Heparanase Accelerates Atherosclerosis In-vivo: New Insights from Genetically Altered Mice Models

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Background: The role of Heparanase, Heparan-sulfate degrading enzyme, in atherosclerosis development and lipid metabolism was evaluated *in vivo.*

Methods: Three different models were used:

- Ubiquitously over expressed heparanase transgenic mice.
- Heparanase knock-out mice on the background of ApoE-/-.
- Heparanase over-expression limited to the hematopoietic system using bone-marrow transplantation model.

Atherosclerosis was assessed quantitatively in all models; lipid profile and metabolism were studied.

Results: Heparanase was proved to be pro-atherogenic in all 3 models: Heparanase over-expressing mice had increased fatty streaks formation compared to control (23984 vs. 4189μm^2, $p<0.001$); heparanase deficient mice (on ApoE-/- background) were relatively resistant to atherosclerosis compared to ApoE-/- mice (40462 vs 84660μm^2, $p=0.035$); and ApoE-/- mice transplanted with bone marrow from heparanase over-expressors had increased atherosclerotic plaque area compared to ApoE-/- mice transplanted with C57BL/6 marrow (30415 vs. 11346μm^2, $p=0.004$).

While in fasting state heparanase over-expression induced only slight elevation in triglycerides and cholesterol level, the difference became striking after oral fat load, while a mirror effect was documented in the heparanase deficient mice. Hepatic uptake of radiolabeled retinol was decreased in transgenic mice while plasma levels were higher - indicating reduced hepatic clearance of remnant lipoproteins, with an opposite effect demonstrated in heparanase deficient mice. No change in lipoprotein profile was demonstrated in the bone marrow transplantation model.

Conclusions: These three complementary models demonstrate, for the first time in-vivo, the pro-atherogenic effect of heparanase. The main mechanism involves reduced hepatic uptake of remnant lipoproteins with increased plasma availability of these atherogenic particles.