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EDITORIAL

Recent advances in vascular biology and their clinical relevance

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Blood vessels provide conduits by which O_2 and nutrients are delivered to and toxic metabolites are removed from every cell in the body. When cells are deprived of O_2, hypoxia-inducible factor 1 (HIF-1) activates the transcription of genes encoding angiogenic growth factors/cytokines such as vascular endothelial growth factor (VEGF), which stimulates angiogenesis and the resulting increase in perfusion corrects the O_2 deficit [1]. Dysregulation of this homeostatic mechanism plays an important role in the pathophysiology of cancer and cardiovascular disease, which are the major causes of mortality in industrialized societies. In this special issue, four outstanding review articles summarize exciting recent advances in the field of vascular biology that have important clinical implications.

Guo-Hua Fong reviews the mechanism by which cells sense O_2 and regulate HIF-1 through the activity of prolyl and asparaginyl hydroxylases that use O_2 as a substrate to modify the HIF-1α and HIF-2α subunits [2]. Prolyl hydroxylation of these proteins, principally by PHD2, induces the binding of the von Hippel–Lindau (VHL) protein, which recruits an ubiquitin protein ligase, resulting in the ubiquitination and proteasomal degradation of HIF-1α and HIF-2α. Asparaginyl hydroxylation blocks the binding of coactivator proteins that are necessary for HIF-1α or HIF-2α to activate gene transcription. Loss of HIF-1α, HIF-2α, VHL, or PHD2 expression in knockout mice results in defects in cardiovascular development and embryonic or perinatal lethality. Dysregulation of the PHD–VHL–HIF-1 pathway also contributes to the pathophysiology of cancer, ischemic cardiovascular disease, diabetes, arthritis, and wound healing.

Peter Carmeliet and colleagues [3] then provide an in-depth analysis of the role of PHD2 in tumor vascularization. Although vascularization is required for tumor growth, the vessels that form are structurally and functionally abnormal, resulting in severe intratumoral hypoxia. Recent work from the Carmeliet laboratory has demonstrated that decreased PHD2 activity in endothelial cells of genetically modified mice results in a normalization of tumor blood vessels, which improves oxygenation and thereby renders tumors less invasive and metastatic. These results stand in contrast to recent studies indicating that treatment of tumor-bearing mice with angiogenic inhibitors that target VEGF signaling induces tumor hypoxia, thereby rendering the tumors more invasive and metastatic [4, 5].

Masahiro Murakami and Michael Simons [6] focus on the factors that determine the stabilization and integrity of newly formed blood vessels and the maintenance of these properties over time. In addition to an analysis of the role of vascular endothelial cells in this process, which complements data presented in the reviews by Fong and Carmeliet, the role of vessel pericytes and the extracellular matrix is also discussed in detail to provide a complete description of the cellular components, secreted factors, and matrix proteins that contribute to the formation of durable blood vessels.

In the final review of this series, Thomas Clemens and colleagues [7] focus on the relationship between osteogenesis and angiogenesis during bone development and regeneration. Analysis of genetically modified mice in his laboratory has produced an elegant model in which O_2-dependent regulation of the PHD–VHL–HIF-1 pathway plays a critical role in initiation of an angiogenic-osteogenic cascade. As in the other reviews in this issue, the potential therapeutic applications of these discoveries are also

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discussed. The rapid pace of progress in the field suggests that vascular biology will remain one of the most active areas of translational research in molecular medicine for some time to come.

References

1. Bosch-Marcé M, Okuyama H, Wesley JB et al (2007) Effects of aging and HIF-1 activity on angiogenic cell mobilization and recovery of perfusion following limb ischemia. Circ Res 101:1310–1318
2. Fong G-H (2009) Regulation of angiogenesis by oxygen sensing mechanisms. J Mol Med 87. doi:10.1007/s00109-009-0458-z
3. De Bock K, De Smet F, Leite De Oliveira R et al (2009) Endothelial oxygen sensors regulate tumor vessel abnormalization by instructing phalanx endothelial cells. J Mol Med 87. doi:10.1007/s00109-009-0482-z
4. Ebos JM, Lee CR, Cruz-Munoz W et al (2009) Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 15:232–239
5. Pàez-Ribes M, Allen E, Hudock J et al (2009) Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 15:220–231
6. Murakami M, Simons M (2009) Regulation of vascular integrity. J Mol Med 87. doi:10.1007/s00109-009-0463-2
7. Riddle RC, Khatri R, Schipani E et al (2009) Role of hypoxia-inducible factor 1α in angiogenic-osteogenic coupling. J Mol Med 87. doi:10.1007/s00109-009-0477-9