Smooth Muscle Cells Are Crucial for Vascular Stem Cell Migration and Vasculogenesis via Keratinocyte Cell-derived Chemokine

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Introduction - Recently, a population of stem/progenitor cells have been identified within the adventitia of vessel walls. While existing data indicate their capacity of differentiation into specific vascular lineages, their migratory roles within vascular diseases remain unknown. Interestingly, smooth muscle cells (SMCs) have been shown to reside within close proximity with the progenitors within the medial layer and thus may have a putative role on the motility of progenitor cells.

Hypothesis- We hypothesize that mouse adventitia-derived resident progenitor cells will migrate in response to SMCs via their secretion of specific chemokine(s).

Methods and Results – In vitro transwell and wound healing migration assays showed significant increases in Sca-1+ vascular progenitor cell migration in response to both SMCs and SMC-conditioned medium (CM). A chemokine ELISA array revealed that keratinocyte cell-derived chemokine (KC) level was markedly increased in SMC-CM. Exogenous recombinant KC significantly increased progenitor cell migration and KC knockdown in SMC-CM using siRNA markedly inhibited progenitor migration. The expression of its receptor, CXCR2, was upregulated following treatment with SMC-CM and treatment with a CXCR2 antagonist was found to significantly inhibit SMC-mediated progenitor migration. Furthermore, we found that the p38 MAP kinase pathway was involved in SMC-mediated migration; the phosphorylation of p38 in response to SMC-CM was partially reduced following knockdown with KC SiRNA. The migration of progenitor cells was also significantly decreased following treatment with a p38 inhibitor. Using a matrigel plug angiogenesis assay in vivo, we found that the KC induced Sca-1+ progenitors migration and enhanced markedly vasculogenesis after 2 weeks. The functional knockdown of KC in C57BL/6 mice using a KC morpholino system potentially reduces Sca-1+ progenitor cell migration compared to corresponding controls (n≥4 per group).

Conclusion – In conclusion, SMCs can induce Sca-1+ progenitor cell migration via the release of KC and subsequent activation of p38 MAPK signalling pathway via CXCR2. The lack of functional KC inhibited progenitor cell migration and vasculogenesis in vivo.