

## RESEARCH INTERESTS - PALMER

Our laboratory examines the regulation of the transcription factor hypoxia inducible factor-1 (HIF-1) by nitric oxide. We are currently examining (1) the mechanism by which NO induces the expression of HIF-1 and (2) the role of NO induced HIF-1 in the development of pulmonary hypertension.

HIF-1 is a transcription factor involved in the regulation of genes induced by low levels of oxygen. It is composed of two subunits, HIF-1 $\alpha$  and HIF-1 $\beta$ . The expression of HIF-1 is primarily determined by the stability of the HIF-1 $\alpha$  subunit. Under normal oxygen concentrations (21%), HIF-1 $\alpha$  mRNA is made but the protein is rapidly degraded by the ubiquitin-proteasome degradation pathway. My lab, along with others, have shown that nitric oxide induces HIF expression in normoxia. The induction is dose and time dependent. The mechanism appears to involve stabilization of the HIF-1 $\alpha$  subunit through a posttranscriptional process. The effect is not mediated through NO directly, but through interaction with the NO<sup>+</sup> (nitrosonium) moiety. The effect can be reproduced by GSNO, an endogenously produced nitrogen oxide and is blocked by acivicin, an inhibitor of GSNO bioactivation. Moreover, this reaction can be reversed by the thiol modifying agent DTT, implying involvement of an S-nitrosylation reaction. Probable sites of interaction under investigation involve modifications of the HIF-1 $\alpha$  protein, the HIF-1 ubiquitin ligase (von Hippel Lindau protein) and the proline hydroxylase believed to be involved in oxygen sensing.

Pulmonary hypertension is a disease characterized by remodeling of the small pulmonary arteries which results in increased vascular pressure, right heart hypertrophy and ultimately death. The mechanism(s) by which this occurs is unknown. HIF-1 regulates the expression of a number of genes that have been implicated in the pathogenesis of this disease. In addition, the vascular remodeling associated with hypoxia-induced pulmonary hypertension is impaired in mice heterozygous for HIF-1 $\alpha$ , consistent with a role for HIF-1 in the upregulation of downstream genes involved in the pathogenesis of this disease. The observation that (1) NO may regulate the expression of HIF-1 and (2) NO have been implicated in the development of this disease has led us to examine the role of NO-induced HIF-1 in the development of this disease. A gamma glutamyl transpeptidase knockout mouse will be examined in the hypoxia induced model of pulmonary hypertension. Lung morphometry measurements, histology and right heart hypertrophy will be evaluated and compared to normal littermates to see if these mice are protected from the development of the disease.