Lack of Mitogen-activated Kinase Phosphatase-5 in Macrophages Protects Ldlr-null Mice against Atherosclerosis

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Background: Mitogen-activated protein kinases, including JNK, ERK, and p38 mitogen-activated protein kinase, are critical in regulating the expression of various proinflammatory and anti-inflammatory cytokines and chemokines. Previous work has suggested that the absence of MAP kinase phosphatase-5 (MKP-5) inhibits oxidized low-density lipoprotein (oxLDL)-induced macrophage foam cell formation without influencing the MAPK activation. The current study is to determine the role of macrophage MKP-5 in the pathogenesis of atherosclerosis and underlying mechanisms.

Methods: Nine-week-old male congenic MKP-5 deficient (MKP-5−/−) and C57Bl/6 control (WT) mice on an low-density lipoprotein (LDL) receptor knock-out (LDLR−/−) background were fed with a high-fat diet containing 125% cholesterol for 14 weeks. Global deficiency of MKP-5 attenuated atherosclerotic plaque formation without altering the lipid profile in vivo. To further elucidate the macrophage-specific effect of MKP-5 in atherosclerosis, lethally irradiated LDLR−/− mice were transplanted with wild-type or MKP-5−/− bone marrow and subjected to high-fat feeding.

Results: Mice transplanted with MKP-5−/− bone marrow developed smaller atherosclerotic lesions compared by decreased lipid deposition and macrophage content compared with wild type. Lack of MKP-5 in macrophages reduced plasma levels of interleukin-1α and IL-7, elevated anti-inflammatory cytokines IL-1 receptor antagonist (IL-1ra) and IL-4. Mechanistically, lack of MKP-5 in macrophages inhibited ox-LDL-induced foam cell formation through enhanced cholesterol efflux mediated by increased expression of ATP-binding cassette transporters ABCA1 and ABCG1.

Conclusion: These data suggest that the myeloid MKP-5 deficiency reduces atherosclerosis progression and foam cell formation by ameliorating cholesterol efflux and inhibiting inflammation.