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The regulation of transcriptional repression in hypoxia

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ABSTRACT

A sufficient supply molecular oxygen is essential for the maintenance of physiologic metabolism and bioenergetic homeostasis for most metazoans. For this reason, mechanisms have evolved for eukaryotic cells to adapt to conditions where oxygen demand exceeds supply (hypoxia). These mechanisms rely on the modification of pre-existing proteins, translational arrest and transcriptional changes. The hypoxia inducible factor (HIF; a master regulator of gene induction in response to hypoxia) is responsible for the majority of induced gene expression in hypoxia. However, much less is known about the mechanism(s) responsible for gene repression, an essential part of the adaptive transcriptional response. Hypoxia-induced gene repression leads to a reduction in energy demanding processes and the redirection of limited energetic resources to essential housekeeping functions. Recent developments have underscored the importance of transcriptional repressors in cellular adaptation to hypoxia. To date, at least ten distinct transcriptional repressors have been reported to demonstrate sensitivity to hypoxia. Central among these is the Repressor Element-1 Silencing Transcription factor (REST), which regulates over 200 genes. In this review, written to honor the memory and outstanding scientific legacy of Lorenz Poellinger, we provide an overview of our existing knowledge with respect to transcriptional repressors and their target genes in hypoxia.

1. The activation and resolution of adaptive responses to hypoxia

The evolution of mitochondrial respiration along with the associated increase in cellular metabolic cap acity, allowed the development of multicellular organisms [1]. Oxygen, the final electron acceptor in the oxidation of organic compounds, is thus essential to sustain essentially all complex life. Hypoxia is the condition which arises when metabolic oxygen demand exceeds it's supply. Exposure to hypoxia can elicit adaptation, such as that observed during ascent to high altitude, where erythropoiesis is induced to counteract the reduced atmospheric oxygen supply [2].

Hypoxia is commonly associated with a range of pathophysiological states including ischemia, chronic inflammatory disease and cancer [3]. Taking inflammatory diseases as an example, upon tissue invasion by a pathogen, resident and recruited inflammatory cells mount a protective response that requires the oxygen-demanding synthesis of inflammatory mediators and oxidative burst therefore creating a hypoxic environment [4]. When inflammation chronic, the associated fibrosis and thrombosis also results in diminished blood delivery, thus exacerbating the hypoxic state [5]. Physiological hypoxic microenvironments are also common and can occur in the developing embryo and the adult [3]. Hypoxic regions arise in a spatio-temporally controlled way in the developing embryo and function as signal to orchestrate embryonic development [6,7]. Physiological hypoxia is also important in the adult where hematopoietic stem cells reside in the most hypoxic niches of the bone marrow [8,9]. Therefore, hypoxia is a relatively commonly encountered threat to the maintenance of metabolic homeostasis in health and disease.

Adaptation to hypoxia involves 3 major responses (Fig. 1): (1) increased glycolysis to cope with ATP depletion, (2) increased oxygen delivery to restore oxidative phosphorylation, and (3) inhibition of energy-demanding processes, to direct the scarce energetic resources to key house-keeping functions. This can be achieved by acute responses that rely on the modification of pre-existing proteins, translational inhibition and transcriptional changes (Fig. 1) that a will be discussed in detail in the next sections.

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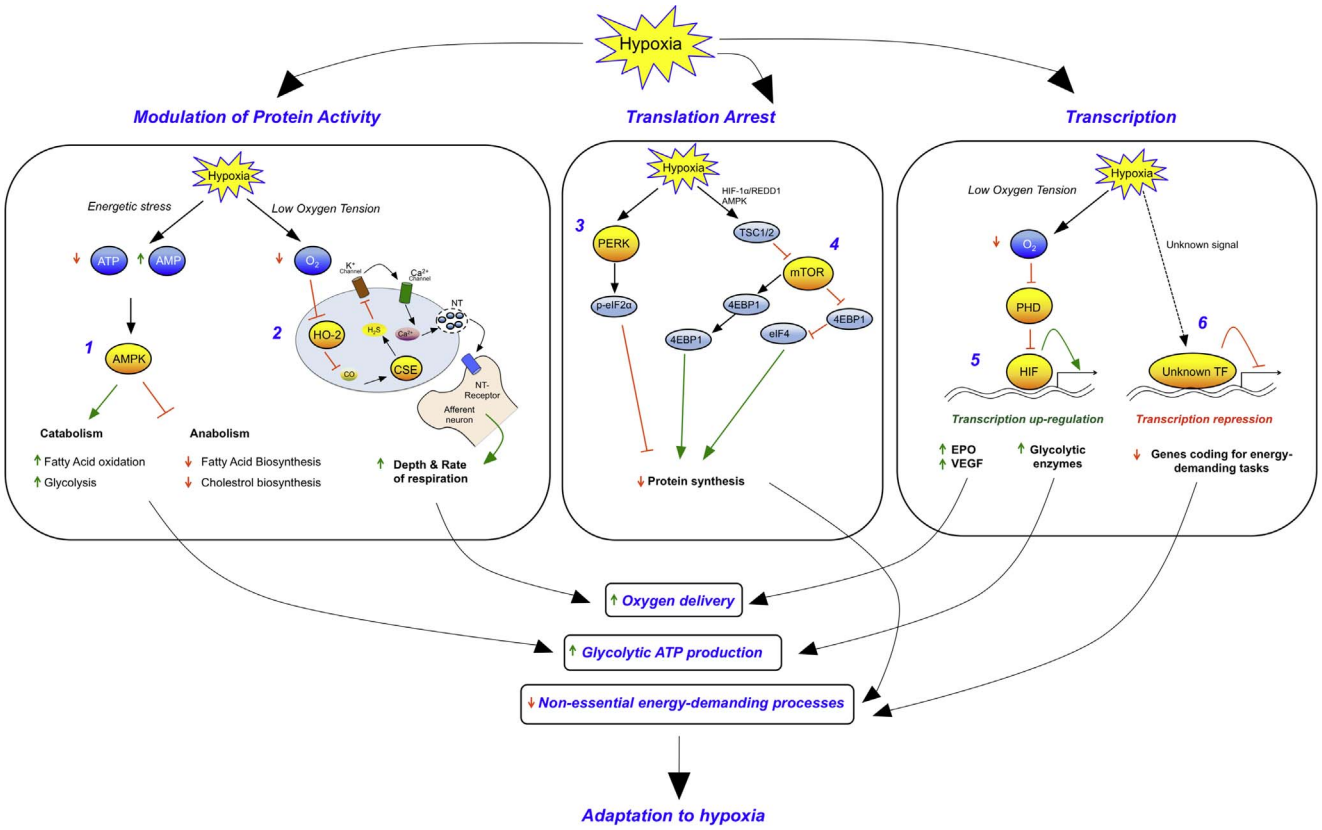

Fig. 1. Molecular mechanisms of adaptation to hypoxia. Adaptation to hypoxia involves 3 major responses: increased glycolysis to cope with ATP depletion, increased oxygen delivery to restore oxidative phosphorylation, and inhibition of energy-demanding processes, to direct the scarce energetic resources to key house-keeping functions. This can be achieved by acute responses that rely on the modification of pre-existing proteins (e.g. AMPK and HO-2), translational inhibition (mediated by mTOR and PERK) and transcriptional changes (mediated by HIF and largely unknown mechanisms for transcriptional repression). Depicted are examples of these mechanisms (from left to right): **(1)** Hypoxia decreases ATP production (energetic stress), this activates AMPK that restores energetic homeostasis by inducing catabolic pathways and inhibiting anabolic pathways. Adapted from [104,105]. **(2)** Haem oxygenase-2 (HO-2)-generated carbon monoxide (CO) is reduced under hypoxia, CO inhibits cystathionine-γ-lyase (CSE)-regulated hydrogen sulfide generation, thus in hypoxia more H2S is generated, inhibiting potassium channels (K+ channel), this leads to increased Ca2+ influx through Ca2+ channels, which initiates neuronal signaling to the central nervous system, ultimately increasing the rate and depth of breathing. Abbreviations: NT, neurotransmitter(s); and NT-R, neurotransmitter receptor. Adapted from [15]. **(3)** Hypoxia activates TSC1/2 via AMPK or HIF-1α/REDD1, TSC1/2 inhibits mTOR leading to an inhibition of 4EBP1, a negative regulator of the eIF4E, thus suppressing protein translation. mTOR also activates P70S6K, which activates ribosomal protein S6. Adapted from [23,106,107]. **(4)** Alternatively hypoxia can activate the effector of the UPR, the kinase PERK, which phosphorylates and inactivates eIF-2α, thus leading to suppression of protein translation. Adapted from [23,106,107]. **(5)** HIF is the master regulator of gene induction in hypoxia. HIF is stabilized by inhibition of the oxygen-dependent PHD enzymes. **(6)** Transcriptional repression is an essential component of adaptation to hypoxia through the inhibition of energy demanding process. However, the mechanisms for transcriptional gene repression in hypoxia are poorly understood.

1.1. Modulation of the activity of pre-existing proteins

The strategies used by a cell to adapt to hypoxia are dependent upon the extent and duration of the challenge. Acute hypoxia can induce rapid and transient effects on the activity of pre-existing proteins [10]. This can be achieved through the regulation of post-translational modifications such as hydroxylation [11–13] and phosphorylation [14], or through a direct effect on enzymes that requires oxygen such haem oxygenase-2 (HO-2). HO-2 activity is reduced in the carotid bodies in response to systemic hypoxia, leading to the modulation of ion channel activity and the subsequent generation of neuronal signals that promote increased depth and rate of breathing to restore systemic oxygen levels to normal [15]. Finally, hypoxia-induced changes in cellular metabolism can indirectly affect enzyme activity. For example, the AMP-activated protein kinase (AMPK), a sensor of AMP:ATP ratios, is activated when ATP levels drop in response to hypoxia, and promotes energetic homeostasis by activating catabolic process and inhibiting anabolic metabolism [16,17]. While the acute responses to hypoxia are mostly mediated by changes in the activity of pre-existing proteins, long lasting adaptation to chronic hypoxia (e.g. high altitude) is achieved through delayed, yet sustained, changes in translation and transcription.

1.2. Inhibition of translation

Down-regulation of energy consuming processes under hypoxic conditions is thought to be part of an energetic adaptation strategy, aimed at redirecting the available energy supply (ATP) to house-keeping functions, especially the maintenance of ionic and osmotic homeostasis in order to prevent membrane depolarization and subsequent cell swelling and necrosis [18]. Protein translation is one of the most energy consuming processes that occurs in cells. In rat cardiomyocytes it can take up to 27% of the total cellular energy capacity. RNA synthesis and Na+/K+ ATPase activity are the two other major energy sinks under normoxic conditions taking 20% and 22% of total energy capacity, respectively [19]. When energy capacity is reduced, translational rates are among the first cellular processes to be down-regulated [20–22]. Hypoxia induces translational arrest by activation of PERK and inhibition of mTOR, two major modulators of the translational machinery [22,23]. Therefore, by reducing the rate of protein translation in hypoxia, energy is conserved and reserved for essential processes.