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14th IVBM Abstracts

Poster section 3. HDL and lipoprotein receptors

A3.01

Prevention of NF-kB activation in macrophages reduces foam cells formation

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Atherosclerosis is an inflammatory disease, characterized by the accumulation of lipid-laden macrophages in the vessel wall. Ample evidence supports a central regulatory role of the transcriptional NF-kB/IkB complex in atherogenesis. However, the function of NF-kB and its downstream gene products in the detrimental conversion of macrophages into 'foam cells' has not been explored. To investigate the relevance of the NF-kB regulatory system for macrophage-derived foam cell formation, transgenic mice were generated in which NF-kB complexes are selectively inhibited in the vascular macrophages. This has been achieved by over-expressing a *trans*-dominant form of IkBa (IkBa 32–36A) under the control of the macrophage-specific SR-A promoter (SR-A/IkBa 32–36A). Three mouse strains with a different degree of inhibition of NF-kB activation were generated. Similarly, stable human THP-1 monocytic cell lines have been generated, harboring copies of the SR-A/IkBa 32–36A construct. Significantly, both in vivo and in vitro, we demonstrate that blocking NF-kB activation largely reduces foam cell formation. Upon treatment with oxidized-LDL, peritoneal thioglycolate-induced murine macrophages, as well as THP1: SR-A/IkBa 32–36A cells, display a dose-dependent decrease in lipid loading. This reduction in lipid accumulation is accompanied by increased mRNA expression of genes known to be involved in the cholesterol efflux pathway such as ABCA1.

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The antiatherogenic and antiinflammatory effect of HDL-associated lysosphingolipids operates via Akt à NF-kappaB signalling pathways in human vascular endothelial cells

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Adhesion of mononuclear cells to the vascular endothelium and their subsequent transmigration into the arterial wall represent key events in the pathogenesis of arteriosclerosis. In previous studies we have shown that high density lipoproteins (HDL) and the HDL-associated sphingosylphosphorylcholine (SPC) have the ability to suppress the TNF-alpha-induced expression of endothelial cell E-selectin. However, the current understanding of the mechanism by which HDL reduces the expression of E-selectin is still incomplete. In the present study we show that interaction of the HDL-associated sphingosylphosphorylcholine and sphingosylgalactosyl-3-sulfate (lysosulfatide, LSF) with the G-protein-coupled EDG receptor initiates a signalling cascade that activates the protein kinase Akt and reduces the E-selectin, ICAM-1 and VCAM-1 expression on protein and mRNA level. This signalling cascade is consistently associated with a reduced translocation of TNF-alpha-activated NF-kappaB into the cell nucleus. The suppressor effect of SPC and LSF is completely reverted by inhibition of the phosphatidylinositol-3-kinase/Akt pathway. We conclude that the antiatherogenic/antiinflammatory effect of lysosphingolipids depends on a competitive interaction of

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