

A role for CD44 in atherosclerosis?

Studies in mice and humans

Akademisk avhandling

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Av

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Avhandlingen baseras på följande delarbeten:

- Paper I **Circulating soluble CD44 is higher among women than men and is not associated with cardiovascular risk factors or subclinical atherosclerosis**
Sjöberg S., Fogelstrand L., Hulthe J., Fagerberg B., Krettek A.
Metabolism 2005. 54: 139-141
- Paper II **Augmented levels of CD44 in macrophages from atherosclerotic subjects: A possible IL-6-CD44 feedback loop?**
Hägg D., Sjöberg S., Mattsson Hultén L., Fagerberg B., Wiklund O., Rosengren A., Carlsson L.M.S., Borén J., Svensson P-A., Krettek A.
Atherosclerosis 2007. 190: 291-297
- Paper III **CD44-deficiency reduces antithrombin, factor X and factor VIII and promotes blood clots with compact structure**
Faxälv L., Sjöberg S., Andersson M., Sellborn A., Lindahl T.L., Krettek A.
Submitted
- Paper IV **CD44-deficiency on hematopoietic cells limits T-cell number but does not protect against atherogenesis in LDL receptor-deficient mice**
Sjöberg S., Eriksson E.E., Tivesten Å., Carlsson A., Klasson A., Levin M., Borén, J., Krettek A.
Under revision
- Paper V **CD44-deficiency reduces mast cell content and affects late but not early atherogenesis in LDL receptor-deficient mice**
Sjöberg S., Wikström J., Lindstedt K., Bourghardt J., Roberts J., Tivesten Å., Gan L-M., Krettek A.
Manuscript

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ABSTRACT

Atherosclerosis is an inflammatory disease that can lead to clinical complications such as myocardial infarction and stroke. Expressed in both vascular and inflammatory cells, adhesion molecule CD44 can be cleaved from the cell surface, and soluble CD44 can be detected in blood. CD44 mediates many inflammatory events, some possibly critical for atherogenesis. However, the role of CD44 in atherosclerosis remains incompletely understood. Therefore, this thesis aimed to investigate the role of CD44 in atherogenesis.

No association between soluble CD44 in serum and atherosclerosis, cardiovascular risk factors, and diabetes was determined, suggesting that soluble CD44 is not a suitable biomarker for atherosclerosis. In contrast, macrophages from patients with subclinical atherosclerosis showed enhanced levels of CD44 compared to healthy controls. CD44 expression associated with increased interleukin-6 secretion, and macrophages treated with interleukin-6 exhibited augmented CD44 expression.

To further examine the potential role of CD44 in atherosclerosis *in vivo*, low-density lipoprotein receptor-deficient (LDLr^{-/-}) mice with or without CD44 expression were used. A bone marrow transplantation in LDLr^{-/-} mice to obtain a mouse model with CD44-deficiency on bone marrow-derived cells was also performed. Surprisingly, and in contrast to published data on CD44 in apolipoprotein-deficient mice, CD44-deficiency in LDLr^{-/-} mice resulted in no or very modest reduction of lesion development. However, both mast cells and T cells, two cell types involved in lesion instability and rupture, decreased due to CD44-deficiency in advanced lesions. Furthermore, altered CD44 expression may influence the extrinsic coagulation cascade and therefore may affect thrombus formation.

Taken together, CD44 expression increased in macrophages from subjects with atherosclerosis. However, its soluble counterpart did not associate with subclinical atherosclerosis and did not hold promise as potential biomarker. Since altered CD44 expression affects cell composition, it may contribute to lesion stability.

Key words: CD44, atherosclerosis, interleukin-6, T cell, mast cell

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