The effect of hypoxia on macrophage proteoglycans: potential role in atherosclerosis

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula på SU/Sahlgrenska, Göteborg torsdagen den 3 december 2009 kl 13.00

av Annika Asplund

Fakultetsopponent: Docent Katarina Öörni, Wihuri Research Institute, Finland

Avhandlingen baseras på följande delarbeten:

I. Hypoxic regulation of secreted proteoglycans in macrophages
Annika Asplund, Pia Stillemark-Billton, Erik Larsson, Ellen Knutsen Rydberg, Jonatan Moses, Lillemor Mattsson Hultén, Björn Fagerberg, Germán Camejo and Göran Bondjers
Glycobiology, 2009 Sep 11. Epub ahead of print

II. Macrophages exposed to hypoxia secrete proteoglycans for which LDL has higher affinity
Annika Asplund, Vincent Fridén, Pia Stillemark-Billton, Germán Camejo and Göran Bondjers
Manuscript

III. Hypoxia increases macrophage motility, possibly by decreasing the heparan sulfate proteoglycan biosynthesis
Annika Asplund, Gunnel Östergren-Lundén, Pia Stillemark-Billton, Germán Camejo and Göran Bondjers
Journal of Leukocyte Biology, 2009. 86: 381-388

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The effect of hypoxia on macrophage proteoglycans: potential role in atherosclerosis

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Abstract

A critical step in the development of atherosclerotic lesions appears to be the retention of low density lipoproteins (LDL) in the arterial wall, mediated by negatively charged proteoglycans (PG). Retained LDL is susceptible to modification and uptake by resident macrophages that are found in hypoxic sites in atherosclerotic lesions (with oxygen levels below 1%). PG are multifunctional proteins and in addition to their interaction with LDL, they bind and regulate the activity of growth factors and cytokines as well as cell migration and adhesion.

The aim of this thesis was to investigate how hypoxia affects PG synthesis in macrophages and the potential consequences on the atherosclerotic process. We found that expression of two large secreted PG, versican and perlecan, was increased in human monocyte-derived macrophages (HMDM) exposed to hypoxia (0.5% O_2) compared with cells in normal cell culture conditions (21% O_2). We found that the hypoxic induction of these two PG involved the hypoxia-inducible transcription factors HIF-1α and HIF-2α, and that HIF-1α and versican co-localized in macrophage-rich areas in human advanced atherosclerotic lesions. The negative charge of PG is on their attached glycosaminoglycans (GAG). We found that GAG secreted under hypoxic conditions bound LDL with higher affinity than GAG secreted under normal cell culture conditions, which could be due to the increased sulfation and size of GAG secreted in hypoxia. In contrast to the hypoxic induction of macrophage-secreted PG, hypoxia decreased the synthesis of the cell-associated heparan sulfate (HS) PG syndecan-1 as well as the HS GAG chains. The general motility of macrophages increased upon hypoxic incubation and was associated with the amount of HS GAG chains.

In conclusion, we found that hypoxia affects the synthesis of the extracellular matrix PG in macrophages with the potential to contribute to increased LDL deposition. Hypoxia also modulates the synthesis of cell-associated PG, with consequences for HMDM cell motility. These results are of importance to understand the role of macrophages in biological processes such as atherosclerosis.

Keywords: atherosclerosis, proteoglycans, glycosaminoglycans, macrophages, hypoxia, hypoxia-inducible transcription factor, LDL binding, cell motility

ISBN 978-91-628-7875-7 Göteborg 2009