Shining the spotlight on cardioprotection: beyond the cardiomyocyte

[1]Sean M Davidson, [2]Ioanna Andreadou, [3]David Garcia-Dorado, [4]Derek J Hausenloy

Affiliations
[1]The Hatter Cardiovascular Institute, University College London, 67 Chenies Mews, London WC1E 6HX, United Kingdom

[2]Laboratory of Pharmacology, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

[3]Department of Cardiology, Vascular Biology and Metabolism Area, Vall d'Hebron University Hospital and Research Institute (VHIR), Universitat Autónoma de Barcelona, Spain; Instituto CIBER de Enfermedades Cardiovasculares (CIBERCV): Instituto de Salud Carlos III, Madrid, Spain.

[4]Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore; National Heart Research Institute Singapore, National Heart Centre, Singapore; Yong Loo Lin School of Medicine, National University Singapore, Singapore; The Hatter Cardiovascular Institute, University College London, London, UK; The National Institute of Health Research University College London Hospitals Biomedical Research Centre, Research & Development, London, UK; Tecnologico de Monterrey, Centro de Biotecnologia-FEMSA, Nuevo Leon, Mexico.

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Corresponding authors:

Prof Derek Hausenloy
Cardiovascular & Metabolic Disorders Program,
Duke-National University of Singapore Medical School,
Singapore
derek.hausenloy@duke-nus.edu.sg

Dr Sean M Davidson
The Hatter Cardiovascular Institute
University College London
67 Chenies Mews, London WC1E 6HX
United Kingdom
Phone: +44 (0) 20344769894
Fax: +44 (0) 2034479505
Email: s.davidson@ucl.ac.uk

Although mortality from acute myocardial infarction (AMI) is on the decline, the incidence and severity of heart failure following AMI is on the rise. As such, there is still an unmet need to discover effective therapies for reducing myocardial infarct (MI) size and preventing adverse left ventricular (LV) remodelling following AMI. Unfortunately, a large number of cardioprotective therapies, which have been demonstrated to be effective in pre-clinical animal studies, have failed to be translated into the clinical setting for patient benefit. The reasons for this are multiple and complex, and have been extensively discussed in the literature.[1] In brief, they include the use of animal acute myocardial ischaemia/reperfusion (I/R) injury models which do not adequately represent the typical AMI patient, lack of rigour in pre-clinical testing of cardioprotective therapies before proceeding to clinical studies, and inappropriate clinical study design. Another key factor relates to the cardioprotective strategy itself, which is more often than not is directed to a single target located within the cardiomyocyte. However, acute myocardial I/R injury is a complex phenomenon, with many non-cardiomyocyte players and factors contributing to the pathophysiology underlying this condition. These include immune cells (such as neutrophils, monocytes/macrophages, lymphocytes and dendritic cells), the innate immune response (such as danger-associated molecular patterns and inflammasomes), platelets, circulating factors (such as extracellular vesicles) and cells (such as erythrocytes), the coronary vasculature and endothelial cells, and cardiac innervation. Therefore, investigating cardioprotective therapies directed to these non-cardiomyocyte cells and factors increase the likelihood of success in terms of translating cardioprotection into the clinical setting for patient benefit.

This spotlight issue which includes several major reviews on cardioprotection by leading researchers in the field, addresses the important question of the role of non-cardiomyocytes in I/R injury and cardioprotection. For instance, it is increasingly recognised that the coronary circulation is both culprit and victim of AMI.[2] Clearly, occlusion of the epicardial coronary artery is the primary cause of ischaemia, and it must be reperfused to salvage the

myocardium. However, coronary microembolisation and soluble factors released from the culprit lesion can directly damage the endothelium resulting in platelet activation and leukocyte adherence, vasoconstriction, and eventually no-reflow, microvascular obstruction and intramyocardial haemorrhage. Therefore, the endothelium represents a critical, yet largely overlooked target in I/R, as reviewed in this issue.[2] Platelets and leukocytes represent additional important targets for cardioprotection that are discussed in a second review in this series.[3] As an example of this, nanoparticles incorporating an inhibitor of toll-like receptor 4 were shown to decrease myocardial I/R injury by inhibiting monocyte-mediated inflammation in mice.[4]

Another type of circulating factor that is exciting a great deal of interest as potential cardioprotective agents are extracellular vesicles (EVs), such as microvesicles and exosomes. Two intriguing research articles in this issue[5, 6] add to the accumulating data that both resident and exogenously administered cells can protect the heart via paracrine mechanisms involving the release of EVs.[7] In the first of these articles, a multitude of data shows that cardiac fibroblasts secrete EVs (exosomes and/or microvesicles) that exert cardioprotection via their delivery of miR-423-3p and effects on the downstream effector RAP2C.[5] In the second article, mesenchymal stromal cell-derived exosomes were found to attenuate acute myocardial I/R injury via miR-182-regulated macrophage polarisation.[6]

Platelets are a major source for a large proportion of circulating EVs and additionally release a smorgasbord of potent vasoactive substances. They are therefore key players in I/R injury and cardioprotection – and they receive particular attention in several of the spotlight reviews.[3, 8, 9] Platelets respond rapidly to vascular damage, are activated early during I/R, interacting with various parts of the immune response. Although the major response of the adaptive immune response typically commences 24-48 h after I/R, it plays a central role in post-AMI LV

remodelling and potential subsequent heart failure as discussed in a review of novel therapeutic opportunities.[10]

The heart is innervated by a dense cardiac network of parasympathetic and sympathetic nerves, that interact with the intrinsic cardiac nerve system to influence myocardial rhythm and contractile function, susceptibility to acute I/R injury and cardioprotection, a fascinating topic which is reviewed in this issue.[11] Importantly, cardiac innervation contributes to endogenous cardioprotective strategies such as ischaemic preconditioning and remote ischaemic conditioning, and nerve stimulation may therefore provide a novel therapeutic strategy for cardioprotection.

In some scenarios, such as pressure overload, the response of the left and right ventricles can be quite different. Although genetic deletion of UCP2 ($UCP2^{-/-}$) protected against cardiac hypertrophy and failure in a classical model of left ventricular pressure overload, hearts from these mice were shown to be well preserved against additional pressure overload (severe pulmonary hypertension), partly due to different effects on fibroblasts.[12] Thus, non-myocytes are important in the adaption of the right ventricle to pressure overload.

A major challenge for successful clinical translation of cardioprotection is the high prevalence of advanced age, co-morbidities (diabetes, hypertension, etc) and co-treatments (platelet inhibitors, statins etc) in the patient population.[13] These factors raise the threshold necessary to attain successful cardioprotection, and have led to the suggestion that multiple combined approaches are necessary, targeting not just the cardiomyocytes, but other cell types in the heart.[14] Interestingly, new data presented here suggests that novel pharmacological inhibitors of GSK3β are able to reduce MI size further than that achieved with an inhibitor of the mitochondrial permeability transition pore.[15] These results offer a glimmer of hope in attaining the elusive goal of optimal cardioprotection.

Reading the reviews in this spotlight issue, it becomes clear that none of these processes act independently, but act as part of a co-ordinated systemic response. Consequently, it is hardly surprising that targeting just one aspect in isolation should be insufficient for maximal protection. It is hoped that these broad reviews of the systemic response to I/R and the identification of the most promising targets for cardioprotection, will provide the inspiration to investigate how non-cardiomyocytes can contribute to cardioprotective strategies.

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Conflicts of Interest
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