**LONG-TERM EXERCISE-DERIVED EXOSOMAL MIRNAS AS NOVEL EXERKINES FOR CARDIOVASCULAR PROTECTION**

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Long-term exercise not only reduces risk factors associated with cardiovascular diseases but also confers direct robust cardiovascular protection in animal models. The underlying mechanisms are being elucidated, especially in the search for exercise factors (i.e. exerkines) that are cardiovascular beneficial. In recent years, several exerkines have been proposed, including irisin, IL-6 and nitric oxide that mediate exercise-induced health effects. Exosomes are endogenous small (30-100 nm) vesicles secreted by multiple cell types transmitting signaling molecules throughout the body. One of its most abundant cargo is non-coding RNAs (especially microRNAs). As such, exosomal miRNAs emerge as novel elements of intercellular communication and have been proposed to mediate cardioprotective effects of stem cells. However, most of the studies so far are based on the exosomes extracted from cell culture supernatant in vitro, while the circulating exosomes in vivo are more complex in content, more diverse in source and very sensitive to changes of internal environment such as exercise. Whether exercise- derived exosomes in circulation mediate the beneficial effects of exercise are still unclear.We recently found that exercise-derived circulating exosomes isolated from the plasma were cardiovascular protective. In the in vitro and in vivo models of myocardial ischemia/reperfusion (MI/R), we found that plasma exosomal miR-342-5p markedly increased after long-term exercise in both human and rats. More importantly, exosomal miR-342-5p significantly reduced myocardial infarction, attenuated cardiomyocyte apoptosis and enhanced myocardial survival signal (p-Akt) via targeting phosphatase Ppm1f in MI/R rats. In addition, long-term exercise increased circulating exosomal miR-486 which restored the vascular endothelial function in diabetic rat through suppression of PTEN.Our findings reveal a novel endogenous mechanism underlying exercise-induced cardiovascular protection and highlights a therapeutic potential of exosomal miRNAs in cardiovascular protection. The results also suggest circulating exosomal miRNAs as a new category of cardiovascular protective exerkine.