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Editorial

Hypoxia in health and disease

Oxygen (O_2) is one of the most abundant elements in the biosphere, and although it is absolutely necessary for most forms of life on earth, it can also be one of the most toxic molecules for life. Adaptive responses have evolved in different animal species to ensure a sufficient supply of O_2 to tissues and to facilitate the survival of cells under transient or sustained conditions of limited O_2 availability (hypoxia). An understanding at the molecular level of how these homeostatic processes are organized and when or why they become maladapted and produce cell damage are among the most appealing challenges facing modern biomedical research. In mammals, hypoxia induces acute reflexes (hyperventilation and sympathetic activation), which can increase the uptake and distribution of O_2 to all tissues of the body within a few seconds. When hypoxia is maintained for long periods (hours or days), a powerful and generalized genetic program is activated, increasing non-aerobic ATP synthesis, erythropoiesis, and the generation of new blood vessels. Our understanding of the molecular basis of adaptation to hypoxia has progressed steadily in the last decades. Studies on the hypoxia-dependent up-regulation of erythropoietin (EPO) gene expression led to discovery of the hypoxia inducible factors (HIFs), master regulators of the transcriptional response to hypoxia (Semenza, 1999). Later, a broadly distributed family of O_2-sensitive prolyl/asparaginyl hydroxylases (PHDs/FIH) was shown to modulate HIF activity in transitions between normoxic and hypoxic conditions (Kaelin and Ratcliffe, 2008). Nowadays, we know that the PHD/FIH-HIF pathway not only underlies the vast majority of homeostatic transcriptional activity induced by hypoxia, but it also has a tremendous impact on the clinical field due to its role in an expanding list of cellular processes involved in the pathogenesis of numerous medical disorders. Some well-known examples are cell proliferation control *via* nutrient supply, autophagy activation, metabolic reprogramming of normal and cancer cells, EMT activation, metastasis promotion, stem cell maintenance and activation of the immune cells during inflammation (Cummins et al., 2016; Hubbi and Semenza, 2015; Pouyssegur et al., 2006).

On the other hand, the fast reflex responses elicited by hypoxia are mediated by a set of O_2-sensitive cells located in specialized organs forming the homeostatic acute O-sensing system (Weir et al., 2005). These cells normally contain O_2-regulated K^+ channels in their plasma membrane, which mediate modulation of cell secretory activity or contractility during exposure to hypoxia (López-Barneo, 1996). Recent work is beginning to unveil the molecular bases of the interaction between the changes in cell O_2 levels and ion channel function, a process that had remained elusive (Peers, 2015). Among the organs that respond acutely to hypoxia, the carotid body, a well-known arterial chemoreceptor located at the carotid bifurcation, is currently attracting renewed medical interest as its over-activation seems to be involved in the autonomous dysfunction that accompanies numerous highly prevalent disorders such as sleep apnea, diabetes, hypertension, and chronic heart failure.

The aim of this special issue of *Molecular Aspects of Medicine* is to provide readers with an authoritative update of the biology and pathophysiology of hypoxia. We have not attempted to assemble a comprehensive volume, but rather to gather together reviews written by leaders in the field that cover some of the most dynamic areas of research on hypoxia. The first series of reviews deal with the effects of hypoxia-driven adaptation in cancer cell metabolism, in stem cell homeostasis and cancer stem cells and well as in cells of the immune system They are followed by an update on the importance of the non-coding genome in key hypoxia-regulated processes and by advances in the design and testing of PHD inhibitors to treat human diseases. The selection is completed by a summary of the role of reactive oxygen species in acute and chronic O_2 sensing and by a report on the mechanisms of acute O_2 sensing by arterial chemoreceptors and their potential medical impact.

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