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Hypercholesterolemia links hematopoiesis with atherosclerosis

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Abstract

Atherosclerosis is characterized by the progressive accumulation of lipids and leukocytes in the arterial wall. Leukocytes such as macrophages accumulate oxidized lipoproteins in the growing atheromata and give rise to foam cells, which can then contribute to a lesion's necrotic core. Lipids and leukocytes interact also in other important ways. In experimental models, systemic hypercholesterolemia is associated with severe neutrophilia and monocytosis. Recent evidence indicates that cholesterol sensing pathways control the proliferation of hematopoietic stem cell progenitors. Here we review some of the studies that are forging this particular link between metabolism and inflammation and propose several strategies that could target this axis for the treatment of cardiovascular disease.

Keywords

hypercholesterolemia; atherosclerosis; hematopoietic stem and progenitor cells; monocytes; neutrophils

Hypercholesterolemia and inflammation orchestrate atherosclerosis

Atherosclerosis is a chronic disease of the vascular wall and a primary cause of myocardial infarction, stroke, and peripheral vascular disease [1, 2]. It has been understood for a long time that atherosclerosis involves the progressive accumulation of lipids in the vascular wall. Numerous experimental and epidemiological studies have linked hypercholesterolemia and high serum levels of low density lipoprotein (LDL) to the development of atherosclerosis and its complications [3, 4]. Randomized clinical trials of lipid-lowering therapy have documented up to 30% reduction of major coronary events, thereby validating the significance of high lipid levels as a major contributing risk factor in atherosclerosis [5]. In one particularly extreme case, in Japan in the 1960s, average LDL levels were only about 100 mg/dl. This was associated with a mortality from cardiovascular diseases that was about 10% of that in the United States and the rest of the developed countries [6] despite high nicotine consumption, a higher incidence of hypertension, and a high prevalence of diabetes.

Moreover, experimental animals, which have naturally low LDL levels of ~50mg/dl [7], are resistant to atherosclerosis. Together, these data have placed hypercholesterolemia as one of the most important factors contributing to atherosclerosis.

In addition to lipids, atheromata (see Glossary) also contain leukocytes. Endothelial dysfunction at sites of disturbed flow, an early event in atherosclerosis' pathophysiology, enhances vascular permeability, heightens cell adhesion and chemotactic molecule expression, and permits arterial leukocyte infiltration [8, 9]. Many different types of circulating leukocytes can accumulate in the growing atheromata. Neutrophils, although infrequent in lesions despite their abundance in the circulation, contribute importantly to early atherosclerotic lesion formation [10] (Box 1). Monocytes, the precursors of the most abundant leukocyte population in atheromata – the macrophage – have received considerable attention. Functionally heterogeneous, monocytes are typically separated into two subsets in both human and mouse: the larger, more numerous human CD16⁺CD14⁺/mouse Ly-6C^{high} (also referred to as inflammatory or classical), and the smaller, less numerous human CD16⁺CD14^{dim} /mouse Ly-6C^{low} (also referred to as resident, reparative, patrolling, or nonclassical) [11, 12]. Of the two subsets, Ly-6C^{high} monocytes dominate inflammatory responses and accumulate in atherosclerotic lesions preferentially, in mice [13] (Box 1). Hyperlipidemia and inflammation thus represent two major pillars in the pathophysiology of atherosclerosis [14]. Studies are now beginning to unravel how hypercholesterolemia influences inflammation and we are learning that lipids affect leukocyte phenotype and consequently *in vivo* behaviour [15] (Box 2).

Hypercholesterolemia-induced monocytosis and neutrophilia promote atherosclerosis

Already in the 1970s it was noticed that peripheral leukocyte counts may predict for future cardiovascular events [16]. Subsequent association studies focusing on circulating neutrophil and monocyte counts and cardiovascular risk correlated leukocytes with the risk for a cardiovascular event [17-19]. In mouse models of atherosclerosis, counts of circulating Ly-6C^{high} monocytes [13, 20, 21] and neutrophils [22, 23] correlate with atherosclerotic lesion burden. Human studies have further shown that hyperlipidemia positively correlates with the expansion of circulating monocytes and neutrophils [24], suggesting that lipids influence the expansion of circulating myeloid cells. Additional associative support for this comes from studies employing lipid lowering drugs. Patients receiving pravastatin have reduced neutrophil and monocyte counts, decreased LDL cholesterol, and increased high density lipoprotein (HDL) cholesterol, after 6 months [25]. Similarly, statins reduce hypercholesterolemia-associated Ly-6C^{high} monocytosis in mice [13]. Hence, clinical studies and observations from animal models point to a pathophysiological loop in which hypercholesterolemia increases the numbers of circulating neutrophils and monocytes which then accumulate in lesions and increase atherosclerosis.

The question that arises from these studies is what orchestrates neutrophilia and monocytosis. Some of the increase in neutrophil counts may depend on facilitated mobilization of neutrophils from the bone marrow and reduced homing into tissue [22]. Neutrophils rely on the CXCR2 chemokine receptor 2 and its chemokine ligands (CXCL8 in

human and KC/Gro- α in mice) to exit the bone marrow [26, 27] and enter atherosclerotic lesions [22]. In both mice and humans, hypercholesterolemia enhances plasma levels of CXCR2 ligands as well as neutrophilic CXCR2 expression, rendering neutrophils prone to mobilization [22, 28]. Deletion of CXCR2 or its ligands, therefore, reduces atherosclerosis [29]. Aged neutrophils can also return to the bone marrow by relying on the CXCR4-CXCL12 axis [26, 27]. CXCR4 inhibitors [30] or high fat diet, which reduces CXCL12 levels in the bone marrow [22], interfere with this axis and contribute to neutrophilia and increased atherosclerosis.

Monocytes on the other hand utilize the chemokine receptor C-C chemokine receptor type 2 (CCR2) to exit the bone marrow [31-33] and enter lesions [20]. In mice lacking CCR2, development of atherosclerosis is impaired [34] and monocytosis does not develop [21, 35]. Clinical studies have shown that hypercholesterolemia is associated with an increase in plasma CCL2, the ligand for CCR2 [28]. However, hypercholesterolemia-associated monocytosis and neutrophilia occur not only in the blood and spleen, but also in the bone marrow [13, 22], the site of neutrophil and monocyte production. This has led investigators to ask whether cholesterol-handling pathways influence myelopoiesis.

Hypercholesterolemia induces proliferation of HSPC

Intracellular cholesterol homeostasis is regulated by the ATP-binding cassette transporter ABCA1, which transports cholesterol from membranes to nascent HDL, and the ATP-binding cassette sub-family G member 1, ABCG1, which transports cholesterol to mature HDL. Deletion of these cholesterol efflux transporters leads to leukocytosis and exaggerated atherogenesis [36, 37]. Mechanistically, Yvan-Charvet *et al* found that leukocytosis in *Abca1*^{-/-} *Abcg1*^{-/-} mice is primarily mediated by increased proliferation of hematopoietic stem and progenitor cells (HSPC) [38]. ABCA1 and ABCG1 are both highly expressed in HSPCs, and their deletion increases the number of Lin⁻Sca+cKit⁺ (LSK) cells, granulocyte-macrophage progenitors (GMP), and common myeloid progenitors (CMP) *in vivo*. Furthermore, the increased proliferation of LSK cells in *Abca1*^{-/-} *Abcg1*^{-/-} mice is associated with increased cholesterol-rich lipid rafts, activation of phospho-Erk, Ras protein, and expression of the interleukin 3 (IL-3) and granulocyte macrophage colony-stimulating factor (GM-CSF) common β subunit receptor, on the plasma membrane [38]. Treatment of *Abca1*^{-/-} *Abcg1*^{-/-} LSK cells with cyclodextrin to disrupt lipid rafts, or with a farnesyl transferase inhibitor to prevent the anchorage of Ras in the plasma membrane, markedly reduces proliferation *in vitro* [38]. Taken together, these data show that increased membrane cholesterol content, secondary to ABC transporter deficiency, increases lipid rafts in stem cell membranes, resulting in increased surface localization of IL-3/ GM-CSF receptor, which leads to increased downstream Ras/Erk signaling and cell proliferation in response to IL-3 and GM-CSF.

HDL can reverse the hyperproliferation of HSPCs *in vitro* and *in vivo* [39]. HDL, but not lipid-poor apoA-I, suppresses IL-3 and GM-CSF-induced proliferation of *Abca1*^{-/-} *Abcg1*^{-/-} bone marrow cells, by promoting cholesterol efflux. Transplantation of bone marrow cells from wild-type (wt) or *Abca1*^{-/-} *Abcg1*^{-/-} mice into wt or apoA-I transgenic recipients, led to a prominent decrease in the frequency, number, and cycling

activity of HSPCs, in the apoA-I transgenic recipients of *Abca1*^{-/-}*Abcg1*^{-/-} bone marrow, but not in the wt recipients, thus confirming the suppressive role of HDL on myeloid progenitor proliferation. Expression of the apoA-I transgene in recipient mice was associated with significantly decreased cell surface expression of the IL-3 receptor β subunit on *Abca1*^{-/-}*Abcg1*^{-/-} bone marrow cells or HSPCs, and complete suppression of myeloid cell infiltration in different organs. In addition, diet-induced atherosclerosis in apoA-I transgenic/*Ldlr*^{+/-} recipient mice receiving *Abca1*^{-/-}*Abcg1*^{-/-} bone marrow was significantly lower compared to *Ldlr*^{+/-} recipient mice not expressing the apoA-I transgene [38]. Overall, this study highlights a novel role for HDL in the regulation of hematopoietic stem cell homeostasis and provides evidence of a hitherto unappreciated mechanism by which it confers cardiovascular protection.

The atheroprotective role of ApoE is well appreciated and has primarily been attributed to its function in the clearance of ApoB lipoproteins as well as local effects on the arterial vessel wall [40, 41]. Recent data indicate that ApoE controls HSPC proliferation [39]. Whereas *ApoE*^{-/-} mice, fed a diet high in fat and cholesterol, respond with pronounced proliferation of HSPCs, neutrophilia, and monocytosis, *Ldlr*^{-/-} or *ApoA1*^{-/-} mice exhibit only modest increases in these parameters [39]. Similarly, subjects with low plasma HDL due to genetic mutations do not develop monocytosis and do not increase their HSPC numbers [39]. These data suggest a specific role by which ApoE suppresses HSPC proliferation. HSPCs secrete ApoE which then anchors to proteoglycans, interacts with ABCA1 and ABCG1, and promotes reverse cholesterol efflux. When HSPCs lack ApoE, cholesterol efflux pathways are disrupted and cholesterol accumulates in cells which then become increasingly responsive to IL-3 and GM-CSF. In the full absence of ApoE, the net effect is increased HSPC proliferation, neutrophilia, and monocytosis, the latter two correlating with increased atherosclerosis [13, 22, 39]. In a therapeutic approach, Murphy and colleagues [39] injected cholesterol-poor phospholipid/ApoA-I complexes as cholesterol acceptors, thereby restoring normal HSPC proliferation and reducing the expansion of circulating neutrophils and monocytes. In addition, treatment with Liver X receptor (LXR) activators, which were previously shown to reduce proliferation of HSPCs and atherosclerotic lesion formation, also increases ApoE on HSPCs, thus reducing myeloproliferation [39].

In summary, HSPCs possess a cholesterol efflux mechanism consisting of the cholesterol transporters ABCA1 and ABCG1 and the acceptor protein ApoE. The close proximity of cell surface ApoE to ABC transporters can modulate plasma membrane free cholesterol and lipid raft content, to fine-tune cellular responses to proliferation signals (*i.e.* IL3 and GM-CSF). This process can function in the absence of exogenous HDL or ApoA-I, and can be enhanced either by an increase in acceptors of free cholesterol (*i.e.* HDL and apoA-I) or by activation of the nuclear hormone receptor LXR.

LXR signaling links lipid metabolism with inflammation

Liver X receptors (LXR α and LXR β) are members of the nuclear family of transcription factors that regulate cellular cholesterol efflux [42]. The natural ligands for LXRs are oxysterols and intermediates in the cholesterol biosynthetic pathway [43]. LXRs regulate the

expression of genes involved in cholesterol metabolism; the net effect of LXR activation is to promote the directional movement of excess cholesterol from peripheral tissues to the liver, bile, and intestinal lumen, for excretion via the feces [44].

Beyond these effects, LXRs have also emerged as important regulators of inflammatory gene expression and innate immunity. LXR activation represses stimulation of inflammatory genes such as toll-like receptor 4 (TLR-4), tumor necrosis factor (TNF), and IL1 β [45-47]. Mechanistically, the anti-inflammatory effects of LXRs have been attributed to nuclear inhibition of nuclear factor kappa B (NFkB) signaling via a process known as transrepression [48]. LXRs contribute to the anti-inflammatory pathway exerted upon engulfment of apoptotic cells [49] and regulate expression of arginase, the M2 marker, in macrophages [50]. Such mechanisms would speak in favor of a protective effect of macrophage LXR in atherosclerotic lesion formation. An important role for the macrophage LXR pathway in atherosclerosis was established by Tangirala and colleagues who showed that transplantation of bone marrow from *Lxr α ^{-/-}* and *Lxr β ^{-/-}* mice into *ApoE^{-/-}* or *Ldlr^{-/-}* mice strongly increased atherosclerotic lesion development [51]. This was further corroborated in studies employing overexpression of LXR α in a macrophage-specific manner leading to reduced atherosclerosis in the absence of changes in plasma lipid levels [52].

Beyond these observations, a link between LXR signaling pathways and neutrophil homeostasis has just recently been identified [53]. With the high turnover of neutrophils, effective clearance of aged neutrophils ensures homeostasis. Ley and colleagues have previously proposed a model wherein clearance of senescent neutrophils exerts a negative feedback loop towards granulopoiesis involving IL23 and IL17 [54, 55], while Hong *et al.* revealed a defect in peripheral neutrophil turnover in LXR-deficient mice. In contrast, systemic administration of GW3965, a synthetic nonsteroidal agonist of both LXR α and LXR β , decreased the number of circulating neutrophils. Mechanistically it was found that phagocytosis of aged neutrophils activated the LXR pathway with concomitant repression of the IL23/IL17 axis. Loss of LXR activity on the other hand perturbed clearance of senescent neutrophils by phagocytes and enhanced expression of IL23/IL17 (Figure 2).

Hypercholesterolemia induces HSPC mobilization and extramedullary hematopoiesis

Monocytes and neutrophils arise in the bone marrow in the steady state from hematopoietic stem cells residing in specialized locations, or niches. Cellular self-renewal, differentiation, survival, and mobilization are tightly controlled processes that rely on a diverse repertoire of cells and molecules necessary to ensure continuous leukocyte replenishment throughout life [56, 57]. In experimental models of atherosclerosis, however, substantial extramedullary hematopoiesis occurs in secondary lymphoid organs. The spleen, which contains a monocyte reservoir in the steady state, produces monocytes and neutrophils that can infiltrate atheromata and contribute to atherosclerosis [58, 59]. After myocardial infarction, monocyte production in the spleen increases and can accelerate atherosclerosis [60]. In response to high fat diet, the number of splenic monocyte and neutrophil progenitors increase over time,

which suggests that hypercholesterolemia, in addition to its effects on proliferation, may also induce progenitor mobilization from the bone marrow.

A recent study has investigated a possible link between lipid metabolism and bone marrow mobilization. Using reverse cholesterol transport-impaired *Abca1*^{-/-}*Abcg1*^{-/-} mice, the authors conclude that cholesterol regulating pathways control HSPC mobilization and extramedullary hematopoiesis [61]. It is a lengthy sequence of events. Defects in cholesterol efflux pathways in macrophages and dendritic cells in the spleens of *Abca1*^{-/-}*Abcg1*^{-/-} mice lead to activation of the IL23/IL17 axis with subsequent production of G-CSF [61]. The use of neutralizing antibodies revealed that G-CSF was responsible for augmented mobilization of HSPCs from the bone marrow of *Abca1*^{-/-}*Abcg1*^{-/-} mice. Mechanistically two primary mechanisms were identified: (1) Increased G-CSF levels skew the myeloid lineage commitment in favor of neutrophils rather than monocytes. This decreases the number of bone marrow macrophages and hence the support network and the abundance of osteoblasts and nestin⁺ mesenchymal stem cells which express the CXCL12, a major retention signal for HSPCs [62, 63]. (2) Increased neutrophil production creates a proteolytic environment allowing for cleavage of CXCR4 on HSPCs. Due to these alterations in the bone marrow stem cell niche, retention of HSPCs in the bone marrow is impaired and as a consequence HSPCs are mobilized.

As described in the previous section, LXR-deficient mice have increased circulating neutrophil counts, but unlike *Abca1*^{-/-}*Abcg1*^{-/-} mice, neutrophilia is caused by impaired clearance. Moreover, LXR-deficient mice also lack evidence for increased medullary or extramedullary hematopoiesis and have normal IL17 and G-CSF levels [53]. Hence, cholesterol flux may regulate myeloid cell homeostasis at several independent levels and a master regulator of HSPC proliferation and mobilization remains to be identified.

Novel approaches for treatment of atherosclerosis

Recent advances at the intersection of lipid metabolism and cellular homeostasis have revealed possible new therapeutic targets for atherosclerosis. Interference with leukocyte accumulation in atherosclerosis has previously focused on inhibition of leukocyte recruitment into large arteries [64, 65]. However, targeting of cell adhesion molecules has so far been largely unsuccessful [65-67]. Reasons for such failures include the striking redundancy of cell adhesion molecules and chemokines during atherogenic recruitment, rendering interference with just one molecule insufficient [20, 21]; prominent off-target effects due to cross-reactivity with receptors of similar structure; discrepancies between animal models and human diseases; and the importance of the targeted molecule in host defense and consequently compromised immune responses [65-67]. Thus, advances described in this review may shift the attention towards the interface between lipid metabolism and leukocyte homeostasis with regard to the control of HSPC proliferation. The aforementioned control of HSPC proliferation may be regulated by LXRs and HDL, but chemokines may also contribute to the regulation of myeloproliferation (Box 3 and Figure 1).

Agonists of LXRs exert anti-atherosclerotic effects in mouse models of atherosclerosis. LXR activation with GW3965 strongly attenuates atherosclerosis in *ApoE*^{-/-} as well as *Ldlr*^{-/-} mice [68, 69]. Several studies have confirmed these findings using not only GW3965 but also other LXR agonists, and others have demonstrated regression of atherosclerotic lesions with LXR agonist treatment [70]. Importantly, LXR agonists alter plaque composition [68, 11]. In several reports, a beneficial effect of LXR activation on lesion development was observed in the absence of changes in plasma lipid levels. These observations are consistent with the idea that LXR activation promotes lipid movement from peripheral cells back to the liver. Given the role of LXR α in promoting hepatic lipogenesis and hypertriglyceridaemia, drug development strategies have focused on LXR β -selective agonists. However it has been challenging to create LXR β -specific ligands to bypass the undesirable effects on lipogenesis because the ligand-binding pockets of the two LXR subtypes differ by only a single amino acid [72, 73]. An important question, then, is whether activation of LXR β alone is sufficient to inhibit atherogenesis. Indeed it has been demonstrated that activation of LXR β in *Lxra*^{-/-}*ApoE*^{-/-} mice did attenuate atherosclerosis, even in the absence of increased triglyceride levels [69].

HDL levels correlate inversely with cardiovascular risk, presumably because HDL increases reverse cholesterol transport and decreases inflammation. Numerous approaches to harness HDL's therapeutic potential therefore exist or are in development. They include direct and indirect augmentation of Apo A-I levels, mimicking the functionality of Apo A-I with Apo A-I mimetic peptides, and enhancing the reverse cholesterol transport pathway via activation of LXRs [74]. Unfortunately, despite considerable understanding of HDL and its metabolism, none of the pharmacological agents designed to raise HDL have succeeded in significantly reducing cardiovascular events. In addition, recent clinical trials involving therapeutic elevations of HDL were prematurely terminated on the basis of futility [75, 76]. In line, a recent human study confirmed that most genetic variants causing changes in LDL cholesterol levels were associated with synchronized changes in coronary heart disease but those associated with HDL cholesterol levels had a weak or nonexistent relationship with coronary heart disease [77]. Hence these data challenge the concept that raising of plasma HDL cholesterol will uniformly translate into reductions of cardiovascular diseases [78]. It will therefore be important to test whether the newly-described intersection of cholesterol metabolism and HSPC activation offers new treatment strategies for atherosclerosis and its complications.

Concluding remarks

Atherosclerosis is a chronic inflammatory disease of the arterial wall involving the accumulation of myeloid cells as a hallmark event. Recent work has revealed multiple mechanisms by which atherosclerotic lesions grow. Endothelial expression of cell adhesion molecules and chemokines controlling leukocyte influx is one major determinant of atherosclerosis. Mechanisms regulating myeloid cell production in the bone marrow and secondary lymphoid organs such as the spleen, myeloid cell mobilization, survival, turnover, and clearance, have all been proposed to be important in the control of arterial leukocyte accumulation. However, the relative importance of the various mechanisms remains unclear so that further studies are required to provide powerful therapeutic targets. In addition, with

the recent studies on cholesterol handling pathways in atherosclerosis, it is important to elucidate how these pathways impact on mechanisms of myeloid cell migration, survival, and egress.

In light of the recent failures of raising HDL cholesterol to reduce cardiovascular risk, attention of future trials may shift towards stimulation of cholesterol efflux. Accordingly, HDL-mediated cholesterol efflux from foam cells to the liver correlates better with atherosclerotic burden than plasma HDL cholesterol levels [78]. Therapeutic stimulation of cholesterol efflux pathways may thus be a promising future direction in the treatment of cardiovascular diseases.

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Glossary

Atheromata	also called atheromatous plaques, are an accumulation of macrophage cells, cholesterol, and fatty acids and fibrous connective tissue in artery walls.
Chemokines	a family of small cytokines, or proteins secreted by cells. They exert their biological effects by interacting with G protein-linked transmembrane receptors called chemokine receptors found on the surfaces of their target cells thereby regulating directed movement of cells.
Chemokine receptors	are 7-transmembrane structure G-protein couple receptors that bind specific chemokine ligands. Binding triggers a flux in intracellular calcium ions that induce chemotaxis. Chemokine receptors are divided into different families that correspond to the 4 distinct subfamilies of chemokines they bind, and include CXC chemokine receptors, CC chemokine receptors, CX3C chemokine receptors and XC chemokine receptors.
Granulocytes	also called polymorphonuclear leukocytes (PMN or PML) are a category of white blood cells characterized by the presence of granules in their cytoplasm.
Hematopoietic stem and progenitor cells (HSPC)	are a heterogeneous population of multipotent stem cells that give rise to all the blood cell types of the myeloid and the lymphoid lineages.
Lin-Sca+cKit+ (LSK) cells	primitive hematopoietic stem cells that possess the capacity to self-renew and can give rise to all mature cell types found in the blood.

Myelopoiesis

is the regulated formation of blood cells in the bone marrow.

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Box 1**Neutrophils and monocytes in atherosclerosis**

Despite their abundance in the circulation, neutrophils are rarely detected in atherosclerotic lesions [10, 79]. Nevertheless, recent evidence indicates that neutrophils contribute to atherogenesis importantly [22]. Neutrophil-derived granule proteins may induce the influx of Ly-6C^{high} monocytes [80] or activate antigen-presenting cells [81, 82]. Other mechanisms of neutrophil-driven atherogenesis may involve the limitation of the bioavailability of nitric oxide (NO) by neutrophil myeloperoxidase as well as the oxidation of lipids to promote foam cell formation [10]. Arterial neutrophil accumulation also associates with signs of plaque destabilization [83, 84], suggesting that neutrophils may also contribute to plaque rupture. However, mechanistic studies on neutrophil-driven atherosclerosis are scant [10].

Monocytes and monocyte-derived macrophages represent the most abundant myeloid cell type in the atherosclerotic plaque. Depletion of monocytes from the circulation reduces plaque formation in rabbits [85]. Depletion of monocytes and macrophages in young animals reduces the number of macrophages in plaques, inhibits lesion development, and alters plaque composition. Depletion of monocytes and macrophages at later time points, however, is less effective in reducing atherosclerosis, suggesting a more prominent role for monocytes in early, rather than later, stages of atherosclerosis [86, 87].

Box 2**Alteration of myeloid cell phenotype and function by hypercholesterolemia**

Crucial to the trafficking of myeloid cells is the expression of adhesion molecules and chemokine receptors. Interestingly, the degree of hyperlipidemia directly correlates with monocytic CD18 and CD54 levels [88]. High LDL levels correlate with higher CCR2 expression on human monocytes [89], whereas a diet high in fat and cholesterol increases CCR2 on Ly-6C^{high} monocytes in mice [20]. Application of statins lowers monocytic CCR2 expression in humans, mice, and rats, and reduces arterial infiltration [90]. Statins influence chemokine and chemokine receptor expression in human endothelial cells and macrophages. In both cell types, treatment with simvastatin decreases CCR4 and MCP-1 dose-dependently. Simvastatin also downregulates the mRNA levels for CCR1, CCR2 and CCR5 [91].

The presence of primed neutrophils in hyperlipidemia was initially reported by Araujo and colleagues who showed a positive correlation between plasma LDL and neutrophil reactive oxygen species (ROS) formation [92]. Recently, Mazor *et al.* reported increased superoxide release and CD11b surface expression in the context of hyperlipidemia [93]. Compared to normocholesterolemic controls, circulating neutrophils in patients with hyperlipidemia discharge myeloperoxidase more readily, as evidenced by an inverse relationship between myeloperoxidase levels detected in cells and those detected in plasma [93].

Box 3**Chemokines control the proliferation of HSPCs**

Chemokines, in addition to their chemotactic functions, may also control HSPC proliferation (Figure 1). The CXCL12/CXCR4 axis is important to HSPC survival [94, 95]. This effect is further increased when CXCL12 acts in combination with other cytokines such as Interferon-gamma (IFN γ) [96]. CXCL12 stimulates the replating and self-renewal capacity of HSPCs, and thus contributes to myelopoiesis [97]. Several other chemokines such as CCL3 and CXCL8 may suppress HSPC proliferation, potentially counteracting ApoE-mediated induction of hematopoiesis [98]. An increase of CXCL1 under hyperlipidemic conditions may either block suppressive effects of other chemokines or directly induce myeloproliferation [99].

Outstanding question box

- What is the relative importance of mechanisms other than cholesterol efflux pathways in the regulation of myeloid cell homeostasis?
- What is the relative contribution of cholesterol efflux pathways in controlling myeloid cell accumulation in atherosclerosis?
- Is targeting of cholesterol efflux pathways a better therapeutic approach compared to HDL-raising approaches?

Figure 1. Regulating of hematopoietic stem cell proliferation by cholesterol efflux pathways and means of therapeutic intervention

A: Endogenous ApoE bound to proteoglycans or lipid-poor ApoA-I interact with ABCA1 and stimulate cholesterol efflux from hematopoietic stem cells to form nascent HDL (nHDL) particles. nHDL or plasma HDL (pHDL) can further interact with ABCG1 to enhance cholesterol efflux mechanisms thereby reducing cellular cholesterol levels. The depletion of cellular cholesterol levels results in diminished lipid raft content. As a consequence, inflammatory and proliferative pathways are inhibited, *e.g.* by reduction of the common beta subunit of the IL3/GM-CSF receptor (IL3R β) in lipid rafts. Ultimately these mechanisms slow down proliferation of hematopoietic stem and progenitor cells. **B:** CCL3 and CXCL8 exert myelosuppressive effects, which are counteracted by CXCL1 or CXCL12. **C:** Treatment with LXR agonists enhances expression of ApoE, ABCA1, and ABCG1, thus stimulating cholesterol efflux and dampening proliferation of myeloid progenitor cells. Similarly, cholesterol-poor phospholipid/ApoA-I complexes (rHDL) inhibit proliferation of myeloid progenitor cells. Red arrows indicate mechanisms of myelosuppressive capacities, whereas green arrows indicate myeloproliferative effects. Modified from [39].

Figure 2. Regulating of hematopoietic stem cell mobilization by cholesterol efflux pathways

Macrophages and dendritic cells in the spleen secrete IL23, which in turn promotes IL17 production in Th17 cells. IL17 drives G-CSF secretion which shifts granulocyte-monocyte-progenitor (GMP) commitment towards neutrophils. Neutrophils create a protease-rich environment in the bone marrow allowing for cleavage of CXCR4 on hematopoietic stem and progenitor cells (HSPCs) thus facilitating the exit from the bone marrow. In parallel, decreases in CXCL12-secreting osteoblasts or nestin+ mesenchymal stem cells ease HSPC bone marrow exit and consequently extramedullary hematopoiesis. In another mechanism, senescent neutrophils are cleared by macrophages, a process that represses the IL23 secretion from macrophages. LXR agonists enhance Gas6 and Mer expression on macrophages, hence promoting clearance of phosphatidylserine (PS)-expressing neutrophils and repressing IL23 secretion. Modified from [100].