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Commentary

Does FFAR4 Agonism have Therapeutic Potential in Cardiometabolic Disease?

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Abbreviations: CVD, cardiovascular disease; FA, fatty acid; FFAR, free fatty acid receptor; LCFA, long-chain fatty acid

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Metabolic conditions, such as diabetes and obesity, are major global health problems, with an increasing incidence and a significant burden on global healthcare. With diabetes and obesity comes a significantly higher risk of developing cardiovascular disease (CVD), which in turn is a major cause of morbidity and mortality among those individuals. As such, there is a pressing need to develop new treatment options which require a better understanding of disease mechanisms and the identification of novel drug targets.

Fatty acids (FAs) have a well-recognized role in metabolic diseases such as diabetes. As well as being a critical energy source, they act as ligands for free fatty acid receptors (FFARs); a group of G protein-coupled receptors, which mediate cellular signaling effects of FAs. One such receptor, FFAR4 (also known as GPR120), has been highlighted as essential in maintaining metabolic homeostasis, with insulin-sensitizing and anti-inflammatory roles as well as controlling adipogenesis (1). As a receptor for long-chain fatty acids (LCFAs), FFAR4 has been shown to mediate some of the protective and beneficial cell signaling effects of omega-3 FAs (1, 2).

In their article, Stuttgen and Sahoo (3) highlight the potential role of FFAR4 in the pathogenesis of cardiometabolic disease, noting that while there is extensive evidence of an involvement of FFAR4 in metabolic and inflammatory

disease (including type 2 diabetes and obesity); the role of FFAR4 in the development of atherosclerosis and CVD is only recently emerging. Given the long-standing associations between FFAR4/GP120 and obesity, diabetes, and inflammation, and the considerable interest in developing therapeutic FFAR4 agonists (4), it is surprising that the role of FFAR4 in atherosclerosis and CVD (particularly in the context of metabolic disease) is not more well studied.

Their article (3) follows a recent publication which reports a cardioprotective role for FFAR4 in models of pressure overload and associations between the R270H polymorphism (affecting Gαq signaling capacity) and eccentric remodeling in patient cohorts (5). Of note, this FFAR4 variant has previously been associated with an increased risk of obesity in European populations (6), though this association has not been consistently observed in different study populations (7) and the loss of FFAR4 expression or activity alone may not be sufficient to induce obesity. The important question also remains as to whether such FFAR4 variants increase the susceptibility to CVD in obese or diabetic individuals.

Another interesting consideration is whether FFAR4 activity could explain at least some of the cardioprotective effects of LCFAs (eg, omega-3), similarly to the effects observed in diabetes, insulin resistance, and inflammation (1, 2), and whether variations in FFAR4 could account for

some of the inconsistencies between association studies of LCFAs and CVD. Of course, LCFAs have multiple biological roles in addition to FFAR4 agonism, and further mechanistic studies are required to untangle the potential cardioprotective effects of LCFAs that are mediated by FFAR4.

Mechanistically, it seems likely that the involvement of FFAR4 in cardiometabolic disease is at least in part due to the role in modulating vascular inflammation. As detailed by Stuttgen and Sahoo (3) there are several lines of evidence supporting a role for FFAR4 in regulating macrophage activation; 1 of the beneficial effects of FFAR4 agonists reported in preclinical models is in improving chronic inflammation associated with insulin resistance, via regulating macrophage activity (4). This potentially makes FFAR4 activation an attractive target for treating vascular damage, atherosclerosis, and CVD, which are driven by chronic, low-grade inflammation. Indeed, there is also evidence that FFAR4 can limit monocyte–endothelial interactions (3), though there is again some contradictory evidence for this role; in a study of FFAR4 in leukocytes, it was concluded that activation by polyunsaturated FAs had no effect in an animal model of atherosclerosis (8). In this instance it is important to note that the concentrations of FAs were comparatively much lower than those in other studies (1, 2) and, crucially, the level of FFAR4 activation achieved by these FAs will not necessarily be comparable to the chronic and consistent FFAR4 activation possible with synthetic agonists. Further detailed studies using small-molecule FFAR4 agonists in preclinical models of atherosclerosis and CVD are therefore warranted.

Important sex-specific differences in the role of FFAR4 have also been noted (3), requiring further investigation and consideration in future studies. It will also be important to delineate the tissue- and cell-specific effects of FFAR4 activation, as the potential roles in chemoresistance and survival of certain cancers (3) suggests therapies based on activating FFAR4 may not always be beneficial.

As discussed by Stuttgen and Sahoo (3), there is a compelling case for a role of FFAR4 in cardiometabolic disease and there is clearly great potential for FFAR4 to be targeted therapeutically. Overall, preclinical studies investigating the effects of FFAR4 agonism in obesity, diabetes, and inflammation are promising, but there is a distinct lack of research investigating the role of FFAR4 in atherosclerosis and CVD; leaving many important questions remaining. It seems variations in FFAR4 (including a loss of activity and expression) could play a role in susceptibility to cardiometabolic

diseases and there is the potential that increasing FFAR4 activation could be protective; but further comprehensive studies, with a triangulation of findings from in vitro systems and preclinical models to larger population-based studies, are needed. Such future work will no doubt shed light on the mechanistic roles of FFAR4 in atherosclerosis and CVD and subsequently, whether FFAR4 agonism has broad therapeutic potential in cardiometabolic disease.

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