
Peer reviewed version
License (if available):
Unspecified
Link to published version (if available):
10.1093/eurheartj/ehab724.3383

Link to publication record in Explore Bristol Research
PDF-document

This is the accepted author manuscript (AAM). The final published version (version of record) is available online via Oxford University Press at 10.1093/eurheartj/ehab724.3383. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/
The SARS-CoV-2 Spike protein alters human cardiac pericyte function and interaction with endothelial cells through a non-infective mechanism involving activation of CD147 receptor signalling.

Authors: Elisa Avolio, Michele Carrabba, Maia Kavanagh Williamson, Rachel Milligan, Kapil Gupta, Monica Gamez, Rebecca Foster, Imre Berger, Massimo Caputo, Andrew Davidson, Darryl Hill, Paolo Madeddu

Topic: COVID-19 and Cardiovascular Disease

Abstract

Background: Human cardiac pericytes (PC) were proposed as the main cellular target for SARS-CoV-2 in the heart due to high transcriptional levels of the angiotensin-converting enzyme 2 (ACE2) receptor. Emerging reports indicate CD147/Basigin (BSG), highly expressed in endothelial cells (EC), is an alternative SARS-CoV-2 receptor. To date, the mechanism by which the virus infects and disrupts the heart vascular cells was not identified yet. Moreover, cleaved Spike (S) protein molecules could be released into the bloodstream from the leaking pulmonary epithelial-endothelial barrier in patients with severe COVID-19, opening to the possibility of non-infective diseases in organs distant from the primary site of infection.

Purposes: (1) to confirm that human primary cardiac PC express ACE2 and CD147; (2) to verify if PC are permissive to SARS-CoV-2 infection; (3) to investigate if the recombinant SARS-CoV-2 S protein alone, without the other viral elements, can trigger molecular signalling and induce functional alterations in PC; (4) to explore which viral receptor is responsible for the observed events.

Methods and results: Cardiac PC express both the ACE2 and CD147 receptors at mRNA and protein level. Incubation of PC for up to 5 days with SARS-CoV-2 expressing the green fluorescent protein (GFP) did not show any evidence of cell infection or viral replication. Next, we exposed the PC to the recombinant S protein (5.8 nM) and confirmed that the protein engaged with cellular receptors (western blot analysis of S protein in treated and control PC). Incubation with the S protein increased PC migration (wound closure assay, P<0.01 vs ctrl) and reduced the formation of tubular structures between PC and EC in a Matrigel assay (P<0.01 vs ctrl). Moreover, the S protein promoted the production of pro-inflammatory factors typical of the cytokine storm in PC (ELISA measurement of MCP1, IL-6, IL-1β, TNFα, P<0.05 vs ctrl), and induced the secretion of pro-apoptotic factors responsible for EC death (Caspase 3/7 assay, P<0.05 vs ctrl). Signalling studies revealed that the S protein triggers the phosphorylation/activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) through the CD147 receptor, but not ACE2, in cardiac PC. The neutralization of CD147, using a blocking antibody, prevented ERK1/2 activation in PC, and was reflected into a partial rescue of the cell functional behaviour (migration and pro-angiogenic capacity). In contrast, blockage of CD147 failed to prevent the pro-inflammatory response in PC.

Conclusions: We propose the novel hypothesis that COVID-19 associated heart’s microvascular dysfunction is prompted by circulating S protein molecules rather than by the direct coronavirus infection of PC. Besides, we propose CD147, and not ACE2, as the leading receptor mediating S protein signalling in cardiac PC.

Funding acknowledgements: (1) BHF PG/20/10285 “Targeting the SARS-CoV-2 S-protein binding to the ACE2 receptor to preserve human cardiac pericytes function in COVID-19”, (2) BHF Centre for Vascular Regeneration II RM/17/3/33381; (3) Elizabeth Blackwell Institute Rapid Response COVID-19 award “COVID-19 S-protein binding to ACE2 negatively impacts on human cardiac pericyte function – a mechanism potentially involved in cardiac and systemic microvascular failure”.