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Protective effect of SOCS1-based therapy in experimental abdominal aortic aneurysm

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Introduction: Abdominal aortic aneurysm (AAA) is a multifactorial vascular disease characterized by chronic inflammation, oxidative stress and proteolytic activity in the aortic wall, which contribute to extracellular matrix degradation and aortic dilation. Altered expression and activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway have been implicated in several cardiovascular diseases including atherosclerosis and aneurysm formation. Suppressors of cytokine signaling (SOCS) are key negative regulators of JAK/STAT pathway and have been considered an attractive target for therapeutic intervention.

AIM
We hypothesize that SOCS1 protein could influence AAA development by inhibiting JAK activity and, consequently, STAT activation and target gene expression. Therefore, this study investigates the effect of a SOCS1-derived synthetic peptide in a rodent model of AAA and in cultured vascular smooth muscle cells (VSMC).

Methods: Experimental AAA was induced in C57BL/6 mice (males, 12 weeks old) by transient elastase perfusion of the aorta. Mice were randomly divided into control (vehicle, i.p.) and treatment (SOCS1 peptide, 3 mg/kg/day, i.p.) groups. Fourteen days after AAA induction, mice were sacrificed, and aorta segments were collected for histology (n=10/group) and mRNA and protein expression analysis (n=8/group).

Results: Compared to the AAA control group, SOCS1-treated mice exhibited a significant decrease in aortic diameter (68±6% vs. control; p<0.005) and aortic wall thickness, (67±3% vs. control; p<0.001). Histological analyses of aortic tissues showed a higher content of VSMC (α-actin) along with reduced leukocyte infiltration (macrophages, neutrophils and T-cells) and oxidative stress markers (superoxide anion and 8-hydroxyguanosine) in SOCS1-treated mice. SOCS1 therapy also attenuated the gene expression of inflammatory cytokines (CCL2, CCL5, TNF, IFNγ) and matrix metalloproteinases (MMP2, MMP9) in aortic lesions, and altered the expression levels of macrophage M1 (ArgII, iNOS) and M2 (ArgI, CD206) polarization markers. In vitro experiments in murine VSMC revealed that SOCS1 peptide prevented the expression of cytokines and chemokines induced by non-toxic dose of elastase (5 ug/ml, 24 hours). Effects of SOCS1 treatment were accompanied by a reduction in STAT1 and STAT3 phosphorylation and gene expression, both in AAA lesions and cultured VSMC.

Conclusion: Our results suggest that SOCS1 peptide presents protective effects in experimental AAA by suppressing JAK/STAT pathway-mediated inflammation.