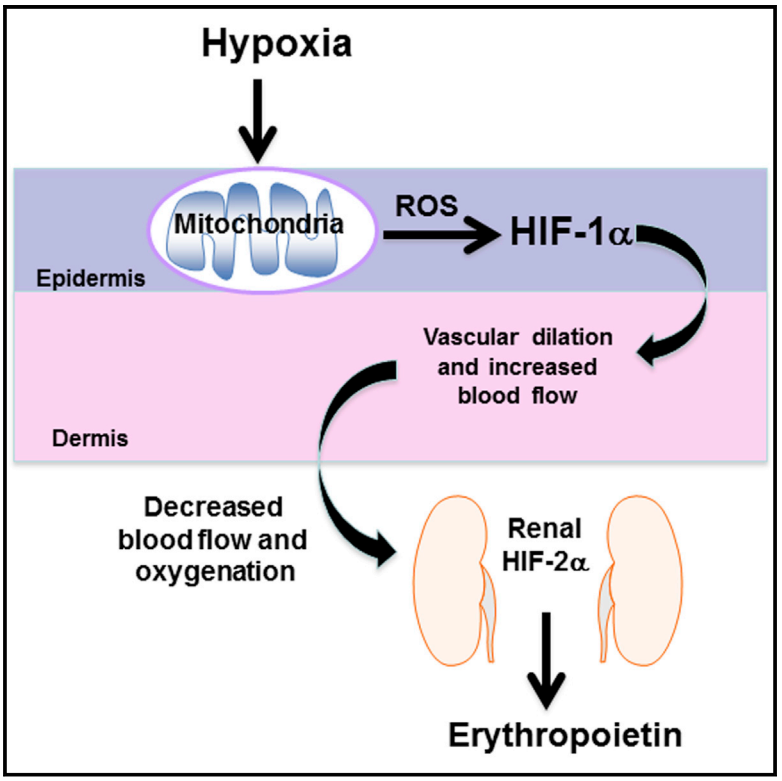
Cell Reports

Report

The Mitochondrial Respiratory Chain Is Required for Organismal Adaptation to Hypoxia

Graphical Abstract



Highlights

- The respiratory chain is essential for hypoxic activation of HIF in keratinocytes
- Respiratory chain production of ROS is necessary for hypoxic activation of HIF in vitro
- Hypoxic activation of HIF in the epidermis requires the respiratory chain in vivo
- Epidermal respiration is essential for hypoxic expression of renal erythropoietin gene

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In Brief

Hamanaka et al. show that loss of mitochondrial respiratory activity in the mouse epidermis impairs hypoxic activation of HIF-1. Since epidermal HIF-1 promotes cutaneous vasodilation and blood flow during hypoxia and potentiates the hypoxic response in the internal organs, mice with loss of TFAM in the epidermis are unable to induce renal erythropoietin expression in response to hypoxia.

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The Mitochondrial Respiratory Chain Is Required for Organismal Adaptation to Hypoxia

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SUMMARY

Hypoxia-inducible factors (HIFs) are crucial for cellular and organismal adaptation to hypoxia. The mitochondrial respiratory chain is the largest consumer of oxygen in most mammalian cells; however, it is unknown whether the respiratory chain is necessary for in vivo activation of HIFs and organismal adaptation to hypoxia. HIF-1 activation in the epidermis has been shown to be a key regulator of the organismal response to hypoxic conditions, including renal production of erythropoietin (Epo). Therefore, we conditionally deleted expression of TFAM in mouse epidermal keratinocytes. TFAM is required for maintenance of the mitochondrial genome, and TFAM-null cells are respiratory deficient. TFAM loss in epidermal keratinocytes reduced epidermal levels of HIF-1α protein and diminished the hypoxic induction of HIF-dependent transcription in epidermis. Furthermore, epidermal TFAM deficiency impaired hypoxic induction of renal Epo expression. Our results demonstrate that the mitochondrial respiratory chain is essential for in vivo HIF activation and organismal adaptation to hypoxia.

INTRODUCTION

The importance of oxygen homeostasis for the survival of eukaryotes has necessitated the evolution of multiple mechanisms by which organisms maintain their oxygen supply. The cellular response to hypoxia is governed largely by a family of transcription factors termed hypoxia-inducible factors (HIFs), which promote the activation of genes involved in glycolysis, angiogenesis, cell-cycle regulation, and survival (Semenza, 2012). Under normoxic conditions, proline residues within the oxygen-dependent degradation domain of HIF-α subunits (HIF-1α, HIF-2α, and HIF-3α) are hydroxylated by a family of 2-oxoglutarate-dependent dioxygenases termed prolyl hydroxylases 1, 2, and 3 (PHD1–3) (Kaelin and Ratcliffe, 2008). This proline-directed hydroxylation targets HIF-α subunits for recognition by a ubiquitin ligase containing the von Hippel-Lindau tumor suppressor protein (VHL). The activity of PHD proteins is inhibited during hypoxia, stabilizing HIF-α subunits, leading to their dimerization with a common β-subunit (HIF-1β) and transactivation of HIF target genes.

Mitochondrial metabolism has been implicated in regulating the hydroxylation reaction carried out by PHDs. Mitochondrial generation of tricarboxylic acid (TCA) cycle intermediates, consumption of oxygen, and production of reactive oxygen species (ROS) have been shown to inhibit the hydroxylation of HIFs, resulting in activation of HIF target genes (Bell et al., 2007; Brunelle et al., 2005; Guzy et al., 2005; Hagen et al., 2003; Isaacs et al., 2005; Mansfield et al., 2005; Pan et al., 2007; Selak et al., 2005; Sullivan et al., 2013). Despite evidence for the role of mitochondrial metabolism in regulating the cellular response to hypoxia, it remains to be demonstrated whether this phenomenon, heretofore observed only in cell culture, plays a physiological role in the mammalian systemic response to hypoxia in vivo.

Epidermal keratinocytes have been shown to play a critical role in regulating the systemic response to hypoxia (Boutin et al., 2008). The epidermis, which obtains oxygen directly from the atmosphere, responds to reductions in atmospheric oxygen by inducing vasodilation in the underlying dermis in a HIF- and nitric-oxide-dependent manner (Boutin et al., 2008; Minson, 2003; Stücker et al., 2002). This hypoxic vasodilation in the skin results in reduced blood flow to the internal organs, increasing internal hypoxia and promoting renal production of erythropoietin (Epo), a glycoprotein hormone that promotes proliferation and differentiation of erythroid progenitor cells into red blood cells, increasing the oxygen carrying capacity of the blood (Boutin et al., 2008; Bunn et al., 1998).

We recently reported on mice that lack expression of transcription factor A, mitochondrial (TFAM) in epidermal keratinocytes (Hamanaka et al., 2013). TFAM is required for transcription and replication of the mitochondrial genome, and cells lacking TFAM are respiratory deficient (Larsson et al., 1998). Loss of TFAM in epidermal keratinocytes resulted in epidermal barrier function defects and lethality 2 weeks after birth. The epidermal defect was due to a decrease in the production of mitochondrial ROS, which is necessary for Notch-dependent epidermal differentiation (Hamanaka et al., 2013). Here, we show that epidermal keratinocytes derived from these TFAM epidermal knockout (TFAM EpiKO) mice display impaired HIF activation upon exposure to hypoxia. Furthermore, neonatal mice displayed diminished HIF-1α protein and target gene induction in their epidermis after exposure to hypoxia. This resulted in an impaired hypoxic induction of Epo expression in the kidneys of these mice. Renal Epo expression could be induced in TFAM EpiKO mice by