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EDITORIAL

# Exercise Protects Sympathetic Stress-Induced Myocardial Fibrosis by Regulating Cytokines

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Cardiovascular diseases are often caused by overactivation of β-adrenergic receptors (β-ARs) during acute sympathetic stress. As cardiomyocytes of adult mammals have lost significant proliferative capacity, the connective tissue replacement occurs once cardiomyocytes are damaged, thereby inducing the progression of myocardial fibrosis. When myocardial fibrosis continues to develop, myocardial contractility decreases, coronary flow reserve decreases, thus causing malignant arrhythmia and cardiac death. Early prevention and reversal of myocardial fibrosis is a key to clinical treatment of various heart diseases. However, there is no effective clinical method for treating myocardial fibrosis.

Alemasi et al. presented that exercise training prevented isoproterenol (ISO)-induced myocardial fibrosis and diastolic dysfunction by inhibiting cytokines in Hedgehog and RAP1 pathways [1]. Their results showed potential application and mechanisms for treatment of acute sympathetic stress-induced cardiovascular disease with physical exercise.

Cytokines are secreted by macrophage. Macrophages are almost always found in the vicinity of myofibroblasts which produce collagen. Macrophages participate in myocardial fibrosis by producing various cytokines such as inflammatory factors, chemokines, and growth factors. Ras-related protein 1 (RAP1) promotes the secretion of inflammatory factors from macrophages, by regulating NF-κB signaling pathway. Inhibition of Rap1 reduces the secretion of TNF-α, IL-6, and MCP-1 in mesenchymal stem cells, which promotes cell survival and therapeutic effects on myocardial infarction, and inhibits the development of atherosclerosis. Epac is an upstream molecule of Rap1. Epac is activated in the presence of cAMP, which in turn catalyzes the conversion of GDP to GTP. One of the most classic Epac/Rap1 functions is regulation of cell adhesion and intercellular connections. Myocardial apoptosis and myocardial fibrosis are reduced in Epac1 knockout mice with ISO-induced chronic stressful heart failure and arrhythmia [2]. Therefore, inhibition of Rap1 pathway has a very positive significance for prevention and treatment of myocardial fibrosis.

In KEGG pathway analysis, growth factors and CDH1 activate Rap, which in turn triggers MAPK pathway and PI3K-Akt pathway. The activation of both MAPK pathway and PI3K-Akt pathway can lead to myocardial fibrosis. In Alemasi et al. 2019's study, exercise inhibited the upregulation of growth factor (IGF1, VEGF2) and CDH1 in ISO-induced myocardial fibrosis. In addition, exercise also inhibited the upregulation of its downstream TNF and IL6. The authors concluded that exercise could improve myocardial fibrosis by inhibiting Rap1 pathway [1]. This provides a promising new approach for relieving stress-induced myocardial fibrosis.

Chemokines are a group of cytokines with specific reinforcing and attracting functions that can promote myocardial fibrosis mainly by participating in the inflammatory response. The representative chemokine, CCL9, is derived from a variety of cells including mononuclear macrophages, neutrophils, endothelial cells, T lymphocytes, and fibroblasts. It is speculated that CCL9 mediates the production of a large number of cytokines, including IL-1β, IL-2, IFN-γ, TNF-α, and IL-6, by

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activating macrophages and Th1 cells when cardiomyocytes are infected by virus [3]. These cytokines disrupt calcium homeostasis in myocardial cells through multiple pathways and aggravate myocardial fibrosis. In Alemasi et al.'s study, exercise inhibited the upregulation of CCL9 expression in ISO-induced myocardial fibrosis [1], which indicated that exercise could protect against cardiac fibrosis by regulating chemokines.

Long-term exercise can induce cardiomyocyte hypertrophy and promote cardiomyocytes proliferation. We previously have reported that exercise induce increasing of miR-222, which promotes cardiomyocyte growth and proliferation by inhibiting Cyclin-dependent kinase inhibitor 1B, Homeobox containing 1, and Homeodomain-interacting protein kinase 1/2. MiR-222 overexpression can protect adverse cardiac remodeling and cardiac dysfunction in ischemic injury models [4].

Alemasi et al. presented that running exercise decreased the expression of 25 cytokines as compared with the sedentary group. These cytokines belong to six cytokine families. Among them, 20 were found significantly upregulated by ISO stimulation; however, running exercise prevented most of these changes induced by ISO. Based on KEGG pathway analysis, it was found that these cytokines were enriched in Hedgehog and RAP1 signaling pathways. Although the role of RAP1 pathway in cardiac fibrosis has been well-documented, Alemasi et al. firstly proposed that exercise might mediate the RAP1 pathway to inhibit cardiac fibrosis. On the other hand, Hedgehog pathway has been reported to be critical for kidney injury and fibrosis. However, related studies on the heart have not been reported. Alemasi et al. found that cytokines in the Hedgehog pathway also changed significantly in ISO-induced myocardial fibrosis, suggesting that Hedgehog pathway may also be involved in the progression of myocardial fibrosis and can be interfered by exercise [1].

Although diseases such as diabetes and myocardial infarction can cause myocardial fibrosis, moderate-intensity continuous exercise and intermittent aerobic exercise can regulate collagen metabolism, correct imbalance of synthesis, and degradation of extracellular matrix, and hence alleviate myocardial fibrosis. With regard to the mechanism by which exercise protects against myocardial fibrosis, multiple miRNAs have been known involved in the regulation, including miR-222, miR-17-3p, and miR-29 [5]. New finding today suggests that exercise can also mediate cytokines to protect against myocardial fibrosis [1]. The search for new molecules and signaling pathways involved in the fibrogenesis process will grow significance in the studies of sports health science.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Research Involving Human Participants and/or Animals** This article does not contain any studies with human participants or animals performed by any of the authors.

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