The role of matrix metalloproteinase-2 on age-dependent arterial stiffness

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Introduction: Arterial stiffness is a well-characterized sign of vascular aging. It strongly predicts the development of several cardiovascular diseases (CVD), such as hypertension, stroke and heart failure. The age-dependent stiffening of elastic arteries is primarily attributed to the loss of interlaminar elastic fibers and the increase of collagen fibers. This process is regulated by matrix metalloproteinases (MMPs), including MMP-2. A strong correlation between MMP-2 levels and arterial stiffness has been previously described. However, the causative link between age-dependent arterial stiffness and MMP-2 remains unclear.

Purpose: In this study, we aimed to prospectively investigate the effect of MMP-2 gene silencing on the development of age-dependent carotid stiffness in wild type (WT) mice.

Methods: Pulse Wave Velocity (PWV), as the gold standard technique to assess arterial stiffness, was assessed in the right common carotid artery (RCCA) of C57BL/6 WT mice of various ages ranging between 3 and 25 months. Plasma and vascular levels of MMP-2 on RCCA were also measured and correlate with PWV. Moreover, aged WT male mice (18–21-month-old) were treated for 4 weeks with either MMP-2 siRNA or Scr siRNA via tail vein injection every 4 days and PWV was assessed at baseline, 2 and 4 weeks.

Results: Mouse carotid PWV increased and was positively correlated with age in our in vivo longitudinal study. Increases of vascular and circulating MMP-2 levels were also observed in this study. MMP-2 knockdown by siRNA treatment reduced vascular MMP-2 level (Fig. 1), which in turn attenuated age-dependent carotid stiffening (data not shown). siMMP-2 treated animals also showed an increase of elastin to collagen ratio. Furthermore, enhanced phosphorylation of the activatory eNOS Ser1177 was observed in the siMMP-2 group without affecting the level of total eNOS and Akt phosphorylation. Interestingly, co-immunoprecipitation experiments demonstrated that MMP-2 directly interacts with eNOS and this interaction is augmented with age.

Conclusion: The silencing of MMP-2 attenuates age-dependent carotid stiffness by affecting elastin to collagen ratio and interfering with eNOS activation. Thus, MMP-2 may mediate ECM remodeling and endothelial-dependent vasorelaxation in the development of age-dependent vascular stiffness.

Figure 1. (A,B) Carotid PWV was measured in 3- (n=8), 8- (n=10), 10- (n=9), 15-17- (n=7) and 23-25-month-old (n=5) male mice to obtain a time course of carotid stiffness development. Carotid PWV gradually increases and positively correlated with age in WT mice. (C) Old WT mice show an increase levels of vascular MMP-2, as compared with young WT mice (n=5-6) (D) Higher level of MMP-2 is also observed in the plasma of old WT mice (n=8-12). Results are presented as mean ± SEM; *p<0.05; **p<0.01 ***p<0.001 vs 3 months. **p<0.01 ***p<0.001 vs 8 months.