Virtual issue: focus on cardiovascular protection

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Introduction

In this issue of Cardiovascular Research, a collection of recently published papers is made available specifically aiming to illustrate recent advances in cardiovascular protection, a topic that is prominent at the 2016 Frontiers in Cardiovascular Biology (FCVB) meeting (http://www.escardio.org/Congresses-&-Events/Upcoming-congresses/Frontiers-in-Cardiovascular-Biology/Frontiers-in-Cardiovascular-Biology).

The papers are freely available online in the ‘Focus on cardiovascular protection’ virtual issue which can be accessed at bit.ly/CVR-FCVB

1. Cardioprotection from ischaemia-reperfusion injury

After the recent disappointment of the CIRCUS trial,1 new ideas for cardioprotection during reperfusion after ischaemia are needed with strong mechanistic support and preclinical evaluation. A meta-analysis of large animal studies further underscores the need for critical evaluation of study design and preclinical data interpretation for translation,2 a principle also advanced by the editors of Cardiovascular Research.3 Novel strategies for cardioprotection need to be tested in a clinically relevant framework, as laid out in the position paper of the ESC Working Groups Cellular Biology of the Heart.4 Novel ideas are generated in mechanistic studies as well as more translational studies.

Mitochondria are main actors involved in I/R injury. Inhibition of mitochondrial permeability transition pore (mPTP) opening is known to be cardioprotective; the role of UCP3 was uncovered through targeted molecular interventions5 while during I/R several activation mechanisms can be distinguished.6 Pharmacological activation of mitochondrial aldehyde dehydrogenase 2 (ALDH2) is not only protective against acute ischaemic injury but also inhibits the progression of cardiac dysfunction in myocardial infarction (MI)-induced heart failure in rats.7

HIF1-a is another mediator in protection against reperfusion injury, either downstream of SUMO-specific protease 1 (SENP1)8 or regulating the expression of renase.9 The protective effect of the inhibition of mPTP opening induced by stabilization of HIF-1α adds further to this concept.10

Innate immunity and inflammation are involved in the early response after ischaemia and in the later adverse remodelling. Several recent papers have demonstrated that immune signalling might comprise promising targets for cardioprotection. Fujii et al. summarized the cardioprotective function of resident cardiac inflammatory M2 macrophages in cardiac homeostasis and tissue maintenance.11 Promising strategies to modulate the inflammatory response include the inhibition of toll-like receptor 2 (TLR2) to reduce macrophage-mediated inflammation12 or the modulation of macrophage migration inhibitory factor (MIF), a key pathway regulating cardioprotective AMP-activated protein kinase (AMPK) signalling, inhibiting pro-apoptotic cascades and decreasing oxidative stress.13 Alternative to targeting the macrophage compartment, blocking complement C5a receptors on circulating leucocytes reduces infarct size and improves cardiac function in a mouse model of I/R injury.14 Finally, more and more evidence is showing an active role of cardiac fibroblasts in modulating the immune system.15

The potential of targeting metabolic pathways against reperfusion injury is illustrated in recent papers and is also reviewed in16. A reversible inhibitor of succinate dehydrogenase, malonate, lowers not only the reactive oxygen species (ROS) production but also mPTP opening17; inhibition of nicotinic acid adenine dinucleotide phosphate (NAADP) signalling reduces reperfusion-induced cell death.18 The combination therapy of remote ischaemic conditioning (RIC) and glucose–insulin–potassium (GIK) or exenatide decreased the infarct size in a pig model due to the activation of diverse cardioprotective pathways different from those activated by RIC alone.19 Fgf21 reduces oxidative stress by the regulation of antioxidant pathways.20

Ion channel targeting could be an alternative approach to cardioprotection as shown for the activation of Kv7.4 in mitochondria,21 while deletion of Kcne2 preconditions the heart, thereby illustrating a role for this channel22 beyond its role in modulating electrical activity of the heart.

Activating protective pathways is the theme of four reviews in the current issue.16,23–25 The report from Bice et al. adds original data showing that NO-independent stimulation or activation of soluble guanylyl cyclase during early reperfusion limits infarct size.23,26

As more upstream modulators, heat-shock proteins and miRNAs are ‘hot’ targets. Overexpression of the muscle-specific chaperone melanin is a dual protective action reducing inflammation and myocyte remodelling early after MI, and preserved contractility, reduced cardiomyocyte loss, and matrix remodelling at a later stage.27 miRNAs can protect the myocardium by promoting cardiomyocyte survival by direct repression of pro-apoptotic genes as shown for mir-15028 and mir-125b.29 Targeting non-myocyte pathways, the mir-15 family was...
found to be an inhibitor of the TGFβ pathway, thereby regulating fibrosis in overloaded hearts. 30

2. Communication and cell–cell interactions

The discovery of microvesicles and exosomes as pathways for communication has generated a lot of excitement. In the heart interaction of cardiac myocytes with inflammatory cells, endothelial cells and fibroblasts have been reported. Direct interaction between fibroblasts and inflammatory cells is involved in fibrosis and repair. 31 32 Cell–cell communication through changing the extracellular vesicles (EVs) content or surface markers is an opportunity to discover the therapeutic potential of these vesicles by interfacing with their biological targets as reviewed in 31. When studied in human cardiac progenitor cells, EVs were the active component of the paracrine secretion that improved cardiac function after MI. 32 Furthermore, cardiomyocyte-derived exosomes are involved in regulation of the glucose transport and metabolism in endothelial cells. 33

3. Common pathways in heart and vessels

Traditionally, the research fields of vascular and cardiac biology follow their own paths and address different communities. Cardiovascular Research, however, is covering all fields in cardiovascular sciences, 34 and it was one of the goals of the FCVB as well to bring together all fields. Therefore, we include in this virtual issue a number of papers that relate to pathways of protection in vessels.

Recent reviews summarize the role of miRNAs and long non-coding RNAs in vascular remodelling, including atherosclerosis, aneurysm formation, and neovascularization after ischaemia. 35–37 A prominent 2013 review discusses the major role of miRNA and their transport in microvesicles in the inflammatory process in atherosclerosis. 38 The important function of specific miRNAs in the vasculature is further illustrated in smooth muscle cells, 39 endothelial cells, 40,41 and macrophages. 42

The role of the immune system in the development of atherosclerosis has been extensively studied. Inhibition of the pro-inflammatory response of the smooth muscle compartment of injured vessels was achieved through depletion of Hsp60,43 In strategy reminiscent of Notch1 signalling 45 or the inhibition of advanced glycation end-products formation in diabetic mice 46 enhances neovascularization after ischaemic events.

Finally, lipid metabolism and interactions with vascular and blood cells are a specific field, but here we make available a number of reviews that relate to the protective role of HDL. 47–50

Conflicts of interest: none declared.

References


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