Myeloid cells regulate plasma LDL-cholesterol levels

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Myeloid cells regulate plasma LDL-cholesterol levels

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Purpose of review
Leukocytosis, elevated blood leukocyte levels, is associated with enhanced cardiovascular risk in humans. Hematopoietic stem and progenitor cells (HSPCs) drive leukocyte production in a process called hematopoiesis, which mainly occurs in the bone marrow, and under certain conditions also in other organs such as the spleen. Cholesterol accumulation in HSPCs enhances hematopoiesis, increasing levels of blood monocytes that infiltrate into atherosclerotic plaques. Although HSPC proliferation and monocytosis enhance atherogenesis in several studies, concomitant decreases in LDL-cholesterol levels have also been reported, associated with anti-atherogenic effects. This review focuses on the link between HSPC proliferation, leukocytosis, plasma LDL-cholesterol levels, and atherogenesis.

Recent findings
Recent studies have shown that an acute infection enhances cholesterol accumulation in HSPCs, driving HSPC proliferation, and leading to the expansion of myeloid cells (monocytes, neutrophils, and macrophages). Enhanced hematopoiesis is associated with low plasma LDL-cholesterol levels in animal models and humans, probably because of the increased number of myeloid cells that take up LDL-cholesterol. Despite low-plasma LDL-cholesterol levels, specific patient populations with enhanced hematopoiesis show increased cardiovascular risk.

Summary
Enhanced hematopoiesis and monocytosis may accelerate atherogenesis. Studies on these processes may lead to the identification of new therapeutic targets for cardiovascular diseases.

Keywords
atherosclerosis, hematopoiesis, inflammation, LDL-cholesterol, leukocytosis

INTRODUCTION

Leukocytosis, the expansion of white blood cells, including monocytes and neutrophils, has been associated with increased cardiovascular risk in humans [1]. Although leukocytosis has originally been attributed to enhanced inflammation [1], enhanced hematopoiesis also plays a key role [2▪▪,3]. During hematopoiesis, hematopoietic stem and progenitor cells (HSPCs) drive the production of several hematopoietic cell types including common myeloid progenitors (CMPs) and granulocyte monocyte/macrophage progenitors (GMPs) that give rise to monocytes and neutrophils, cells of the myeloid lineage [4]. Cholesterol accumulation in HSPCs enhances hematopoiesis, leading to monocytosis and neutrophilia [2▪▪,3]. These findings have been reviewed extensively in [5] and are summarized briefly in this review.

Although several studies in animal models have shown that HSPC proliferation and leukocytosis enhance atherogenesis [2▪▪,3,6–8], a series of studies has reported concomitant decreases in apolipoprotein B (apoB)-containing lipoproteins, associated with antiatherogenic effects [9–12]. This link was first described in patients with myeloproliferative disorders (MPD) [13]. MPD patients show continuous hematopoietic cell proliferation, described as myeloproliferation, accompanied by low plasma LDL-cholesterol levels [13]. Fifty to ninety percent of MPD patients are carriers of the *JAK2* p.Val617Phe

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KEY POINTS

- The *JAK2* p.Val617Phe mutation, present in 50–90% of patients with myeloproliferative diseases, enhances cardiovascular risk in humans despite low-plasma LDL-cholesterol levels.
- Cholesterol accumulation in hematopoietic stem and progenitor cells (HSPCs) enhances monocytosis and neutrophilia, accelerating atherogenesis.
- An acute infection enhances cholesterol accumulation in HSPCs, expanding the population of myeloid cells, potentially linking infections with atherogenesis.

mutation [14–18]. Interestingly, recent studies have shown that carriers of the *JAK2* p.Val617Phe mutation have an increased cardiovascular risk despite low-plasma LDL levels [19▪▪]. In this review, we will discuss the link between hematopoiesis, myeloid cell expansion, plasma VLDL/LDL-cholesterol, and atherosclerosis.

CHOLESTEROL EFFLUX PATHWAYS SUPPRESS MONOCYTOSIS WITH ANTI-ATHEROGENIC EFFECTS

The cholesterol transporters, ATP-Binding Cassette A1 and ATP-Binding Cassette G1 (ABCA1 and ABCG1) mediate cholesterol efflux to apolipoprotein A1 (apoA1) and HDL, respectively [20–22]. ABCA1 and ABCG1 act in several cell types to mediate cholesterol efflux, including monocytes, macrophages, and HSPCs [5]. Although the anti-atherogenic effects of these cholesterol efflux pathways were initially attributed to their role in macrophages [8], later studies suggested a key atheroprotective role for cholesterol efflux pathways in HSPCs [2▪▪,12]. HSPCs secrete ApoE, which interacts with ABCA1 and ABCG1 at the cell surface to facilitate cholesterol efflux in a cell-intrinsic manner [3]. Hematopoietic *Abca1/g1* or *Apoe* deficiency enhances cholesterol accumulation in HSPCs, increasing HSPC proliferation, which drives production of monocytes, accelerating atherogenesis [2▪▪,3,23]. Mechanistic studies showed that enhanced *Abca1/g1* or *Apoe*-deficient HSPC proliferation was accompanied by increased surface expression of the common β subunit to the interleukin-3/granulocyte macrophage-colony-stimulating factor (IL-3/GM-CSF) receptor [2▪▪,3,24]. Hematopoietic deficiency of this receptor suppressed HSPC proliferation, monocytosis, and atherosclerosis in $Ldlr^{-/-}$ mice transplanted with $Apoe^{-/-}$ bone marrow [23]. Thus, cholesterol efflux pathways suppress HSPC proliferation and expansion by decreasing surface expression of the common β subunit to the IL-3/GM-CSF receptor. Further studies have shown that increased levels of HDL either as a consequence of overexpression of the *APOA1* transgene or via injection of reconstituted HDL (rHDL) suppress HSPC proliferation and monocytosis in mice [2▪▪,3], whereas *Apoa1* deficiency leads to the opposite phenotype [7]. An inverse correlation of plasma HDL levels with blood monocytes was also found in children with familial hypercholesterolemia, indicating that HDL-mediated cholesterol efflux pathways also suppress monocytosis in humans [7].

Abca1/g1 or *Apoe*-deficient mice may represent extreme phenotypes; however, downregulation of *Abca1/g1*-occurs during diabetes or in the setting of an infection [25–27]. Interestingly, a recent study has shown that in a model of trained immunity, injection of β-glucan and subsequently lipopolysaccharide (LPS) led to cholesterol accumulation in HSPCs, driving HSPC expansion and monocytosis [26▪▪]. HSPC expansion was accompanied by decreased expression of *Abca1* and increased expression of several cholesterol-synthesis genes. Experiments using statins and GM-CSF antibodies showed that HSPC expansion was dependent on cholesterol accumulation and increased surface expression of the common β subunit to the IL-3/GM-CSF receptor [26▪▪]. These studies [26▪▪] suggest that cholesterol accumulation in HSPCs may drive the production of myeloid cells during infections, suggesting broader implications of the mechanisms identified in mice with hematopoietic *Abca1/g1* or *Apoe* deficiency [2▪▪,3]. In addition, these findings [26▪▪] may also offer an explanation for the increased susceptibility to atherogenesis in the setting of an infection [28].

PLASMA APOLIPOPROTEIN B-CONTAINING LIPOPROTEINS ARE DECREASED IN PATIENTS WITH MYELOPROLIFERATIVE DISORDERS

Although several studies in animal models have shown that HSPC proliferation and leukocytosis enhance atherogenesis [2▪▪,3,6,8], a series of studies has reported concomitant decreases in apoB-containing lipoprotein levels, associated with anti-atherogenic effects [9–12]. The link between myeloproliferation and low LDL-cholesterol plasma levels was first described in MPD patients [13]. An overview of studies in these patients is given in Table 1.

MPD patients show higher fractional catabolic rate of LDL Apo-B [29], most likely accounting for their low LDL-cholesterol plasma levels [29–31]. MPD patients present with splenomegaly and extramedullary hematopoiesis (i.e. hematopoiesis occurring outside of the bone marrow) [30,31]. Their

Table 1. Myeloproliferative disorders inversely correlate with plasma LDL-cholesterol levels in humans

Study	Study population	Plasma cholesterol levels (ApoB-containing lipoproteins)
Characterization of hypocholesterolemia in myeloproliferative disease [31]	32 MPD patients; controls from the Framingham study	Lower plasma TC levels reflected by decreased plasma LDL-C levels; Splenectomy, chemotherapy, or splenic irradiation increased LDL-C by >17%
Increased low-density lipoprotein catabolism in myeloproliferative disease [29]	7 MPD patients and 5 healthy controls	TC 44% ↓; LDL-C 53% ↓; ApoB 27% ↓; Fractional catabolic rate of LDL ApoB 70% ↑
Increased low-density lipoprotein levels after splenectomy: a role for the spleen in cholesterol metabolism in myeloproliferative disorders [30]	34 MPD patients (14 splenomegaly, 10 normal sized spleen, 10 underwent splenectomy), and 10 healthy controls	TC 30% ↓ Splenectomy increased plasma TC levels by 34% (mainly LDL-C)
Exome-wide association study of plasma lipids in >300,000 individuals [19▪▪]	Screen variants in more than 300 000 individuals; JAK2 p.Val617Phe mutation	LDL-C ↓

ApoB, apolipoprotein B; LDL-C, LDL-cholesterol; MPD, myeloproliferative disorders; TC, total cholesterol.

spleen size inversely correlates with plasma LDL-cholesterol levels [31]. Importantly, splenectomy normalizes plasma LDL-cholesterol [30,31], suggesting a direct link between splenic myeloproliferation and LDL-cholesterol catabolism. Several studies have been performed to identify the mechanism for this link.

LDL-uptake studies using ^{99m}Technetium LDL (^{99m}Tc-LDL) have shown marked splenic and bone marrow ^{99m}Tc-LDL-uptake in MPD patients opposed to predominant liver ^{99m}Tc-LDL-uptake by controls [32▪▪]. High ^{99m}Tc-LDL-uptake was observed in hypercellular areas of the bone marrow, suggesting a link between LDL-uptake and myeloproliferation [32▪▪]. Studies in mice have shown that HSPCs utilize LDL-cholesterol to enhance their proliferation, and take up LDL-cholesterol via LDL receptor dependent and independent mechanisms [7]; the latter presumably mediated by macropinocytosis, a mechanism that has been described in macrophages [33], but could also mediate LDL-uptake in HSPCs. We propose a mechanism where continuous uptake of

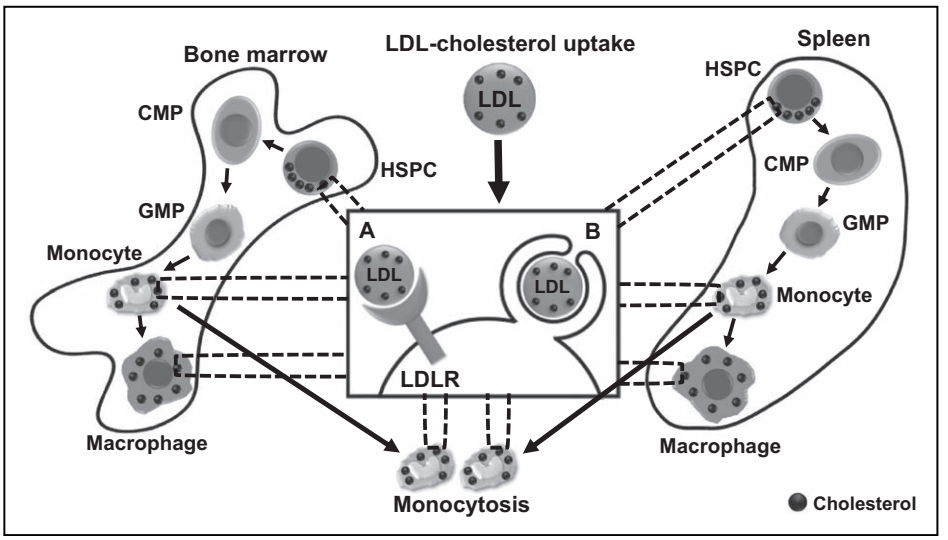

FIGURE 1. LDL-cholesterol uptake in hematopoietic stem and progenitor cells enhances hematopoiesis. HSPCs take up LDL-cholesterol in an LDL receptor (LDLR) dependent (a) and independent manner (b) in bone marrow and spleen, enhancing their proliferation, and driving production of common myeloid progenitors (CMPs), granulocyte monocyte/macrophage progenitors (GMPs), monocytes, and macrophages, eventually leading to monocytosis. In bone marrow, blood, and spleen, monocytes and macrophages take up LDL-cholesterol, lowering LDL-cholesterol in the setting of excessive hematopoiesis. HSPCs, hematopoietic stem and progenitor cells.

LDL by HSPCs fuels myeloproliferation in bone marrow and spleen of MPD patients (Fig. 1). HSPC proliferation drives the production of monocytes/macrophages [2▪▪,3] that efficiently store LDL-cholesterol [34]. It has been suggested that monocytes/macrophages are the predominant cell type contributing to low-plasma LDL-cholesterol levels in MPD patients [32▪▪]. This would imply that LDL-cholesterol drives HSPC proliferation in bone marrow and spleen of MPD patients, giving rise to monocytes and macrophages that subsequently accumulate LDL-cholesterol in these organs and lower plasma LDL-cholesterol levels (Fig. 1).

MYELOPROLIFERATIVE DISEASES ENHANCE CARDIOVASCULAR RISK

MPDs are associated with a decreased life expectancy [35]. The causes of death in MPD patients have been studied in the Swedish population in a cohort consisting of 9285 MPD patients and 35 769 controls. Interestingly, MPD patients in the groups of 18–49 years or 50–59 years at age of diagnosis showed a significantly elevated risk of cardiovascular death compared with the control group [36]. Even though confined to a specific age group, these results may suggest that myeloproliferation in bone marrow and spleen enhances cardiovascular risk in humans, similar to observations in animal models [2▪▪,3].

Interestingly, a recent study has shown that carriers of the *JAK2* p.Val617Phe mutation, which occurs in 50–90% of MPD patients [14–18], have low-plasma LDL-cholesterol levels [19▪▪]. Strikingly, the *JAK2* p.Val617Phe mutation is associated with enhanced cardiovascular risk [37]. These observations may suggest that myeloproliferation in carriers of the *JAK2* p.Val617Phe mutation predicts cardiovascular risk independently of plasma LDL-cholesterol. The mechanisms underlying these observations warrant further investigation.

ADMINISTRATION OF GROWTH FACTORS THAT STIMULATE MYELOID CELL PRODUCTION DECREASES PLASMA LEVELS OF APOLIPOPROTEIN B-CONTAINING LIPOPROTEINS

Several growth factors stimulate HSPC proliferation, including granulocyte monocyte/macrophage-colony stimulating factor (GM-CSF) [38]. GM-CSF skews HSPCs towards production of myeloid cells [39]. Macrophage-colony stimulating factor (M-CSF) skews GMPs towards monocyte/macrophage production [40]. Patients with defects in hematopoiesis have been treated with these growth factors for hematopoietic recovery [41–43]. The detailed outcome of these studies is shown in Table 2. In summary, these studies show that administration of GM-CSF or M-CSF to stimulate production of myeloid cells in humans is associated with myeloproliferation and low-plasma LDL-cholesterol levels (Table 2) [41,42,44,45], similar to findings in MPD patients.

Table 2. Granulocyte-macrophage-colony-stimulating factor and monocyte/macrophage-colony stimulating factor administration decreases plasma levels of apoB-containing lipoproteins in humans

Study	Study population	Intervention	Blood leukocyte levels, bone marrow/spleen cellularity	Plasma cholesterol levels (ApoB-containing lipoproteins)
Serum cholesterol-lowering activity of human monocytic colony-stimulating factor [42]	7 children with chronic neutropenia	Injections of native human M-CSF (2×10^5 units/kg) for 7 days	Increased neutrophil counts in five patients and monocyte counts in one patient	TC 20.6%↓
Serum cholesterol-lowering activity of granulocyte-macrophage colony-stimulating factor [41]	8 patients with refractory aplastic anemia	Continuous intravenous infusion of GM-CSF for ~4 weeks (escalating dose: 4–64 μg/kg/day)	Increased leukocyte counts in all patients, increased bone marrow cellularity	TC 27–53%↓ reflected by decreased plasma LDL-C levels [45]
Safety and efficacy of subcutaneous-only granulocyte-macrophage colony-stimulating factor for collateral growth promotion in patients with coronary artery disease [44]	14 patients with chronic stable coronary artery disease	Subcutaneous injections of GM-CSF or placebo for 2 weeks	Leukocyte count 4-fold; ↑ neutrophils 4.4-fold ↑ Monocytes 1.8-fold ↑	TC 25% ↓

ApoB, apolipoprotein B; GM-CSF, granulocyte-macrophage-colony-stimulating factor; LDL-C, LDL-cholesterol; M-CSF, monocyte/macrophage colony-stimulating factor; TC, total cholesterol.

Table 3. Monocyte/macrophage colony-stimulating factor inversely correlates with plasma levels of apoB-containing lipoproteins in animal models

Study	Model	Intervention	Blood leukocyte levels, bone marrow/spleen cellularity	Plasma cholesterol levels (ApoB-containing lipoproteins)
Human monocyte colony-stimulating factor enhances the clearance of lipoproteins containing Apolipoprotein B-100 via both low density lipoprotein receptor-dependent and -independent pathways in rabbits [46]	Male NZW and WHHL (deficient in LDL receptor) rabbits	Intravenous injection of recombinant human M-CSF (NZW: 100 μg, WHHL: 500 μg)	Increased cellularity of bone marrow and spleen	TC 33–36% ↓; Clearance of plasma ApoB-100 containing lipoproteins 1.56–1.97 fold ↑
Effects of recombinant human macrophage colony-stimulating factor on plasma cholesterol levels [11]	Female NZW and WHHL rabbits, and cynomolgus monkeys	Recombinant human M-CSF	Cholesterol-laden blood monocytes ↑ Hepatic and splenic macrophages ↑ Extramedullary hematopoiesis in liver and spleen ↑	Monkeys: TC 16–55%↓; NZW rabbits: TC 25% ↓; WHHL rabbits: TC 40% ↓; all reflected by decreased LDL-C
Heterozygous osteopetrotic (op) mutation reduces atherosclerosis in LDL receptor-deficient mice [47]	*Ldlr*$^{-/-}$ mice homozygous (*op/op*) for the *M-Csf* mutation and their *Ldlr*$^{-/-}$ littermates fed a high-fat high-cholesterol diet	–	*M-Csf* mutation: blood monocytes 55% ↓	*M-Csf* mutation: TC 50% ↑ increases in VLDL/LDL-C

ApoB, apolipoprotein B; LDL-C, LDL-cholesterol; M-CSF, monocyte/macrophage colony-stimulating factor; NZW, New Zealand white rabbits; TC, total cholesterol; VLDL-C, VLDL-cholesterol; WHHL, Watanabe heritable hyperlipidemic rabbits.

Findings in animal models confirm these observations and shed more light on the underlying mechanisms (Table 3). M-CSF administration lowers LDL-cholesterol and enhances LDL apoB-catabolic rate independent of the LDL receptor in rabbits [46], and stimulates extramedullary hematopoiesis in liver and spleen leading to increased cholesterol-laden blood monocytes and hepatic and splenic macrophage foam cells in rabbits and monkeys [11]. Conversely, *Ldlr*$^{-/-}$ mice deficient in *M-Csf* show depletion of blood monocytes and hypercholesterolemia [47]. These results indicate that GM-CSF and M-CSF enhance myeloproliferation, expanding the number of myeloid cells that take up LDL-cholesterol (Fig. 1). These findings share similarities with those in MPD patients, and reveal that LDL-cholesterol uptake in myeloid cells occurs independent of the LDL receptor, suggesting a role for other pathways in LDL-uptake, perhaps including macropinocytosis [33].

MYELOID CELLS DECREASE PLASMA APOLIPOPROTEIN B-CONTAINING LIPOPROTEINS

Studies in *Ldlr*$^{-/-}$ mice with HSPC or myeloid cell expansion offer additional insights on the link of apoB-containing lipoproteins with HSPC proliferation, leukocytosis, and atherogenesis. Whole body *Apoa1* deficiency, myeloid *Abca1* or *Abca1/g1* deficiency, hematopoietic *Abca1/g1* deficiency, or combined deficiency of *Abca1* and *Scavenger Receptor B1* (*Srb1*) decrease plasma VLDL/LDL-cholesterol levels in *Ldlr*$^{-/-}$ mice fed a cholesterol-rich diet to levels of 25–50% of the controls [10,12,48–50]. Plasma VLDL/LDL-cholesterol levels are not affected in *Ldlr*$^{-/-}$ mice on chow [10,12,48–50]. These findings lead us to propose that whenever VLDL/LDL levels are in the range of 200–300 mg/dl in *Ldlr*$^{-/-}$ mice fed chow diet, the main clearance route for VLDL/LDL cholesterol is the liver. Whenever plasma cholesterol levels increase further, additional pathways involving monocytes and macrophages contribute to plasma VLDL/LDL clearance. One possible explanation could be that deficiency of cholesterol efflux pathways [10,12,48,49] or an almost complete deficiency of HDL [50] promotes myelopoiesis and extramedullary hematopoiesis, which may decrease VLDL/LDL-cholesterol plasma levels via accelerated clearance of the apoB-containing lipoprotein particles by expanded myeloid cells. This is in line with studies on MPD patients.

MYELOID CELLS DECREASE VERY LOW DENSITY LIPOPROTEIN PRODUCTION

The decreased VLDL/LDL cholesterol levels in the models described above could also be attributed to decreased VLDL production. Myeloid *Abca1* deficiency and hematopoietic *Abca1/Srb1* deficiency decreased VLDL production in *Ldlr*$^{-/-}$ mice fed cholesterol-rich diets [48,49]. Hematopoietic *Abca1/g1* deficiency decreased the hepatic mRNA expression of *sterol regulatory element binding protein 1c* (*Srebp-1c*), a main pathway for VLDL production [51], in *Ldlr*$^{-/-}$ mice fed Western-type diet [52].

Several explanations could account for the decreases in VLDL production or *Srebp-1c* expression

in these models. Hematopoietic *Abca1/g1* deficiency led to a two-fold increase in the expression of glucose transporter 1 (GLUT-1) in leukocytes, which enhances glucose uptake. As a consequence, hematopoietic *Abca1/g1* deficiency shows enhanced glucose tolerance and hypoglycemia [53]. Hematopoietic *Abca1/g1* deficiency may decrease insulin levels and phosphorylation of Akt in the liver, decreasing *Srebp-1c* expression and VLDL production. It would be of interest to investigate these mechanisms further.

ENHANCED MYELOID CELL INFLAMMATION DECREASES APOLIPOPROTEIN B-CONTAINING LIPOPROTEINS

Several of these models also show increased plasma cytokines [12,48,50], which may have accounted for decreased plasma VLDL/LDL cholesterol levels. Also hematopoietic deficiency of microRNA-146a in *Ldlr*$^{-/-}$ mice increases plasma levels of IL-6, and decreases plasma VLDL/LDL cholesterol levels, accompanied by dramatic extramedullary hematopoiesis [9]. Tocilizumab, which binds to the IL-6 receptor to inhibit IL-6 signaling, increases plasma LDL-cholesterol levels in rheumatoid arthritis patients [54], presumably linked to increased LDL-catabolism [54]. Conversely, increased levels of IL-6 may thus decrease plasma LDL-cholesterol. Also enhanced IL-1β signaling decreases VLDL/LDL-cholesterol plasma levels in hypercholesterolemic mice [55,56]. Of note, both IL-1β and IL-6 stimulate hematopoiesis [9,57], which may explain their plasma VLDL/LDL cholesterol-lowering effects, although exact mechanisms warrant further investigation.

CONCLUSION

MPD patients show myeloid cell expansion. 50–90% of the MPD patients are carriers of the *JAK2* p.Val617-Phe mutation [14–18]. The *JAK2* p.Val617Phe mutation is associated with enhanced cardiovascular risk, despite low-plasma LDL-cholesterol levels [19▪▪], suggesting that myeloid cell expansion increases cardiovascular risk in humans. Studies in mice have shown that cholesterol accumulation in HSPCs enhances monocytosis and atherogenesis [2▪▪,3], indicating that pathways decreasing cholesterol accumulation in HSPCs may be anti-atherogenic. Injections of reconstituted HDL (rHDL) enhance cholesterol efflux and suppress HSPC proliferation [3]. These studies suggest that patients at cardiovascular risk, especially MPD patients, may benefit from rHDL injections to suppress HSPC proliferation. The rHDL CSL-112 is currently in clinical trials for acute coronary syndrome (ACS) [58].

Recent studies have also shown that acute infections enhance cholesterol accumulation in HSPCs, leading to HSPC proliferation [26▪▪]. This was reversed by statins [26▪▪], suggesting that local inhibition of cholesterol synthesis in HSPCs, which can perhaps be achieved by injection of statins in nanoparticles [59] targeted to bone marrow and/or spleen, may suppress HSPC proliferation. Also anti-inflammatory drugs may have the potential to decrease myeloid cell expansion, suppressing atherogenesis.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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