Molecular responses to hypoxia: ancient pathways, clinical promises

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Oxygen is a staple of life, but like most things, is best consumed in moderation. Too much oxygen, hyperoxia, leads to the excess accumulation of toxic reactive oxygen species (ROS) and has been linked to acute lung injury as well as the retinopathy of prematurity. Conversely, ineffective delivery of oxygen to tissues leads to too little oxygen, hypoxia. Generically, hypoxia is a consequence of an imbalance in oxygen supply and demand and is a central feature of several disease states, including cardiac ischemia, stroke, cancer, congenital heart malformations and chronic obstructive pulmonary disease. In total, these diseases take an enormous socioeconomic toll on our populace.

The supply of oxygen is tightly monitored at both the cellular and organism level and the first clues about the mechanisms that underlie oxygen sensing were sought by early 20th century biologists. Indeed, it has been known for many decades that physiologic oxygen sensing in mammals occurs primarily in the carotid body as well as the juxtaglomerular apparatus of the kidney [1]. Over the last 15 years, the fog over oxygen sensing at a cellular level has largely dispersed as we have come to realize the staggering complexity of the molecular response to variations in oxygen tension. Hypoxia results in alterations in the expression of hundreds of genes and modulation of other complex subcellular processes such as the unfolded protein response, mRNA translation and ion channel function.

Despite this ever increasing complexity however, master regulators of the hypoxic response have been identified. With respect to the transcriptional response to hypoxia, the hypoxia-inducible

factor (HIF) family of transcription factors and their ubiquitin ligase, the von Hippel-Lindau tumour suppressor protein (pVHL), appear to central mediators of the cellular oxygen-sensing pathway [2]. When oxygen becomes limiting (during specific stages of development, or in pathological settings), HIF orchestrates a complex transcriptional response, involving networks of hundreds of genes, activated or repressed, coding and no coding. The direct oxygen sensors in this system are the prolyl-4-hydroxylase domain proteins (PHDs), which belong to the Fe(II) and 2-oxoglutarate-dependent oxygenase family [3]. The PHDs coordinately react to changes in oxygenation by hydroxylating the α subunits of HIF on conserved prolyl residues, resulting in their polyubiquitination by pVHL, and their destruction by the proteasome [4–7]. Additional substrates of the PHD family are likely but have yet to be defined.

Given the central role of mitochondria in cellular metabolism and energy production it seems fitting that they too play a role in both mediating and responding to hypoxia. Intermediates of the Krebs cycle such as 2-oxoglutarate are a cofactor for the PHDs while others such as succinate and fumarate have been noted to inhibit PHD enzymatic activity [8, 9]. As well, growing evidence suggests that ROS can promote the accumulation of HIF [9].

Cancer biologists have come to a more precise understanding of the role of hypoxia in solid tumorigenesis as well as its ability to impart both chemo and radioresistance [10]. Importantly, these insights have led to the development of novel strategies targeting the HIF pathway (either HIF itself, or selected downstream targets)

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and therapeutic successes in cancers such as renal cell carcinoma [11]. Additionally, inhibitors of the HIF prolyl hydroxylases have emerged as candidate drugs in a variety of pathological settings that can benefit from HIF stabilization such as chronic anaemia or vascular disease.

In this series hosted by the *Journal of Cellular and Molecular Medicine*, we present reviews from highly prolific groups with seminal contributions in the field, focused on the recent advances in our understanding of the response to both physiologic and pathologic hypoxia.

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