Vascular Cell Lineage Determination and Differentiation

Y. Eugene Chen

This issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* contains a review series describing the regulation of vascular cell lineage determination and differentiation. In this miniseries, we also focus on the vascular cells involved in the pathology and pathogenesis of vascular injury, including endothelial cells (EC), smooth muscle cells (SMC), monocytes/macrophages, and adventitial cells.

One of the central themes of this review series is the molecular mechanisms underlying vascular cell determination and differentiation. This review series highlights the available in vivo and in vitro model systems currently being used for the study of mechanisms pertaining to vascular cell differentiation. Next, this series integrates several concepts related to the mechanistic study of vascular cell determination and differentiation, vascular development, and vascular pathophysiology.

EC, which are known to be multifunctional, play a critical role in maintaining normal vascular homeostasis, as well as participating in physiological and pathophysiological processes, including the regulation of vascular tone, inflammatory signaling, vascular wall remodeling, and vasculogenesis. This series, which includes 8 reviews, begins with the review by De Val, which provides a detailed description of the development of the vascular system. This review focuses on the mechanisms regulating gene expression during early-stage EC differentiation and vascular development. Next, Jain and colleagues emphasize the major signaling cascades related to EC differentiation. The first part of this review discusses the molecular mechanisms that determine EC specification to an arterial, venous, or lymphatic fate. The second part of the review focuses on EC phenotypic heterogeneity between organs and vascular beds, as well as within a single vascular bed. Compared with other vascular cells, the molecular mechanisms regulating EC differentiation are currently better characterized.

The next 2 reviews highlight the importance of elucidating the molecular mechanisms facilitating vascular SMC differentiation. A greater understanding of the signaling pathways culminating in SMC differentiation will allow us to gain valuable insight into the SMC-specific role being played in cases of vascular pathophysiology, as well as the functional consequences of an altered SMC phenotype in abnormal vascular conditions. The review by Chen and colleagues provides a detailed description of the current cell-based models and systems used for the study of SMC differentiation. This review also emphasizes the most recent progress in terms of uncovering the complex molecular network driving embryonic stem cell-derived SMC differentiation. Next, the review by Mack provides an in-depth examination of the molecular mechanisms involved in the initiation and maintenance of SMC differentiation. This review also discusses coordinated cell signaling in SMC that not only promotes inhibition of SMC differentiation but also stimulates proliferation and migration of vascular SMC; this coordinated interaction of signaling pathways serves to enhance SMC phenotypic modulation.

Next, Ley and colleagues describe the role of monocytes and monocyte-derived macrophages in the initiation and...
development of atherosclerosis. Recent findings concerning monocyte recruitment, monocyte differentiation to macrophages following endothelial transmigration, and dynamic changes in macrophage phenotypes in the atherosclerotic vessel wall are the major focus of this review. Also, a review by Swirski discusses the nature and complexity of monocyte/macrophage heterogeneity. This review enriches the initial assertions of the van Furth and Cohn model by providing up-to-date information that adds to the complexity of monocyte/macrophage biology. For example, monocytes may have tissue- and cell-specific duties other than a transitional role, and macrophage differentiation may occur without a monocyte intermediate. Further unravelling of the monocyte/macrophage regulatory signaling network will be a critical component for maximizing the capabilities of tracking and imaging macrophages in vivo, which will likely provide new insights for future drug development.

Historically, the role of adventitial cells in vascular biology has been underappreciated. There is now evidence supporting the idea that adventitial cells can be programmed to differentiate into other vascular cells. Recent studies have shed light on the critical importance of adventitial progenitor/stem cells in vascular homeostasis. Furthermore, the identification of adventitial progenitor/stem cells as major players during the progression of vascular injury may have important clinical implications for diagnosing and treating vascular diseases. The review by Xu and colleagues reports that adventitial progenitor/stem cells, in addition to maintaining normal vascular function, can differentiate into endothelial and SMC in response to stimuli. Under pathophysiological conditions, inflammatory-induced cytokine release has been shown to result in the mobilization and differentiation of progenitor/stem cells in the adventitia. The review also addresses the role of adventitial cells in vascular repair and vascular pathologies, including atherosclerosis and vascular lesion formation. Finally, Majesky and colleagues highlight the multifaceted roles of adventitial cells, namely progenitor/stem cells, fibroblasts, and macrophages. This review, with a particular focus on progenitor/stem cells residing in the adventitial layer, discusses the notion that these vascular precursor cells may have the potential to play a role in microvascular network formation. In addition, these adventitial progenitor/stem cells may have the ability to be induced to differentiate toward a SMC-like population and also act as a contributing source of precursor cells in vascular lesions.

In closing, it is of significant interest to further elucidate the molecular mechanisms governing vascular cell determination and differentiation to fully define and appreciate the potential roles of these cell types in vascular biology and function. Furthermore, combining the knowledge derived from studies examining vascular cell determination and differentiation with the knowledge obtained from clinical vascular events will undoubtedly provide a clearer understanding regarding the contributory role of vascular cells in physiological and pathophysiological conditions. A greater understanding of the specific roles and differentiation capabilities of the various vascular cells will enable more effective therapeutic management of vascular diseases.

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