

PATHOPHYSIOLOGY OF RESPIRATION (REVIEW)

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Summary

Normal tissue function in mammals depends on adequate supply of oxygen. A discrepancy between oxygen supply and consumption (hypoxia) induces a variety of specific adaptation mechanisms. These mechanisms are in part governed by the activation of hypoxia-inducible transcription factors (HIF-1, HIF-2, HIF-3) [Marti, 2004]. HIF-1 α is activated at physiologically relevant oxygen levels [Jiang et al., 1996], ensuring fast and adequate response to hypoxia. HIF-1 α targets include genes involved in angiogenesis, vasomotor control, energy metabolism, apoptosis, innate immune defence. As a consequence of these various functions, HIF-1 α is also implicated in the pathophysiology of many human diseases [Semenza, 2000].

HIF-1 is a heterodimer, composed of α and β subunits which are both members of the basic helix-loop-helix-PAS family of proteins. HIF-1 α is an oxygen-labile protein that is very rapidly stabilized under hypoxic conditions. Upon stabilization, the HIF-1 heterodimer binds to specific DNA sequences located in hypoxia-response elements associated with oxygen-regulated genes such as erythropoietin and vascular endothelial growth factor [Wenger, 2002]. Delineation of HIF-hydroxylation pathways provides new targets for therapeutic intervention. There is increasing evidence that activation of HIF is protective in ischemic/hypoxic disease, Parkinson's disease [Masson & Ratcliffe, 2003] and can generate a productive angiogenic response [Elson et al., 2001; Vincent et al., 2000]. A novel and essential role for HIF-1 α in regulation of several important polymorphonuclear leukocyte functions is described [Zarembek & Malech, 2005]. At the same time, the inhibition of HIF-1 could provide new strategy for the treatment and prophylaxis of pulmonary hypertension and high-altitude edema as well as prevent alveolar epithelial cells from the destruction. Thus, the functions of HIF-1 α in the organism are polysemantic and demand further scrupulous investigations.