GS03-4

Investigation of the novel mechanism of vascular fibrosis inhibition by xanthine oxidase inhibitor

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OBJECTIVE Several reports from basic researches and clinical studies have suggested that xanthine oxidase (XO) inhibitors have suppressive effects on cardiovascular diseases. However, the roles of a XO inhibitor, febuxostat (FEB), in the pathogenesis of vascular remodeling and hypertension independent of the serum uric acid level remain unclear. In this study, we investigated the mechanism of FEB for vascular remodeling and hypertension. METHODS To induce vascular remodeling in mice, angiotensin II (Ang II) was infused for 2 weeks with a subcutaneously implanted osmotic minipump. FEB was administered every day during Ang II infusion. Aortic fibrosis was assessed by EVG staining. Mouse macrophage RAW264.7 cells (RAW) and mouse embryonic fibroblasts were used for in vitro studies. RESULTS FEB suppressed Ang II-induced blood pressure elevation and aortic fibrosis. Immunostaining showed that Ang II-induced macrophage infiltration in the aorta tended to be suppressed by FEB, and XO was mainly colocalized in macrophages, not in fibroblasts. Transforming growth factor- β 1 (TGF- β 1) mRNA expression was induced in the aorta in the Ang II alone group, but not in the Ang II + FEB group. Ang II induced α -smooth muscle actin-positive fibroblasts in the aortic wall, but FEB suppressed them. XO expression and activity were induced by Ang II stimulation alone but not by Ang II + FEB in RAW. FEB suppressed Ang II-induced TGF- β 1 mRNA expression in RAW. CONCLUSIONS Our results suggested that FEB ameliorates Ang II-induced aortic fibrosis via suppressing macrophage-derived TGF- β 1 expression.