Interleukin-4 regulates macrophage polarization via the MAPK signaling pathway to protect against atherosclerosis

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ABSTRACT. Our study aimed to investigate the effects of interleukin-4 (IL-4) on macrophage polarization, as well as its role in the development of atherosclerosis. Human peripheral blood mononuclear cells (PBMCs) were isolated and randomly divided into 3 groups: control group, ox-LDL group, and ox-LDL + IL-4 groups. The expression of M1/M2 macrophage surface markers such as TNF-α, CD68, and CD206 were analyzed by western blot. Cell viability was determined using the MTT assay. Measurement of CD86/CD206 expression ratio (M1/M2 ratio) was performed via flow cytometry. In addition, ApoE−/− mice on a C57BL/6 background were subjected to high-fat diets, and were used as a model of atherosclerosis. Atherosclerotic lesion area was quantified after mice were treated with ox-LDL and IL-4. Finally, expression of phosphorylated MAPK signaling molecules such as p-ERK and p-JNK was quantified using western blot. The expression of TNF-α and CD86 markedly increased after cells were treated with ox-LDL, whereas the expression of CD206 markedly increased after PBMCs were treated with IL-4. It is possible that IL-4 could decrease ox-LDL-induced cell viability and the CD86/CD206 (M1/M2) ratio. Additionally, IL-4 intervention attenuated
ox-LDL-induced atherosclerotic lesions in ApoE−/− mice, and decreased ox-LDL-induced expression of p-ERK and p-JNK. Our findings indicate that IL-4 may induce macrophages to take on an M2 phenotype in order to resolve inflammation via inhibition of MAPK signaling pathways, thereby protecting against atherosclerosis. IL-4 may serve as an intervention target for atherosclerosis.

**Key words:** Atherosclerosis; Interleukin-4; M2 macrophage; MAPK signaling pathway