The ApoM/S1P-complex: its role in vascular inflammatory disease and interaction with S1P-receptors

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2016

Document Version:
Publisher's PDF, also known as Version of record

HDL is believed to be protective against cardiovascular disease (CVD) via the reverse cholesterol transport and anti-inflammatory actions in the vessel. Apolipoprotein M (apoM) is an apolipoprotein mainly associated with HDL. Recently ApoM was proven to be the main carrier of Sphingosine 1-phosphate (S1P) in circulation. SIP is a signaling phospholipid involved in the immune system, exerting most of its effects through signaling via 5-G-protein coupled receptors; SlP_{l-5}.

The aim of this thesis is to investigate the role of the apoM/SlP-complex in vascular inflammatory diseases such as atherosclerosis and sepsis. We also want to study the interaction between the apoM/SlP-complex and the SlP-receptors.

We developed a liquid chromatography-tandem mass spectrometry method for SlP-quantification in plasma and cell extracts. We found that plasma levels of SIP and apoM were decreased in sepsis, levels reflecting the severity of the disease. The apoM/SlP-complex contributes to the anti-inflammatory effects exerted by HDL as shown *in vitro* by its inhibiting potential of pro-inflammatory adhesion molecules on the endothelial surface and by its increment of the endothelial barrier function. Plasma levels of apoM and SIP in type-l-diabetes (TlD)- patients (who have increased risk of developing CVD) were not altered compared to healthy controls. However, HDL-particles from TlD showed decreased anti-inflammatory effects which was not related to reduced presence of apoM and S1P. The apoM/S1P-complex could interact with all SlP-receptors as shown by internalization of fluorescently labelled S1P-receptors overexpressed in HEK293-cells. Interestingly, extracellular levels of apoM and SIP could detemine which receptor was available at the cellular surface.

ln conclusion, our data suggest apoM and SlP to have a role in acute and chronic inflammation. Future research could help us clarify how the apoM/SlP-complex signals through the different SlP-receptors in different inflammatory disorders and hence contribute in developing new therapies against diseases in the vasculature.