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Invited Review Article

Environmental and behavioral regulation of HIF-mitochondria crosstalk

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ABSTRACT

Reduced oxygen availability (hypoxia) can lead to cell and organ damage. Therefore, aerobic species depend on efficient mechanisms to counteract detrimental consequences of hypoxia. Hypoxia inducible factors (HIFs) and mitochondria are integral components of the cellular response to hypoxia and coordinate both distinct and highly intertwined adaptations. This leads to reduced dependence on oxygen, improved oxygen supply, maintained energy provision by metabolic remodeling and tapping into alternative pathways and increased resilience to hypoxic injuries.

On one hand, many pathologies are associated with hypoxia and hypoxia can drive disease progression, for example in many cancer and neurological diseases. But on the other hand, controlled induction of hypoxia responses via HIFs and mitochondria can elicit profound health benefits and increase resilience.

To tackle pathological hypoxia conditions or to apply health-promoting hypoxia exposures efficiently, cellular and systemic responses to hypoxia need to be well understood. Here we first summarize the well-established link between HIFs and mitochondria in orchestrating hypoxia-induced adaptations and then outline major environmental and behavioral modulators of their interaction that remain poorly understood.

1. Introduction

The cellular utilization of oxygen enables highly efficient energy production but also puts cells and tissues at risk for oxidative damage. Almost all human cell types depend on oxygen and cannot rely solely on anaerobic energy generation. In mammals, most of the inspired oxygen is consumed by mitochondria for the generation of molecular energy; an estimated 85–90% of cellular oxygen is used for mitochondrial oxidative phosphorylation [1].

On the other hand, toxic byproducts of the utilization of oxygen are hazardous for cellular and tissue function and are involved in the pathogenesis of numerous diseases and normal aging processes. The utilization of oxygen in mitochondria also makes them major producers of such toxic byproducts, particularly mitochondrial reactive oxygen species (ROS). This is the case in physiological and normoxic conditions but even more in some pathological and/or hypoxic (reduced oxygen supply due to reduced ambient oxygen availability, biological compartment specific hypoxia or "critical-function induced" hypoxia [2]) or hyperoxic (increased oxygen supply) conditions. Hypoxia and subsequent reoxygenation phases are frequently associated with an increased ROS-burden, although hypoxia transiently also can lead to reduced ROS production. In addition, low oxygen supply limits mitochondrial respiration and thus ATP production, leading to energy-deficiency.

Cells, tissues and organisms thus require effective mechanisms to adapt, when oxygen is scarce and to generate protection from associated hazards. Accordingly, they use different strategies to maintain cellular and tissue homeostasis, preserve energy levels and avoid hypoxia-induced damage, including by ROS. These strategies involve non-transcriptional mechanisms (e.g., cardiorespiratory responses [3]) and

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the regulation of gene-expression and enzyme activities. They are mediated by biochemical reactions, chemosensors and signaling molecules, including the transcription factors hypoxia inducible factors (HIFs). Notably, the same substances that jeopardize cellular integrity during hypoxia (notably ROS) are also essential for the induction of many protective cellular mechanisms. Whether they are detrimental or beneficial – by inducing adaptive processes – largely depends on the dose of these substances, as well as on the resilience of the cells, tissues or organisms.

The aim here is to review how HIFs and mitochondria interact and how this reciprocal interplay is modulated by various environmental conditions and behaviors that all modulate physiological responses [4]. Consideration of these factors is not only important to understand HIF-mitochondria crosstalk in different environments but is also essential for emerging clinical applications of therapeutic hypoxia-interventions.

HIFs orchestrate a wide array of transcriptional responses leading to reduced dependence of cells and tissues on oxygen and to improved oxygen supply by regulating metabolic reprogramming, blood and vessel adaptations [5]. Many of these actions modulate mitochondrial functions and reverse effects (mitochondrial regulation of HIFs) also occur. Based on the potential of adaptations to hypoxia to induce either resilience or pathological alterations, the understanding of how HIF-mitochondria interactions are regulated in health and disease are crucial for risk-reduction and optimization of hypoxia-based treatments for clinical applications or performance enhancement [6,7].

2. Cellular responses to hypoxia

Low oxygen availability directly affects mitochondrial function by reducing electron transfer [8] and thus limiting adenosine triphosphate (ATP) generation by oxidative phosphorylation. Cells counteract detrimental ATP reductions in response to acute hypoxia in various ways via both defence and rescue mechanisms [9], including (i) switches between metabolic pathways, (ii) down-regulation of energy metabolism, (iii) minimization of hypoxia-associated damage and (iv) cellular and tissue adaptations to increase the resilience to future hypoxic insults. In addition, the efficiency of oxygen-dependent reactions can be increased, including for oxidative phosphorylation [10]. Gnaiger and colleagues [11] demonstrated the sensitive equilibrium of adenosine biphosphate (ADP) and oxygen availability on the coupling efficiency of mitochondrial bioenergetics. If ADP levels are limiting, mitochondrial oxygen fluxes will be higher in comparison to ADP and the reverse is true, if oxygen levels are limited. The increase of coupled versus uncoupled mitochondrial respiration (i.e., not used for ATP generation) thus is a means to maintain ATP-levels in oxygen-limited conditions.

Cellular responses to prolonged hypoxia include mechanisms leading to decreased dependence on oxygen or to more efficient oxygen supply. In addition, protective processes are initiated and include for example the upregulation of antioxidant defenses or the modulation of inflammation. These effects are importantly regulated by the hypoxia-sensitive transcription factors nuclear factor erythroid-2 related factor 2 (Nrf2) [3] and nuclear factor κB (NF-κB) [12].

HIFs play important roles in many of these strategies to counteract hypoxia-induced energy-deficits and often impinge on mitochondrial functions, as discussed in the following chapters. Beside the HIF-regulated improvements of oxygen supply, however, numerous other pathways, revolving for example around the cellular energy sensor AMP-activated protein kinase (AMPK) and mammalian target-of-rapamycin (mTOR) also counteract hypoxia-induced ATP-depletion independently of – but often overlapping with - HIFs. While rising AMP/ATP levels (indicating low cellular energy levels) are well-established AMPK activators, hypoxia is increasingly recognized to stimulate AMPK as well, possibly also independently of AMP/ATP levels [13]. AMPK upregulation leads to endocytosis of energy-intensive Na/K-ATPases [14] and to repression of ATP-consuming mRNA translation via inhibition of mTOR, eukaryotic initiation factor 2α (eIF2α) and eukaryotic translation elongation factor 2 (eEF2) [15]. AMPK further is involved in the activation of mitochondrial biogenesis pathways via transcription factor EB [16] and in the regulation of mitophagy in conjunction with the serine/threonine kinase Unc-51-like kinase 1 (ULK1) [17] following energetic stress/mitochondrial damage. Because of partially overlapping functions of AMPK- and HIF-pathways in cellular responses to energetic and hypoxic stress, an interplay between them has been suggested but is not yet well understood [13]. mTOR, on the other hand, activates HIF-1 directly via an mTOR signaling motif in the HIF-1α N-terminus [18].

3. HIFs orchestrate cellular hypoxia responses

HIFs are central regulators of oxygen homeostasis and are crucially involved in mediating molecular and tissue remodeling to ensure oxygen supply in response to low oxygen levels. Active HIFs are heterodimers consisting of oxygen-regulated α-subunits (e.g., HIF-1α [19,20]) and their constitutive β-subunits, termed aryl hydrocarbon receptor nuclear translocator (ARNT) subunits. In mammalians, HIF-1α has proven to be essential for both vascular and brain development [21].

HIFs' α-subunits (of the basic helix-loop-helix/Per ARNT SIM transcription factor family) are degraded in normoxia and get stabilized in hypoxic conditions (Fig. 1). In normoxia – dependent on α-ketoglutarate and ferrous iron –, prolyl hydroxylase (PHDs) mark HIF α-subunits [22–25] for recognition by VanHippel-Lindau proteins (VHL) that in turn effect their poly-ubiquitinylation and proteasomal degradation [26–28]. Among the PHDs 1–3, PHD2 is likely the most important for the hypoxic response [29].

Moreover, the asparaginyl hydroxylase factor inhibiting HIF-1 (FIH) hydroxylates HIF α-subunits in normoxia and thereby prevents HIF transactivation [30–32]. PHDs and FIH hydroxylate different residues of

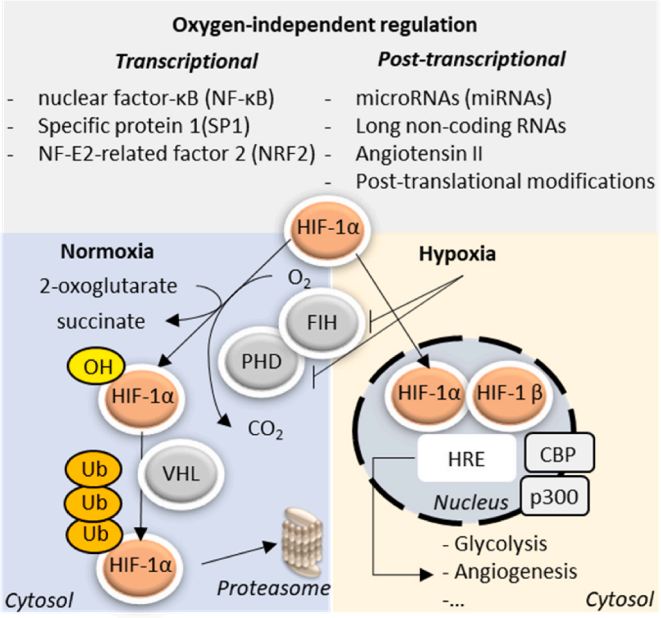

Fig. 1. Regulation of hypoxia inducible factor 1 (HIF-1) stability. HIF-1α subunits are continuously degraded in normoxia by prolyl hydroxylases (PHD) and factor inhibiting HIF (FIH) in the cytosol. These enzymes hydroxylate (OH) HIF-1α, leading to its poly-ubiquitinylation (Ub) by VanHippel-Lindau proteins (VHL) and proteasomal degradation. In hypoxia, HIF-1α stabilizes, translocates to the nucleus, dimerizes with HIF-1β and via transactivation of hypoxia responsive elements (HREs) and recruitment of co-activators like CREB binding protein (CBP) or p300 to gene promoters, orchestrates transcription of many hypoxia-regulated genes. Apart from its regulation by oxygen levels, several oxygen independent mechanisms regulate HIF-1 transcription and stability.

HIF α-subunits; the former prolyl residues and the latter asparagyl residues. While PHD activity is reduced already at small declines of oxygen levels, FIH regulates HIF at higher hypoxia severity, as recently reviewed [3].

Hypoxia allows the stabilization of HIF α-subunits within minutes and in a hypoxic dose-dependent manner [33], their dimerization with HIF β-subunits, subsequent translocalization of the dimers to the nucleus and transactivation of hypoxia responsive elements (HREs). The activation of HREs triggers a transcriptional response of hundreds of target genes [34], affecting primarily the regulation of glycolysis, iron homeostasis, erythropoiesis, angiogenesis and cell survival [35,36].

The two HIF-1 paralogues HIF-2 and HIF-3 also regulate responses to altered oxygen availability. HIF heterodimers recruit to the gene promoters co-activators like cyclic AMP response element-binding protein (CREB) binding protein (CBP) or p300, which recruit additional co-activators [37–40]. HIF-1 and HIF-2 bind the same HREs [41] and both are involved in decreasing the cellular reliance on oxidative phosphorylation, yet they also exert differential effects, with HIF-1 primarily evoking adaptations to acute and HIF-2 to chronic hypoxia [42]. Furthermore, HIF-1 and HIF-2 act partly independently, in some cases seemingly antagonizing each other, due to differential co-activators or temporal differences of HIF-1 and HIF-2 activity [26], distinct DNA binding properties [43] and differential expression patterns; HIF-1α is continuously expressed in most cells but HIF-2α expression is restricted to only some cell types. HIF-1 mainly upregulates expression of genes expressing glucose transporters and glycolytic enzymes, including phosphofructokinase-liver type, aldolase, phosphoglycerate kinase-1, enolase and lactate dehydrogenase-A, increasing conversion of pyruvate to lactate [44]. HIF-1 further induces pyruvate dehydrogenase kinase 1 (PDK1) [45,46], which inhibits pyruvate dehydrogenase, the enzyme catalyzing acetyl coenzyme A production and upregulates a subset of monocarboxylate transporters (MCTs), including MCT4 [47], which shuttles lactate out of cells. Together, these effects shift cellular energy metabolism towards glycolysis [44,48], reduce tricarboxylic acid cycle activity and thus lower availability of reducing equivalents for the mitochondrial electron transfer system.

HIF-2 regulates primarily erythropoietin expression and genes involved in vessel function and remodeling [49]. Regulation of angiogenesis, glucose transport, lipid metabolism and immune functions are shared between HIF1 and 2 [49]. The upregulation of HIF-1 in hypoxia is faster with maximal levels being detected in endothelial cells after 4 h, followed by decreasing levels, whereas HIF-2 levels peaked at 8 h and remained elevated after 24 h [50]. In addition, HIF-1 and HIF-2 play differential roles in pathologies, for example, HIF-1α deficiency in endothelial cells has been shown to delay tumor cell migration by reducing nitric oxide synthesis, while loss of HIF-2α exacerbates tumor cell migration in hypoxic conditions [51] and both HIF isoforms promote different oncogene activation patterns in cancer cells [52]. A third α-subunit, HIF-3α binds - but does not strongly activate - HREs and might suppress HRE binding of HIF-1 and HIF-2. A HIF-3α splice variant, inhibitory PAS domain protein is a dominant negative suppressor of HIF signaling [26].

HIF activities are not only regulated by hydroxylases. Gene expression is under the control of the transcription factors Nrf2, NF-κB and specific protein 1 (SP1) and various microRNAs and non-coding RNAs regulate transcript levels [53]. In particular, Nrf2-and HIF-signaling in response to hypoxia are intimately linked and cross-regulated [3,54]. On the transcriptional level, it has recently been shown that in hypoxic breast cancer cells silencing of the *NRF2*-gene impaired HIF-1α stabilization and HIF-mediated gene responses to hypoxia via miR181-c upregulation [55]. Similarly, in human colon cancer cells, stable knockdown of Nrf2 RNA decreased HIF-1α stabilization and associated tumor angiogenesis [56]. Post-translational modifications of HIF proteins regulate their stability and DNA-binding and co-factors their activity [26,57], which in turn are modulated by environmental and metabolic conditions, as discussed in later chapters. Exemplifying post-translational HIF regulation is nicotinamide adenine dinucleotide (NAD^+)-dependent regulation of the stress-inducible deacetylase sirtuin 1. Deacetylation leads to inactivation of HIF-1α [58] but to the activation of HIF-2α [59], thus representing a further mechanism of distinct HIF-1 and HIF-2 signaling. Sirtuin 1 regulates several stress-induced cellular adaptations by deacetylating various transcription factors, including the mitochondrial biogenesis regulator peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α), p53 and heat shock factor 1 (HSF1) [60,61].

Carbon monoxide and nitric oxide prevent normal accumulation of HIF in hypoxia [62], although high nitric oxide levels (<1 microM) have also been shown to stabilize HIF-1α apparently independent of oxygen concentration [63]. Mechanistically, nitric oxide inhibits PHDs, leading to accumulation of HIF-1α [64]. Interactions of HIF signaling with many signaling pathways, including Wnt, mTOR, PPARγ, Myc and Notch, the delta opioid receptor system, NMDARs and the sphingosine system, have been reported, as previously summarized [26,65]. In cancer-related Myc signaling, for example, HIF-1 may displace Myc at Myc-activated promoters, thereby downregulating Myc-activated genes leading to cell cycle arrest [66]. HIF-2 is thought to oppose these HIF-1 effects [26]. In addition, cytokines and growth factors regulate HIF-*α* subunits in cell type-specific manners [5]. The focus of this review, however, is the regulation of HIFs by mitochondria.

4. Mitochondrial regulation of HIFs

Among important mitochondria-derived molecules potentially affecting HIF levels are mitochondrial ROS and mitochondrial metabolites, which are discussed in this section.

4.1. Mitochondrial respiration, reactive oxygen species and HIFs

Although experiments demonstrating reduced HIF-stabilization in cells without functional mitochondria [67], without cytochrome *c* [68] or when mitochondrial respiration was inhibited in hypoxia, the mitochondrial control over hypoxia-activated HIF pathways remains debated. Inhibition of complex I by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), diphenylene iodonium or rotenone [69–71] or other respiratory complexes [70,71] compromised normal HIF-1α stabilization in hypoxia in the hands of some groups. Results for the complex III inhibitor antimycin A, are conflicting and indicate either increased [71] or decreased [70] HIF-1α levels in hypoxia. Other groups did not observe modulation of hypoxic HIF-1α levels by inhibition of respiratory chain components [72].

Respirational control of HIF stability has been suggested to be due to competition of mitochondria for oxygen [70], withdrawing substrate for the hydroxylases PHD and FIH. This idea was corroborated by results in primary human skeletal muscle myotubes overexpressing PGC1α [73]. The resultant increase of mitochondrial mass was associated with reduced intracellular oxygen levels and elevated HIF-1α levels, likely due to oxygen-limited HIF-1α hydroxylation by PHD [73].

Several mitochondria-derived molecules also modulate HIF-stability and -activity. ROS were previously considered major candidates to induce HIF-1α stabilization even in normoxia [67]. Although still insufficiently understood [74,75], ROS derived from complexes of the mitochondrial respiratory chain, especially from complex III [71,76], may be major negative regulators of PHD2 and FIH and therefore of HIFs [77–80]. In line with this assumption, oxidation of iron (Fe^{2+} to Fe^{3+}) by ROS inhibits [81], while reduction of Fe^{3+} by ascorbic acid preserves PHD-activity [82]. Supporting the regulation of HIF-levels by ROS, hydrogen peroxide (H_2O_2) stabilized HIF-1α also in normoxia [67] and the upregulation of the antioxidant enzyme catalase attenuated HIF-1α accumulation in hypoxia [67]. Conversely, deficiency of the H_2O_2 generating mitochondrial superoxide dismutase (SOD2) resulted in reduced HIF-1α RNA levels in chronic hypoxia in cells [83]. Other groups did not observe a modulatory effect of the mitochondrial

respiratory system integrity on HIF regulation [72,84]. These apparently contradictory results reflect the complex regulation of HIF on the transcriptional, translational and post-translational level but also highlight the importance of temporal patterns (e.g., changing levels of ROS from acute to chronic) and potential confounding technical factors. If HIFs are regulated by ROS this would also mean that ROS control mitochondrial remodeling, through HIFs (as discussed in chapter 5) or independently. Likely cell type characteristics and manipulation of mitochondrial respiration are crucial factors for the reported differences but conditions of cell culturing and hypoxia have been identified as a main methodological problem. While usual cell culturing conditions represent rather hyperoxic conditions (oxygen levels of 18.6% at sea level in standard incubators [85], as compared to much lower oxygen availability *in vivo* [86]), they can also result in hypoxic conditions for cells due to diffusion limitations of oxygen [85]. For example, partial oxygen pressures of 2 mmHg have been reported for confluent HepG2 cells in cell cultures in a ("normoxic") air/5% CO2 environment [87]. The oxygen gradient largely depends on mitochondrial respiration and thus can be influenced by modulation of mitochondrial function, thereby regulating HIFs [88]. Preserving experimental oxygen concentrations using gas-permeable culture dishes abolished modulation of HIF levels by electron transfer system inhibitors [88].

Taken together, several confounding factors impair interpretation of crosstalk between mitochondria and mitochondrial ROS with HIFs from *in vitro* results. The understanding of *in vitro* limitations together with unprecedented technical opportunities to study hypoxia *in vivo* will facilitate future studies on the inter-regulation of mitochondria and HIFs *in vivo*.

4.2. Mitochondrial metabolites and HIFs

Hypoxia leads to the accumulation of various mitochondrial tricarboxylic acid intermediates, which also affect HIF-1α stability. Apart from oxygen, the tricarboxylic acid cycle metabolite 2-oxoglutarate (or α-ketoglutaric acid) is required for the hydroxylation of HIF-α subunits by PHDs and thus for their degradation. Oxidative breakdown of 2-oxoglutarate yields the co-products CO_2 and succinate, as well as oxygen species responsible for hydroxylation of the substrate, e.g. HIF-α subunits [89]. Resulting increased levels of succinate should therefore inhibit hydroxylation by mass action product inhibition leading to higher HIF levels. HIF-1α upregulation independently of hypoxia has indeed been shown for succinate [90] and also for fumarate [91] and isocitrate [29], all through inhibition of PHDs. The mechanism by which succinate stabilizes HIF-1α thus is outcompeting of 2-oxoglutarate for PHD's catalytic domain by succinate [92]. HIF-1α stabilization by succinate recently has also been linked to mitochondrial ROS, which inhibit succinic dehydrogenase, leading to the accumulation of succinate [93]. In addition, high succinate levels lead to increased activation of succinate receptor 1, an important regulator of inflammation [94], further contributing to physiological and pathophysiological hypoxia responses and adaptations. Disruption of oxoglutarate dehydrogenase due to mutations in the genes oxoglutarate dehydrogenase itself or lipoic acid synthase has further been shown to increase formation of L-2-hydroxyglutarate, which inhibits PHDs and thereby stabilizes HIFs also in normoxia [95].

Additionally, glucose-dependent HIF-1α stabilization (glucose is not required for hypoxia-induced HIF-1α stabilization) and HIF-1-related gene expression by the glycolysis end-product pyruvate (and lactate, if converted to pyruvate) has been demonstrated [96]. This may be an important mechanism of cancer cell survival and malignancy [96].

Different mitochondrial dysfunctions, also unrelated to direct deficits in the electron transfer system or tricarboxylic acid cycle modulate HIF levels. In cells deficient of enzyme 2-enoyl thioester reductase/mitochondrial enoyl-CoA reductase (MECR) or SOD2 lower HIF-1α levels were observed in chronic hypoxia of 20 h, while knockout of mitochondrial DNA depletion syndrome channel protein Mpv17 increased HIF-1α protein in normoxia and hypoxia [83].

5. HIFs regulate mitochondrial function

Cellular adaptations to hypoxia include the HIF-mediated metabolic reprogramming (e.g., the discussed upregulation of components for glycolytic ATP generation [26]) as well as a structural and functional remodeling of mitochondria, including the mitochondrial respiratory system [27]. While HIFs mediate many mitochondrial and other cellular adaptations to hypoxia – and are the topic of this review –, not all hypoxia responses depend on HIFs. Important other pathways have been reviewed elsewhere [27,97]. ROS likely are modulators of both HIFs (see chapter 4.1) and mitochondrial structure and function and partially mediate HIF-mitochondrial crosstalk but in addition are also regulated by HIF and mitochondria [3,98].

5.1. HIFs modulate oxidative phosphorylation

Mitochondrial oxidative phosphorylation consists of the generation of a proton gradient across the inner mitochondrial membrane via the electron transfer system, and phosphorylation of ADP to ATP, as well as adenylate transport, via the mitochondrial phosphorylation system. The electron transfer system comprises the mitochondrial complexes I-IV, coenzyme Q and cytochrome C, and is arranged in super-complexes for efficient electron transfer. Hypoxia induces structural and functional adaptations of all mitochondrial complexes, as previously reviewed in more detail [74].

Upon acute hypoxia exposure, HIFs play an important role in increasing oxidative phosphorylation efficiency by modulating complex IV activity. This effect is achieved by different mechanisms remodeling complex IV and includes the HIF-1-mediated substitution of the complex IV subunit COX4I1 with COX4I2, which increases efficiency of electron transferal from complex IV to O_2 [10]. Moreover, the induction of gene domain family member 1A by hypoxia activates complex IV, and, thereby, augments oxidative phosphorylation [99]. In mice, on the other hand, HIF-1α-dependent repression of complex IV's COX5B subunit in white adipose tissue elicited adipocyte enlargement, a phenomenon associated with aging [100]. While increased oxidative phosphorylation efficiency is beneficial to optimally use remaining oxygen, prolonged hypoxia requires a downregulation of oxygen utilization in the electron transfer system.

HIFs effectuate such downregulation via multiple mechanisms, partly impinging on complex I. Low oxygen levels result in decreased mitochondrial electron transfer. This is mediated in part by the HIF-1-mediated induction of the mitochondrial gene product, NADH dehydrogenase [ubiquinone] 1 α subcomplex 4-like 2, an inhibitor of respiratory complex I [101]. Furthermore, the hypoxia-activated microRNA miR-210 inhibits electron transfer by repressing iron-sulfur cluster assembly [102–104] or synthesis of respiratory complex I, II [104] and IV [103] subunits. A HIF-1 mediated transient upregulation of complex II-linked succinate utilization in hypoxia may partially compensate for reduced NADH oxidation by complex I [105].

A complex and not fully understood relationship between HIFs and mitochondria concerns mitochondrial ROS formation. While mitochondrial ROS may contribute to HIF-1α stabilization (see above), HIF-induced remodeling of mitochondria is initially associated with higher ROS levels [106]. However, HIF-induced upregulation of antioxidant defense mechanisms and downregulation of oxidative phosphorylation is associated with reduced oxidative stress [107]. HIF-2 plays an important role in the coordination of antioxidant defenses, including by transactivation of the gene for SOD2 [108], although also HIF-1 has been shown to regulate SOD2 [109]. As discussed above, SOD2-deficiency in return reduces HIF-transcription, indicating a reciprocal regulation [83].

HIF-1 also supports antioxidant actions of glutathione, as recently reviewed [92]. In addition, reduced ROS production may be caused by

HIF-1-mediated downregulation of oxidative phosphorylation (see above).

5.2. HIFs regulate mitochondrial mass, shape and cellular location

HIF-1α is involved in metabolic reprogramming in hypoxia. It increases glycolysis by upregulating glycolytic components [110] and reduces oxidative phosphorylation by downregulating mitochondrial respiration efficiency and mass, at least in renal carcinoma cells lacking VHL [106]. HIF-2 seems to have similar effects in this model, also reducing mitochondrial biogenesis by reducing PGC1α expression via the negative PGC1α regulators deleted in esophageal cancer 1 (DEC1) and MAX-interactor 1 (MXI1) [111]. PGC1α mRNA levels, however, were not altered by hypoxic conditions (1% oxygen for 24 h) in Hela cells or myotubes [73]. Mitochondrial biogenesis is a complex process that requires the production, import and integration of proteins and lipids and the replication of mitochondrial DNA, in which PGC-1α plays a central role [112].

Chronic hypoxia results in reduced mitochondrial mass by upregulated mitophagy, the selective autophagic clearance of mitochondria. Although this process partly depends on HIFs [74,113], mitophagy in response to hypoxia probably also occurs independently of HIF-1 or -2 [97]. In this study, human macrophages were exposed to hypoxia until HIF-α-subunit accumulation and expression of HIF-target genes reached a new steady state (>72 h in 1% O_2) after acute hypoxia perturbation. HIF-1-signaling has been demonstrated before to lead to upregulation of BCL2 Interacting Protein 3 (BNIP3) and BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L/NIX), which boost clearance of mitochondria [113,114]. Hypoxia-induced mitophagy has been shown to depend on the mitochondrial outer membrane protein FUN14 domain containing 1 (FUNDC1) that enables interaction with light chain 3 (LC3) and autophagosome formation [115].

In pulmonary arterial smooth muscle cells, HIF-1 mediated hypoxia-induced mitochondrial fragmentation, likely through direct regulation of the mitochondrial fission regulator dynamin-related protein 1 (Drp1) [116]. Conversely, HIF-1 has been shown to protect kidney cells by preventing excessive mitochondrial fission in hypoxia [117]. This suggests that in healthy cells, HIF-1 is involved in hypoxia-related mitochondrial fission, while at the same time preventing exuberant mitochondrial fragmentation. Cancer cells, in contrast, have been reported to upregulate mitochondrial fusion via the mitochondrial fusion factor Mfn1 in a HIF-1 dependent manner in chronic hypoxia, which conferred protection from cell death [118].

Hypoxia also leads to changes in the intra-cellular location of mitochondria, leading to accumulation of mitochondria close to the nucleus. HIF-1 regulates this mitochondrial trafficking by upregulating mitochondrial movement regulator (HUMMR) [119]. Finally, some reports indicate non-transcriptional, direct interactions of HIF-proteins with mitochondria [120,121]. In hypoxia, non-phosphorylated HIF-1α has been shown to bind the protein mortalin (also known as GRP75 or HSPA9), the complex then translocated to the outer mitochondrial membrane and produced a C-terminally truncated form of the major mitochondrial porin voltage-dependent anion channel 1 (VDAC1) with anti-apoptotic effects [121].

In summary, HIFs (especially HIF-1) regulate mitochondrial shape, mass and location. A summary of the complex interplay between HIF-1 and HIF-2 with mitochondria is provided in Fig. 2.

6. Regulation of HIF-mitochondria interactions by environment and behavior

While the crosstalk between HIFs and mitochondria is well established, their inter-dependent regulation by environmental, dietary and behavioral factors is highly complex and less well understood. Obviously, oxygen availability (such as hypobaric hypoxia in high altitude) influences this interplay, but many other factors play roles too and will only be briefly listed here. An understanding of the regulation of HIF-mitochondria crosstalk is important to assess risks and opportunities of ambient hypoxia exposure but also is needed for the development of safe and efficient treatment strategies for diseases associated with hypoxic conditions and mitochondrial functions, notably including cancers [122] or neurodegenerative diseases [123].

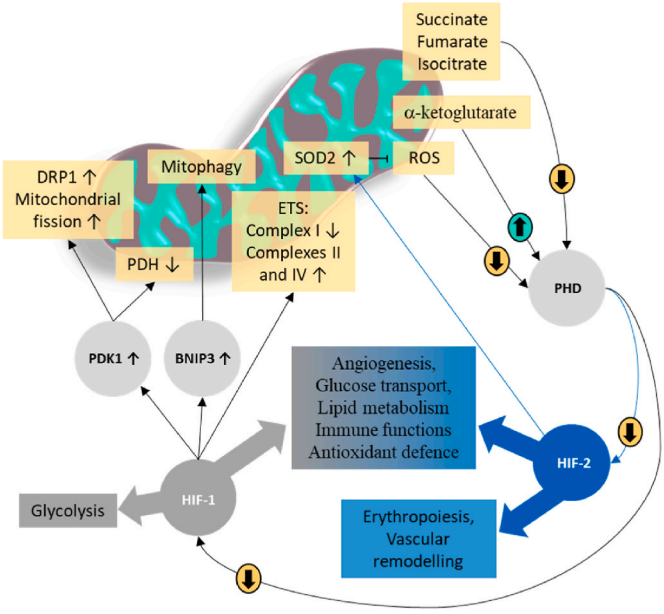

Fig. 2. Hypoxia inducible factor (HIF)-mitochondria interactions. PHD; prolyl hydroxylases, ROS; reactive oxygen species, SOD2; mitochondrial superoxide dismutase, CI – CIV; complexes of the respiratory system, DRP1; dynamin-related protein 1, PDK1; pyruvate dehydrogenase kinase 1, PDH; pyruvate dehydrogenase, BNIP3; BCL2 Interacting Protein 3.

6.1. The regulation of HIF-mitochondrial crosstalk by circadian rhythms

Circadian rhythms are oscillations of molecular and physiological processes that depend on the time of day, are driven by biological clocks and modulate metabolism, physiology and behavior [124,125]. Accordingly, HIFs and mitochondria are also under the control of circadian rhythms, partly due to day-time-dependent variations of tissue oxygenation [126]. In mammals, the hypothalamic suprachiasmatic nuclei exert central control of systemic circadian rhythms, but in addition almost every cell is regulated by cell-autonomous circadian clocks.

In mice, it has been demonstrated that suprachiasmatic nuclei control transcription of oxidative phosphorylation components in a circadian rhythm-dependent fashion, likely to prepare individuals for periods of expected increased energy demand [127]. The circadian control of oxidative phosphorylation was previously reviewed [128,129], and the rhythmicity of mitochondrial uncoupling [130], autophagy [131] and ATP production [132] are well-established. Mitochondrial generation of ATP and NAD^+, in turn, feed back to the modulation of clock gene expression via AMPK [128,133].

HIF-1 and mitochondrial functions are tightly regulated by the circadian clock in the form of feedback cycles. More specifically, hypoxia reduces the amplitude of the circadian oscillator, and HIF-1 expression - and therefore the hypoxic response – depend on the time of day, hence are under strict circadian regulation [134–136]. Among the manifold interconnections between cellular metabolism and the circadian clock [129], also ROS signaling itself is clock controlled. Therefore, mitochondrial as well as cytosolic ROS accumulation appear to have a circadian pattern [132,137,138]. H_2O_2 in turn, is known to have the potential for resetting the circadian clock and, thus, to feedback into the circadian rhythm [139,140]. Interestingly, the circadian clock

and associated HIF-1 protein were shown to respond to low intensity magnetic fields [141–143]. This magneto sensitivity relies on the radical pair mechanism (RPM), a now well accepted quantum based model [144]. The center of the RPM is formed by the electron transfer occurring at the core clock flavoprotein CRYPTOCHROME, and most probably also other (mitochondrial) flavoproteins, when their Cofactor FAD^+ is excited by blue light wavelengths. The subsequent electron transfer leads to the generation of the radical pairs $FADH^{\cdot}$ and Tryptophan $H^{\cdot}$, which are spin correlated and therefore sensitive to changes of the external magnetic field. Altered magnetic field intensities consequently lead to changes in the relative yields of superoxide $O^{\cdot-}$ and H_2O_2 [144,145]. The resulting amounts of specific ROS were demonstrated to not only affect the circadian clock, but also basic cellular metabolism by altering the ratio between glycolysis and mitochondrial respiration [141–143,146–148], indicating therewith a huge therapeutic potential of low intensity electromagnetic fields. Remarkably, a central role for magnetic field induced cell signaling was recently assigned to $O^{\cdot-}$ and its conversion to the secondary radical peroxynitrite $ONOO^-$ [149]. $ONOO^-$, in turn, was reported to affect levels of HIF-1 under hypoxic conditions by acting as an alternative donor of oxygen for activated PHDs, leading to the degradation of HIF-1 protein [150]. $ONOO^-$ was also demonstrated to affect mitochondrial energy production and calcium homeostasis and to promote the opening of the mitochondrial permeability transition pore [151,152]. Due to the complex feedback regulation of hypoxic signaling, mitochondrial function, the circadian clock and ROS signaling, the exact role of HIF-1 for the circadian clock and magnetic sensing is just starting to be unveiled.

6.2. Altitude, hypoxia and HIF-mitochondrial interactions

Terrestrial altitude is associated with numerous specific physical characteristics, including temperature and irradiation, which can influence HIF-mitochondria interactions. The major environmental stressor impacting on this crosstalk is hypobaric hypoxia due to decreasing atmospheric pressure with increasing altitude. This hypoxia most clearly induces the described HIF-dependent or -independent physiological adaptations. Since hypoxia both limits oxidative phosphorylation due to reduced amounts of the terminal electron acceptor oxygen, and initially increased ROS formation [1,67,107], altitude exposure modulates mitochondrial functions, which in turn may influence HIF-stability and activity. In parallel, altitude-related hypoxia activates HIF-pathways by reduced hydroxylation of HIFs requiring molecular oxygen for degradation by PHD and FIH, initiating metabolic reprogramming and mitochondrial alterations. In hypoxia, the activity of other 2-oxoglutarate-dependent hydroxylases, such as Jumonji C domain-containing histone demethylases, is also reduced. The resulting increased histone methylation is often associated with facilitation of transcriptional activation by HIFs [153,154].

Besides the plain reduction in oxygen availability, the acute paradoxical increase of mitochondrial ROS at lower oxygen levels [71,155] is an important factor for hypoxia-induced modulation of HIF-mitochondria interactions. It may be explained by (i) accumulation of electrons in the electron transfer system due to the lack of reducible oxygen [67], (ii) a prolonged lifespan of the mitochondrial complex III-associated transient free radical ubisemiquinone [156], (iii) a switch of mitochondrial complex I from NADH-ubiquinone oxidoreductase to Na^+/H^+ antiporter activity that may lead to increased ROS formation [157] and (iv) increased succinate oxidation in hypoxia [158]. Chronic hypoxia can induce cell death via ROS, for example in endothelial cells, where mitochondrial ROS mediated NLR family pyrin domain containing 3 (NLRP3) inflammasome activation and the associated inflammatory response caused apoptosis [159]. ROS are further involved in hypoxia-induced pulmonary hypertension [160].

Various illnesses that can arise due to altitude exposure, such as acute mountain sickness [161] or high altitude pulmonary or cerebral edemas [162], have therefore unsurprisingly been linked to ROS. Importantly, pharmacological strategies to prevent or treat these diseases usually will also alter HIF-mitochondria interactions. The carbonic anhydrase inhibitor acetazolamide is commonly used to prevent acute mountain sickness [163]. Carbonic anhydrases are regulated by HIF and acetazolamide induces HIF-1α [164]. Carbonic anhydrases have also been demonstrated to regulate mitochondrial biogenesis, as well as glucose and lipid metabolism in human Sertoli cells [165]. The glucocorticoid dexamethasone is indicated for severe acute mountain sickness and high altitude cerebral edemas and it is efficient to prevent these illnesses and high altitude pulmonary edemas [163,166]. Intriguingly, it is also an inhibitor of mitochondrial complex I [167]. Dexamethasone modulates HIF-1α activity as well, although the outcomes can be diverging. While reduced transactivation activity of HIF-1α, despite increased cytosolic levels, have been reported in HepG2 cells [168], while transcription of HIF-1α target genes was increased in human and zebrafish liver cells [169].

Moreover, altitude exposure is associated with hypoxia-dependent changes in substrate preferences for energy metabolism and appetite, which also modulate HIF-mitochondria interactions.

6.3. The influence of diet and appetite on HIF-mitochondrial crosstalk

Appetite and associated nutrient availability are factors tightly linked to mitochondrial function and determined by oxygen- (and therefore HIF-) levels, physical activity and circadian rhythms.

Although hypoxia also affects systemic nutrient supply by modulating appetite and appetite- and metabolism-regulating hormones, such as ghrelin, leptin and insulin [170,171], it thus likely alters nutrient utilization by its effects on mitochondrial functions and structure (discussed above). Mitochondria are essential in nutrient sensing, e.g., of glucose in pancreatic beta cells [172], and adapt in response to the availability of specific nutrients in order to increase the efficiency of nutrient utilization [173]. These adaptations are tissue-specific and involve bioenergetic efficiency, mitochondrial dynamics and the regulation of mitochondrial numbers/mass [173]. The metabolic responses to hypoxia in most organs acutely lead to increased uptake of glucose that is most likely primarily used for anaerobic processes, as recently shown in mice by positron emission tomography (PET) and isotope-labeled tracer experiments [174]. Conversely, skeletal muscles and brown adipose tissues exhibited reduced glucose uptake [174]. Chronic hypoxia (fraction of inspired oxygen 8% over 3 weeks) in this study led to robust metabolic remodeling that included 2-3-fold increased fatty acid uptake and oxidation in kidney, brain and liver, while the heart was the only organ that showed persistently increased glucose oxidation in hypoxia [174]. In different cell lines and tumor animal models, hypoxia also resulted in the increased expression of proteins for fatty acid import and storage [175] and upregulated lipogenesis [176]. The increased lipid storage may be protective against oxidative stress in hypoxia [175].

Intestinal hypoxia, which – partially mediated by HIF-1 – regulates intestinal metabolism, intestinal epithelial barrier function and host-gut microbiome interactions with consequences on systemic nutrient availability and inflammatory processes [177]. How these functions are affected by acute or long-term intermittent or continuous ambient hypoxia, remains to be elucidated.

While hypoxia clearly changes substrate preferences in different tissues [174], how specific diets affect responses to hypoxia and metabolic consequences, e.g., regulation of mitochondria by dietary strategies [178], remains to be investigated. Dietary strategies vary depending on individual (e.g., genetic predisposition, fitness, acclimatization state) and contextual factors (e.g., exercise, hypoxia severity, temperature). The scarce available recommendations for high altitude expedition nutrition and hydration have recently been summarized [179].

6.4. Exercise and HIF-mitochondria interactions in skeletal muscle

Increasing cellular ATP and oxygen demand during exercise leads to physiological responses to optimize oxygen delivery and oxygen consumption by mitochondria in working skeletal muscles. High oxygen demand in skeletal muscle can lead to "functional hypoxia" and associated stabilization of HIFs [180]. Especially HIF coordination of mitochondrial functions, improvement of oxygen supply by increasing angiogenesis and erythropoiesis and facilitation of glycolysis and glucose uptake highlight its potential role in mediating exercise-adaptations [181]. These adaptations depend on the type and duration of the exercise [182] and especially endurance exercise is well known to result in increased mitochondrial biogenesis and angiogenesis, partially resulting from upregulation of PGC-1α and vascular endothelial growth factor (VEGF), respectively [183,184].

Therefore, while HIFs may synergistically support some exercise adaptations, they may counteract other consequences of exercise, such as mitochondrial biogenesis. For continuous beneficial exercise adaptations, gradual downregulation of HIF-1 levels in long-term exercise via negative regulators, including PHDs and FIH [181], may therefore be necessary.

PGC-1α-induced mitochondrial biogenesis has been suggested to indirectly stabilize HIF-1α by reducing oxygen availability for PHD-mediated HIF hydroxylation [73]. Conversely, PGC-1α is a robust positive transcriptional regulator of HIF-2α in skeletal muscle [185]. Increased HIF-2α levels in turn regulate muscle fiber type composition by promoting gene expression programs for slow twitch fibers [185].

Despite the activation of HIFs by exercise and although exercise in hypoxic conditions has become an important training modality, as preparation for competitions in high altitude [186], to increase general athletic performance (although this remains debated [187,188]) or as a potential alternative to heavy training for load-compromised individuals [189], the interplay of mitochondria and HIFs during exercise is not well understood yet.

6.5. Temperature and HIF-mitochondrial crosstalk

Besides other environmental stressors, temperature changes induce mitochondrial adaptations and regulate HIF stability. These effects are closely related to the previously discussed factors, since body temperature is intimately linked with metabolism, physical activity levels and controlled by ambient temperatures and circadian rhythms [190].

Like by physical activity or fasting, PGC-1α is rapidly upregulated by environmental temperature changes, modulating mitochondrial biogenesis and respiration [191]. Cold exposure activates the sympathetic nervous system and induces adrenergic stimulation of brown adipose tissue, and increased cyclic adenosine monophosphate (cAMP) and cAMP-dependent pathways [i.e. protein kinase A (PKA), p38 mitogen-activated protein kinase (MAPK), and transcription factors cAMP response element-binding (CREB)/activating transcription factor 2 (ATF2)], stimulating PGC-1α [192]. To counteract the cold, PGC-1α and CREB/ATF2 induce the thermogenic uncoupling protein (Ucp)-1, which uses the mitochondrial proton gradient to generate heat [192,193]. Additionally, increases in thyroid hormone levels (T3 and T4) associated with cold exposures can stimulate upregulated PGC-1α and, as a result, mitochondrial biogenesis [191,194].

PGC-1α activation can be mediated from various upstreaming signaling molecules, including AMPK, p38 MAPK, and mTORC1 [195–197]. Interestingly, it has been shown that heat stress can activate p38 MAPK and mTORC1 [198].

Temperature also regulates HIF stability, with dose dependent outcomes. Liver HIF-1α levels were increased more than 3-fold in extreme condition, when mice were exposed to either an ambient temperature of 0 °C for 10 days or to a hypoxic environment (6% oxygen) for 3 days and were accompanied by HIF-1 mediated elevations of transferrin levels and hypercoagulability [199]. Mild hypothermic conditions (atmospheric temperature of 18 °C for 5 h, reducing body temperature to about 32 °C), on the other hand, suppressed HIF-1 induction and upregulation of its target gene expression (EPO and GLUT1) in hypoxic conditions (10% oxygen) in mouse brain [200].

Heat stress has been reported to upregulate a form of HIF-1α *in vitro* and in various mouse tissues that – unlike hypoxia-upregulated HIF-1α – did not get phosphorylated [201]. Unlike for cold stress, the addition of heat stress (42 °C) appeared to strongly increase HIF-1α induction by hypoxia (3% oxygen) in HepG2 cells [201].

Mitochondrial functions may be central in the complex joint effects of hypoxia and temperature. Cold [199,202] and hypoxia can both stabilize HIFs, downregulate mitochondrial respiration and thereby probably protect mitochondrial functions from damage, including due to oxidative stress.

The regulation of HIF-levels by temperature has profound clinical implications since controlled hypothermia is an important tool to protect from hypoxia-induced neurological damage [202,203].

In summary, environmental and behavioral factors importantly regulate mitochondria and HIFs separately and their interaction (Fig. 3), an aspect that must be considered particularly in emerging clinical applications of hypoxia exposures.

7. Conclusions

In this review, we explored the complex crosstalk between HIFs and mitochondria and highlighted some relevant environmental conditions and behaviors modulating these interactions. Not only are these important parameters to take into consideration for high altitude acclimatization and general physiological responses to hypoxia, but their understanding is also paramount to advance safe and efficient hypoxia interventions for athletic performance-enhancement and clinical applications. While altitude/hypoxia training is being discussed and applied since decades [204], the last years have seen a steep increase in the interest in hypoxia-based therapeutic approaches targeting numerous diseases and risk factors, from hypertension [205] to pulmonary diseases [206] to a range of potential applications in neurological [123] and psychiatric diseases [207]. Both mitochondrial and HIF-mediated adaptations are thought to be at the core of hypoxia-induced benefits [3] and their interplay determines the

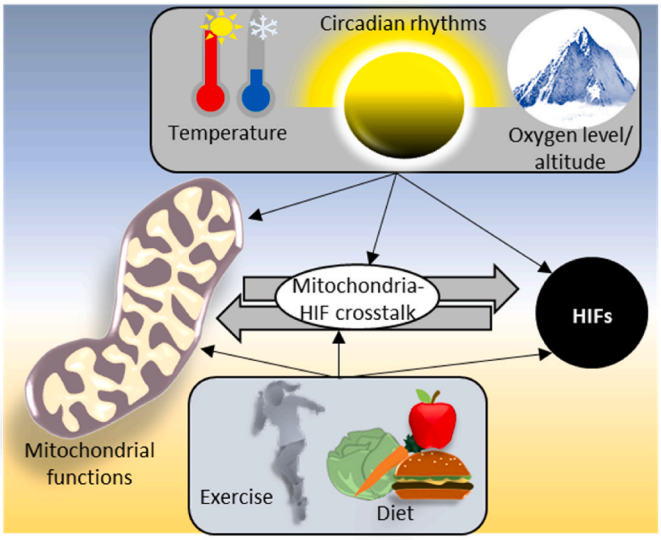

Fig. 3. Environmental and behavioral factors influence hypoxia inducible factor (HIF)-mitochondria interactions. Interdependent environmental factors (e.g., circadian period, ambient temperature or ambient oxygen concentration) and behavioral factors (e.g., exercise and diet) modulate mitochondrial functions, HIF stability and activity and HIF-mitochondrial crosstalk.

efficiency of the responses.

The potential of adequate hypoxia-based interventions is increasingly acknowledged but the optimization of protocols will be a major challenge for the future. Apart from great individual variation in chemosensitivity and hypoxia responses [3], not only the hypoxic dose (intensity, duration, frequency) but also the environmental conditions, circadian period and nutritional/activity status of the subject will determine outcomes of hypoxia exposure. The investigation of the complex interplays of relevant parameters and the disentanglement of synergistic versus inhibitory effects will become increasingly important for the design of optimal hypoxia protocols.

We know much about HIF-mitochondria interactions from cell culture studies. These are not only great simplifications of actual physiological hypoxia responses (tissue-complexities and inter-organ crosstalk usually not reflected, highly constant and artificial environmental and nutrient conditions) but also technical limitations of classical research (i.e., the discussed required precise control of oxygen levels in cell culturing as crucial determinant of HIF-levels) make it necessary to interpret these results carefully and considering potential confounding conditions.

Declaration of competing interest

The authors declare no conflicts of interest related to the topic of this review.

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