GW23-e0381 **APOLIPOPROTEIN E SUPPRESSES IL-12 PRODUCTION IN MACROPHAGES**

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Objectives Accumulation of T cells and macrophages in atherosclerotic plaques and the formation of antibodies directed against plaque proteins suggests that adaptive immunity contributes to the development of atherosclerosis. Apolipoprotein E (apoE) exerts potent anti-inflammatory effects that may contribute to protection against atherosclerosis independent of its role in lipid metabolism. Here, we investigated the expression of pro-inflammatory cytokine interleukin-12 (IL-12) in macrophages of apoE$^{-/-}$ mice and then further explored the molecular mechanisms.

Methods In this study, peritoneal macrophages and bone marrow-derived macrophages elicited from wild-type (WT) or apoE knockout (apoE$^{-/-}$) mice were stimulated with low-dose lipopolysaccharide (LPS), interferon-r (IFN-r) or LPS plus IFN-r for 24 h, followed by collection of culture supernatants for measurement of IL-12 p40 and p70 protein secretion by ELISA. Meanwhile, cells treated with these stimuli for 4 h were used for RNA isolation and IL-12 p35 and p40 mRNA detection by quantitative real-time PCR. Then, we transiently co-transfected a human IL-12 p35 promoter luciferase construct with different amounts of apoE expression vector or $PTYB_2$ vector into THP-1 cells (a human macrophage cell line) by electroporation, followed by measurement of luciferase activity in cell lysates.

Results The expression of IL-12 were upregulated to a significantly greater extent in apoE-deficient mice than in WT mice at both the mRNA and protein levels following administration of LPS or LPS plus IFN-r. ApoE suppressed IL-12 p35 promoter in a dose-dependent manner, indicating that apoE-mediated p35 gene suppression is regulated at the level of transcription. Moreover, cells co-transfected with the p35 promoter and the apoE-expressing vector showed decreased promoter activities in response to IFN-r and LPS treatments compared with cells co-transfected with the empty vector, $PTYB_2$, further demonstrating that apoE suppressed IL-12 p35 gene transcription under both basal and inducible conditions.

Conclusions Our study reveals that apoE suppresses IL-12 production at the level of transcription in macrophages, this effect may represent a novel anti-inflammatory activity of apoE.