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Editorial overview: Hypoxia

Hesham A Sadek and Gregg L Semenza

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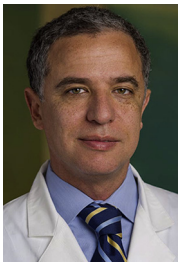
Hesham A Sadek



Center for Regenerative Science and Medicine, The University of Texas Southwestern Medical Center, United States

Sadek obtained his medical degree from Ain Sham University in Cairo, Egypt, and his PhD from Case Western Reserve University in Cleveland, Ohio. He completed clinical training in Internal Medicine and cardiology at the University Hospitals of Cleveland, and post doctoral-fellowship in cardiac regeneration at UT Southwestern Medical Center. Dr. Sadek's research focuses on mammalian heart regeneration, and the link between metabolism and cell cycle regulation. He is currently an Associate Professor of Internal Medicine, and Associate Director of Center for Regenerative Science and Medicine at UT Southwestern Medical Center, where he holds the J. Fred Schoellkopf, Jr. Chair in Cardiology. The Sadek laboratory is funded by grants from NIH, AHA, CPRIT, CRSM and Fondation Leducq.

Oxygen homeostasis, which is maintenance of the balance between oxygen supply and demand, is critical for survival. Erythropoietin (EPO) is the hormone that controls red blood cell production and thereby determines the blood oxygen-carrying capacity. A decrease in tissue oxygenation as a result of hemorrhage or ascent to high altitude leads to increased EPO production. Studies investigating *EPO* gene regulation led to elucidation of molecular mechanisms that underlie many cellular and systemic physiological responses required to maintain oxygen homeostasis. Hypoxic induction of *EPO* transcription required a *cis*-acting hypoxia response element (HRE) located in the 3′-flanking region of the gene. Hypoxia-inducible factor 1 (HIF-1) binds to the HRE under hypoxic conditions. HIF-1 is a heterodimer composed of HIF-1α and HIF-1β subunits. O_2-dependent hydroxylation of a proline residue in HIF-1α leads to ubiquitination and proteasomal degradation of the protein. Catalytic activity of the prolyl hydroxylase domain (PHD) proteins is inhibited under hypoxic conditions, and non-hydroxylated HIF-1α cannot be bound by the von Hippel–Lindau protein (VHL), which is the recognition subunit of the ubiquitin ligase, leading to accumulation of HIF-1α, dimerization with HIF-1β, binding to the HRE, and transcriptional activation. Now, over 4 000 target genes are known to be directly regulated by HIF-1 and/or family members HIF-2 and HIF-3, which are heterodimers of HIF-1β with HIF-2α or HIF-3α subunits that are also regulated by O_2-dependent hydroxylation, ubiquitination, and degradation.

The critical role of the HIF–PHD–VHL system in controlling erythropoiesis and other responses to hypoxia has been dramatically demonstrated by genetic studies of individuals with congenital polycythemia, as reviewed by Tsewang Tashi, Jihyun Song, and Josef Prchal. Excess red blood cell production increases the hematocrit leading to an increased risk for venous or arterial thrombosis. A mutation in the gene encoding PHD2, VHL, or HIF-2α has been identified in many affected individuals. Molecular analysis of the mutant alleles has in all cases demonstrated that they impair O_2-dependent degradation and increase HIF activity at any given O_2 concentration, which leads to polycythemia and pulmonary hypertension. Even the normal erythropoietic response appears to be maladaptive under conditions of chronic hypoxia associated with life at high altitude. In fact, polycythemia and pulmonary hypertension are cardinal signs of chronic mountain sickness, a life threatening condition observed in many lowlanders who sojourn to high altitude and even some high altitude inhabitants. Prchal *et al.* describe the genetic studies that have identified DNA variants at the loci encoding HIF-2α and PHD2 that are associated with a blunted erythropoietic response to chronic hypoxia in Tibetan highlanders and thereby represent an evolutionary adaptation to life at high altitude.

Gregg L Semenza

Johns Hopkins Institute for Cell Engineering, United States

Gregg L Semenza, M.D., Ph.D. is the C. Michael Armstrong Professor of Genetic Medicine at Johns Hopkins, with appointments in Pediatrics, Medicine, Oncology, Radiation Oncology and Biological Chemistry, and founding Director of the Vascular Program in the Johns Hopkins Institute for Cell Engineering. He is an elected member of the Society for Pediatric Research, American Society for Clinical Investigation, Association of American Physicians, National Academy of Medicine, and National Academy of Sciences. Dr. Semenza discovered hypoxia-inducible factor 1 (HIF-1), a master regulator that directs transcriptional responses to decreased oxygen availability in metazoans. HIFs play important roles in cardiovascular disorders, cancer, COPD, diabetes, sleep apnea, ocular neovascularization and hematologic disorders. HIF stabilizers and inhibitors are in clinical trials for the treatment of anemia and cancer, respectively.

Larissa Shimoda, Xin Yun and Gautam Sikka describe pulmonary hypertension as a maladaptive response to hypoxia associated with chronic lung disease or high altitude. In contrast to systemic arterioles, which dilate in response to hypoxia, pulmonary arterioles constrict. This is an adaptive response in the context of pneumonia, in which a single lobe of the lung is consolidated by bacterial and inflammatory cells. Pulmonary arterial constriction shunts blood away from affected areas that are not ventilated, thereby maximizing O_2 uptake by uninvolved areas. However, when the entirety of both lungs is subjected to hypoxia, constriction is maladaptive and leads to reduced O_2 uptake, right heart failure, and eventually death. Shimoda *et al.* describe how HIF-dependent responses to hypoxia in pulmonary arterioles play a critical role in the pathogenesis of hypoxic pulmonary hypertension.

Cardiac adaptation to chronic hypoxia is discussed by Mike Stembridge and Benjamin Levine. Decreased filling of the left ventricle leads to decreased stroke volume and a compensatory increase in heart rate in order to maintain cardiac output. Stembridge and Levine describe the complex physiological responses to hypoxia that may contribute to decreased stroke volume at high altitude.

Whereas chronic continuous hypoxia leads to pulmonary hypertension, chronic intermittent hypoxemia associated with obstructive sleep apnea leads to systemic hypertension and is the major cause of treatment-resistant hypertension. Nanduri Prabhakar, Jayasri Nanduri, Ying-Jie Peng, and Ning Wang describe the molecular mechanisms they have elucidated from the analysis of rodents exposed to chronic intermittent hypoxia, which begins with the carotid body, a small sensory organ, which is located at the bifurcation of the common carotid artery and contains glomus cells that sense arterial O_2 levels and stimulate the sympathetic nervous system in response to hypoxemia. As in the case of chronic continuous hypoxia due to high altitude, chronic intermittent hypoxia due to obstructive sleep apnea results in a maladaptive response. Remarkably, whereas continuous hypoxia increases both HIF-1α and HIF-2α in pulmonary vessels, Prabhakar *et al.* describe how intermittent hypoxia increases HIF-1α and decreases HIF-2α in glomus cells, which plays a critical role in sympathetic nervous system activation leading to systemic hypertension.

As described with respect to pneumonia, bacterial infection results in the recruitment of inflammatory cells to sites of infection. The resulting increase in cells and their consumption of O_2 invariably leads to hypoxia in the affected tissue. Eilise Ryan, Moira Whyte, and Sarah Walmsley describe how both the host immune cells and the invading bacteria adapt to hypoxia. Novel insights into this important aspect of host–pathogen interaction may lead to novel therapeutic approaches.

Changes in gene transcription are critical for both adaptive (physiologic) and maladaptive (pathologic) responses to hypoxia. These changes involve both DNA-binding proteins, such as HIF-1 and HIF-2, as well as chromatin-modifying enzymes that allow DNA binding proteins and RNA polymerase to access the DNA and transcribe it into RNA. Hye Jin Nam and Sun Hee Baek describe the effect of hypoxia on several large families of chromatin modifying enzymes, either because the proteins are products of HIF target genes, or the proteins require O_2 for their catalytic activity. In addition, modification of RNA by methylation of adenosine residues has recently been shown to affect RNA stability, splicing and translation, and one of the two known adenosine demethylases is an O_2-dependent enzyme encoded

by a HIF target gene. The complexity of molecular mechanisms by which cells adapt to hypoxia provides further evidence of the essential role of oxygen homeostasis in human physiology.

Phototransduction, the process of converting photons into chemical signals in the retina, is an energetically demanding process, and thus highly sensitive to hypoxia and ischemia. Seth Fortmann and Maria Grant provide elegant insights into the molecular mechanisms of retinal ischemia, and its role in retinal pathology. Their article highlights recent advances in understanding how maladaptive mechanisms that are designed to protect the retina from the consequences of hypoxia, mediate a variety of retinal pathologies including exudation, neovascularization and vessel growth.

The hypoxic metabolic phenotype of cancer cells has long been recognized, with recent discoveries linking the metabolic phenotype of cancer cells to tumor immunity. Ronghui Yan, Linchong Sun, and Huafeng Zhang outline the concept of 'metabolic rewiring' of cancer cells, and how the diverse metabolic phenotypes of cancer cells influence tumor progression and serve as potential therapeutic targets.

A less studied aspect of the metabolic adaptation to hypoxia is its effect on pH. Long thought to be a deleterious side effect of hypoxia, recent evidence suggests that acidosis may have significant cytoprotective effects, which has become known as the 'pH Paradox'. In this issue, Eric Swenson outlines the effects of hypoxia and ischemia-induced pH changes on cellular adaptation and survival, and the potential therapeutic opportunities that this offers both in critically ill patients as well as cancer patients.

Organ transplantation remains the mainstay of therapy in many end stage diseases; however as the number of patients on transplant lists grows, organ transplantation continues to be limited by the availability of organs. Unfortunately, almost all successfully transplanted organs eventually fail due to a variety of etiologies, with decreased tissue perfusion being a leading cause of eventual organ failure. This issue is particularly important in case of lung transplant which is the only solid organ allograft in which the major native blood supply is not restored at the time of transplantation. Shravani Pasnupneti and Mark Nicolls discuss the evolution of airway tissue hypoxia following lung transplantation, and how it plays a critical role in graft survival and patient outcomes.

An intriguing and highly relevant aspect of the hypoxic response is the mechanism of adaptation to environmental hypoxia. Elite mountaineers can for example survive the severe hypoxic environment at the summit of Everest without supplemental oxygen if appropriately acclimatized. However, exposure to the same oxygen level is invariably lethal in the absence of acclimatization. In this issue, Robert Roach provides a view of acclimatization studies in humans, and how this phenomenon can be leveraged to develop novel therapies for high altitude sickness, as well as circulatory and pulmonary diseases.

A widely accepted view of the role of iron in cellular damage during oxidative stress is that related to Fenton reaction-mediated reactive oxygen species formation. Rajiv Ratan provides an overview of the growing body of evidence supporting alternative roles of iron in oxygen homeostasis as well as cellular damage. This thought provoking review outlines the role of iron in oxygen sensing through prolyl hydroxylases and in ferroptosis, an iron-dependent type of programmed cell death.

The field of oxygen biology is continuing to evolve with the discovery of novel mechanisms that regulate adaptive and maladaptive responses to this fundamental environmental stress. While hypoxia research initially focused on understanding the deleterious effects of hypoxia, it has become clear that a deeper understanding of the mechanisms of hypoxia adaptation has provided a wide array of therapeutic opportunities in fields ranging from cancer, to vascular diseases as well as organ transplant and regenerative medicine. In the current edition, we present a series of cutting edge, thought provoking articles that highlight the current state of the field, and a forward-looking view of the challenges and opportunities that lie ahead.