Angiogenesis in Development & Cancer

Guest Editors

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Preface

Angiogenesis in Development and Cancer Today

The cardiovascular system plays a crucial role in vertebrate development and homeostasis. During embryonic development, vasculature is formed by both vasculogenesis and angiogenesis. Vasculogenesis, which consists of *de novo* vessel formation from angioblasts, provides the nascent vascular network, particularly during early embryonic life. Angiogenesis, which refers to expansion of a pre-existing vascular bed through sprouting, bridging and intussusceptive growth, intervenes mostly during later stages of embryogenesis. Recent experimental studies have demonstrated that bone-marrow-derived stem and endothelial progenitor cells can in principle contribute to tissue repair by induction of neo-angiogenesis.

Several genetic and epigenetic mechanisms are involved in the early development of the vascular system and there is an extensive literature on the genetic background and the molecular mechanisms responsible for blood vessel formation. Evidence is now emerging that blood vessels themselves have the ability to provide instructive regulatory signals to surrounding non-vascular target cells during organ development. Thus, endothelial cell signaling is currently believed to promote fundamental cues for cell fate specification, embryo pattering, organ differentiation and postnatal tissue remodeling. The ability of vessels to influence surrounding non-vascular cells may depend on the intrinsic heterogeneity of endothelial cells. Understanding the concept of vascular bed specificity represents a major challenge for future investigations. Indeed, one of the most interesting theoretical perspectives and practical applications of endothelial cell signaling is the possibility for these cells to maintain their inductive potential during adult life.

Angiogenesis is an important process by which new blood vessels are formed, both in health and disease. Over the past 25 years, the number of Medline publications dealing with angiogenesis has risen in a nonlinear fashion; almost 40,000 publications which included "angiogenesis" as a key word, were published in the year 2009, reflecting the interest among basic scientists and clinicians in this field.

Starting with the hypothesis of Judah Folkman (1933-2008) that tumor growth is angiogenesis dependent, this area of research has a solid scientific foundation. More than 30 years ago, Folkman found a revolutionary new way to think about cancer. He postulated that in order to survive and grow, tumors require blood vessels and that by cutting off the blood supply, a cancer could be starved into remission. Several clinical studies have shown a positive correlation between the number of vessels in the tumor, metastasis formation and prognosis. The genetic instability of tumor cells permits the occurrence of multiple genetic alterations that facilitate tumor progression and metastasis, and cell clones with diverse biological aggressiveness may coexist within the same tumor. These two properties allow tumors to acquire resistance to cytotoxic agents. Inhibiting angiogenesis is a major area of therapeutic development for the treatment of cancer. Whereas conventional chemotherapy, radiotherapy and immunotherapy are directed against tumor cells, antiangiogenic therapy is aimed at the vasculature of a tumor and will either cause total tumor regression or keep tumors in a state of dormancy. Even though numerous compounds inhibit angiogenesis, few of them have proved effective *in vivo*, and only a couple of agents have been able to induce tumor regression. Bevacizumab is considered to be the first specific angiogenesis inhibitor for clinical oncology. However, the results from clinical trials have not shown the dramatic antitumor effects that were expected following preclinical studies, which revealed a much higher efficacy

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of these type of agent in animal models. Patients with different types of tumors respond differently to antiangiogenic therapy. While colorectal, lung and breast cancer patients have responded, pancreatic cancer patients have not shown survival advantages when treated with antiangiogenic monotherapy or combinations of antiangiogenic agents with chemotherapy. Additionally, preclinical and clinical data have shown the possibility that tumors may acquire resistance to antiangiogenic drugs or may escape antiangiogenic therapy via compensatory mechanisms. Most of the FDA-approved drugs, as well as those in phase III clinical trials, target a single proangiogenic protein. However, multiple angiogenic molecules may be produced by tumors, and tumors at different stages of development may depend on different angiogenic factors for their blood supply. Therefore, blocking a single angiogenic molecule might have little or no impact on tumor growth. Cancer genomics and proteomics are likely to identify novel, tumor-specific endothelial targets and accelerate drug discovery.

In this Special Issue of *"The International Journal of Developmental Biology" (Int. J. Dev. Biol.)*, several leading investigators report new findings about angiogenesis in development and cancer. We express our gratitude to all our colleagues who have contributed to this issue and to Juan Aréchaga for the opportunity to present this work in a single Special Issue of the *Int. J. Dev. Biol.*

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