Analysis of Blood Vessel Formation and Self-Renewal of Hematopoietic Stem Cells

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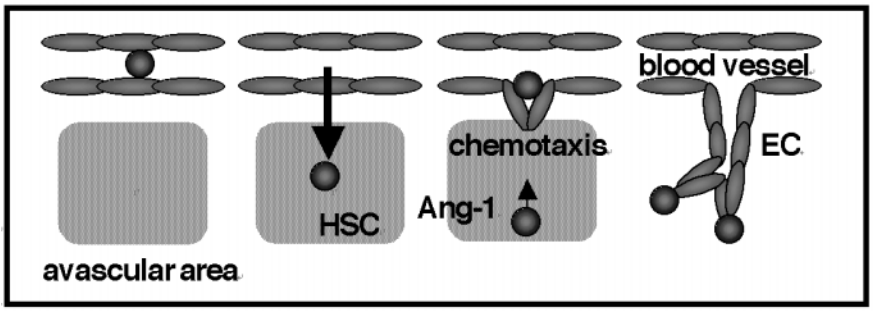
Blocking tumor angiogenesis has become a promising approach in managing cancer. In recent years, a large number of anti-angiogenic drugs and recombinant proteins have entered clinical trials, and some of them are already in the final phase of testing. In the future, for remarkable progress in this anti-angiogenic therapy, it is important to know molecular mechanism of blood vessel formation precisely. We have focussed on the relationship between vasculogenesis-angiogenesis and hematopoiesis for better understanding in blood vessel formation. So far we found 1) Hematopoietic stem cells (HSCs) produce angiopoietin-1 and regulate angiogenesis, 2) NP-1 on hematopoietic cells delivers VEGF to Flk-1/VEGFR2 on endothelial cells and regulates vasculogenesis. 3) Moreover, we have analyzing the molecular mechanism how vein and artery are developed separately. On the other hand, we have hoped to translate our research into clinical trial especially in various regeneration therapies focusing on 4) the molecular mechanism of self-renewal of HSC for the in vitro expansion of HSCs, 5) transdifferentiation from mesenchymal stem cells into endothelial cells, and 6) identification of vascular stem cells those can differentiate into endothelial cells and vascular smooth muscle cells (these 5), 6) for regenerative angiogenesis). In this report, we present data that have been already confirmed and published elsewhere.

1) Role of hematopoietic stem cells (HSCs) in promoting angiogenesis.

As shown in Figure, when hypoxia and avascular area occur in the location, HSCs migrate in such region at first. Following the migration of HSCs, endothelial cells start to sprout toward HSCs. Finally, endothelial cells form capillary and ischemic region is vasculized. This effect of endothelial cell migration is promoted by angiopoietin-1 produced from HSCs.



2) Role of neuropilin-1 on hematopoietic cells (HCs) in enhancing the stimulation of Flk-1/VEGFR2

Neuropilin-1 (NP-1) is co-receptor for Flk-1 on endothelial cell, binds VEGF, and enhance the phosphorylation of Flk-1. Monomer form of soluble NP-1 saturates VEGF and inhibit VEGF-Flk-1 signal. By contrast, dimer form of soluble NP-1 stimulates FLk-1 exogenously and enhances the FLk-1 signal. We recently found that HCs express NP-1 and work as dimer form of soluble NP-1 and enhance blood vessel formation.