Cell Death and Differentiation (2008) 15, 619–620

www.nature.com/cdd

Editorial

Hypoxia-inducible factor: roles in development, physiology, and disease

NS Chandel*[,1,2] and MC Simon[3]

Cell Death and Differentiation (2008) **15,** 619–620. doi:10.1038/cdd.2008.11

Multi-cellular organisms have evolved multiple mechanisms to respond to decreased oxygen levels (hypoxia).[1] Healthy individuals typically encounter hypoxia at high altitudes, where at least three prominent physiological responses take place: neurotransmitter release by the carotid body to increase breathing; pulmonary vascular constriction to shunt blood to better oxygenated regions of the lung; and production of the hormone erythropoietin to enhance red blood cell mass and hemoglobin concentration in the blood.[2] Hypoxia is also a feature of many diseases such as pulmonary hypertension, chronic obstructive pulmonary disease, sepsis, myocardial ischemia, and cancer.[3–4]

Although physiological responses to hypoxia at the organismal and tissue level have been appreciated for decades, the molecular and cellular biology of hypoxia have only been elucidated in the past 15 years. Notably, the discovery of the transcription factor hypoxia-inducible factor (HIF)-1, by Gregg Semenza and colleagues in the 1990s provided a molecular platform to investigate the mechanisms underlying responses to O_2 deprivation. HIF-1 was discovered as a nuclear factor bound to a cis-acting hypoxia response element in the 3′flanking region of the erythropoietin gene during hypoxia.[5] Further biochemical purification experiments led to the identification of genes encoding the HIF-1α and HIF-1ß subunits.[6] HIF-1α protein is only detectable under hypoxic conditions, while HIF-1ß subunit is constitutively stable. Subsequently, HIF-2α and HIF-3α were discovered, which show similar regulation in response to hypoxia.[7–8]

The biological consequences of HIF activity have been determined utilizing HIF-gene targeting experiments. The HIF-1α and HIF-1ß knockout mice demonstrated embryonic lethality by day 8.5–10.5 due to cardiac malformations, vascular regression hematopoietic abnormalities, and placental defects.[9–12] Conditional knockouts of HIF-1α and HIF-1ß subunits have highlighted the importance of HIF-1 and HIF-2 in normal vascular and hematopoietic development as well as in tumorigenesis, pulmonary hypertension, myocardial ischemia, and inflammatory diseases.

A major research focus in the hypoxia field for the past 10 years has revolved around identifying the regulators and biological consequences of HIF activation. A major breakthrough in the regulation of HIFs came from studies demonstrating that complexes containing the tumor suppressor von Hippel–Lindau protein serves as an E3 ubiquitin ligase for the degradation of HIF-α protein during normoxia.[13] Subsequent studies demonstrated that HIF-α protein is hydroxylated at proline residues by prolyl hydroxylases under normoxia to allow von Hippel–Lindau protein interaction.[14–16] HIF-α protein is also hydroxylated at an asparagine residue by the asparaginyl hydroxylase FIH under normoxia to prevent interactions with co-activators such as p300 and aberrant transcriptional activation.[17–18] Hypoxia suppresses the hydroxylation of proline and asparagine residues, thereby allowing full HIF transcriptional activation. Mechanism(s) by which hypoxia prevents hydroxylation are not fully understood. Recent evidence indicates that in addition to the prolyl hydroxylases and FIH, reactive oxygen species from the mitochondrial electron transport chain and mitochondrial metabolites are also likely to regulate hydroxylation of the HIF-α protein.[19–20] Thus, multiple inputs likely regulate the HIF-α hydroxylation.

This collection of reviews discusses our current knowledge of how hypoxia regulates HIFs through the prolyl hydroxylases, von Hippel-Lindau protein, FIH, and the mitochondrial electron transport chain, as well as many normal and pathophysiological roles of HIF protein.[21–27] The series also includes articles related to three new areas for HIFs, namely stem cells, non-transcriptional functions, and regulation of microRNAs.[28–30] Like all rapidly evolving fields, we hope this series is timely in discussing progress in the past 15 years in the hypoxia field as well as projecting important new directions. We hope the readers of *Cell Death and Differentiation* will find these reviews useful for both research and teaching purposes.

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[1]Department of Medicine, Northwestern University Medical School, Chicago, IL, 60611, USA; [2]Department of Cell and Molecular Biology, Northwestern University Medical School, Chicago, IL, 60611, USA and [3]Abramson Family Cancer Research Institute, Cell and Molecular Biology Graduate Group and Howard Hughes Medical Institute, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104, USA
*Corresponding author: NS Chandel, Department of Medicine and Department of Cell and Molecular Biology, Northwestern University Medical School, McGaw Pavillion, 240 East Huron Avenue, M-334, Chicago, IL 60611, USA. Tel: +1 312 503 2549; Fax: +1 312 908 8163; E-mail: nav@northwestern.edu

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