

Hypoxia-inducible factors (HIFs) and biological responses, in hypoxia, inflammation and embryonic vascular development.

Akademisk avhandling

som för avläggning av medicine doktorexamen
vid Sahlgrenska akademien vid Göteborgs universitet
kommer att offentligen försvaras i Arvid Carlsson salen,
Academicum, Medicinaregatan 3
torsdagen den 8 maj 2008 kl. 9.00

av
Maria Hägg

Opponent:
Professor Sven Pålman
Molekylär medicin, Universitetssjukhuset i Malmö, Malmö

This thesis is based on the following papers:

- I. Activation of hypoxia-induced transcription in normoxia. (2005) **Hägg, M.** and Wennström, S. *Exp. Cell Res.*306, 180-191.
- II. Hypoxia-inducible factor-2 α (HIF-2 α) modulates formation of vascular/hematopoietic progenitors in differentiating embryonic stem cells. ***Hägg, M.**, *Nilsson, I., Carmeliet, P., Claesson-Welsh, L. and Wennström, S. Manuscript
*Authors contributed equally to the manuscript
- III. Hypoxia-inducible factor-1 α (HIF-1 α) activation and hypoxia following catheter implantation and a single peritoneal dialysis dwell. **Hägg, M.**, Cavallini, N. and Braide, M. Manuscript.



UNIVERSITY OF GOTHENBURG

Hypoxia-inducible factors (HIFs) and biological responses, in hypoxia, inflammation and embryonic vascular development.

Maria Hägg

Department of Medical Biochemistry and Cell Biology, Institute of Biomedicine, the Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden.

Abstract

Low oxygen tension (hypoxia) is a major inducer of neovascularisation and evidence emerging has indicated that oxygen tension and hypoxia-inducible factors (HIFs), a family of oxygen-regulated heterodimeric transcription factors, may play important roles in vascular and hematopoietic development. This thesis has focused on studying molecular and cellular mechanisms, by which cells and organisms sense changes in oxygen tension, and how this signal is transduced by HIFs into downstream signalling.

Cells, tissues, and organisms experience reduced oxygen (O_2) tension, or hypoxia under both physiologic and pathologic conditions. The total of all signals are integrated in the nucleus of the target cell, activating transcription of genes necessary for modulating cell function. HIF-1 is a key regulator of VEGF mediated angiogenesis, glycolysis and differentiation among a range of cellular responses to hypoxia. HIF-1 is also activated by non-hypoxic stimuli, like growth factors, hormones and cytokines i.e. IL-1 and TNF- α .

To investigate the possibility to induce HIF under non-hypoxic conditions, we made a construct, denoted the saturating domain (SD), based on a domain of HIF-1 α . As hoped for, expression of the SD, saturated degradation of endogenous HIF-1 α proteins, resulting in activation of HIF-1 mediated transcription in normoxia. Aggregates of differentiating embryonic stem (ES) cells, denoted embryoid bodies form blood vessels in a manner faithfully recapitulating vascular development and angiogenesis *in vivo*. By using ES cells lacking HIF-1 α or HIF-2 α , we show that HIF-1 α is required for vascularisation. The related HIF-2 α protein plays a role in regulating the number and activity of early endothelial and hematopoietic cells. Peritoneal dialysis (PD) induces fibrosis and angiogenesis in the peritoneal membrane, leading to ultrafiltration failure. The mesenteric-window angiogenesis model was used to study the role of the HIF-system in experimental PD. We showed that PD fluid exposure lead to hypoxia and activation of HIF-1 α in various resident and inflammatory cell types. The increased HIF levels, either induced by hypoxia or inflammation, points out different cellular sources of VEGF.

The HIF-system is an interesting target for pharmacological intervention aiming at inhibition of VEGF-mediated angiogenesis in inflammatory disorders (PD) and at stimulation of blood vessel formation in ischemic diseases.

Keywords: Embryonic stem cell, embryoid body, HIF-1 α , hypoxia, VEGF, angiogenesis, vasculogenesis, peritoneal dialysis

50 pages

ISBN 978-91-628-7446-9

Göteborg 2008