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Forum Editorial

Hypoxia: Life on the Edge

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ABSTRACT

Hypoxia and its corollaries pose both negative and positive pressures to multicellular eukaryotes. Evolutionarily, life developed under hypoxia, and the building blocks were established under conditions close to anaerobiosis; therefore, reason exists to expect that certain biologic processes may perform preferentially under hypoxia. Evolving evidence suggests that by providing an environment of reduced oxidative stress, hypoxia may help preserve the biologic functions of some cells and prevent senescence. Hypoxia provides essential signals for development, trimming redundant tissue by inducing apoptosis and driving the growth and development of oxygen and nutrient delivery systems, as well as those for waste management. The pathologic consequences of hypoxia and ischemia, including acidosis and oxidative stress associated with hypoxia–reoxygenation, form the basis of most of the major diseases confronting humans, including heart disease, cancer, and age-related degenerative conditions. The 11 articles in the forum touch on multiple aspects of hypoxia, in particular, signaling responses, adaptations, and diseases that result from imbalance and fluctuations of supply and demand. Although we have developed elaborate processes to combat hypoxia and oxidative damage, it is clear that oxygen and our environment still control us, perhaps even more than they did our unicellular ancestors 2 billion years ago. *Antioxid. Redox Signal.* 9, 1303–1307.

HYPOXIA, EVOLUTION, AND DEVELOPMENT

PHYSIOLOGIC OXYGEN TENSIONS of adult mammalian tissues range from 150 mm Hg at the lung apices to ~40 mm Hg in mixed venous blood and most organs, to <20 mm Hg in parts of the bone marrow and to <10 mm Hg in pathologic conditions involving ischemia (1, 9, 16, 20, 31). Endothelial cells in contact with arterial blood (80–100 mm Hg) are more highly oxygenated than are those in contact with venous blood (35–42 mm Hg). One of the most dramatic changes in oxygen tension occurs during birth in human alveolar epithelium, where oxygen tension increases abruptly from 23 mm Hg in the fetus to 100 mm Hg in the newborn (1). The impressive range of oxygen tension under which mammalian cells exist illustrates the high degree of flexibility and tolerance of these cells to pO_2. Such a tolerance is perhaps a reflection or in some instances a recapitulation of early evolution that began in an oxygen-free environment but changed course dramatically when oxygen appeared. Atmospheric oxygen during the Archean period was <1% of the current level; by ~1.8 billion years ago, it was 15% and had probably increased to the current level by 0.5 billion years ago. It has been estimated that as much as 99% of the existing anaerobic life forms were extinguished by the toxic byproducts of oxygen in the late Precambrian period (2, 3, 17). Oxygen supported a rapid diversification and expansion of survivors because of the increased energy made available from oxidative metabolism. The main expansion occurred within the eukaryotic kingdom, stimulated by the mitochondria, a highly efficient energy generator partially insulated from other cellular functions. Metabolic and gene regulatory pathways, including responses to hypoxia, adapted in parallel to integrate and coordinate mitochondrial and glycolytic functions (38, 40).

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Central to our evolution from single-cell obligate anaerobes to oxygen-utilizing, and ultimately complex multicellular eukaryotes was the acquisition of efficient gas and small-molecule transport systems to supply oxygen and other nutrients and remove waste products (CO_2, lactate) from cells situated beyond the diffusion limit for these molecules. As a consequence, most mammalian cells are no more than one or two cells away from blood and lymph vessels (10). In parallel with the acquisition of efficient oxygen-delivery systems, most eukaryotic cells retain the capability to survive even extended periods of hypoxia through multifaceted hypoxia-adaptation programs. The response to hypoxia has two obvious primary functions: (a) developmentally, it provides signals that stimulate the oxygen-delivery system; and (b) in the adult, it provides a mechanism to respond in a coordinated way to a failure of the delivery system. Both of these functions include mechanisms to activate cell death or survival pathways depending on the context of the hypoxia signal. Articles in this Forum by Fisher and Burggren (8) and Dore-Duffy and Lamanna (7) elegantly document these responses in the heart and brain, respectively. Hypoxia stimulates both angiogenesis and apoptosis in the myocardial outflow tract of developing chick embryos, the former to relieve hypoxia, and the latter to remove surplus tissue and accommodate remodeling. VEGF and SDF-1 have been identified as playing key roles in the recruitment of endothelial precursors for angiogenesis; the pathway of hypoxia-activated apoptosis in this context is not known. Hypoxia-driven angiogenesis and apoptosis are also central to responses of the adult brain to mild hypoxia. Exposure of rats to low oxygen tension for 3 weeks promotes a doubling of capillaries in the cerebral cortex by pathways that require HIF-1, VEGF, angiopoietin-2, and cyclooxygenase-2. The first event in this response involves hypoxia-mediated migration of pericytes to the vessel walls where they secrete growth and remodeling factors. The capillary networks rapidly regress to the prehypoxic levels when the animals are returned to normoxia, a process that involves endothelial cell apoptosis that is activated by angiopoietin-2 when VEGF levels decline. In addition to new vessel recruitments, cardiac and skeletal muscles also activate mitochondrial biogenesis when exposed to hypobaric hypoxia. The article by Lynn *et al*. (26) discusses some of the remarkable molecular genetic consequences of chronic hypoxia combined with intermittent normoxia and exercise. In addition to activating an ischemic preconditioning-like response, intermittent hypobaric hypoxia combined with training (live low, train high) promotes mitochondrial biogenesis, increased antioxidants and glucose oxidation, and increased $V_{O_{2max}}$. Hypobaric hypoxia also mediates an increased level of oxidative stress probably caused by elevated superoxide production from the mitochondria.

HYPOXIA AND DISEASE

The hypoxia response has features that are probably remnants of anaerobic Archean biology combined with more recent acquisitions, akin to antioxidant systems that were under strong selection pressure during the Vendian period of evolution, and that are essential for oxygen-dependent life (38). In support of the latter possibility, all eukaryotic cells have retained the capability to generate ATP through glycolysis, even to the exclusion of oxidative phosphorylation. Cardiac myocytes isolated from neonatal rodent hearts survive normally and retain synchronous contractions for several weeks when cultured under oxygen tensions of $\leq$2 mm Hg, equivalent to Precambrian pO_2 levels, provided they are supplied continuously with glucose and a mechanism to remove extracellular acid (11). This suggests that these cells are threatened not so much by hypoxia as by the secondary consequences of hypoxia that can include glucose depletion, waste buildup, return of oxygen (reoxygenation), and possibly oxidative damage from hypoxic mitochondria (22, 39). The latter effect is almost certainly a recent Cambrian acquisition, with no equivalent in pre-Vendian life. Retention of an independent anaerobic energy-generating capability by modern multicellular eukaryotes also appears to be more than a mere relic of Archean biology, or just a precaution against ischemia. Embryonic stem cells and cancer cells preferentially use glycolysis even under aerobic conditions, and differentiation can promote the switch from glycolytic energy production to oxidative phosphorylation (19). Imbalance between oxidative phosphorylation and glycolysis in the human heart can result in cardiomyopathy (5).

Hypoxia is an ever-present threat to the animal kingdom. The requirement for oxygen-breathing apparatus to support expeditions to the highest altitudes of our planet is a forceful reminder that the mantle of oxygen surrounding the earth is thin. It is also evidenced by the delicate relations between capillary networks and oxygen consuming cells, disruption of which is the most frequent cause of human disease (37). Hypoxia is obligatorily associated with all forms of blood and vascular disorders, including anemia; hemophilia; sickle cell diseases; coronary and peripheral arterial diseases including stroke, myocardial and limb ischemia; lung disorders; diabetes; and renal and liver ischemia. Severe hypoxia is also found in the core region of solid tumors where capillary networks are insufficiently organized to supply the rapidly growing tissue with oxygen. Tumor cells represent a unique case of surviving severe hypoxia. The microenvironment around the necrotic core of the tumor is both hypoxic and acidotic, conditions that are lethal to other cells and tissues (22). Tumor cells preferentially use glycolysis to produce ATP (the Warburg effect) and avoid intracellular acidosis and probable death by aggressively secreting protons. In these cells, the disadvantage of inefficient fuel use appears to be outweighed by the positive impact of more-rapid generation of ATP, and perhaps lower oxidative stress. Kurtoglu *et al*. (23) in this Forum describe how the Warburg effect is being exploited for therapeutic purposes to treat hypoxic tumors. Blocking glucose metabolism with analogues, such as 2-deoxyglucose and 2-fluoro-deoxyglucose, selectively kills cells inside a hypoxic tumor probably by two mechanisms, inhibiting the sole source of energy, and blocking protein glycosylation.

HYPOXIA AND CELL DEATH

Microarray analyses of different cell types, including stem cells, cancer cells, and cardiac myocytes, reveal 100–200 genes that respond positively to exposure to hypoxia (11, 28, 33).

More than 100 of these appear to be regulated directly by HIF-1 (18). Many induced genes fall into logical categories associated with adaptation to hypoxia (glucose transporters, glycolytic enzymes) and the generation of signals to enhance oxygen delivery by promoting erythropoiesis and angiogenesis and modulating vascular tone. Hypoxia and HIF-1 also induce growth factors, such as the insulin-like growth factor-2 and transforming growth factor-α. (21). Heme oxygenase is a powerful prosurvival gene that is induced by hypoxia. Not quite so obvious in the context of adaptation is the simultaneous activation of proapoptosis genes. Hypoxia has been shown to stimulate Fas and its ligand, depress antiapoptotic Bcl-2, and activate caspases (35). HIF-1 directly activates the BH3-only proapoptotic genes *Bnip3*, *NOXA*, *RTP801*, *HGTD-P*, and perhaps *PUMA* (36). Hypoxia-mediated apoptosis is decreased in embryonic stem cells that contain an ablated HIF-1 gene (4). Therefore, by activating HIF-1, hypoxia simultaneously induces prosurvival and prodeath genes.

The outcome of the mixed signals generated by hypoxia is cell specific and determined by the severity of hypoxia as well as by the presence of ancillary conditions associated with hypoxic metabolism. Schroff and Chandel in this Forum (32) describe a pathway whereby severe but not moderate hypoxia promotes apoptosis. The antiapoptotic gene Mcl-1 is induced by hypoxia through HIF-1; however, under severe hypoxia, Mcl-1 is targeted for degradation by the proteasome, whereas under mild hypoxia, it is not and remains elevated, favoring survival. Death decisions are determined by the balance of multiple prosurvival (Bcl-2/XL, Mcl-1, Bcl-w, A1) and prodeath Bcl-2 family proteins, each subjected to independent regulation. The commitment of a cell to suicide is a complex decision, usually taken only when all survival options are overridden. One safety mechanism that can switch from prosurvival to prodeath, depending on the stress level, is autophagy. Autophagy normally has a protective role, conserving energy by recycling damaged proteins and removing damaged organelles. The activity is increased under stress, when more damage occurs to intracellular structures. Takagi *et al*. in this forum (34) present compelling arguments that autophagy mediates both prosurvival and prodeath pathways in the heart subjected to ischemia or reperfusion stress. Autophagy is probably activated by starvation-like signals generated during ischemia, and during reperfusion by other pathways connected with mitochondrial ROS or ER stress or both, possibly involving the prodeath Bcl-2 family protein Bnip3. The article by Graham *et al*. in this Forum (12) describes a pathway for reoxygenation-mediated induction and phosphorylation of Bnip3 that may initiate both autophagy and necrotic cell death.

ROS, HYPOXIA, AND INTERMITTENT HYPOXIA

The injury caused when hypoxic cells or tissues are reoxygenated is perhaps the supreme example of pathologic atavism in which intracellular ROS generated by the resurgence of mitochondrial electron transport exceeds the cellular defenses and can trigger massive death to affected cells, reminiscent of the anaerobes that perished by oxidative stress in the late Precambrian. The cell-death pathways that are activated by reoxygenation highlight the central role played by the mitochondria in the response to hypoxia as both the source and ultimately the targets of ROS. Mitochondrial ROS are implicated not only as the perpetrators of all of the major human pathologies, including cardiovascular disease, stroke, cancer and aging, but are also essential signaling intermediates and, appropriately, sensors for cellular responses to hypoxia. The concept that mitochondrial ROS are molecular oxygen sensors was pioneered by Paul Schumacher's group, based on their observations that ROS production by mitochondria paradoxically increases under conditions of hypoxia and is required for the induction of some hypoxia-regulated genes (13). Three articles in this forum discuss this fascinating aspect of hypoxia. Guzy *et al*. (14) present original data that ROS from mitochondrial complex III, already implicated in the response of mammalian cells to hypoxia, are also required for activation of hypoxia-responsive genes in yeast. The transcription factors Yap1p, Msn2p, and Mga2p, required for the induction of multiple hypoxia-regulated genes, are inactivate in yeast mutants affecting complex III or when ROS are quenched by antioxidant treatment. Such regulation is evident only in yeast grown without glucose when glycolysis is not an option. These results suggest close parallels between these yeast transcription factors and mammalian HIF-1 and indicate that oxygen sensing by mitochondrial ROS predates HIF-1, which probably first appeared during the Silurian period of evolution (38). Semenza and Prabakhar (30) and Prabakhar *et al*. (29) describe another critical role for HIF-1 in the response to chronic intermittent hypoxia (CIH), a condition believed to be contribute to the pathophysiologic consequences (hypertension, metabolic syndrome) of sleep apnea. The target of CIH appears to be the carotid body, the primary chemoreceptor for sensing changes in arterial pO_2 and secreting the catecholamines that regulate vascular tone and blood pressure. The CIH response critically involves HIF-1 and ROS; scavengers of reactive oxygen block the responses, and heterozygous HIF-1α ($-/+$) knockout mice do not respond to CIH. These results suggest that HIF-1α not only requires ROS to sense oxygen but also has an essential role in generating it.

REGULATION OF HIF-1 AND PERCEIVED HYPEROXIA

The molecular events that mediate the global responses to hypoxia are still unclear. Activation of the HIF-1 complex and its dependent genes requires hypoxia-mediated mitochondrial ROS and oxygen-dependent regulation of the prolyl and arginyl hydroxylases that target both HIF-1α and HIF-2α. The mechanism of ROS as oxygen sensors is not clear but may include activation of protein kinases that are required for HIF-1–mediated transcription. As described by Nyko *et al*. in this Forum (27), the activities of the prolyl hydroxylases are themselves subject to regulation not only by oxygen availability, but also by multiple other metabolites that contribute to the redox state of the cell. Such regulation may contribute to the wide range of oxygen tensions that resident cell types can interpret as normoxic or hypoxic. Chronic hypoxia can change the pO_2 that a cell perceives as normoxic; in the postinfarct heart, this can re-

sult in perceived hyperoxia, a condition that promotes healing in periinfarct tissue (31). pO_2 is clearly an important parameter in regulating cell biology, and the standard practice in the research community to culture cells at a pO_2 of 150 mm Hg (21% oxygen) may lead to artifacts of hyperoxia. For example, oxygen tension is an important determinant of proliferation and differentiation of hematopoietic cells from the bone marrow. Reduced oxygen tension (40 mm Hg) enhances the production of erythroid, megakaryocytic, and granulocytic-monocytic progenitors *in vitro*, whereas the formation of mature erythrocytes and megakaryocytes is more extensive at 150 mm Hg (15, 24, 25). Low oxygen tension has also been shown to preserve the stem cell phenotype of human bone marrow (6).

Investigators using these, as well as other progenitor and mature cells in culture for physiological studies, should perhaps consider using oxygen tensions more similar to those under which these cells normally reside.

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ABBREVIATIONS

CIH, chronic intermittent hypoxia; ER, endoplasmic reticulum; HIF-1, hypoxia-inducible factor 1; ROS, reactive oxygen species; SDF-1, stromal cell–derived factor 1; VEGF, vascular endothelial growth factor.

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