Sphingosine 1-Phosphate And Atherosclerosis: New Evidence From Transgenic Animal Models

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OBJECTIVES - Recent evidence suggests that atheroprotective effects of HDLs can be partly attributed to the sphingosine 1-phosphate (S1P), a lysosphingolipid able to bind and activate specific G-protein coupled receptors (GPCRs). Out of five receptor subtypes identified to date, S1PR1 and S1PR3 isoforms appear to be the most relevant in the cardiovascular system. Our work aimed to clarify the impact of endogenous S1P on atherosclerosis in vivo using specific transgenic mouse models that overexpress S1PR1 and S1PR3 isoforms in a tissue-specific way.

MATERIALS AND METHODS - The overexpression of S1PR1 and S1PR3 receptors in cells relevant for atherosclerosis, such as macrophages and endothelium, was obtained by generating transgenic mice based on Cre-LoxP technology. Animals on genetic background susceptible to atherosclerosis (ApoE +/- or chimeras LDLR -/-) were subjected to Western diet for 16-24 weeks and then sacrificed. The analysis of atherosclerotic lesionswas performed on cryosections of the heart at the aortic roots level and on the brachiocephalic artery after Oil-Red-O/hematoxylinstaining and expressed as total area of lesions or ratio between the area of the plaque and the total intima area (mean ± SD).

RESULTS - The animals overexpressing S1PR1 in macrophages show a massive reduction of atherosclerotic lesions as compared to controls, both at the level of the aortic root (719749,75 ± 76145,30 vs 378623,85 ± 98072,97) and the brachiocephalic artery (47383.53 ± 20251.24 vs 11288.12 ± 11085.16). Similarly, in the endothelium, the overexpression of S1PR1 (0.35 ± 0.28 vs 1.38 ± 0.53) or S1PR3 (0.30 ± 0.13 vs 1.38 ± 0.53) induced a significant reduction of lesions compared to controls.

CONCLUSIONS - Our study shows, for the first time, that the amplification of the endogenous S1P signaling is a protective factor against atherogenesis and such effectcan be attributed, at least in part, to both S1PR1 and S1PR3 receptors.