Oxygen sensing in health and disease

Oxygen sensing is critical for cell survival and for a living organism’s ability to adapt to changing environments or physiological conditions. Cellular responses to oxygen are complex, involving multiple genes and signaling pathways. Clinical consequences of impaired oxygen sensing presumably include cancer, hypertension, sleep apnea, congestive heart failure, stroke, and sudden infant death syndrome. This issue of the Journal of Applied Physiology introduces the “Oxygen Sensing in Health and Disease” Highlighted Topic series. In the January through March issues, this series will present original research and mini-reviews that explore the wide range of cellular and molecular mechanisms underlying oxygen sensing, as well as the physiological impact of oxygen sensing in terms of health and disease.

This issue includes a Historical Perspective article by Dr. N. Cherniack, who reviews the changing concepts of oxygen sensing through the years. Recent research indicates that oxygen sensing is not a property unique to special receptors such as the carotid body but is a common property of tissues. Researchers have made astonishing progress toward unraveling the intracellular mechanisms involved in the sensing of oxygen, particularly in nonchemoreceptors. However, the study of oxygen sensing by tissues other than chemoreceptors complicates our analysis of human responses to hypoxia and our ability to separate responses of the carotid body from the effects of hypoxia on both the brain and the neural pathways that connect the carotid body to the brain. Understanding the cellular and molecular pathways triggered by hypoxia and hyperoxia allows us to identify therapeutic targets for treatment of diseases such as cancer. Although we also have a better understanding of the complexities of the human respiratory responses to hypoxia, major deficiencies remain in our ability to alter, or even measure, human ventilatory responses to oxygen deficiency.

The mini-reviews included in this issue focus on peripheral and central nervous system oxygen sensing. Peripheral chemoreceptors, particularly the carotid bodies, are primarily responsible for monitoring changes in arterial blood oxygen and the resultant maintenance of homeostasis in response to hypoxic conditions. Drs. N. Prabhakar and Y.-J. Peng highlight the role of carotid bodies in altitude acclimatization, exercise, and pregnancy in their mini-review entitled “Peripheral chemoreceptors in health and disease.” In addition to the role of carotid bodies in these normal conditions, these investigators also discuss evidence for altered function of carotid bodies in chronic disorders of the cardiorespiratory system, including sleep apnea, congestive heart failure, and hypertension.

Also in this issue, Drs. J. Neubauer and J. Sunderram discuss oxygen-sensitive sites in the brain stem in their mini-review entitled “Oxygen sensing neurons in the central nervous system.” This mini-review highlights recent work showing evidence of highly sensitive regions within the brain stem that, along with peripheral chemoreceptors, coordinate respiratory and sympathetic responses to acute, chronic, and intermittent hypoxia. Although the mechanisms by which these oxygen-sensitive neurons sense hypoxia remain largely unknown, these investigators point out that the present data indicate that oxygen-sensing mechanisms used by other hypoxic chemosensors are possibly conserved. Exploration into the physiological and clinical relevance of these oxygen-sensitive neurons in the brain is only just beginning to evolve.

In the February issue, Drs. D. Millhorn and K. Seta explore the many genes and signaling pathways involved in the complex cellular response to hypoxia in a mini-review entitled “Functional genomics approach to hypoxia signaling.” These authors note that a thorough understanding of this cellular response requires the use of high-throughput technologies that allow global views of the processes and genes involved. These investigators describe a unique approach to the study of hypoxia signaling that couples subtractive suppressive hybridization to microarray analysis. Used in conjunction with high-throughput functional assays for cell survival and apoptosis, this approach promises a rapid method for discovering validated therapeutic targets for the treatment of cardiovascular disease, stroke, and tumors.

Signal transduction by heme-based sensors is the most common physiological strategy for detection of oxygen, carbon monoxide, and nitric oxide. In the February issue, in a mini-review entitled “Signal transduction by heme-containing PAS-domain proteins,” Drs. M.-A. Gilles-Gonzalez and G. Gonzalez discuss recent findings of the role of heme-Per-ARNT-Sim (heme-PAS) domains, the most common of the many possible heme-binding domain structures in heme-based sensors. This mini-review includes an examination of the factors that determine the range of detection of heme-based sensors and how they transduce oxygen signals. Capable of ligand-dependent switching of a variety of activities in widely divergent partner domains including histidine kinase, phosphodiesterase, and DNA-binding activities, proteins containing heme-binding PAS domains are found in all kingdoms of life and display tremendous diversity in their physiological roles.

Also in the February issue, Dr. J. Dean and colleagues revisit evidence for the long-recognized, but seldom acknowledged, paradox of respiratory control known as hypoxic hyperventilation in a mini-review entitled “Hypoxia, reactive O2 species, and hyperventilation: evaluating oxygen sensitivity of brain stem neurons.” This mini-review recaps recent evidence substantiating the hypothesis that increased production of reactive oxygen species (ROS) during hyperoxia directly stimulates central CO2 chemoreceptors in the brain stem. These authors propose that oxygen-induced hyperventilation provides clues about the fundamental role of redox signaling and reactive oxygen species in central control of breathing. They also discuss the possible role of oxidative stress in respiratory control dysfunction. These authors suggest that future respiratory control studies using hyperoxia will benefit by consideration of the central excitatory effects of oxygen and reactive oxygen species on brain stem neurons, effects that occur simultaneously with the inhibitory effects of oxygen on peripheral chemoreceptors.

In the March issue, Dr. G. Semenza discusses the mediating effects of hypoxia-inducible factor 1 (HIF-1) on changes in gene expression involved in physiological responses to hypoxia in a mini-review entitled “Oxygen-regulated gene expression: transcriptional control of cardiorespiratory physiology by HIF-1.” By analyzing mice heterozygous for a knockout allele
at the locus encoding the oxygen-regulated HIF-1α or HIF-2α subunits, Dr. Semenza provides evidence that these proteins play vital roles in physiological responses to chronic hypoxia, ranging from erythrocytosis to vascular remodeling. Whereas brief episodes of intermittent hypoxia are sufficient to induce production of erythropoietin in wild-type mice that protects the heart against apoptosis after ischemia-reperfusion, intermittent hypoxia did not induce erythropoietin production for cardiac protection in mice with partial HIF-1α deficiency. Dr. Semenza highlights the importance of HIF-1 as a mediator of critical physiological responses to hypoxia. The elucidation of such homeostatic mechanisms may lead to novel therapies for the most common causes of mortality within the U.S. population.

Systemic responses to hypoxia are intrinsically associated with altered cellular functions. Exploring these cellular responses to hypoxia, Drs. G. Kumar and J. Klein review the present understanding of the complex protein changes that occur during chronic and intermittent hypoxia in a mini-review entitled “Analysis of protein expression in hypoxia.” A large body of evidence suggests that hypoxia initiates a plethora of functional changes in various organelles, including the plasma membrane, cytosolic compartment, nucleus, and mitochondria. These functional changes could, in part, be attributed to alterations in the expression, structure, and activity of proteins associated with the cellular compartments, thus enabling the system to function properly under conditions of reduced oxygen availability. Approaches generally categorized as proteomics are increasingly being applied as a means to understand hypoxia-induced alterations in protein expression and function. Results derived from such analyses show that hypoxia, in general, affects the levels of a subset of proteins associated with such cellular functions as metabolism, stress response, cell injury, development, and apoptosis.

Also in the March issue, Dr. J. López-Barneo and colleagues summarize the present knowledge of ion channels as effectors of cellular responses to hypoxia in their mini-review entitled “Regulation of oxygen sensing by ion channels.” Oxygen-sensitive K+ channels, whose activity is inhibited by low oxygen tension, participate in acute cardiorespiratory adjustments to hypoxia. These channels, initially described in carotid body glomus cells, have also been found in other oxygen-sensitive cells such as those in the neuroepithelial bodies of the lung, chromaffin cells, and pulmonary arterial myocytes. However, the mechanisms underlying oxygen sensing and the interactions between oxygen sensors and ion channels remain enigmatic. In this mini-review, López-Barneo and colleagues describe the participation of ion channels in the chronic cellular adaptations to hypoxia. These authors also consider the involvement of oxygen-regulated ion channels in the pathogenesis of human diseases.

Oxygen sensing is an everyday part of our lives and our physiological responses to the environment. It is therefore not surprising that impaired oxygen sensing has many far-reaching and serious clinical consequences. This Highlighted Topic series only touches the surface of this extremely important area of research. Clearly, exploring the mechanisms of oxygen sensing is crucial, not only to a better understanding of normal physiology but also to an understanding of many serious common diseases. As always, the Associate Editors and I hope that the mini-reviews and original research highlighted within this Topic series have provided a basis for encouraging the continued publication of research on oxygen sensing in the Journal of Applied Physiology.