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EDITORIAL

A new strategy to decrease cardiac injury in aged heart following ischaemia-reperfusion: enhancement of the interaction between AMPK and SIRT1

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This editorial refers to 'Cardiomyocyte-specific deletion of *Sirt1* gene sensitizes myocardium to ischaemia and reperfusion injury' by L. Wang *et al.*, pp. 805–821.

Myocardial injury is increased in aged hearts during ischaemia-reperfusion (IR) and accelerates the transition to post-infarct heart failure.[1] Although many therapeutic interventions can effectively decrease cardiac injury in younger adult hearts, strategies to decrease cardiac injury in aged hearts are still limited.[1] Therefore, understanding the mechanisms of injury in the aged heart during IR is critical to develop potential strategies to protect the high-risk aged heart.[2]

The impairment of substrate flexibility (balance between glucose usage and fatty acid oxidation) contributes to cardiac injury during IR as well as heart failure development.[3] Limitation of glucose utilization and oxidation with concomitant increased fatty acid oxidation during reperfusion enhances cardiac injury.[3] Dr Li *et al.* found that the substrate flexibility was markedly impaired in aged hearts following IR compared with young hearts.[4] They further found that the decreased substrate flexibility was due in part to impairment of the AMPK (AMP-activated protein kinase) signalling pathway activation. Glucose uptake and utilization was decreased in parallel with enhanced fatty acid oxidation.[4] AMPK contributes an essential role in the regulation of glucose and lipid metabolism. Activation of the AMPK leads to increased glucose uptake and enhances insulin sensitivity.[5] Liver kinase B1 (LKB1) is an AMP-activated kinase that activates AMPK through phosphorylation of the alpha subunit of AMPK.[6] The activity of LKB1 is regulated by SIRT1 (sirtuin 1), a member of the sirtuin (NAD-dependent deacetylase) family.[7] Activation of SIRT1 leads to deacetylation and activation of LKB1 that increases AMPK phosphorylation and activity. Thus, SIRT1-dependent activation of LKB1 stimulates AMPK activity. Dr Li's study clearly showed that the impaired AMPK activation in aged hearts was at least in part due to decreased SIRT1 activity.[4] Increased expression of SIRT1 via adenoviral transfection rescued the attenuation of AMPK activation and reduced ischaemic injury, providing key mechanistic support. Interestingly, they also found that there was a feedback interaction between AMPK and SIRT1 activation. AMPK can act as an upstream enzyme to stimulate SIRT1 activity through modulation of intracellular NAD^+ concentration.[6] Sestrin 2 is another protein that forms a complex with AMPK and LKB1.[8] Knockout of Sestrin 2 leads to decreased AMPK activation and enhanced ischaemic injury.[9] Pharmacologic activation of AMPK or restoration of SIRT1 activity in aged hearts led to decreased cardiac injury during IR, indicating that restoration of the signalling defect in aged hearts is a promising strategy to decrease cardiac injury. The potential role of Sestrin 2 in modifying the AMPK-SIRT1 interaction will await further research (Figure 1).

Mitochondrial dysfunction contributes to increased cardiac injury in aged hearts.[1] Aging impairs electron transport chain (ETC) activity in the interfibrillar population of mitochondria located between the fibrils (IFM). The Complex III activity is decreased in IFM isolated from the aged hearts. Complex III is one of the key sites to generate the reactive oxygen species (ROS).[10] The defect of Complex III in aged hearts increases ROS generation that augments cardiac injury during IR. Dr Li *et al.* found evidence for increased ROS generation and deteriorated mitochondrial morphology after IR in aged hearts. Mitochondrial DNA (mtDNA) was further damaged in aged hearts by IR.[4] Cytochrome *b*, a key catalytic subunit of Complex III, is encoded by mtDNA. Age-related defects in Cytochrome *b* lead to decreased Complex III activity in aged hearts.[10] Thus, these results suggest that the aging-induced mtDNA damage contributes to the increased cardiac injury in aged hearts. It will be interesting to consider if activation of AMPK or SIRT1 can restore the Complex III defect present in aged hearts.

Pyruvate dehydrogenase (PDH) is a key enzyme to regulate glucose vs. fatty acid utilization. Inhibition of PDH leads to decreased glucose oxidation by diminishing the entry of acetyl-CoA into the tricarboxylic acid cycle. PDH activity is decreased in hearts following IR. PDH activity is affected by post-translational modification.[11] Is impaired PDH activity involved in the decreased glucose oxidation in aged hearts? Is PDH more

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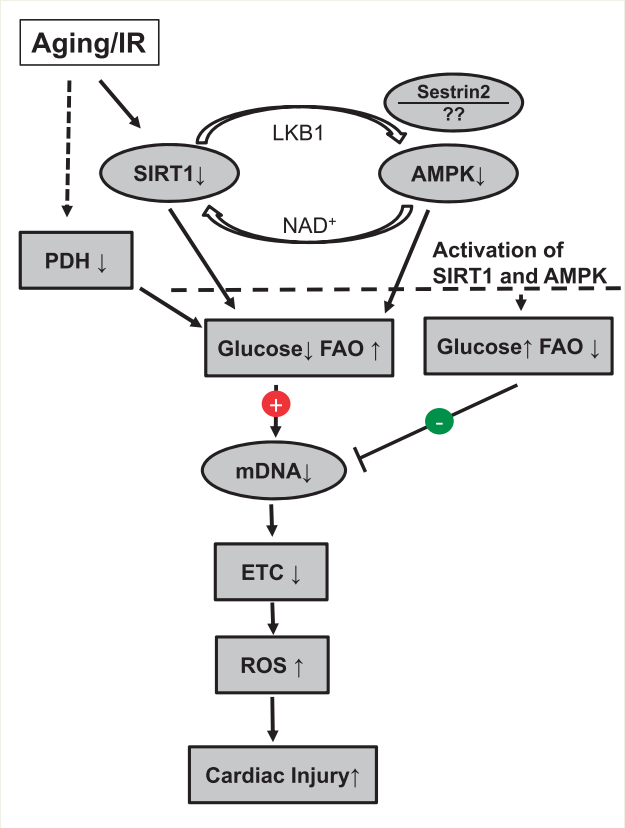

Figure 1 Activation of SIRT1 and AMPK decreases cardiac injury in aged hearts following IR. Aging and IR decreases SIRT1 activity that leads to decreased AMPK activity through acetylation and subsequent inhibition of LKB1. Deactivation of AMPK also affects SIRT1 activity due to altered NAD^+ concentration. Sestrin 2 may also interact and affect AMPK activation. Deactivation of SIRT1 and AMPK leads to decreased glucose oxidation and increased fatty acid oxidation (FAO) that contribute to increased injury in aged hearts following IR. Aging also impairs mtDNA that increases ROS generation by inhibiting Complex III at mitochondrial ETC. IR leads to decreased PDH activity that also leads to altered metabolism in hearts with decreased glucose oxidation and increased FAO. Activation of SIRT1 and AMPK is a promising approach to decrease cardiac injury in aged hearts following IR.

sensitive to IR damage in aged hearts? Does activation of AMPK or SIRT1 protect PDH activity in aged hearts following IR?

The key finding in this study is the clear crosstalk between decreased AMPK activity and the defect of SIRT1 in aged hearts. Metformin, a traditional AMPK activator, leads to decreased cardiac injury in hearts during IR.[12,13] Activation of SIRT1 also decreases cardiac injury in aged hearts. These results are consistent with the notion raised in this study.

Interestingly, a recent study showed that metformin–leucine co-treatment can activate both AMPK and SIRT1.[6] Addition of leucine to metformin increases the effect of metformin on insulin sensitivity and glycemic control in that both AMPK and SIRT1 contribute to the regulation of glucose and lipid metabolism. Metformin is the most commonly prescribed drug for the treatment of Type 2 diabetes. It is also known that metformin decreases cardiac injury during IR.[12,13] Co-treatment of metformin–leucine improves insulin sensitivity and improves glucose metabolism.[6] Does metformin–leucine co-treatment provide better protection in aged hearts following IR compared with individual AMPK activation or SIRT1 activation?

Clearly, this study which identifies the mechanisms of AMPK deficiency in aged hearts provides guidance to develop potential pharmacological approaches to decrease cardiac injury and subsequent heart failure development in aged hearts.

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