Oxygen: Both a Passenger and a Biological Determinant in the Vasculature

Frank J. Giordano

Cells have an extensive repertoire of "sensors" that monitor and respond to signals from their internal and external environments. As a fundamental substrate for cellular respiration, crucial biological pathways have developed to sense and respond to oxygen availability. In this Arteriosclerosis, Thrombosis, and Vascular Biology review series, several of these crucial oxygen-sensing biological transduction pathways are explored, with a special emphasis on their relevance to vascular biology. Given that one of the primary functions of the circulatory system is to deliver oxygen to cells and tissues, how the component cells of the vasculature themselves respond to oxygen is of particular interest and importance.

In the section by Taylor and Moncada, the coordinate roles of nitric oxide and cytochrome c oxidase in vascular oxygen sensing are addressed. Dr Moncada is a major figure in the field of nitric oxide biology and pioneered the concept that nitric oxide influences mitochondrial biogenesis and energy production. In this contribution to the series, the interactions between nitric oxide levels, oxygen and cytochrome c oxidase redox state, oxygen and nitric oxide consumption, and vascular tone are discussed. How these parameters relate to the generation of reactive oxygen species and the consequent effects on vascular cell signaling are also elegantly illuminated.

In the contribution by Gregg Semenza, the oxygen-sensing role of the classic hypoxia-inducible factor (HIF) pathway and its relevance in the vasculature are discussed. As the discoverer of HIF1α, Dr Semenza is one of the foremost experts on how oxygen levels influence transcription and gene expression. In his section, Dr Semenza delineates how the HIF pathway, in response to alterations in oxygen availability, alters the expression of cytokines and growth factors that influence vascular remodeling and inflammation and how the cellular receptors for these factors are also regulated by the HIF-pathway. His piece also addresses how impairments in HIF-dependent responses contribute to abnormal vascular responses in aging and diabetes.

The roles of the NADPH oxidases in the vasculature are elucidated in the contribution by Bernard Lassegue and Kathy Griendling. Dr Griendling is an authority on the biological significance of reactive oxygen species in the vasculature, their role in signaling, and the function of NADPH oxidases in defining vascular reactive oxygen species levels and reactive oxygen species–dependent signaling. In their contribution to this series, Drs Lassegue and Griendling elegantly delineate the various molecular components of the NADPH oxidase enzyme family and discuss how they are regulated and how they are involved in various vascular pathologies.

Finally, Jonathan Shoag and Zolt Arany write about the regulation of hypoxia-inducible genes by a relatively recently recognized component of the cellular oxygen-sensing machinery, PGC-1. Dr Arany recently defined a crucial HIF-independent role for PGC-1 in oxygen-sensitive regulation of vascular endothelial growth factor expression and angiogenesis. In their piece, Drs Shoag and Arany review the biology of PGC-1, its role as a transcriptional regulator of mitochondria and oxidative metabolism, and its biological significance as a unique HIF-independent regulator of cellular responses to oxygen levels.
As illustrated in this series, the vasculature not only transports oxygen to cells and tissues but is also itself dependent on and crucially influenced by oxygen. It is not a passive conduit but rather a biologically active “organ” that requires oxygen for cellular respiration and responds to changes in oxygen availability by altering cellular gene expression and signaling. As research in this area moves forward, it is likely that involvement of oxygen-responsive pathways will be found in many crucial adaptive and maladaptive biological processes in the vasculature.\textsuperscript{13–15}

**Disclosures**

None.

**References**

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