Abstract Title
Superior Proangiogenic Characteristics of Human Neonatal Thymus Mesenchymal Stem Cells

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Abstract
Mesenchymal stem/stromal cells (MSCs) are being evaluated as proangiogenic agents for ischemic and vascular disease in adults, but not in children. Newborns with congenital heart disease who undergo cardiac surgery already have or are at risk of developing conditions related to inadequate tissue perfusion. We have recently discovered that MSCs can be isolated from discarded thymus tissue from neonates undergoing cardiac surgery, and that these MSCs are proangiogenic. The primary objective of this study was to assess the therapeutic potential of thymus MSCs by comparing their proangiogenic characteristics to those of bone derived MSCs. A secondary objective was to determine the mechanism explaining any difference in proangiogenic potency between the two MSC types. We first compared neonatal thymus MSCs to adult bone marrow derived MSCs in their ability to promote endothelial cell (EC) proliferation, EC migration, MSC:EC spheroid sprouting and angiogenic gene expression. We found that thymus MSCs were superior in promoting EC migration and spheroid sprouting, but there was no difference in the targeted gene analysis. We then compared these two MSC types in a subcutaneous implant model in immune deficient mice and found that thymus MSCs were superior in promoting the formation of perfused human neovessels. Because age of the MSC could have affected the above studies, we performed a patient-matched in vitro comparison using sternal bone derived MSCs. We found that thymus MSCs were also superior to matched bone MSCs in promoting EC migration and spheroid sprouting. To gain insight into the differences between thymus and bone MSCs, we performed a genome wide, patient-matched-comparison and found a significant increase expression of SLIT3, a potent angiogenic factor, in thymus MSCs, which was then confirmed by qPCR and Western blotting. Finally, soluble ROBO4 was able to inhibit the angiogenic sprouting promoted by thymus MSCs in vitro. Collectively, these data indicate that discarded thymus tissue from neonatal heart surgery is a clinically relevant source of proangiogenic thymus MSCs, and that these proangiogenic qualities may be mediated by an increased expression of SLIT3. Further evaluation of thymus MSCs in models of cardiovascular disease is warranted.