Pharmacological Reviews 77 (2025) 100033

Pharmacological Reviews

journal homepage: www.pharmrev.aspetjournals.org

REVIEW ARTICLE

Shared molecular, cellular, and environmental hallmarks in cardiovascular disease and cancer: Any place for drug repurposing?

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https://doi.org/10.1016/j.pharmr.2024.100033

ARTICLE INFO

Associate Editor: Ali Eid

ABSTRACT

Cancer and cardiovascular disease (CVD) are the 2 biggest killers worldwide. Specific treatments have been developed for the 2 diseases. However, mutual therapeutic targets should be considered because of the overlap of cellular and molecular mechanisms. Cancer research has grown at a fast pace, leading to an increasing number of new mechanistic treatments. Some of these drugs could prove useful for treating CVD, which realizes the concept of cancer drug repurposing. This review provides a comprehensive outline of the shared hallmarks of cancer and CVD, primarily ischemic heart disease and heart failure. We focus on chronic inflammation, altered immune response, stromal and vascular cell activation, and underlying signaling pathways causing pathological tissue remodeling. There is an obvious scope for targeting those shared mechanisms, thereby achieving reciprocal preventive and therapeutic benefits. Major attention is devoted to illustrating the logic, advantages, challenges, and viable examples of drug repurposing and discussing the potential influence of sex, gender, age, and ethnicity in realizing this approach. Artificial intelligence will help to refine the personalized application of drug repurposing for patients with CVD.

Significance Statement: Cancer and cardiovascular disease (CVD), the 2 biggest killers worldwide, share several underlying cellular and molecular mechanisms. So far, specific therapies have been developed to tackle the 2 diseases. However, the development of new cardiovascular drugs has been slow compared with cancer drugs. Understanding the intersection between pathological mechanisms of the 2 diseases provides the basis for repurposing cancer therapeutics for CVD treatment. This approach could allow the rapid development of new drugs for patients with CVDs.

I. Introduction: Epidemiology of cardiovascular disease and cancer

Despite advancements in early detection and treatment modalities, cardiovascular disease (CVD) and cancer continue to pose significant challenges to healthcare systems worldwide. According to the World Health Organization, CVD stands as the leading cause of mortality, followed by cancer, with estimated death rates of 17.9 and 9.6 million per year, respectively. The epidemiology of both diseases shares a complex interplay of genetic, environmental, and lifestyle risk factors that must be addressed through a multifaceted approach encompassing primary prevention, early detection, personalized treatment strategies, and long-term surveillance.

In the last 10 years since the seminal report by Hasin et al (2013), there has been increasing evidence of the interconnectedness of these 2 major killers (Pushpakom et al, 2019). CVD and cancer often intersect clinically because individuals with cancer are at increased risk of developing cardiovascular complications caused by various factors, including the consequences and side effects of chemotherapy, immunotherapy, and radiation therapy, as studied in the developing field of cardio-oncology (Florido et al, 2022). Reciprocally, patients with heart failure (HF) have a significantly higher risk of developing cancers compared with subjects with normal heart function. This observation justifies and supports the emerging field of "reverse" cardio-oncology (Ameri et al, 2018; Aboumsallem et al, 2020). Despite this being an emerging and interesting topic, reverse

cardio-oncology goes beyond the scope of this manuscript. Hence, we invite the readers to read a recent review article that extensively addressed the potential effects of HF pharmacotherapeutics on cancer (Sayour et al, 2024). Furthermore, the presence of comorbidities, such as diabetes and hypertension, can exacerbate the risk of developing both CVD and cancer, amplifying their impact on overall morbidity and mortality. For a detailed description of shared risk factors of cancer and CVD from a clinical perspective, please see a recent manuscript from Wilcox et al (2024).

An advanced understanding of the overlapping pathological mechanisms and molecular pathways between CVD and cancer underscores the importance of implementing a holistic management strategy. Repurposing anticancer drugs for the management of CVD represents a promising avenue. Several anticancer drugs have garnered research attention for their cardioprotective effects, leveraging their mechanisms of action to target pathological processes underlying CVD (Atallah et al, 2007; Trent et al, 2010; Avolio et al, 2022; Mohammed et al, 2024).

CVD, as a general term, encompasses a variety of cardiac and vascular pathologies (Chavez-Castillo et al, 2020). Their heterogeneity and differential pathophysiological molecular mechanisms require disease-tailored therapeutic approaches. Likewise, this diversity poses a challenge to personalized drug repurposing applications.

This review focuses on the rationale and opportunities for repurposing anticancer drugs to treat CVD, specifically ischemic heart disease—including myocardial infarction (MI) and atherosclerosis—and HF and associated cardiomyopathies. We thoroughly illustrate the features and molecular mechanisms shared by CVD and cancer. Significant attention is devoted to presenting the logic, advantages, challenges, and viable examples of drug repurposing and discussing the potential influence of sex, gender, age, and ethnicity in realizing this approach. The effects of pharmacodynamics (PD) and pharmacokinetics (PK) will also be given attention. We conclude with an overview of innovative strategies and emerging technologies that, in the future, together with personalized medicine, could help realize the full potential of drug repurposing. This is a timely topic because with the slow development of new cardiovascular drugs, repositioning cancer drugs could boost the introduction of novel therapeutics for patients with CVD, helping to fill a central clinical gap in managing these patients.

II. Drug repurposing

A. Introduction

Drug repurposing or repositioning uses approved or investigational drugs to treat pathologies different from the original target (Ashburn and Thor, 2004; Pushpakom et al, 2019; Abdelsayed et al, 2022). Advantages of drug repurposing include a low risk of failure and reduced time and costs for full development. From a commercial viewpoint, repurposed drugs provide a more rapid return on the investment. The costs of bringing a repurposed drug to market have been projected to be US$300 million on average, compared with an estimated ~$2−3 billion for a new chemical entity (Pushpakom et al, 2019). Bringing a repurposed drug to market could take around half the time needed for a new drug (Nosengo, 2016). Finally, repurposed drugs may reveal new targets and pathways that can be further exploited.

Generic drugs are the easiest and most attractive target for repositioning, having been tested for efficacy and safety for many years and cheap to obtain for clinical assessment because their original patents have expired. Generic drugs attract the interest of companies because patent coverage is still possible, and market exclusivity can be granted for 3 years by the US Food and Drug Administration (US FDA). Repurposing was also developed on drugs abandoned by companies having failed to pass phase 1 trials or showing off-target effects. The UK Medical Research Council and the National Institutes of Health's National Center for Advancing Translational Sciences have made large investments and struck deals with major pharmaceutical companies to allow academic groups to study some abandoned compounds (Nosengo, 2016). Significant barriers to successful repurposing include patentability and regulatory and organizational hurdles. These aspects are out of the scope of this article, being extensively covered by a recent report (Pushpakom et al, 2019).

More recently, computational and omics approaches have been employed to obtain meaningful interpretations for repurposing hypotheses (Pushpakom et al, 2019). Experimental approaches can also be used to identify repurposing options. The growing scientific interest in drug repurposing is reflected by the increasing number of publications, with 12,819 reported in PubMed since 1996 and a peak of 2900 in 2021. Interestingly, a minor fraction refers to cardiovascular repurposing applications (4.8%) or can be retrieved by combining drug repurposing, cardiovascular, and cancer (1.6%) as keywords. Likewise, the association of drug repurposing and angiogenesis results in 222 publications (1.7%). These data indicate that the field is novel and worth further research.

Cancer drug repurposing for the treatment of CVD is still in the very early developmental stages. Advancing this strategy is particularly important because the development of new cardiovascular drugs is slow. Indeed, in 2020, the FDA approved 36 new drugs for cancer therapy versus only 2 for CVD (Abdelsayed et al, 2022). These numbers suggest that repurposing cancer drugs for CVD applications could accelerate the development of new treatments for patients with CVD.

B. Role of pharmacokinetics and pharmacodynamics in drug repurposing

Management of CVD and cancer almost invariably requires multipharmacological therapies. For instance, in patients with HF, the therapeutic regimen includes a combination of drugs targeting various pathogenic mechanisms, such as mineralocorticoid antagonists, angiotensin receptor/neprilysin inhibitors, and sodium-glucose cotransporter-2 inhibitors. These treatments are now extended to a large population of patients with mild to moderate reduction of ejection fraction (McDonagh et al, 2021; Vaduganathan et al, 2022). Severe medication-related adverse events are up to 4 times more frequent in the elderly than in the general population (Alhawassi et al, 2014). Extended prescription of polypharmacy in this high-risk category will increase medication regimen complexity and predispose to adverse events. Multimorbidity can also significantly affect a drug's therapeutic efficacy and safety regardless of age (Laatikainen et al, 2022). Drug repurposing poses significant challenges in frail, multimedicated patients and requires accurate assessment of PK and PD interactions.

PK refers to the action a medication causes once given to a living organism and comprises drug absorption, distribution, metabolism, and elimination (ADME) profiles. Drug formulation, crafting the composition, structure, and delivery of pharmaceuticals, can help refine ADME profiles and improve a repurposed drug's efficacy and safety.

PD refers to the relationship between the drug concentration at the site of action and the biological effect. Therefore, it is paramount to prefer new repurposing compounds that reach specific targets (enzymes, receptors, and ion channels) in a selective and timely manner. For instance, several mitogen-activated protein kinase (MAPK) pathways control fundamental cellular processes, including cell proliferation, differentiation, and survival. When

dysregulated, these kinases participate in the induction and maintenance of various pathologies, primarily cancer and CVD (Kong et al, 2019; Bhagwat et al, 2020; Mohammed et al, 2024). Small molecule screening can help select the most promising candidates to modulate specific Raf/MAPK kinase (MEK)/extracellular signal-regulated kinase 1/2 (ERK1/2) cascade pathways in vascular cells to treat ischemic disease (Avolio et al, 2022; Schanbacher et al, 2022). Moreover, recent research focuses on designing new molecules capable of interfering with the duration and intensity of the Raf/MEK/ERK1/2 signals and dynamic subcellular localization that classify the components of the cascade. In resting cells, ERK1/2 molecules are retained in the cytoplasm. In cancerous cells, rapid and robust translocation to the nucleus allows the phosphorylation and modulation of the activity of many nuclear proteins, mainly implicated in cell proliferation. At the same time, the cytosolic molecules primarily regulate other ERK1/2-dependent processes. Compounds preventing nuclear translocation improve the outcome of BRAF- and N/K-Ras-transformed cancers and overcome the side effects of unspecific ERK inhibitors (Plotnikov et al, 2015; Maik-Rachline et al, 2019). Similar PD approaches could be used to refine anticancer drug indications in CVD.

Drug interaction (DI) encompasses the pharmacological or clinical response to the administration or coexposure to multiple therapeutic agents that can change the patient's outcome beneficially or detrimentally, improving or reducing the efficacy and impinging upon toxicity (Fatunde and Brown, 2020). When reusing a drug for new therapeutic indications, the clinical relevance of possible DI with concomitant therapy can be quantified using functional parameters. For instance, a definition of cancer therapy-related cardiac dysfunction reportedly referred to a decrease in the left ventricular (LV) ejection fraction of $>$ 10% points to a value of $<$ 53% (Volkova and Russell, 2011). A PD-DI may occur whenever a given repurposed drug shares mechanisms of action similar to concomitant medications. This type of interaction, either positive or negative, may be additive, synergistic, or antagonistic.

Extending or repurposing a drug to a larger user population may reveal unexpected DIs after market approval. Most cardiovascular and cancer drugs have multifaceted pharmacological profiles, including a narrow therapeutic index and a steep dose-toxicity curve. These features may be further modified and amplified by intrapatient and interpatient variability to make the case more complex (Beijnen and Schellens, 2004). Other substances or factors can affect medication disposition, including food, supplements, formulation excipients, and environmental factors. The reader is directed to specialized review articles and scientific statements that describe PD-DI in the context of various CVDs (eg, hypertension, cardiomyopathy, and HF) common to cardio-oncology (Mangoni and Jarmuzewska, 2019; Beavers et al, 2022).

Patients with HF represent a paradigmatic example of how a disease state can modify drug PK-PD characteristics. One crucial aspect regards changes in the expression of drug-metabolizing enzymes and transporters, such as cytochrome P450 (CYP) and UDP-glucuronosyltransferases (UGTs). CYP enzymes are responsible for a significant part of drug phase 1 metabolism, while UGTs are the most important enzyme families involved in phase 2 metabolism. New cardiovascular therapies and repurposed drugs should be scrutinized for their DI with concomitant medications affecting the CYP- and UGT-regulated metabolism (Beavers et al, 2022).

Moreover, hepatic, gastrointestinal, and renal perfusion deficits result in drug absorption and elimination problems. Reviewing reported clearance changes, Ogawa et al (2014) showed that multiple treatments can lead to significant differences in PK-PD characteristics in patients with HF. HF is also associated with alterations in the intestinal microbiota, which can impact drug PK-PD characteristics and cause the formation of toxic metabolites interfering with drug response (Tuteja and Ferguson, 2019). Hypoalbuminemia is common in patients with HF, creating changes in the PK profile for drugs highly bound to albumin.

Comorbidities are also important variables to consider when introducing a new drug to a patient with HF. In EMPEROR trials, plasma concentrations of empagliflozin, an antidiabetic drug repurposed to treat CVD (Zinman et al, 2015), were higher in patients with HF compared with patients with type 2 diabetes (T2D) and CVD (Rascher et al, 2024). The observed difference between the different patient populations could only partly be explained by the influence of baseline and demographic characteristics. It was suggested that the changes in PK profiles were caused by changes in HF-induced pathophysiology. The conclusion was that 10 mg is the appropriate empagliflozin dose for patients with HF, 2.5-fold less than the dose recommended for patients with T2D (Rascher et al, 2024).

Many other patient-specific factors contribute to individual variation in response to medications. Pharmacogenetics and pharmacogenomics, which study differences in drug response caused by specific gene variants or multiple gene interactions, have been widely applied in cancer. Cardiac pharmacogenomics has progressed, even at a slower pace, after discoveries that variants are associated with modified effects or metabolism of common drugs, such as β-blockers, angiotensin-converting enzyme inhibitors, statins, and antiplatelet and anticoagulant drugs. Recently, some centers have started performing genetic testing routinely to inform the risk of statins and clopidogrel (Sleder et al, 2016). For the scope of drug repurposing, genetic testing may help identify patients who may benefit from targeting an inherited molecular alteration.

C. *Influence of sex, gender, ethnicity, and age*

As discussed in the previous section, during drug development and repurposing, a comprehensive approach necessitates the evaluation of several critical variables. Genetic, epigenetic, and environmental factors, such as sexual chromosomes, sexual hormone levels, body weight, fat percentage, total body water, and many others, influence drug PK and PD characteristics, thus the body's response (Valodara and Sr, 2019; Lee et al, 2021; Pathak et al, 2023). Among these, sex, gender, ethnicity, and age represent key aspects that often remain understudied in clinical trials and drug efficacy and safety investigations (Klein and Flanagan, 2016; Guerrero et al, 2018). This lack of consideration for demographic characteristics limits the generalizability of findings and may lead to the erroneous assessment of the drug's risks and benefits for the less-represented subgroups (Ramamoorthy et al, 2022).

Below are discussed some key examples of subgroup-specific differences in physiological and pathological mechanisms contributing to CVDs and cancer onset, progression, and treatment.

The immune system, which is a key player in cancer and CVDs, is strongly influenced by age, sex, gender, and ethnicity. The major difference between men and women consists in the T-cell ratio, where women display a higher percentage of $CD4^+$ T cells to $CD8^+$ T cells compared with men (Abdullah et al, 2012; Sankaran-Walters et al, 2013; Klein and Flanagan, 2016; Guerrero et al, 2018). The number and function of T cells are also strongly impaired with aging, which causes immunosenescence (Lewis et al, 2022). Differences in immune response have also been observed related to ethnicity (Martin et al, 2023a).

Angiogenesis, another main actor in CVDs and cancer progression, has also shown sub-group differences. For example, white adipose tissue-derived endothelial cells (ECs) from women display a higher proliferation rate compared with males (Rudnicki et al,

2023). Another study demonstrates that a significant portion (14%–25%) of EC RNA transcripts exhibit sex bias, which could potentially influence coronary artery disease profile later in life, contributing to the observed differences in cardiovascular health between men and women (Hartman et al, 2021; Regitz-Zagrosek and Gebhard, 2023).

Furthermore, the role of melanocortin 1 receptor signaling in stimulating angiogenic pathways is well-established (Freilikhman et al, 2021). Given the reported link between melanocortin 1 receptor activity and skin pigmentation (Swope and Abdel-Malek, 2018), it is reasonable to hypothesize that skin pigmentation may influence the angiogenic process, thus impacting drug repurposing (Freilikhman et al, 2021).

Sex hormones, like estrogens and androgens, are also key players in drug response (Valodara and Sr, 2019). They regulate gene expression through the binding of their receptor to specific regions on gene promoters or enhancer regions on DNA (Wang et al, 2011). This regulation impacts transporters, receptors, and enzymes related to drug metabolism, affecting drug absorption, distribution, metabolism, and elimination directly and indirectly (Moyer et al, 2019). Divergences in sex hormone levels are evident not only between the sexes but also among different ethnicities and age groups (Rohrmann et al, 2007; Horstman et al, 2012; Lopez et al, 2013).

Notably, estrogens and androgens are strongly involved in breast and prostate cancer progression, respectively (Keshamouni et al, 2002; Klein and Flanagan, 2016). These hormone-modulated genes influence a vast array of biological processes, including those discussed in this review. Myc proto-oncogene protein (MYC) levels and ERK1/2 activation have shown a positive correlation with estrogen levels. Additionally, MYC and androgen receptor expression seem to influence each other (Wang et al, 2011; Ludwik et al, 2020).

In estrogen receptor (ER)α-positive luminal breast cancer, δ-like ligand 1 (DLL1)/neurogenic locus notch homolog protein (NOTCH) signaling appears particularly important. Higher DLL1 levels correlate with poorer prognosis in this type of cancer. The estrogen pathway stabilizes the DLL1 protein, preventing its degradation (Kumar et al, 2019).

Sex hormones also influence the cardiovascular system in a sex-specific manner. Cardiac tissue treated with 17β-estradiol (E2) shows that E2 regulates gene expression differently between men and women (Kararigas et al, 2012). Also, the response to cancer therapy is modulated by sex. Immune checkpoint inhibitors (ICIs) show greater efficacy in females with non–small cell lung cancer, while the opposite is true for colorectal cancer, where males receiving ICIs have a higher survival rate compared with females. Similarly, male patients with melanoma display significantly better survival rates than females (Haupt et al, 2021). These few examples merely scratch the surface of the vast field of sex dimorphism, ethnic differences, and aging, emphasizing the crucial need for subpopulation stratification in clinical and preclinical studies.

III. Shared cellular hallmarks in CVD and cancer

Despite arising from distinct pathological processes, both CVD and cancer share several pathophysiological features at the molecular, cellular, and systemic levels supporting the rationale of cancer drug repurposing for the treatment of CVD.

Many of the shared alterations in cancer and CVD convey similar dysregulation of cellular signaling pathways, resulting in uncontrolled inflammation and immune response, vascular alterations, unbalanced proliferation or cell death, and aberrant healing/repair capabilities (Fig. 1).

A. Inflammation

Inflammation represents a key mechanism of defense of the organism, requiring the close interaction of molecules (already available or neo-synthetized, following given insults) and cellular effectors of innate and adaptive immunity (Mantovani and Garlanda, 2023). The acute inflammatory process is characterized by 2 main events involving (1) vascular changes and (2) recruitment and activation of immune cells mediating inflammation. These events are closely interconnected. In the event of failure to resolve acute inflammation (for example, because of failure to eliminate the triggering agent), the inflammatory process shifts from the acute to the chronic phase (Mantovani and Garlanda, 2023).

Humoral soluble factors regulating the inflammatory response include cytokines, that orchestrate immune cell recruitment into injured tissues and their polarization and effector activities, preformed soluble immunoglobulins (that favor the opsonization process, the recognition of aptens, and the generation of immunocomplexes), and soluble mediators of inflammation (Mantovani and Garlanda, 2023). These latter can be preformed, such as histamine, serotonin, lysosomal enzymes, immunoglobulins, or can be de-novo generated starting from the arachidonic acid processing (prostaglandins, prostacyclins, thromboxanes), nitric oxide, platelet-activating factor (Mantovani and Garlanda, 2023).

The cytokine/chemokine milieu within damaged tissue, together with their circulating counterpart, strongly impacts all events orchestrating inflammation and is also crucial in the shift from acute to chronic inflammation, this latter largely known as a host-dependent hallmark of cancers and CVDs.

Tumor necrosis factor-α (TNF-α) represents one of the earliest and most potent mediators of inflammation because it is necessary for the production of other inflammatory mediators and promotes the activation of immune cells, vascular permeability, and the recruitment of leukocytes to the site of infection or damage (van Loo and Bertrand, 2023).

Interleukin (IL)-1 (IL-1) family member proteins, which include IL-1α and IL-1β, are crucial in the acute phase of inflammation to boost the release of additional inflammatory cytokines that cooperate for the activation of ECs, support the recruitment of leukocytes to the damaged tissues and are responsible for the systemic effects of inflammation, including fever (Dinarello, 2018).

IL-6 is produced by diverse immune and nonimmune cells, during inflammation, and promotes the acute phase response in the liver, including the production of C-reactive protein (CRP); also IL-6 is one of the major activators of the signal transducer and activator of transcription 3 (STAT3) signaling, another relevant inflammatory-related pathway shared by cancers and CVDs (Hunter and Jones, 2015).

IL-8 is one of the key mediators of chemotaxis, guiding neutrophils and other immune cells to areas of tissue damage or infection via chemokine receptors C-X-C motif chemokine receptors 1 and 2. IL-8-activated neutrophils release granule-stored enzymes and reactive oxygen species (ROS), necessary to eliminate pathogens and clean the inflammatory tissues from damaged cells. Like other cytokines, IL-8 is also implicated in the cascade activation by amplifying the release of diverse proinflammatory cytokines, including TNF-α and IL-1 (Apostolakis et al, 2009).

Interferon-γ (IFN-γ) represents a key cytokine during inflammation. IFN-γ is secreted by effector cells of innate and adaptive immunity, namely natural killer (NK) cells, $CD4^+$ T-helper, and $CD8^+$ T-cytotoxic effector cells, and is also involved in the polarization of M1 macrophages, directly contributing in the clearance of intracellular pathogens (Zhang, 2007).

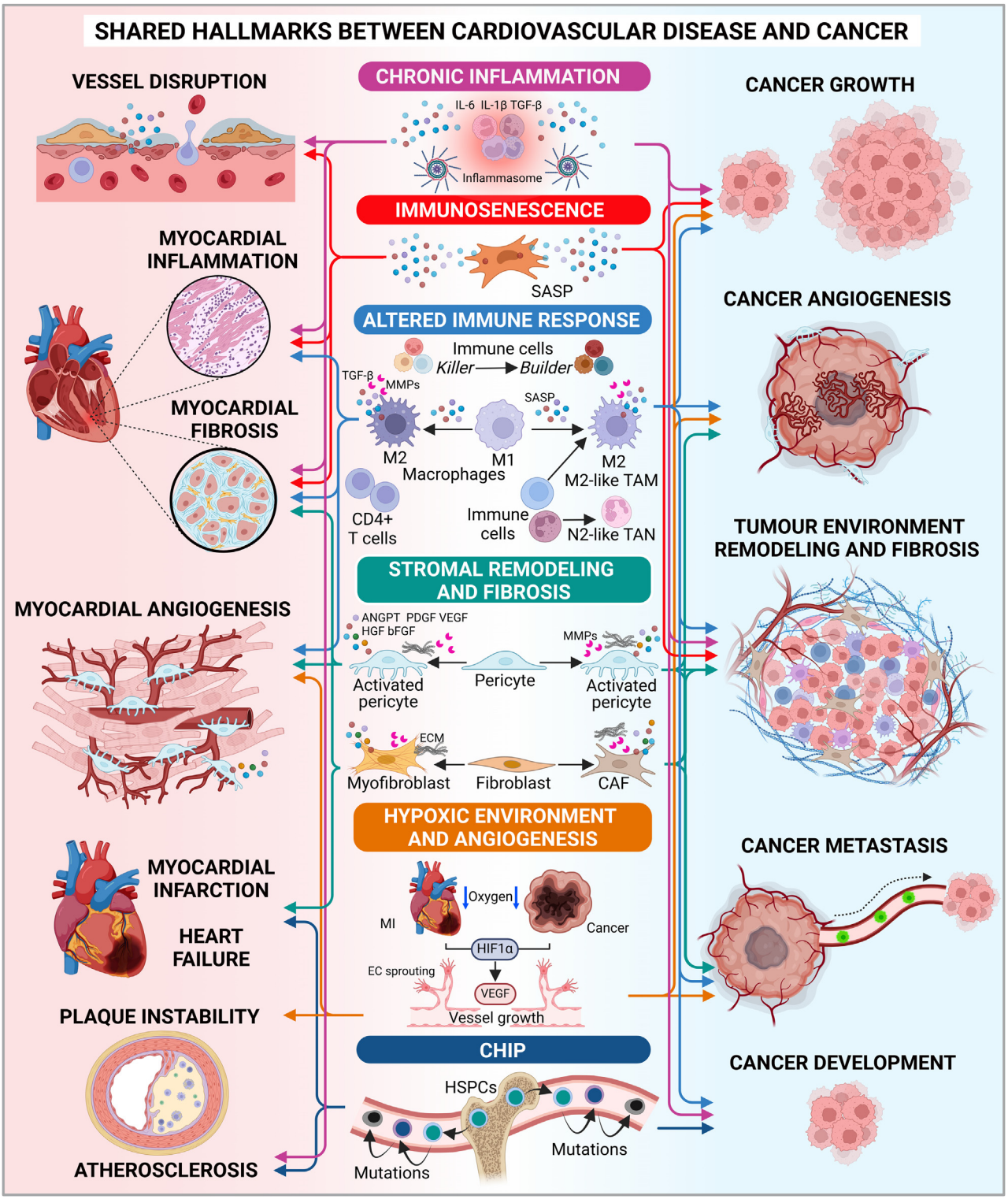

Fig. 1. Shared hallmarks between cancer and CVD. Cartoon illustrating the features and cellular and molecular mechanisms shared by cancer and ischemic heart disease (including MI, HF, and atherosclerosis) that contribute to the development or progression of the 2 diseases. Shared hallmarks (summarized in the central panel) include chronic inflammation, immunosenescence, altered immune response, stromal remodeling and fibrosis, hypoxia, angiogenesis, and CHIP. In the context of CVD (left panel), these processes contribute to the disruption of vascular integrity and function, the pathogenesis of myocardial inflammation and fibrosis, as well as the pathogenesis and progression of MI, heart failure, and atherosclerosis. Moreover, they also participate in the beneficial reparative pro-angiogenic response after injury. While in cancer (right panel), they play a role in cancer development, growth, and metastatic spread, in addition to promoting cancer angiogenesis and tumor environment remodeling, including fibrosis. bFGF, basic fibroblast growth factor; TAM, tumor-associated macrophages; TAN, tumor-associated neutrophils. Created with BioRender.com.

Among the mechanisms immediately instructed for rapid responses against pathogens, inflammasomes, defined as large multiprotein complexes of the innate immune system, have a crucial role in the inflammatory response (Yao et al, 2024). Inflammasomes are composed of a sensor and a caspase recruitment domain, linked together, directly or via an adapter. The mechanisms of action of

these complexes were well-reviewed by Yang et al (2019). Briefly, a pattern-recognition receptor is activated by pathogen-associated molecular patterns or damage-associated molecular patterns; this induces the priming of the inflammasome, which consists of the expression of IL-1β and inflammasome sensor component. Then, the sensors sense the pathogen-associated molecular pattern/ damage-associated molecular pattern molecules, and the inflammasome starts to assemble. Once the inflammasome is assembled, it permits the autocatalytic activity of the caspases that bind to it, leading to caspase cleavage and activation. Activated caspases trigger gasdermin-D cleavage, which translocates to the cell membrane, where it generates pores that determine programmed cell death through pyroptosis and the release of IL-1β and IL-18 in the extracellular environment. IL-1β and IL-18 transmit the inflammatory signal and recruit other immune cells (Yang et al, 2019).

The association between cardiovascular risk factors, inflammation, and cancer has been long and last established. Persistent inflammation (ie, chronic inflammation) plays a pivotal role in the pathogenesis of many cancers, by modulating the early tumor microenvironment and facilitating cancer initiation and progression (Wang and DuBois, 2018). This intricate process entails a complex interaction between tumor cells and immune cells and may be partly attributed to impaired resolution of inflammation (Mantovani et al, 2008).

Cancer and CVD are characterized by the chronic release of major proinflammatory cytokines, such as IL-6, IL-1β, and transforming growth factor-β (TGF-β) (Wei et al, 2019; Zhao et al, 2021a) that can aberrantly activate different downstream pathways, including STAT3, Nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), and suppressor of mothers against decapentaplegic (SMAD). This inflammatory signaling promotes the continuous recruitment and induction of altered phenotypes and functions of immune cells in a phenomenon termed immune cell polarization (Johansson et al, 2008; Bruno et al, 2014; Sun et al, 2021a; Steffens et al, 2022).

NOD-like receptor (NLR) protein 3 (NLRP3)-inflammasome accounts as another inflammatory mediator representing a shared system in cancers and CVDs (Zheng, 2022; Sharma and Kanneganti et al, 2021; Mauro et al, 2023).

Increased expression of the NLRP3-inflammasome signaling pathway in the salivary gland of patients with Sjogren's syndrome could predict the development of non-Hodgkin's lymphoma (Baldini et al, 2017). Inflammasome pathway gene expression is modulated in urine sediments of bladder cancer (Poli et al, 2015). Inflammasomes are thought to play a role also in colorectal cancer, where NLRP3-mediated activation of IL-18 and IL-1β induces macrophage stimulation of interferon genes (*STING*) signaling and supports 4-1BBL/4-1BBL-dependent NK cell antitumor properties (Dupaul-Chicoine et al, 2015; Sun et al, 2023; Si et al, 2024). NLR nucleotide-binding oligomerization domain-like receptor family caspase recruitment domain containing 5 (NLRC5) is involved in both the transcriptional activation of major histocompatibility complex class I and serves as a sensor in the inflammasome. It is associated with multiple tumor types and has been suggested as a promising prognostic and therapeutic target (Yoshihama et al, 2016). Furthermore, increased expression of caspase1 and NLRP3 has been identified in bone marrow-derived mononuclear cells from patients with leukemia resistant to glucocorticoids (Paugh et al, 2015).

In CVD, inflammasome has been linked to multiple conditions such as hypertension, MI, ischemic injury, cardiomyopathies, HF, and atherosclerosis (Pellegrini et al, 2021). One example is represented by the detected enhanced levels of proteins involved in the NLRP3 pathway in monocytes associated with the severity of coronary artery disease (Wang et al, 2014). Moreover, Altaf et al (2015) demonstrated that the higher levels of inflammasome molecules detected in patients with acute MI and unstable angina could be reverted by rosuvastatin, a drug used to control cholesterol, suggesting a possible role of cholesterol in inflammasome activation. Moreover, several drugs known to reduce inflammation signals and potentially modulate the inflammasome pathway have been demonstrated to exert cardiovascular protection, including canakinumab, discussed later in this article, and others that are thoroughly described in a recent review article by Pellegrini et al (2021).

B. Altered immune response

Cancer and CVD share several immunological features. In both cases, immune cells of the innate and adaptive systems are initially recruited to recognize and eliminate the noxious agent and are endowed with "killer" activities. Later, based on the plasticity of immune cells, the chronic proinflammatory state turns them into "builder" cells (Johansson et al, 2008; Bruno et al, 2014; Steffens et al, 2022). This shift from killer to builder also occurs during the wound healing and repair processes (Laurent et al, 2017; Abnave and Ghigo, 2019; Moon et al, 2023), but it is uncontrolled in both cancer and CVD.

Cancer tissues, because of immunosuppression, block the infiltration of antitumor effector cells of both innate (NK cells) and adaptive ($CD8^+$ T cells) immunity, while privileging the infiltration of myeloid cells, such as myeloid-derived suppressor cells, M2-like/ tumor-associated macrophages, N2-like/tumor-associated neutrophils. Cancer cells also regulate the phenotype and functions of tissue-resident immune cells, by polarizing them into protumor cells, such as M2-like/ tumor-associated macrophages, that further support immunosuppression and tumor angiogenesis. Angiogenesis is a crucial event for cancer maintenance, progression, and metastatic spread (Mantovani et al, 2002; Sica et al, 2008; Parisi et al, 2018). Immune cells are active orchestrators of the angiogenic switch in tumors, shifting from killer to builder effector cells (Bruno et al, 2014; Stockmann et al, 2014; Ebeling et al, 2023).

Similar immune responses can be observed in CVD and cancers. Macrophages have been extensively studied, being the most numerous leukocytes in the heart and for their role in the response to injury (Mosser et al, 2021). A dual role of macrophages, based on their polarization state, can be also found in the heart, under pathophysiological conditions. For example, in the steady state, tissue-resident macrophages exert homeostatic functions, including defending against infection and removing senescent or damaged cells, acquiring the typical M1-like phenotype, and exerting proinflammatory and phagocytic activities.

Following myocardial damage, proinflammatory M1-like macrophages are generated to eliminate damaged cells and contain possible infections occurring in the injured heart. In the latter phases, M1-like macrophages are turned and/or replaced by M2-like macrophages, which are generated to start the myocardium remodeling process (Yap et al, 2023; Shen et al, 2024b). When this process of M2-like macrophage generation is uncontrolled, based on their capability to produce TGF-β and matrix metalloproteinases (MMPs), the fibrogenic process is induced, resulting in myofibroblast activation and extracellular matrix (ECM) remodeling (Yap et al, 2023; Shen et al, 2024b).

Neutrophils also have a dichotomous role in CVD (Sreejit et al, 2022). N1 neutrophils show proinflammatory activities (killer) during MI but can be found also in an N2 form, exerting pro-repairing (builder) functions (Prabhu and Frangogiannis, 2016). Following MI, neutrophils produce the alarmin S100A8/A9 that induces the expression of Nr4a1 in inflammatory monocytes, supporting their shift to reparative M2-like macrophages (Marinkovic et al, 2020). The shift from N1-like to N2-like neutrophils has been

found to occur following 1 day of MI. Finally, neutrophils can express proreparative factors, including oncostatin M, lipocalin, and annexin A1 (Lorchner et al, 2015; Horckmans et al, 2017; Ferraro et al, 2019).

In addition to macrophages and neutrophils, adaptive immune cell populations, including T-cell subsets, can be found in the infarcted heart (Hofmann and Frantz, 2016). The fine-tuning of T-cell response is crucial to avoid a subsequent maladaptive response. Concerning the profibrogenic activity of T cells in the heart, it has been observed that CD4+ T cells, accumulating in the myocardium, exacerbate cardiac fibrosis in response to pressure overload (Nevers et al, 2015). Another example of a T-cell builder-to-killer shift in the CVD setting is represented by acute viral myocarditis, where persistent T-cell-mediated responses can participate in the development of dilated cardiomyopathy through an autoimmune mechanism (Stephenson et al, 2017).

Perturbations of the immune system might be considered shared features in cancer and CVDs; however, some implications are different, based on the extreme plasticity of immune cells. For example, similar cytokines, in a time and (pathology) context-dependent manner, can result in different behaviors for the same immune cell subset. In line, while in cancer, immunosuppression leads to tumor evasion from the immune surveillance, in CVD, immune activation may be damaging.

Finally, both cancer and CVD show senescence as a shared hallmark. Because individuals age, all tissues and organs undergo the senescence process that impacts efficient immunosurveillance (ie, in cancers) and repairing capabilities (ie, in CVDs). Also, the immune system, during aging, acquires compromised and often aberrant phenotypes and functional alterations. In this scenario, immunosenescence—consisting of the gradual impairment of essential responses typical of "physiologic" aging—acts as a relevant shared feature between cancer (Pawelec et al, 2010; Liu et al, 2023a; Wang et al, 2023c) and CVD (Ghamar Talepoor and Doroudchi, 2022; Puspitasari et al, 2022; Liu et al, 2023a). Several factors produced by tumors and shared in CVDs can enhance the immunosenescence process, making the immune system impaired, caused by the induction of anergy and cell exhaustion. A peculiar secretory feature of cancerous cells and cardiovascular cells, termed senescence-associated secretory phenotype (SASP), contributes to the generation of a chronic inflammatory state and a tissue microenvironment promoting immune cell dysfunction (Coppe et al, 2010; Faget et al, 2019; Song et al, 2020; Sun et al, 2022b).

C. Angiogenesis

Angiogenesis is the process through which new blood vessels form from pre-existing vessels. It is essential to ensure continuous provision of nutrients and oxygen to tissues. It has contrasting roles in CVD and cancer: while angiogenesis is beneficial to sustain tissue healing and repair following MI and preserve myocardial viability in HF, unwanted angiogenesis is detrimental in cancer because it promotes tumor cell growth and metastatic spread. Abnormal blood vessel function, metabolism, and remodeling are typical hallmarks and contributors to disease progression in both cancer and MI. Therefore, understanding the complex mechanisms underlying angiogenesis in cancer and ischemic heart disease is crucial for developing effective therapeutic strategies for patients.

Solid cancer and the ischemic heart are united by a common hypoxic microenvironment contributing to angiogenesis (Krock et al, 2011). Low oxygen levels trigger hypoxia-inducible factor 1 (HIF-1) activation. HIF-1 regulates the transcription of vascular endothelial growth factor (VEGF), a potent proangiogenic factor. Other angiogenic factors produced by cancer cells, cardiac stromal cells, and vascular cells include basic fibroblast growth factor (FGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and angiopoietin (ANGPT)-1 and 2 (Vimalraj, 2022). These angiogenic factors promote EC proliferation, migration, and tube formation, leading to the sprouting of new blood vessels from pre-existing ones. The balance between angiogenic inducers and inhibitors is critical. In cancer, inhibitors of angiogenesis (eg, angiostatin, endostatin, and thrombospondin) are being explored as therapeutic targets to block tumor growth (Ferrara and Kerbel, 2005).

In the heart, this adaptive tissue response to ischemia is usually beneficial in promoting tissue perfusion and survival. Accordingly, inhibition of key angiogenic pathways promotes the transition from compensatory cardiac remodeling—such as cardiac hypertrophy—to HF (Izumiya et al, 2006; Sano et al, 2007; Groarke et al, 2014). However, angiogenesis is not always a positive event in some CVDs. For example, within atherosclerotic plaques, it can lead to plaque instability and rupture, increasing the risk of ischemic events for the patient (Virmani et al, 2005; Camare et al, 2017). In addition, spontaneous angiogenesis is often defective in the ischemic heart, with this reparative dysfunction being a hallmark of a pre-existing endothelial dysfunction and microvascular disease. Proangiogenic therapies aimed to aid the spontaneous vascular response to ischemia often resulted in leaky and immature neovascularization, favoring more inflammation and tissue edema (Pettersson et al, 2000; Annex and Simons, 2005; Rubanyi, 2013; Tan et al, 2022).

In cancer, oxygen consumption by tumoral cells reaches a critical threshold as the cancer mass increases, leading to hypoxia. Angiogenesis within the tumor facilitates tumor progression as well as cancer cell migration and metastatic colonization of other organs, a detrimental event for the host (Bielenberg and Zetter, 2015). Tumor vessels show abnormal structure and function with typically chaotic organization, with irregular and tortuous serpentine-like shapes. Abnormal tumor blood vessels are highly permeable, which contributes to edema (swelling) and facilitates tumor cell invasion into surrounding tissues. This permeability is often driven by VEGF and other factors (Nagy et al, 2009; Forster et al, 2017).

Important for effective therapeutic approaches, arterial-venous identity is ill-defined, and shunting compromises flow, limiting immune cell recruitment and proper drug delivery in the tumor mass. Thus, a paradigm shift from the idea of therapies contrasting vasculature formation in cancer to those improving vascular maturation and normalization is warranted because it could aid chemotherapy by boosting the delivery of drugs within the tumor (Yang et al, 2021). By analogy, therapeutic products capable of stabilizing neovascularization in the ischemic heart could overcome the current limitations of therapeutic angiogenesis (Avolio et al, 2022).

In this context, the biology of pericytes, vascular stromal cells controlling the maturation and stabilization of newly formed capillaries, is attracting attention for angiogenic-based therapies. Pericytes are key cells of the vascular niche that support angiogenesis and vascular maturation. They wrap around blood vessels and are essential to preserving vascular integrity, stability, and function. During the initial phases of angiogenesis, nascent vessels are only partially covered by pericytes. The subsequent recruitment and enrichment of pericytes lead to structural and functional vascular maturation (Payne et al, 2020). This phenomenon aids in functional vascularization post-MI (Avolio et al, 2024). Noteworthy, in cancer, pericytes remain detached from ECs, thus promoting vascular instability (Sun et al, 2021b). Hence, pericytes may represent preferential targets for stabilizing tumoral and ischemic vascularization. In both the hypoxic microenvironments of cancer and MI, quiescent pericytes are activated and produce more angiogenic factors to support a quick angiogenic response, but also ECM,

matricellular proteins, and MMPs to sustain the remodeling of the surrounding environment. In the ischemic heart, this process supports tissue perfusion and repair (Avolio et al, 2024). Manipulating pericyte phenotype or behavior could be therapeutically valuable in encouraging functional vascularization of the infarcted heart (Avolio et al, 2022) as well as limiting tumoral cell intravasation into blood vessels and metastases in the context of cancer (Sun et al, 2021b). On the other hand, additional aspects, such as the pericytes' contribution to premetastatic niche formation, should be considered (Paiva et al, 2018).

D. Stromal remodeling

Remodeling of the tissue stroma is another overlapping mechanism in cancer, ischemic heart disease, and postischemic HF, characterized by profound alterations of the extracellular microenvironment. Degradation of ECM components by MMPs facilitates EC migration and new vessel formation. A common feature is fibroblast activation into myofibroblasts or, in the context of cancer, cancer-associated fibroblasts (CAFs). Activated fibroblasts increase the deposition of collagen, fibronectin, and other matrix proteins, leading to the build-up of fibrotic tissue. Within the tumor, the formation of thick layers of fibrotic tissue creates a physical barrier that limits drug penetration and immune cell infiltration, reducing treatment efficacy (Choi et al, 2013). CAFs also secrete growth factors, cytokines, and chemokines, favoring tumor growth and vascularization (Pape et al, 2020). Stromal remodeling in cancer often results in increased ECM stiffness, which can influence tumor cell behavior such as invasion, particularly through the activation of focal adhesion kinase (FAK) and Src family kinases, and epithelial-to-mesenchymal transition (Levental et al, 2009).

Excessive ECM secretion in the heart leads to pathological fibrosis; stiff fibrotic tissue impedes normal myocardial contractility, ultimately causing alterations in LV function and HF (Hinderer and Schenke-Layland, 2019). Although these observations put fibrosis into the enemy field, fibrotic repairs could be advantageous in some circumstances. For example, after MI, the fibrotic scar is vital to "fill the gap" generated by the sudden loss of viable myocardial tissue. Activated fibroblasts play a crucial role in tissue repair and remodeling following MI (Humeres and Frangogiannis, 2019). By contributing to the formation of granulation tissue, they prepare a scaffold for angiogenesis and the migration of other cell types involved in the repair process. The creation of a compact ECM after heart ischemia promotes a stable scar formation crucial to preventing cardiac rupture (Fu et al, 2018).

Stromal cells secrete a plethora of soluble factors that are released in situ and into the systemic circulation. The cell secretome is influenced by the extracellular environment and changes to reflect the disease status of organs and tissues. Interestingly, recalling the concept of reverse cardio-oncology, some molecular alterations induced by CVD favor cancer development. Caller et al (2024) demonstrated that small extracellular vesicles produced by cardiac mesenchymal stromal cells in infarcted and failing hearts carry protumorigenic factors that speed up cancer growth when uptaken by cancer cells. In another study, the induction of HF promoted the growth of intestinal tumors in mice (Meijers et al, 2018). The same study reported that patients with HF present significantly higher levels of plasmatic serpinA3, a protumorigenic factor reportedly implicated in human colon cancer cell growth (Meijers et al, 2018).

E. Altered cellular metabolism

Among the others, the shift from oxidative phosphorylation to glycolysis during nutrient deprivation was the first metabolic reprogramming recognized in tumors. This metabolic adaptation, known as the "Warburg effect," supports rapid proliferation in cancer cells and affects tumor growth and dissemination potential (Zhao et al, 2023).

Tumoral ECs undergo a metabolic reprogramming characterized during the high-energy stage of sprouting by a hyperglycolytic phenotype and enhanced lactic acid production. Lactate accumulation in the tumor environment, apart from generating an immunosuppressive environment, facilitates excess lactate uptake by the vascular endothelium, with subsequent conversion to pyruvate for further oxidation and an ROS-mediated NF-κB and IL-8 induction (Vegran et al, 2011). Moreover, lactate reportedly directly modulates receptor tyrosine kinases (RTKs) (including VEGF receptor 2) in angiogenic ECs (Ruan and Kazlauskas, 2013). Glycolysis also provides intermediates for the branched pentose phosphate pathway, leading to the anabolic synthesis of nucleotides. A study using pathway mapping and heatmap analysis revealed that transcripts of most glycolytic genes were upregulated in tumoral ECs, including 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), the glucose-transporter GLUT1, and rate-limiting enzymes of glycolytic side-pathways, such as the pentose phosphate pathway glucose-6-phosphate dehydrogenase, hexose-6-phosphate dehydrogenase, and serine biosynthesis pathway phosphoglycerate dehydrogenase, involved in biomass (nucleotide) synthesis.

Another important metabolite produced by the Warburg effect is methylglyoxal, a precursor of advanced glycation end products. In cancer, methylglyoxal has been reported to play a dual role, displaying a hormetic potential, which in part justifies the conflicting results regarding its antitumor or protumorigenic roles that have been shown so far. Indeed, although anticancer properties were initially ascribed to methylglyoxal because of its cytotoxicity, increasing evidence has highlighted its protumorigenic role in several types of cancer (Leone et al, 2021).

Furthermore, alterations in cancer cell metabolism can extend beyond the tumor microenvironment and impact the cardiovascular system. In this context, somatic mutations in IDH1 and IDH2 (encoding cytosolic isocitrate dehydrogenase [NADP] [IDH1] and mitochondrial isocitrate dehydrogenase [NADP] [IDH2], respectively) have been identified in several cancer types, including gliomas (Yan et al, 2009), acute myeloid leukemia (Kattih et al, 2021), colorectal cancer (Huang et al, 2021), and prostate cancer (Mehra et al, 2023). Variants in IDH1 and IDH2, converting α-ketoglutarate into D-2-hydroxyglutarate (D2-HG), result in the accumulation of D2-HG in cancer cells that release this oncometabolite into the bloodstream, thereby also affecting distant organs. D-2HG acts as a competitive inhibitor of α-ketoglutarate-dependent dioxygenases, including HIF-regulating prolyl hydroxylases, DNA-, RNA-, and histone demethylases, promoting cancer progression through epigenetic and metabolic pathways, also influencing the immune microenvironment, and favoring immune escape. In a model of glioma, Bunse et al (2018) demonstrated that D-2HG is imported into T cells by specific solute carrier transporters and inhibits nuclear translocation of nuclear factor of activated T cells, impairing T-cell proliferation and production of effector cytokine production. Accordingly, Notarangelo et al (2022) showed that D-2HG, altering glycolysis and reducing lactate dehydrogenase activity in CD8+ T cells, significantly impairs their cytotoxicity, limiting IFN-γ production.

Mitophagy plays multiple roles in tumor development and progression (Liu and Wu, 2022). It can serve as a tumor suppressor, maintaining the balance between mitochondria amount/activity by removing damaged or dysfunctional mitochondria in certain cancer subtypes (Rocca et al, 2023). Mitophagy can play an oncosuppressor role, inhibiting the accumulation of damaged mitochondria and,

therefore, preventing tumor development. In a murine model of colorectal cancer, phosphatase and tensin homolog-induced kinase 1 overexpression was associated with the reduction of acetyl-CoA levels that was partly because of HIF-1α-pyruvate dehydrogenase (PDH) kinase 1-pyruvate dehydrogenase kinases-pyruvate dehydrogenase E1α subunit axis activation, leading to increased apoptotic cell death and limited tumor growth. Treating mice with acetate, therefore increasing acetyl-CoA levels, rescued phosphatase and tensin homolog-induced kinase 1-suppressed carcinogenesis (Yin et al, 2021). On the other hand, mitophagy can also contribute to drug resistance onset, promoting cancer cell survival under cytotoxic stress by degrading damaged mitochondria and reducing mitochondrial ROS (Yan and Li, 2018).

Recent research showed that the Wartburg effect is not limited to cancer but also occurs in CVD, as extensively reviewed by Kuspriyanti et al (2021). During ischemia, when the oxygen supply is limited, cells are forced to rely on anaerobic glycolysis for ATP production. However, it is thought that glycolysis continues even after that reperfusion reestablishes oxygen back to normal levels. In HF, cardiomyocytes switch from oxidative phosphorylation to glycolysis even when oxygen is available, as part of an adaptive response to maintain ATP levels under stress conditions (Doenst et al, 2013; Kuspriyanti et al, 2021). Increased glycolysis rates were associated with atherosclerosis progression (Kumar et al, 2020; Li et al, 2022). In vascular smooth muscle cells (VSMCs), Kruppel-like factor-induced increase in PFKFB3 expression enhances the metabolic shift to glycolysis, determining the VSMC phenotypic switch toward a proatherogenic phenotype (Zhang et al, 2022b).

Metabolic alterations are also found in diabetic cardiomyopathy, even in the early stages before transition to HF. We recently performed a multiomics characterization of T2D mice hearts in comparison with nondiabetic controls. We found that 493 cardiac metabolites were differentially modulated between the 2 groups, primarily related to lipid metabolism (Faulkner et al, 2020). Indeed, diabetic mice present higher levels of intramyocardial lipid accumulation compared with controls (Dang et al, 2020; Gu et al, 2023). Underlying metabolic alterations in diabetic individuals include the loss of flexibility in myocardial substrate utilization, toxicity from nonoxidative lipid pathway intermediates, mitochondrial dysfunction, and the activation of inflammatory and fibrotic pathways (McGavock et al, 2007; Schulze et al, 2016; Faulkner et al, 2020; Peterson and Gropler, 2020; Gu et al, 2023).

F. Clonal hematopoiesis

Common molecular mechanisms in cancer and CVD include genetic susceptibility, low-grade chronic inflammation, and repetitive stress. Moreover, recently, research efforts have been devoted to the phenomenon of clonal hematopoiesis of indeterminate potential (CHIP), an age-related condition affecting less than 1% of individuals under 60 years old, but notably escalating to nearly 20% in those over 90 years old (McKerrell et al, 2015). CHIP is characterized by the establishment of clonal populations of bone marrow hematopoietic stem progenitor cells (HSPCs) carrying specific somatic mutations. Interestingly, CHIP correlates with cancer development and poor cardiometabolic disease outcomes (Jaiswal et al, 2014). Indeed, individuals with CHIP display a higher risk of developing myeloid or lymphoid leukemia (Laurie et al, 2012; Jaiswal et al, 2014; Zink et al, 2017). CHIP mutations often involve acute myeloid leukemia-associated genes, which confer increased fitness (Challen and Goodell, 2020; Watson et al, 2020). The most common mutations affect the DNA methyltransferase 3A (DNMT3A) and tet methylcytosine dioxygenase 2 (TET2) genes, which are involved in epigenetic regulation. Other known CHIP-related genes are additional sex combs-like 1, splicing factor 3b subunit 1, serine and arginine rich splicing factor 2, tumor protein P53, and protein phosphatase Mg2+/Mn2+ dependent 1D (Jaiswal et al, 2014; Fabre et al, 2022).

DNMT3A is a transcription suppressor that interacts with MYC, a known proto-oncogene involved in cell cycle regulation and inhibits the expression of its target genes (Hervouet et al, 2009). Thus, loss of DNMT3A activity could result in increased proliferation and inhibited differentiation of HSPCs in CHIP, as was observed in mice (Reed et al, 2023). TET2 loss has a similar effect on HSPCs and, in mice, induces a premature differentiation toward the monocyte/macrophage lineage (Reed et al, 2023).

From the cardiovascular point of view, CHIP elevates the chances of developing coronary heart disease and ischemic stroke (Jaiswal et al, 2014, 2017), as well as ischemic and nonischemic HF (Sikking et al, 2023) and early-onset MI (Jaiswal et al, 2017). Moreover, in patients with ischemic origin-chronic HF, CHIP represents significantly worse long-term clinical outcomes (Dorsheimer et al, 2019; Svensson et al, 2022). In vivo and in vitro studies were essential to partially elucidate CHIP mechanisms driving the adverse outcomes associated with this condition. Intracellular stress and inflammation, well-known drivers of cancer and CVD, have been identified as the leading players in CHIP development and pathophysiology. Endogenous and exogenous stressors, such as aging and pathogen infections, lead to HSPC mutagenesis. Some of these mutations increase inflammation, inducing HSPC proliferation and accelerating clonal population consolidation. In atherosclerosis, experimental evidence suggests that the loss of function of TET2 stimulates the transcription of IL-1β and its secretion mediated by inflammasomes in macrophages. The increased level of IL-1β results in enhanced leukocyte recruitment from activated ECs at the atherosclerotic plaque site (Kohnke and Majeti, 2021; Tall and Fuster, 2022; Avagyan and Zon, 2023).

In humans, CHIP is associated with cytokine level modulation (Bick et al, 2020; Gibson et al, 2022). Gibson et al (2022) investigate the effects of CH-carrying donors in allogeneic hematopoietic cell transplantation. They found dysregulation of cytokines in recipients of DNMT3A-CH donors characterized by an increase in IL-12p70, IL-1β, IL-4, IL-5, and IFN-γ levels and decreased IL-8, IL-22, TNF-α, and IL-10 levels. Surprisingly, this profile is associated with improved survival because of a lower relapse risk. Overall, these findings suggest that CHIP is a potential therapeutic target for cancer prevention and CVD treatment.

IV. Shared mechanisms and therapeutic approaches in CVD and cancer

Several molecular pathways involved in the processes described above play similar roles in CVD and cancer. Here, we will focus on selected ones, namely ERK1/2, STAT3, NOTCH, TGF-β, MYC, adenosine 5' monophosphate-activated protein kinase (AMPK), and phosphatidylinositol 3-kinase (PI3K)/protein kinase b (AKT), based on their crucial role and being some of the most druggable pathways (Figs. 2 and 3). The knowledge of common cellular and molecular mechanisms paves the way for mutual and reciprocal therapeutic strategies. In the following sections, we illustrate 2 main approaches: the use of different drugs to target common mechanisms and anticancer drugs to treat CVD.

A. Common target approach on shared cellular and molecular mechanisms

1. Inflammation and immune response

Diverse clinical trials are studying the effects of modulating inflammatory and immune responses in cancer and patients with

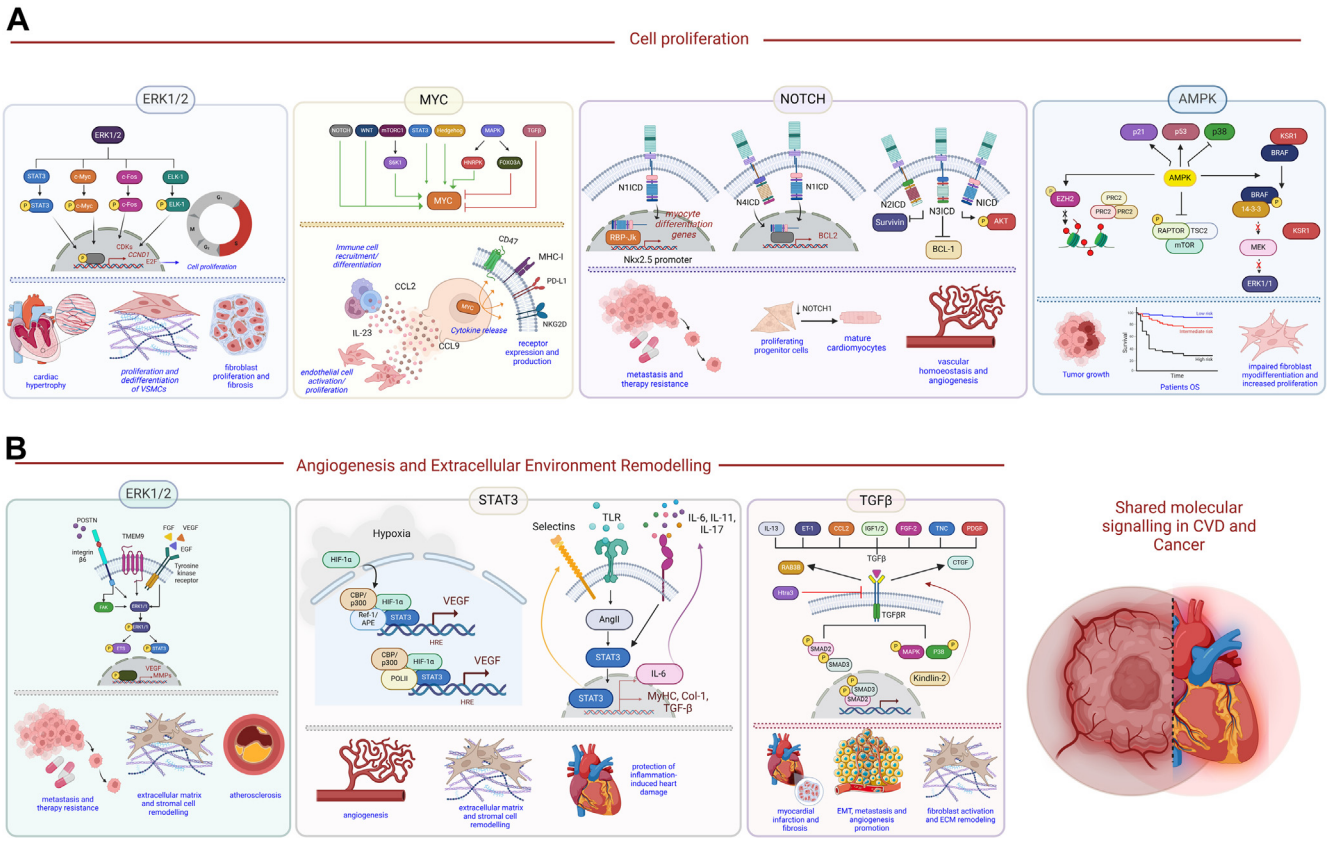

Fig. 2. Shared molecular mechanisms between cancer and CVD affecting cell proliferation, angiogenesis, and extracellular microenvironment remodeling. (A) ERK1/2, MYC, NOTCH, and AMPK as key molecular pathways regulating tumor cell, cardiomyocyte, fibroblast, and endothelial cell proliferation. (B) ERK1/2, STAT3, and TGF-β as relevant molecular pathways contributing to angiogenesis and extracellular environment remodeling and as crucial drivers for cancer/heart fibrosis, atherosclerosis, and tumor cell dissemination. Created with BioRender.com and Servier medical art (https://smart.servier.com/). APE, apurinic/apyrimidinic endonuclease; CCL2, monocyte chemotactic protein 1; CCND1, cyclin D1; CDK, cyclin-dependent kinase; Col-1, collagen type I; CTGF, connective tissue growth factor; ET-1, endothelin-1; FAK, focal adhesion kinase; FOXO3A, forkhead box O3; HNRNPK, heterogeneous nuclear ribonucleoprotein K; HRE, hypoxia-response element; IGF, insulin growth factor; KSR1, kinase suppressor of Ras 1; mTORC1, mechanistic target of rapamycin complex I; NICD, notch intracellular domain; NKG2D, natural killer group 2, member D; PDGF, platelet-derived growth factor; POLII, RNA polymerase II; POSTN, periostin; PRC2, polycomb repressive complex 2; RAPTOR, regulatory-associated protein of mTOR; RBP-Jk, recombination signal binding protein for immunoglobulin kappa J region; REF-1, redox effector factor-1; S6K, S6 kinase; TLR, toll-like receptor; TMEM, transmembrane protein; TNC, tenascin C; TSC2, tuberous sclerosis complex 2.

CVDs, for instance, using inflammasome pathway inhibitors on cardiovascular risk in patients with CHIP (Sikking et al, 2023). Among them, a phase 2 clinical trial is evaluating the reduction in inflammatory markers in patients with coronary heart disease following the administration of the NLRP3 inhibitor DFV890 or MAS825, a bispecific IL-1β/IL-18 monoclonal antibody (ClinicalTrials.gov ID: NCT06097663). Moreover, multiple clinical trials have also addressed the protective role of IL-1 inhibitors in cancer (Lust et al, 2009, 2016) and CVDs (Pellegrini et al, 2021).

Results from the clinical trial Canakinumab Anti-Inflammatory Thrombosis Outcome Study ("CANTOS"), a randomized, double-blind trial of canakinumab—a therapeutic monoclonal antibody targeting IL-1β, involving high-risk patients with CVD risk to study efficacy on nonfatal MI, nonfatal stroke, or cardiovascular death—showed that patients with the TET2 CHIP variant display a better response to the monoclonal antibody against IL-1β canakinumab (Ridker et al, 2017a; Svensson et al, 2022). Of note, in the CANTOS cohort that was composed of patients with a history of previous MI and a baseline CRP level of 2 mg/L or greater, patients with cancer were excluded; canakinumab reduced inflammation without affecting low-density lipoprotein (LDL) cholesterol levels (Baylis et al, 2017). Interestingly, exploratory results suggest that the blockage of IL-1β signaling substantially decreases the occurrence of lung cancer and mortality associated with lung cancer (Ridker et al, 2017b). The effects of canakinumab were dose-dependent, with a 67% decrease in total lung cancer risk ($P <$ .0001) and a 77% reduction in fatal cases ($P =$ .0002) at the 300 mg dose. Patients with high levels of high-sensitivity CRP and IL-6 faced the greatest lung cancer risk, while smokers and those with the largest drops in these markers benefited the most. Canakinumab had no notable impact on cancers beyond the lung but reduced overall cancer mortality by over 50% compared with placebo ($P =$ .0009). However, because lung cancer was not a formally pre-specified study endpoint, the results need to be confirmed in a dedicated study. A further analysis was conducted to gain molecular insights into the tumor risk in the CANTOS cohort, finding that circulating tumor DNA and soluble inflammatory biomarkers were higher in patients who developed lung cancer (Wong et al, 2020). This result suggests that the reduced cancer incidence observed between the treated and placebo groups pertains to patients at an early stage of lung cancer. In summary, IL-1β inhibition is an example of a common target between cancer and cardiovascular pathologies.

Immunosenescence and inflammaging (aging-associated inflammation) jointly affect cancer and CVD. Senolytics are drugs that target selectively senescent cells inducing their death. By reducing the number of senescent cells, and associated SASP production, senolytics have the potential to reduce tissue and systemic inflammation in both CVD and cancer. Senotherapy can attenuate age-related CVD (Owens et al, 2021; Dookun et al, 2022). A recent

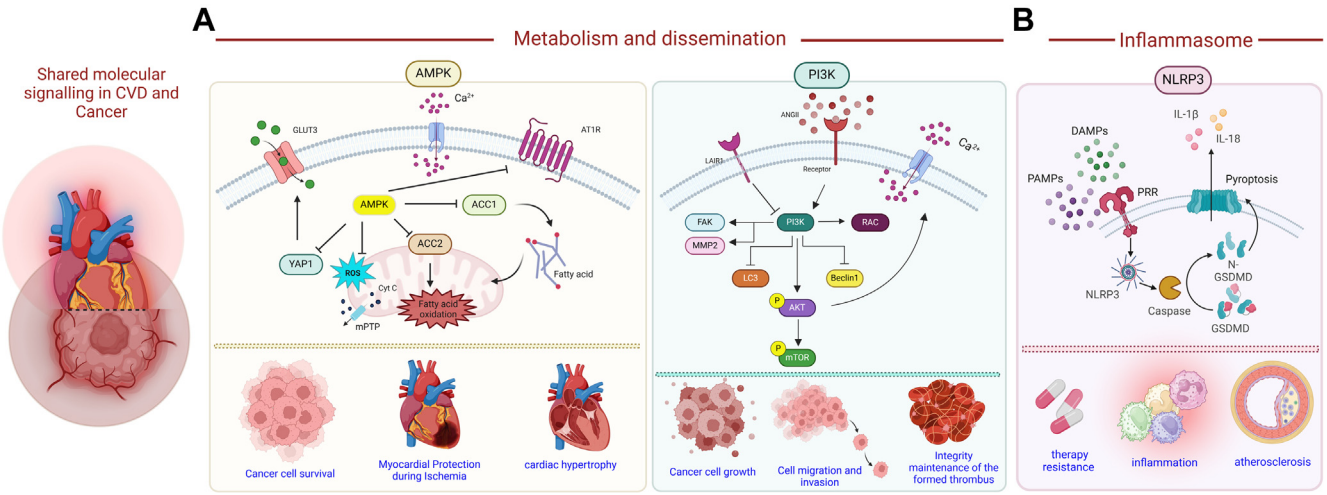

Fig. 3. Shared molecular mechanisms between cancer and CVD are involved in cell metabolism, dissemination, and inflammation. (A) AMPK and PI3K as crucial players in different pathways regulating cell metabolism and dissemination, contributing to cancer growth, cell migration and invasion, myocardial protection, and thrombus formation. (B) NLRP3/inflammasome as a key signaling pathway involved in therapy resistance, inflammation, and atherosclerosis. Created with BioRender.com. ACC, acetyl-coa carboxylase; ATR1, angiotensin II receptor type 1; DAMP, damage-associated molecular patterns; FAK, focal adhesion kinase; GSDMD, gasdermin-D; LAIR1, leukocyte-associated immunoglobulin-like receptor 1; mTORC1, mechanistic target of rapamycin complex I; PAMP, pathogen-associated molecular patterns; PRR, pattern-recognition receptors; RAC1, Ras-related C3 botulinum toxin substrate 1.

study showed that the eradication of SASP-cardiomyocytes improves heart function after MI (Redgrave et al, 2023). Post-MI treatment of mice with the senolytic navitoclax reduced myocardial inflammation and infarct size and improved perfusion and LV function (Dookun et al, 2020). Dasatinib reduced cardiac cell senescence and improved diastolic heart function in a mouse model of diabetic cardiomyopathy (Gu et al, 2023). In cancer, senolytics can achieve therapeutic benefits by lowering the number of senescent immune cells, thereby contrasting immune evasion and enhancing the overall immune response to cancer. The benefits of the combination of conventional chemotherapy and immunotherapy with senolytic agents have been reviewed recently (Malayaperumal et al, 2023). Of note, in cancer, cellular senescence can be a double-edged sword. While it serves as a tumor-suppressive mechanism by permanently arresting cancer cell growth, at the same time cancer therapy-induced senescence can paradoxically promote tumorigenesis, cancer cell survival, and reactivation. Rapid elimination of therapy-induced senescent cells is crucial for improving outcomes in patients with cancer (Xiao et al, 2023).

Inflammaging could soon be tackled with innovative therapies. Interestingly, Puca et al (2020) are developing an innovative treatment involving the horizontal transfer of the longevity-associated variant of the bactericidal/permeability-increasing fold-containing family B member 4 (BPIFB4) gene, found in healthy centenarians, to the elderly and patients with CVDs. Preclinical studies conducted so far showed that the longevity-associated variant-bactericidal/permeability-increasing fold-containing family B member 4, delivered either as a gene or a protein, reduces inflammation and exerts therapeutic benefits in preclinical models of atherosclerosis, diabetic cardiomyopathy (Dang et al, 2020; Alvino et al, 2024), MI (Cattaneo et al, 2023a), and aging cardiomyopathy (Cattaneo et al, 2023b; Alvino et al, 2024). The same gene acted as a senotherapeutic agent, reducing senescence in patients' glioblastoma and T cells, and favoring cell sensitivity to chemotherapeutic drugs (Puca et al, 2022).

2. *Angiogenesis and metabolism*

The mechanism of action of angiogenesis inhibitors on tumor blood vessels can be classified into 3 categories: (1) vessel depletion, (2) vessel normalization, and (3) immune activation (Carmeliet and Jain, 2011).

Antiangiogenic therapy is often used in combination with chemotherapy, immunotherapy, or other anticancer therapeutics in the treatment of various solid cancers to prevent tumor growth. Most therapeutics involve anti-VEGF monoclonal antibodies (such as bevacizumab) but also tyrosine kinase inhibitors (TKIs—such as sunitinib and sorafenib) (Guo et al, 2024). Conversely, antibodies neutralizing ANGPT-2, another well-known angiogenic factor—are still in the preclinical development phase (Leow et al, 2012).

One notable side effect associated with antiangiogenic drugs is represented by changes in blood pressure (BP). Hypertension—an increase in systemic BP—occurs because inhibition of VEGF reduces the ability of blood vessels to dilate properly, causing their narrowing and stiffening, thus increasing flow resistance and leading to elevated BP. Anti-VEGF monoclonal antibodies and TKIs targeting the VEGF and other receptors are particularly known to induce hypertension (Pucci et al, 2019; Coschignano et al, 2021). Antihypertensive treatment is therefore recommended in patients treated with these drugs.

Conversely, antiangiogenic drugs have not found application in the context of CVD yet, though they could be used for those conditions characterized by abnormal angiogenesis, such as in atherosclerosis, to reduce intraplaque neovascularization and increase plaque stability. So far, therapy with anti-VEGF monoclonal antibodies (bevacizumab, ranibizumab, and aflibercept) has mainly found application in the treatment of retinal vascular conditions—such as diabetic macular edema and age-related macular degeneration—associated with abnormal blood vessel growth or leakage and that are one of the leading causes of blindness (Zong et al, 2024). Rather than antiangiogenic therapies, a stabilizing approach has been proposed for therapeutic angiogenesis in ischemic heart disease, and we refer the reader to recent reviews on this topic (Eelen et al, 2020; Perez-Gutierrez and Ferrara, 2023; Avolio et al, 2024).

Although combination treatment blocking or enhancing distinct angiogenic signals is promising, compensation by other angiogenic or antiangiogenic factors can reduce this therapeutic strategy in cancer and CVD. Modulation of aberrant metabolism in cancerous and cardiovascular cells represents a complementary strategy. Traditional antidiabetic or lipid-lowering agents, aimed at shifting

the balance of cardiac metabolism from utilizing fatty acids to glucose, have shown conflicting results and may cause adverse cardiovascular events, as in the case of thiazolidinediones. Therefore, different solutions have been investigated. Recent advances in metabolic therapy for CVD were extensively treated in previous reviews (Kolwicz et al, 2013; Zuurbier et al, 2020); therefore, we limit this section to a few examples.

Partial inhibition of glycolysis, for instance, interfering with the pentose phosphate pathway by targeting its rate-controlling enzyme glucose-6-phosphate dehydrogenase, is enough to stabilize the chaotic tumor vessel formation. Boosting the pentose phosphate pathway by supplementing the vitamin B1 analog benfotiamine proved beneficial in improving the recovery from limb ischemia in mice (Gadau et al, 2006). A small exploratory clinical trial conducted by Dr Gary E. Gibson's laboratory at the Burke Neurological Institute in collaboration with physicians at the Burke Rehabilitation Hospital indicated that Benfotiamine can improve cognitive outcomes among people with mild cognitive impairment and mild Alzheimer's disease (Gibson et al, 2020).

Several metabolic therapies focused on the promotion of glucose oxidation. One key target has been carnitine palmitoyltransferase I, the enzyme that is the gateway for long-chain fatty acid uptake into the mitochondria. A clinical trial evaluating etomoxir in patients with chronic HF showed improved stroke volume and ejection fraction. Another trial evaluated the effect of perhexiline in patients with HF and observed improved Vo2max, ejection fraction, and tolerance to dobutamine stress. In hypertrophic cardiomyopathy, perhexiline, together with medical management, increased the phosphocreatine (PCr)/ATP ratio, correcting energy-dependent LV diastolic relaxation (Schmidt-Schweda and Holubarsch, 2000; Lee et al, 2005).

Conditions of high shear stress activate the transcription factor Krüppel-like factor 2 (KLF2), which serves to repress the expression of the glycolytic regulator PFKFB3 in normal, quiescent ECs, limiting glycolytic flux. In atherosclerosis, alterations to flow in macrovessels, caused by atherosclerotic plaque encroachment into the blood vessel lumen or in atherosclerotic plaque neovessels, which, like tumor vessels, are often leaky and hypoperfused, lead to the cessation of KLF2-mediated repression of PFKFB3, thus enhancing glycolytic flux, perturbing macrovascular barrier function, and promoting plaque angiogenesis. Limiting glycolysis by targeting PFKFB3 may be a promising therapeutic strategy to limit pathological endothelial alterations in atherosclerosis (Zhou et al, 2021).

3. *ERK1/2*

The ERK1/2 signaling—also called MAPK signaling—plays a central role in cell proliferation and survival and is also implicated in other important processes such as angiogenesis, ECM remodeling, and fibrosis. Some CVDs and cancers are united by persistent ERK1/2 activation, failing to regulate the above-mentioned biological processes within physiological levels. This evidence suggests that both cancer and CVD may benefit from treatments aiming to normalize ERK activity.

ERK1/2 is the final component of the RAS-RAF-MEK-ERK 3-tiered kinase cascade, also called the MAPK pathway, in which each kinase phosphorylates and activates the downstream kinase. This pathway is activated by the engagement of extracellular ligands with growth factor RTKs and hormone and chemokine G protein-coupled receptors on the cell surface (Shaul and Seger, 2007; Mendoza et al, 2011; Mohammed et al, 2024). Once activated, ERK1/2 directly (by phosphorylation) or indirectly (by phosphorylating intermediate targets) activates hundreds of cellular targets.

ERK1/2 phosphorylates and directly activates several transcription factors regulating the cell cycle: STAT3, C-MYC, C-FOS, and ETS-like 1 protein (ELK-1). STAT3 and C-MYC will be reviewed below. Briefly, phosphorylation of STAT3 on Tyr705 and Ser727 by ERK promotes cell cycling through the transcriptional activation of the cyclin D gene (*CCND1*) (Zhang and Liu, 2002). Cyclin D is a key regulator of the cell cycle. By forming complexes with cyclin-dependent kinases (CDKs), primarily CDK4 and CDK6, cyclin D promotes the progression from the G1 to the synthesis (S) phase. Cyclin D-CDK4/6 complexes phosphorylate and inactivate the retinoblastoma protein. This leads to the release of retinoblastoma protein-bound E2F transcription factors, allowing E2F to activate the expression of genes required for entry into the S phase (Vermeulen et al, 2003). Upon phosphorylation on Ser62 by ERK1/2, C-MYC increases the transcription of key gene targets promoting proliferation, including cyclins, CDKs, and E2F (Garcia-Gutierrez et al, 2019; Zuo et al, 2023). Moreover, by phosphorylating MYC at Ser62, ERK prevents its proteasomal degradation, resulting in MYC accumulation and favoring uncontrolled cell proliferation (Beroukhim et al, 2010). C-FOS modulates the expression of multiple cell cycle regulators, including cyclin D1, p53, p21CIP1/WAF1, and p16INK4A (Murphy et al, 2002). ELK-1 induces cell proliferation through the transcriptional activation of key cell cycle genes such as *CCND1* (Sharrocks, 2006).

a. ERK1/2 in cancer. Aberrant activation of the RAS-RAF-MEK-ERK pathway is observed in at least 40% of human cancers (Guo et al, 2020). Genetic mutations or overexpression of the pathway components cause ERK1/2 hyperactivation, resulting in sustained cell proliferation, cancer growth, and enhanced metastatic potential (Burotto et al, 2014). Single base replacement mutations at amino acid residues 12, 13, or 61 in the RAS genes result in constitutive RAS activation and are the most common, detected in 30% of cancers, among which are colorectal, lung, bladder, thyroid, and biliary tract carcinomas; pancreatic adenocarcinomas; leukemia; melanomas; and salivary gland tumors (Bos, 1989; Fernandez-Medarde and Santos, 2011; Forbes et al, 2011; Santarpia et al, 2012). BRAF mutations, most of which are missense and determine the kinase activation, account for 7%–10% of all cancers and are frequently found in melanoma, papillary thyroid, colorectal, and ovarian cancer (Davies et al, 2002; Fransen et al, 2004; Libra et al, 2006). Conversely, MEK and ERK mutations are rare and only found in less than 1% of cancers (Yaeger and Corcoran, 2019). Prolonged ERK signaling can also cause the repression of cell cycle inhibitors, thus establishing a vicious cycle aiding continual cell proliferation (Sharrocks, 2006). Moreover, aberrant cyclin D expression, activity, gene splicing, or mutations that confer it with resistance to degradation are commonly observed in cancer (Tashiro et al, 2007; Wang et al, 2023a). Examples of cancers with increased MYC expression are ovarian, breast, colorectal, and pancreatic cancers. C-FOS phosphorylation by ERK at Thr325, Thr332, and Ser374 results in transcription factor stabilization and neoplastic transformation (Murphy et al, 2002). C-FOS stabilization and cell transformation are also promoted by RSK, another important ERK substrate phosphorylated and activated by ERK at Thr573 (Chen et al, 1996; Dalby et al, 1998). Pharmacological inhibition of the ERK pathway aimed at halting cell proliferation and inducing cell apoptosis is a keystone of cancer therapy.

ERK signaling also regulates ECM remodeling, fibrosis, and stromal cell activation in several ways. For example, it regulates the expression and activity of MMPs, proteolytic enzymes that hydrolyze and remodel the ECM. Moreover, by promoting fibroblast proliferation and differentiation, ERK supports the synthesis of ECM proteins, which favor the formation of fibrotic tissue (Umbarkar et al, 2022).

ERK1/2 phosphorylates and activates the erythroblast transformation specific (ETS) transcription factor. In cancer, ETS binding

to the promoter regions of MMP genes enhances their transcription, promoting breast cancer cell invasion (Shin et al, 2023). Matrix rigidity is a critical contributor to tumor progression. Increased matrix stiffness activates yes-associated protein 1 (YAP) and promotes periostin secretion in CAFs. Periostin triggers the integrin/FAK/ERK mechanotransduction pathway, induces ECM remodeling, and promotes breast cancer cell invasion (Wu et al, 2023). In pancreatic ductal adenocarcinoma, integrin β6 upregulation induces ERK/ETS1 phosphorylation and MMP9 activation, promoting cancer cell invasiveness (Li et al, 2016).

The ERK pathway is a key signaling modulator of cancer and postischemic angiogenesis (Liu et al, 2023b; Song et al, 2023b). The cellular and molecular mechanisms implicated in cancer and CVDs are similar. The intracellular transduction of signaling originated from the engagement of angiogenic growth factors (ie, VEGF, PDGF, and HGF) with their cell surface RTK receptors, as well as ANGPT/Tie2 and adhesion molecules/ECM/integrins, all involving downstream ERK1/2 activation (Liu et al, 2023b). VEGF is the master proangiogenic factor regulating both physiological and pathological angiogenesis. Upon binding to its receptors on ECs, VEGF activates ERK1/2 and stimulates EC proliferation, migration, and tube formation, essential steps in angiogenesis (Melincovici et al, 2018). Inhibition of ERK1/2 in ECs restrains the cell migration and angiogenic activity in tube formation assays in vitro (Zuo et al, 2010; Avolio et al, 2022).

In cancer, the ERK-VEGF axis retains a predominant role, with the 2 factors mutually activating each other. VEGF-induced ERK1/2 activation contributes to cancer angiogenesis, as described in esophageal and ovarian cancer (Su et al, 2014; Bhattacharya et al, 2018). ERK1/2 activated by other growth factors—such as HGF—favors the expression of VEGF, as documented in human colorectal cancer cells (Zhang et al, 2007), contributing to establishing a positive loop that sustains the development of tumor blood vessels. Upregulation of transmembrane protein 9 in lung adenocarcinoma activates the MEK/ERK/STAT3 pathway, resulting in upregulated VEGF expression and enhanced tumor microvascular density (Wang et al, 2024b). Gain- and loss-of-function approaches showed that the A disintegrin and metalloproteinase with thrombospondin motifs 12 protein supports angiogenic activity in gastric cancer cells by activating ERK and upregulating VEGF. Suppression of ERK1/2 phosphorylation by using peptides inhibiting the epithelial growth factor (EGF) and FGF receptors activation resulted in decreased tumor cell growth and angiogenesis in bladder and prostate cancer (Wang et al, 2024c; Zheng et al, 2024). Downregulation of MEK1 using siRNA in triple-negative breast cancer cells led to decreased angiogenesis and tumor regression (Ferreira et al, 2023).

Drugs targeting the ERK pathway have already been adopted to arrest cancer proliferation and angiogenesis. Classical and long-term-used anticancer drugs target and inhibit upstream RTKs on the cell surface (such as VEGF, EGF, and FGF receptors) (Huang et al, 2020), thus switching off the entire pathway. Pharmacological inhibitors under preclinical or clinical development include small molecules targeting specifically 1 component of the pathway: RAS, RAF, MEK, and ERK inhibitors, extensively described in dedicated review articles (Chang et al, 2003; Santarpia et al, 2012; Pan et al, 2022; Bahar et al, 2023; Ram et al, 2023). Here, we will present some of these drugs with the potential to be repurposed for CVD therapy below, in section B.

b. ERK1/2 in CVD. The ERK1/2 pathway is well-known for its pro-survival effects. In the heart, it protects cardiomyocytes, particularly under conditions of stress such as ischemia, oxidative stress, and HF, and it is also involved in the adaptation of cells to stress. By inhibiting proapoptotic proteins such as B-cell lymphoma 2 (BCL-2)-associated agonists of cell death and activating anti-apoptotic proteins like BCL-2, ERK1/2 protects cells from programmed death (Korshunova et al, 2021). ERK1/2 activation also protects against mitochondrial dysfunction by maintaining mitochondrial integrity and function during ischemia and oxidative stress (Zhao et al, 2021b). In line, ERK1/2 activation before ischemia can protect the cardiomyocytes from reperfusion injury by inducing antiapoptotic pathways and reducing oxidative stress (Lips et al, 2004; Kong et al, 2019). In response to pressure or volume overload, ERK1/2 signaling is involved in the process of cardiomyocyte hypertrophy (increase in heart muscle cell size), which helps the heart adapt to increased workload (Bueno et al, 2000; Mutlak et al, 2018). This hypertrophic response involves ERK1/2-activating transcription factors GATA binding protein 4 and NF-κB, which regulate genes associated with cell growth and survival.

Nonetheless, abnormal ERK1/2 signaling can be pathological even in the cardiovascular context. When ERK1/2 signaling is aberrantly activated, promoting excessive cardiomyocyte growth, cardiac hypertrophy, which was initially a positive response to help cells cope with stressors, becomes pathological. The development of pathological hypertrophy involves ELK-1/C-FOS activation (Babu et al, 2000; Gallo et al, 2019). A mutation of the RAS gene resulting in continuous MEK-ERK activation causes hypertrophic cardiomyopathy and HF in patients with the genetic Costello syndrome (Geddes et al, 2023). In VSMCs, ERK signaling promotes cell proliferation and shifting from the contractile to the synthetic phenotype. Proliferative VSMCs are key players in neointima formation, a negative process contributing to vascular stenosis, both in native vessels and in vascular grafts such as veins and arteries used for coronary artery bypass after MI (Koyama et al, 1998; Yu et al, 2007).

Like in cancer, ERK1/2 regulates the production of ECM, MMP-2 and -9, and tissue inhibitors of MMPs in various cardiovascular cells to balance ECM synthesis and degradation (Nagata et al, 2003; Cui et al, 2012; Yijing et al, 2013). In the arterial wall, proliferative synthetic VSMCs produce high amounts of ECM proteins, eg, collagen and fibronectin, and MMPs, causing a structural, profibrotic remodeling of the vascular wall. These structural alterations promote vascular cell migration toward the intimal layer and into the atheromatous plaque, contributing to the progression of atherosclerosis (He et al, 2019; Tao et al, 2021; Yan et al, 2021). In the heart, endothelin-1-induced ERK activation promotes fibroblast proliferation and differentiation into myofibroblasts, which release higher amounts of ECM proteins, favoring myocardial fibrosis (Umbarkar et al, 2022; Duangrat et al, 2023). In the postischemic or failing heart, as well as in cancer, arresting ERK signaling using drugs inhibiting the various components of the pathway could be adopted to attenuate pathological fibrotic remodeling, with benefits for patients.

Contrary to the consensus of a detrimental role for aberrant ERK signaling in cancer angiogenesis, controversy arose from preclinical studies regarding ERK and post-MI myocardial repair. In our study, the inhibition of ERK1/2 phosphorylation promoted the revascularization and perfusion of infarcted mouse hearts, decreased scar size, and increased animal survival (Avolio et al, 2022). Similar results were collected by Jin et al (2018) in rats. Conversely, in the other 2 older studies in rats and swine, ERK inhibition resulted in bigger infarct scars (Hausenloy et al, 2005; Strohm et al, 2000). The reasons for these discrepancies remain unknown but are probably caused by the different animal species, MI models, and drug administration protocols, including the duration of treatment.

4. STAT3

The STAT family includes 7 members, all with a well-recognized transcription factor activity, namely STAT1, STAT2, STAT3, STAT4,

STAT5A, STAT5B, and STAT6. Among the others, STAT3 activation is downstream of several pathways regulated by different cytokines and growth factors, including IL-6 (Catlett-Falcone et al, 1999; Johnson et al, 2018; Gu et al, 2020), VEGF, and EGF (Qin et al, 2019). Constitutive activation of STAT3 signaling can be associated with malignant transformation, can promote cell proliferation, fibrosis, resistance to apoptosis, immune evasion, and sustain angiogenesis and tumor cell dissemination and metastasis.

Over the past 20 years, different drugs have been developed to directly inhibit STAT3 activity, including Stattic, Napabucasin, STX-0119, STA-21, LY-5, S31-201, PYM, WP1066, TTI-101, DSSP-0337, OPB-51602, OPB-31121, and OPB-11107 (Yang et al, 2023). To date, some of these inhibitors, such as napabucasin have been explored in clinical trials, showing encouraging results in the oncologic field, even if, so far, no STAT3 inhibitor has been approved for clinical use (Yang et al, 2023). As discussed above, given the contribution of STAT3 in the pathogenesis of both tumors and CVDs, regulating proliferation, angiogenesis, and fibrosis, it is reasonable to hypothesize that inhibiting this transcription factor could yield advantages in both contexts. Indeed, from a pharmacological point of view, either preclinical studies or preliminary results from clinical trials have not reported any significant cardiotoxic events following the administration of STAT3 inhibitors, indicating the safety of these agents for the cardiovascular compartment. Some studies in the literature demonstrated a cardioprotective role of STAT3, because of its role in regulating antiapoptotic protein expression and its ability to decrease ROS production in cardiomyocytes, suggesting that pharmacological combination between STAT3 inhibitors and conventional chemotherapy deserves increased caution (Harhous et al, 2019). Indeed, different reports pointed out that STAT3 overexpression in the heart exerts a protective role against the development of doxorubicin-induced cardiotoxicity. In this context, Rong et al (2016) demonstrated that STAT3 activation might increase the expression of antioxidant proteins, such as metallothionein 1 and 2, reducing heart damage. In line, S-propargyl-cysteine counteracts doxorubicin-induced cardiotoxicity by activating STAT3 via glycoprotein 130, enhancing cardiomyocyte viability, decreasing apoptosis and oxidative stress, and it antagonizes mitochondrial dysfunction and intracellular calcium overload, therefore reducing cardiomyopathy and HF upon doxorubicin treatment (Wu et al, 2016).

a. STAT3 in cancer. Alterations in oxygen levels are closely associated with STAT3 activation. In pancreatic and prostate carcinomas, hypoxia-induced VEGF expression via Src activation leads to increased steady-state levels of HIF-1α and induces STAT3 phosphorylation. In this context, STAT3 and HIF-1α bind simultaneously to the VEGF promoter, forming a molecular complex with the transcriptional coactivators cAMP response element-binding protein (CBP/p300) and redox effector factor-1/apurinic/apyrimidinic endonuclease ((Gray et al, 2005). Likewise, in triple-negative breast cancer cells and Hep3B hepatoma cell lines, STAT3, CBP/p300, RNA polymerase II, and HIF-1α complexes have been shown to regulate HIF-1α target genes, including VEGF (Pawlus et al, 2014), suggesting a close link between STAT3 and VEGF-mediated angiogenesis. The direct regulation of VEGF by STAT3 was demonstrated using an activated STAT3 mutant (STAT3C), which has been shown to increase VEGF expression by binding to the VEGF gene promoter, while the dominant-negative STAT3 protein or STAT3 antisense oligonucleotide in tumor cells downregulates VEGF expression (Niu et al, 2002).

The intercellular communication between cancer and ECs is aided by STAT3. Indeed, ECs are the primary targets of the paracrine production of cytokines and factors, including VEGF, produced by cancer cells. VEGF stimulates lymphatic EC migration and tube formation in a STAT3-dependent manner in vitro (Okazaki et al, 2011). Oncostatin M, a member of the IL-6 family, was able to induce angiogenic sprouting in ECs, also increasing human umbilical cord EC (HUVEC) migration in vitro by activating STAT3 (Rapp et al, 2023). Stimulation of ECs with lung cancer cell-conditioned media induced STAT3 activation that, in turn, was shown to upregulate cell adhesion molecule expression, including E-selectin and P-selectin, in vitro and in premetastatic lungs of tumor-bearing mice in vivo (Kim et al, 2017).

Besides its effects on angiogenesis, accumulating evidence, recently reviewed by Allam et al, highlighted STAT3 activity in regulating fibroblast functions during the oncogenic process. Indeed, STAT3 is often activated in CAFs and other stromal cells within the tumor microenvironment because of the high levels of IL-6, IL-11, and IL-17 that mediate the conversion of normal fibroblasts to CAFs. Once activated, CAFs shape the tumor microenvironment stiffness, remodeling ECM and promoting matrix cross-linking by releasing protumorigenic factors, including IL-6, VEGF, TGF-β, IL-15, and IL-11 (Du et al, 2017; Allam et al, 2021), that can also impact neighboring ECs, promoting tumor angiogenesis (Du et al, 2017).

b. STAT3 in CVD. In cardiomyocytes, STAT3 plays a significant role in survival, growth, sarcomere architecture, energetics, and metabolism (Haghikia et al, 2014). Although the specific deletion of STAT3 in cardiomyocytes resulted in no phenotype alterations in mice under baseline conditions, cardiac response to neurohumoral activation, ischemia, chemotherapy treatment, and lipopolysaccharides (LPS) are compromised (Haghikia et al, 2014).

Deletion of STAT3 in cardiomyocytes leads to a progressive impairment of capillary density and increased interstitial fibrosis because of alterations in the ECM composition in the aging hearts of mice (Jacoby et al, 2003; Hilfiker-Kleiner et al, 2004). Consistent with these findings suggesting the protective role of STAT3 in the cardiovascular system, overexpression of the constitutively active form of STAT3 in cardiomyocytes was associated with increased VEGF-mediated angiogenesis both in vitro and in vivo (Osugi et al, 2002).

STAT3 has also been reported to play a critical role in protecting from inflammation-induced heart damage. Indeed, LPS induced more apoptosis in STAT3-deficient mice than in their wild-type counterparts. At the cellular level, this was associated with the increased release of TNF in response to LPS by STAT3-knockout cardiomyocytes (Jacoby et al, 2003). In line, conditioned media from STAT3-deficient cardiomyocytes decrease EC proliferation while increasing fibroblast proliferation. In parallel, STAT3-deficient mice showed enhanced susceptibility to MI/reperfusion injury and MI with enhanced cardiac apoptosis, infarct sizes, and impaired cardiac function and cell survival (Hilfiker-Kleiner et al, 2004).

In cardiomyoblasts, STAT3 activation by angiotensin-II (Ang-II) via toll-like receptors has been demonstrated to increase IL-6 production, which creates a positive feedback loop leading to a second STAT3 activation through the IL-6/glycoprotein 130/Janus-family tyrosine kinases 2 pathway, ultimately resulting in the upregulation of genes involved in cardiac remodeling, including myosin heavy chain, collagen-1, and TGF-β. In vivo, STAT3 inhibition reduces Ang-II-induced cardiac fibrosis and hypertrophy, thereby pointing out the relevance of STAT3 activation in heart remodeling (Han et al, 2018b).

Accordingly, nuclear factor-erythroid factor 2-related factor 2 expression loss exacerbates Ang-II-triggered hypertrophy and inflammation via IL-6/STAT3 signaling, resulting in cardiac fibrosis, increased hypertrophy-related biomarkers, oxidative stress, and enhanced serum concentration of lactate dehydrogenase and

creatine kinase-MB, all markers of cardiac tissue lesion (Chen et al, 2019).

5. NOTCH

The Notch pathway is one of the most highly conserved through evolution, and, in physiological contexts, it regulates cell proliferation and differentiation, thus playing a relevant role already in early cell development, including embryogenesis (Ferrari and Rizzo, 2014). Notch signaling is activated by the Notch ligand/receptor binding, mostly mediated by cell/cell contact. This interaction triggers 2 proteolytic cleavages that, in turn, result in the release of the Notch active form. Given the crucial role of this pathway in regulating cellular homeostasis and proliferation, Notch inhibitors raised significant interest in cardio-oncology. However, while effective as an anticancer therapy, it also poses significant risks to the cardiovascular system, leading to complications such as cardiotoxicity, vascular dysfunction, and HF. Several studies, that have been comprehensively summarized by Rizzo et al (2014), reported whether the inhibition of the Notch pathway can be effective in the oncology setting caused by the impairment of tumor cell survival, proliferation, and dissemination properties, but it can potentially affect the cardiovascular system, inducing toxicity. Inhibition of Notch signaling negatively impacts angiogenesis, therefore impairing the neo-vascularization and wound healing capabilities, worsening atherosclerotic and diabetes mellitus patients' outcomes.

Despite the cardiotoxic events observed in oncologic patients and the disruptive effects on postischemic reparative angiogenesis, Notch inhibitors have been considered and displayed beneficial effects in preclinical studies for the treatment of atherosclerosis. Indeed, Notch receptor inhibitors improved the antiatherosclerotic activity of LXR ligand agonists in ApoE$^{-/-}$ mice also limiting lipid accumulation within the liver and hypertriglyceridemia (Hao et al, 2020). In line, activation of Notch signaling in macrophages is associated with an inflammatory and unstable plaque phenotype; therefore, Notch inhibition can represent a promising strategy for atherosclerosis (Rizzo and Ferrari, 2015; Vieceli Dalla Sega et al, 2019).

a. NOTCH in cancer. Either ligands or Notch receptors have been found overexpressed in many cancer types, including ovarian and breast cancers and gliomas (Hopfer et al, 2005; Stockhausen et al, 2010; Yousefi et al, 2022), negatively impacting patients' prognosis and outcomes. The oncogenic role of Notch signaling was first proposed by Ellisen et al (1991), showing that the t(7;9) chromosomal translocation results in the expression of a NOTCH1 constitutively active form in T-cell acute lymphoblastic leukemia (ALL). It is now well known that more than 50% of patients with T-cell ALL harbored NOTCH1 point mutations or other genetic events that lead to Notch activation (Weng et al, 2004) that directly promote cell growth, proliferation, and self-renewal. Other than in hematological malignancies, the oncogenic role of Notch has also been pointed out in solid tumors. In breast cancer, the dysregulation of Notch signaling is reported as an early event. Notch downstream gene aberrant activation was described in a broad range of cancer subtypes, including ductal carcinoma in situ and epithelial hyperplasia. Moreover, aberrant signaling has also been associated with the triple-negative breast cancer subtype, demonstrating the involvement of Notch in the promotion of aggressiveness, dissemination, and therapy resistance phenotype (Edwards and Brennan, 2021).

b. NOTCH in CVD. Notch plays a key role in cardiomyocyte survival, cell proliferation, and angiogenesis. In the ischemic limb muscles, DLL4 is upregulated in sprouting ECs, and the Notch/DLL4 signaling is pivotal to functional reparative angiogenesis. Accordingly, in mice, inhibiting the endogenous DLL4 resulted in a chaotic, leaky, and low-perfused capillary network in ischemic muscles (Al Haj Zen et al, 2010). Moreover, treating cultured human monocytes with the Notch inhibitor DAPT resulted in increased proinflammatory IL-8 production (Al Haj Zen et al, 2010). This evidence suggests that Notch inhibition could also negatively affect myocardial repair, exacerbating the myocardium pathological remodeling.

As in cancer, mutations in the Notch pathway have been recognized in human congenital heart defects and cardiomyopathies (Luxan et al, 2013). The most common alterations, including point mutation driving myocardial dysfunctions, are associated with Notch1 and Jagged1, the 2 Notch family members mainly expressed by adult myocytes (Croquelois et al, 2008).

Notch1 has been shown to regulate myocardial remodeling. Indeed, its inhibition was associated with Ang-II overproduction that induced an altered remodeling with a hypertrophic response in preclinical models (Gude et al, 2008; Oie et al, 2010). Forcing Notch1 or Jagged1 expression in cardiomyocytes resulted in reduced myocardium damage and remodeling (Gude et al, 2008; Nemir et al, 2014).

Actively proliferating progenitor cells of mature cardiomyocytes express high levels of active Notch1 that are progressively lost during culture passages, thereby suggesting that the activation of this signaling is required for progenitor proliferation, while decreased Notch1 expression is necessary to achieve terminal differentiation. Because of Notch1 activation, the Notch1 intracellular domain, complexed with RBP-Jk, binds to the Nkx2.5 promoter, promoting transcription and myocyte differentiation. On the contrary, activation of the Notch1 pathway by Jagged1 leads to the downregulation of transcription factors in vascular cells (Boni et al, 2008).

In the cardiovascular system, Notch receptors 1, 2, and 4, as well as DLL1, 4, and JAG1, 2, are all expressed in the endothelium and contribute to maintaining vascular homeostasis, impacting EC survival and proliferation, hence regulating angiogenesis (Ferrari and Rizzo, 2014). The basic mechanisms of Notch signaling in angiogenesis are almost conserved between cardiovascular development and tumor growth and include direct and indirect regulation of VEGF receptor and Ephrin pathways (Akil et al, 2021). The Notch pathway significantly regulates EC proliferation and survival. In this context, Notch receptors play opposite roles in the endothelium. For instance, Rizzo et al (2013) demonstrated that Notch1 and Notch4 prevent LPS-induced Bcl2 upregulation and apoptosis. Notch activation in HUVECs by estrogens promotes EC survival in response to TNF-α because of Notch1-mediated AKT phosphorylation (Fortini et al, 2017). On the other hand, Notch2 sensitizes ECs to apoptosis, downregulating survivin expression (Quillard et al, 2009). Furthermore, during vascular remodeling, the activation of Notch signaling can induce EC apoptosis, hence disrupting EC proliferation/regeneration balance (Dejana et al, 2017). Notch3 increase negatively affects the expression of the Bcl-2 antiapoptotic gene in ECs, thereby inducing apoptosis (Solaimani Kartalaei et al, 2015; Dejana et al, 2017).

6. TGF-β

The TGF-β superfamily includes over 35 members, such as TGF-βs, activins, bone morphogenetic proteins, and nodal, and growth differentiation factors. These secreted proteins play pleiotropic roles in regulating the development, survival, proliferation, differentiation, and functions of diverse cell types in health and diseases (Wang et al, 2023b).

TGF-β1 plays an important role in tissue repair, promoting both tissue regeneration and repair. The mechanism involves inducing

proangiogenic M2 macrophages and activating fibroblast proliferation, production of ECM molecules, and ECM deposition.

Given the crucial role of TGF in cancer, multiple strategies have been developed to target this signaling in different tumors, including the inhibition of TGF-β production, neutralization of TGF-β activity, interference between TGF-β ligand and its receptors binding, or inhibition of the TGF-β receptor kinase (ALK) activity. While preclinical studies have pointed out promising results, the outcomes from clinical trials have shown only minor survival benefits and highlighted side effects in the cardiovascular compartment.

Specific inhibition of ALK5 by several small molecules resulted in undesired side effects, especially cardiotoxic effects (Anderton et al, 2011). Anti-TGF-β administration 1 week before or 5 days after coronary artery ligation enhanced mice mortality because of increased LV dilatation that was associated with a decrease in collagen production and promotion of MMP expression (Frantz et al, 2008). TGF-β2 is the most abundant TGF-β isoform in human plaques and is involved in plaque stability by decreasing inflammation and matrix degradation. Moreover, TGF-β2-high patients also displayed a lower risk of suffering from future cardiovascular events (Edsfeldt et al, 2023).

Targeting TGF-β poses several challenges, mainly caused by its dual role in cancer, acting as a tumor suppressor in early phases of tumor growth while inhibiting cell proliferation and promoting apoptosis in later stages, also decreasing epithelial-mesenchymal transition, immune evasion, and tumor dissemination to distant organs. This dual effect was also found in CVDs during MI. Indeed, in the early phases, TGF-β signaling has been demonstrated to be protective against ischemic myocardial damage, while the prolonged pathway activation resulted in LV remodeling and failure after MI (Ikeuchi et al, 2004).

a. TGF-β in cancer. In different cancer types, acute and chronic stimuli promote the aberrant expression of TGF-β from various cell types, therefore fostering collagen deposition and epithelial-to-mesenchymal transition (Peng et al, 2022). In a model of hepatocellular carcinoma, Yu et al. showed that TGF-β1 activated hepatic stellate cells (HSCs), also resulting in Kindlin-2 upregulation via the p38 and ERK/MAPK pathways. In mice and patients, high levels of Kindlin-2 correlate with liver fibrosis, and its downregulation limited the TGF-β1-mediated fibrotic process. Mechanistically, kindlin-2 promotes TGF-β signaling, enhancing Smad2/3 phosphorylation (Yu et al, 2018). Gastric fibroblast-to-CAF transition induced by TGF-β1 also promoted in vitro migration and the metastatic process in vivo (Yoon et al, 2021).

The TGF-β1 signaling pathway also plays a relevant role in forming new blood vessels in the injury area for subsequent revascularization or in cancers. During ER-breast cancer progression, TGF-β can induce the expression of angiopoietin-like 4 (ANGPTL4), which disrupts vascular endothelial junctions and induces lung metastasis (Padua and Massague, 2009).

In addition, TGF-β supports the angiogenic process in hypoxic tissues, including tumor tissues, promoting the expression of TGF receptors ALK1 and ALK5 (Oh et al, 2000), which upregulate angiogenic factors such as PDGF, IL-1, and basic FGF. Furthermore, TGF-β induces the production of VEGF (Ferrari et al, 2009), a potent stimulator of blood vessel formation.

b. TGF-β in CVD. TGF-β1 is associated with cardiac fibrosis. Indeed, following MI, TGF-β expression is increased, with TGF-β1 and TGF-β2 mainly upregulated in the early phases, while TGF-β3 increased in a later stage post-MI (Dewald et al, 2004). During HF, TGF-β1 is upregulated, resulting in increased cardiac fibrosis and inducing myocardial dysfunction through DNA damage accumulation and secretory phenotype generation in failing cardiomyocytes. In this context, TGF-β1 signaling is dampened by high-temperature requirement A serine peptidase 3 (Htra3), which promotes TGF-β1 degradation, preventing the activation of cardiac fibroblasts, therefore ameliorating cardiac function (Ko et al, 2022).

Likewise, Mmp14f/f:Lyz2-Cre mice, characterized by the genetic deletion of Mmp14 in macrophages, displayed limited cardiac dysfunction post-MI, reduced fibrosis, and preserved cardiac capillary network.

As comprehensively reviewed by Goumans et al (2009), several studies have pointed out the role of TGF-β in different non-ischemic CVDs, including hereditary hemorrhagic telangiectasia, primary pulmonary hypertension, and Marfan syndrome. It has been shown that inhibitory SMADs, SMAD-6, and SMAD-7 are highly expressed in specific heart regions, and when induced by TGF-β, they can promote the generation of a negative feedback loop. Either SMAD-6 or SMAD-7 deficient mice are characterized by significant cardiovascular defects, including hyperplasia of the cardiac valves and outflow tract septation defects, ossification of the aorta, and display high BP, abnormality in the ventricular septum and non-compaction (Galvin et al, 2000; Chen et al, 2009). Shen et al (2024a) have also demonstrated that MEOX1, a TGF-β1 downstream gene, is mainly expressed in the microvascular endothelium of the infarct and peri-infarct myocardium. Following MI, MEXO1 is upregulated and results in angiogenesis inhibition and induction of fibrosis (Shen et al, 2024a).

7. MYC

C-MYC, L-MYC, and N-MYC are transcription factors that belong to the MYC family. MYC heterodimerizes with Myc-associated factor X (MAX) and binds to DNA enhancer boxes where recruiting cofactors induces gene transcription. The MYC family potentially regulates more than 15% of the human genome and is implicated in numerous biological processes, spanning from protein translation to cell metabolism, development, proliferation, and differentiation (Dhanasekaran et al, 2022; Zacarias-Fluck et al, 2024). The expression and production of several immune molecules, as well as immune ligands or receptors, such as programmed death-ligand 1, CD47, MHC classes I and II, and killer cell lectin-like receptor subfamily k member 1, are regulated by MYC. MYC also stimulates the production of multiple cytokines, such as C-C motif chemokine ligand (CCL)-2, IL-23, and CCL9. These cytokines play a role in shifting the antitumor M1 macrophages to the protumor M2 phenotype. Additionally, these cytokines inhibit the activation and recruitment of B cells, NK cells, and CD4+ and CD8+ T cells. Angiogenesis is prompted by CCL9-induced activation of mast cells, together with active neutrophils and CCL-2/IL-23-stimulated M2 macrophages (Dhanasekaran et al, 2022). The MYC proto-oncogene is under the regulation of major growth-regulatory and oncogenic signaling pathways. MYC transcription is stimulated by Notch, WNT, Hedgehog, and Janus kinase—signal transducer and STAT3 signaling pathways, while TGF-β signaling inhibits it. The mammalian or mechanistic target of rapamycin (mTOR) complex 1 (mTORC1)—S6K1 and MAPK—HNRPK enhance, while MAPK—FOXO3A inhibits, MYC translation efficiency acting on MYC mRNA. At the protein level, the MYC stability is increased by the combined action of the PI3K and RAS signaling pathways (Kress et al, 2015).

a. MYC in cancer. In cancer, MYC participates in a series of pathological processes, such as immune surveillance, invasiveness, and angiogenesis, regulating the tumor microenvironment and concurring with malignancy progression (Dhanasekaran et al, 2022; Donati and Amati, 2022). A very high percentage of human cancers present deregulation of MYC expression, which often

implies MYC overexpression (Duffy et al, 2021). *MYC* overexpression can result from various mechanisms, primarily including gene amplification, translocation, mutation, enhancer activation, alteration of protein stability, and P53 loss (Duffy et al, 2021). In breast cancer, *MYC* gene amplification relates to a higher risk of relapse and death, as found in a meta-analysis of 29 studies (Deming et al, 2000). Meanwhile, the number of *N-MYC* copies determines neuroblastoma aggressiveness (Seeger et al, 1985; Jung et al, 2017b).

b. MYC in CVD. MYC expression and protein level changes were also observed in other pathologies (Marin et al, 1993; Kaizer et al, 2007; Wolfram et al, 2011; Ernst et al, 2017; Hou et al, 2022; Hojjati et al, 2023; Zacarias-Fluck et al, 2024). In patients affected by diabetic nephropathy, a pathology that involves a strong increase in cardiovascular risk, elevated MYC levels were detected in tumor biopsy and are thought to be partly responsible for the endothelial inflammation triggered by hyperglycemia (Hou et al, 2022; Hojjati et al, 2023). On the other hand, Kaizer et al (2007) suggest that MYC overexpression is not simply a response to high glucose because it was identified in peripheral blood mononuclear cells derived from patients with type 1 diabetes but not in those from T2D (Kaizer et al, 2007). MYC levels are increased inside the plaque of patients with atherosclerosis (Marin et al, 1993). This high concentration of MYC could be responsible for VSMC proliferation. VSMC-derived cells have been recently proven to account for 30% of cells forming the lesion and play a crucial role in plaque pathogenesis (Shankman et al, 2015). Notably, the presence of MYC-associated zinc finger protein in the serum may predict ischemic heart disease and inflammatory atherosclerotic lesions, suggesting its suitability as a CVD biomarker (Ernst et al, 2017). In the myocardium, a reduction of C-MYC levels, which are usually enhanced in cardiac hypertrophy and LV dysfunction in patients with chronic aortic regurgitation, was observed after aortic valve replacement. These findings suggest a potential correlation between MYC and the reversibility of myocardial cellular hypertrophy and LV dysfunction (Taketani et al, 2001). Rodríguez et al (2021) noticed elevated MYC protein in bone marrow HSPCs from patients affected by Fanconi anemia, which relates to overexpression of p53 and the TGF-β pathway.

Despite all the above studies emphasizing the detrimental effects of elevated MYC levels, a comparative analysis based on Gene Expression Omnibus datasets reveals the downregulation of MYC, C/EBPβ, and their downstream targets in failing heart tissues (Wang et al, 2020a). Altogether, these data suggest that a dysregulation of the MYC family concurs with cancer and cardiovascular pathologies, encouraging researchers to develop MYC target therapies.

8. AMPK

AMPK is a key energy sensor in eukaryotic cells. AMPK exists as a heterotrimeric complex, composed of catalytic α subunits and regulatory β and γ subunits. Its subunits are encoded by multiple genes, generating 2 α (α1, α2), 2 β (β1 and β2), and 3 γ subunits (γ1, γ2, and γ3), thereby resulting in 12 different combinations that display slightly different subcellular localization and functions or tissue-specific distribution (Hsu et al, 2022). For instance, α1 and regulatory β2 subunits are mainly expressed in the human liver, while γ2 subunits are highly expressed in the human heart (Wu et al, 2013). In rats, α1 and α2 subunits are expressed with comparable levels within the liver, with β1 and γ1 representing the major regulatory subunit isoforms, while the isoforms with the γ1 subunit are more predominant in the rodent heart (Woods et al, 1996). AMPK can be activated through different mechanisms. As a major energy sensor, the increased ratio of AMP/ATP or ADP/ATP mediates the induction of the upstream regulator liver kinase B1 (LKB1), which in turn activates AMPK. It can also be activated by the calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2 or CaMKKβ) or by the exercise-activated atypical protein kinase C, which can directly phosphorylate AMPK. Pharmacological compounds such as metformin, 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside, and small molecule compounds like A-769662 can also trigger AMPK signaling. Post-translational modification, particularly threonine 172 phosphorylation of AMPK, has been demonstrated to play a crucial role in AMPK complex stability, also directly impacting its enzymatic activity and fostering its activation (Hsu et al, 2022). AMPK activation leads to the phosphorylation of target proteins, including fructose-2-kinase/fructose-2, 6-bisphosphatase (PFKFB2 and PFKFB3), acetyl-CoA carboxylase (ACC), mitochondrial fission factor, unc-51-like autophagy-activating kinase 1, and mTOR complex, thereby inhibiting lipid metabolism while enhancing glycolysis and fatty-acid oxidation to produce energy, inducing mitochondrial fission and mitophagy, inhibiting protein synthesis and steroid synthesis to limit energy employment, inducing autophagy and cell cycle arrest, and further suppressing cell proliferation (Hsu et al, 2022; Wang et al, 2024a).

During the past 2 decades, several agents have been developed to target AMPK, including metformin and salicylate. Recently, sodium-glucose cotransporter-2 inhibitors canagliflozin, PF-739, PF-06409577, and PAN-AMPK activator (MK-8722) have demonstrated efficacy in reducing blood glucose, with effects comparable to metformin and phenformin (Villani et al, 2016; Myers et al, 2017; Steinberg and Carling, 2019). Based on AMPK's role in regulating metabolic processes, AMPK inhibitors have gained significant relevance in the treatment of metabolic disorders, including T2D and obesity. However, AMPK's ability to impact cell proliferation by regulating cell cycle and apoptosis suggests the possible use of AMPK-targeting drugs also in oncology, even if this repurposing remains controversial in different cancer types.

a. AMPK in cancer. As comprehensively reviewed by Hsu et al (2022), the role of AMPK in cancer is context-dependent, suppressing tumor growth by restricting energy use and growth signals while promoting tumor survival under metabolic stress. AMPK can directly inhibit the mTOR pathway through phosphorylation of TSC2 and RAPTOR, arresting the cell cycle and negatively impacting cell growth and proliferation, as well as inducing p21 and p53. During glucose deprivation, AMPK activation closely cooperates with the Hippo tumor-suppressive signal to induce phosphorylation and inactivation of yes-associated protein (YAP), a major regulator of glucose-transporter 3 expression (Wang et al, 2015). In LKB1- or AMPK-deficient fibroblasts, HIF1α levels and their downstream targets are increased compared with wild-type counterparts. A similar increase of HIF1α is also found in the epithelia of gastrointestinal hamartomas from LKB1 heterozygous mice (Shackelford et al, 2009). In response to energy stress, AMPK phosphorylates BRAF at Ser729, disrupts its interaction with the KSR1 scaffolding protein, and promotes the association of BRAF with 14-3-3 proteins, thereby inhibiting MEK-ERK signaling, resulting in the impairment of cell proliferation and cell cycle progression (Shackelford et al, 2009). Moreover, in patients with breast and ovarian cancer, it has been shown that AMPK-mediated phosphorylation of EZH2 suppresses PRC2 oncogenic function and is associated with improved survival (Wan et al, 2018). Besides its oncosuppressive role in tumors, increased AMPK, AKT, and SKP2 phosphorylation have been found in advanced breast cancer and significantly correlate with poor disease-specific and metastasis-free survival (Han et al, 2018a), highlighting the clinical implication of AMPK activation, also impacting resistance to therapy. Jeon et al (2012), demonstrated that, during energy stress, AMPK activation prolongs the cell survival of cancer cells through the

inhibition of acetyl-CoA carboxylases ACC1 and ACC2, resulting in NADPH level maintenance by decreasing NADPH consumption in fatty-acid synthesis and increasing NADPH generation using fatty-acid oxidation.

b. AMPK in CVD. In the cardiovascular system, AMPK activation has been reported to exert a protective role in the ischemic heart. Several studies showed that, in murine models lacking AMPKα2 or expressing a dominant-negative AMPK isoform, the myocardial recovery is dampened after ischemia and during ischemia-reperfusion (Russell et al, 2004; Paiva et al, 2011; Zaha et al, 2016). The protective role of AMPK is mainly associated with its ability to preserve mitochondrial integrity and function during reperfusion. Indeed, during ischemia-reperfusion, matrix calcium accumulation, adenine nucleotide depletion, and oxidative stress induce the mitochondrial permeability transition pore opening, which results in ROS production, cytochrome c release, and mitochondrial matrix swelling, all phenomena that can be counteracted by AMPK activation (Paiva et al, 2011; Zaha et al, 2016). Noppe et al (2014) also showed a crucial role of AMPKα1 in cardiac fibroblasts. Using in vivo and in vitro approaches, the authors demonstrated that AMPKα1 loss was associated with an impaired myodifferentiation of fibroblasts caused by the downregulation of the TGF-β1/p38 MAPK, together with the increased fibroblast proliferation in infarcted areas. Although infarct size was comparable between AMPK-knockout and wild-type mice subjected to MI, the genetic downregulation of AMPKα1 leads to compromised scar contractility, defective scar collagen maturation, and uncontrolled adverse remodeling, as indicated by increased LV diastolic dimension, 30 days after MI (Noppe et al, 2014). Moreover, AMPK activation reduces cardiac hypertrophy by downregulating AT1R and preventing mitochondrial dysfunction via the SIRT1/eNOS/p53 pathway (Hernandez et al, 2014).

9. PI3K

PI3K signaling is one of the main pathways involved in the regulation of cell homeostasis, proliferation, cell metabolism, and cell migration. Three classes of PI3Ks, class I, class II, and class III, have been identified, each of which is characterized by distinct effectors, in addition to the common substrate AKT, including protein kinase C, 3-phosphoinositide-dependent kinase 1 (, serum and glucocorticoid-regulated kinase 1, and others for class I PI3K; small GTPase and myotubularins for class II PI3K; and liver kinase B1 (LKB1) and serum and glucocorticoid-regulated kinase 3 for class III PI3K (He et al, 2021). As major effectors downstream of RTKs and G protein-coupled receptors, PI3Ks transduce signals from several cytokines and growth factors into intracellular messages by generating phospholipids, which in turn activate the serine/threonine kinase AKT and other downstream effector pathways (Liu et al, 2009).

a. PI3K in cancer. The PI3K/AKT/mTOR pathway is frequently activated in different cancer types, including breast, gastric, ovarian, colorectal, prostate, glioblastoma, and endometrial cancers. Therefore, several compounds aiming at targeting this pathway have been developed so far (Sirico et al, 2023). PI3K inhibitors can be classified into 2 main categories, including Pan-PI3K Inhibitors and Isoform-Selective PI3K Inhibitors. The first generation of PI3K targeting drugs, namely pictilisib (GDC-0941), buparlisib (BKM120), and copalinsib, target all 4 catalytic isoforms of class I PI3Ks (α, β, γ, and δ). These small molecules have demonstrated a broad spectrum of activities and are characterized by severe adverse events and treatment discontinuation. Among the isoform-selective PI3K inhibitors, Alpelisib (BYL719) was the first oral inhibitor targeting the p110α isoform of wild-type PI3Kα to be approved by the US FDA and by the European Medical Agency. Taselisib (GDC-0032) is a novel effective inhibitor of PI3Kα, exerting its blocking activity on p110*a*, p110γ, and p110δ isoforms (Sirico et al, 2023).

The *PIK3CA* gene, encoding p110α, is frequently mutated in different types of cancer, such as colorectal, glioblastoma, gastric, breast, lung, and kidney cancers. The genetic alterations, commonly because of somatic missense mutations, lead to aberrant activation of this pathway, enhancing PI(3,4,5)P3 levels and activating AKT signaling, thereby promoting cellular proliferation and transformation (Liu et al, 2009). Recently, it has also been shown that the *PIK3R1* gene, encoding the p85α regulatory subunit, was mutated in up to 10% of glioblastomas, thus representing one of the most frequently altered genes in this kind of tumor (Parsons et al, 2008). Together with cell proliferation and survival, PI3K has been shown to promote cell migration as well as angiogenesis, thereby promoting tumor progression. Dolecek et al (2012) have reported that the hyperactivation of the PI3K/AKT pathway is associated with a poor prognosis in the central nervous system and brain cancers. PI3K knockdown in glioblastoma cells results in the reduction of FAK activity and decreased MMP2 levels, negatively affecting cell migration and invasion, also impairing cell proliferation (Weber et al, 2011). Qiao et al (2023) demonstrated that sennoside A inhibited DU-145 and PC-3 prostate cancer cell viability and concomitantly increased light chain 3 β (LC3B) expression and the relative protein expression of LC3II/LC3I and beclin-1 via PI3K inhibition, thus negatively impacting tumor growth in vitro and in vivo. Using ovarian cancer cell lines, Liu et al (2020) demonstrated that leukocyte-associated immunoglobulin-like receptor 1 overexpression decreased cell proliferation by suppressing PI3K-AKT-mTOR. They also developed a lipid metabolism score system and identified a potential sensitizing agent, MK1775, which targets lipid metabolism and enhances the effects of anti-PD-1 treatment. The authors demonstrated that MK1775 inhibits tumor progression by influencing lipid crosstalk between tumor cells and tumor-associated macrophages and CD8+ T cells, thereby increasing the effectiveness of anti-PD-1 treatment. Using in vitro and in vivo approaches, Chen et al (2024) demonstrated that MK1775 was able to reduce lung cancer growth by inhibiting the PI3K/AKT/mTOR pathway, resulting in the decrease of fatty-acid synthesis and oxidation of tumor-associated macrophages and promotion of the interferon regulatory factor 1-mediated release of CXCL10 and CXCL11, thereby supporting CD8+ T-cell infiltration.

b. PI3K in CVD. PI3K signaling plays a crucial role in the cardiovascular system, regulating different processes, such as angiogenesis, hypertension, thrombosis, and HF. Human platelets express all class I PI3K isoforms, with PI3Kβ expressed at the highest level (Kim et al, 2014). Laurent et al (2015) have shown that PI3Kβ expression in platelets is not essential for thrombus formation at normal arterial shear, while it is crucial for the integrity maintenance of the formed thrombus. Indeed, using transgenic mice carrying a selective p110β deletion in the megakaryocyte lineage, the authors demonstrated increased thrombus instability at a high shear rate in PF4-Cre/p110βflox/flox (p110βnull) mice, not only compared with the WT p110βflox/flox counterpart but also with PF4-Cre/p110αflox/flox mice carrying the deletion of p110α in platelets. Using human samples treated with the PI3Kβ inhibitor AZD6482, the authors also showed that PI3Kβ is required for the incorporation of new platelets into an existing thrombus under a high shear rate. Fougerat et al (2008) also demonstrated that PI3Kγ plays a crucial role in the pathogenesis of atherosclerosis. The pharmacological inhibition of PI3Kγ, using AS605240, was shown to significantly reduce early atherosclerotic lesions in apolipoprotein E (ApoE)-null mice, also dampening advanced atherosclerotic lesion

formation in LDL receptor-deficient mice. Moreover, PI3Kγ loss in mice prevents hypertension induced by Ang-II, which can induce smooth muscle contraction via the RAC pathway and promotes AKT-driven extracellular calcium entry via L-type calcium channels (Vecchione et al, 2005).

B. Examples of anticancer drug repurposing

Here we report a few examples of how cancer therapeutics could be repositioned in the CVD context, targeting key mechanisms and pathways described above (Fig. 4). While some drugs have undergone initial clinical trials on patients, these studies remain mainly in the preclinical phase.

1. MEK inhibitors

MEK inhibitors (MEKIs) have been developed as cancer drugs for their inhibitory activity on cell proliferation. They are small molecules that prevent ERK1/2 phosphorylation by inhibiting the upstream MEK1/2 catalytic activity (Cheng and Tian, 2017; Ram et al, 2023). New-generation MEKIs bind with very high specificity to a site near the ATP-binding pocket of MEK1/2; because they do not compete with ATP for binding to MEK, they do not produce unwanted off-target effects deriving by simultaneous binding to conserved ATP-binding sites of other cellular kinases (Ohren et al, 2004; Cheng and Tian, 2017). MEKIs are indicated for the treatment of solid tumors, such as melanoma, lung, pancreatic, liver, and colorectal cancer. While most MEKIs are still undergoing preclinical development and some of them are tested in clinical

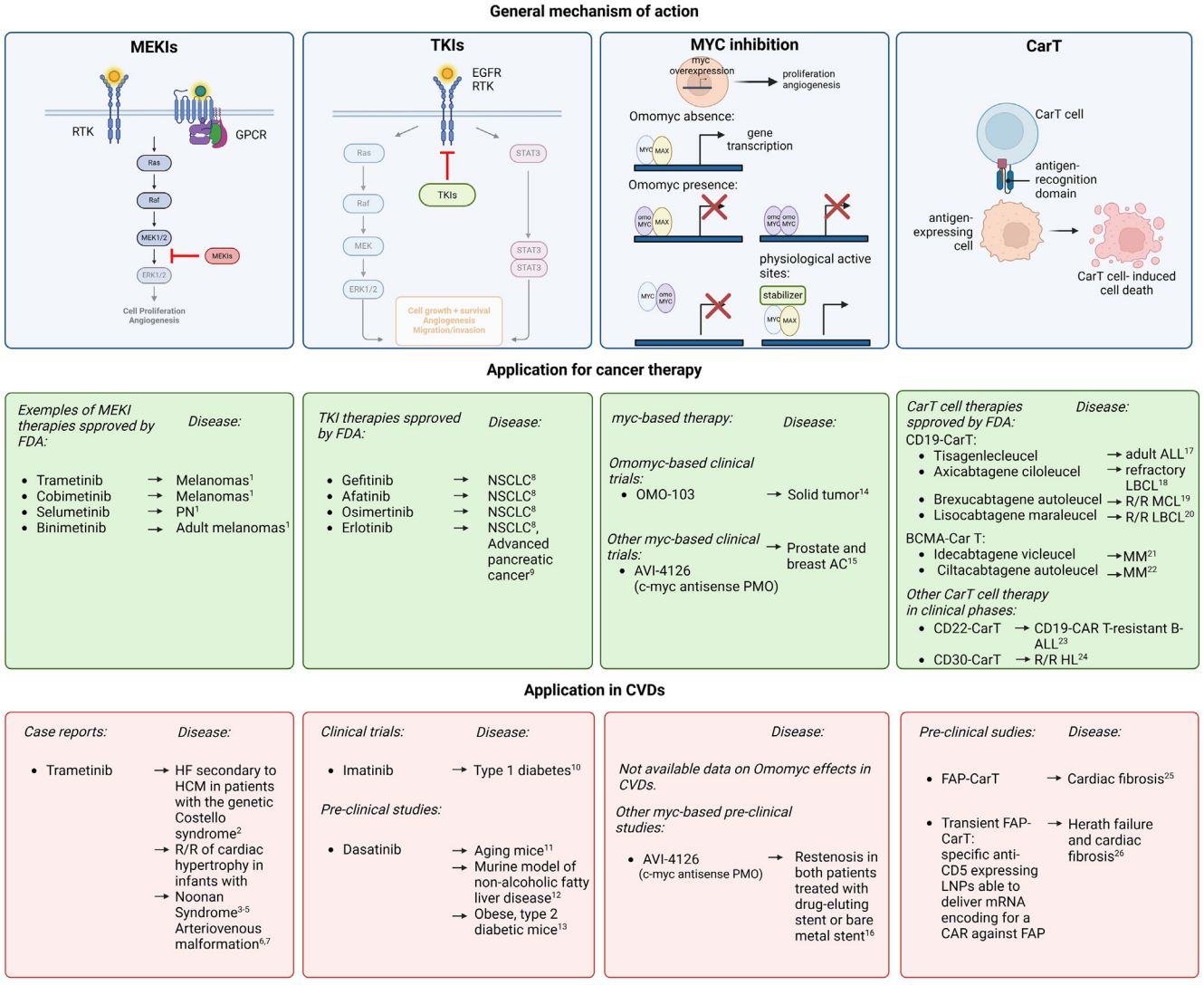

Fig. 4. Cancer therapeutics repurposed for CVDs. Schematic drawing of the general molecular mechanisms (top row), the approved therapies from the US FDA or, if not available, the ongoing clinical trials as cancer therapies (middle), and preclinical studies or case reports for potential use as CVD therapies (bottom) of the 4 therapeutic approaches discussed in the review: *MEK inhibitors (MEKIs), Tyrosine kinase inhibitors (TKIs), Myc inhibitors, and CAR-T cells*. Created with BioRender.com. Numbers refer to references listed in the text: (1) Cheng and Tian (2017); (2) Geddes et al (2023); (3) Andelfinger et al (2019); (4) Leegaard et al (2022); (5) Mussa et al (2021); (6) Edwards et al (2020); (7) Lekwuttikarn et al (2019); (8) Solassol et al (2019); (9) Carter and Tadi (2024); (10) Gitelman et al (2021); (11) Islam et al (2023); (12) Elsayed et al (2021); (13) Gu et al (2023); (14) Garralda et al (2024); (15) Devi et al (2005); (16) Kipshidze et al (2007); (17) Maude et al (2018); (18) Locke et al (2019); (19) Wang et al (2020b); (20) Abramson et al (2020); (21) Munshi et al (2021); (22) Martin et al (2023b); (23) Fry et al (2018); (24) Ramos et al (2020); (25) Aghajanian et al (2019); (26) Rurik et al (2022). AC, adenocarcinoma; ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; HCM, hypertrophic cardiomyopathy; EGFR, epidermal growth factor receptor; FAP, fibroblast-activated protein; HL, Hodgkin lymphoma; LBCL, large b-cell lymphoma; LNPs, lipid nanoparticles; MAX, myc-associated factor X; MCL, mantle-cell lymphoma; MM, multiple myeloma; NSCLC, non–small-cell lung cancer; PMO, phosphorodiamidate morpholino oligomer; PN, plexiform neurofibromas; PRAD, prostate adenocarcinoma; R/R, refractory/relapsed.

trials, 4 compounds—trametinib, cobimetinib, selumetinib, and binimetinib—were approved by the US FDA for clinical use in cancer patients.

More recently, MEKIs have attracted researchers' attention for their possible application in treating CVDs characterized by aberrant ERK activation. We recently reviewed the preclinical studies conducted so far to test the MEKI therapeutic efficacy in animal models of MI, cardiac hypertrophy, HF, and aortic aneurysm (Mohammed et al, 2024).

Briefly, the MEKIs PD0325901 and PD98059 showed therapeutic benefits associated with smaller infarct scars in 2 preclinical MI models using mice and rats (Jin et al, 2018; Avolio et al, 2022). In our study, PD0325901 also had a clear effect on vascularization, promoting LV arteriogenesis by inducing pericyte differentiation (Avolio et al, 2022). However, in the 2 studies in rats and swine, treatment with the MEKI PD98059 and U0126 resulted in larger infarct scars (Strohm et al, 2000; Hausenloy et al, 2005). The MEKI pimasertib attenuated cardiac hypertrophy and prevented HF in mice with continuous EGF receptor activation (Sala et al, 2016). PD0325901 prevented or reduced carotid neointima formation in a mouse model of neurofibromatosis type 1 with mechanical carotid injury, corroborating the concept that the same anticancer drug could be used to treat both cancer and vascular conditions (Stansfield et al, 2014). In the context of atherosclerosis, the MEKI U0126 blunted the atherogenic process in mice with advanced atherosclerotic lesions by reducing macrophage and foam cell formation (Chen et al, 2015). MEKIs can also modulate macrophage polarization toward the anti-inflammatory M2 phenotype, thus promoting macrophage reparative properties (Long et al, 2017). Interestingly, a recent drug repurposing algorithm (OCTAD) aimed at identifying the shared transcriptional risk patterns between cancer and atherosclerosis pointed to the MEKI PD0325901 as the top compound with predicted therapeutic benefits in atherosclerosis (Baylis et al, 2023).

To date, MEKI application in clinical trials remains limited and restricted to trametinib. Trametinib reversed HF secondary to hypertrophic cardiomyopathy in patients with the genetic Costello syndrome, characterized by a mutation of the RAS gene resulting in continuous MEK activation (Geddes et al, 2023). The drug proved successful in inducing the remission or regression of cardiac hypertrophy in infants with Noonan syndrome, characterized by severe early-onset eccentric hypertrophy and congestive HF (Andelfinger et al, 2019; Mussa et al, 2021; Leegaard et al, 2022). It was also effective in improving arteriovenous malformation, a congenital vascular anomaly that causes complications including HF, in 2 patients (Lekwuttikarn et al, 2019; Edwards et al, 2020). Finally, there are currently 2 clinical trials investigating the therapeutic effects of trametinib in children and adults with arteriovenous malformation (ClinicalTrials.gov IDs NCT04258046 and NCT06098872). These preliminary clinical studies suggest that MEKIs, administered for limited periods to avoid toxicity, could offer new hope for treating selected cardiovascular conditions in the future.

2. Tyrosine kinase Inhibitors

As key regulators, tyrosine kinases drive the activation of mitogenic factors explored in this paper, with a pivotal role in orchestrating the ERK1/2, STAT3, and MYC pathways. TKIs are pivotal drugs to fight cancer. In the last few years, there have been significant technological advances in computational tools, chemoproteomics, and microfluidics, providing more efficient and selective TKIs (Pottier et al, 2020). While their efficacy in cancer treatment is well-established, with TKIs such as gefitinib, erlotinib, afatinib, and osimertinib already approved by the US FDA for oncology (Solassol et al, 2019; Carter and Tadi, 2024), the potential benefits of these agents in CVDs remain largely unexplored, with emerging studies beginning to shed light on their possible role in this context. Phase 2 clinical trial with the first-generation TKI imatinib conducted in patients without cancer with recent-onset type 1 diabetes showed improvement in β-cell function and peripheral insulin sensitivity (Gitelman et al, 2021). Dasatinib is a second-generation TKI used to treat chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. The association of dasatinib and the flavonoid quercetin reduced adipose tissue inflammation and senescence and improved systemic metabolic function in aging mice (Islam et al, 2023). In a murine model of nonalcohol misuse fatty liver disease, dasatinib reportedly inhibited liver steatosis, inflammation, fibrosis, and hepatocellular ballooning by attenuating lipogenesis and inducing M2 macrophage polarization with antifibrotic activity (Elsayed et al, 2021). Additionally, TKIs increase the antilipolytic activity of insulin, thereby reducing the mobilization of free fatty acids from visceral fat depots (Elsayed et al, 2021). Importantly, we showed that dasatinib also attenuates lipid accumulation and interstitial fibrosis in the heart and improves cardiac function in obese, T2D mice. This TKI may have important implications for the treatment of diabetic cardiomyopathy (Gu et al, 2023).

3. OmoMyc

Omomyc is a developed peptide that acts as a MYC-dominant negative. It can form homodimers and heterodimers with MYC or MAX proteins. These dimers can bind to DNA, inhibiting MYC target gene transcription (Jung et al, 2017a; Masso-Valles and Soucek, 2020). Unexpectedly, Omomyc appears to repress mainly the non-physiological gene activation, probably thanks to stabilizing cofactors interacting with MYC/MAX on physiologically active sites (Masso-Valles and Soucek, 2020), revealing an exceptional therapeutic potential in pathologies associated with MYC upregulation. In vitro and in vivo studies have also demonstrated the role of Omomyc in inducing apoptosis, but only when exogenous Myc is provided (Soucek et al, 2002), suppressing Myc-induced transactivation and potentiating Myc-induced transrepression (Savino et al, 2011). These results outline Omomyc's ability to suppress Myc's pro-oncogenic actions while enhancing its antioncogenic ones. Its antitumor therapeutic potential was convincingly proved in mouse models of papillomatosis (Soucek et al, 2004), insulinoma (Sodir et al, 2011), lung adenocarcinoma (Soucek et al, 2013), glioma (Annibali et al, 2014), and pancreatic ductal adenocarcinoma (Sodir et al, 2020).

Omo-103 is currently under evaluation in a phase 1/2 clinical trial (ClinicalTrials.gov ID NCT04808362) for its antitumoral efficacy on solid tumors. The first results revealed its safety. PK investigations determined that OMO-103's half-life in serum samples was at least 40 hours (Garralda et al, 2024). Other molecules deriving from Omomyc are under preclinical phase investigation (Masso-Valles and Soucek, 2020). MYC inhibitors have been tested to treat cancer, and the results have been well-reviewed by Whitfield et al (2017). AVI-4126 represents an exciting example. AVI-4126 is a c-myc antisense phosphorodiamidate morpholino oligomer, initially tested in oncology patients, where it exhibited excellent safety and localized accumulation within tumor tissues (Devi et al, 2005). Subsequently, additional clinical trials have been initiated to evaluate its potential application in CVDs, such as restenosis in patients treated with drug-eluting or bare metal stents (NCT00244647 and NCT00248066).

Given the demonstrated in vitro role of C-MYC in restenosis, because of its capacity to induce VSMC proliferation, the AVAIL study aimed to assess the efficacy of AVI-4126 in reducing restenosis in patients undergoing percutaneous coronary intervention. Initial findings revealed an inferior reduction in artery diameter post-treatment, associated with a diminished risk of restenosis (Kipshidze et al, 2007).

4. Chimeric antigen receptor T cells

Immunotherapy emerged as a revolutionary next-generation approach to the fight against cancer, based on the concept that the same immune system of the host can be reawakened and reactivated against cancer cells. Cancer immunotherapy is now characterized by different tools and approaches, ranging from cytokines and (immune)cytokines, anticancer vaccines, bi/tri-specific monoclonal antibodies, and autologous and/or heterologous cell therapy. This latter approach deals with the reactivation of circulating or tumor-infiltrating T cells from patients with cancer or with the possibility of arming T cells with the correct arsenal to redirect them against tumors (specific antigens).

In line with this, in the last decade, chimeric antigen receptor (CAR)-T cell therapy has been introduced as an innovative immunotherapy strategy. It involves the genetic modification of autologous T cells, which are engineered using synthetic CAR receptors that allow for improved recognition and elimination of target cells expressing the specific corresponding antigen. The synthetic receptor is composed of an antigen-recognition domain (typically derived from an antibody), a transmembrane domain, and intracellular signaling domains. Once modified, CAR-T cells are cultured and expanded in vitro and then infused into the patient with prior lymphodepletion. After infusion, CAR-T cells proliferate and recognize their target antigen, resulting in effective T-cell activation, release of cytokines, and target cell elimination (Sterner and Sterner, 2021). The intracellular domain classifies CARs into 5 generations (Tokarew et al, 2019). A single activation domain, a cytoplasmic domain, mostly CD3 ζ (CD3ζ), and the γ-chain of the Fc receptors characterize the first. The second generation introduced one costimulatory domain obtained using 4-1BB or CD28 linked to an activator domain (CD3ζ/γ chain of Fc receptor) to enhance both cell proliferation and activation. The third generation introduced multiple costimulatory domains with CD3ζ, such as 4-1BB and CD28, CD134, and CD137. The fourth generation, namely T cells redirected for universal cytokine-mediated killings, were engineered to release transgenic cytokine-like IL-12, IL-15, and IL-18, overcoming immunosuppression and granting an effective activation within the tumor microenvironment. The fifth generation of CARs is similar to the second generation while containing a truncated cytoplasmic receptor (IL-12) and a β-chain domain (IL-2Rβ truncated intracellular interleukin 2β chain receptor) along with the transcription factor STAT3/5 binding motif (Alnefaie et al, 2022).

CAR-T cell therapy is a promising alternative approach for the treatment of different hematological malignancies, such as large B-cell lymphomas and lymphoblastic leukemia. The first CAR-T cell therapy approved by the US FDA was tisagenlecleucel (Kymriah), a CD19-CAR-T cell, in 2017, for the treatment of pediatric and young adult acute lymphoblastic leukemia (Maude et al, 2018). Furthermore, the US FDA approved 3 other CD19-specific CAR-T cells for the treatment of different B-cell malignancies: (1) axicabtagene ciloleucel (Yescarta) for the treatment of refractory large B-cell lymphoma (Locke et al, 2019), (2) brexucabtagene autoleucel (Tecartus) in relapsed or refractory mantle-cell lymphoma (Wang et al, 2020b), and (3) lisocabtagene maraleucel (Breyanzi) for patients with relapsed or refractory large B-cell lymphomas (Abramson et al, 2020). In 2021 and 2022, 2 B-cell maturation antigen-specific CAR-T cell therapies were approved for the treatment of multiple myeloma, namely idecabtagene vicleucel (Abecma) (Munshi et al, 2021) and ciltacabtagene autoleucel (Carvykti) (Martin et al, 2023b), showing 33% and 82.5% of complete response, respectively. Other T-cell therapies have proved effective, including the CD22-targeted CAR-T cell therapy for CD19-CAR T-resistant B-ALL (Fry et al, 2018) or anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma (Ramos et al, 2020).

Besides hematological malignancies, research has focused its attention on the possibility of extending CAR-T cell therapy to solid tumors. However, as comprehensively reviewed by Maher and Davies, the efficacy of CAR-T in this field is limited and has presented greater challenges and complexities (Maher and Davies, 2023). Indeed, although different clinical trials considered several potential targets on cancer cells (such as human epidermal growth factor 2, EGF receptor, CD133, prostate-specific membrane antigen, prostate stem cell antigen and carcinoembryonic antigen), identifying suitable antigens that are exclusive to cancer cells and minimally expressed on healthy tissues encounters significant challenges (Patel et al, 2022; Maher and Davies, 2023). Despite these issues, ongoing research and clinical trials explore novel strategies to optimize CAR-T therapy for solid tumors, including combination therapies and localized delivery (Maher and Davies, 2023).

More recently, some studies have also extended the application of CAR-T cell therapies to CVD, with a particular focus on cardiac fibrosis (Ferrer-Curriu et al, 2023). In a mouse model of hypertensive cardiac injury and fibrosis, Aghajanian et al (2019) engineered CAR-T cells to specifically target fibroblast-activated protein, therefore leading to myofibroblast elimination and resulting in a reduction of cardiac fibrosis and restoration of cardiac functions. Rurik et al (2022) also developed a therapeutic approach to generate transient antifibrotic CAR-T cells in vivo. Indeed, they generated specific anti-CD5-expressing lipid nanoparticles, able to deliver mRNA encoding for a CAR against fibroblast-activated protein. These lipid nanoparticles, when injected into a mouse model of HF, specifically interact with T cells. mRNA was released into the T-cell cytoplasm and translated to obtain a fibroblast-activated protein CAR that efficiently eliminated myofibroblasts in vivo, reducing fibrosis and improving heart function (Rurik et al, 2022).

C. Side effects of repurposed cancer drugs on the cardiovascular system

As mentioned above, several studies highlighted the potential positive effects of anticancer therapies such as MEKIs, TKIs, Omo-Myc, and CAR-T cells on the cardiovascular system. However, to have a broader image, it is essential to recognize the potential cardiovascular side effects associated with these treatments.

The MEK/ERK pathway is essential for normal cardiac and vascular physiological function, and its activation is mandatory for cardio-protection during acute stress such as MI (Zhang et al, 2022a). Therefore, patients with cancer receiving MEKi treatments show a range of cardiovascular complications, including hypertension, left-sided HF, thrombo-embolic events, and arrhythmias (Glen et al, 2022). Likewise, TKIs, especially imatinib and sunitinib, have been linked to right-sided HF and heart block (Shyam Sunder et al, 2023).

In CAR-T cell cancer immunotherapy, cytokine release syndrome that occurs as a result of CAR-T cell activation can lead to severe cardiovascular complications, including hypotension, capillary leak syndrome, and arrhythmias (Cobb and Lee, 2021).

Moreover, it has been reported that 7.5% of patients receiving MYC inhibitors therapy showed off-target cardiovascular adverse effects such as myocarditis (El-Cheikh et al, 2023) and that MYC inhibition has a strong association with HF (Wang et al, 2020a).

V. Future directions and current challenges

A. Emerging drug discovery/repurposing technologies

Drug discovery and development is a complex and expensive process requiring over a decade from initial molecule identification to regulatory approval and introduction in the clinic (Fig. 5). Each stage of drug development is associated with a high risk of failure,

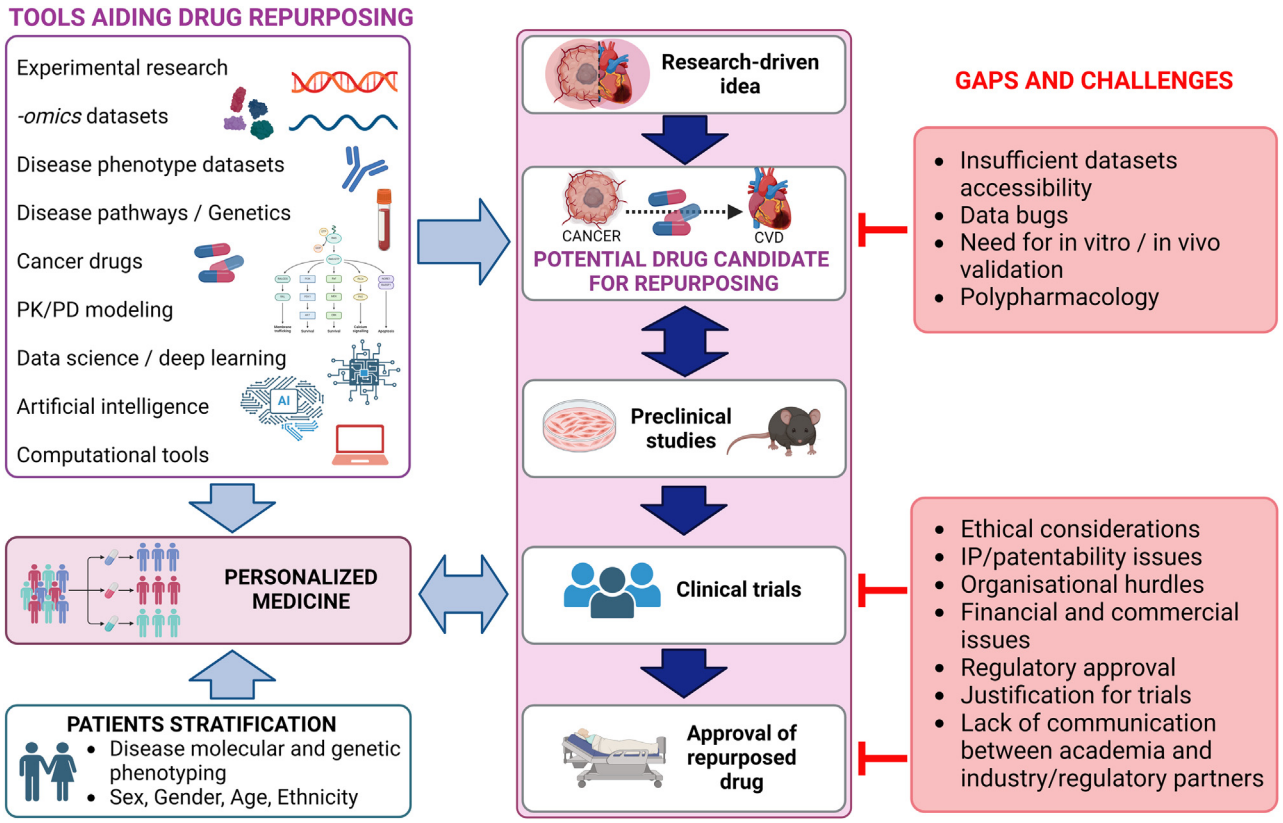

Fig. 5. Diagram summarizing the steps involved in drug repurposing. On the left, are tools aiding the identification of potential drug candidates for repurposing, including common methodologies, innovative technologies under development, and novel approaches such as personalized medicine. In the center, the flow is from research ideas to the approval of repurposed drugs. On the right are unsolved gaps and challenges that hinder the potential of drug repurposing. Created with BioRender.com. IP, intellectual property.

and the majority of drug candidates—about 90%—do not reach the market, leading to financial burdens and inefficiencies (Sun et al, 2022a). In this context, artificial intelligence (AI) is gaining great attention in the scientific and medical communities. AI models span from unsupervised clustering, which groups drugs or patients without predefined labels to identify potential drug compounds or suitable patient populations, to supervised machine-learning approaches that improve the accuracy of drug monitoring (van der Lee and Swen, 2023).

The rapidly advancing field of AI shows great potential in drug discovery and development, largely thanks to the vast amounts of chemical and biological data stored in public libraries and platforms. This data includes essential information for exploring potential toxicity and side effects associated with specific drug candidates (Paul et al, 2021; Kokudeva et al, 2024). AI predictions can be critical in identifying which candidate compounds are more likely to be repurposed safely and effectively, potentially saving considerable time and resources. This aspect can be particularly relevant in the cardio-oncology field and drug repurposing to screen different compounds and select those displaying the lowest potential for adverse effects on the cardiovascular system. In line, in 2018, Bayer and Merck received US FDA approval to use AI algorithms to support clinical decision-making for chronic thromboembolic pulmonary hypertension. In the same period, Cyclica, in collaboration with Bayer, explored the use of AI in identifying the polypharmacological profiles of small molecules and developing more affordable drugs. This resulted in the generation of an integrated network of cloud technologies expanded with AI, namely Ligand Express, that supported drug design, screening, and personalized medicine (Kokudeva et al, 2024).

The Connectivity Map (cMap), created by the Broad Institute in 2006, is a resource of gene expression profiles from over 1300 compounds tested in various cell lines, serving as a proxy phenotypic screen to aid drug repurposing for multiple diseases (Lamb et al, 2006).

Public repositories, such as Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) and Array Express (https://www.ebi.ac.uk/biostudies/arrayexpress), collect raw transcriptomic and genomic data from hundreds of disease conditions in humans and animal models. These computational tools, together with cMap, can be interrogated to identify similar molecular signatures between cancer and CVDs and disease-drug connections to aid drug repurposing.

Matching transcriptomic signatures can be used to compare drug-disease similarities. By analyzing how a drug alters gene expression in cells or tissues and comparing it to the gene expression in diseased and healthy states, researchers can identify whether the drug's effects oppose the disease's gene expression patterns. A strong negative correlation suggests the drug might have therapeutic potential. This method relies on the signature reversion principle, which assumes that when a drug can reverse disease-related gene expression changes to resemble a healthy state, it could potentially counteract the disease (Dudley et al, 2011).

ProHarMeD, a novel computational tool generated in 2023, allows the harmonization and comparison of proteomics data gathered in multiple studies, the extraction of potential disease mechanisms, and the prediction of drug repurposing candidates (Adamowicz et al, 2023).

Another computational approach adopted in drug discovery is represented by cell docking, which predicts the ligand conformation and orientation within a targeted binding site (Kitchen et al,

2004). Perhaps, once established, the target involved in a certain CVD, cell docking could be used to interrogate a library of cancer drugs against that target.

Genome-wide association studies (GWAS) have risen in the last 15 years. GWAS identifies genetic variants linked to common diseases, offering biological insights and potential novel targets that can overlap with existing drug-treated conditions, enabling drug repositioning opportunities (Sanseau et al, 2012).

The drug directionality Map is a computational tool that analyzes the effects of drugs on gene activity (activation or inhibition) via protein interactions, based on 24,121 PubChem compounds and 5196 Uniprot proteins, establishing over 438,000 drug-protein relationships. It ranks drug-drug and drug-protein interactions to identify repurposing candidates by comparing similar features of drugs (Huang et al, 2015).

Modern PK-PD modeling and its application to the specific case of drug repurposing will take advantage of AI's capacity to process complex datasets. AI has the potential not only to perform such analyses with greater speed, accuracy, and efficiency but also to enhance the predictions of molecular targets for personalized treatment, marking a shift from static to dynamic modeling that continuously learns and reworks the PK-PD domain (van der Lee and Swen, 2023). PK-PD modeling could help refine the application of drug repurposing. This approach attempts to predict the concentration-driven drug efficacy and toxicity, considering the drug's distribution across multiple compartments represented by various organs, tissues, and cells. With an increasing understanding of system biology and the fast development of computational and bioinformatic capacities, quantitative systems pharmacology could more precisely explain between-subject variability and predict a repurposed drug's efficacy and safety (Azer et al, 2021).

Regulatory agencies, including the US FDA, Japan Pharmaceutical and Medical Device Agency, China Food and Drug Administration, and the UK Medicines and Healthcare Products Regulatory Agency, use Phoenix WinNonlin software to evaluate drug submissions. The NONMEM/PREDPP/NM-TRAN package provides tools for basic nonlinear regression analyses and powerful subroutines for population- and patient-type PK data analyses. Other software, like Monolix and GastroPlus, can predict PK characteristics based on molecular properties. GastroPlus, for instance, can simulate disease-specific modeling by integrating physicochemical properties, biological data, and PK processes (Almukainzi et al, 2016).

B. Personalised medicine

Personalized or precision medicine tailors treatment to the patient's characteristics to maximize patients' benefits. Patient stratification, accounting not only for the disease but also for other factors such as age, comorbidities, and genetic background, is a crucial step in drug development (Fig. 5), but sadly, personalized cardiovascular medicine is still in its early stages of development (Madeddu et al, 2019). On the other side, precision oncology, which tailors treatments to patients with cancer, is more advanced. For example, in clinical trials for cancer therapeutics, patients are often matched with targeted therapies based on their tumor's molecular profile (Song et al, 2023a). In the future, cancer drug repurposing for CVD may find its best application in the context of personalized medicine.

Refined protocols to adapt the PK properties of anticancer drugs to the therapeutic finalities of acute cardiovascular ischemic events could increase the benefit/adverse response ratio. While patients with cancer undergo long, harsh, and repeated treatments with drugs that kill cancer cells, we can expect that short treatments and lower doses are sufficient to achieve the desired effects in patients with CVD. The treatment of chronic HF, however, poses more difficulties.

Systemic and cardiac toxicity of cancer drugs represents an obvious barrier to drug repurposing (Mincu et al, 2019; Jin et al, 2020; Arangalage et al, 2021; Grela-Wojewoda et al, 2022). However, with the advancements in targeted therapy, which enables increasingly precise targeting of specific tissues and cells, coupled with the rise of personalized medicine, it is possible to significantly reduce side effects for patients (Krzyszczyk et al, 2018; Abdelsayed et al, 2022).

C. Outstanding challenges and gaps

The above technologies and approaches have the potential to accelerate drug repurposing, resulting in the development of new therapeutics. However, knowledge and technological gaps and challenges still hinder its full potential (Fig. 5).

Data-driven approaches using big data repositories have significantly advanced drug repurposing efforts by linking molecular, phenotypical, and pharmacological data. However, although resources like cMap and GWAS have been developed, more extensive and accessible data sets are needed to enhance drug repurposing. Moreover, these bioinformatic tools need further refinement to improve accuracy and reduce reliance on traditional in vitro and in vivo screening methods (Gns et al, 2019).

The new AI revolution carries challenges, particularly regarding the heterogeneous and dynamic nature of PK/PD data bases featuring new drugs or therapeutic indications (Wright, 2022). Robust algorithms capable of processing and selecting these datasets must be developed to ensure that the analysis validly supports clinicians. Nonetheless, as suggested in a recent position article, AI models cannot replace doctors' expertise and critical decision-making because their output is only as good as the quality of the data analyzed (Davies, 2023).

Polypharmacology, the ability of drugs to interact with multiple targets, can hinder drug repurposing because of the complexity of predicting multiple drug-target interactions, which can result in unwanted off-target effects, jeopardizing the new drug's application (Chopra and Samudrala, 2016).

Ethical considerations, such as privacy, data security, and the risk of biased outcomes, are paramount and must be addressed because AI paves the way toward individualized treatments (Ghayoor and Kohan, 2024).

Beyond the technological challenges, other factors that can hinder the process of drug repurposing are organizational hurdles, regulatory approval, intellectual property, financial and commercial considerations, and justification for randomized controlled trials, reviewed in (Pushpakom et al, 2019; Begley et al, 2021).

Finally, some considerations about the role of academia. Academic research represents an important ring of the chain leading to drug discovery. Experimental work carried out by academic researchers fuels drug repurposing ideas. However, academics often neglect the above-mentioned challenges, which results in wasting considerable resources to carry out pointless studies and the failure to translate preclinical findings into clinical drug repurposing (Begley et al, 2021). Filling this knowledge gap within the academic research community and enhancing communication with industrial and regulatory partners could expand the potential of drug repurposing.

VI. Conclusions

Cancer and CVD, the leading global causes of death, share common features and underlying cellular and molecular mechanisms. These diseases often overlap clinically, with individuals having one condition reciprocally at higher risk of developing the other. While therapies for both exist, cardiovascular drug

development lags behind advancements in cancer treatments. Therefore, exploring the shared pathological mechanisms between the 2 diseases could enable the repurposing of cancer drugs for CVD treatment. Drug repurposing, supported by experimental approaches, data-driven methods, and AI, accelerates therapeutic development but faces challenges such as limited datasets, ethical and intellectual property concerns, and regulatory and commercial barriers. Additionally, the potential toxicity of cancer drugs on the cardiovascular system remains a key hurdle. Integrating drug repurposing with the emerging fields of personalized medicine and targeted therapies could represent a promising path toward the development of novel high-benefit/low-risk CVD therapeutics.

Abbreviations

AI, artificial intelligence; ALK, TGF-β receptor kinase; AKT, protein kinase b; AMPK, 5' monophosphate-activated protein kinase; Ang-II, angiotensin II; ANGPT, angiopoietin; BCL2, B-cell lymphoma 2; BP, blood pressure; CAF, cancer-associated fibroblast; CANTOS, Canakinumab Anti-Inflammatory Thrombosis Outcome Study; CAR-T, chimeric antigen receptor T cell; CCL, C-C Motif Chemokine ligand; CDK, cyclin-dependent kinases; CHIP, clonal hematopoiesis of indeterminate potential; CREB, cAMP response element; CRP, C reactive protein; CVD, cardiovascular disease; CYP, cytochrome P450; D2-HG, D-2-hydroxyglutarate; DAMPs, damage-associated molecular patterns; DI, drug interaction; DLL, δ-like ligand; DNMT3A, DNA methyltransferase 3A; EC, endothelial cell; ECM, extracellular matrix; EGF, epithelial growth factor; ELK-1, ETS-like 1 protein; ER, estrogen receptor; ERK1/2, extracellular signal-regulated kinase ½; ETS, erythroblast transformation specific; US FDA, United States Food and Drug Administration; GPCR, chemokine G protein-coupled receptor; GWAS, genome-wide association studies; HER2, human epidermal growth factor 2; HGF, hepatocyte growth factor; HF, heart failure; HIF-1, hypoxia-inducible factor 1; HSPC, hematopoietic stem progenitor cells; HUVEC, human umbilical cord endothelial cell; ICI, immune checkpoint inhibitor; IDH, isocitrate dehydrogenase; IFN-γ, interferon γ; IL, interleukin; KLF, rüppel-like factor; LPS, lipopolysaccharides; LV, left ventricular; MAPK, mitogen-activated protein kinase; MAX, Myc-associated factor X; MHC, major histocompatibility complex; MDSC, myeloid-derived suppressor cell; MEK, MAPK kinase; MEKI, MAPK kinase inhibitor; MI, myocardial infarction; MMPs, matrix metalloproteinases; MYC, Myc proto-oncogene protein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; NLRP3, NOD-like receptor protein 3; NOTCH, Neurogenic locus notch homolog protein; PAMP, pathogen-associated molecular patterns; PD, pharmacodynamics; PDGF, platelet-derived growth factor; PD-L1, programmed death-ligand 1; PFKFB3, 6-phosphofructokinase/2,6-bisphosphatase 3; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetics; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; SASP, senescence-associated secretory phenotype; SMAD, suppressor of mothers against decapentaplegic; STAT3, signal transducer and activator of transcription 3; T2D, type 2 diabetes mellitus; TAM, tumor-associated macrophages; TET2, tet methylcytosine dioxygenase 2; TGF-β, transforming growth factor β; TKI, tyrosine kinase inhibitor; TLR, Toll-like receptor; TNF-α, tumor necrosis factor α; UGT, UDP-glucuronosyltransferase; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; VSMC, vascular smooth muscle cell.

Acknowledgments

We would like to thank all funding agencies for their financial support to carry out this study. We thank Biorender.com for creating all the Figures.

Financial support

Elisa Avolio is the recipient of a British Heart Foundation Intermediate Basic Science Research Fellowship [FS/IBSRF/23/25173]. Barbara Bassani, Marzia Campanile, Paola Muti, Antonino Bruno, and Gaia Spinetti are funded by the Italian Ministry of Health, Ricerca Corrente to the I.R.C.C.S. MultiMedica and 5Xmille. Khaled AK Mohammed is supported by a PhD scholarship from the Ministry of Higher Education of the Arabic Republic of Egypt [MM24/21]. Antonino Bruno has received research grants funded by the Italian Association for Cancer Research [AIRC-MFAG, ID 22818], the Italian Ministry of University and Research PRIN-2022 [ID-2022RK9X2K], and Fondi di Ateneo per la Ricerca FAR2022 and FAR2023 - University of Insubria, Varese, Italy.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

There are no datasets presented in this paper.

Authorship contributions

Wrote or contributed to the writing of the manuscript: Avolio, Bassani, Campanile, Mohammed, Muti, Bruno, Spinetti, Madeddu.

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