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Vascular niche signals in organotypic stem cell regeneration

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Stem cell self-renewal and fate determination are dependent on niche-derived signals. However, the source of the niche cells and mechanism by which these signals regulate regeneration are not fully defined. Tissue-specific endothelial cells (ECs) by production of angiocrine factors establish an instructive vascular niche that choreographs stem cell homeostasis and organ regeneration. During development and regenerative processes, vascular niche cells oscillate the supply of (stimulatory)/(inhibitory) angiocrine factors and others are yet unknown factors. These angiocrine signals coordinate the self-renewal and differentiation of organotypic stem cells, such as hematopoietic stem cells (HSCs). To uncover the mechanism by which these angiocrine signals regulate stem cell reconstitution, we have devised an *in-vivo* tissue-specific vascular niche platform for expansion of HSCs and for generating vascularized cardiac, epithelial, hepatic and neural 3D organoids. Employing this vascular niche model, we show that ECs deploy signals that are essential for the specification, self-renewal and differentiation of human, mouse and non-human primate HSCs. Co-culture of adult marrow-derived hematopoietic cells with ECs results in 25 to 50 fold clonal HSC self-renewal with the capacity of long-term, multi-lineage engraftment in mice and non-human primate hosts. Vascular niche cells are also essential for pluripotent-independent conversion of readily accessible adult ECs into engraftable HSCs. To prove this point, we transduced human or mouse adult mature ECs with *Runx1/Spi1/Gfi1/FosB* transcription factors along with vascular niche-induction enabling step-wise conversion of these ECs into long-term repopulating immunocompetent HSCs. Clonal populations of converted HSCs expanded on vascular niche in-vitro, and fully reconstituted multi-lineage hematopoiesis in rodents. Co-infusion of the ECs along with HSCs augmented hematopoietic recovery, underscoring the significance of vascular niche-signals in stem cell reconstitution *in-vivo*. To translate the potential of vascular niche to the therapeutic setting, we have engineered generic ECs capable of vascularizing epithelial, hepatic, neural and cardiac 3D organoid cultures. Cross talk of ECs with tissue-specific stem cells promotes proper patterning and remodeling of these organoids into functional tissues. Using *in-vivo* regenerative models, we showed that transplantation of ECs stimulates hematopoietic, hepatic and lung repair without provoking maladapted fibrosis. These approaches have allowed us to uncover the molecular determinants of vascular heterogeneity; bringing us closer to translate the regenerative potential of ECs for organ repair to the clinic. Tissue-specific vascular-stem cell organoid cultures facilitate screening by gene-editing and small molecule libraries to identify unknown vascular niche signals that coordinate stem cell self-renewal and differentiation for functional organ repair.

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