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Angiogenic, arteriogenic, and vasculogenic properties of sonic hedgehog gene therapy in an experimental model of ischemia

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We have previously shown that the signaling pathway of the embryonic morphogen sonic hedgehog (Shh) is recapitulated in the postnatal skeletal muscle in response to ischemia. We have also demonstrated that Shh is an indirect angiogenic agent upregulating various families of angiogenic growth factors and that Shh gene therapy improves angiogenesis and heart function in experimental models of myocardial ischemia. Based on these findings, we hypothesized that Shh gene therapy is beneficial in an experimental model of peripheral ischemia.

The amino-terminal domain of human Shh coding sequence was selected to make a Shh plasmid, using a pCMV-ScriptPCR mammalian expression vector. The human Shh plasmid (phShh) that we used is a 4,878-bp plasmid that contains the 600 bp amino-terminal domain coding sequence of the human Shh gene.

We found that intramuscular treatment with phShh increased blood flow, capillary density, and arteriole density in mice in which peripheral circulation of the hindlimb was disrupted by removal of the common femoral artery. Shh gene therapy also enhanced vasculogenesis, by increasing the number of circulating bone marrow (BM)-derived endothelial precursors and improving the contribution of these cells to the process of neovascularization. Finally, phShh treatment induced upregulation of prototypical angiogenic, arteriogenic, and vasculogenic factors, such as vascular endothelial growth factor (VEGF), angiopoietin 1 (Ang-1), and stromal cell-derived factor-1 (SDF-1α). These data suggest that phShh gene therapy merits further investigation for its ability to trigger the expression of potent trophic factors and stimulate pleiotropic aspects of neovascularization in the setting of ischemia.

Biography

Palladino received an MD degree in 2003, she completed a Residency Program in "Hematology" in 2007 and she received a PhD in "Oncology/ Hematology" from the Catholic University School of Medicine (UCSC), Rome, Italy, in 2011. Currently, she works as Post-Doctoral Fellow in the Laboratory of Vascular Biology & Genetics at the Department of Medicine-UCSC, Rome, Italy. She has published several papers in peer-reviewed international scientific journals. She has trained in the Division of Cardiovascular Research at St. Elizabeth's Medical Center/ Tufts University, Boston, MA, USA. She has presented at many national and international meetings and has received several awards.

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