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Functional deficiency in activating fegamma receptor protects against aortic abdominal aneurysm in mice

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BACKGROUND AND AIM: Abdominal aortic aneurysm (AAA) is a degenerative disorder characterized by a localized and permanent dilation of the aorta. Pathological features of AAA include proteolysis, vascular smooth muscle cells (VSMC) apoptosis, oxidative stress and inflammation. Previous studies have demonstrated the role of innate and adaptive immunity in the initiation and progression of AAA. However, the specific mechanisms of humoral, antibody-mediated, immune response elicited by self and non-self-antigens are not completely known. IgG Fc receptors (FcgammaR) play an important role in the initiation and regulation of many immunological and inflammatory processes, thus providing a link between humoral and cellular immune responses. In this work, we focus on IgG immune response against antigens exposed in the damaged vessel, analysing the specific role played by FcgammaR in the pathogenesis of AAA.

METHODS AND RESULTS: AAA was induced by aortic elastase perfusion in wild-type (WT) C57BL/6 mice (n=24 males, 12 weeks old). Compared with healthy aortas, AAA tissue showed IgG and IgM deposition and increased expression levels of activating (IA, IIIA and IVA) and inhibitory (IIB) FcgammaR (5-, 3-, 10, and 2-fold increases; p<0.005) at day 14 post-elastase perfusion. To explore the functional contribution of activating FcgammaR to AAA formation, parallel experiments were performed in mice deficient in gamma-chain (gamma-KO), the common signalling subunit of FcgammaRI, III and IV. Compared with WT mice, gamma-KO mice (n=21) exhibited lower IgG and IgM deposits (21±4% and 28±12% vs WT, respectively; p<0.02) and decreased AAA lesions with reduced aortic expansion (% vs WT: aortic wall thickness, 67±3%; aortic diameter, 55±3%; p<0.0001). AAA lesions from gamma-KO mice showed less disruption of elastin layers (Verhoeff-van Gieson staining) and reduced loss of medial VSMC (α-actin immunofluorescence). Inflammatory markers such as leukocyte content (CD68+ macrophages, Ly6G+ neutrophils, CD45R+ B cells, and CD3+ T lymphocytes) and the gene expression of chemokines (MCP-1, RANTES), adhesion molecules (ICAM-1), cytokines (TNFa, IFNg, IL-10) and metalloproteinases (MMP9) were all significantly lower in AAA lesions from gamma-KO mice than those from WT mice. In vitro, cross-linking of FcgammaR with fibrinogen-containing immune complexes triggers the gene expression of proinflammatory cytokines and chemokines in both VSMC and bone marrow-derived macrophages.

CONCLUSION: Activating FcgammaR participate in AAA formation by promoting inflammatory cell recruitment, and cytokine and matrix-degrading protease expression. Therefore, modulation of FcgammaR-dependent responses could be a promising therapeutic option for the treatment of AAA.