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Turning the Oxygen Dial: Balancing the Highs and Lows

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Abstract

Oxygen is both vital and toxic to life. Molecular oxygen is the most used substrate in the human body and is required for several hundred diverse biochemical reactions. The discovery of the PHD-HIF-pVHL system revolutionized our fundamental understanding of oxygen sensing and cellular adaptations to hypoxia. It deepened our knowledge of the biochemical underpinnings of numerous diseases, ranging from anemia to cancer. Cellular dysfunction and tissue pathology can result from a mismatch of oxygen supply and demand. Recent work has shown that mitochondrial disease models display tissue hyperoxia and that disease pathology can be reversed by normalization of excess oxygen, suggesting that certain disease states can potentially be treated by modulating oxygen levels. In this review, we describe cellular and organismal mechanisms of oxygen sensing and adaptation. We provide a revitalized framework for understanding pathologies of too little or too much oxygen.

Reflections on the Early Adventures of Oxygen Research

Oxygen was introduced into Earth's atmosphere nearly 2.5 billion years ago, marking a new era in the evolution of complex life forms. The appearance of photosynthetic cyanobacteria led to the Great Oxidation Event and caused a mass extinction of anaerobic species [1]. Eventually, this selective pressure gave rise to the first oxygen-sensing and detoxifying pathways, while simultaneously allowing for hundreds of oxygen-dependent biochemical reactions and highly efficient ATP production through oxidative phosphorylation (Box 1). The apparent trade-off between the pros and cons of an oxygen-rich environment are a constant theme in human development, health, and disease. Here, we discuss several key concepts central to this theme: (i) How do cells and organisms sense changes in oxygen levels? (ii) How do cells and organisms adapt to variations in oxygen levels? (iii) What happens when oxygen supply and demand are mismatched? (iv) Which diseases and pathologies arise from such an imbalance? (v) How can we modulate oxygen levels for therapeutic benefit?

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Before delving into the biochemistry of oxygen metabolism, we look to the past and draw inspiration from the rich history of the oxygen research field. Oxygen was first discovered in 1774 by the British experimental chemist, Joseph Priestley, who described ‘dephlogisticated air’ as a highly reactive, colorless gas that supported combustion. Soon after, Antoine Lavoisier named this element ‘oxygen’ from the Greek term for ‘acid-former’ [2]. The decades that followed were characterized by colorful stories of high-altitude expeditions and hot air balloon rides to study the physiological effects of low oxygen, or **hypoxia** (see Glossary). In the mid-19th century, the aeronaut and French chemist Gaston Tissandier experienced the life-threatening effects of acute hypobaric hypoxia when he survived the rise to an elevation of 8600 meters. His colleagues, Joseph Crocé-Spinelli and Théodore Sivel, were less fortunate and perished [3]. In a more controlled environment, Paul Bert, the French physiologist, demonstrated the acute central nervous system (CNS) effects of oxygen toxicity on larks [4]. Recently, researchers have focused on problems related to oxygen sensing and adaptation, from the carotid body at the whole-body level to the hypoxia transcriptional factor (HIF) program at the molecular scale.

The Goldilocks Oxygen Principle

Here, we review the recent advances in the field and propose a revitalized framework for oxygen metabolism: ‘The Goldilocks Oxygen Principle’. Every tissue has an ideal **oxygen tension** (PO_2) that allows it to maintain metabolic homeostasis, which is regulated by extrinsic variables (e.g., temperature, barometric pressure) and intrinsic factors (e.g., metabolic rate, fuel preferences, physiological reserve). Tissue PO_2 is regulated by oxygen delivery, oxygen consumption, and blood flow, which are controlled by complex interactions of the cardiovascular, respiratory, and nervous systems. Under normal conditions, the partial pressure of oxygen (PO_2), varies widely in the human body, ranging from 100 mmHg (13.2% O_2) in arterial blood, 34 mmHg (4.4% O_2) in the brain, and 30 mmHg (3.8% O_2) in skeletal muscle [5]. Certain organs, such as the brain and heart, are highly aerobic and sensitive to hypoxia, whereas others, such as the skeletal muscle, are more tolerant of prolonged hypoxia. Not only do different tissues have different ‘set-points’ for oxygen, we believe that different individuals and disease states also have an optimal oxygen set-point. By understanding such states of hypoxia or hyperoxia, we can better understand the interplay between homeostasis and disease pathology, allowing us to achieve the ideal set-point by ‘turning the oxygen dial’ as a therapy.

Cellular Oxygen Sensors

At the molecular level, oxygen sensors can either directly sense oxygen or respond to redox reactions (e.g., cysteine oxidation, Fe-S cluster oxidation). Here, we define oxygen sensors as: (i) having a physiologically relevant $\boldsymbol{K_M}$ for O_2, (ii) transducing O_2-dependent reactions into a signaling cascade, and (iii) resulting in adaptive or stress responses in hypoxic conditions. The canonical PHD-HIF-pVHL pathway is conserved across all metazoans and its components have been extensively characterized as master regulators of oxygen homeostasis (Figure 1). Gregg L. Semenza, William G. Kaelin, Jr., and Sir Peter J. Ratcliffe were awarded the Nobel Prize in Physiology or Medicine in 2019 for delineating the biochemical details of this elegant stress response pathway. The three HIF-α isoforms (1α,

2α, and 3α) are basic helix-loop-helix, PAS domain-containing, oxygen labile proteins that form heterodimers with the constitutively expressed HIF-1β (ARNT) [14]. Three PHD proteins (PHD 1,2,3), which are also known as egg-laying defective nine (EglN 2, 1, and 3, respectively) isoenzymes, regulate HIF-α abundance via prolyl hydroxylation [15–17]. Of these, PHD2 is the main oxygen sensor and has the lowest O_2 affinity. Under normoxic conditions, HIF-α undergoes oxygen-dependent hydroxylation on two highly conserved prolyl residues. This hydroxylated form of HIF is recognized by the E3 ligase and tumor suppressor protein, pVHL, which marks the protein for degradation [18,19]. Factor inhibiting HIF (FIH-1) is an additional regulator that serves as a fine-tuner of the HIF response. More specifically, FIH-1 impairs HIF-1 α transcriptional activity by hydroxylating the C terminal transactivation domain of HIF-1α, thus inhibiting its interaction with its transcriptional coactivators, p300 and CREP binding protein (CBP) [20–22]. For comprehensive reviews of the PHD-HIF pathway, refer to [23–25].

Recently, researchers have discovered several additional oxygen-sensing pathways that appear to be HIF-independent. As mentioned above, there are 60+ enzymes that belong to the same enzyme family as PHDs: the -ketoglutarate-dependent dioxygenases. Of these, several histone demethylase enzymes have been shown to sense oxygen and induce changes in histone methylation, thereby affecting gene expression. KDM5A and KDM6A are O_2-sensitive Jumonji C domain histone lysine demethylases that directly control chromatin and cell fate by regulating histone methylation homeostasis [26,27]. Other members of this family are also likely to be oxygen sensors that coordinate cellular adaptations to hypoxia.

Cysteamine dioxygenase (ADO) is a cysteine dioxygenase that transduces responses to hypoxia in both animals and plants via an O_2-dependent pathway for protein degradation [28]. More specifically, in normoxia, an O_2-dependent modification of an N terminal cysteine residue triggers degradation of a subset of proteins. In *Arabidopsis thaliana*, a conserved N terminal amino acid sequence of the ethylene response factor transcription factor, RAP2.12, can undergo post-translational modification in response to oxygen; in hypoxic conditions, RAP2.12 translocates to the nucleus and activates anaerobic gene expression. In normoxia, this transcription factor is degraded via the N-end rule pathway [29]. In this manner, hypoxia can be sensed on a shorter timescale, directly affecting the protein stability of targets. This oxygen-sensing pathway may serve as a bridge to HIF-dependent adaptations that require an orchestrated transcriptional response over a longer timescale (Figure 1).

Lower organisms that lack PHD-HIF enzymes have other unique methods of sensing and adapting to hypoxia. The gram-negative nitrogen-fixing bacterium, *Rhizobium meliloti*, utilizes a two-component system oxygen sensor, FixL (sensor kinase)/FixJ (transcriptional activator), to control expression of nitrogen fixation genes, *nifA and fixK*, in response to hypoxia via a heme-binding region [30,31]. *Escherichia coli* can sense oxygen levels using the Aer redox flavoprotein, enabling migration towards or away from oxygen gradients [32]. This behavior allows *E. coli* to respond to changes in PO_2 and optimize energy utilization [33]. The fission yeast, *Schizosaccharomyces pombe,* uses homologs of the sterol regulatory SREBP pathway, mga2 (functionally analogous to SREBP-1) and sre1 (SREBP-2), to

stimulate transcription of sterol synthesis genes and other O_2-dependent enzymes that are required for anaerobic growth (Figure 1) [34–36].

Whole-Body Oxygen Sensors

In addition to cellular oxygen sensing, there are whole-body mechanisms of oxygen sensing and adaptation. A few notable examples exist during developmental transition from the hypoxic womb to the relatively O_2-rich atmosphere after birth. Placental trophoblasts are cells that provide nutrients to the early embryo and first-trimester placenta, which is characterized by cellular hypoxia (PO_2 <20 mmHg). In the second trimester, PO_2 levels rise, driving trophoblast differentiation and placental maturation [37]. As another example, fetal blood circulation bypasses the nonfunctional pulmonary circulation via the foramen ovale and the ductus arteriosus [38]. Upon the first few breaths of the newborn, PO_2 rapidly rises and pulmonary vascular resistance decreases, leading to the anatomical closure of the ductus. Failure of this O_2-dependent closure can lead to pulmonary hypertension (PH).

Postdevelopment, mammals can acutely sense and adapt to oxygen levels, largely via cardiorespiratory responses. The carotid body is a neural crest-derived organ located at the bifurcation of the common carotid artery that senses arterial blood O_2 tension and lactate by type I (glomus) cells and acts as the principal arterial chemoreceptor. In hypoxia, hyperventilation is triggered via inhibition of O_2-sensitive K+ channels in glomus cells and subsequent afferent nerve activation to the brainstem respiratory center [39,40]. Hypoxia-induced hyperventilation increases the alveolar ventilation rate, thereby causing respiratory alkalosis and a leftward shift of the hemoglobin saturation curve. Additional hypoxia sensors include intrapulmonary neuroepithelial bodies (NEB), which respond to changes in airway oxygenation. NEB are composed of innervated clusters of cells that regulate NADPH oxidase-O_2 sensitive K+ channels and downstream intracellular signaling pathways in response to hypoxia [41]. It is likely that additional tissues sense and respond to O_2. Future work is needed to discover additional oxygen sensors that integrate the cellular and whole-body oxygen-sensing mechanisms.

Cellular Oxygen Adaptations

Hypoxia-induced HIF activity initiates a robust transcriptional program of more than 200 genes. Broadly, many of these adaptations are aimed at either increasing oxygen delivery or decreasing oxygen consumption, in order to meet metabolic demands and normalize local PO_2. For example, HIF induction triggers erythropoiesis [erythropoietin (EPO)] and iron homeostasis [e.g., transferrin (TF)] to increase circulating red blood cell (RBC) levels [42,43]. Additional adaptations are aimed at shifting carbon flux from oxidative phosphorylation to anaerobic glycolysis (e.g., induction of nearly all glycolytic enzymes, glucose transporters, and lactate transporters). Hypoxia results in phosphorylation and inactivation of pyruvate dehydrogenase (via HIF-dependent upregulation of PDK1), to downregulate glucose-derived oxidative phosphorylation and tricarboxylic acid (TCA) cycle flux [44]. Hypoxia-induced reductive carboxylation is a process by which glutamine-derived carbons are used to run the TCA cycle in reverse, in order to generate citrate for *de novo* fatty acid synthesis [45,46]. In *Caenorhabditis elegans*, hypoxia leads to H_2S accumulation

and promotes interaction of PHD and CYSL-1, a member of the cysteine synthase/sulfhydrylase gene family, thus stabilizing HIF-1 transcriptional activity [47]. Additionally, several isoform/subunit switches have been reported in the electron transport chain that regulate more efficient electron flux during hypoxia, including the HIF-dependent induction of NDUFA4L2 and COX4I2 subunits [48,49]. Together, such adaptations redirect fuel sources for biosynthetic and energy-producing reactions, in a manner that minimizes dependence on the O_2-dependent electron transport chain (Figure 2) [50].

Additional cellular adaptations are HIF-independent. These include chromatin remodeling, epigenetic changes (TETs and DNA methylation) [51], miRNA expression (also known as 'hypoxamirs') [52,53], post-translational processes (e.g., cysteine thiol redox status) [54], and induction of additional stress responses (e.g., NF-κβ, CEBP, and AP-1 stress responses) [55]. For example, hypoxia can cause a secondary ATP crisis, resulting in a high AMP/ATP ratio. This is sensed by AMP-activated protein kinase (AMPK), which results in mammalian target of rapamycin (mTOR) inhibition and downregulation of energy-intensive processes, such as translation and lipid synthesis, and upregulation of autophagy. Hypoxia also inhibits mTOR1 independently of AMPK by induction of the HIF-1α target genes, DNA damage response 1 and 2 (*REDD1, REDD2*) [56]. Lipid homeostasis is also tightly regulated by hypoxia since sterol synthesis and fatty acid desaturation are oxygen-requiring processes (e.g., formation of monounsaturated fatty acids by SCD1) and are important to maintain proper cell integrity and membrane fluidity in hypoxia [57] Figure 2). We recently found that genes involved in lipid metabolism (e.g., *AMFR, SREBF1*), peroxisomal biogenesis (e.g., *PEX10, ACSL4*), and ether phospholipid biosynthesis (e.g., *FAR1, AGPS*) can be selectively essential in low oxygen, likely in part to protect against saturated fatty acid toxicity in hypoxia [113]. Focused discussions of cellular adaptations to hypoxia are reviewed elsewhere [58].

Whole-Body Oxygen Adaptations

Several non-human animals are particularly tolerant of hypoxic environments. We highlight a few of these organisms that have developed unique adaptive mechanisms of extreme hypoxia tolerance (Figure 3). The naked mole rat (*Heterocephalus glaber*) lives in subterranean, unventilated environments with extremely low O_2 levels [59]. It is also the longest-living rodent with a similar longevity quotient to humans [60]. It has several interesting adaptations, such as unique O_2-binding globins in the brain, enhanced ammonia detoxication, and expression of genes associated with DNA damage repair that allow it to be relatively insensitive to low oxygen levels [61]. More recently, it was found to uptake large amounts of fructose via increased expression of ketohexokinase and the fructose transporter GLUT5 as an alternative entry point into glycolysis [62]. High-altitude birds (e.g., *Gyps rueppelli*) have four hemoglobins with a wide range of O_2 affinities, permitting oxygen loading along a broad spectrum of O_2 tensions [63]. Turtles (e.g., *Chrysemys picta*) use their mineralized shells to buffer against increased lactate levels from hypoxic tissues by releasing calcium and magnesium carbonates [64]. Diving mammals, such as Weddell seals (*Leptonychotes weddellii*), are able to acutely increase tissue oxygen delivery by triggering contractions of their spleen during deep dives, which release stored RBCs into circulation [65]. In these animals, the circulating hemoglobin concentration can increase 25–60%

during dives due to splenic contraction. Interestingly, human elite apneic-divers (e.g., professional Korean diving women) are able to adapt to prolonged breath-holds by splenic contractions during deep dives to transiently increase circulating RBCs [66,67]. It is likely that future research will uncover even more creative adaptations that exist in nature across extreme organisms. Perhaps, remnants of these adaptations exist in humans or can serve as inspiration for future therapeutic approaches for states of ischemia.

Human whole-body hypoxia adaptions lead to an increase of oxygen supply and decrease of oxygen demand at the tissue level (Figure 3). Acute physiologic changes that augment oxygen supply include hyperventilation mediated by the chemosensory cells in the carotid body, systemic vasodilation, and increased cardiac output. The pulmonary arteries are unique in their ability to vasoconstrict in response to hypoxia, allowing blood to be shunted away from hypoxic alveoli and subsequently correcting ventilation-perfusion mismatch. More chronic adaptations include erythropoiesis mediated by HIF-2α stabilization, angiogenesis, suppression of whole-body O_2 consumption, decreased food intake, and decreased body temperature [68,69]. Chronic hypoxia also increases 2,3-diphosphoglycerate, which is a glycolytic intermediate that shifts the oxygen-hemoglobin dissociation curve to the right and improves oxygen off-loading in peripheral tissues at lower O_2 tensions [70].

Toxicity of Low Oxygen

Hypoxia can have deleterious effects on the acute, chronic, and intermittent timescales. Acute, severe hypoxia exposure, which occurs when healthy individuals ascend rapidly to high altitudes (>2500 m), can cause acute mountain sickness, high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE) (Table 1). In general, these adverse effects subside with acclimatization and are reversed upon return to normoxia [71]. The metabolic and physiologic susceptibility risk factors for HAPE and HACE are unknown.

Ischemia, defined as the lack of oxygen coupled with nutrient deprivation (e.g., glucose, glutamine, fatty acids) from restriction of blood flow, is characteristic of myocardial infarction and stroke, which are leading causes of morbidity and mortality worldwide [72]. While the upstream pathology may differ, organ dysfunction and tissue necrosis ultimately result from a lack of oxygen and nutrients. The critical thresholds and responses to ischemia, including tissue metabolic rate, fuel use, oxygen extraction, inflammation, and antioxidant responses, in different organs need to be better studied to elucidate mechanisms of intrinsic ischemia tolerability.

Chronic hypoxia is linked to both systemic and tissue-level adaptation and pathology. Approximately 140 million people live at 2500 meters above sea level or higher. At moderate altitudes, children are born significantly underweight and at extreme altitudes, childbirth is no longer possible [73,74]. The causes of developmental issues and infertility are unknown. The adaptive effects of chronic hypoxia can also result in PH from endothelial HIF-2α upregulation and right-sided heart failure [75,76]. A proportion of individuals living at high altitude suffer from chronic mountain sickness, which is a disease secondary to polycythemia and hypoxia [77]. However, many individuals are disease-free and others (e.g.,

Tibetan high-dwellers), have acquired genetic adaptations in the *HIF2a* (*EPAS1*) and the *PHD2* genes, thereby decreasing erythrocytosis and PH [78,79].

At the tissue level, tissue-specific genetic activation of the HIF transcriptional response can have pathologic effects (Table 1). HIF activation and hypoxia are not synonymous and artificially activating HIF in normoxia can paradoxically lead to increased oxygen delivery, thereby potentially causing tissue hyperoxia. Furthermore, chronic hypoxia in solid tumors and the tumor microenvironment has been linked to aberrant angiogenic signaling, tumor proliferation and survival, resistance to chemotherapy, increased metastatic potential, and poor prognosis [80,81]. The majority of cases of clear cell renal cell carcinoma (ccRCC), the most common type of kidney cancer, are caused by *VHL* gene inactivation, leading to aberrant HIF accumulation. Recently, studies have shown that two pVHL targets, the transcription factors zinc fingers and homeoboxes 2 (ZHX2) and Scm-like with four malignant brain tumor domains 1 (SFMBT1), contribute to ccRCC carcinogenesis by promoting NF-κβ activation and sphingosine kinase 1 transcription, respectively [82,83]. Both of these transcription factors undergo prolyl hydroxylation (SFMBT1 by PHD2), demonstrating that the pro-oncogenic phenotype driven by solid tumor hypoxia is regulated by both HIF-dependent and HIF-independent downstream pathways. For recent reviews on hypoxia and tumor metabolism, refer to [84–86].

Toxicity of High Oxygen

At the other extreme, hyperoxia (>21% O_2) has harmful effects at the cellular, tissue, and whole-body levels (Table 2). The mechanisms of hyperoxic injury are not completely understood; increased O_2 levels cause superoxide radical formation, followed by dismutation to H_2O_2 by superoxide dismutase. In the presence of Fe^{2+}, H_2O_2 is catalyzed into the highly reactive hydroxyl free radical via the Fenton reaction and serves as a membrane-permeable signaling molecule. Oxidative stress can lead to lipid peroxidation of cellular membranes, protein dysfunction, and inactivation of critical cellular enzymes, all of which contribute to cellular dysfunction, autophagy, and cell death [87,88]. However, it is largely unknown how cells adapt to hyperoxia and the pathways affected by excess oxygen independent of signaling related to reactive oxygen species (ROS).

In premature infants with immature lung development, supplemental oxygen is often delivered to support normal gas exchange. However, excess oxygen can cause retinopathy of prematurity, a pathological vasoproliferative disorder of the retina that can lead to blindness [89]. In adults, hyperoxia causes vasoconstriction, reduction in coronary blood flow, and decreased cardiac output. Chronic hyperoxia can cause adverse effects involving the CNS (e.g., altered mental status, seizures), eyes (e.g., cataracts), and lungs (e.g., pulmonary interstitial fibrosis) (Table 2). Relative hyperoxia from oxygen influx in the setting of restoration of blood flow after ischemia, known as ischemia/reperfusion (I/R), causes cell death and tissue injury through various mechanisms, including generation of ROS, lactate, and succinate accumulation, release of proinflammatory eicosanoids and cytokines, and dysregulation of nitric oxide signaling (Table 2).

Supplemental oxygen is one of the most common therapies provided in hospitalized patients, often without clear evidence of hypoxia or in excess of what is needed by the human body [i.e., arterial partial pressure of oxygen (P_aO_2) >100 mmHg] [90]. There is increasing clinical evidence that this therapy is not benign. In critically ill patients, excess oxygen is associated with increased intensive care unit (ICU) mortality, decrease in ventilator-free days, and neurologic disability in patients with traumatic brain injury and following cardiac resuscitation (Table 2). More rigorous prospective clinical trials are needed to delineate the toxicities associated with hyperoxia.

Hypoxia as a Therapy

The imbalance between oxygen supply and demand, coupled with organ-specific set points for (low or high) oxygen tolerance, results in negative effects from hypoxia and hyperoxia, as described. Understanding the pathologies of low or high oxygen provides us with a unique therapeutic opportunity. There is emerging preclinical evidence that oxygen can be modulated for therapeutic benefit and that hypoxia can ameliorate certain disease phenotypes, decrease the risk of cardiovascular disease, and even significantly improve survival in rare genetic disorders such as mitochondrial disease.

Hypoxia and Aging

The potential benefits of hypoxia are apparent across species from yeast to *C. elegans* to humans. In *C. elegans*, the hypoxia response via loss of VHL-1 increases lifespan, enhances resistance to β-amyloid toxicity, and improves protein homeostasis [91–93]. Hypoxia improves replicative lifespan in yeast and delays senescence in patient fibroblasts [94,95]. Indeed, almost all the hallmarks of aging are known to be ameliorated by low oxygen in cell culture settings: stem cell exhaustion, senescence, telomere attrition, and mitochondrial dysfunction [96–99]. The *in vivo* and organismal relevance of hypoxia on aging and age-associated pathologies remains to be determined.

Moreover, there is epidemiological data suggesting that systemic hypoxia might improve longevity in humans, as well. For example, the number of centenarians is significantly higher in Tibetans who have lived at altitude for centuries compared with the Han Chinese who ascended in more recent times [100]. The mechanism of improved longevity is unclear and might be secondary to a range of factors, including lower temperature, decreased basal metabolic rates, and adaptations of aging-associated genes in hypoxia. Furthermore, there is extensive epidemiologic data that demonstrate decreased cardiovascular disease and age-related risk factors, including diabetes, hypertension, ischemic heart disease, and obesity, in populations that live at or have been adapted to high altitude [101–104]. Interestingly, patients with cyanotic heart disease (e.g., tetralogy of Fallot) also seem to be protected from atherosclerosis and dyslipidemia [105,106]. More rigorous epidemiological studies will be needed to determine correlations between high altitude, chronic hypoxia, and disease incidence.

Hypoxia and Mitochondrial Disease

We have several lines of evidence that support using hypoxia or the hypoxia response as a potential therapeutic strategy for specific metabolic disorders. Recently, we showed that hypoxia can prevent and even reverse disease pathologies associated with mitochondrial dysfunction in rodent models of disease. In a mouse model of the pediatric mitochondrial disease, Leigh syndrome, exposure to chronic normobaric hypoxia (11% O_2) rescued body weight, behavior, and neuropathology [107]. Moreover, the lifespan of this complex 1 disease mouse model was extended by fivefold. Amazingly, hypoxia exposure was even able to reverse neuropathology at a very late stage of neurologic disease. These benefits were not observed with a more conservative degree of continuous normobaric hypoxia (17% O_2) or **intermittent hypoxia** and quickly reversed upon return to normoxia [108].

While cellular studies suggested that HIF activation could rescue the effects of electron transport chain deficiency, this did not translate *in vivo.* Though hypoxia exposure itself rescued disease in the Leigh syndrome mouse model, activating the HIF response was insufficient to rescue disease [109]. Instead, it appears that a broken electron transport chain leads to decreased tissue oxygen consumption, thereby causing brain hyperoxia. Indeed, others have previously observed decreased oxygen extraction and venous hyperoxia in mitochondrial disease patients upon exercise [110]. Exactly how elevated oxygen leads to tissue damage remains to be determined. We believe we have identified some of the first metabolic disorders of ‘excess oxygen’. It will be interesting to characterize which additional genetic disorders result from tissue hyperoxia.

And so the question remains: Will this therapeutic approach generalize to additional mitochondrial disorders, unrelated metabolic disorders, and common conditions? More recently, researchers showed that an additional genetic model of Leigh syndrome caused by a mutation in the complex 2 subunit succinate dehydrogenase (SDHC) could be rescued by hypoxia [111]. Additionally, hypoxia delayed symptoms in a disease model of Friederich’s ataxia [112]. In order to prioritize additional diseases for hypoxia therapy, we recently performed a genome-wide CRISPR knockout (KO) screen comparing cell growth and survival at 21% O_2 versus 1% O_2 [113]. This revealed over 75 monogenic disorders whose gene KO could be rescued by hypoxia. Potential disease candidates for hypoxia therapy include pyruvate dehydrogenase (PDH) deficiency, sideroblastic anemia (GLRX5), autosomal dominant optic atrophy (OPA1), and monogenic forms of Parkinson’s disease (HTRA2), among others. Future preclinical work is needed to determine whether these cellular findings extend to *in vivo* models of disease. In addition to mitochondrial diseases, there are preclinical studies that suggest therapeutic benefit of hypoxia or the hypoxia response in fatty liver disease [114], insulin sensitivity [115], obesity [116,117], kidney injury [118,119], chemotherapy-related toxicities [120], multiple sclerosis [121], colitis [122], and transplant allograft vasculopathy [123,124].

Ischemic Preconditioning

Due to potential long-term complications associated with chronic hypoxia, shorter-duration therapy could be safer in specific contexts. Local and remote ischemic preconditioning

(RIPC) are two techniques that utilize hypoxia to protect against ischemic injury. Numerous preclinical studies demonstrate that ischemic preconditioning can attenuate subsequent ischemic injury in animal models of focal brain ischemia [125], ischemic and fibrotic kidney injury [126,127], neurodegenerative diseases (e.g., Parkinson's disease) [128], and myocardial infarction [129]. Patients who experience stable angina prior to myocardial infarction have smaller infarctions and fewer cardiac complications [130]. This protection is partially conferred by hypoxia-induced angiogenesis and arteriogenesis, with development of collateral arteries [131].

In RIPC, brief episodes of hypoxia to an organ, for example, the skeletal muscle, can provide ischemic protection to a distant organ (e.g., heart from ischemia-reperfusion injury). The mechanisms are not fully understood, though an increase of protective secreted factors, including interleukin (IL)-10 and kynurenic acid, and reduction of proinflammatory cytokines, such as IL-6, have been implicated [132–135]. Clinical applications of RIPC in patients undergoing elective coronary artery bypass grafting surgery have largely been negative, possibly due to interaction of protective factors with hepatically metabolized anesthetic agents [136,137]. Future trials should assess the role of RIPC in acute and chronic conditions (e.g., stroke, myocardial infarction, neurodegenerative disease).

Regenerative Medicine

Most stem cells exist in hypoxic niches within the body [138]. Severe hypoxia has also been shown to cause proliferation of fetal cardiomyocytes and allow adult mammalian cardiomyocytes to exit cell cycle arrest [139,140]. Hypoxic cardiomyocytes display characteristics of proliferative neonatal cardiomyocytes and are less sensitive to oxidative DNA damage. In a preclinical adult mouse model, hypoxia can induce heart regeneration and decrease infarct size after I/R injury through mechanisms that are not fully understood [141]. PHD2 inactivation in skeletal progenitor cells supports postimplantation bone repair and survival by preserving redox balance via HIF-1α mediated conversion of glutamine to glutathione [142]. The mechanisms by which hypoxia activates stem cell niches or quiescent cells need further investigation and can potentially be widely applicable to human diseases related to aging, senescence, and tissue injury.

HIF Response as a Therapy

Recent drug developments have taken advantage of the HIF response for therapeutic benefit [143]. PHD inhibitors, which partially stabilize HIF levels and upregulate expression of HIF target genes, have shown promise in patients with chronic kidney disease (CKD)-related anemia (Figure 4). EPO is a glycoprotein hormone and specific HIF-2α target that is produced by renal interstitial fibroblasts. In patients with CKD, treatment with the PHD inhibitor, FG-4592, induces EPO as a therapeutic strategy for anemia and also decreases cholesterol levels through unclear mechanisms [144,145]. In a preclinical mouse model, PHD inhibition increases hepatic cholesterol elimination and ceramide catabolism [146]. It remains unknown what other diseases could be treated with PHD inhibition.

Furthermore, the downregulation of the HIF response using selective and orally active HIF-1 and HIF-2 antagonists has demonstrated therapeutic potential in preclinical studies and human Phase I and II clinical trials for various neoplasms (Figure 4). A subset of patients with ccRCC, which is driven by pVHL inactivation and constitutive overexpression of HIF-2α have shown clinical benefit with oral HIF-2α inhibitors. VEGF inhibitors, including VEGF ligand antibodies and tyrosine kinase inhibitors, are FDA approved systemic therapies for advanced renal cell carcinoma [147]. Preclinical models of PHD inhibition or HIF activation suggest therapeutic potential for neuroprotection following brain ischemia [148], allograft dysfunction [149,150], chemotherapy-related adverse effects [120], cardiac dysfunction [151], inflammatory bowel diseases [122]. Alternatively, HIF inhibition could be a therapeutic strategy for chronic hypoxia-induced WHO group III PH [152,153] and certain malignancies characterized by abnormal hypoxia signaling [154]. FIH inhibitors might be helpful for amelioration of metabolic syndromes, including diabetes and obesity [155]. Future research should further delineate which diseases can be treated by targeted manipulation of the hypoxia response, such as HIF stabilization, versus hypoxia itself, which involves numerous interrelated regulatory pathways.

Implementation of Hypoxia Therapy

Hypobaric hypoxia can be achieved by living at altitude or by gradual reduction of atmospheric pressure in a hypobaric chamber. As a reference, there is 15% O_2 at 2400 meters above sea level (Aspen, CO, USA), 14% O_2 at 3400 meters (Cusco, Peru), and 7% O_2 at 8840 meters (Mount Everest). Commercially available at-home systems mimic altitude training by decreasing the oxygen percentage of air using pressure swing adsorption. Hypoxic air can be created by mixing nitrogen and oxygen gases at different ratios and it is feasible to make this system portable, comparable with portable oxygen tanks with delivery via nasal cannula. We can also imagine small-molecule approaches to causing tissue hypoxia. For example, left shifters of the oxyhemoglobin dissociation curve are already being developed for sickle cell anemia and can cause tissue hypoxia when given at high doses (Figure 4) [156,157].

The hypoxia response can also be targeted by medications or small-molecule inhibitors, such as PHD inhibitors and pVHL inhibitors (Figure 4). Drugs that target the HIF pathway have already shown great potential for treating anemia and renal cell carcinoma and future drug development should aim to discover druggable HIF and non-HIF targets involving the hypoxia response [83]. Prior to implementation of hypoxia therapy, future studies will need to determine which organs and diseases are most amenable to hypoxia therapy, as well as the risks of chronic use that could lead to prohibitive treatment-related adverse events or treatment resistance. Therefore, additional mechanistic studies might allow us to develop more specific and targeted small-molecule therapies.

Concluding Remarks

Oxygen is both vital and toxic to life. Hypoxia is a double-edged sword that can have detrimental and beneficial effects at the cellular, tissue, and systemic levels. Every tissue, disease state, and individual has an optimal oxygen set-point. A mismatch in oxygen supply

and demand disrupts this set-point and can result in pathology. Several important questions remain unanswered about the mechanisms of how hypoxia and the hypoxia response can treat certain diseases and how to target the hypoxia pathway in select disease states. For hypoxia therapy, the degree and duration of hypoxia will need to be carefully determined to maximize the benefit to risk ratio. On the opposite end of the spectrum, much remains unknown about cellular responses to hyperoxia. There is mounting evidence that excess oxygen is toxic at the cellular and systemic levels for reasons that are not fully understood. Oxygen delivery should be considered a therapy that should be administered when indicated, titrated to meet tissue oxygen demands, and discontinued when no longer required to minimize toxic systemic side effects. Importantly, supplemental oxygen should be avoided unless absolutely indicated in patients with mitochondrial disease, with evidence indicating that pathology and disease progression are related to tissue and venous hyperoxia and that normalization of hyperoxia can have dramatic phenotypic improvements, including prolongation of life. Future research should aim to unravel how cells and tissues sense, respond, and adapt to hyperoxia, and the mechanisms by which certain organs are more tolerant of hyperoxia than others. The horizon of oxygen research looks bright as it may unlock clues to treatment for neurological and cardiovascular disease, mitochondrial dysfunction, proteotoxic conditions, dopaminergic neurodegeneration, malignancies driven by abnormal hypoxia signaling, and aging. We have come a long way since the days of hot-air balloon rides and high-altitude expeditions. Yet, boundless unchartered territory remains to explore the highs and lows of oxygen metabolism (see Outstanding Questions).

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Glossary

Hypoxia	in the atmosphere, defined as less than 21% oxygen. Hypobaric hypoxia results from decreased barometric pressure (e.g., high altitude). Normobaric hypoxia results from decreased inspired fraction of oxygen (F_iO_2).
Intermittent hypoxia	alternating episodes of normoxia and hypoxia, leading to cyclical bursts of deoxygenation and reoxygenation. Intermittent hypoxia is a feature of obstructive sleep apnea and central sleep apnea.
Ischemia	severe hypoxia or anoxia (complete lack of oxygen), coupled with reduced availability of nutrients, including glucose, fatty acids, amino acids, and vitamins. In tissues, ischemia results from inadequate blood flow due to arterial blood flow restriction, leading to accumulation of metabolic waste products, cellular dysfunction, and tissue damage.

K_M	the Michaelis constant value at which the substrate concentration permits a reaction rate that is half of V_{max}, the maximum rate ofan enzymatic reaction when saturated by the substrate. Enzymes with high K_M have low affinity for their substrates. As an example, PHD proteins have low oxygen affinities (high K_M), enabling them to sense oxygen in physiological ranges.
Oxygen tension	the partial pressure of oxygen (PO_2). The partial pressure of oxygen at sea level is 21% of the standard atmospheric pressure of 760 mmHg, equivalent to 160 mmHg. At sea level, Earth's atmosphere is composed of 78% nitrogen, 21% oxygen, 0.9% argon, 0.03% carbon dioxide, and trace amounts of other gases.

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Outstanding Questions

Which additional α-ketoglutarate-dependent dioxygenases are able to sense physiological changes in oxygen and coordinate stress responses under hypoxic conditions?

What are novel cellular adaptations to hypoxia that are independent of the transcriptional response regulated by the PHD-HIF-pVHL pathway?

Which oxygen-dependent reactions fail during states of ischemia and lead to adaptive metabolic changes that improve cell survival?

Are there metabolic adaptations in animals tolerant of extreme hypoxia that are widely evolutionarily conserved and applicable to human disease?

Which diseases can be treated by modulating oxygen tensions or the related stress responses, such as HIF stabilization or HIF inhibition?

How do cells and organisms sense and adapt to hyperoxia? Are there human diseases that are defined by tissue hyperoxia that can be corrected by normalization of tissue pO_2 by hypoxia?

Highlights

Molecular oxygen is an essential substrate in mammalian metabolism. Imbalances in oxygen levels are associated with a wide range of conditions in human health and disease.

The Jumonji C domain histone lysine demethylases, KDM5A and KDM6A, are recently discovered oxygen sensors that regulate histone demethylation and cellular differentiation.

Some animals are tolerant of extreme hypoxia and have developed unique adaptations that might have relevance to oxygen sensing and adaptation in humans.

Hypoxia can have both beneficial and toxic effects depending on the severity and duration of hypoxia, in combination with cell- and tissue-specific metabolic demands.

In a mouse model of pediatric mitochondrial disease, hypoxia itself, but not activation of the hypoxia transcriptional factor (HIF) response, is sufficient to rescue disease. Decreased tissue oxygen consumption and resulting excess oxygen contributes to pathology, which can be reversed with normalization of oxygen levels by hypoxia.

Preclinical and early clinical studies demonstrate that hypoxia or manipulation of the hypoxia response can potentially be used to treat various diseases, including mitochondrial diseases, neurodegenerative and cardiovascular diseases, anemia, and malignancies, among others.

Box 1.

Oxygen-Dependent Reactions

Oxygen is the most used substrate in the human body and is required for several hundred different biochemical reactions. Yet, little is known about which reactions are affected as a function of O_2 tension. Oxygen-dependent enzymes include over 60 different α-ketoglutarate (2-oxoglutarate)-dependent dioxygenases [6]. Such enzymes are obligate steps in a diverse set of pathways, including collagen maturation (e.g., LOX), carnitine synthesis (e.g., TMLHE), histone demethylation (e.g., KDM and JMJ enzymes), DNA methylation (e.g., TET enzymes), protein hydroxylation [e.g., prolyl hydroxylase domain (PHD) hydroxylases], and ribosome modifications (e.g., OGFOD1), to name a few [7–11].

Oxygen is also central to amino acid catabolism and lipid metabolism. For example, tryptophan dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO1) shunt tryptophan towards *de novo* NAD+ synthesis and separately, tryptophan hydroxylase (TPH) produces serotonin from tryptophan. Tyrosine hydroxylase (TH) is O_2-dependent and responsible for the synthesis of catecholamines such as dopamine, epinephrine, and norepinephrine [12]. Additionally, aerobic conditions are needed for fatty acid and sterol metabolism. The cytochrome P450 hydroxylases use molecular oxygen to introduce hydroxyl groups at multiple steps in the mevalonate pathway for steroid and cholesterol synthesis (e.g., Cyp51A). Cholesterol synthesis is a highly O_2-consuming process, requiring 11 molecules of O_2 for every cholesterol molecule in eukaryotes. Furthermore, fatty acid desaturation is O_2-dependent (e.g., SCD1) and is needed to maintain an optimal ratio of saturated to unsaturated fatty acids, thereby regulating cell membrane fluidity and preventing lipotoxicity [13].

And perhaps most well-known is the role of O_2 as the final electron acceptor in the mitochondrial electron transport chain. Electron transport chain dysfunction can have secondary metabolic effects, including a collapse in membrane potential, impaired NADH oxidation, and secondary stress responses. As is evident from this discussion, O_2 enabled a great diversification of biochemistries during the transition from anaerobic to aerobic conditions. In fact, oxygen plays a key role in nearly every aspect of mammalian metabolism. As a result, hundreds of oxygen-dependent reactions can fail during states of **ischemia**. The challenge ahead lies in more comprehensively studying such reactions and related adaptations as a function of PO_2.

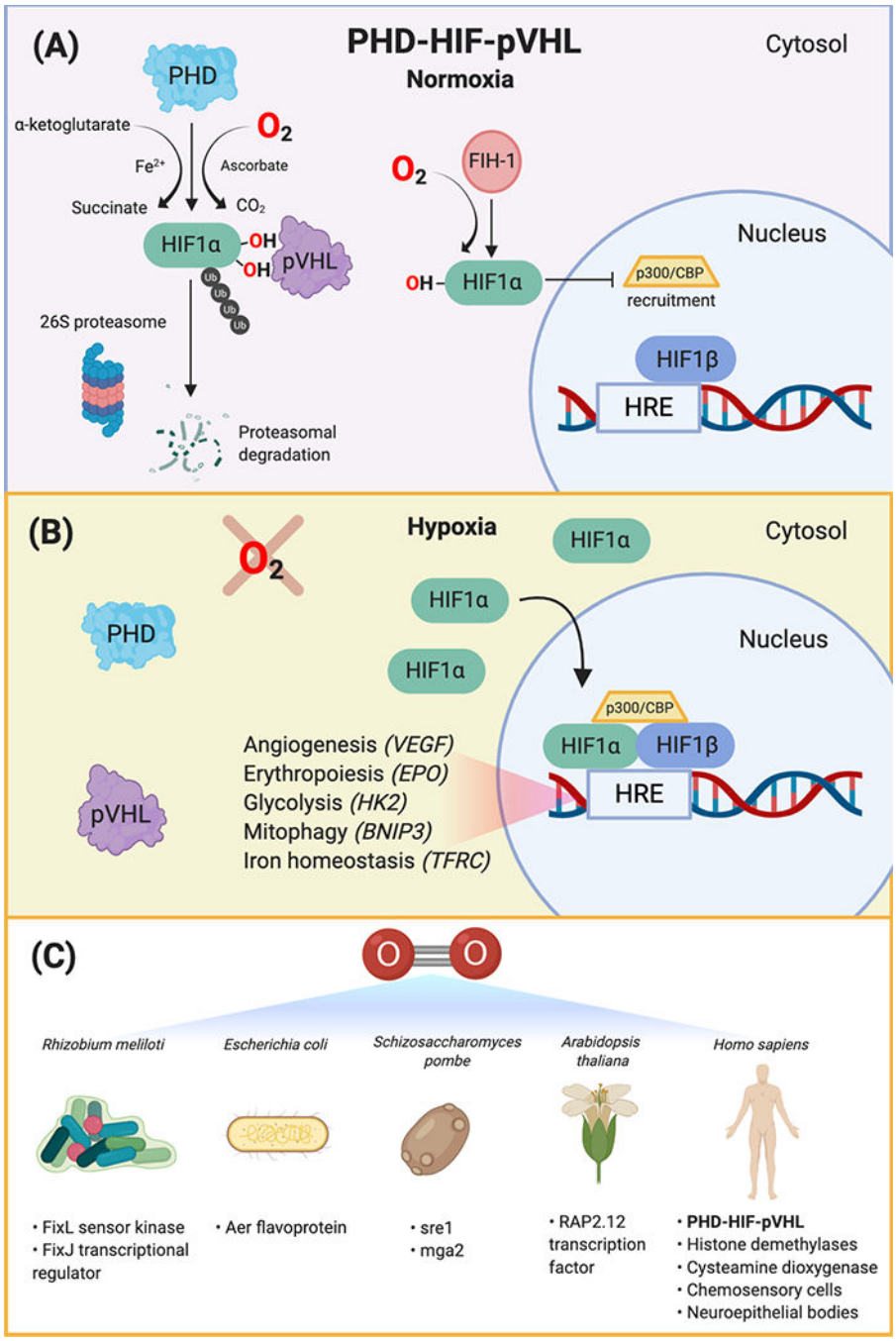

Figure 1. Cellular Oxygen Sensors.

(A)The PHD-HIF-pVHL oxygen sensing pathway is conserved across all metazoans. Under normoxic conditions, PHD proteins hydroxylate the HIF-α transcription factor at two highly-conserved prolyl residues on the oxygen-dependent degradation domain, leading to its recognition by the tumor suppressor, pVHL. pVHL is the recognition component of a ubiquitin E3 ligase complex that polyubiquitylates HIF-α, marking it for proteasomal degradation by the 26S proteasome. Factor inhibiting HIF1 (FIH-1) is an asparagine hydroxylase that hydroxylates HIF in normoxia and prevents recruitment of the transcription

coactivators, p300 and CBP. (B) Under hypoxic conditions, HIF-α is not degraded. HIF-α accumulates in the cytosol and translocates to the nucleus, where it binds to the conserved HRE sequence on DNA, its constitutively active and oxygen-insensitive partner, HIF-1β (ARNT), and the transcription coactivators, p300 and CBP. This complex transcriptionally activates hundreds of genes that allow cells to adapt to hypoxic environments, including *VEGF, EPO, HK2, BNIP3*, and *TFRC*. (C) There are various oxygen sensors across organisms, including Gram-negative bacteria (*Rhizobium meliloti* and *Escherichia coli*), fission yeast (*Schizosaccharomyces pombe*), plants (*Arabidopsis thaliana*), and metazoans (e.g., *Homo sapiens*). These systems, including the FixL sensor kinase and FixJ transcriptional response regulator, Aer flavoprotein, sre1 and mga2 transcriptional regulators, RAP2.12 transcription factor, histone demethylases, chemosensory cells in the carotid body, and intrapulmonary neuroepithelial bodies, transduce oxygen-dependent reactions into a signaling cascade that result in adaptive responses in hypoxic conditions. Abbreviations: BNIP3, BCL2 interacting protein 3; CBP, cyclic-AMP response element binding protein (CREB) binding protein; EPO, erythropoietin; TFRC, transferrin receptor; HIF, hypoxia-inducible factor; HK2, hexokinase-2, HRE, hypoxia response element; PHD, prolyl hydroxylase domain; pVHL, von-Hippel-Lindau tumor suppressor protein; VEGF, vascular endothelial growth factor.

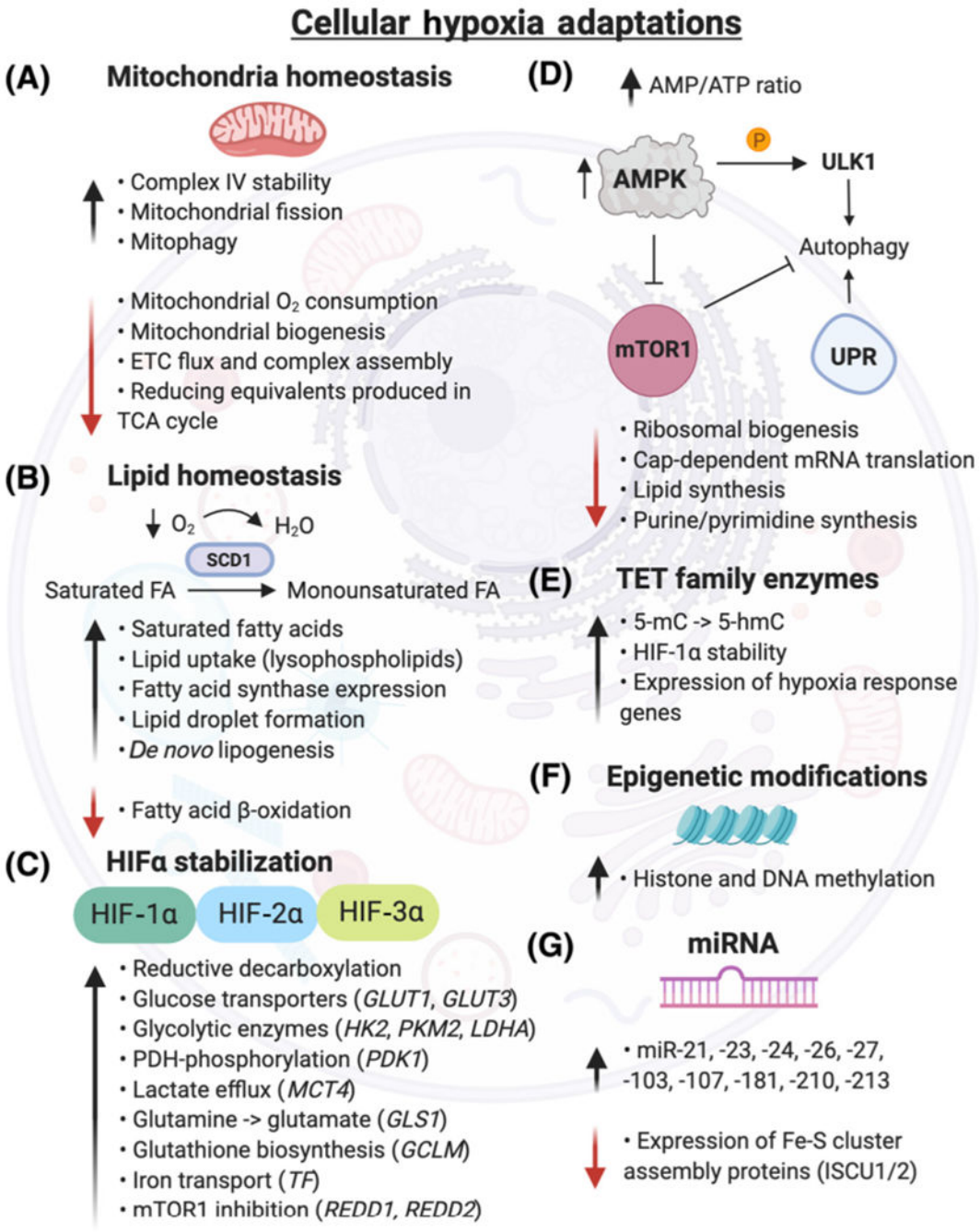

Figure 2. Cellular Hypoxia Adaptations.

(A) Mitochondria adapt to hypoxia by increasing cytochrome c oxidase (complex IV) stability, which facilitates electron transport to O_2. Mitochondria biogenesis, ETC flux, and respiration are downregulated, reducing O_2 consumption and reactive oxygen species production [223]. Hypoxia induces mitochondrial fission by increasing the activity of the E3 ubiquitin ligase, SIAH2, which degrades AKAP121, subsequently increasing Drp1/Fis1 interaction [224]. (B) Under hypoxia, cells become deficient in unsaturated fatty acids by reduced O_2-dependent desaturation of saturated fatty acids by stearoyl-CoA desaturases

(e.g., SCD1). Hypoxic cells increase uptake of lysophospholipids and formation of lipid droplets, which serve as extra supply stores for lipids and help buffer against saturated lipid species [225]. Hypoxia downregulates fatty acid β-oxidation [226]. (C) Gene expression of several HIF targets are highlighted, though hundreds of genes are regulated by HIF stabilization [24]. (D) Hypoxia andthe subsequent energy deficiency (elevated AMP/ATP ratio) inhibit mTOR1 through AMP-activated protein kinase (AMPK). The downstream pathways regulated by mTOR1, including ribosomal and lipid synthesis, are downregulated in hypoxia, while apoptosis is increased. Unc-51-like kinase 1 (ULK1), an autophagy initiation serine/threonine protein kinase, is directly phosphorylated by AMPK in hypoxia, initiating a proautophagy signal [227]. Severe hypoxia (<0.01% O_2) promotes the transcriptional response of essential autophagy genes and activates the UPR in a HIF-independent manner [228]. (E) Ten-eleven translocation methylcytosine dioxygenases (TET) catalyze the conversion of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), increasing DNA methylation and gene expression of hypoxia responsive genes [8]. (F) Hypoxia induces changes in histone and DNA methylation via KDM and TET enzymes, respectively, which regulate chromatin and methylation homeostasis. (G) Numerous microRNAs are induced by hypoxia. miR-210 is increased in a HIF-1α-dependent manner and represses iron-sulfur cluster assembly proteins (ISCU1/2), resulting in decreased integrity of Fe-S cluster proteins [53]. Abbreviations: ETC, electron transport chain; FA, fatty acid; GCLM, glutamate-cysteine ligase modifier subunit; GLS1, glutaminase; GLUT, glucose transporter; HIF, hypoxia-inducible factor; HK2, hexokinase 2; KDM, lysine demethylase; LDHA, lactate dehydrogenase A; MCT4, monocarboxylate transporter 4; mTOR, mammalian target of rapamycin; PDK1, pyruvate dehydrogenase kinase; PKM2, pyruvate kinase muscle isozyme 2; REDD1/2, DNA damage response; TCA, tricarboxylic acid cycle; TF, transferrin; UPR, unfolded protein response.

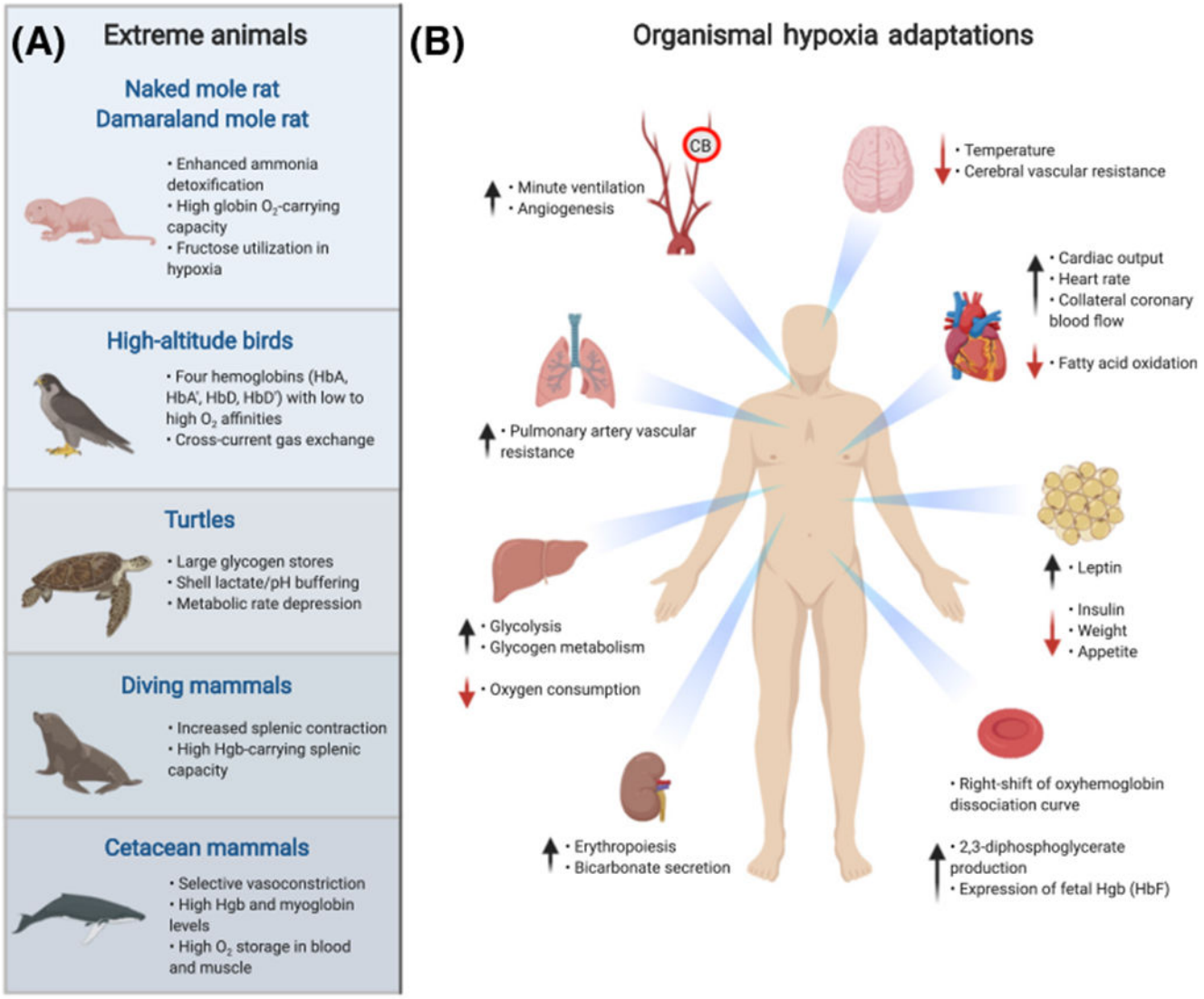

Figure 3. Organismal Hypoxia Adaptations in Extreme Animals and *Homo sapiens*.

(A) The naked mole rat (*Heterocephalus glaber*), high-altitude birds (e.g., *Gyps rueppelli*), turtles (e.g., *Chrysemys picta*), diving mammals (e.g., *Leptonychotes weddellii*), and cetacean mammals (e.g., *Tursiops truncatus*) [229], have developed unique metabolic and physiologic adaptations to extreme hypoxic environments. (B) Hypoxia induces whole-body physiologic and tissue metabolic adaptations in *Homo sapiens* involving the brain, heart, adipose tissue, kidney, liver, pulmonary and systemic vasculature, and carotid body (CB). Hypoxia induces generalized vasodilation with the exception of HIF-2α-mediated vasoconstriction of pulmonary arteries, leading to pulmonary hypertension. Metabolic changes include increased circulating leptin levels, decreased insulin levels, and increased glycogen metabolism [230]. Cardiac adaptations include increased heart rate, cardiac output, and coronary artery blood flow, and decreased fatty acid oxidation rate [231]. Chemosensory type I glomus cells in the CB sense hypoxia and increase the ventilation rate via activation of action potentials in the glossopharyngeal nerve that excite central chemoreceptors in the

brain. Kidneys adapt by increasing bicarbonate secretion and erythropoiesis via HIF-2α-dependent induction of erythropoietin, augmenting oxygen-carrying capacity to tissues. The oxyhemoglobin dissociation curve shifts to the right, facilitating unloading of oxygen into tissues. Hypoxia promotes erythroid expansion of mature red blood cell (RBC) precursors containing fetal hemoglobin (HbF) [232]. Abbreviation: Hgb, hemoglobin.

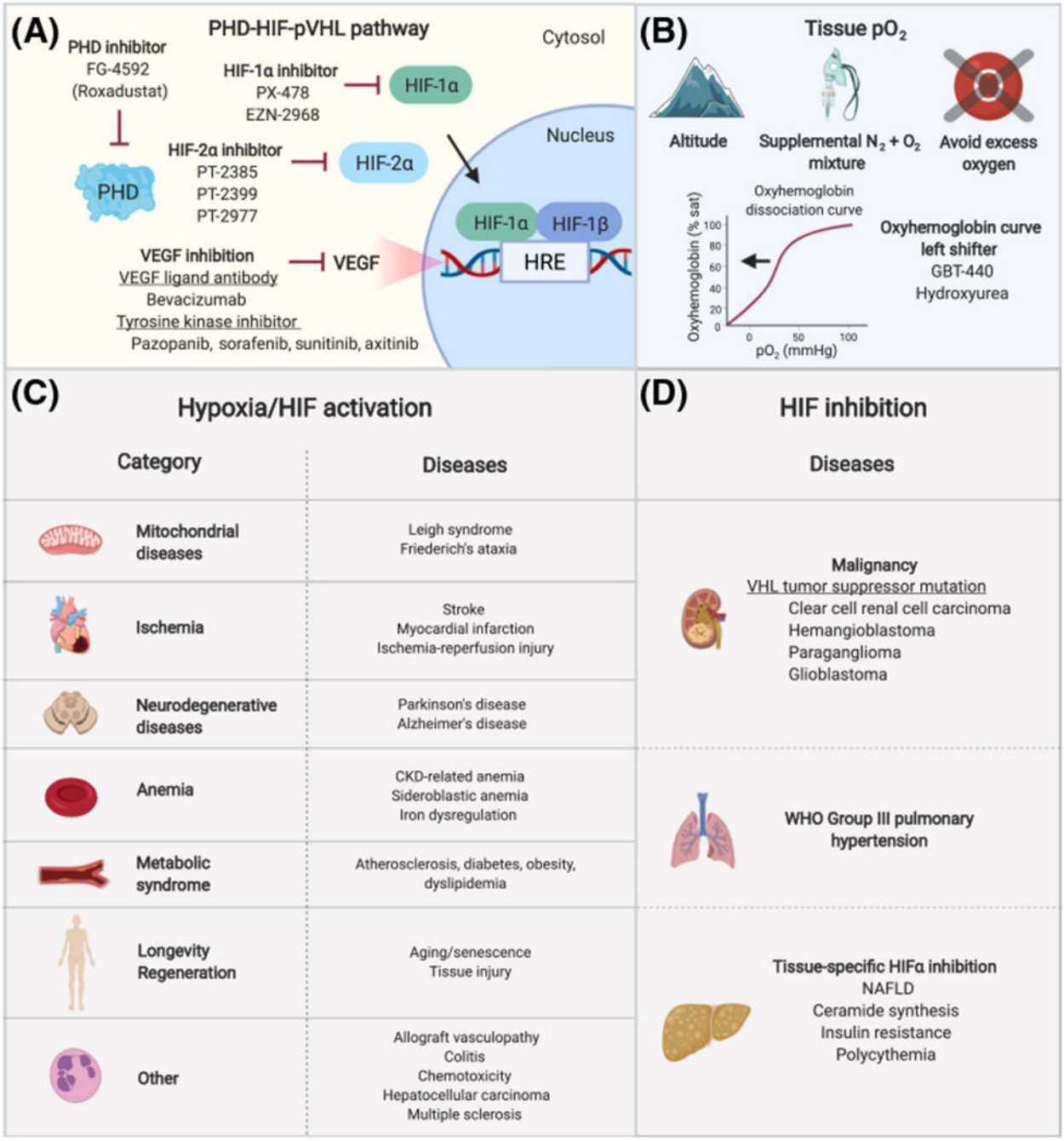

Figure 4. Hypoxia Response Therapy and Candidate Diseases Amenable to Hypoxia/HIF Activation or HIF Inhibition.

(A) Medications and novel small-molecule compounds that inhibit prolyl hydroxylase domain (PHD) proteins, HIF-1α, HIF-2α, and VEGF have shown clinical benefit in preclinical models and clinical trials [153,154,183,185,233]. PHD inhibition increases the HIF transcriptional response by preventing HIF hydroxylation, whereas HIF-1α and HIF-2α inhibition downregulate the HIF response. (B) Hypobaric hypoxia can be achieved by ascent to altitude or use of hypobaric hypoxia chambers, which simulate hypoxia by reducing atmospheric pressure. Normobaric hypoxia can be achieved by delivery of a mixture of

nitrogen and oxygen gases and pressure swing adsorption systems. Tissue hypoxia can be mimicked by administration of oxyhemoglobin curve left shifters. Certain mitochondrial diseases are associated with tissue hyperoxia and preclinical studies show that pathologic phenotypes can be ameliorated by hypoxia exposure. In these conditions, excess oxygen should be avoided unless clinically indicated. (C) Category and examples of diseases that can potentially be treated with hypoxia or HIF activation (e.g., PHD inhibition). (D) Candidate diseases that can be treated with inhibition of the HIF response (e.g., HIF or VEGF inhibition). Abbreviations: CKD, chronic kidney disease; HIF, hypoxia-inducible factor; HRE, hypoxia response element; NAFLD, non-alcoholic fatty liver disease; PHD, prolyl hydroxylase domain protein; pO_2, oxygen tension; VEGF, vascular endothelial growth factor; VHL, von Hippel-Lindau tumor suppressor protein; WHO, World Health Organization.

Table 1.

Toxicity of Low Oxygen or the Hypoxia Response

Type	System/organ	Exposure/condition	Effect	Refs
Acute	Systemic	- High altitude - Carbon monoxide poisoning	- Acute mountain sickness - High altitude pulmonary edema (HAPE) - Pulmonary hypertension, pulmonary edema, hypoxic respiratory failure - High altitude cerebral edema (HACE) - Cerebellar ataxia, retinal hemorrhages, unconsciousness, death	[158,159]
Chronic	Systemic	- High altitude - Hypoxic diseases - Chronic obstructive pulmonary disease - Emphysema - Diffuse parenchymal lung disease - *VHL* loss of function mutation (e.g., 598C->T Chuvash polycythemia) - Germline *VHL* deficiency (homozygous synonymous mutation C.222C->A, p.V74V) - *PHD2* loss of function mutations - *HIF-2α, EPOR* gain of function mutations	- Chronic mountain sickness - Decreased fertility - Low birth weight - Erythrocytosis - World Health Organization Group III pulmonary hypertension - Right-sided heart failure - Hypotension - Persistent hypoglycemia	[160–168]
Intermittent	Systemic	- Obstructive sleep apnea - Central sleep apnea - Cheyne-Stokes respiration - Intermittent hypoxia	- Hypertension - Obesity - Non-alcoholic fatty liver disease (NAFLD) and steatohepatitis - Insulin resistance - Dyslipidemia - Atrial fibrillation - Ventricular arrhythmias - Sudden cardiac death	[169–175]
Ischemia	Myocardium Brain Acute limb ischemia Renal infarction	- Non-ST segment elevation myocardial infarction (MI), ST-elevation MI - Acute coronary syndrome - Ischemic stroke - Thromboembolic event	- MI - Ischemic stroke - Kidney infarction - Peripheral arterial thrombosis - Pulmonary embolus	[176–179]
Local	White adipose tissue	- Overexpression of constitutively active form of *Hif-1α* - Adipocyte-specific *Vhl* KO - High-fat diet-induced obesity and adipose hypoxia	- Increased local inflammation and fibrosis - Increased proinflammatory cytokines, pathologic cardiac hypertrophy - Increased expression of inflammatory genes - Decreased expression of adiponectin - Increased adipose tissue inflammation and uncoupled respiratory state	[180–184]
	Intestine	- Distal ileum *HIF-2α* expression in obese subjects - Intestinal epithelium-specific *Vhl* disruption	- Increased obesity, NAFLD, hepatic steatosis - Increased colon tumor multiplicity and progression from adenomas to carcinomas	[185,186]
	Myocardium	- Chronic cardiac-specific *Phd* inactivation - Cardiac-specific *Hif-1α* and *Vhl* KO mouse model	- Dilated cardiomyopathy - Increased cardiac steatosis, fatty acid uptake, and eccentric hypertrophy	[187,188]
	Kidney	- Conditional inactivation of *Vhl* in Pepck-Cre mutants - Kidney-specific *Vhl* KO - *Pkd1* and *Hif-1α* co-deletion in kidney epithelium - Podocyte-specific *Vhl* gene loss	- Increased renal cyst development - Polycythemia - Increased interstitial fibrosis and kidney cyst growth - Glomerulomegaly and glomerulosclerosis	[189–192]
	Brain	- Controlled cortical impact traumatic brain injury mouse model - Mouse cerebral hypoxia-ischemia model	- Induction of LRRK2, exacerbation of neuronal cell death - Increased expression of TIM-3 and inflammatory immune cells	[193,194]

Type	System/organ	Exposure/condition	Effect	Refs
	Liver	- Temporal liver-specific *Vhl* disruption - *Vhl-Hif-1α* mutant mice	- Increased hepatic lipid accumulation, steatosis, and inflammation - Severe steatohepatitis, impaired fatty acid β-oxidation - Increased circulating cholesterol levels	[117,195,196]
	Lung	- Alveolar type 2 cells-specific *Hif-1α* conditional KO with closed-chest unilateral lung contusion	- Increased acute proinflammatory cytokines (IL-1β, IL-6, macrophage inflammatory protein-2)	[197]
Malignancy	Tumor	- Inactivation of *VHL* tumor suppressor gene - Hypoxia in solid tumors	- Clear cell renal cell carcinoma - Sporadic hemangioblastoma - Paraganglioma - Pheochromocytoma - Increased chemoresistance, metastatic potential, and treatment resistance - Poor prognosis marker for malignancies, including cervical cancer, breastcancer, colorectal cancer, lymphoma, glioblastoma multiforme	[81,198–202]

Table 2.

Toxicity of High Oxygen

Type	System/ organ	Exposure/cond ition	Effect	Refs
Acute	Systemic Lungs Brain Heart Ocular	- Supplemental oxygen in excess - Deep diving with supplemental nitrox	- Irritability, disorientation, seizures, ataxia, coma, death (Paul Bert effect) - Pulmonary edema, alveolar and bronchial damage - Activation of lung inflammasome - Decreased cardiac output - Higher systemic vascular resistance - Decreased coronary artery blood flow - Increased coronary vascular resistance - Increased cardiac biomarkers and larger infarct size on cardiac magnetic resonance imaging following myocardial infarction - Worse short-term functional outcomes after traumatic brain injury - Higher in-hospital mortality	[203–207]
Subacute	Systemic Brain	- Supplemental oxygen	- Increased intensive care unit mortality - Worse functional outcomes after mechanical thrombectomy - Neurologic disability	[208–210]
Chronic	Brain	- *Ndufs4* KO mouse model of complex I deficiency	- Increased tissue hyperoxia leading to neurologic disease and decreased lifespan	[109]
Ischemia-reperfusion	Systemic Heart Brain Lung Kidney Gut Skeletal muscle	- Ischemia followed by reoxygenation - Organ-specific ischemia-reperfusion injury - Organ allogeneic transplant	- Induction of cytochrome p450 and increased oxidation of polyunsaturated fatty acids into eicosanoids - Increased production of reactive oxygen species (e.g., superoxide) - Leukocyte and neutrophil infiltration - Opening of the mitochondrial permeability transition pore and subsequent apoptotic cell death - ATP depletion - Increased MCT4 expression and lactate extrusion - Decreased nitric oxide bioavailability - Succinate accumulation	[210–218]
Infants	Retina Lungs	- Supplemental oxygen	- Retinopathy of prematurity - Bronchopulmonary dysplasia Airway injury and inflammation Airway smooth muscle hypertrophy - Lower alveolar density, enlargement of parenchymal air spaces	[219–222]