Exercise-Induced Myonectin Protects Against Ischemia-Reperfusion Injury

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The physiological benefits of exercise on the cardiovascular system have long been well established. In fact, for the past 5 decades, there have been several animal and human studies demonstrating the benefits of moderate exercise to cardiovascular health, including blood pressure reduction, attenuated obesity, decreased hyperlipidemia, and improved insulin tolerance.[1] In fact, sedentary lifestyle and lack of physical exercise have been linked to the insurgence type II diabetes mellitus and cardiovascular morbidities in North America.[2] In particular, studies have shown that short-term,[3] as well as long-term,[4] aerobic physical activity can dramatically increase the myocardial tolerance to ischemia-reperfusion (I/R), decrease myocardial infarct size and arrhythmias. Although the mechanism of cardioprotection conferred by exercise is poorly understood, several theories have been purported to explain this phenomenon; these include, the involvement of HSPs (heat shock proteins), opioid system, COX-2 (cyclooxygenase-2), mitochondrial ATP-sensitive potassium channels (K_{ATP}), NO, and antioxidant production.[5]

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Given the global benefits of exercise on the body's organs systems, the release of humoral factors from skeletal muscle or other cell types could account for the positive effects of exercise training on the cardiovascular health. In this regard, there is growing evidence that chemokines, bioactive molecules secreted during exercise may protect against cardiovascular disease. Recently, myokines which are skeletal muscle–derived cytokines induced by physical activity have been purported to protect against certain forms of cellular stress.[6] Myokines also play a role in regulating oxidative metabolism in the liver hepatocytes and adipose tissue, as well as influence proliferation of muscle satellite cells.[6]

Notably, the first myokine to be identified was IL (interleukin)-6.[6] IL-6 is an anti-inflammatory cytokine whose induction can inhibit the expression of TNF-α (tumor necrosis factor-α).[7] IL-6 can be detected in the blood after physical activity and can alleviate glucose uptake through and AMPK (AMP-activated protein kinase) dependent mechanism.[7]

It is noteworthy that the mechanisms of action of myokines in the cardiovascular system and their reported protective role are incompletely understood. Although certain myokines can target direct components of the cardiovascular system, including cardiomyocytes, endothelial cells, and vascular smooth muscle cells, others are believed to influence cardiovascular function indirectly, by altering cell metabolism.[8] For example, FSTL1 (follistatin-like 1) is an extracellular glycoprotein that is secreted by both the skeletal muscles and cardiac muscles.[9] Secretion of FSTL1 is induced under conditions of Akt-mediated hypertrophy and injury.[10] Moreover, circulating levels of FSTL1 in mice were also shown to be increased after exercise and protect against I/R injury through Akt- mediated suppression of apoptosis.[10] Conversely to FSTL1, which targets directly the cardiovascular system, the myokine irisin protects the heart indirectly through metabolic pathways. Irisin is a peptide that acts mainly on white adipose tissue and is induced by physical activity. Irisin is a PPAR-γ (peroxisome proliferator-activated receptor-γ) PGC1-α (PPAR-γ coactivator-1α)-dependent myokine which also influences UCP1 (uncoupling protein 1) expression. Studies of aerobic physical activity in obese individuals showed a link between increased plasma irisin levels and positive effects on the muscle mass.[11] Moreover, irisin was shown to accelerate the transition of white to brown fat in adipose tissue, which led to alleviations in the lipid oxidation balance and improved the overall metabolic status. Together, these metabolic changes led to improved cardiovascular function and promoted indirect cardioprotection.[12]

Recently, Otaka et al[13] described a novel exercise-induced myokine in skeletal muscle, referred to as myonectin. Myonectin, also known as C1q/TNF-related protein 15/erythroferrone, is a paralogue to adiponectin and was shown to modulate iron homeostasis and fatty acid metabolism. Notably, myonectin was recently shown to be upregulated in skeletal muscles during endurance exercise.[13] Despite these observations, there remains a paucity of information on how myokines, such as myonectin, influence the pathogenesis of cardiovascular disease outcomes. In this issue of *Circulation Research*, Otaka et al[14] reveal a novel link between induction of myonectin during exercise and cardioprotection against acute myocardial ischemic injury that involves modulation of inflammation and apoptosis pathways.

The authors showed that endurance treadmill training of wild-type mice increased myonectin levels in skeletal muscle and the blood which coincided with smaller infarct sizes after I/R injury compared with corresponding sedentary controls. Next, using a global myonectin knockout mouse model, the authors showed that mice deficient for myonectin exhibited significantly greater incidence of cardiac injury demonstrated by

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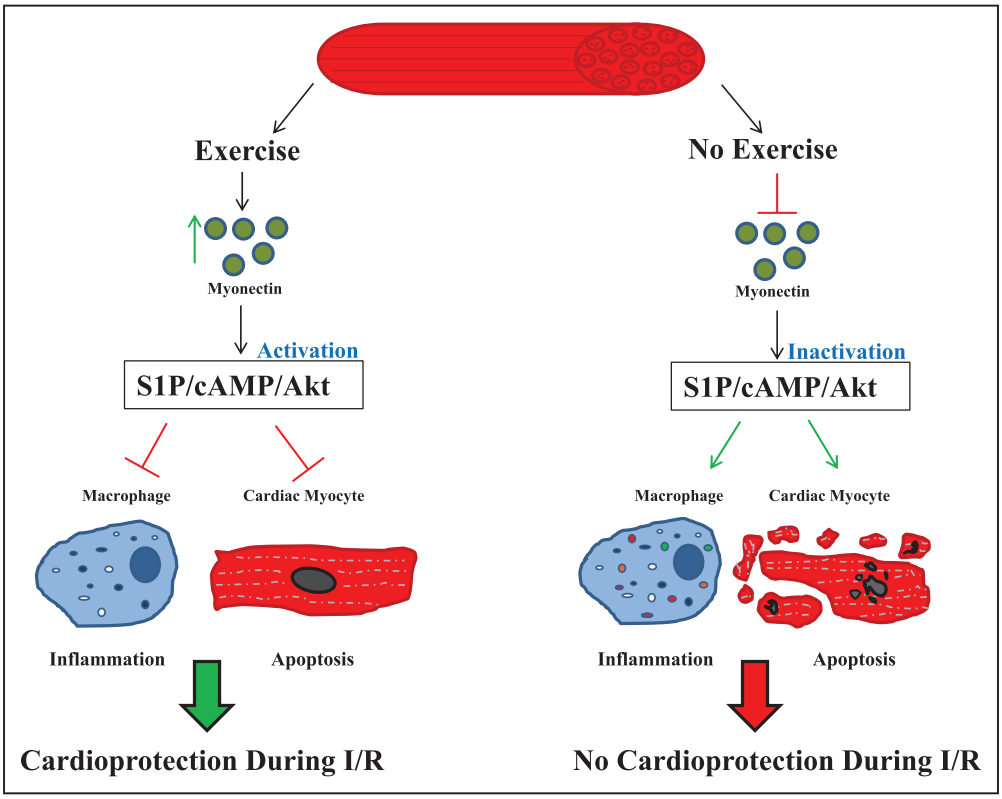

Figure. Cardioprotective mechanism of the exercise-induced myonectin. Secretion of myonectin from the skeletal muscle during exercise activates the S1P (sphingosine-1-phosphate)/cAMP/Akt (protein kinase B) pathway and confers cardioprotection through suppression of inflammatory processes (**left**). In the absence of exercise, secretion of skeletal muscle–derived myonectin is suppressed resulting in increased macrophage-mediated inflammation and apoptosis (**right**). I/R indicates ischemia-reperfusion injury.

larger infarcts, cardiac dysfunction, increased apoptosis, and expression of inflammatory genes after I/R injury than wild-type mice. In fact, loss of myonectin completely abrogated the cardioprotective effect of exercising training. Conversely, gain of function of myonectin in mice overexpressing myonectin in skeletal muscle exhibited less myocardial damage and associated inflammatory cytokines, autophagy, and apoptosis after I/R compared with wild-type mice. Interestingly, when Otaka et al[14] pretreated cardiac myocytes in vitro with myonectin before hypoxia/reoxygenation, apoptosis was diminished by a mechanism that was contingent on S1P (sphingosine-1-phosphate)-dependent activation of cAMP/Akt (protein kinase B) signaling pathway. Furthermore, lipopolysaccharide-induced macrophage activation and inflammatory cytokine production was dramatically suppressed by myonectin treatment. However, the authors went on to show that cytoprotective effects of myonectin on lipopolysaccharide macrophage activation involves S1P/cAMP/Akt-dependent cascade because pharmacological inhibition of either of S1P, cAMP, or Akt completely attenuated beneficial effect of myonectin resulting in increased macrophage activation. Perhaps most compelling finding was that inhibition of the S1P/cAMP/Akt pathway in vivo in exercise-trained mice resulted in greater infarcts after I/R, proving that the S1P/cAMP/Akt-dependent pathway is required for the cardioprotective effects of myonectin.

Collectively, this novel work demonstrates that exercise-induced skeletal muscle myonectin mitigates I/R injury by suppressing inflammation from macrophage activation and apoptosis of cardiac myocytes.

Although the data presented provides convincing evidence that myonectin can modulate the anti-inflammatory response and antiapoptotic signaling cascades in an endocrine manner, the underlying mechanism to explain the cardioprotection conferred by myonectin was not addressed. For example, it is unknown, if myonectin signals through its own receptor or can engage other myokine/cytokine receptors, such as adiponectin, irisin, or FSTL1 during exercise. Moreover, how myonectin influences S1P synthesis or other signaling pathways related to sphingosine metabolism was not determined. The authors showed that myonectin suppressed I/R induced apoptosis; however, how myonectin influences apoptosis or other cell death programs remains unknown. It also is unclear how myonectin influences autophagic processes linked to AMPK-mTOR (mammalian target of rapamycin) signaling pathway or mitochondrial metabolism. Moreover, the impact of exercise-induced myonectin and S1P signaling on biochemical and molecular pathways that influence mitochondrial density (PGC1α), substrate metabolism, protein synthesis or cell survival mechanisms were not examined in this study.

Nevertheless, the findings of Otaka et al[14] provide an excellent opportunity to address the potential cardioprotective role of myonectin in other forms of cardiac disease. It will be intriguing to determine whether the cardioprotection conferred by myonectin is universally conserved or a restricted phenomenon to I/R injury or whether myonectin can protect

against other cardiac stress conditions, such as hypertension, diabetes mellitus, coronary diseases, or heart failure. Lastly, it would be important to know whether the type of exercises, such as running, walking, swimming, or whether a given threshold of physical activity, endurance versus interval training influences myonectin expression, and cardioprotection. In the present study, the authors used treadmill exercised mice to study the effects of myonectin on cardioprotection which begs the question: are myonectin levels and associated cardioprotection regulated differently in athletes, such as sprinters, who utilize fast twitch glycolytic muscle fibers versus weightlifters who recruit large slow twitch oxidative muscle fibers? Addressing these questions may prove beneficial in establishing how an exercise-induced myonectin can be applied clinically to curtail cardiac dysfunction in high-risk individuals after myocardial infarction.

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Disclosures

None.

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