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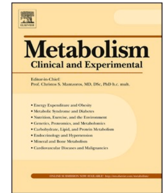

Bone marrow rewired: Trained immunity and clonal hematopoiesis in metabolic disease☆

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ABSTRACT

Diseases associated with obesity and metabolic dysregulation, such as diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD) promote chronic low-grade inflammation, which in turn, may enhance the risk for cardiovascular disease. Emerging evidence in recent years suggests that chronicity of inflammation involves alterations in bone marrow homeostasis. Obesity-related inflammation and metabolic stress, including hyperglycemia or hyperlipidemia, may trigger rewiring of hematopoietic stem and progenitor cells (HSPCs) in the bone marrow, driving production of myeloid cells with heightened inflammatory capacity that in turn fuel and sustain chronic inflammation. This process is akin to trained immunity and may promote an inflammatory memory that links metabolic disorders to their cardiovascular complications. Clonal hematopoiesis of indeterminate potential (CHIP) is characterized by aging-related emergence of somatic mutations in hematopoietic cells that clonally expand and bear higher inflammatory potential. Importantly, a bidirectional link between CHIP and metabolic disorders as well as their cardiovascular sequelae emerges. Here, we review current concepts regarding the links between bone marrow biology and metabolic diseases and associated chronic inflammation.

1. Introduction

Hematopoiesis is the generation of all blood and immune cells and occurs in the bone marrow (BM) microenvironment. Hematopoietic stem cells (HSCs) reside in the specialized BM niche, composed of mesenchymal stromal cells (MSCs), adipocytes, endothelial cells, osteoblasts, and extracellular matrix components; this environment collectively maintains HSC quiescence, self-renewal, and lineage-specific differentiation to support systemic homeostasis and immunocompetence [1,2]. Hematopoietic stem and progenitor cells (HSPCs) in the BM express Toll-like receptors (TLRs) recognizing pathogen-derived stimuli, as well as a series of receptors interacting with growth factors, such as macrophage colony-stimulating factor (M-CSF), and with cytokines, such as interferons (IFNs), tumor-necrosis factor (TNF), interleukin-1β (IL-1β) or IL-6 [3–5]. This allows them to sense and react to inflammation by proliferation and differentiation towards enhanced production of mature myeloid immune cells; this process, termed emergency myelopoiesis, ensures sufficient replenishment of myeloid cells under inflammatory or stress conditions [3,4].

The inflammatory regulation of hematopoiesis is also involved in the induction of trained immunity (TRIM), a form of innate immune memory, defined by long-lasting rewiring leading to enhanced inflammatory reaction of innate immune cells to subsequent challenges, whether related or unrelated to the original stimulus [6,7]. Specifically, TRIM can be initiated in the BM, via sustained metabolic and epigenetic adaptations in HSPCs, resulting from inflammatory stimuli or infectious pathogen-derived factors, that trigger myeloid lineage skewing and the generation of progeny myeloid cells with elevated inflammatory

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potential, when exposed to future challenges [7,8]. While TRIM can confer protection against infection and cancer, TRIM may also contribute to the establishment of inflammatory memory underlying the development or progression of inflammatory and cardiometabolic disorders [7,9–15].

An additional facet of the interface between inflammation and BM hematopoiesis is clonal hematopoiesis of indeterminate potential (CHIP). CHIP refers to clonal hematopoiesis involving somatic mutations in myeloid malignancy–associated genes detected in the blood or BM at a variant allele fraction (VAF) of at least 2% in individuals who otherwise have no overt or diagnosed hematologic malignancy or unexplained cytopenia [5,16]. These mutations – most commonly occurring in genes encoding epigenetic regulators such as *DNMT3A* and *TET2* – enable HSCs to clonally expand and produce a substantial fraction of circulating blood cells [5,17]. Although by definition CHIP is a non-malignant condition, it increases the risk not only of hematologic neoplasias, but also of cardiovascular and inflammatory pathologies [5,17,18].

Metabolic disorders, such as diabetes mellitus, particularly type-2 diabetes (T2D), and metabolic dysfunction-associated steatotic liver disease (MASLD), formerly named non-alcoholic fatty liver disease (NAFLD), constitute a major global health burden and are strongly associated with elevated cardiovascular disease (CVD) risk [19,20]. These conditions are linked to obesity, insulin resistance and dyslipidemia, and may underlie the development of systemic chronic low-grade inflammation, which in turn, accelerates CVD progression [19–22]. Mounting evidence suggests that hyperglycemia- and hyperlipidemia-associated vascular inflammation may involve alterations in BM biology and function [23–25]. Such metabolic insults reshape the cellular and molecular landscape of the BM niche, reprogram HSPCs, and may bias hematopoietic output towards myelopoiesis [12,23,25–27]. This leads to the expansion of myeloid cells poised for heightened pro-inflammatory responses that perpetuate chronic inflammation and vascular dysfunction [12,23,25,27]. In other words, such alterations mirror the hallmarks of TRIM [6,28]. Indeed, emerging evidence suggests that maladaptive TRIM may be induced by metabolic disorders, thereby fueling chronic inflammation, atherosclerosis, and CVD [7,12,23,27,29].

The objective of this review is to synthesize current knowledge from recent studies on the role of the BM, including processes emanating thereof, such as TRIM and CHIP, in the context of metabolic disorders and related chronic inflammation.

2. Bone marrow changes in obesity

Metabolic dysfunction linked to obesity and diabetes drives intersecting and often synergistic mechanisms that alter BM homeostasis and function. Obesity and aging promote BM adipose tissue (BMAT) expansion through the preferential activation of adipogenic lineages while impairing osteogenic differentiation of BM stem cell-like mesenchymal precursor cells ($CD45^{-}$ $CD31^{-}$ $Sca1^{+}$ $CD24^{+}$) [26]. This adipocyte accumulation disrupts niche homeostasis, dysregulates hematopoiesis, and compromises skeletal repair, in part, though excessive secretion of dipeptidyl peptidase-4 (DPP4) from committed adipogenic progenitors [26] (Fig. 1). Complementing these findings, obesity-induced hyperinsulinemia promotes significant BMAT expansion and decreases trabecular and cortical bone thickness in the tibia [30]. These findings suggest that obesity imposes a metabolic pressure on the BM niche associated with BM adiposity and reduced bone integrity.

Building on these insights into BMAT expansion, adipocytes are increasingly recognized as active BM regulators, secreting key factors such as stem cell factor (SCF) besides leptin and adiponectin [26,31,32]. While factors like SCF typically support HSC maintenance and regeneration [31], adipocyte-derived signals can also exert maladaptive effects on hematopoiesis and immune function. For instance, leptin, which is elevated in obesity, drives maladaptive TRIM in monocytes through epigenetic reprogramming resulting in amplified pro-inflammatory responses such as enhanced TNF production upon secondary stimulation [33]. Accordingly, circulating leptin positively correlates with IL-1β and IL-6 production in a sex-dependent manner, with stronger associations observed in men, exacerbating cardiometabolic risk and inflammation [33].

At the cellular level, obesity alters HSC functions through multiple mechanisms. In both murine models and humans, obesity skews hematopoiesis towards myelopoiesis, which contributes to systemic inflammation [21,34–37]. Oxidative stress during obesity elevates the expression of the transcription factor *Gfi1*, resulting in increased HSC proliferation, reduced HSC regenerative capacity, and a sustained

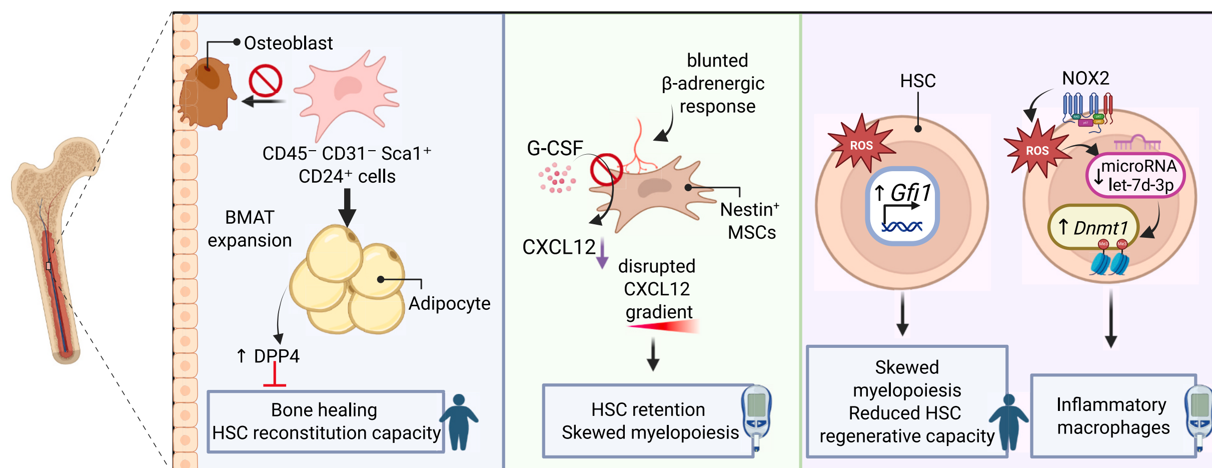

Fig. 1. Schematic representation of obesity- and diabetes-associated bone marrow niche alterations. **Left panel:** In obesity, bone marrow (BM) stem cell-like mesenchymal precursor cells ($CD45^{-}$ $CD31^{-}$ $Sca1^{+}$ $CD24^{+}$ cells) undergo preferential differentiation into adipocytes while concurrently osteoblastogenesis is suppressed. The generated adipocytes secrete dipeptidyl peptidase-4 (DPP4), contributing to impaired bone healing and reduced HSC reconstitution potential. **Middle panel:** In diabetes, granulocyte colony-stimulating factor (G-CSF) fails to downregulate CXCL12 in $nestin^{+}$ mesenchymal stromal cells (MSCs) due to blunted β-adrenergic signaling. This disrupts the CXCL12 gradient required for hematopoietic stem cell (HSC) egress from the BM, thereby promoting HSC retention and skewed myelopoiesis. **Right panel:** Oxidative stress-mediated upregulation of *Gfi1* in HSCs in obesity impairs long-term HSC fitness and regenerative capacity while sustaining a myeloid bias. In diabetes, NADPH oxidase 2 (NOX2)-induced oxidative stress in HSCs decreases microRNA let-7d-3p expression, resulting in DNA methyltransferase 1 (DNMT1) upregulation that controls an epigenetic mechanism skewing macrophages towards inflammatory phenotypes.

myeloid bias even after returning to a normal diet [37] (Fig. 1). High-fat diet (HFD) feeding of mice elevates IL-1β levels in the BM niche, activating the p38/mitogen-activated protein kinase (MAPK) pathway in HSPCs to promote myelopoiesis [36]. Moreover, short-term HFD exposure disrupts plasma membrane raft–like microdomain organization and transforming growth factor-β (TGF-β) signaling in HSCs, impairing their long-term reconstitution potential, favoring myelopoiesis, and altering BM niche interactions that compromise HSC maintenance in a cell-autonomous manner [38]. Complementarily, short-term HFD exposure upregulates neutrophil elastase in mice, activating the C/EBPα-GFI-1 pathway in HSPCs to drive emergency myelopoiesis, endothelial hyperpermeability and vascular leakage, and systemic inflammation [34]. Prolonged HFD consumption further impairs neutrophil function in obese mice by expanding BM neutrophils while reducing TNF release, phagocytosis, bacterial killing, and upregulating lipid metabolism (including *Acot1*, *Cpt1a*, and *Plin2* expression) that hinder hematopoietic regeneration following myeloablation [39]. TLR4 and its downstream adaptors, TIR domain–containing adapter protein–inducing interferon-β (TRIF) and MyD88, are essential for HSPC responses to free fatty acids (FFAs) and the generation of pro-inflammatory CD11c$^+$ adipose tissue macrophages, further linking innate immune signaling to obesity-associated metabolic inflammation [40,41] (Fig. 2). This TLR4 dependency may operate through precursor cell-autonomous mechanisms, wherein obesity skews hematopoiesis towards myelopoiesis marked by enhanced myeloid gene expression (e.g., *Csf1r, Spi1, Runx1*) in lineage$^-$c-kit$^+$Sca-1$^-$ (LKS^{neg}) progenitors and concomitantly suppressed lymphoid gene expression (e.g., *Flt3, Tcf3, Ebf1*) in common lymphoid progenitor cells [42]. Macrophages of the adipose tissue in obesity foster myelopoiesis via elevated NLR family pyrin domain containing 3 (NLRP3)-dependent IL-1β production, resulting in monocytosis that further aggravates adipose tissue inflammation and insulin resistance [41] (Fig. 2). Importantly, the NLRP3 inflammasome also contributes to TRIM associated with obesity-related metabolic dysfunction. Western diet-feeding triggers NLRP3-dependent TRIM in myeloid cells and granulocyte-monocyte progenitors (GMPs), inducing persistent epigenetic reprogramming through altered chromatin accessibility, and thereby enhancing inflammatory responses and exacerbating atherosclerosis, even after returning to a chow diet [12].

In addition to HSPC-intrinsic and niche-mediated mechanisms, extrinsic factors such as the gut microbiota further modulate hematopoiesis in obesity. Microbiota from obese mice, characterized by an altered community structure with enhanced energy-harvesting and pro-inflammatory capacity compared with microbiota from lean mice, influence hematopoietic output by altering the BM niche via peroxisome proliferator-activated receptor-γ2 (PPARγ2) activation in MSCs, suppressing osteoblastogenesis while enhancing adipogenesis, downregulating niche factors, e.g., Jag-1, SDF-1 (CXCL12) and IL-7, and biasing HSC differentiation towards myeloid lineage [43]. These effects are transferable via fecal transplantation from HFD-fed mice to normal diet fed mice and partially reversed by antibiotic treatment [43]. Moreover, transient metabolic challenges, such as repeated weight cycling and intermittent HFD exposure, can also imprint long-lasting changes on BM function or innate immune cell phenotypes [44–47]. Alternating HFD exposure also exacerbates atherosclerosis through IL-1β-dependent epigenetic reprogramming of BM myeloid progenitors upon dietary re-exposure, triggering emergency myelopoiesis, neutrophilia, enhanced neutrophil plaque infiltration and neutrophil extracellular traps (NETs), thereby promoting plaque instability [29]. Short-term caloric restriction increases *Fcgr4*$^+$ macrophages in white adipose tissue (WAT) and atherosclerotic plaques, facilitating necrotic core clearance, while weight regain on a high-fat high-cholesterol diet promotes inflammatory reprogramming of BM progenitors leading to increased monocyte-derived macrophage accumulation in plaques and disease progression [48]. Furthermore, in dietary-cycling mouse models, CD7$^+$ BM monocytes preferentially migrate to subcutaneous WAT where they activate protein kinase A (PKA) signaling through

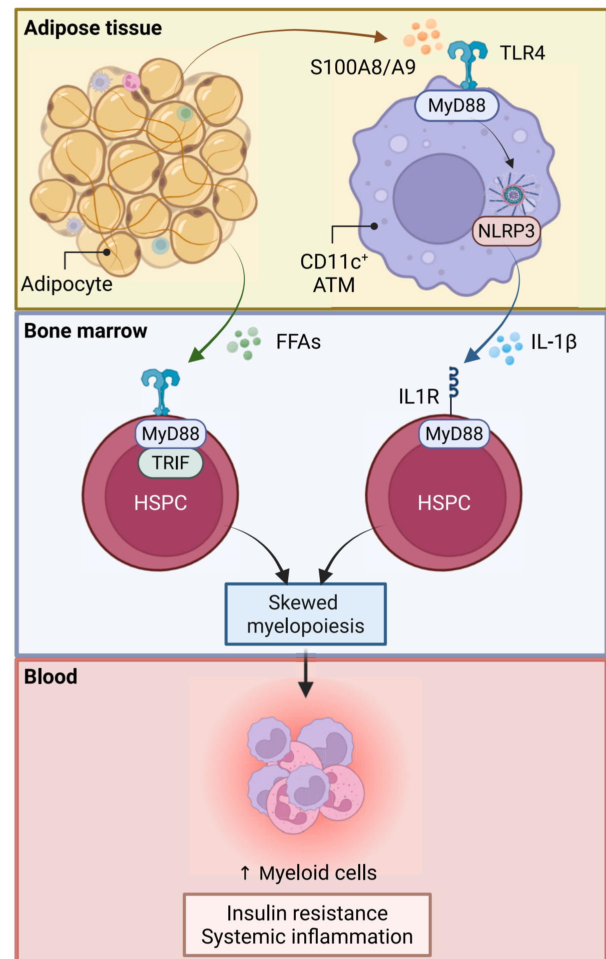

Fig. 2. Contribution of adipose tissue to systemic inflammation in obesity. Free fatty acids (FFAs) from adipose tissue may stimulate the Toll-like receptor 4 (TLR4)/MyD88/TIR domain–containing adapter protein–inducing interferon-β (TRIF) pathway in HSPCs, contributing to enhanced myelopoiesis in the bone marrow. Moreover, S100A8/A9 in the adipose tissue binds TLR4 on adipose tissue macrophages (ATMs), triggering NLR family pyrin domain containing 3 (NLRP3) inflammasome-mediated interleukin-1β (IL-1β) secretion that acts on IL-1 receptor-expressing precursors of myeloid cells in the bone marrow, driving myelopoiesis and increased production of circulating monocytes and neutrophils. The resulting myeloid skewing in both mechanisms enhances systemic inflammation and contributes to insulin resistance in obesity.

fibrinogen-like protein 2 secretion to promote beige fat thermogenesis, thereby attenuating post-diet adipose tissue expansion and limiting weight regain [47]. Weight cycling also induces innate immune memory in adipose tissue macrophages, resulting in exaggerated inflammatory responses (e.g., enhanced TNF production) upon subsequent metabolic stress, such as weight regain, that persist upon weight normalization and contribute to worsened glucose tolerance [44]. In summary, these findings underscore the sensitivity of the BM to nutritional fluctuations and highlight the potential consequences of dietary patterns and obesity on driving long-term hematopoietic reprogramming and systemic inflammation.

Beyond the effects on myelopoiesis, obesity also reshapes the lymphoid cell landscape, as extensively reviewed elsewhere [49–51]. In particular, obesity promotes the expansion of adipose tissue Th1 and Th17 subsets while reducing Th2 cells and regulatory T cells (Tregs) [49]. CITE-seq (Cellular Indexing of Transcriptomes and Epitopes by Sequencing) analysis in visceral adipose tissue from lean, obese (HFD), weight-loss, and weight-cycling (weight regain) mice revealed a decline in Treg number and function – including loss of IL-33/ST2 signaling

capacity – that failed to recover after weight loss [46]. Moreover, adipose tissue effector-memory $CD8^+$ T cells exhibit an exhaustion signature characterized by expression of *Pdcd1, Tox, Tigit, Lag3, and Entpd1*; this signature persists through weight loss and is amplified by weight regain [46]. In addition to T cells, innate lymphoid cells (ILCs) play a critical role in metabolic regulation and inflammation [50]. In adipose tissue, ILC2s maintain metabolic homeostasis and protect against insulin resistance; however, their numbers and function are markedly reduced with obesity [50]. On the contrary, increased numbers of adipose tissue NK cells/ILC1s in obesity promote insulin resistance by skewing macrophages towards a pro-inflammatory phenotype [50]. B1a lymphocytes have been shown to reduce inflammation through IL-10 secretion and IgM antibody-dependent mechanisms, improving obesity-associated glucose intolerance [52]. In contrast, B2 and T-bet$^+$ B cells expand in obesity and promote insulin resistance, inflammation, and metabolic complications [53,54]. Collectively, obesity-driven alterations in lymphocyte composition and function may regulate chronic inflammation, insulin resistance, and metabolic dysfunction.

3. Bone marrow remodeling in diabetes

Dysmetabolism in diabetes, including hyperglycemia and insulin resistance, exerts significant stress on the BM niche, fostering dysregulated hematopoiesis that could amplify CVD risk [23,24,55]. A defining feature of this disruption involves the compromised interactions between HSCs and supportive niche components, culminating in impaired HSC mobilization [24,55,56]. In both human patients and murine models of diabetes, hyperglycemia impairs the mobilization of $CD34^+$ cells (in humans) or $Lin^-Sca\text{-}1^+c\text{-}Kit^+$ (LSK) cells (in mice) in response to granulocyte colony-stimulating factor (G-CSF) [56]. This impairment is mediated by the dysregulation of nestin$^+$ MSCs, expressing CXCL12, a critical chemokine regulating HSPC retention [56]. Specifically, diabetes-related dysregulated β-adrenergic signaling disrupts the G-CSF-mediated decrease in CXCL12 and hence the gradient necessary for HSPC egress from the BM [56] (Fig. 1). Complementing these insights, hyperglycemia also induces endothelial dysfunction via the down-regulation of *Cxcl12* expression and the upregulation of epidermal growth factor receptor signaling via adipose-derived amphiregulin [24]. This cascade accelerates HSPC proliferation and myelopoiesis, leading to aggravated vascular complications, such as impaired wound healing and atherosclerosis [24]. Furthermore, BM-MSCs from patients with T2D display a constitutive adipogenic bias [57]. In this altered microenvironment, monocyte chemoattractant protein-1 (MCP-1) secreted by BM adipocytes further exacerbates BM adiposity [57]. Moreover, hyperglycemia affects osteopontin-positive (OPN$^+$) osteoblastic niche cells and thereby long-term HSCs (LT-HSCs) [55]. In streptozotocin (STZ)-induced diabetic mice, elevated glucose levels lead to a reduction in OPN$^+$ cells and LT-HSCs while promoting differentiation towards short-term HSCs and multipotent progenitors [55]. These changes are associated with reduced expression of Tie2, β-catenin, and N-cadherin on LT-HSCs, as well as a decrease in β-catenin, β1-integrin, angiopoietin-1, and CXCL12 on OPN$^+$ cells resulting in impaired HSC quiescence, and self-renewal [55]. Together, these findings underscore diabetes-induced niche remodeling as a driver of HSPC dysfunction.

Beyond these niche-specific alterations, obesity and diabetes may induce broader transcriptomic, epigenetic, and metabolic changes in HSPCs that are associated with a heightened pro-inflammatory state [58–60]. For instance, hyperglycemia triggers a NADPH oxidase 2 (NOX2)-dependent increase in HSC oxidative stress, resulting in a decrease in microRNA let-7d-3p that upregulates DNA methyltransferase 1 (DNMT1) and leads to dysregulated HSC differentiation towards monocytes/macrophages [60] (Fig. 1). This results in reduced macrophage wound infiltration and a bias towards pro-inflammatory macrophage polarization that compromises tissue repair [60]. Similarly, in T2D, reduced levels of the repressive histone methylation marker H3K27me3 at the IL-12 promoter in BM LSK cells persist in bone marrow-derived macrophages (BMDMs) and amplify macrophage inflammatory potential, further delaying wound healing [58]. Additionally, elevated levels of histone deacetylase 3 in macrophages from diabetic atherosclerotic lesions positively correlate with serum low-density lipoprotein (LDL) and triglycerides [61]. In vitro, high glucose conditions enhance macrophage metabolism, marked by increased glucose utilization, succinate accumulation, lactate production, and oxygen consumption, while increasing inflammatory cytokine gene expression, ultimately accelerating atherosclerotic plaque development [61]. Transcriptomic analysis of LSK cells from *db/db* mice corroborates these findings, revealing upregulated expression of pro-inflammatory factors (e.g., *Tlr4, Tnf*) and downregulation of anti-inflammatory *Il10*, accompanied by enrichment of pathways related to inflammation, leukocyte migration, and macrophage activation that may exacerbate vascular complications associated with diabetes [62]. Hyperglycemia increases enrichment of H3K4me3 at promoters of inflammatory genes in HSCs that persists in macrophages to promote proatherogenic functions such as enhanced uptake of modified LDL and foam cell formation [23]. In vivo, transplantation of BM from STZ-induced diabetic donors into normoglycemic *Ldlr*$^{-/-}$ recipients exacerbates aortic root atherosclerosis, consistent with lasting hyperglycemia-induced immune memory that links metabolic dysfunction to CVD [23]. Similarly, diet-induced obesity enhances the activating histone marker H3K4me3 in HSPCs, thereby promoting myelopoiesis and persistent inflammation, mirroring features of BM reprogramming observed in hyperglycemic environments [63]. Moreover, transient high-glucose exposure in both human monocytes and murine BMDMs induces TRIM, which is characterized by sustained hyperresponsiveness to secondary LPS stimulation [64]. This hyperglycemia-induced innate immune memory is marked by elevated TNF and IL-6 secretion and driven by the mixed lineage leukemia (MLL) family that regulates transcription through H3K4 methylation [64]. In alloxan-induced diabetes, chronic hyperglycemia dysregulates LPS-induced cytokine production, including increased IL-6 and IL-1β but decreased TNF and IL-10 in diabetic BMDMs [65]. LPS-stimulated diabetic BMDMs also exhibit impaired phagocytosis, reduced nitric oxide and hydrogen peroxide production, and reduced TLR4 expression [65]. Together, these changes indicate a persistent "glycemic memory" in HSPCs and their progeny that exacerbates chronic inflammation in diabetes through multifaceted innate immune dysfunction.

Dysregulated BM-derived immune cells arising in diabetic settings also exacerbate vascular dysfunction by producing inflammatory mediators that disrupt endothelial integrity and promote oxidative stress [66,67]. In *db/db* mice, hyperhomocysteinemia promotes Ly6C$^+$ monocyte differentiation and inflammatory macrophage polarization, exacerbates insulin intolerance, oxidative stress with elevated reactive oxygen species (ROS) production, endothelial dysfunction, and vascular sequelae [66]. In STZ-induced diabetic mice, BM-derived Ly6C^{high} monocytes exhibit aberrant activation and preferential differentiation towards pro-inflammatory macrophages [67]. These monocytes infiltrate metabolic tissues, such as the liver and adipose tissue, where they contribute to impaired glucose tolerance and systemic inflammation [67]. Similarly, in *db/db* mice and mice fed a HFD, Ly6C^{high} monocytes upregulate inflammatory gene expression (e.g., *gp91phox, Tlr4, S100a8, S100a9*), which enhance their infiltration into metabolic tissues, and adoptive transfer of these monocytes from obese *db/db* donors exacerbates glucose intolerance and insulin resistance in recipient mice [67]. Beyond monocytes, neutrophil-derived S100A8/A9 proteins bind to the receptor for advanced glycation end products (RAGE), expressed on the cell surface of hepatic Kupffer cells, amplifying the pro-inflammatory milieu through IL-6-mediated hepatic thrombopoietin production, driving reticulated thrombocytosis and enhancing atherogenesis in diabetes [68]. In parallel, hyperglycemia sustains myelopoiesis through S100A8/A9–RAGE signaling in myeloid progenitors, perpetuating monocytosis and neutrophilia while impairing atherosclerosis resolution in diabetic *Ldlr*$^{-/-}$ mice [69]. Notably, antioxidants such as

astaxanthin reverse hyperglycemia-induced oxidative stress in BM cells, restoring HSC maintenance and function, and normalizing hematopoiesis in STZ-diabetic mice [70].

Supporting these vascular and inflammatory findings, advanced imaging techniques, reveal profound abnormalities in the diabetic BM niche of STZ-induced mice including vascular remodeling, enhanced endothelial cell proliferation, sprouting angiogenesis, and hypoxia that promote myelopoiesis, leukocytosis, and systemic inflammation [71]. These niche alterations, in turn, may promote complications such as diabetic retinopathy, a leading cause of vision loss in diabetic patients, where altered myeloid responses play a central role [72,73]. In Akita mice, which model long-term diabetes, deficiency of the pattern-recognition receptor NOD1 attenuates retinopathy progression through reduced retinal BMDM infiltration and CXCL1/CXCL2 secretion, resulting in reduced neutrophil recruitment and NET release [72]. Collectively, these studies highlight the role of myelopoiesis in propagating diabetes-related complications.

4. Bone marrow and other metabolic disorders

Emerging evidence indicates that maternal metabolic perturbations, including obesity and gestational diabetes mellitus (GDM), can reprogram fetal hematopoiesis, resulting in long-term alterations in HSC fate and function in the offspring. Notably, these hematopoietic changes persist into adulthood, even in the absence of overt metabolic disease, suggesting a form of innate immune memory that originates in utero that may predispose offspring to chronic inflammation and cardiometabolic dysfunction later in life [74–76]. For instance, maternal obesity or Western diet may drive intrinsic HSC dysfunction and myeloid skewing that predispose offspring to glucose intolerance, insulin resistance, hepatic steatosis, and CVD in adulthood, even when maintained on a standard chow diet [75,77–79]. Mechanistically, maternal HFD remodels the fetal liver niche, the primary site of hematopoiesis during mid-gestation, promoting the preferential expansion of myeloid progenitors [78]. Single-cell RNA sequencing and epigenomic profiling have shown that maternal HFD induces persistent transcriptomic and metabolic changes in HSPCs, including upregulation of genes associated with inflammatory signaling, oxidative stress pathways, and myeloid differentiation [74,76,77]. Furthermore, STZ-induced GDM in mice induces hematopoietic memory in offspring via maternal RAGE and NLRP3 inflammasome activation that promotes placental inflammation and DNMT1-dependent epigenetic modifications in HSPCs that persist into adulthood [75]. These changes result in increased myelopoiesis, upregulated inflammatory markers in BMDMs, and heightened atherosclerosis susceptibility [75]. Similarly, maternal consumption of a high-fat Western diet in rhesus macaques remodels the transcriptional landscape of fetal HSPCs at the single-cell level, inducing pro-inflammatory responses in HSPCs and fetal macrophages with enriched inflammatory gene signatures and suppressed B cell development genes that culminate in poor engraftment of fetal HSPCs in immunodeficient mice [77]. Moreover, myeloid cells from offspring of obese dams exhibit profound lipidomic and metabolomic remodeling, characterized by increased diacylglycerols, triacylglycerols, sphingolipids, and phospholipids, decreased cholesteryl esters, and age-dependent mitochondrial dysfunction, independent of sex [74]. Maternal obesity and HFD consumption induce long-lasting innate immune reprogramming of resident immune cell populations as well, such as liver-resident Kupffer cells, promoting a pro-inflammatory phenotype that contribute to the early onset and progression of pediatric MASLD [78,80]. While these findings underscore the importance of developmental hematopoietic reprogramming in shaping susceptibility to disease during adulthood, intergenerational inheritance due to maternal metabolic status as well as the precise mechanisms driving this hematopoietic memory require further investigation.

Other metabolic stressors, such as hypercholesterolemia and dyslipidemia, also modulate hematopoiesis. High-density lipoprotein and ATP-binding cassette transporters facilitate cholesterol efflux from HSCs, thereby suppressing HSC proliferation and attenuating myeloid expansion [81]. Oxidized LDL induces TRIM in monocytes by enhancing glycolysis and oxidative phosphorylation in a glutaminolysis-dependent manner, contributing to persistent inflammation that exacerbates atherosclerosis [82]. Furthermore, defective cholesterol metabolism within HSCs enhances myelopoiesis and accelerates atherosclerosis progression, particularly in inflammatory conditions such as rheumatoid arthritis [83]. Similarly, lipoprotein lipase deficiency impairs BM myelopoiesis and reduces circulating monocyte numbers, highlighting the links between lipid metabolic pathways and hematopoietic progenitor dynamics and homeostasis [84]. Mechanistically, metabolic intermediates produced from cholesterol biosynthesis via the mevalonate pathway have been implicated in the induction of TRIM, linking dyslipidemia and immune memory [28]. Collectively, these findings establish a nexus between dyslipidemia, sustained innate immune rewiring, and chronic inflammation, providing a mechanistic foundation for therapeutic strategies aimed at restoring BM homeostasis, modulating hematopoietic reprogramming, and ultimately mitigating CVD risk.

5. CHIP and metabolic dysfunction

CHIP has emerged as a significant risk factor for a spectrum of cardiometabolic and inflammation-associated chronic diseases, including cardiovascular disease, diabetes, MASLD, rheumatoid arthritis, and periodontitis [85–90]. Experimental studies from animal models support a causal role for CHIP in exacerbating these conditions through heightened inflammatory responses [87,91–95]. Furthermore, evidence from both animal studies and human cohorts suggests that CHIP may not only drive chronic inflammatory dysregulation, but may also be promoted by it, indicating a bidirectional relationship [96–102]. Similarly, while CHIP can worsen metabolic disorders, metabolic dysfunction may promote the expansion of CHIP clones. Indeed, beyond aging and genetic predisposition [103–106], unhealthy diet (low in vegetables and fruits, high in red meat), obesity and metabolic imbalance may also influence CHIP development [107–110]. Reflecting these influences, elevated coronary artery disease risk associated with CHIP was observed in individuals with intermediate or unfavorable lifestyle scores — based on BMI, smoking, physical activity, diet, and sleep duration per AHA's Life's Essential 8 recommendations [111] — but not in those with favorable scores [112].

A normal body mass ($18.5\ kg/m^2 \leq BMI < 25\ kg/m^2$) was associated with a lower prevalence of CHIP as compared with being obese (BMI $>30\ kg/m^2$) [108]. Consistently, the prevalence of CHIP was associated with increased waist-to-hip ratio (WHR), a marker of central obesity [109]. The higher prevalence of CHIP-associated mutations in obesity is likely driven by obesity-induced inflammation [109]. In support of a causal link, studies in obese mice with CHIP (driven by heterozygosity of *Tet2, Dnmt3a, Asxl1,* or *Jak2*) showed that a fatty bone marrow (FBM) environment promotes clonal expansion [109]. In further support of causation, a 20-year prospective study showed that CHIP clone size (VAF) increased with age in obese individuals receiving standard care but not in those who underwent bariatric surgery, with clone growth correlating negatively with HDL-cholesterol [110]. Human *DNMT3A*$^{R882H/+}$ HSCs and HSCs from a mouse model expressing the human DNMT3A R882H mutation exhibit enhanced self-renewal in FBM environment, an effect suppressed by IL-6 neutralization, implicating FBM-derived inflammatory signals as paracrine drivers of CHIP clonal expansion [113].

Obesity has been associated also with an increased risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [114,115]. Given that CHIP is a premalignant state with potential progression to MDS and/or AML [116], it is plausible that obesity contributes to this association, at least in part, through its capacity to promote CHIP. In this regard, obesity creates a pro-inflammatory, metabolically stressed BM environment that favors the emergence and

expansion of CHIP-mutant HSPCs. Indeed, studies in obese mice with CHIP driven by *Tet2*, *Dnmt3a*, *Asxl1*, or *Jak2* mutations show that FBM augments mutant clone expansion, an effect suppressed by anti-inflammatory treatments [109]. Human and mouse *DNMT3A*-mutant HSCs also exhibit increased self-renewal in FBM, mediated by IL-6 [113]. Age-related hormonal decline promotes FBM accumulation [117], recapitulated by castration or ovariectomy and reversed by estrogen [113,118,119]. A 20-year study showed that CHIP clone size increased with obesity but not after bariatric surgery, correlating with insulin resistance and reduced HDL [110]. Together, these studies indicate that inflammatory, niche-derived cues accelerate CHIP progression, potentially reinforced by obesity-induced FBM remodeling of stromal and adipocyte-derived signals. The CHIP-promoting effects of obesity [109,110], combined with its established role as a major risk factor for diabetes and MASLD [113,120,121], suggest that obesity may function as a common upstream driver linking CHIP to inflammation-associated metabolic disease.

Diet may influence CHIP by modulating systemic inflammation and the BM microenvironment [122]. Western-type diets, through obesity and hyperglycemia, promote expansion of myeloid progenitors and drive myelopoiesis [12,35]. Key micronutrients, such as vitamins A and D, are essential in hematopoiesis [123,124]. Elevated serum B12 has been linked to clonal hematopoiesis [125], while vitamin C serves as a cofactor for TET2, thereby limiting aberrant HSPC self-renewal [126]. Consistently, inadequate plasma vitamin C levels in older adults are significantly associated with CHIP involving *TET2* mutations [127]. These findings underscore that CHIP is not solely a consequence of aging or genetics, but is also shaped by metabolic and inflammatory states, which influence clonal dynamics and disease outcomes. Understanding and targeting these pathways may enable personalized interventions to mitigate CHIP-related comorbidities. In the following sections, we explore links between CHIP, diabetes, and MASLD.

6. CHIP and diabetes

Accumulating evidence indicates that CHIP may contribute to the pathogenesis of T2D and its complications. While cross-sectional studies have yielded conflicting results [89,128] — partly due to uncertainty about the timing of CHIP onset relative to diabetes diagnosis — a large prospective study involving 17,637 participants followed for an average of 9.8 years found that individuals with CHIP at baseline had a significantly higher risk of developing T2D compared to non-carriers [86]. In support, additional studies showed that the incidence of new-onset diabetes, as well as diabetic microvascular complications, is significantly higher in CHIP carriers than in individuals without CHIP [129,130]. Furthermore, CHIP mutations are more common in individuals with T2D, with *TET2* mutations showing the strongest association with increased mortality [131]. Interestingly, bidirectional Mendelian randomization analyses suggest that T2D may predispose to CHIP development, whereas CHIP does not seem to accelerate diabetes onset [131]. Longitudinal monitoring of CHIP in obese individuals further revealed that clonal growth correlates positively with insulin levels and insulin resistance [110]. Together, although current evidence supports an association between CHIP and T2D, further research is needed to clarify this relationship.

A study in a mouse model suggested a causal link between CHIP and diabetes [132]. Specifically, clonal hematopoiesis driven by TET2-deficiency exacerbated insulin resistance in aged or obese mice. This phenotype was attributed to IL-1β overproduction from TET2-deficient macrophages, which impaired insulin signaling in adipocytes. Consistently, conditioned medium from TET2-deficient macrophages reduced insulin receptor substrate 1 (IRS1) expression and glucose uptake in cultured adipocytes; both effects were reversed by IL-1β-neutralizing antibodies. Moreover, pharmacological inhibition of the NLRP3 inflammasome, which mediates IL-1β maturation, alleviated insulin resistance in mice with TET2-driven CHIP [132]. The biological relevance of IL-1β in this context is supported by increased circulating IL-1β levels in individuals carrying *TET2*-CHIP mutations [106].

An independent study showed that *Tet2*$^{-/-}$ mice with concomitant genetic obesity due to leptin-deficiency (*Tet2*$^{-/-}$ *ob/ob* mice) exhibit greater weight gain than *ob/ob* mice, and increased inflammatory blood cells compared to *Tet2*$^{-/-}$ mice [109]. These compound mutants also developed a myeloproliferative neoplasm (MPN)-like condition, marked by elevated myeloid blasts and progenitor cells in the BM and extensive infiltration of *Tet2*$^{-/-}$ myeloid cells in the spleen and liver, disrupting normal organ architecture [109]. Similar findings were obtained in *Dnmt3a*$^{+/-}$ *ob/ob* mice, further supporting that obesity synergizes with CHIP-associated loss-of-function mutations to drive metabolic dysfunction and MPN-like pathology [109].

TET2-mutant pre-leukemic HSPCs require additional hits to progress to AML or MPNs, and hyperglycemia may serve as an environmental driver. In a mouse model combining *Tet2* haploinsufficiency with hyperglycemia induced by the *Ins2*$^{Akita/+}$ mutation, compound mutants developed lethal MPN and/or AML [133]. Hyperglycemia amplified systemic inflammation and synergized with *Tet2* heterozygosity to promote myeloid skewing and chronic inflammation. Transcriptomic analysis revealed upregulation of pro-inflammatory pathways, including the antiapoptotic long noncoding RNA *Morrbid*, whose deletion rescued lethality and mitigated disease progression in the compound mutants [133].

If TET2-driven CHIP exacerbates insulin resistance in human obesity, as shown in experimental models [132], then — together with studies suggesting that metabolic dysfunction may promote clonal hematopoiesis [110,131] — this points to a potential feed-forward loop. In this hypothetical vicious cycle that warrants investigation, metabolic dysfunction accelerates CHIP clonal expansion, which in turn worsens insulin resistance, thereby amplifying disease progression in obesity. The observed association between metabolic dysfunction and clonal growth may stem from increased HSC proliferation driven by impaired TET2 function and stability. Notably, high glucose levels reduce AMP-activated protein kinase (AMPK) activity in T2D, leading to diminished phosphorylation of TET2 at Ser99 and subsequent destabilization [134]. This mechanism thus mirrors the CHIP-related defect of TET2 that promotes HSC clonal expansion.

Interestingly, in the aforementioned prospective study linking CHIP to increased risk of T2D, the association was statistically significant for total CHIP and for gene-specific CHIP driven by mutations in *TET2, ASXL1, JAK2*, and *TP53*, but not *DNMT3A* [86]. The absence of significant association for DNMT3A-driven CHIP may be explained by recent findings in both human and mouse models. HSCs harboring the most common CHIP-associated *DNMT3A* mutation — at position R882 in humans and its mouse equivalent R878 — exhibit elevated mitochondrial respiration, which underlies their enhanced expansion relative to wild-type (WT) controls [135–137]. The expansion advantage of *Dnmt3a*$^{\mathrm{R878H}}$ clones is suppressed by metformin, an anti-diabetic drug that inhibits complex I of the electron transport chain [138], as demonstrated in mouse models of DNMT3A-driven CHIP [135,136]. Consistently, patients treated with metformin show a lower prevalence of R882-mutant *DNMT3A* CHIP compared to non-metformin-treated individuals [135], potentially explaining the observed lack of association between *DNMT3A* mutations and T2D. Mechanistically, metformin promotes the methylation capacity in *DNMT3A*-mutant HSPCs, correcting their aberrant CpG and histone methylation landscapes [136]. An additional, non-mutually exclusive mechanism may involve metformin's inhibition of mammalian target of rapamycin (mTOR) signaling [139,140], which is critical for the expansion of *Dnmt3a*$^{\mathrm{R878H}}$ clones, as shown by the suppression of these clones by rapamycin in a mouse model of *DNMT3A*-driven CHIP [87]. *TET2* mutations are well established to drive potent NLRP3/IL-1β responses [106], whereas *DNMT3A* mutations trigger a broader and more heterogeneous inflammatory program rather than a dominant NLRP3/IL-1β axis [141]. Given the central role of IL-1β as a causal link between CHIP and diabetes [132]

these mutation-specific biological differences offer an additional plausible explanation for the weaker epidemiological association between *DNMT3A* mutations and T2D.

Nevertheless, experimental studies suggest that mutated DNMT3A can drive metabolic dysfunction in the context of CHIP. Mice transplanted with *Dnmt3a*$^{+/-}$ BM cells and fed a HFD develop increased body weight, impaired glucose tolerance, and heightened inflammation, including increased abundance of *Dnmt3a*$^{+/-}$ macrophages in adipose tissue and pancreas, as compared to HFD-fed controls receiving WT BM cells [142]. In another study, mice transplanted with BM containing 20% *Dnmt3a*$^{+/-}$ or *Dnmt3a*$^{R878H/+}$ cells exhibited progressive weight gain and subcutaneous white adipocyte hypertrophy, even without HFD exposure — although the diet further intensified these effects [143]. These metabolic abnormalities were more pronounced in *Dnmt3a*$^{+/-}$-driven CHIP. When challenged with a HFD, these mice showed elevated fasting glucose, hyperinsulinemia, and impaired glucose tolerance compared to WT controls, indicating a DNMT3A/CHIP-associated predisposition to metabolic dysfunction [143].

CHIP may also affect the development of diabetic complications. Specifically, a UK Biobank-based prospective cohort study found that CHIP, particularly with mutations in TET2 and the RNA splicing factor SF3B1, is significantly associated with increased CVD risk in individuals with diabetes [144]. This risk remained elevated even in diabetic patients with ideal health indicators (BMI, HbA1c, BP, LDL) [144]. Thus, CHIP increases the risk of CVD in diabetic patients regardless of metabolic health, underlining the necessity for targeted screening approaches and therapeutic strategies beyond conventional metabolic control.

7. CHIP and MASLD

CHIP was associated with a significantly elevated risk of both pre-existing and incident chronic liver disease [95]. Individuals with CHIP — particularly those carrying mutations in *TET2* and *JAK2* — were more likely to exhibit hepatic inflammation and fibrosis. Mendelian randomization analyses demonstrated that inherited predisposition to CHIP increases susceptibility to chronic liver disease. Further support for a potential causal relationship between CHIP and hepatic inflammation and fibrosis, came from mechanistic studies in a dietary mouse model of metabolic dysfunction-associated steatohepatitis (MASH), induced by a choline-deficient, amino acid-defined high-fat diet (CDAHFD). Transplantation of *Tet2*-deficient hematopoietic cells to CDAHFD-fed mice led to exacerbated liver inflammation and fibrosis, as well as elevated disease activity score, relative to controls receiving WT cells. Notably, these pathological features were markedly attenuated in CDAHFD-fed mice receiving BM deficient in both *Tet2* and *Nlrp3*, implicating NLRP3-dependent inflammatory signaling as a key driver of CHIP-associated liver injury [95] (Fig. 3). Consistent with this, an earlier study showed that knock-in mice expressing a hyperactive NLRP3 variant (D301N; ortholog of D303N in human *NLRP3*) exhibited severe liver inflammation and fibrosis, effects that were partially attenuated by IL-1 receptor antagonism [145]. In the above-discussed CDAHFD dietary model, transplantation of *Dnmt3a*-deficient hematopoietic cells similarly resulted in increased liver inflammation and higher disease activity scores relative to WT controls [95]. Consistent findings were reported in an independent study, where HFD-fed mice transplanted with BM containing 20% *Dnmt3a*$^{+/-}$ cells developed features of MASLD/MASH, including aggravated steatosis, inflammation, fibrosis, and elevated disease activity score compared to mice receiving exclusively WT BM cells [143]. These observations align with mechanistic evidence that CHIP-associated mutations potentiate liver inflammation and fibrosis through altered macrophage function. Hematopoietic TET2 deficiency drives expansion of pro-inflammatory monocyte-derived macrophages

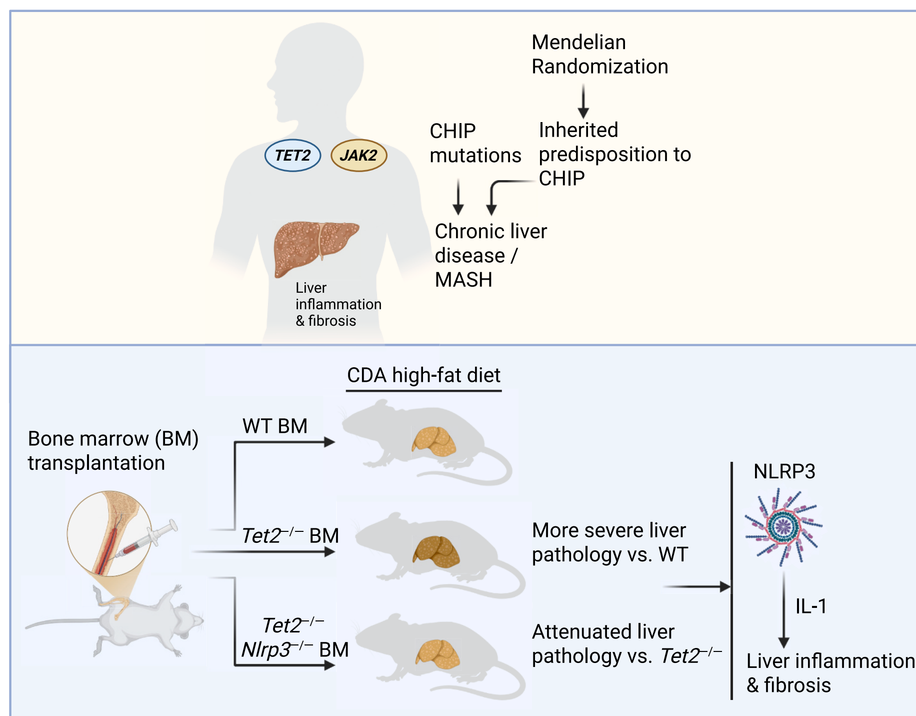

Fig. 3. Proposed mechanistic link between clonal hematopoiesis and chronic liver disease. **Top panel**: Schematic representation of the proposed connection between clonal hematopoiesis (CHIP) and chronic liver disease. CHIP-associated mutations in genes such as *TET2* and *JAK2* increase susceptibility to liver inflammation and fibrosis, as supported by Mendelian randomization analyses. These mutations contribute to metabolic-associated steatohepatitis (MASH) and chronic liver pathology. **Bottom panel**: Experimental evidence from mouse models. Bone marrow transplantation of *Tet2*$^{-/-}$ cells into wild-type recipients, followed by feeding with a choline-deficient, amino acid-defined (CDA) high-fat diet, results in exacerbated liver pathology compared to wild-type bone marrow. In contrast, combined deficiency of TET2 and NLRP3 attenuates liver inflammation and fibrosis, highlighting the critical role of the NLRP3 inflammasome and IL-1 signaling in mediating CHIP-driven liver disease.

that accumulate in injured liver via enhanced CCL2/CCR2 signaling. These mutant macrophages secrete elevated IL-6, which activates hepatic stellate cells and promotes extracellular matrix deposition, whereas blocking chemokine signaling or IL-6 attenuates macrophage accumulation and fibrosis [146]. In a different fibrotic context (cardiac fibrosis), DNMT3A loss in macrophages enhances secretion of heparin-binding EGF-like growth factor, which activates local fibroblasts [147]. This supports a plausible paracrine mechanism that could similarly operate in the liver, where macrophage derived growth factors or cytokines may activate hepatic stellate cells and reinforce fibrogenesis.

8. Therapeutic interventions

Therapeutic interventions that modulate BM function may mitigate inflammation associated with metabolic disorders and reduce CVD risk. For instance, in diabetic *Ldlr*$^{-/-}$ mice, transgenic overexpression of apolipoprotein AI promotes atherosclerosis regression, partly by suppressing hyperglycemia-driven myelopoiesis [148]. This effect is mediated through enhanced cholesterol efflux from BM progenitors and downregulated S100A8/A9–RAGE signaling resulting in reduced HSC proliferation, monocytosis, neutrophilia and NET formation in plaques [148]. In STZ-induced diabetic *ApoE*$^{-/-}$ mice fed a HFD, BM mesenchymal stem cell–derived extracellular vesicles (BMSC-EVs) alleviate diabetes-induced atherosclerosis by suppressing mTOR signaling and thereby promoting autophagy, driving macrophage polarization towards a reparative phenotype and resulting in reduced plaque area and foam cell formation [149]. Clinical translation of such approaches warrants further investigation.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, have shown significant cardiovascular benefits in clinical trials. For example, in the landmark SELECT trial involving overweight patients or patients with obesity and preexisting CVD with no history of diabetes, semaglutide reduced major adverse cardiovascular events (MACE) compared to placebo [150]. In the SEMA-VR CardioLink-15 randomized trial that included patients with T2D and/or obesity with CVD or high CVD risk, semaglutide reduced pro-inflammatory granulocyte precursors – particularly those expressing CD66b and CXCR2 – and downregulated serum proteins enriched in TNF and interleukin signaling pathways [151]. Additionally, tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptor agonist, has shown substantial cardiovascular protective effects and weight management in individuals with metabolic disorders [152]. The beneficial effects of the GIP component are further supported by murine studies showing that GIP receptor signaling on myeloid cells suppresses excessive myelopoiesis and adipose-tissue inflammation by directly reducing S100A8/A9 in adipose tissue macrophages [153].

In parallel, lifestyle modifications such as physical exercise and nutritional interventions beneficially influence BM-driven inflammation. Regular aerobic activity reduces HSPC proliferation and lowers systemic inflammation by modulating leptin signaling in murine models [154]. Moreover, long-term moderate exercise reprograms monocyte/macrophages towards anti-inflammatory phenotypes through metabolic shifts in favor of oxidative phosphorylation, thereby dampening BM-driven inflammation and lowering CVD risk in mice [155]. Nutritional strategies, such as caloric restriction and intermittent fasting, further modulate BM function. Short-term fasting in both mice and humans reduces the number of circulating monocytes by engaging a hepatic AMPK–peroxisome proliferator-activated receptor alpha (PPARα) axis that suppresses CCL2 production and limits BM monocyte mobilization without impairing monocyte recruitment and function during acute inflammation or infection [156]. Furthermore, in murine models of diabetes, intermittent fasting and fasting-mimicking treatments activate sirtuin 1 and liver X receptor alpha (SIRT1/LXRα) signaling pathways, thereby reducing myeloid skewing and inflammatory cytokine production in the BM and restoring microvascular function [73].

Further pharmacological treatments for metabolic disease also exert important effects on BM homeostasis. Clinically relevant pharmacological agents, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors and metformin, may reduce CVD risk via BM modulation [157,158]. Metformin enhances cholesterol efflux from HSPCs via increased *Abca1* expression, thereby limiting maladaptive myelopoiesis and attenuating macrophage-driven inflammation [158]. SGLT2 inhibitors in turn reduce glucose toxicity, suppress myelopoiesis, and attenuate atherosclerosis progression [157]. Collectively, these findings underscore the complex interplay between BM niche remodeling, immunometabolism, and vascular pathology in metabolic disorders, paving the way for novel therapeutic avenues focused on modulating hematopoiesis to attenuate CVD risk.

9. Conclusions

As summarized herein, BM homeostasis is affected by different metabolic disorders, highlighting their role in perpetuating chronic inflammation, skewed myelopoiesis, and CVD progression via mechanisms akin to maladaptive TRIM [6,8]. Hyperglycemia, hyperlipidemia, and obesity-associated inflammatory cues remodel BM architecture and trigger persistent epigenetic and metabolic reprogramming in HSPCs and their progeny, resulting in myeloid cells with enhanced pro-inflammatory phenotypes that fuel chronic low-grade inflammation, and accelerate vascular dysfunction and atherosclerosis/CVD [6,8,25]. Such alterations during maternal obesity or GDM may be transmitted to fetal HSPCs, predisposing offspring to glucose intolerance, heightened inflammation, and cardiometabolic risks later in life [75]. Therapeutic interventions such as metformin, apolipoprotein A-I supplementation, as well as lifestyle modifications, including exercise have shown considerable potential in preclinical models by restoring BM homeostasis, suppressing aberrant myelopoiesis, and promoting atherosclerosis regression [148,154,158]. The interplay between CHIP and metabolic disorders further reveals a complex bidirectional relationship between BM homeostasis, chronic inflammation, and metabolic imbalance [95,109]. CHIP mutations, particularly in TET2 and DNMT3A, drive clonal expansion and generate hematopoietic progeny with heightened inflammatory potential; this, promotes a pro-inflammatory BM milieu that further amplifies CHIP and may exacerbate cardiometabolic dysfunction that, in turn, may further reinforce clonal hematopoiesis [110,131,132]. FBM environments and inflammatory signals (e.g., IL-6, IL-1β) in obesity and hyperglycemia also promote clonal expansion; in turn, CHIP worsens insulin resistance, glucose intolerance, and hepatic fibrosis [95,113,143]. Inflammation modulators (e.g., targeting NLRP3 inflammasome or IL-1β antagonism) and dietary changes (e.g., optimizing vitamin C intake to support hematopoiesis, enzymatic functions of TET2, and reduce inflammation) may help mitigate CHIP-related comorbidities [95,127,132]. Although the studies summarized above provide insightful mechanistic links among metabolic disease, hematopoiesis and chronic inflammation, significant translational limitations persist. The majority of the findings discussed in this review derive from preclinical rodent models that recapitulate only certain aspects of human metabolic disease and lack individual heterogeneity seen in patients with obesity and T2D. Nevertheless, by enabling rigorous testing of specific and overlapping mechanistic hypotheses, these models collectively provide valuable and often highly insightful biological and translational inferences. Additionally, direct examination of human BM HSCs and HSPCs in obese or diabetic individuals is technically challenging, making most human data correlative rather than causative. Consequently, while pathways such as TLR4, NLRP3, S100A8/A9–RAGE are appealing targets based on mouse experiments, whether these mechanisms can be effectively modulated as therapeutic interventions in cardiometabolic disease in humans requires clinical investigation. Nevertheless, emerging clinical evidence with metabolic targets, such as GLP-1RAs, which have potential BM modulating effects, provide an optimistic outlook for such approaches. Taken together, by addressing the BM as a central hub of maladaptive TRIM and CHIP in

metabolic disorders, novel therapeutic strategies may be streamlined to reduce chronic inflammation and alleviate the global burden of diabetes- and obesity-associated CVD.

CRediT authorship contribution statement

Julia Chronopoulos: Writing – review & editing, Writing – original draft, Conceptualization. **George Hajishengallis:** Writing – review & editing, Writing – original draft, Conceptualization. **Triantafyllos Chavakis:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Triantafyllos Chavakis reports financial support was provided by Deutsche Forschungsgemeinschaft. George Hajishengallis reports financial support was provided by NIH - NIDCR. Triantafyllos Chavakis reports financial support was provided by co-funded by the European Union and cofinanced from tax revenues on the basis of the budget adopted by the Saxon State Parliament. Triantafyllos Chavakis reports a relationship with Sanofi that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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