Plasma exosomes protect the myocardium from ischemia-reperfusion injury.

Exosomes are nanometer-sized vesicles released from cells into the blood, where they can transmit signals throughout the body. Shown to act on the heart, exosomes' composition and the signaling pathways they activate have not been explored. We hypothesized that endogenous plasma exosomes can communicate signals to the heart and provide protection against ischemia and reperfusion injury. This study sought to isolate and characterize exosomes from rats and healthy volunteers, evaluate their cardioprotective actions, and identify the molecular mechanisms involved. The exosome-rich fraction was isolated from the blood of adult rats and human volunteers and was analyzed by protein marker expression, transmission electron microscopy, and nanoparticle tracking analysis. This was then used in ex vivo, in vivo, and in vitro settings of ischemia-reperfusion, with the protective signaling pathways activated on cardiomyocytes identified using Western blot analyses and chemical inhibitors. Exosomes exhibited the expected size and expressed marker proteins CD63, CD81, and heat shock protein (HSP) 70. The exosome-rich fraction was powerfully cardioprotective in all tested models of cardiac ischemia-reperfusion injury. We
identified a pro-survival signaling pathway activated in cardiomyocytes involving toll-like receptor (TLR) 4 and various kinases, leading to activation of the cardioprotective HSP27. Cardioprotection was prevented by a neutralizing antibody against a conserved HSP70 epitope expressed on the exosome surface and by blocking TLR4 in cardiomyocytes, identifying the HSP70/TLR4 communication axis as a critical component in exosome-mediated cardioprotection. Exosomes deliver endogenous protective signals to the myocardium by a pathway involving TLR4 and classic cardioprotective HSPs.