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Microvascular plasticity: angiogenesis in health and disease.

Preface

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Abstract

This Special Topic Issue is concerned with the mechanisms that determine the structure of microvascular networks. The vast number of vessels and the highly plastic character of the microcirculation give evidence that microvascular network structures emerge as a result of responses of individual vessels and cells to the local stimuli that they experience, through a combination of angiogenesis, remodeling and pruning. The articles in this issue of *Microcirculation* address a range of cellular and molecular mechanisms involved in these processes.

The total length of blood vessels in the human body is of the order of 10^7 m (4)*. Nearly all of this length consists of microvessels. How is this vast network of vessels organized to perform its function of transporting oxygen and other materials throughout the tissues of the body? This broad question motivates the contributions included in this Special Topic Issue of *Microcirculation*.

Two basic observations support the view that the microcirculation is in fact a largely self-organizing system. Firstly, given the enormous length and number of vessels forming the microcirculation, it is not plausible that the specific geometrical configurations of all microvessels are predetermined by genetic information. This contrasts to the situation for the major blood vessels, whose arrangement is largely predetermined. Secondly, the microcirculation is highly plastic, capable of continuous structural change during growth and development, and in response to varying functional demands and disease. Therefore, the structure of the microcirculation must emerge as the collective outcome of a myriad of responses at the level of individual vessels and cells, each governed by its local environment and the stimuli that it experiences (6).

The self-organization of the microcirculation takes place on multiple spatial scales. On the scale of networks, the main processes have been identified (7) as vasculogenesis (initial formation of a vascular plexus), angiogenesis (addition of vessels), remodeling and maturation (changes in vessel diameter and wall structure) and pruning (removal of vessels).

*Data of Mall (4) scaled up from a 13 kg canine to a 70 kg human.

Angiogenesis can occur by sprouting from existing vessels or by splitting of existing vessels (intussusception). Each of these processes requires a specific set of cellular behaviors that are coordinated at the level of existing or newly formed vascular segments. These cellular behaviors are driven by a variety of external stimuli, which may be mechanical, such as wall shear stress or circumferential wall tension, or molecular, such as growth factors, metabolites and other signaling molecules. It is likely that direct cell-cell communication via gap junctions plays an important role in coordinating these cellular responses, although direct evidence for this remains sparse.

Changes in vascular structure are central to numerous physiological and pathophysiological processes. Therefore, improved understanding of the underlying processes has great potential to lead to advances in biomedicine. A notable example is the concept that the inhibition of angiogenesis would prevent growth of solid tumors (4). This promise has stimulated numerous investigators to work in this area. However, despite extensive efforts, a comprehensive understanding of the mechanisms controlling microvascular structure remains an elusive goal. The multiplicity of biological processes and agents obviously presents an enormous challenge. Moreover, while a tremendous amount of research has focused on the cellular and mechanisms of sprouting angiogenesis, other key aspects of microvascular plasticity, such as intussusceptive angiogenesis, vascular remodeling and pruning have been relatively neglected, at least until recently. We suggest that an integrated view, in which angiogenesis, remodeling and pruning are considered as continuous, coexistent processes, can provide a useful perspective for motivating and interpreting studies that address the specific mechanisms involved in controlling microvascular structure (6).

The contributions in this issue of *Microcirculation* address a range of cellular and molecular processes. Two papers discuss the role of stromal derived cells. Corliss et al. (1) consider the role of macrophages in angiogenesis and lymphangiogenesis, and Stallcup et al. (8) examine contributions of stromal cells to tumor vascularization. Key signaling molecules involved in vascular remodeling are discussed by Yuan and Kevil (9) (hydrogen sulfide and nitric oxide), and by Olfert (5) (vascular endothelial growth factor). Finally, LeBlanc and Hoying (3) discuss the decline in plasticity of the coronary microcirculation that occurs in aging. All these papers provide insights into particular aspects of microvascular plasticity, while contributing to the broad challenge of understanding of how the microcirculation organizes itself.

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