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Anti-inflammatory adipokine, omentin, attenuates angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein-E knockout mice

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Topic(s):
Atherosclerosis, Cerebrovascular Diseases, Aneurysm, Restenosis

Citation:
European Heart Journal (2019) 40 (Supplement), 753

Background: Abdominal aortic aneurysm (AAA) is an increasing and life-threatening disease. Obesity is associated with an increased risk of AAA. Omentin is a circulating adipokine, which is downregulated by obesity. Recently we have demonstrated that omentin is an anti-inflammatory adipokine that prevents the development of atherosclerosis in apolipoprotein-E knockout (apoE-KO) mice. Here we examined whether omentin could modulate angiotensin II-induced AAA formation in apoE-KO mice.

Methods and results: To overexpress human omentin in apoE-KO mice, apoE-KO mice were crossed with transgenic mice expressing the human omentin gene in fat tissue under the control of AP2 promoter (OMT-Tg mice). Circulating levels of human omentin in apoE-KO/OMT-Tg mice were approximately threefold higher than those in healthy human subjects, whereas human omentin was undetectable in apoE-KO mice. There were no differences in body weight, blood pressure and heart rate between apoE-KO/OMT-Tg and apoE-KO mice. We also subjected apoE-KO/OMT-Tg and apoE-KO mice at 24 weeks of age to continuous angiotensin II-infusion by using osmotic mini pumps for 4 weeks, which is a widely-accepted model of experimental AAA. ApoE-KO/OMT-Tg mice exhibited a lower incidence of AAA formation and a reduced maximal diameter of AAA determined by direct measurement and ultrasound imaging as compared with apo-E KO mice. In histological analyses with van Gieson staining, apoE-KO/OMT-Tg mice showed attenuated disruption of medial elastic fibers in response to angiotensin II compared with apo-E KO mice. ApoE-KO/OMT-Tg mice also displayed reduced mRNA levels of matrix metalloproteinase (MMP) 2 and MMP9 as well as pro-inflammation genes including interleukin (IL)-6 in aortic walls compared with apo-E KO mice. Treatment of human monocyte-derived macrophages with human omentin protein attenuated LPS-stimulated expression of MMP9, TNF-α and IL-6. Omentin treatment also reduced LPS-induced activation of MMP9 in cultured media of human macrophages as evaluated by gelatinolytic zymography. Omentin treatment increased phosphorylation levels of Akt in human macrophages. The suppressive effects of omentin on inflammatory response in macrophages were reversed by treatment with LY294002, which is an inhibitor of PI3 kinase/Akt signaling.

Conclusion: These data suggest that omentin acts as an adipokine that can attenuate angiotensin II-induced development of AAA through suppression of MMP activation and inflammatory response in the vascular wall.