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EFFECTS OF FC γ RIIIA ON AORTIC ATHEROSCLEROTIC PLAQUE DESTABILISATION IN APOE $^{-/-}$ MICE

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Objectives Our previous studies suggest that Fc receptor III A of immunoglobulin G (Fc γ RIIIA, also named CD16) is closely correlated to coronary heart disease (CHD). However, the mechanism responsible for Fc γ RIIIA's in contribution to CHD development remains largely unclear. Atherosclerosis, a chronic inflammatory

state, is implicated in the pathogenesis of CHD. Thrombosis induced by atherosclerotic plaque destabilisation is the leading cause of the incidence of acute cardiovascular events. Herein, we investigated the possible role of Fc γ RIIIA in the atherosclerotic plaque destabilisation using an aortic atherosclerosis mouse model of ApoE^{-/-} mice in vivo.

Methods Twenty wt C57BL/6J mice were chosen as the control group, and 60 ApoE^{-/-} mice were randomly divided into three groups, ApoE^{-/-} group, ApoE^{-/-}+ IVIG group, ApoE^{-/-}+ Simvastatin (Sm) group, with 20 mice in each group. Mice in ApoE^{-/-}+IVIG group received an intraperitoneal injection of IVIG (1 mg/g) daily over a 5-day period prior to the exposure to high-fat diet. Mice in the ApoE^{-/-}+Sm group received Sm (0.026 g/kg) per gavage for 10 weeks. Mice in C57 group and ApoE^{-/-} group received PBS. Pathomorphological changes of aorta were observed by Masson staining evaluating plaques collagen content, immunohistochemical staining α -actin and CD68 evaluating contents of plaques vascular smooth muscle cells and macrophages, and oil red O staining evaluating plaques adipose tissue contents. Fc γ RIIIA expression changes in mice with atherosclerotic plaque were determined by assaying the protein level of membrane CD16 on monocytes using immunofluorescent staining and FACS analysis. To verify the potential role of Fc γ RIIIA in atherosclerotic plaque destabilisation and inflammatory response, matrix-metalloproteinase-9 (MMP-9) in aorta at protein level and mRNA expression and TNF- α , IL-1 and soluble E-selectin (sE-selectin) levels in sera were observed, respectively.

Results Aortic atherosclerotic plaque formation was induced in ApoE^{-/-} mice after feeding on high-fat diet for 10 weeks which was confirmed by assessment of blood lipid levels and histological examination of aortic roots. The protein level of membrane CD16 on monocytes reflected by the percentage of CD16-positive cells in ApoE^{-/-} mice was significantly increased compared to the control, and that in IVIG pretreatment mice was decreased compared to the ApoE^{-/-} mice. Similarly, both the mRNA and protein levels of MMP-9 of aorta were increased in ApoE^{-/-} mice. The role of Fc γ RIIIA inhibition by IVIG in atherosclerotic plaque destabilisation in ApoE^{-/-} mice was similar to that with Simvastatin treatment. Additionally, we observed increased serum levels of TNF- α , IL-1 and sE-selectin in ApoE^{-/-} mice, compared to the C57 mice, and the effect of Fc γ RIIIA inhibition by IVIG on inflammation was similar to the ApoE^{-/-} mice treated with simvastatin.

Conclusions Collectively, our data demonstrate that Fc γ RIIIA is involved in the atherosclerotic formation by stimulating expression of inflammatory cytokines and triggering the atherosclerotic plaque destabilisation.