Macrophage-derived MMP-9 enhances the progression of atherosclerotic lesions and vascular calcification in transgenic rabbits

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Background:
Accumulation of monocytes and macrophage-derived foam cells in the intima of large arteries is a hallmark of human and experimental animal atherosclerosis. Macrophages and macrophage-derived foam cells in the arterial wall secrete large amounts of matrix metalloproteinases (MMPs). One of these MMPs is MMP-9, gelatinase. MMP-9 in concert with other MMPs has been considered to participate in the pathogenesis of atherosclerosis and plaque rupture. However, it is not clear whether macrophage-derived MMP-9 is directly involved in the initiation or progression of atherosclerosis although increased expression of MMP-9 was detected in the lesions of human atherosclerosis.
In this study, we generated MMP-9 transgenic (Tg) rabbits in which MMP-9 was overexpressed in macrophages. We hypothesized that macrophage-derived MMP-9 is involved in the development and progression of atherosclerosis.
We fed Tg rabbits along with non-Tg rabbits with a cholesterol diet for 16 and 28 weeks. During the period, plasma lipids including total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDLC) were measured. After a cholesterol diet, the aorta and heart tissue were collected and fixed in formalin solution for pathological analysis.

Main findings:
We have successfully generated MMP-9 transgenic rabbits that expressed human MMP-9 in the macrophage lineage as confirmed by Northern blotting. We found that increased expression of MMP-9 did not affect the early stage of atherosclerosis but significantly enhanced the progression of atherosclerosis. In addition, Tg rabbits showed prominent vascular calcification, suggesting that MMP-9 not only enhanced atherosclerosis but also participated in the vascular calcification. We further found that MMP-9 overexpression was associated with osteoclastogenesis, which may be the critical mechanisms for MMP-9 mediated vascular calcification.

Conclusion:
We have successfully created Tg rabbits that overexpress MMP-9 specifically in macrophage lineage. Increased expression of MMP-9 in macrophages enhances the formation of advanced atherosclerotic lesions in Tg rabbits, which exhibited marked vascular calcification. We were the first to demonstrate

that macrophages are also involved in the vascular calcification possibly through increased osteoclastogenesis in the bone and reduced osteoclastogenesis in the arterial wall or increased cell death in the lesions. Therefore, macrophage-derived MMP-9 in the arterial wall may exert other physiological functions beyond its classical gelatinase activity. Although the molecular mechanisms remain yet to be clarified, it will be interesting to investigate in the future whether inhibition of MMP-9 expression functions as a therapeutic method to inhibit vascular calcification.

Chen Y, Waqar AB, Nishijima K, Ning B, Kitajima S, Matsuhisa F, Chen L, Liu E, Koike T, Yu Y, Zhang J, Chen YE, Sun H, Liang J and Fan J: Macrophage-derived MMP-9 enhances the progression of atherosclerotic lesions and vascular calcification in transgenic rabbits. Journal of Cellular and Molecular Medicine, 2020; n/a:1-14