Exercise and cardioprotection: A "HIP" side of HIPK2 in the heart

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It is widely accepted that physical inactivity or lack of exercise is associated with an increase in cardiovascular diseases worldwide, evidenced by an inverse relationship between physical activity and cardiovascular events in both healthy individuals and cardiovascular patients.[1] It has been proposed that the benefits of exercise are mediated via either modifiable cardiovascular risks such as blood pressure, lipid and glucose levels, or direct effects on atherosclerotic processes and cardiovascular function.[2] Although it has been shown that exercise exerts anti-inflammatory and anti-oxidative effects,[3] the underlying mechanisms behind its cardioprotection are still unclear. In addition, since pro-inflammatory effects of exercise in sedentary healthy young volunteers have been reported,[4] it raises the question about whether different types and conditions of exercise would alter the course of anti-inflammatory processes in those healthy individual and also in patients with cardiovascular disease. These findings are also supported by a recent report on the effects of differing exercise intensities on cardiac autonomic balance.[5] Since clear conclusions regarding the pathological response to exercise remain inconclusive at this time,[6] it is essential the mechanisms driving the benefits conferred by the types and intensities of exercise for cardiovascular disease prevention are investigated.

Homeodomain-Interacting Protein Kinase 2 (HIPK2) is a protein kinase involved in important cellular processes including cell proliferation, apoptosis, and mitochondrial function.[7] Recently, its roles in cardiovascular function have been explored in various models including HIPK2 loss-of-function and transaortic constriction-induced heart failure mouse models.[7,8] In this issue of *EBiomedicine*, Zhou and colleagues[9] further demonstrate the important association between HIPK2 and exercise, and the underlying mechanisms responsible for cardioprotection. In mice with acute myocardial infarction (AMI), increased expression of cardiac HIPK2 and decreased miR-222 (an upstream regulator of HIPK2) were observed, and both correlated with adverse cardiac remodeling following AMI.[9] The beneficial effects of exercise through HIPK2 on adaptive hypertrophy and prevention of adverse cardiac remodeling were clearly shown since exercise led to suppression of HIPK2, decreased P53 phosphorylation, and attenuated cardiac apoptosis, culminating in a reduction of infarct size and adverse cardiac remodeling after AMI. Although these cardioprotective effects of exercise were associated with cardiac HIPK2 suppression, possibly through increased cardiac miR-222, these benefits decreased shortly after discontinuing the exercise.[9] Interestingly, supportive findings were observed in AMI patients who had decreased levels of serum miR-222, when compared to healthy controls, and serum miR-222 level was even lower in AMI patients with adverse outcomes.[9] Despite these significant findings, whether the low level of miR-222 increases the risk of atherosclerosis and AMI, or vice versa requires elucidation.

Zhou and colleagues demonstrated the detrimental effects of HIPK2 expression and cardioprotective effects of HIPK2 inhibition in AMI mice,[9] however the essential roles of HIPK2 in maintaining physiologic cardiovascular function have been previously demonstrated.[7,8] In HIPK2 Knockout (KO) mice, time-dependent effects of HIPK2 suppression on cardiac structure and function were observed.[7,8] Decreased cardiac function was demonstrated in HIPK2 KO mice aged 5 months,[8] while increased cardiac size, cardiomyocyte hypertrophy and myocardial fibrosis being observed at 18 months.[7] These findings indicate the essential roles of HIPK2 in regulating cardiac development and function. In addition, decreased cardiac HIPK2 expression was reported in the hearts of patients with end-stage ischemic cardiomyopathy, compared to the normal hearts.[8] Taking all these findings into account, it appears contradictory findings regarding HIPK2 exist. However, it may be that cardiac HIPK2 expression is up-regulated following acute cardiac insults such as AMI or acute pressure overload, whereas its expression is significantly reduced in advanced cardiac dysfunction. These postulations need testing in future studies to elucidate the complex roles of HIPK2 in the heart.

Regular exercise has long been an important part of the advocacy for maintaining health, however,

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appropriate type and intensity of exercise differ between demographics. In healthy mice, even after cardiac insult, Zhou et al report that regular exercise, partly via HIPK2 suppression, could exert cardioprotection.[9] However, the effects of HIPK2 inhibition in conditions with low cardiac HIPK2 expression, such as in patients with advanced heart failure, have not been investigated, despite demonstration of the beneficial effects of exercise on functional capacity in these patients.[10] Further studies into various types and intensities of exercise in different cardiac pathological conditions in both preclinical and clinical settings are essential to warrant the safety and efficacy of exercise prescription in patients with heart disease. At this time, these findings strongly indicate that exercise continues to be on the "HIP" side for a healthy lifestyle for the foreseeable future.

Contributors

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Declaration of Competing Interest

The authors declare no conflict of interest.

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