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The developing endothelium in action

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Blood vessel formation is an evolutionary adaptation to the increase in size of organisms. Single cell or primitive life forms, from bacteria to flatworms, use the cellular surface as a simple point of exchange of gases and nutrients with the outside world. As organisms and their tissues increase in size and complexity, however, cells deep within those tissues can no longer rely on simple diffusion. Consequently, an internal 'plumbing' of blood vessels arose to perfuse every tissue and service every living cell. Blood vessels are consequently highly heterogeneous in size and character, as they adapt to different tissue microenvironments.

How does a blood vessel form? This question presents many exciting challenges, as vascular endothelial cells must carry out a variety of behaviors to assemble and grow properly, which are different in different vessels at different times and places. However, some unifying concepts do exist. Initially, migrating endothelial progenitors, or angioblasts, must assemble into lumenless cords at precise embryonic locations, and then open up lumens and transition into blood-carrying tubes. These tubes can then sprout and generate new vessels from old ones. In both cases, vessel formation depends on an amazing orchestration of numerous events, such as cell specification and migration, cell–cell adhesion and cell shape changes, cell polarization and sprouting, reception of extracellular cues—both positive and negative, oriented cell divisions, as well as response to biomechanical forces such as from blood flow. Together, these events coordinate to create an intricate, seamless and essential system of functional blood vessels. Understanding blood vessel formation, growth and plasticity will be critical to the successful development of therapies for a wide range of diseases, including tumor angiogenesis, cardiac ischemia, macular degeneration and diabetic retinopathy, as well as organ transplantation and tissue engineering.

This special issue of *Seminars in Cell and Developmental Biology* presents a set of eight reviews from leaders in the field investigating basic mechanisms of endothelial behavior during blood vessel formation. With a range of model systems, including amphibian, avian, fish and mammalian embryos, this issue provides an overview of current research on vascular development. In chapter 1, *Stryder Meadows*, *Candace Myers* and *Paul Krieg* introduces angioblast specification with a comprehensive review of the ETS family of transcription factors, of which *Etv2* is required for all endothelial gene expression. In chapter 2, *Robert Garriock* and *Takashi Mikawa* introduce the concept of vascular patterning with the powerful vascular repulsion of angioblasts that occurs in the vicinity of

the chick notochord. In chapter 3, *Ke Xu* and *Ondine Cleaver* describe recent studies of *in vivo* blood vessel lumen formation and its dependence on Rho family GTPase regulation of cell adhesion contacts and cell shape. In chapter 4, *John Chappell*, *David Wiley* and *Victoria Bautch* covers recent advances in understanding regulation of vessel sprouting via environmental cues and lateral cell–cell communication. In chapter 5, *David Wiley* and *Suk-Won Jin* introduce BMP signaling as a critical and context-dependent angiogenic cue, which can substitute for VEGF signaling in certain vessels. In chapter 6, *Jennifer James* and *Yohsuke Mukoyama* discuss neuronal control of vascular patterning and establishment of the neuro-vascular interface throughout development and into adulthood. In chapter 7, *Elizabeth Jones* describes the events leading to onset of blood flow and how this important physiological signal is required for vascular development. In chapter 8, *Joan Zape* and *Ann Zovein* cover how specialized regions of the endothelium give rise to hematopoietic lineages.

These contributions provide cutting edge overviews of mechanisms underlying normal endothelial development. They also provide insights into how blood vessel growth might be manipulated therapeutically in different pathological settings. The myriad approaches in varied model systems have combined to advance our understanding of growing blood vessels. Continued basic research in vascular biology will continue to lay the foundations for seminal discoveries as to the cellular and molecular basis of cardiovascular development and disease.