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

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Abstracts

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 MAKP 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/6j control (WT) mice on a 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 accompanied by decreased lipid deposition and macrophage content compared with wild type. Lack of MKP-5 in macrophages reduced plasma levels of interleukin-1α (IL-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 ABCB1.

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


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Imatinib Promotes Reverse Cholesterol Transport and Elevates Scavenger Receptor BI

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Abstracts

Background: Dyslipidemia is a cardiovascular risk factor for coronary artery disease and atherosclerosis that is characterized by elevated serum cholesterol and lipid levels. Although high-density lipoprotein-associated cholesterol (HDL-C) is associated with a reduced risk of cardiovascular events, targeted therapy to increase HDL-C levels has been unsuccessful in altering outcomes of associated atherosclerotic disease. Single nucleotide polymorphisms in SCARB1 the gene that encodes HDL receptor scavenger receptor B1 (SR-BI), are associated with dyslipidemia and atherosclerotic cardiovascular disease. We were the first to identify inherited mutations in SCARB1 that segregate with disease in a family with severe coronary artery disease and dyslipidemia, including elevated HDL. Our findings suggest that HDL function (vs HDL-C concentration) may be a promising target for cholesterol-based therapy.

Methods: Here, we performed an unbiased high throughput drug screen with ~788 US Food and Drug Administration-approved compounds, using HepG2 cells to measure endogenous HDL binding. We identified five compounds that significantly increased endogenous HDL binding: imatinib, trimethoprim, eszopiclone, clemastine, and mepenzolate, of which imatinib was the only compound to increase SR-BI expression. Imatinib is a tyrosine kinase inhibitor that is a chemotherapeutic agent designed to treat individuals with chronic myeloid leukemia.

Results: Limited clinical evidence suggests a reduction in total cholesterol with 400 mg/day imatinib. Additionally, imatinib treatment (150 mg/kg) in mouse models of atherosclerosis reduces total cholesterol. Yet, no data are available on the effects of imatinib on HDL and reverse cholesterol transport. We have found that imatinib promotes HDL binding and SR-BI expression in vitro. Furthermore, in wildtype C57Bl/6j mice on a high-fat, high cholesterol diet, imatinib treatment (50 mg/kg) was sufficient to decrease plasma total cholesterol, HDL-C and triglyceride levels and elevate hepatic SR-BI expression.

Conclusions: Our data support the exploration of imatinib-mediated SR-BI induction and RCT pathway to identify new therapeutic targets for dyslipidemia.