Commentary: Circulating factors released after myocardial infarction: Beneficial or detrimental?

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F.J.A. is supported by a Canadian Institutes of Health Research Post-doctoral Fellowship. R.-K.L. is supported by a grant from the Canadian Institutes of Health Research (332652) and holds a Tier 1 Canada Research Chair in Cardiac Regeneration.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 29, 2018; accepted for publication Oct 29, 2018; available ahead of print Nov 30, 2018.

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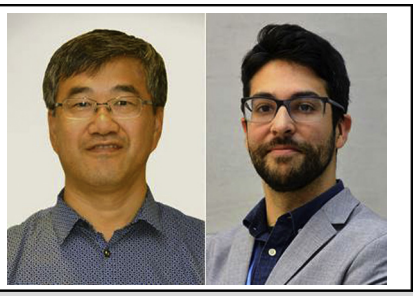
J Thorac Cardiovasc Surg 2019;157:2270-1

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2018.10.128



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Central Message

Reperfusion after myocardial ischemia leads to the release of multiple factors that are essential for cardiac repair and regeneration, but can also accelerate cardiac injury.

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Restoring coronary blood flow is a crucial step in minimizing the extent of myocardial infarction (MI) after coronary artery occlusion. Reperfusion restores the delivery of essential substrates and oxygen to the ischemic myocardium. Accumulating research evidence has shown that factors released from the ischemic myocardium mediate postreperfusion responses. These factors can be beneficial to infarct healing and include cytokines and proangiogenic factors that act to home stem cells and limit cell death to enhance cardiac repair. However, reperfusion itself can have adverse effects, such as myocardial cell death, myocardial stunning, and reperfusion arrhythmias.[1] Ischemia–reperfusion injury was first introduced in 1960 by Jennings and colleagues,[2] and since then a number of mechanisms have been proposed to mediate the injury process. After reperfusion, there is a rapid increase in oxidative stress leading to the production of reactive oxygen species. These toxic species react nonspecifically within surviving cells and promote cell death. Early approaches involved targeting reactive oxygen species by providing antioxidants such as trimetazidine[3] or recombinant superoxide dismutase-1[4]; however, clinical studies failed to demonstrate beneficial effects. This has led to a more targeted approach to block the effect of detrimental factors released from the ischemic myocardium because they can initiate proinflammatory responses and mediate reperfusion injury. One such factor is DNA, which has emerged as a key danger-associated molecular pattern that initiates inflammatory responses.[5]

In this issue of the *Journal*, Tian and colleagues[6] investigate the mechanisms by which cell-free DNA mediates ischemia–reperfusion injury using a short-term myocardial ischemia–reperfusion mouse model. They demonstrate that HMGB1 facilitates the transfer of cell-free DNA to immune cells within the spleen to initiate proinflammatory responses and reperfusion injury. By using knockout mouse models, Tian and colleagues reveal an important mechanism in which HMGB1 interacts with RAGE and TLR9 to mediate immune cell activation by DNA. Together, the authors suggest that HMGB1 is a key factor responsible for facilitating DNA transfer; however, other mechanisms independent of HMGB1 also may exist to enable the transfer of cell-free DNA to inflammatory cells. Extracellular vesicles (EVs) from cardiomyocytes[7] and endothelial cells[8] are rapidly released into the circulation post-MI, where they interact with inflammatory cells in the spleen.[8] EVs are capable of facilitating intercellular DNA transfer,[9,10] and this transfer can initiate proinflammatory responses.[11] Of note, EV DNA mediated activation of inflammatory responses signals through TLR9-dependent pathways,[11] suggesting that HMGB1 and EVs use common downstream pathways to initiate immune cell activation. EVs also carry a number of other biologically active factors such as proteins, lipids, and noncoding RNAs, all of which have established roles in regulating the function of multiple cell types.[12] Therefore, additional factors that are released into the circulation and carried by EVs may play important roles in the regulation of inflammatory responses and infarct healing post-MI.

It is important to note that in this study infarct size was examined 1 hour after reperfusion. Myocardial repair is a complex process involving sequential phases of

inflammation, angiogenesis, and scar maturation; temporal coordination of these phases is critical in determining outcome.[13] Future long-term studies will be able to examine how targeting these early events will affect ventricular dilation and the progression to heart failure. Although much work remains to define the mechanisms underlying reperfusion injury, Tian and colleagues have provided important insights into the contributions of HMGB1 and cell-free DNA in mediating this process.

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