Microparticles carrying Sonic hedgehog favor neovascularization through the activation of nitric oxide pathway in mice

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BACKGROUND: Microparticles (MPs) are vesicles released from plasma membrane upon cell activation and during apoptosis. Human T lymphocytes undergoing activation and apoptosis generate MPs bearing morphogen Shh (MPs(Shh+)) that are able to regulate in vitro angiogenesis. METHODOLOGY/PRINCIPAL FINDINGS: Here, we investigated the ability of MPs(Shh+) to modulate neovascularization in a model of mouse hind limb ischemia. Mice were treated in vivo for 21 days with vehicle, MPs(Shh+), MPs(Shh+) plus cyclopamine or cyclopamine alone, an inhibitor of Shh signalling. Laser doppler analysis revealed that the recovery of the blood flow was 1.4 fold higher in MPs(Shh+)-treated mice than in controls, and this was associated with an activation of Shh pathway in muscles and an increase in NO production in both aorta and muscles. MPs(Shh+)-mediated effects on flow recovery and NO production were completely prevented when Shh signalling was inhibited by cyclopamine. In aorta, MPs(Shh+) increased activation of eNOS/Akt pathway, and VEGF expression, being inhibited by cyclopamine. By contrast, in muscles, MPs(Shh+) enhanced eNOS expression and phosphorylation and decreased caveolin-1 expression, but cyclopamine prevented only the effects of MPs(Shh+) on eNOS pathway. Quantitative RT-PCR revealed that MPs(Shh+) treatment increased FGF5, FGF2, VEGF A and C mRNA levels and decreased those of α5-integrin, FLT-4, HGF, IGF-1, KDR, MCP-1, MT1-MMP, MMP-2, TGFβ1, TGFβ2, TSP-1 and VCAM-1, in ischemic muscles. CONCLUSIONS/SIGNIFICANCE: These findings suggest that MPs(Shh+) may contribute to reparative neovascularization after ischemic injury by regulating NO pathway and genes involved in angiogenesis.

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