The Hypoxia-Inducible Factor-2alpha Is Stabilized by Oxidative Stress Involving NOX4.

Abstract

Abstract The hypoxia-inducible factor-2alpha (HIF-2alpha) contributes to the vascular response to hypoxia. Hypoxia inhibits prolyl hydroxylation of the N-terminal transactivation domain (N-TAD), thus preventing binding of the von Hippel-Lindau protein (pVHL) and proteasomal degradation; additionally, hypoxia inhibits asparagyl hydroxylation of the C-TAD, thus diminishing cofactor recruitment.

Reactive oxygen species (ROS) derived from NADPH oxidases (NOXs) have been shown to control vascular functions and to promote vascular remodeling. However, whether HIF-2alpha, ROS, and NOXs are linked under such nonhypoxic conditions is unclear. We found that activation of NOX4 by thrombin or H(2)O(2) increased HIF-2alpha protein because of decreased pVHL binding in pulmonary artery smooth muscle cells (PASMCs). Thrombin, H(2)O(2), and NOX4 overexpression increased HIF-2alpha N-TAD and C-TAD activity, which was prevented by ascorbate treatment or mutation of the hydroxylation sites in the TADs. HIF-2alpha also mediated induction of plasminogen activator inhibitor-1 and the proliferative response to thrombin, H(2)O(2), or NOX4 overexpression. Thus, ROS derived from NOX4 in response to thrombin stabilize HIF-2alpha by preventing hydroxylation of the N- and C-TAD, thus allowing formation of transcriptionally active HIF-2alpha, which promotes PASMC proliferation.
Together, these findings present the first evidence that HIF-2alpha is critically involved in the ROS-regulated vascular remodeling processes. Antioxid. Redox Signal. 13, 425-436.