Karolinska Institutet

Institutionen för Mikrobiologi, Tumör och Cell Biologi

Angiogenic mechanisms in adipose tissue and tumor

AKADEMISK AVHANDLING
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av

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ABSTRACT

Angiogenesis is involved in the development and progression of many human diseases, including cancer, cardiovascular diseases, chronic inflammation, and metabolic diseases. Despite differences in microenvironment under various pathological settings, angiogenic blood vessels share some common features in numerous diseases. This thesis reveals novel molecular mechanisms of angiogenesis in tumors and adipose tissues, as well as defining potential therapeutic targets for treatment of cancer and obesity-associated metabolic diseases.

In Paper I, we showed that PDGF-BB is a tumor-derived vascular remodeling factor that promotes tumor growth through activation of stromal fibroblasts and perivascular cells in tumor microenvironment. Tumor-derived PDGF-BB activates stromal fibroblasts to produce erythropoietin (Epo), which in turn triggers extramedullary hematopoiesis thereby enhancing oxygen perfusion in tumor vasculatures leading to an accelerated tumor growth rate. Epo is also known as a potent angiogenic factor which acts directly on endothelial cells (ECs) to induce tumor neovascularization. Therefore, PDGF-BB modulates tumor angiogenesis, vascular remodeling and hematopoiesis, via activation of the Epo signaling pathway, thus facilitating tumor growth, invasion and possibly reduces drug responsiveness. Understanding the role of Epo in promoting tumor growth and angiogenesis not only provides novel mechanistic insights into the complex interplay between various signaling pathways involved in the stimulation of angiogenesis, but also highlights the risk associated with using Epo in treatment of cancer-associated anemia.

In Paper II, we used mouse tumor models to propose a novel mechanism underlying the combination therapy consisting of anti-angiogenic and chemotherapeutic agents commonly used in human patients. We showed that tumor-derived VEGF induces severe aplastic anemia in mice, and delivery of chemotherapeutics to these tumor-bearing mice led to an earlier demise due to the synergistic or additive suppression of bone marrow hematopoiesis by VEGF and chemotherapy. Switching to a sequential delivery of anti-angiogenic drugs prior to administration of chemotherapeutics drugs resulted in significant recovery of bone marrow hematopoiesis, and thus markedly increased tolerance to chemotoxicity. Given the fact that a significant number of cancer patients die of chemotoxicity, our findings provide an important mechanism in which anti-angiogenic drugs decreases chemotoxicity.

In Paper III, we discuss the novel methods we developed for the study of adipose angiogenesis, which are becoming increasingly used by other scientists. In Paper IV, we showed for the first time that cold acclimation of mice markedly activates an angiogenic phenotype via sympathetic upregulation of VEGF expression. Importantly, inhibition of angiogenesis significantly modulates adipose metabolism. This work provides the first example where targeting adipose vasculature might provide a novel therapeutic approach for the treatment of obesity and metabolic diseases.

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