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Review

Interleukin-1-mediated inflammatory memory: Protective training or maladaptive tumor imprinting?

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ABSTRACT

Interleukin-1 (IL-1) exerts a pivotal role in the regulation of innate immune responses and inflammatory processes. Beyond its local effects at the site of inflammation, IL-1 acts as a systemic regulator of hematopoiesis by reprogramming hematopoietic stem and progenitor cells (HSPCs), thereby shaping the functional properties of the myeloid progeny. Through induction of emergency myelopoiesis and inflammatory memory, IL-1 can imprint durable epigenetic, metabolic and transcriptomic changes within the hematopoietic compartment, altering immune output well beyond the initial inflammatory trigger. This systemic effect of IL-1 signaling is particularly relevant in the context of cancer, since tumors are now viewed as inflammatory entities providing persistent inflammatory factors that can influence hematopoiesis and imprint an immunosuppressive phenotype in myeloid cells. In parallel, aging and clonal hematopoiesis (CH) are characterized by chronic low-grade inflammation in which IL-1 signaling may amplify mutant progenitor expansion, linking inflammaging to increased susceptibility to both hematological malignancies and solid cancers. Here, we discuss the role of IL-1 signaling in emergency myelopoiesis and both central and peripheral inflammatory memory, and how these processes shape cancer progression. We also highlight the therapeutic potential of targeting IL-1-mediated hematopoietic reprogramming.

1. Introduction

Inflammation is a fundamental immune response that enables host defense and tissue repair, but when sustained, it can profoundly reshape immune homeostasis [1]. Beyond its local effects at sites of infection or injury, inflammation also acts systemically on the hematopoietic system, thereby regulating the production, composition, and functional state of immune cells [2]. In this context, the bone marrow (BM) emerges as an active immune organ that dynamically adapts the hematopoietic output in response to inflammatory cues [3,4].

Myelopoiesis represents a central arm of this systemic adaptation. Under steady-state conditions, myeloid cell production is tightly regulated to maintain immune surveillance and tissue homeostasis [5]. In response to inflammatory stress, the hematopoietic system rapidly adjusts to the demands of the host through the process of emergency myelopoiesis, which is characterized by increased proliferation and differentiation of myeloid progenitors to meet heightened demand for innate immune cells [5–7]. While this process is essential for host protection, persistent or dysregulated inflammatory signaling can lead to sustained alterations in myeloid output, with consequences that extend beyond the resolution of the initial insult [8–11].

Recent advances have shed light to the concept of trained immunity, also referred to as inflammatory memory, by demonstrating that inflammatory signals can induce durable functional reprogramming of progenitors and of their progeny [9–15]. Rather than representing a transient activation state, trained immunity describes a form of innate immune memory in which prior inflammatory exposure imprints epigenetic, transcriptomic and metabolic changes in innate immune cells [15]. Importantly, accumulating evidence indicates that this rewiring can occur at the level of hematopoietic stem and progenitor cells (HSPCs), a process termed as central trained immunity, thereby influencing myelopoiesis and shaping the functional properties of myeloid progeny over extended periods [11,13,14,16–21]. These findings position the hematopoietic compartment as a reservoir of inflammatory memory.

Mechanistically, trained immunity is associated with long-lasting

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changes in chromatin accessibility in regions associated with inflammatory and myeloid-associated genes, thereby modulating the binding of key transcription factors (TFs) and subsequently the transcriptional responsiveness of HSPCs and mature myeloid cells upon secondary stimulation [15,22]. Among the most extensively described epigenetic changes associated with trained immunity are histone marks, including the histone 3 lysine 27 acetylation (H3K27ac), the histone 3 lysine 4 monomethylation (H3K4me1), and the histone 3 lysine 4 trimethylation (H3K4me3), which are associated with active enhancers and promoters of inflammatory genes [15,22]. Importantly, these epigenetic adaptations are tightly linked to cellular metabolism. Inflammatory stimulation induces metabolic rewiring, including enhanced glycolysis, cholesterol biosynthesis, amino acid and fatty acid metabolism and oxidative phosphorylation, which alters the availability of key metabolites that modulate chromatin structure and influence TF activity [23]. Metabolites such as fumarate, mevalonate, alpha-ketoglutarate and itaconate have been implicated in the induction of trained immunity in mature myeloid cells through regulating the function of DNA and histone modifying enzymes [24–27]. Consistently, induction of trained immunity is associated with increased aerobic glycolysis and glutaminolysis, which subsequently promote histone modifications and sustained inflammatory gene expression, highlighting the close interplay between metabolic and epigenetic regulation [24,28,29]. In addition to metabolic rewiring, epigenetic reprogramming during trained immunity induction is associated with persistent transcriptional changes in HSPCs and mature myeloid cells as revealed by transcriptomic and single-cell epigenomic analysis [13,14,16,18,19,30,31]. Central trained immunity, which involves reprogramming of HSPCs, is associated with transcriptional changes in genes linked to inflammatory signaling pathways, including type I and type II interferon (IFN) signaling, metabolic pathways such as glycolysis, and genes linked to myeloid lineage differentiation [13,14,18,19,30,32]. Notably, these epigenetic and transcriptomic changes upon induction of trained immunity establish a poised state in HSPCs, enabling their myeloid progeny to exhibit enhanced effector responses [14].

The interleukin−1 (IL−1) family comprises 11 cytokines that play central roles in the regulation of innate immunity and inflammatory processes [33]. Among them, IL−1 alpha (IL−1α) and IL−1 beta (IL−1β) are central mediators of inflammatory responses and orchestrate both local and systemic immune responses [34]. Although IL−1α and IL−1β exert similar pro-inflammatory effects, they differ significantly in their localization, expression, processing mechanisms, and biological functions [35]. IL−1α is expressed in a constitutive manner by a broad range of cell types, including epithelial, endothelial cells and hematopoietic stem cells (HSCs). Both the precursor, pro-IL−1α, and mature form of IL−1α are biologically active. Pro-IL−1α contains a nuclear localization sequence and can translocate to the nucleus, where it regulates the expression of inflammatory cytokines and chemokines [35]. Moreover, membrane-associated or released IL−1α can act locally by binding to IL−1 receptor (IL−1R) on neighboring cells and triggering inflammatory responses. Since IL−1α can be expressed by a wide range of cells, its release is regarded as an alarmin, as it promotes the recruitment of immune cells to sites of inflammation and orchestrates inflammatory responses. In particular, IL−1α is rapidly released from injured or activated cells and functions as an early danger signal that activates surrounding immune and stromal cells [35,36]. Unlike IL−1α, IL−1β becomes biologically active only after cleavage and exerts its function only as a secreted protein. IL−1β is predominantly produced by activated myeloid cells. Upon inflammatory stimulation, immune cells express the precursor of IL−1β, pro-IL−1β, which is subsequently cleaved in a NLR family pyrin domain containing 3 (NLRP3)-caspase 1 dependent manner. Secreted IL−1β binds to its receptor, IL−1R, on the surface of target cells, leading to the activation of nuclear factor κB (NF-κB) pathway and downstream inflammatory programs [37].

Beyond their well-established effects on innate immune cells at the sites of inflammation, IL−1 family ligands can directly act on HSPCs. These cells express IL−1R type I (IL−1RI), and type II (IL−1RII), IL−18 receptor (IL−18R) and ST2, enabling them to sense IL−1α, IL−1β, IL−18 and IL−33, respectively [38–42]. In response to ligand binding to IL−1 receptor, conformational changes in the IL−1R extracellular domain enable the recruitment of IL−1R accessory protein (IL−1RAP) [43]. Sequentially, IL−1R and IL−1RAP recruit via their shared cytosolic regions, named Toll- and IL−1R-like (TIR) domains, two signaling proteins, the myeloid differentiation primary response gene 88 (MYD88) and interleukin−1 receptor–activated protein kinase (IRAK) 4 [44,45]. This signaling cascade activates downstream NF-κB signaling, p38 mitogen-activated protein kinase (p38MAPK), c-Jun N-terminal kinases (JNK) and extracellular signal-regulated kinases (ERK) ultimately leading to the transcription of IL−1-responsive genes [44,45].

Within this cytokine family, IL−33 signaling through ST2 has been shown to contribute to steady-state hematopoiesis [46]. Beyond this, IL−1 signaling exerts a prominent role during inflammatory stress by acutely promoting emergency myelopoiesis and, under sustained exposure, imprints long-term inflammatory memory in progenitors, thereby linking systemic inflammation to reprogramming of myelopoiesis and long-lasting alterations in the functional properties of myeloid progenitors [7,31,47–51]. Thus, IL−1 emerges not only as a pro-inflammatory cytokine but as a systemic mediator of hematopoietic reprogramming.

Cancer represents a pathological context in which tumor-associated inflammation, IL−1-mediated immune responses, emergency myelopoiesis and innate immune memory acquire particular relevance by shaping local and systemic immune responses, thereby affecting cancer outcome [52–56]. Tumors function as chronic inflammatory entities that generate persistent cytokine signals, including IL−1, primarily IL−1α and IL−1β, capable of reshaping immune responses within the tumor microenvironment (TME) [57–59] and systemically influencing hematopoiesis in the BM [47]. Consistent with this, elevated IL−1α and IL−1β cytokine levels have been reported in many solid tumors, such as melanoma [60], colon [61], lung [62] and breast cancer [59] as well as hematological malignancies [63]. In this context, IL−1 signaling can exert both pro-tumorigenic and anti-tumorigenic effects during tumor initiation and progression, as well as angiogenesis and metastasis [64,65]. Beyond cancer-associated inflammation, chronic inflammatory states such as aging and clonal hematopoiesis (CH) are also characterized by persistent IL−1 signaling, which may contribute to increased susceptibility to malignant transformation [45,66,67]. Whereas IL−1β has been extensively implicated in the induction of emergency myelopoiesis and inflammatory memory, with either protective or maladaptive outcomes, both IL−1α and IL−1β participate in cancer-driven systemic immune reprogramming, exerting context-dependent effects that can either promote or suppress cancer progression [13,16,19,31,47,48,68].

In this review, we discuss the role of IL−1 signaling in emergency myelopoiesis and inflammatory memory, explore its implications in disease outcome and particularly cancer development, and highlight therapeutic strategies aimed at selectively modulating IL−1-imprinted hematopoiesis.

2. IL−1-mediated emergency myelopoiesis and trained immunity

2.1. Emergency myelopoiesis as an inflammatory adaptation

Under homeostatic conditions, HSPCs reside within specialized BM niches in a predominantly quiescent state, entering the cell cycle in a tightly regulated periodic manner to sustain blood cell production [69,70]. Despite this semi-quiescent state, HSPCs retain the capacity to directly sense inflammatory signals and translate them into adaptive changes in their hematopoietic output [4,71].

HSPCs express pattern recognition receptors (PRRs), as well as receptors for inflammatory cytokines and growth factors, such as IL−1,

IFN-γ, IL−6, tumor necrosis factor alpha (TNF-α), IL−3, IL−11, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF), enabling them to directly sense systemic inflammatory signals, rapidly respond and differentiate [4,51,72]. In response to infection, tissue damage, or other types of inflammatory stress, such as chronic inflammation, aging and cancer, the BM rapidly shifts from steady-state hematopoiesis to an inflammation-adapted program of emergency myelopoiesis [55,68,73]. During inflammatory signaling within the BM niche, HSCs initiate emergency myelopoiesis by altering the dynamics and lineage bias of multipotent progenitors (MPPs). In this process, lymphoid-biased MPP4 cells undergo molecular reprogramming toward a myeloid-biased MPP3 fate, thereby providing a source for rapid expansion of granulocyte/macrophage progenitors (GMPs) to support hematopoietic regeneration [51]. In addition, stress conditions further drive the development of a myeloid-primed MPP3 subset that functions as a GMP reservoir through a combination of lineage priming and distinct cytokine secretion that exerts both paracrine and autocrine effects within the BM niche [74]. During acute infections, cytokines such as G-CSF and IL−3 act on HSPCs, including common myeloid progenitors (CMPs) and GMPs and orchestrate the accelerated generation of neutrophils required for host defense, a process termed emergency granulopoiesis [75–77]. This dynamic adaptation underscores that emergency myelopoiesis is not merely increased output, but a coordinated reprogramming of progenitor hierarchy. Beside the BM, hematopoiesis takes place also in other organs, such as spleen, liver, or lymph nodes, a process termed extramedullary hematopoiesis [78]. While physiologically active during fetal development, extramedullary myelopoiesis can also be activated under inflammatory conditions during which BM-derived HSPCs migrate to peripheral organs and contribute to local myeloid cell generation to provide to their enhanced demand in the periphery [48,78,79].

However, when inflammatory signaling is sustained or recurrent, emergency myelopoiesis can become maladaptive. Chronic activation of HSPCs can result in prolonged myeloid skewing, impaired self-renewal capacity and exhaustion [51,80–82].

2.2. IL−1 as a central regulator of emergency myelopoiesis

Among inflammatory mediators, IL−1 has emerged as a key cytokine linking systemic inflammation to emergency myelopoiesis [31,51,83,84]. Experimental studies demonstrate that IL−1 promotes HSPC proliferation and accelerates differentiation toward the myeloid lineage [13,38,42,51,82,85,86].

Locally produced in the BM niche, IL−1β binds to IL−1R expressed on HSPCs and initiates emergency myelopoiesis, through expansion of myeloid-biased MPP3 cells at the expense of lymphoid-biased MPP4 cells [13]. Specifically, IL−1R signaling in HSCs activates downstream transcriptional programs, including induction of the myeloid regulator PU.1, thereby promoting a myeloid lineage bias [50,51,86]. In addition to PU.1, IL−1R signaling in HSCs activates key master regulators of myeloid differentiation, namely CCAAT/Enhancer binding protein alpha (C/EBPα) and beta (C/EBPβ), which have been implicated in IL−1β-induced myeloid differentiation under chronic inflammatory conditions and lipopolysaccharide (LPS)-driven epigenetic reprogramming of HSCs, respectively [49,87]. Consistent with this, IL−1β treatment of $CD34^{+}$ human HSPCs drives the generation of granulocyte-macrophage (GM) colonies upon colony-forming assays [31]. *In vivo*, IL−1RI signaling is further required for emergency granulopoiesis and reactive neutrophilia during acute inflammation, further highlighting the role of IL−1 family in emergency myelopoiesis [42,85]. Notably, chronic exposure of long-term HSCs (LT-HSCs) to IL−1 drives the repression of genes involved in cell cycle progression and protein synthesis genes which was associated with increased PU.1 levels [50]. As a regulatory mechanism, IL−1 signaling can also trigger negative feedback pathways, including proteasomal degradation of the adaptor protein MYD88, thereby limiting excessive HSC proliferation and preventing stem cell exhaustion [88]. Importantly, the impact of IL−1 is highly context dependent. While acute IL−1 exposure supports the replenishment of HSPCs upon myeloablation and transplantation [51], chronic IL−1 signaling in the BM niche drives aberrant HSPCs division and differentiation, impairing their self-renewal capacity and driving their exhaustion [46,49–51,82].

These observations position IL−1 not simply as an inflammatory cytokine, but as a temporal regulator that determines whether emergency myelopoiesis remains an adaptive response or becomes pathological.

2.3. Inflammatory memory and central trained immunity

The concept of trained immunity, also referred to as inflammatory memory, has fundamentally reshaped our understanding of how innate immune responses adapt over time [8–10,15,89]. Rather than a transient activation state, trained immunity describes durable epigenetic, metabolic, and transcriptional rewiring that enhances responses upon subsequent challenges [11,13,14,16,17,90–93].

Initially described in mature myeloid cells (peripheral trained immunity), inflammatory memory is now recognized to originate at the level of HSPCs (central trained immunity), where inflammatory exposure imprints long-term changes that persist through differentiation from the progenitor to the progeny [11,13,14,17,30]. This central reprogramming explains how innate immune memory can persist long-term and outlast the short lifespan of terminally differentiated myeloid cells such as neutrophils [94].

Diverse environmental and inflammatory stimuli, such as Bacillus Calmette-Guerin (BCG) vaccine [17–19], fungus-derived β-glucan [13,14], viral infections [95], physiological stress [96,97], sleep deprivation [98], acute stimulation with LPS [87], and western diet (WD) or oxidized forms of low-density lipoprotein (oxLDL) [99,100], are proven to induce trained immunity in myeloid cells, by provoking epigenetic, transcriptomic and metabolic reprogramming of HSPCs and myeloid progenitor cells. While trained immunity on the one hand enhances host defense against infections [16,101–103], and improves immune responsiveness in conditions such as sepsis-associated immunoparalysis [104] and cancer [14,18,19,104–106], on the other hand, chronic inflammation drives maladaptive training of myelopoiesis leading to the generation of hyperinflammatory myeloid cells that exacerbate chronic inflammatory diseases, such as periodontitis, arthritis and cardiovascular diseases [11,107–111]. This maladaptive immune memory represents also a key mechanism underlining the link between inflammatory comorbidities [11,109,112].

Taken together, trained immunity represents a double-edged sword, as its consequences depend on the disease context and the inflammatory mediators that shape hematopoiesis and subsequently myeloid responses.

2.4. IL−1 as an inducer of trained immunity

Among inflammatory mediators, IL−1 has emerged as a pivotal cytokine linking systemic inflammation to emergency myelopoiesis and hematopoietic reprogramming. Evidence suggests that IL−1 family cytokines contribute to both peripheral and central trained immunity [13,16,31,113–115]. Experimental studies demonstrate that IL−1β induces immunological memory, particularly in HSCs, giving rise to a pool of epigenetically reprogrammed mature cells [13,16,31].

During β-glucan-induced trained immunity, elevated IL−1β levels within the BM niche promote HSPCs proliferation, myeloid skewing and metabolic rewiring [13,16]. Importantly, since HSPCs do not directly sense β-glucan due to lack of expression of the β-glucan receptor Dectin−1 [116,117], IL−1β acts as mediator of the established β-glucan-mediated central trained immunity effects. In support of this, loss of IL−1 signaling blocks the β-glucan training effects by inhibiting the

proliferation of HSPCs and myeloid progenitors and by altering their cell metabolism [13,16].

Similarly, BCG vaccination enhances pro-inflammatory cytokine secretion, including IL−1β and TNF-α even 3 months after vaccination through epigenetic reprogramming in circulating immune cells from vaccinated volunteers, which may represent the mechanism underlying the long-term regulation of cytokine production [118,119]. In addition, HSPC exposure to IL−1β results in altered responsiveness of differentiated mature monocytes upon LPS and Pam3Cys rechallenge, characterized by increased production of cytokines, such as TNF-α and IL−1β, respectively [31]. Stimulation of HSPCs with high dose of IL−1β augments the phagocytosis capacity of HSPCs-derived macrophages, potentially through transcriptional reprogramming of their monocyte and macrophage progeny, a defining feature of trained immunity [31].

Beyond IL−1β, other IL−1 family members have been implicated in the induction of innate immune memory. In particular, IL−18 promotes memory-like reprogramming of natural killer (NK) cells with high proliferating capacity and potent anti-tumor effector functions [113–115]. Other IL−1 superfamily members, such as IL−33 and IL−36, are recognized as activators of innate immune responses and regulators of inflammatory signaling cascades [33]. Although their capacity to induce trained immunity has not yet been formally demonstrated, their roles suggest potential involvement in inflammatory memory programs that warrants further investigation.

In contrast, the anti-inflammatory IL−1R antagonist (IL−1Ra) (anakinra) functions as a physiological regulator that restrains excessive IL−1 signaling [13]. Notably, IL−1Ra is secreted upon restimulation of β-glucan-trained monocytes [120], suggesting the existence of intrinsic feedback mechanisms that temper excessive inflammatory responses following induction of trained immunity.

Importantly, IL−1-mediated training is context dependent (Fig. 1). While transient IL−1 signaling may enhance protective immunity, chronic exposure can drive maladaptive myelopoiesis, HSPC exhaustion and exacerbation of inflammatory pathologies [11,16,99,103,121–129].

2.4.1. *IL−1-dependent trained immunity in host protection against infections*

Early evidence supporting the role of IL−1 in the establishment of non-specific immune memory emerged from studies demonstrating that exogenous IL−1 administration confers protection against subsequent infections. In a seminal study, granulocytopenic mice pretreated with a single dose of IL−1β one day prior to lethal *Pseudomonas aeruginosa* infection exhibited significantly improved survival [123]. Subsequent studies have shown the protective effects of IL−1 pre-treatment against various pathogens, such as *Candida albicans* and *Plasmodium berghei* [124,125]. In parallel, IL−18 has been reported to mediate flagellin-induced cross-protection against heterologous infections [126]. Taken together, these findings support the notion that IL−1 can promote innate immune memory and confer broad non-specific host protection against multiple pathogens (Fig. 1).

Clinical data reinforce this concept, as BCG vaccination has been reported to provide non-specific protection against multiple subsequent infections [130]. In a randomized placebo-controlled clinical trial, individuals that had previously received BCG vaccine displayed enhanced protection against viral infection caused by yellow fever vaccine. Interestingly, this protection was positively correlated with increased IL−1β levels after BCG vaccination [103]. In a human study, in which participants were vaccinated intradermally with BCG, analysis of BM aspirates revealed significant modifications in gene expression of human HSPCs and hematopoiesis bias toward the myeloid lineage, that was detected 3 months after the BCG vaccination [30,119]. Production of pro-inflammatory cytokines, including IL−1β and TNF-α, was found to be enhanced when peripheral blood mononuclear cells (PBMCs) from BCG-vaccinated volunteers were exposed to mycobacterial and non-mycobacterial stimuli [118,119]. Notably, the increased IL−1β production persisted for 3 months after vaccination, consistent with the BCG-mediated long-term epigenetic reprogramming of myeloid progenitors and altered innate immune responses of mature myeloid cells [30,118,119]. Taken together, this evidence indicates that IL−1 may contribute to the BCG-mediated protection against infections (Fig. 1).

Similarly, β-glucan-conferred protection against Mycobacterium

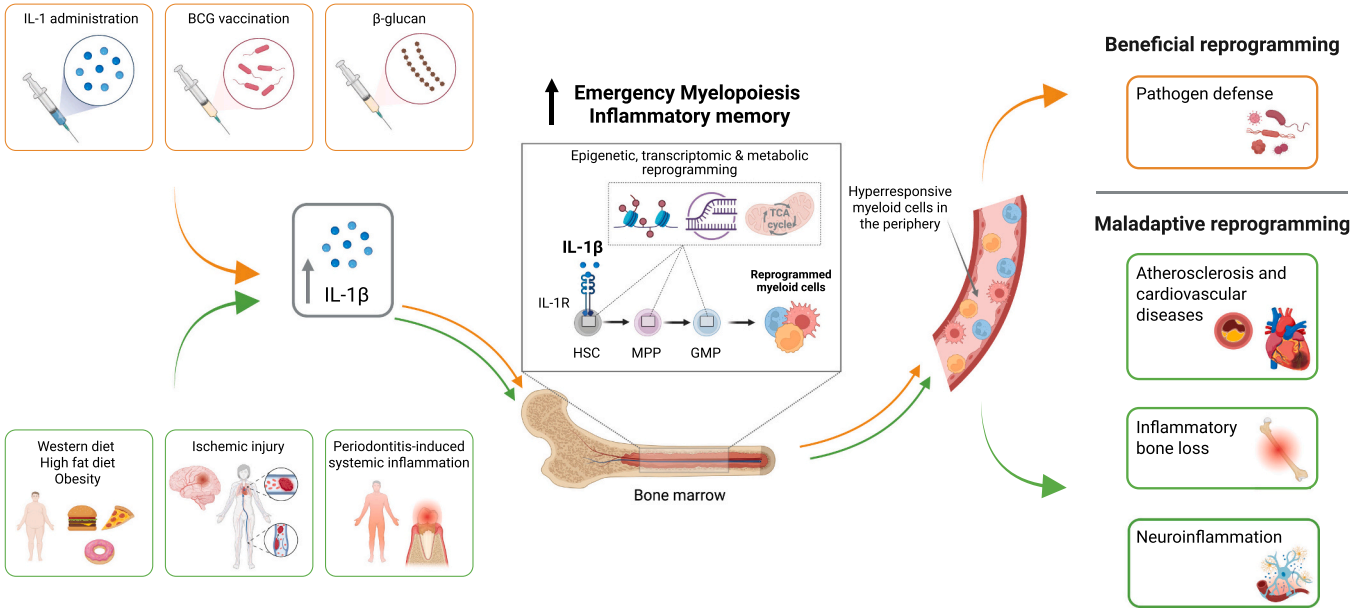

Fig. 1. IL−1β as a central regulator of emergency myelopoiesis and inflammatory memory. Multiple inflammatory stimuli, including IL−1 administration, BCG vaccine, β-glucan, diet-associated metabolic stress, ischemic injury and periodontitis-induced systemic inflammation increase IL−1β levels within the BM niche. HSPCs sense high IL−1β levels through IL−1R signaling and initiate emergency myelopoiesis, accompanied by epigenetic, transcriptomic and metabolic reprogramming. This central IL−1β-mediated imprinting of inflammatory memory leads to the generation of hyperresponsive myeloid cells in the periphery. Depending on the inflammatory context, IL−1β-driven hematopoietic reprogramming can confer enhanced protection against heterologous infections or promote maladaptive outcomes, including atherosclerosis, advanced cardiovascular events, inflammatory bone loss and neuroinflammation.

tuberculosis infection was shown to depend on IL−1R signaling [16]. The suggested mechanism of β-glucan-mediated protection is that β-glucan promotes IL−1β production within the BM, which binds to the IL−1R on HSPCs and induces transcriptional rewiring of the progenitors [13]. HSPCs respond to high IL−1β levels by inducing myelopoiesis and shifting the metabolism toward glycolysis and cholesterol synthesis [13, 16]. Collectively, these findings position IL−1 signaling as a central driver of trained immunity-mediated enhanced protection against infections (Fig. 1).

2.4.2. IL−1-dependent diet-induced trained immunity

Studies have revealed that diet can induce maladaptive inflammatory memory by exposing mature and progenitor cells to inflammatory nutrients, such as saturated fatty acids, palmitic acid and stearic acid, which eventually leads to increased mortality upon infection or increased susceptibility to inflammatory comorbidities [99,128,131, 132].

In obesity, NLRP3 inflammasome activation promotes IL−1β production in visceral adipose tissue, which targets IL−1R on CMPs and GMPs in the BM, resulting in monocytosis and neutrophilia [127]. Eventually, these IL−1β-dependent changes contribute to adipose tissue inflammation and insulin resistance, both observed in obese patients [127]. Diet-induced obesity drives epigenetic and transcriptomic reprogramming of adipose tissue macrophages (ATMs) toward a more pro-inflammatory and pro-angiogenic phenotype, thereby promoting retinal inflammation. These obesity-induced changes in ATMs persist even after switching to normal diet, highlighting the capacity of diet-induced obesity to imprint innate immune memory in resident myeloid cells. This pro-inflammatory phenotype is also observed in BM monocytes from obese mice, which retain the capacity to repopulate ATMs in recipient mice following BM transplantation. Importantly, chow-fed recipient mice receiving BM cells from obese donors also exhibit increased retinal inflammation, suggesting that obesity induces reprogramming at the BM level, which subsequently alters ATM function and promotes neuroinflammation (Fig. 1) [128].

WD enriched in saturated fatty acids and sucrose has been implicated in inducing inflammatory memory and correlated with increased severity and susceptibility upon LPS-driven sepsis [131]. Feeding with WD in LDL receptor-deficient (*Ldlr*$^{-/-}$) mice induces systemic inflammation that resolves upon dietary switch to normal diet [99]. However, WD-induced transcriptomic and epigenetic reprogramming of GMPs and emergency myelopoiesis persist even after diet removal [99]. The inflammasome and IL−1 signaling pathway were found to be highly implicated in GMP reprogramming after feeding with WD [99], identifying IL−1 as a mechanistic link between metabolic stress and long-lasting inflammatory memory (Fig. 1).

Similarly, intermittent consumption of high fat diet (HFD) has been implicated in atherosclerosis development independently of the adaptive immune system or gut microbiota, through the reprogramming of GMP in the BM. In *Ldlr*$^{-/-}$ mice, switching from HFD to chow diet, followed by re-exposure to HFD, leads to elevated levels of immature neutrophils exhibiting a highly pro-inflammatory phenotype, along with increased neutrophil extracellular traps (NET) formation in the aorta. These changes are mediated by IL−1β-driven reprogramming of GMPs in the BM and are associated with more severe atherosclerotic lesions, indicating that HFD-induced neutrophilia accelerates atherosclerosis development [129]. Notably, discontinuing of HFD induces epigenetic reprogramming of GMPs, characterized by reduced *Runt-related transcription factor 1* (*Runx1)* expression, thereby promoting inflammatory signaling in the progenitors within the BM. Upon re-challenge with HFD, elevated levels of IL−1β within the BM niche trigger emergency myelopoiesis and GMPs reprogramming, including decreased expression of *Runx1*, ultimately promoting the expansion of IL−1β-producing neutrophils that drive atherosclerosis development [129]. Collectively, these findings highlight IL−1 as a potential therapeutic target to counteract diet-associated comorbidities, including cardiovascular diseases and atherosclerosis (Fig. 1).

2.4.3. Role of IL−1 in ischemia-induced innate immune training

Acute sterile inflammation can also induce IL−1-dependent inflammatory training (Fig. 1). Following ischemic stroke, rapid elevation of IL−1β alters BM cellularity and induces epigenetic reprogramming of HSPCs, leading to sustained inflammatory changes in peripheral monocytes and macrophages [121]. These reprogrammed cells subsequently infiltrate the heart, where they differentiate into cardiac macrophages characterized by a pronounced extracellular matrix remodeling signature and increased expression of *Matrix metalloproteinase−19 (Mmp19)*, thereby promoting cardiac fibrosis and contributing to post-stroke cardiac dysfunction [121]. Importantly, neutralization of IL−1β or blocking of caspase−1 activation, thereby preventing IL−1β release, are sufficient to prevent post-stroke myelopoiesis and epigenetic reprogramming of HSPCs and of their progeny, and protect against cardiac complications, demonstrating a causal role for IL−1 signaling in ischemia-induced trained immunity [121].

Consistent with these findings, hind limb ischemia in Apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice fed with WD increased HSPC abundance in vascular BM niches, and induced their epigenetic reprogramming associated with emergency myelopoiesis and aggravation of atherosclerosis [122]. Notably, HSPCs upregulated IL−1R following hind limb ischemia, and genetic or pharmacological inhibition of IL−1R reversed the maladaptive effects of ischemia-induced trained immunity and attenuated atherosclerosis progression [122]. These findings underscore IL−1-signaling as a central axis linking sterile injury to long-term hematopoietic reprogramming and cardiovascular diseases (Fig. 1).

2.4.4. Role of IL−1 signaling in periodontitis-induced inflammatory memory

Chronic inflammatory diseases can similarly induce IL−1-dependent maladaptive training [109,112]. Periodontitis, an inflammatory disease of the soft and bone tissues, induces chronic low-grade systemic inflammation, by promoting enhanced production of IL−1β by activated neutrophils within the BM [11]. In turn, IL−1β binds to the IL−1R on HSPCs and induces epigenetic reprogramming of the progenitors and of their progeny, resulting in persistent myeloid skewing and exacerbation of inflammatory arthritis (Fig. 1). Consistently, IL−1 signaling pathway is important for periodontitis-induced maladaptive training of HSPCs and for the periodontitis-arthritis axis, since blocking of IL−1 signaling ablates this maladaptive training and decreases inflammatory bone loss [11]. These findings suggest that chronic IL−1 exposure within the hematopoietic niche enforces long-lasting imprinting that amplifies inflammatory comorbidities (Fig. 1).

3. IL−1-driven hematopoietic rewiring from premalignant states to cancer development and progression

3.1. IL−1-mediated age-associated systemic inflammation as a driver of premalignant hematopoiesis

Aging is marked by chronic, low-grade inflammation (“inflammaging”) within the BM, fueled by accumulated cellular damage, enhanced senescence-associated secretory phenotype (SASP), and dysregulated immune responses, thereby contributing to increased cancer susceptibility [66,80,133]. Hematopoietic aging is characterized by impaired self-renewal of HSCs, and a progressive skewing of hematopoiesis toward the myeloid lineages [134]. Chronic inflammatory conditions can reinforce these aging-related changes, indicating that inflammaging is not merely a result of aging but an important driver of hematopoietic rewiring [66].

Among the inflammatory mediators implicated in inflammaging, IL−1 has emerged as a central regulator of age-associated hematopoietic rewiring (Fig. 2). Elevated IL−1β production has been reported in the BM of aged mice, originating from different BM cell types, namely

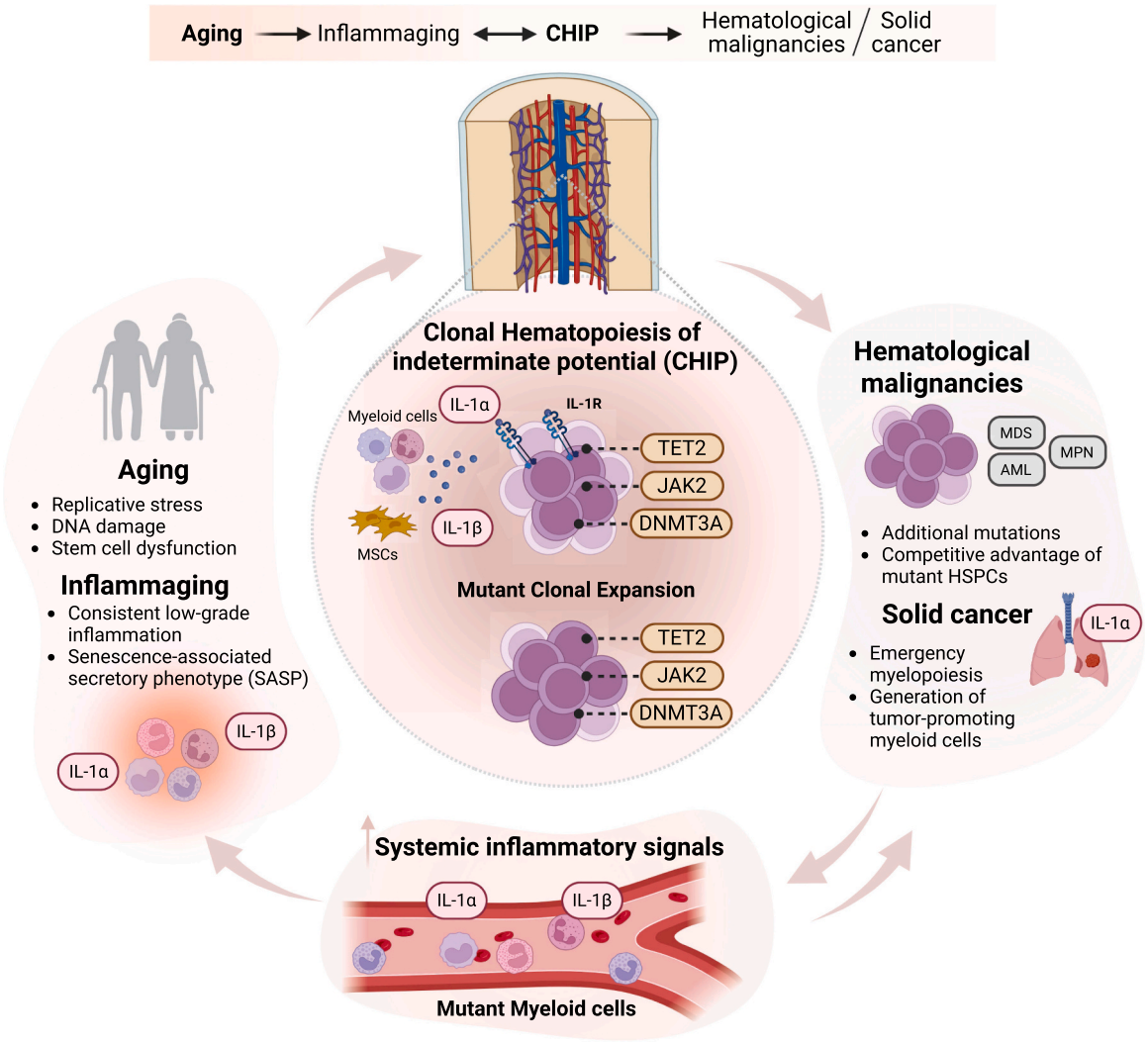

Fig. 2. IL−1-driven inflammaging promotes CH and facilitates progression of hematological and non-hematological malignancies. Aging is characterized by replicative stress, accumulation of DNA damage and stem cell dysfunction, favoring the development of CHIP. Age-related chronic low-grade inflammation ("inflammaging") is marked by elevated pro-inflammatory cytokines, including IL−1α and IL−1β. IL−1α and IL−1β are key mediators in reshaping the hematopoietic niche, by providing selective advantage to HSPCs carrying CHIP-associated mutations in genes, such as *Tet2*, *Jak2* and *Dnmt3a*, thereby driving mutant clonal expansion. Expanded mutant myeloid cells further amplify systemic inflammation, reinforcing a feed-forward loop between CHIP and the inflammatory microenvironment. Sustained IL−1-driven inflammation facilitates clonal evolution, acquisition of additional mutations, generation of tumor-promoting myeloid cells and malignancy development, ultimately contributing to the development of hematological malignancies such as MDS, MPN, AML and non-hematological malignancies such as lung adenocarcinoma.

macrophages, monocytes, neutrophils, dendritic cells (DCs), platelets as well as stromal niche cells, including mesenchymal stromal cells (MSCs) [135–140]. Chronic IL−1β production by MSCs induces hematopoietic remodeling and drives emergency myelopoiesis, which ultimately prevents hematopoietic regeneration in old mice [135,138]. Moreover, during aging MSCs produce IL−33, which signals via ST2 receptor expressed on BM-resident type 2 innate lymphoid cells (ILC2s), which in turn produce IL−6 and GM-CSF and initiate emergency myelopoiesis while impairing HSPC self-renewal capacity [46]. Plasma cells were reported to regulate the production of inflammatory factors, including IL−1 and TNF-α, by BM stromal cells, thereby enhancing myelopoiesis during aging, whereas inhibition of these cytokines rebalances hematopoiesis [136]. In addition, high levels of microbiome-derived compounds in blood of aged mice result in increased IL−1α and IL−1β production by BM myeloid cells, mostly monocytes and neutrophils [138]. In parallel, aged HSPCs upregulate IL−1R and exhibit an IL−1-dependent inflammatory transcriptional signature. Functionally, IL−1 sensing skews aged HSPCs toward myeloid lineage differentiation, whereas treatment with IL−1Ra restores hematopoiesis [138]. Together, these findings identify IL−1 as a major driver of inflammaging-associated myelopoiesis.

Within the aged and inflamed hematopoietic environment, replicative stress and DNA damage result in the accumulation of somatic mutations in HSCs that confer a competitive advantage, resulting in clonal expansion and altered output of mutant progeny [66]. This phenomenon, termed as clonal hematopoiesis of indeterminate potential (CHIP), is detected in more than 10% of individuals above 65 years of age, is associated with increased risk of hematological malignancies and has also been linked to adverse outcomes in solid tumors [67,141–144]. Thus, CHIP can be considered as a premalignant hematopoietic state that emerges in the context of inflammaging.

The most frequent CHIP-associated mutations affect epigenetic modifiers, such as DNA methyltransferase 3 A (DNMT3A) and ten eleven translocation 2 (TET2), although mutations also occur in genes encoding inflammatory signaling mediators including Janus kinase 2 (JAK2), splicing factors and DNA damage repair genes [145,146]. Notably, CHIP-related variants have been identified in tumor-infiltrating leukocytes from patients with solid cancers and hematological malignancies,

and their presence has been associated with adverse clinical outcomes [145,147–149]. Beyond malignant transformation of hematopoietic clones, CHIP may influence tumor initiation and progression through sustained systemic inflammation and tumor-promoting myelopoiesis [68,145,147–149].

Importantly, CHIP and inflammaging appear to reinforce one another (Fig. 2). CHIP can amplify systemic inflammation and thereby reinforce inflammaging [68]. In turn, chronic inflammatory signaling within the aged BM can promote the preferential expansion of mutant HSPC clones, contributing to their dominance over normal HSPCs [67, 150]. Thus, aging establishes an inflammatory environment in which mutant clones are both generated and selected, positioning IL−1 signaling during inflammaging as a key driver of premalignant CH (Fig. 2).

Mechanistic insight into the link between IL−1 signaling and CH has emerged particularly in TET2-mutant associated CHIP. TET2 is a dioxygenase that regulates HSCs function by modifying DNA methylation status via converting 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) [151]. Loss-of-function mutations in *Tet2* are amongst the most prevalent observed in patients with CHIP and are also frequently found in hematological malignancies including myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPNs) and acute myeloid leukemia (AML) [152–156]. Multiple studies demonstrate elevated IL−1β levels in patients or experimental mouse models with *Tet2* loss-of-function mutation, suggesting a role of IL−1 in CHIP-associated inflammation [150,157–161]. Mechanistically, IL−1β acts as a selective pressure that accelerates age-related CHIP and myeloid skewing of TET2-mutant HSPCs (Fig. 2). By employing transgenic mouse models with hematopoietic-specific TET2 deletion, researchers demonstrated that IL−1β administration can promote self-renewal and lineage differentiation of mutant HSPCs via IL−1 signaling [150,162]. Chronic IL−1β exposure induces transcriptional reprogramming of TET2-deficient HSCs, which display enrichment of transcriptional signatures related to cancer, myelopoiesis, and dysregulated lymphopoiesis and hemopoiesis [162]. Furthermore, epigenetic analysis of lineage$^-$ Sca−1$^+$ c-Kit$^+$ (LSKs) hematopoietic progenitors, CMPs and GMPs has revealed that IL−1β-driven inflammation markedly increased global methylation and expanded hypermethylated differentially methylated regions (DMR), particularly at lineage-associated enhancers and TF binding sites [162]. Importantly, genetic or pharmacological inhibition of IL−1R attenuated TET2-associated HSPCs alterations, reduced premalignant progression, and improved survival of the TET2-deficient mice [162,163]. Notably, Canakinumab Anti-inflammatory Thrombosis Outcomes Trial (CANTOS) was the first large-scale randomized, placebo-controlled clinical study to demonstrate that Canakinumab therapy, which targets IL−1β, reduces lung cancer incidence and mortality in a dose-dependent manner, with particularly strong benefit observed in patients with TET2 associated CHIP [158,164]. These findings support the notion that individuals harboring TET2 variants may experience greater therapeutic benefit from IL−1β neutralization compared to individuals without CHIP [158, 164]. In addition, loss of TET2 in HSPCs results in the generation of neutrophils with altered effector functions, including reduced phagocytic capacity, altered NET-related functions, and enhanced inflammatory responses [160]. These TET2-mutant neutrophils display impaired antimicrobial clearance capacity, potentially predisposing individuals to infection-related hematological malignancies [165]. In addition, TET2-mutant neutrophils produce increased levels of pro-inflammatory cytokines, such as IL−1β and IL−6, which may contribute to the heightened inflammatory state observed in patients with CH [160].

Collectively, these findings position IL−1-mediated inflammaging as a key mechanism linking aging to premalignant hematopoiesis. By remodeling the aged BM niche, promoting myeloid-biased hematopoiesis and favoring the expansion of CHIP-associated mutant clones, persistent IL−1 signaling creates a permissive environment for malignant development and increases susceptibility to both hematological and solid cancers (Fig. 2).

3.2. IL−1 as an inflammatory driver of dysregulated myelopoiesis in chronic myeloid neoplasms

Sustained IL−1 signaling within the hematopoietic niche, driven by chronic inflammatory signals associated with aging or CHIP, promotes the clonal expansion of mutant HSPCs and increases the risk of hematological malignancies, primarily myeloid malignancies, including MPNs, MDS and AML (Fig. 2) [63,166,167]. In addition, IL−1 signaling has also been implicated in the development of other hematological malignancies such as Juvenile myelomonocytic leukemia (JMML) and chronic myeloid leukemia (CML), which arise independently of inflammaging or CHIP.

3.2.1. Role of IL−1 signaling in MPNs

Evidence suggests that MPNs can arise in the context of chronic inflammation, which drives aberrant clonal expansion of either erythroid, megakaryocytic or myeloid lineages [168]. Elevated levels of IL−1β in MPN patients correlate with poor prognosis and decreased survival [169,170]. IL−1β produced by myelomonocytic cells and megakaryocytes promotes MPN disease by favoring the clonal expansion of *Jak2*^{V617F} mutant HSCs [171]. In turn, mutant HSCs produce high levels of IL−1β, leading to neuronal damage and apoptosis of nestin$^+$ MSCs, thereby further promoting uncontrolled mutant HSC expansion [172]. Importantly, this excessive expansion and differentiation of HSPCs can be reversed upon administration of IL−1Ra, highlighting the pathological role of IL−1β in MPN disease progression [172,173].

3.2.2. Role of IL−1 signaling in MDS

MDS represents another age-associated myeloid malignancy characterized by a disrupted pro-inflammatory BM microenvironment, with IL−1 signaling playing a significant role in the disease progression [174]. In low-risk MDS patients, BM-resident DCs were identified as the main source of IL−1β following Toll-like receptor−1 (TLR1) and TLR2 induction, suggesting that DCs-derived IL−1β may contribute to altered HSPC function and mobilization observed in these patients [139]. BM stromal dysfunction is increasingly recognized as a driver of HSPC impairment in MDS. In particular, sensing of IL−1 cytokines by BM stromal cells reduces their ability to support HSPCs functions [174,175]. Moreover, MDS blasts can secrete inflammatory mediators, such as IL−1α, and suppress factors important for supporting hematopoiesis and angiogenesis, resulting in remodeling of the stromal niche that further impairs HSPC function and stemness while favoring malignant cell survival and disease progression [176]. Notably, inhibition of IL−1 signaling can restore the function of BM stromal cells, support normal HSPC activity and prevent MDS development [177].

3.2.3. Role of IL−1 signaling in AML

Inflammation within the BM has also been implicated in the pathogenesis of AML, a hematological malignancy characterized by expansion of mutant myeloid-biased progenitors [178]. More broadly, studies in leukemic models have shown that persistent inflammatory cytokines within the inflamed leukemic BM niche, particularly IL−1β and G-CSF, promote the sustained expansion of multipotent progenitor subsets such as MPP2 and MPP3. These progenitors are primed and committed to generate GMPs and, in the absence of quiescence-enforcing cytokine signals, continue to proliferate without appropriate regulatory restraint [73]. Consequently, the chronically activated leukemic niche hijacks normal myelopoiesis by exploiting and deregulating hematopoietic pathways, resulting in impaired differentiation and excessive myeloid output [73]. Moreover, elevated IL−1β levels, along with an enhanced proliferative response of AML cells to IL−1β, are associated with poor patient prognosis [179,180]. Upon broad cytokine screening, monocyte-derived IL−1 was found to trigger a marked expansion of myeloid progenitor cells of AML patients via IL−1R signaling, and

downstream phosphorylating p38MAPK [178]. Inhibition of p38MAPK reversed this effect, providing a strong rationale for developing IL−1/IL−1RI/p38MAPK-targeted therapies for AML [178]. Moreover, low levels of the IL−1Ra have correlated with poor prognosis in patients with AML [86]. Loss of IL−1Ra caused IL−1β-induced pre-leukemic myelopoiesis, which was therapeutically targeted upon administration of exogenous IL−1Ra [86]. In addition, IL−1RAP-IL−1 axis plays a significant role in AML [181]. Increased levels of IL−1RAP present in patients with AML, were positively correlated with a leukemic GMP signature. IL−1β-induced activation of IL−1RAP on both AML cells and stromal cells resulted in induction of an inflammatory secretome, which affected normal hematopoiesis while leukemic cell proliferation remained unaffected [181]. The pro-tumorigenic effect of IL−1β was eliminated by IL−1Ra treatment, indicating that inhibition of IL−1-IL−1RAP signaling pathway could be a potential therapeutic strategy to decrease inflammation in the BM niche and thereby support normal hematopoietic recovery over AML proliferation after chemotherapy [181].

3.2.4. Role of IL−1 signaling in JMML

JMML is a rare, aggressive MDS/MPN that occurs early in childhood and is driven by mutations in Rat sarcoma virus (RAS) pathway genes, resulting in the hyperresponsiveness of progenitor cells to GM-CSF [182]. Activating mutation in tyrosine-protein phosphatase non-receptor type 11 (*Ptpn11),* which encodes the protein tyrosine phosphatase SHP2, plays a significant role in initiation and progression of JMML [182]. MSCs and progenitor cells of osteoclasts bearing *Ptpn11* mutation recruit monocytes within the BM niche via secretion of the chemokine (C-C motif) ligand 3 (CCL3) [183]. BM-infiltrating monocytes and JMML malignant cells secrete increased levels of IL−1β, which triggers the HSPCs hyperresponsiveness, stem cell exhaustion and myeloid-lineage differentiation that contribute to JMML progression [183,184]. Importantly, disruption of IL−1 signaling ameliorates disease outcome by restoring hematopoiesis and rescuing stem cells from exhaustion, offering a therapeutic strategy to combat abnormal hematopoiesis in JMML [184].

3.2.5. Role of IL−1 signaling in CML

CML is a myeloproliferative disorder driven by BCR-ABL fusion tyrosine kinase, which arises when HSPCs acquire the BCR-ABL chromosomal translocation, leading to uncontrolled cell proliferation [185]. Even though aging and CHIP do not promote the development of CML, high levels of IL−1α and IL−1β have been positively correlated with disease progression, aberrant *ex-vivo* expansion of CML leukemia stem cells (LSCs) and decreased survival in patients [186,187]. Although IL−1 is dispensable for CML initiation, IL−1 signaling is vital for the survival and expansion of CML LSCs within the BM through phosphorylation and activation of NF-κB, JNK, and p38MAPK pathways downstream of IL−1R [188]. Even though BCR-ABL tyrosine kinase inhibitors (TKIs) show remarkable efficiency in disease remission [189], residual LSCs remain refractory to TKI therapy [190]. However, elevated IL−1R expression in LSCs renders them susceptible to combined IL−1Ra and TKI therapy [188]. IL−1RAP plays a significant role in CML progression, since it is ubiquitously expressed in leukemic cells of CML patients; inhibition of this co-receptor induces cell-mediated cytotoxicity [191, 192].

Taken together, these studies support the concept that prolonged IL−1 signaling in the BM acts as a maladaptive inflammatory driver, driving expansion of HSPCs, disruption of normal hematopoiesis, and progression toward hematological malignancies (Fig. 2).

3.3. IL−1 signaling linking age-associated hematopoietic rewiring to solid tumor progression

Beyond its role in driving premalignant hematopoiesis and hematological malignancies, IL−1-mediated reprogramming of the hematopoietic system can also influence the progression of solid tumors. Recent work provides a mechanistic connection between age-associated inflammatory hematopoiesis, IL−1-driven myelopoiesis, and solid tumor progression [68]. In a mouse model of non-small cell lung cancer (NSCLC), inflammaging in HSPCs was linked to enhanced emergency myelopoiesis, leading to the accumulation of a myeloid progenitor-like population with an IL−1α signature in lung tumor lesions of these mice. The existence of progenitor-like cells in the tumor resulted in the generation of tumor-promoting monocyte-derived macrophages, which exhibited decreased expression of DNMT3A, which is also one of the most frequently mutated genes reported in individuals with CHIP. Downregulation of DNMT3A enhanced the production of IL−1α by the monocyte-derived macrophages and contributed to the progression of lung adenocarcinoma, pancreatic adenocarcinoma and colorectal carcinoma [68]. This study proposes a feed-forward circuit whereby IL−1α produced at the tumor site sustains age-induced emergency myelopoiesis [68]. Notably, early intervention with IL−1Ra restored myelopoiesis and prevented aberrant lung tumor growth [68]. Together, these data may provide mechanistic insights into the relationship between CHIP-associated variant *Dnmt3a*, IL−1-driven inflammaging, and solid cancer (Fig. 2).

Collectively, these observations position IL−1 as a critical mediator linking inflammaging, CH and premalignant hematopoietic development. Persistent IL−1 signaling within the aged BM niche not only drives maladaptive myelopoiesis but also creates a selective environment that favors the expansion of CHIP-mutant clones, thereby increasing susceptibility to hematological and solid malignancies (Fig. 2).

3.4. IL−1-mediated trained immunity reshapes tumor-associated myeloid cell function

3.4.1. Tumor-driven IL−1-dependent maladaptive training of myelopoiesis

Beyond aging and CHIP, established tumors themselves function as chronic inflammatory organs that systemically reprogram hematopoiesis. Cancer-associated systemic inflammation profoundly reshapes hematopoiesis and hijacks myeloid cell function contributing to tumor progression and metastasis [52,53]. Rather than reflecting a strong anti-tumor immune response, accumulation of tumor-infiltrating myeloid cells strongly correlates with poor prognosis in cancer patients and resistance to immune checkpoint blockade therapies [193, 194]. In this context, neutrophils are reprogrammed toward pro-tumoral states in the TME that support tumor progression, consistent with clinical observations that increased neutrophil abundance, often reflected to an elevated neutrophil-to-lymphocyte ratio, is associated with adverse outcomes across multiple malignancies [195–198]. In addition, within the TME, inflammatory cues including TNF-α and prostaglandin E_2 (PGE_2) can synergistically reprogram tumor-infiltrating monocytes into IL−1β-producing tumor-associated macrophages (TAMs), whose abundance correlates with poor prognosis in patients with pancreatic ductal adenocarcinoma [58], highlighting how tumor-derived signals actively shape myeloid effector programs.

Importantly, tumor-driven myeloid reprogramming is not confined to the TME. Cancer-derived inflammatory factors including IL−1β, G-CSF, GM-CSF, IL−6 and vascular endothelial growth factor A (VEGFA) can reach the hematopoietic niche and initiate emergency myelopoiesis, altering progenitor differentiation trajectories to favor the production of immunosuppressive myeloid cells that subsequently infiltrate the TME [47,55,199,200]. Cancer-driven systemic immune alterations favoring tumor growth were positively associated with increased tumor cell-derived IL−1α production. Importantly, blockage of IL−1α prevented the cancer-mediated reprogramming of splenic immune composition, by reducing splenic neutrophils and mature myeloid cells [201]. Moreover, persistent inflammation caused by mammary tumors was shown to skew hematopoiesis toward myelopoiesis and induce immunosuppressive reprogramming of granulopoiesis (Fig. 3A) [47].

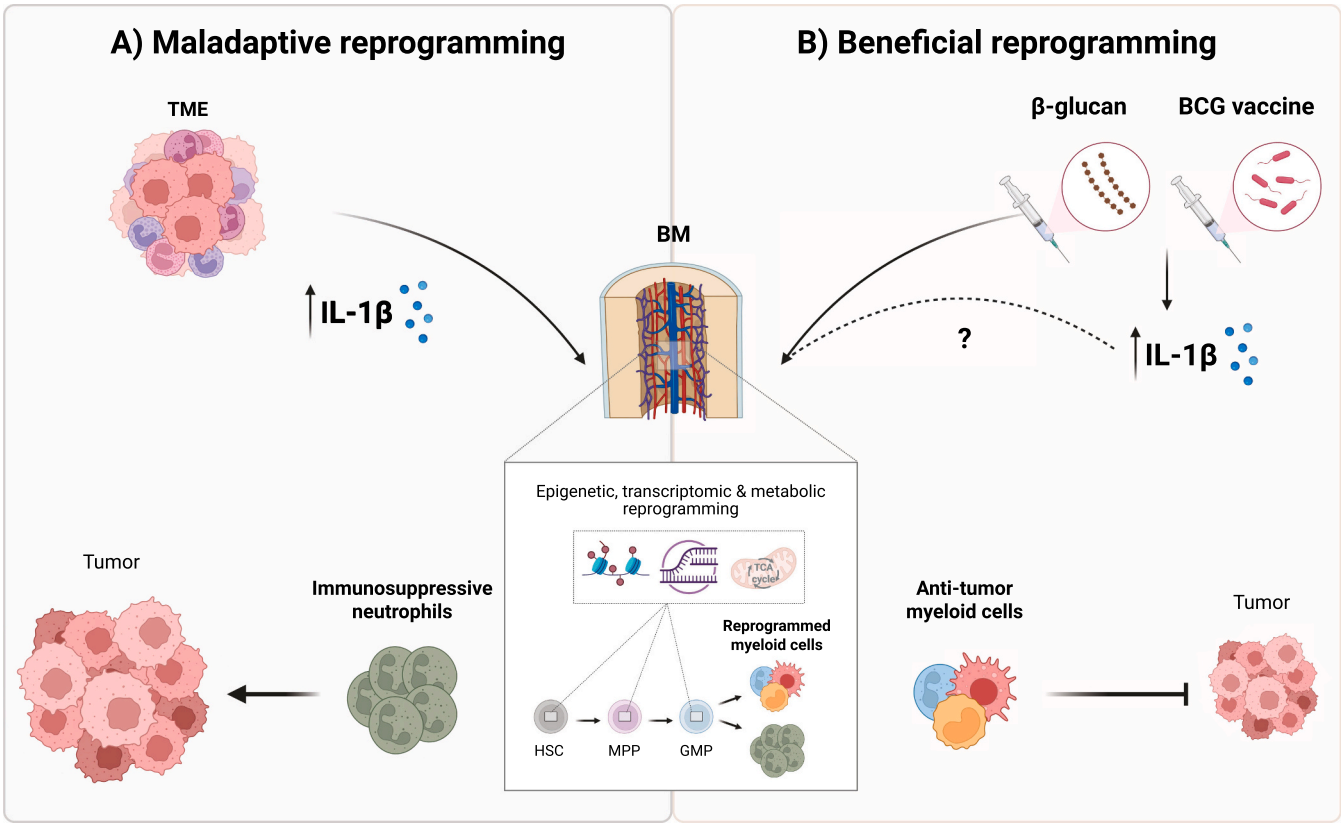

Fig. 3. Context-dependent role of IL−1β in beneficial and maladaptive myeloid reprogramming in cancer. Different stimuli including β-glucan, BCG vaccine and TME-derived inflammatory factors can induce long-term functional reprogramming of the innate immune system through epigenetic, transcriptomic, and metabolic rewiring of HSPCs in the BM, leading to the generation of reprogrammed myeloid cells that will ultimately infiltrate the tumor and affect tumor progression. A) Maladaptive reprogramming. In the context of cancer-associated inflammation, TME-derived IL−1β drives maladaptive reprogramming of HSPCs, resulting in the expansion of immunosuppressive neutrophils that facilitate tumor growth and suppress anti-tumor immunity. B) Beneficial reprogramming. Trained immunity induced by stimuli such as β-glucan and BCG vaccine promotes the generation of reprogrammed myeloid cells with enhanced anti-tumor activity. Administration of these training agents induce elevated levels of IL−1β; however, the precise mechanisms linking increased IL−1 signaling to myeloid anti-tumor reprogramming remain incompletely understood (indicated by the dashed arrow and question mark).

Cancer-derived CCL2 reprograms TAMs to produce high levels of IL−1β which in turn induces an inflammatory cascade resulting in elevated levels of G-CSF, an important growth factor for neutrophil development [202,203]. HSPCs respond to IL−1β signaling which leads to their epigenetic reprogramming by increasing chromatin accessibility for master TF important for granulopoiesis, namely C/EBPα, while closing sites for the master regulators of erythroid lineage, GATA-binding factor 1 (GATA1). Moreover, in response to IL−1β, HSPCs upregulate genes associated with an immunosuppressive phenotype, leading to the generation of immunosuppressive neutrophils during granulopoiesis in the BM niche [47]. The immunosuppressive signature of mature neutrophils was traced back to the transcriptional reprogramming of LT-HSCs (Fig. 3A). Blockade of IL−1β signaling restored hematopoietic balance, reversed the pro-tumoral reprogramming of neutrophils and reduced tumor-induced neutrophilia resulting in decreased metastatic spread, highlighting the functional importance of this pathway mediating the crosstalk between TME and HSPC reprogramming during cancer [47].

Along the same line, tumor-associated inflammation can trigger extramedullary hematopoiesis in other lymphoid organs, particularly in the spleen, which further sustains the systemic supply of tumor-promoting myeloid cells [48,204,205]. Extramedullary hematopoiesis is present in many solid tumors, including breast, renal and lung cancer, and contributes to tumor progression by reinforcing a chronic, tumor-supporting myelopoietic output [205,206]. Interestingly, tumor-derived IL−1 was shown to be implicated in splenic HSPCs reprogramming increasing the myelopoietic capacity of the spleen during cancer, suggesting IL−1 as a possible mechanism of tumor-associated myelopoiesis [48]. In line with this, tumor-derived IL−1α induces TNF-α expression by HSPCs to reprogram the hematopoietic niche into favoring increased myelopoiesis [48].

Collectively these observations support the concept that cancer can impose a form of maladaptive inflammatory memory on the hematopoietic system. Persistent tumor-induced IL−1 signaling reprograms HSPCs and their progeny, biasing myelopoiesis toward immunosuppressive, tumor-promoting phenotypes that reinforce tumor progression (Fig. 3A).

3.4.2. Role of IL−1 signaling in trained immunity-mediated anti-tumor response

In contrast to tumor-mediated maladaptive inflammatory imprinting, innate immune training can also promote protective anti-tumor myeloid responses. Stimuli that induce trained immunity, such as β-glucan and BCG can reprogram myeloid cells toward anti-tumoral phenotypes, providing a rationale for therapeutic targeting [14,18,19,101,105,207–213].

In experimental models, β-glucan induces central reprogramming of granulopoiesis, resulting in sustained production of rewired anti-tumor neutrophils. These reprogrammed neutrophils infiltrate the TME, where they exhibit enhanced effector functions, including increased reactive oxygen species (ROS) production, and can serve as a therapy when administered systemically into tumor-bearing mice [14]. In addition to neutrophils, peripheral trained immunity induced by β-glucan can reprogram mature monocytes and macrophages, enabling cytotoxic activity leading to tumor reduction [207–209].

Administration of β-glucan has been shown to activate IL−1 signaling which is associated with induction of central trained immunity [13]. However, whether IL−1 is mechanistically required for the β-glucan-driven anti-tumor effects of trained immunity remains unclear (Fig. 3B). Consistent with a potential contribution of IL−1 signaling, administration of γ-irradiated β-glucan mediates peritoneal macrophage reprogramming, leading to increased production of pro-inflammation cytokines, such as TNF-α, IL−6, and IL−1β through NF-κB and MAPK signaling pathways, resulting in significant inhibition of tumor growth and lung metastasis in mice bearing B16BL6 tumors [209]. In an experimental model of pancreatic cancer, therapeutic administration of β-glucan induces the reprogramming of tumor-infiltrating macrophages/monocytes with a prominent IL−1β signature [208]. Clinically, combined treatment of β-glucan with immune checkpoint inhibitors has been shown to improve efficacy of immune checkpoint blockade among patients with advanced cancer [210]. Of note, serum levels of IL−1β were found to be elevated in these patients after combination therapy, indicating that IL−1β could facilitate anti-tumor immune responses in this setting [210].

On the other hand, a recent study explored whether β-glucan-mediated IL−1β signaling plays a role in the training phenotype of macrophages and thereby affecting the control of lung tumor metastasis [207]. Global genetic deletion of IL−1R showed that IL−1 signaling is dispensable in this context as the anti-tumor effect of β-glucan-induced trained immunity was not abrogated in IL−1R deficient mice [207]. Moreover, the same study assessed whether the NLRP3 inflammasome pathway, which mediates the release of IL−1β [214], plays a role in the β-glucan-mediated tumor protection. However, similar results were shown in the NLRP3-deficient mouse model, indicating that the IL−1β–IL−1R pathway does not mediate the tumor protection which is acquired upon β-glucan-mediated trained immunity [207].

Consistent with the anti-tumor effect of β-glucan observed in experimental mouse models, β-glucans are also being used as immunotherapy adjuvants to enhance treatment efficacy in patients [212,215,216]. A clinically advanced example is Imprime PGG, a soluble yeast-derived β-glucan currently being evaluated in multiple clinical trials as an adjuvant to cancer immunotherapy [216]. In murine cancer models Imprime treatment was associated with enhanced anti-tumor responses accompanied by increased inflammatory mediators, including IL−1β [212]. However, IL−1 cytokine levels were not significantly elevated in treated patients [212].

Intravesical BCG administration as cancer immunotherapy for non-muscle-invasive bladder cancer (NMIBC) has long been established and remains the only bacterial-based treatment approved for cancer [217]. Considering its well-established adjuvant effects in activating the innate immune system, it is plausible that its anti-tumor effects involve mechanisms of trained immunity, especially in light of the well-established capacity of BCG to induce both peripheral and central immune training [17,30,91,101,105,119,213,218,219]. Studies show that systemic administration of BCG results in increased levels of IL−1α and IL−18 in urine specimens and correlate with better prognosis [220–223]. In addition, recent studies show that therapeutic intravesical administration of BCG in tumor-bearing mice resulted in reprogramming of HSPCs, increased serum levels of IL−1β and promoted the anti-tumor effects of mature myeloid cells [19,211]. However, whether IL−1 is an indispensable mediator of this effect remains unknown (Fig. 3B). In patients with NMIBC, intravesical administration of BCG induced functional reprogramming of circulating monocytes, as evidenced by elevated production of TNF-α and IL−1β after heterologous *ex vivo* stimulation [101,219]. Along the same line, recent work suggests one possible mechanism underlying the BCG-mediated anti-tumor effect of trained immunity. BCG induces differential TF activity and gene transcription in HSPCs, promotes hematopoiesis bias toward myeloid lineage and increases chromatin accessibility in CMPs, ultimately leading mature myeloid cells to secrete elevated levels of IL−1β which confers protection against cancer [119].

Taken together, these findings highlight a critical distinction: whereas chronic tumor-derived IL−1 signaling enforces maladaptive inflammatory memory that sustains immunosuppressive myelopoiesis, transient or therapeutically induced innate immune training can harness related pathways to generate protective anti-tumor myeloid responses (Fig. 3). Thus, IL−1 signaling operates as a context-dependent hematopoietic checkpoint whose impact on tumor immunity depends on timing, duration, and source of inflammatory cues.

4. Potential therapeutic implications and concluding remarks

The evidence discussed throughout this review reframes IL−1 as more than a classical pro-inflammatory cytokine. Rather, IL−1 emerges as a central regulator of hematopoietic adaptation to stress and inflammatory memory, integrating environmental, infectious, metabolic, and tumor-derived cues into durable alterations of myeloid cell function [83]. By reshaping epigenetic, metabolic and transcriptomic programs in HSPCs, IL−1 signaling may lead to protective immunity or maladaptive myelopoiesis that fuels various diseases including cancer progression [11,13,16,19,30,47,48,68,99,101,121,122,127–129,208–212,219].

This duality carries significant therapeutic implications. In aging, CH and established malignancies, persistent IL−1 exposure sustains emergency myelopoiesis, promotes the expansion of mutant clones, and reinforces immunosuppressive myeloid output [47,68,135,150,162]. In these contexts, pharmacological inhibition of IL−1 signaling represents a rational strategy to interrupt the self-reinforcing loop between inflammation and clonal selection. Importantly, the CANTOS trial provides a key translational link between these mechanistic insights and clinical outcomes. Although, originally designed to evaluate the effects of IL−1β blockade on cardiovascular outcomes, CANTOS unexpectedly demonstrated that neutralization of IL−1β with canakinumab reduces lung cancer incidence and mortality in a dose-dependent manner, with particularly pronounced benefit observed in individuals with CHIP [158,164]. As the first large-scale randomized placebo-controlled study to demonstrate that targeting IL−1β-driven inflammation can reduce cancer incidence, CANTOS provided a critical clinical proof-of-concept for anti-IL−1 therapeutic strategies. In this context, CANTOS serves as an important bridge between mechanistic insights into IL−1-mediated immune reprogramming and its potential therapeutic exploitation in cancer. Consistent with this, IL−1R antagonists and IL−1 neutralizing antibodies restore balance of hematopoiesis and limit tumor-driven myeloid reprogramming in preclinical settings [13,47,51,68,150,162]. However, whether IL−1 blockage can reverse the imprinting in HSPCs, or whether such interventions are effective during early premalignant states or as a preventive strategy, remains unclear.

At the same time, IL−1 cannot be viewed solely as a pathological driver. In controlled settings of innate immune training, such as β-glucan or BCG-induced reprogramming, IL−1 signaling can amplify anti-tumor effector functions [19,101,208,209,211,212,219]. The observation that IL−1 may promote tumor control when engaged transiently, yet facilitate tumor progression when chronically activated, underscores the importance of context, timing, and source. A major unresolved question is how these divergent outcomes are encoded at the molecular level. It remains to be defined which epigenetic, metabolic or transcriptional signatures distinguish protective from maladaptive IL−1-associated imprinted states, how stable these programs are within the HSCs, and whether they can be selectively reprogrammed without compromising host defense.

The prospect of cell-specific modulation of IL−1 signaling further expands therapeutic possibilities. Advances in nucleic acid-based delivery systems, including apolipoprotein nanoparticles that incorporate small interfering RNA (siRNA) into their core for silencing genes *in vivo* has emerged as a therapeutic approach [224]. To directly target HSPCs, researchers have developed c-kit (CD117) antibody-targeted lipid nanoparticles for delivery of siRNA [225]. C-kit is a cell surface receptor

and marker of both human and mouse HSPCs, essential for the HSC quiescence and self-renewal capacity [226]. This approach would enable targeted delivery of *Il1α*, *Il1β* or *Il1r* siRNA to c-kit$^+$ HSPCs, potentially inhibiting the pro-tumoral effects mediated by IL−1-driven inflammatory memory. Moreover, RNA interference (RNAi) represents an emerging therapeutic strategy for selectively inhibiting pathways or gene expression implicated in trained immunity [227]. However, studies exploring the use of RNAi-based therapeutic approaches to suppress trained immunity are limited. Although RNAi-mediated silencing of IL−1β has been successfully demonstrated *in vitro* [228], the lack of robust *in vivo* preclinical evidence currently hampers clinical translation of this strategy. In general, such strategies could theoretically suppress IL−1-driven maladaptive training while preserving essential peripheral inflammatory responses. Yet, the *in vivo* consequences of selectively dampening IL−1 signaling within HSPCs remain largely unexplored. How such interventions would influence lineage plasticity under inflammatory challenges, clonal expansion in CHIP, or responsiveness to immunotherapy is not yet known.

The field still lacks biomarkers capable of identifying IL−1-dependent hematopoietic imprinting in patients. Whether signatures of IL−1-driven inflammatory memory can predict cancer risk, for instance in aged individuals, disease progression and outcome, or therapeutic responsiveness represents an important avenue for future investigation. Furthermore, although we focus here on the role of IL−1 in these processes we should not neglect that it operates in a complex inflammatory network that also includes other mediators such as IL−6, TNF-α, G-CSF between others [34]. Dissecting how these pathways cooperate or compete in shaping myeloid output and inducing inflammatory memory will be essential for designing rational combination therapies.

Collectively, the current data support a unifying model in which IL−1 functions as a hematopoietic checkpoint of inflammatory memory [84]. In acute infection or therapeutically induced training, IL−1 enables adaptive reprogramming that enhances host defense and anti-tumor immunity [16,19,101,208,212,219]. In contrast, during aging, CH, chronic inflammatory conditions, and cancer, sustained IL−1 signaling imprints maladaptive programs that facilitate immune suppression and tumor progression [47,66,68,135,150,162]. Understanding how to selectively modulate this checkpoint, dampening chronic, tumor promoting IL−1 signaling while preserving or harnessing beneficial training represents a central challenge in the field.

In light of the aforementioned, targeting IL−1 is not merely an anti-inflammatory intervention. It is an opportunity to re-educate hematopoiesis itself and to reshape inflammatory memory that underlies cancer development and progression.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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References

[1] R. Medzhitov, Origin and physiological roles of inflammation, Nature 454 (7203) (2008) 428–435.
[2] J. Wang, M. Erlacher, J. Fernandez-Orth, The role of inflammation in hematopoiesis and bone marrow failure: What can we learn from mouse models? Front. Immunol. 13 (2022) 951937.
[3] E. Zhao, et al., Bone marrow and the control of immunity, Cell. Mol. Immunol. 9 (1) (2012) 11–19.
[4] T. Chavakis, I. Mitroulis, G. Hajishengallis, Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation, Nat. Immunol. 20 (7) (2019) 802–811.
[5] J.L. Schultze, E. Mass, A. Schlitzer, Emerging Principles in Myelopoiesis at Homeostasis and during Infection and Inflammation, Immunity 50 (2) (2019) 288–301.
[6] I. Mitroulis, et al., Regulation of the Bone Marrow Niche by Inflammation, Front. Immunol. 11 (2020) 1540.
[7] I. Mitroulis, et al., Myelopoiesis in the Context of Innate Immunity, J. Innate Immun. 10 (5-6) (2018) 365–372.
[8] L. Kalafati, et al., The role of neutrophils in trained immunity, Immunol. Rev. 314 (1) (2023) 142–157.
[9] G. Hajishengallis, M.G. Netea, T. Chavakis, Trained immunity in chronic inflammatory diseases and cancer, Nat. Rev. Immunol. 25 (7) (2025) 497–514.
[10] G. Hajishengallis, T. Chavakis, Central trained immunity and its impact on chronic inflammatory and autoimmune diseases, J. Allergy Clin. Immunol. 154 (5) (2024) 1113–1116.
[11] X. Li, et al., Maladaptive innate immune training of myelopoiesis links inflammatory comorbidities, Cell 185 (10) (2022) 1709–1727, e18.
[12] N. Haacke, et al., Innate immune training of osteoclastogenesis promotes inflammatory bone loss in mice, Dev. Cell. 60 (13) (2025) 1854–1870, e6.
[13] I. Mitroulis, et al., Modulation of Myelopoiesis Progenitors Is an Integral Component of Trained Immunity, Cell 172 (1-2) (2018) 147–161, e12.
[14] L. Kalafati, et al., Innate Immune Training of Granulopoiesis Promotes Anti-tumor Activity, Cell 183 (3) (2020) 771–785, e12.
[15] M.G. Netea, et al., Defining trained immunity and its role in health and disease, Nat. Rev. Immunol. 20 (6) (2020) 375–388.
[16] S. Moorlag, et al., beta-Glucan Induces Protective Trained Immunity against Mycobacterium tuberculosis Infection: A Key Role for IL-1, Cell. Rep. 31 (7) (2020) 107634.
[17] E. Kaufmann, et al., BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis, Cell 172 (1-2) (2018) 176–190, e19.
[18] L.F. Jurado, et al., A fungal-derived adjuvant amplifies the antitumoral potency of Bacillus Calmette-Guerin via reprogramming granulopoiesis, Immunity 58 (8) (2025) 1984–2001, e6.
[19] A.W. Daman, et al., Microbial cancer immunotherapy reprograms hematopoiesis to enhance myeloid-driven anti-tumor immunity, Cancer Cell. 43 (8) (2025) 1442–1459, e10.
[20] N. Khan, et al., beta-Glucan reprograms neutrophils to promote disease tolerance against influenza A virus, Nat. Immunol. 26 (2) (2025) 174–187.
[21] N. Khan, et al., M. tuberculosis Reprograms Hematopoietic Stem Cells to Limit Myelopoiesis and Impair Trained Immunity, Cell 183 (3) (2020) 752–770, e22.
[22] C. van der Heijden, et al., Epigenetics and Trained Immunity, Antioxid. Redox Signal. 29 (11) (2018) 1023–1040.
[23] A.V. Ferreira, et al., Metabolic Regulation in the Induction of Trained Immunity, Semin. Immunopathol. 46 (3-4) (2024) 7.
[24] R.J. Arts, et al., Glutaminolysis and Fumarate Accumulation Integrate Immunometabolic and Epigenetic Programs in Trained Immunity, Cell. Metab. 24 (6) (2016) 807–819.
[25] S. Bekkering, et al., Metabolic Induction of Trained Immunity through the Mevalonate Pathway, Cell 172 (1-2) (2018) 135–146, e9.
[26] P.S. Liu, et al., alpha-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming, Nat. Immunol. 18 (9) (2017) 985–994.
[27] M. Bambouskova, et al., Electrophilic properties of itaconate and derivatives regulate the IkappaBzeta-ATF3 inflammatory axis, Nature 556 (7702) (2018) 501–504.
[28] S.C. Cheng, et al., mTOR- and HIF-1alpha-mediated aerobic glycolysis as metabolic basis for trained immunity, Science 345 (6204) (2014) 1250684.
[29] R.J.W. Arts, et al., Immunometabolic Pathways in BCG-Induced Trained Immunity, Cell. Rep. 17 (10) (2016) 2562–2571.
[30] B. Cirovic, et al., BCG Vaccination in Humans Elicits Trained Immunity via the Hematopoietic Progenitor Compartment, Cell. Host Microbe 28 (2) (2020) 322–334, e5.

[31] D. Flores-Gomez, et al., Interleukin-1beta induces trained innate immunity in human hematopoietic progenitor cells in vitro, Stem Cell. Rep. 19 (12) (2024) 1651–1664.
[32] W. Li, et al., A single-cell view on host immune transcriptional response to in vivo BCG-induced trained immunity, Cell. Rep. 42 (5) (2023) 112487.
[33] C. Garlanda, C.A. Dinarello, A. Mantovani, The interleukin-1 family: back to the future, Immunity 39 (6) (2013) 1003–1018.
[34] C. Garlanda, I. Di Ceglie, S. Jaillon, IL-1 family cytokines in inflammation and immunity, Cell. Mol. Immunol. 22 (11) (2025) 1345–1362.
[35] N.C. Di Paolo, D.M. Shayakhmetov, Interleukin 1alpha and the inflammatory process, Nat. Immunol. 17 (8) (2016) 906–913.
[36] A. Malik, T.D. Kanneganti, Function and regulation of IL-1alpha in inflammatory diseases and cancer, Immunol. Rev. 281 (1) (2018) 124–137.
[37] S.G. Ford, et al., The secretion of interleukin-1b, eta. Cytokine Growth Factor. Rev. 84 (2025) 101–113.
[38] C. Orelio, et al., Interleukin-1 regulates hematopoietic progenitor and stem cells in the midgestation mouse fetal liver, Haematologica 94 (4) (2009) 462–469.
[39] J.E. Howard, et al., IL-18R-mediated HSC quiescence and MLKL-dependent cell death limit hematopoiesis during infection-induced shock, Stem Cell. Rep. 16 (12) (2021) 2887–2899.
[40] M.L. Capitano, et al., The IL-33 Receptor/ST2 acts as a positive regulator of functional mouse bone marrow hematopoietic stem and progenitor cells, Blood Cells Mol. Dis. 84 (2020) 102435.
[41] C.M. Dubois, et al., vivo interleukin-1 (IL-1) administration indirectly promotes type II IL-1 receptor expression on hematopoietic bone marrow cells: novel mechanism for the hematopoietic effects of IL-1, Blood 78 (11) (1991) 2841–2847.
[42] Y. Ueda, et al., IL-1R type I-dependent hemopoietic stem cell proliferation is necessary for inflammatory granulopoiesis and reactive neutrophilia, J. Immunol. 182 (10) (2009) 6477–6484.
[43] R. Casadio, et al., Model of interaction of the IL-1 receptor accessory protein IL-1RAcP with the IL-1beta/IL-1R(I) complex, FEBS Lett. 499 (1-2) (2001) 65–68.
[44] A. Weber, P. Wasiliew, M. Kracht, Interleukin-1 (IL-1) pathway, Sci. Signal. 3 (105) (2010) cm1.
[45] F. Caiado, M.G. Manz, IL-1 in aging and pathologies of hematopoietic stem cells, Blood 144 (4) (2024) 368–377.
[46] P. Naef, et al., IL-33/ST2 signaling in ILC2s drives exhaustion and myeloid skewing of HSCs in response to hematopoietic stress and aging, iScience 28 (5) (2025) 112378.
[47] H. Garner, et al., Understanding and reversing mammary tumor-driven reprogramming of myelopoiesis to reduce metastatic spread, Cancer Cell. 43 (7) (2025) 1279–1295, e9.
[48] D.A.G. Barisas, et al., Tumor-derived interleukin-1alpha and leukemia inhibitory factor promote extramedullary hematopoiesis, PLoS. Biol. 21 (5) (2023) e3001746.
[49] K.C. Higa, et al., Chronic interleukin-1 exposure triggers selection for Cebpa-knockout multipotent hematopoietic progenitors, J. Exp. Med. 218 (6) (2021).
[50] J.S. Chavez, et al., PU.1 enforces quiescence and limits hematopoietic stem cell expansion during inflammatory stress, J. Exp. Med. 218 (6) (2021).
[51] E.M. Pietras, et al., Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal, Nat. Cell. Biol. 18 (6) (2016) 607–618.
[52] K. Taniguchi, M. Karin, NF-kappaB, inflammation, immunity and cancer: coming of age, Nat. Rev. Immunol. 18 (5) (2018) 309–324.
[53] H. Zhao, et al., Inflammation and tumor progression: signaling pathways and targeted intervention, Signal. Transduct. Target. Ther. 6 (1) (2021) 263.
[54] C. Garlanda, A. Mantovani, Interleukin-1 in tumor progression, therapy, and prevention, Cancer Cell. 39 (8) (2021) 1023–1027.
[55] K. Aliazis, et al., Emergency myelopoiesis in solid cancers, Br. J. Haematol. 205 (3) (2024) 798–811.
[56] J. Qu, et al., The significance of trained immunity in cancer, Front. Immunol. 16 (2025) 1665099.
[57] A. Mantovani, I. Barajon, C. Garlanda, IL-1 and IL-1 regulatory pathways in cancer progression and therapy, Immunol. Rev. 281 (1) (2018) 57–61.
[58] N. Caronni, et al., IL-1beta(+) macrophages fuel pathogenic inflammation in pancreatic cancer, Nature 623 (7986) (2023) 415–422.
[59] T. Wu, et al., Modulation of IL-1beta reprogrammes the tumor microenvironment to interrupt oral carcinogenesis, Sci. Rep. 6 (2016) 20208.
[60] M. Okamoto, et al., Constitutively active inflammasome in human melanoma cells mediating autoinflammation via caspase-1 processing and secretion of interleukin-1b, eta. J. Biol. Chem. 285 (9) (2010) 6477–6488.
[61] O. Dmitrieva-Posocco, et al., Cell-Type-Specific Responses to Interleukin-1 Control Microbial Invasion and Tumor-Elicited Inflammation in Colorectal Cancer, Immunity 50 (1) (2019) 166–180, e7.
[62] D. Matanic, et al., Cytokines in patients with lung cancer, Scand. J. Immunol. 57 (2) (2003) 173–178.
[63] L. Arranz, M.D.M. Arriero, A. Villatoro, Interleukin-1beta as emerging therapeutic target in hematological malignancies and potentially in their complications, Blood Rev. 31 (5) (2017) 306–317.
[64] A.M. Malkova, et al., Pathogenetic role and clinical significance of interleukin-1beta in cancer, Immunology 168 (2) (2023) 203–216.
[65] H. Van Gorp, M. Lamkanfi, The emerging roles of inflammasome-dependent cytokines in cancer development, EMBO Rep. 20 (6) (2019).
[66] G. Hajishengallis, T. Chavakis, Inflammageing and clonal haematopoiesis interplay and their impact on human disease, Nat. Rev. Mol. Cell. Biol. (2026).
[67] W.E. Schleicher, et al., CHIP: a clonal odyssey of the bone marrow niche, J. Clin. Invest. 134 (15) (2024).
[68] M.D. Park, et al., Hematopoietic aging promotes cancer by fueling IL-1α-driven emergency myelopoiesis, Science 386 (6720) (2024) eadn0327.
[69] A. Wilson, et al., Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair, Cell 135 (6) (2008) 1118–1129.
[70] C.M. Sawai, et al., Hematopoietic Stem Cells Are the Major Source of Multilineage Hematopoiesis in Adult Animals, Immunity 45 (3) (2016) 597–609.
[71] A. Collins, C.A. Mitchell, E. Passegue, Inflammatory signaling regulates hematopoietic stem and progenitor cell development and homeostasis, J. Exp. Med. 218 (7) (2021).
[72] K.A. Matatall, et al., Chronic Infection Depletes Hematopoietic Stem Cells through Stress-Induced Terminal Differentiation, Cell. Rep. 17 (10) (2016) 2584–2595.
[73] A. Herault, et al., Myeloid progenitor cluster formation drives emergency and leukaemic myelopoiesis, Nature 544 (7648) (2017) 53–58.
[74] Y.A. Kang, et al., Secretory MPP3 reinforce myeloid differentiation trajectory and amplify myeloid cell production, J. Exp. Med. 220 (8) (2023).
[75] M.G. Manz, S. Boettcher, Emergency granulopoiesis, Nat. Rev. Immunol. 14 (5) (2014) 302–314.
[76] M. Aglietta, et al., Granulocyte-macrophage colony stimulating factor and interleukin 3: target cells and kinetics of response in vivo, Stem Cells 11 (2) (1993) 83–87.
[77] B. Bajrami, et al., G-CSF maintains controlled neutrophil mobilization during acute inflammation by negatively regulating CXCR2 signaling, J. Exp. Med. 213 (10) (2016) 1999–2018.
[78] J.L. Johns, M.M. Christopher, Extramedullary hematopoiesis: a new look at the underlying stem cell niche, theories of development, and occurrence in animals, Vet. Pathol. 49 (3) (2012) 508–523.
[79] V. Fernandez-Garcia, et al., Contribution of Extramedullary Hematopoiesis to Atherosclerosis. The Spleen as a Neglected Hub of Inflammatory Cells, Front. Immunol. 11 (2020) 586527.
[80] R. Bogeska, et al., Inflammatory exposure drives long-lived impairment of hematopoietic stem cell self-renewal activity and accelerated aging, Cell. Stem Cell. 29 (8) (2022) 1273–1284, e8.
[81] S.S. Burns, R. Kapur, Turning the clock forward: Inflammation accelerates the aging of hematopoietic stem cells, Cell. Stem Cell. 29 (8) (2022) 1156–1158.
[82] M. Weisser, et al., Hyperinflammation in patients with chronic granulomatous disease leads to impairment of hematopoietic stem cell functions, J. Allergy Clin. Immunol. 138 (1) (2016) 219–228, e9.
[83] A. Mantovani, et al., Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity, Immunity 50 (4) (2019) 778–795.
[84] S. Moorlag, et al., The role of the interleukin-1 family in trained immunity, Immunol. Rev. 281 (1) (2018) 28–39.
[85] D.W. Cain, et al., Inflammation triggers emergency granulopoiesis through a density-dependent feedback mechanism, PLoS. One 6 (5) (2011) e19957.
[86] A. Villatoro, et al., Endogenous IL-1 receptor antagonist restricts healthy and malignant myeloproliferation, Nat. Commun. 14 (1) (2023) 12.
[87] B. de Laval, et al., C/EBPbeta-Dependent Epigenetic Memory Induces Trained Immunity in Hematopoietic Stem Cells, Cell. Stem Cell. 26 (5) (2020) 657–674, e8.
[88] M. Guillamot, et al., The E3 ubiquitin ligase SPOP controls resolution of systemic inflammation by triggering MYD88 degradation, Nat. Immunol. 20 (9) (2019) 1196–1207.
[89] M.G. Netea, J. Quintin, J.W. van der Meer, Trained immunity: a memory for innate host defense, Cell. Host Microbe 9 (5) (2011) 355–361.
[90] S.L. Foster, D.C. Hargreaves, R. Medzhitov, Gene-specific control of inflammation by TLR-induced chromatin modifications, Nature 447 (7147) (2007) 972–978.
[91] L. Kong, et al., Single-cell transcriptomic profiles reveal changes associated with BCG-induced trained immunity and protective effects in circulating monocytes, Cell. Rep. 37 (7) (2021) 110028.
[92] J. Quintin, et al., Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes, Cell. Host Microbe 12 (2) (2012) 223–232.
[93] S. Saeed, et al., Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity, Science 345 (6204) (2014) 1251086.
[94] A.A. Patel, F. Ginhoux, S. Yona, Monocytes, macrophages, dendritic cells and neutrophils: an update on lifespan kinetics in health and disease, Immunology 163 (3) (2021) 250–261.
[95] J.G. Cheong, et al., Epigenetic memory of coronavirus infection in innate immune cells and their progenitors, Cell 186 (18) (2023) 3882–3902, e24.
[96] T.J. Barrett, et al., Chronic stress primes innate immune responses in mice and humans, Cell. Rep. 36 (10) (2021) 109595.
[97] T. Heidt, et al., Chronic variable stress activates hematopoietic stem cells, Nat. Med. 20 (7) (2014) 754–758.
[98] C.S. McAlpine, et al., Sleep exerts lasting effects on hematopoietic stem cell function and diversity, J. Exp. Med. (11) (2022) **219**.
[99] A. Christ, et al., Western Diet Triggers NLRP3-Dependent Innate Immune Reprogramming, Cell 172 (1-2) (2018) 162–175, e14.
[100] S. Bekkering, et al., Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes, Arterioscler. Thromb. Vasc. Biol. 34 (8) (2014) 1731–1738.
[101] J.H. van Puffelen, et al., Intravesical BCG in patients with non-muscle invasive bladder cancer induces trained immunity and decreases respiratory infections, J. Immunother. Cancer 11 (1) (2023).

[102] C.L. Stothers, et al., beta-Glucan Induces Distinct and Protective Innate Immune Memory in Differentiated Macrophages, J. Immunol. 207 (11) (2021) 2785–2798.
[103] R.J.W. Arts, et al., BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity, Cell. Host Microbe 23 (1) (2018) 89–100, e5.
[104] L. Yin, et al., Trained immunity alleviates the progression of melanoma during sepsis-associated immunoparalysis, Cell Oncol (Dordr) 48 (4) (2025) 1047–1065.
[105] J.H. van Puffelen, et al., Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer, Nat. Rev. Urol. 17 (9) (2020) 513–525.
[106] B. Priem, et al., Systemically inducing trained immunity overcomes solid tumors' immunosuppressive microenvironment, Sci. Adv. 12 (1) (2026) eadu0292.
[107] S. Bekkering, et al., Trained Immunity: Linking Obesity and Cardiovascular Disease across the Life-Course? Trends Endocrinol. Metab. 31 (5) (2020) 378–389.
[108] T. Chavakis, B. Wielockx, G. Hajishengallis, Inflammatory Modulation of Hematopoiesis: Linking Trained Immunity and Clonal Hematopoiesis with Chronic Disorders, Annu. Rev. Physiol. 84 (2022) 183–207.
[109] G. Hajishengallis, et al., Maladaptive trained immunity and clonal hematopoiesis as potential mechanistic links between periodontitis and inflammatory comorbidities, Periodontol 2000 89 (1) (2022) 215–230.
[110] A.J. Merbecks, et al., Western lifestyle linked to maladaptive trained immunity, Elife 15 (2026).
[111] S. Chen, et al., Maladaptive trained immunity of adipose tissue macrophages unraveling the link to obesity, T2DM, and beyond, Am. J. Physiol. Endocrinol. Metab. 329 (1) (2025) E117–E130.
[112] G. Hajishengallis, T. Chavakis, Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities, Nat. Rev. Immunol. 21 (7) (2021) 426–440.
[113] J.W. Leong, et al., Preactivation with IL-12, IL-15, and IL-18 induces CD25 and a functional high-affinity IL-2 receptor on human cytokine-induced memory-like natural killer cells, Biol. Blood Marrow Transplant. 20 (4) (2014) 463–473.
[114] J. Ni, et al., Sustained effector function of IL-12/15/18-preactivated NK cells against established tumors, J. Exp. Med. 209 (13) (2012) 2351–2365.
[115] J.G. van den Boorn, et al., Inflammasome-Dependent Induction of Adaptive NK Cell Memory, Immunity 44 (6) (2016) 1406–1421.
[116] J. Herre, S. Gordon, G.D. Brown, Dectin-1 and its role in the recognition of beta-glucans by macrophages, Mol. Immunol. 40 (12) (2004) 869–876.
[117] B. Mirshekar-Syahkal, et al., Dlk1 is a negative regulator of emerging hematopoietic stem and progenitor cells, Haematologica 98 (2) (2013) 163–171.
[118] J. Kleinnijenhuis, et al., Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes, Proc. Natl. Acad. Sci. USA 109 (43) (2012) 17537–17542.
[119] S.J. Sun, et al., BCG vaccination alters the epigenetic landscape of progenitor cells in human bone marrow to influence innate immune responses, Immunity 57 (9) (2024) 2095–2107, e8.
[120] S. Bekkering, et al., Vitro Experimental Model of Trained Innate Immunity in Human Primary Monocytes, Clin. Vaccin. Immunol. 23 (12) (2016) 926–933.
[121] A. Simats, et al., Innate immune memory after brain injury drives inflammatory cardiac dysfunction, Cell 187 (17) (2024) 4637–4655, e26.
[122] E. Coppin, et al., Peripheral Ischemia Imprints Epigenetic Changes in Hematopoietic Stem Cells to Propagate Inflammation and Atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 43 (6) (2023) 889–906.
[123] J.W. van der Meer, et al., A low dose of recombinant interleukin 1 protects granulocytopenic mice from lethal gram-negative infection, Proc. Natl. Acad. Sci. USA 85 (5) (1988) 1620–1623.
[124] J.H. Curfs, et al., Low dosages of interleukin 1 protect mice against lethal cerebral malaria, J. Exp. Med. 172 (5) (1990) 1287–1291.
[125] R.A. Pecyk, E.B. Fraser-Smith, T.R. Matthews, Efficacy of interleukin-1 beta against systemic Candida albicans infections in normal and immunosuppressed mice, Infect. Immun. 57 (10) (1989) 3257–3258.
[126] B. Zhang, et al., Viral infection. Prevention and cure of rotavirus infection via TLR5/NLRC4-mediated production of IL-22 and IL-18, Science 346 (6211) (2014) 861–865.
[127] P.R. Nagareddy, et al., Adipose tissue macrophages promote myelopoiesis and monocytosis in obesity, Cell. Metab. 19 (5) (2014) 821–835.
[128] M. Hata, et al., Past history of obesity triggers persistent epigenetic changes in innate immunity and exacerbates neuroinflammation, Science 379 (6627) (2023) 45–62.
[129] J.R. Lavillegrand, et al., Alternating high-fat diet enhances atherosclerosis by neutrophil reprogramming, Nature 634 (8033) (2024) 447–456.
[130] J. Chen, et al., BCG-induced trained immunity: history, mechanisms and potential applications, J. Transl. Med. 21 (1) (2023) 106.
[131] B.A. Napier, et al., Western diet regulates immune status and the response to LPS-driven sepsis independent of diet-associated microbiome, Proc. Natl. Acad. Sci. USA 116 (9) (2019) 3688–3694.
[132] A.L. Seufert, et al., Enriched dietary saturated fatty acids induce trained immunity via ceramide production that enhances severity of endotoxemia and clearance of infection, Elife 11 (2022).
[133] L. Ferrucci, E. Fabbri, Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty, Nat. Rev. Cardiol. 15 (9) (2018) 505–522.
[134] L.V. Kovtonyuk, et al., Inflamm-Aging of Hematopoiesis, Hematopoietic Stem Cells, and the Bone Marrow Microenvironment, Front. Immunol. (7) (2016) 502.
[135] C.A. Mitchell, et al., Stromal niche inflammation mediated by IL-1 signalling is a targetable driver of haematopoietic ageing, Nat. Cell. Biol. 25 (1) (2023) 30–41.
[136] P.D. Pioli, et al., Plasma Cells Are Obligate Effectors of Enhanced Myelopoiesis in Aging Bone Marrow, Immunity 51 (2) (2019) 351–366, e6.
[137] B.J. Frisch, et al., Aged marrow macrophages expand platelet-biased hematopoietic stem cells via Interleukin1B, JCI Insight 5 (10) (2019).
[138] L.V. Kovtonyuk, et al., IL-1 mediates microbiome-induced inflammaging of hematopoietic stem cells in mice, Blood 139 (1) (2022) 44–58.
[139] S. Li, et al., IL-1beta expression in bone marrow dendritic cells is induced by TLR2 agonists and regulates HSC function, Blood 140 (14) (2022) 1607–1620.
[140] T.C. Luis, et al., Perivascular niche cells sense thrombocytopenia and activate hematopoietic stem cells in an IL-1 dependent manner, Nat. Commun. 14 (1) (2023) 6062.
[141] S. Jaiswal, et al., Age-related clonal hematopoiesis associated with adverse outcomes, N. Engl. J. Med. 371 (26) (2014) 2488–2498.
[142] G. Genovese, et al., Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence, N. Engl. J. Med. 371 (26) (2014) 2477–2487.
[143] X. Cai, R.L. Bowman, J.J. Trowbridge, Clonal hematopoiesis in myeloid malignancies and solid tumors, Nat. Cancer 6 (7) (2025) 1133–1144.
[144] B. Zheng, et al., The role of clonal hematopoiesis of indeterminate potential in non-hematological malignancies of various origins, Biochim. Biophys. Acta Rev. Cancer 1880 (5) (2025) 189442.
[145] M. Kleppe, et al., Somatic mutations in leukocytes infiltrating primary breast cancers, NPJ Breast Cancer 1 (2015) 15005.
[146] M.A. Florez, et al., Clonal hematopoiesis: Mutation-specific adaptation to environmental change, Cell. Stem Cell. 29 (6) (2022) 882–904.
[147] M.M. Buttigieg, et al., Inflammatory reprogramming of the solid tumor microenvironment by infiltrating clonal hematopoiesis is associated with adverse outcomes, Cell. Rep. Med. 6 (3) (2025) 101989.
[148] W.G. Dunn, M.A. McLoughlin, G.S. Vassiliou, Clonal hematopoiesis and hematological malignancy, J. Clin. Invest. 134 (19) (2024).
[149] C.C. Coombs, et al., Therapy-Related Clonal Hematopoiesis in Patients with Non-hematologic Cancers Is Common and Associated with Adverse Clinical Outcomes, Cell. Stem Cell. 21 (3) (2017) 374–382, e4.
[150] F. Caiado, et al., Aging drives Tet2+/- clonal hematopoiesis via IL-1 signaling, Blood 141 (8) (2023) 886–903.
[151] K.P. Koh, et al., Tet1 and Tet2 regulate 5-hydroxymethylcytosine production and cell lineage specification in mouse embryonic stem cells, Cell. Stem Cell. 8 (2) (2011) 200–213.
[152] H. Kunimoto, H. Nakajima, TET2: A cornerstone in normal and malignant hematopoiesis, Cancer Sci. 112 (1) (2021) 31–40.
[153] A. Nazha, et al., Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes, J. Clin. Oncol. 39 (33) (2021) 3737–3746.
[154] A.M. Jankowska, et al., Loss of heterozygosity 4q24 and TET2 mutations associated with myelodysplastic/myeloproliferative neoplasms, Blood 113 (25) (2009) 6403–6410.
[155] S.M. Langemeijer, et al., Acquired mutations in TET2 are common in myelodysplastic syndromes, Nat. Genet. 41 (7) (2009) 838–842.
[156] F. Delhommeau, et al., Mutation in TET2 in myeloid cancers, N. Engl. J. Med. 360 (22) (2009) 2289–2301.
[157] S. Sano, et al., Tet2-Mediated Clonal Hematopoiesis Accelerates Heart Failure Through a Mechanism Involving the IL-1beta/NLRP3 Inflammasome, J. Am. Coll. Cardiol. 71 (8) (2018) 875–886.
[158] E.C. Svensson, et al., TET2-Driven Clonal Hematopoiesis and Response to Canakinumab: An Exploratory Analysis of the CANTOS Randomized Clinical Trial, JAMA Cardiol. 7 (5) (2022) 521–528.
[159] J.J. Fuster, et al., Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice, Science 355 (6327) (2017) 842–847.
[160] H. Huerga Encabo, et al., Loss of TET2 in human hematopoietic stem cells alters the development and function of neutrophils, Cell. Stem Cell. 30 (6) (2023) 781–799, e9.
[161] A.G. Bick, et al., Inherited causes of clonal haematopoiesis in 97,691 whole genomes, Nature 586 (7831) (2020) 763–768.
[162] J. McClatchy, et al., Clonal hematopoiesis related TET2 loss-of-function impedes IL1beta-mediated epigenetic reprogramming in hematopoietic stem and progenitor cells, Nat. Commun. 14 (1) (2023) 8102.
[163] S.S. Burns, et al., Il-1r1 drives leukemogenesis induced by Tet2 loss, Leukemia 36 (10) (2022) 2531–2534.
[164] P.M. Ridker, et al., Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial, Lancet 390 (10105) (2017) 1833–1842.
[165] H. Zeng, et al., Antibiotic treatment ameliorates Ten-eleven translocation 2 (TET2) loss-of-function associated hematological malignancies, Cancer Lett. 467 (2019) 1–8.
[166] M. Yamashita, et al., Dysregulated haematopoietic stem cell behaviour in myeloid leukaemogenesis, Nat. Rev. Cancer 20 (7) (2020) 365–382.
[167] S.Y. Kristinsson, et al., Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes, J. Clin. Oncol. 29 (21) (2011) 2897–2903.
[168] A. Morotti, et al., Modeling myeloproliferative neoplasms: From mutations to mouse models and back again, Blood Rev. 31 (3) (2017) 139–150.
[169] V. Skov, et al., Molecular profiling of peripheral blood cells from patients with polycythemia vera and related neoplasms: identification of deregulated genes of significance for inflammation and immune surveillance, Leuk. Res. 36 (11) (2012) 1387–1392.
[170] R. Vaidya, et al., Plasma cytokines in polycythemia vera: phenotypic correlates, prognostic relevance, and comparison with myelofibrosis, Am. J. Hematol. 87 (11) (2012) 1003–1005.

[171] S. Rai, et al., IL-1beta promotes MPN disease initiation by favoring early clonal expansion of JAK2-mutant hematopoietic stem cells, Blood Adv. 8 (5) (2024) 1234–1249.
[172] L. Arranz, et al., Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms, Nature 512 (7512) (2014) 78–81.
[173] M.F. Rahman, et al., Interleukin-1 contributes to clonal expansion and progression of bone marrow fibrosis in JAK2V617F-induced myeloproliferative neoplasm, Nat. Commun. 13 (1) (2022) 5347.
[174] Y. Kawano, et al., IL-1R1 and IL-18 signals regulate mesenchymal stromal cells in an aged murine model of myelodysplastic syndromes, Blood 145 (15) (2025) 1632–1644.
[175] E. Pronk, M. Raaijmakers, The mesenchymal niche in MDS, Blood 133 (10) (2019) 1031–1038.
[176] K.D. Prummel, et al., Inflammatory stromal and T cells mediate human bone marrow niche remodeling in clonal hematopoiesis and myelodysplasia, Nat. Commun. 16 (1) (2025) 10042.
[177] H. Kawano, et al., Interleukin-1/Toll-like Receptor Inhibition Can Restore the Disrupted Bone Marrow Microenvironment in Mouse Model of Myelodysplastic Syndromes, Blood 138 (2021).
[178] A. Carey, et al., Identification of Interleukin-1 by Functional Screening as a Key Mediator of Cellular Expansion and Disease Progression in Acute Myeloid Leukemia, Cell. Rep. 18 (13) (2017) 3204–3218.
[179] K.R. Katsumura, et al., GATA Factor-Dependent Positive-Feedback Circuit in Acute Myeloid Leukemia Cells, Cell. Rep. 16 (9) (2016) 2428–2441.
[180] K. Ezaki, et al., Interleukin-1 beta (IL-1 beta) and acute leukemia: in vitro proliferative response to IL-1 beta, IL-1 beta content of leukemic cells and treatment outcome, Leuk. Res. 19 (1) (1995) 35–41.
[181] B. De Boer, et al., The IL1-IL1RAP axis plays an important role in the inflammatory leukemic niche that favors acute myeloid leukemia proliferation over normal hematopoiesis, Haematologica 106 (12) (2021) 3067–3078.
[182] A.K. Gupta, et al., Juvenile myelomonocytic leukemia-A comprehensive review and recent advances in management, Am. J. Blood Res. 11 (1) (2021) 1–21.
[183] L. Dong, et al., Leukaemogenic effects of Ptpn11 activating mutations in the stem cell microenvironment, Nature 539 (7628) (2016) 304–308.
[184] Y. Yan, et al., JMML tumor cells disrupt normal hematopoietic stem cells by imposing inflammatory stress through overproduction of IL-1b, eta. Blood Adv. 6 (1) (2022) 200–206.
[185] C.L. Sawyers, Chronic myeloid leukemia, N. Engl. J. Med. 340 (17) (1999) 1330–1340.
[186] M. Wetzler, et al., Altered levels of interleukin-1 beta and interleukin-1 receptor antagonist in chronic myelogenous leukemia: clinical and prognostic correlates, Blood 84 (9) (1994) 3142–3147.
[187] B. Zhang, et al., Altered microenvironmental regulation of leukemic and normal stem cells in chronic myelogenous leukemia, Cancer Cell. 21 (4) (2012) 577–592.
[188] B. Zhang, et al., Inhibition of interleukin-1 signaling enhances elimination of tyrosine kinase inhibitor-treated CML stem cells, Blood 128 (23) (2016) 2671–2682.
[189] J. Cortes, et al., Front-line and salvage therapies with tyrosine kinase inhibitors and other treatments in chronic myeloid leukemia, J. Clin. Oncol. 29 (5) (2011) 524–531.
[190] S. Chu, et al., Persistence of leukemia stem cells in chronic myelogenous leukemia patients in prolonged remission with imatinib treatment, Blood 118 (20) (2011) 5565–5572.
[191] M. Jaras, et al., Isolation and killing of candidate chronic myeloid leukemia stem cells by antibody targeting of IL-1 receptor accessory protein, Proc. Natl. Acad. Sci. USA 107 (37) (2010) 16280–16285.
[192] H. Agerstam, et al., IL1RAP antibodies block IL-1-induced expansion of candidate CML stem cells and mediate cell killing in xenograft models, Blood 128 (23) (2016) 2683–2693.
[193] X. Cheng, et al., Tumor-associated myeloid cells in cancer immunotherapy, J. Hematol. Oncol. 16 (1) (2023) 71.
[194] A.J. Gentles, et al., The prognostic landscape of genes and infiltrating immune cells across human cancers, Nat. Med. 21 (8) (2015) 938–945.
[195] D.R. Powell, A. Huttenlocher, Neutrophils in the Tumor Microenvironment, Trends Immunol. 37 (1) (2016) 41–52.
[196] L.A. Garcia-Flores, et al., Increased neutrophil counts are associated with poor overall survival in patients with colorectal cancer: a five-year retrospective analysis, Front. Immunol. 15 (2024) 1415804.
[197] J. Dong, et al., Correlation between the neutrophil-to-lymphocyte ratio and clinicopathological parameters in epithelial ovarian cancer patients and its effect on prognosis-a retrospective cohort study, Gland. Surg. 11 (8) (2022) 1367–1373.
[198] M.S.F. Ng, et al., Deterministic reprogramming of neutrophils within tumors, Science 383 (6679) (2024) eadf6493.
[199] A.J. Casbon, et al., Invasive breast cancer reprograms early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils, Proc. Natl. Acad. Sci. USA 112 (6) (2015) E566–E575.
[200] S.S. McAllister, R.A. Weinberg, The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis, Nat. Cell. Biol. 16 (8) (2014) 717–727.
[201] B.M. Allen, et al., Systemic dysfunction and plasticity of the immune macroenvironment in cancer models, Nat. Med. 26 (7) (2020) 1125–1134.
[202] S.B. Coffelt, et al., IL-17-producing gammadelta T cells and neutrophils conspire to promote breast cancer metastasis, Nature 522 (7556) (2015) 345–348.
[203] K. Kersten, et al., Mammary tumor-derived CCL2 enhances pro-metastatic systemic inflammation through upregulation of IL1beta in tumor-associated macrophages, Oncoimmunology 6 (8) (2017) e1334744.
[204] Z. Chen, et al., Mechanism and effects of extramedullary hematopoiesis on anti-tumor immunity, Cancer Biol. Med. 20 (7) (2023) 477–482.
[205] C. Wu, et al., Spleen mediates a distinct hematopoietic progenitor response supporting tumor-promoting myelopoiesis, J. Clin. Invest. 128 (8) (2018) 3425–3438.
[206] Y. Bao, et al., Extramedullary hematopoiesis secondary to malignant solid tumors: a case report and literature review, Cancer Manag. Res. 10 (2018) 1461–1470.
[207] C. Ding, et al., Inducing trained immunity in pro-metastatic macrophages to control tumor metastasis, Nat. Immunol. 24 (2) (2023) 239–254.
[208] A.E. Geller, et al., The induction of peripheral trained immunity in the pancreas incites anti-tumor activity to control pancreatic cancer progression, Nat. Commun. 13 (1) (2022) 759.
[209] E.B. Byun, et al., Gamma-irradiated beta-glucan induces immunomodulation and anticancer activity through MAPK and NF-kappaB pathways, J. Sci. Food Agric. 96 (2) (2016) 695–702.
[210] M. Wang, et al., beta-Glucan Combined With PD-1/PD-L1 Checkpoint Blockade for Immunotherapy in Patients With Advanced Cancer, Front. Pharmacol. 13 (2022) 887457.
[211] Q.L. Tan, et al., Immunotherapy of Bacillus Calmette-Guerin by targeting macrophages against bladder cancer in a NOD/scid IL2Rg-/- mouse model, Mol. Med. Rep. 22 (1) (2020) 362–370.
[212] A.S.H. Chan, et al., Imprime PGG Enhances Anti-Tumor Effects of Tumor-Targeting, Anti-Angiogenic, and Immune Checkpoint Inhibitor Antibodies, Front. Oncol. 12 (2022) 869078.
[213] L.S. Helder, et al., Bacillus Calmette-Guerin-induced trained immunity potentiates TH17 responses in vitro, J. Leukoc. Biol. 117 (9) (2025).
[214] E.K. Jo, et al., Molecular mechanisms regulating NLRP3 inflammasome activation, Cell. Mol. Immunol. 13 (2) (2016) 148–159.
[215] L. Steimbach, et al., Fungal beta-glucans as adjuvants for treating cancer patients - A systematic review of clinical trials, Clin. Nutr. 40 (5) (2021) 3104–3113.
[216] M. Thomas, et al., A randomized, open-label, multicenter, phase II study evaluating the efficacy and safety of BTH1677 (1,3-1,6 beta glucan; Imprime PGG) in combination with cetuximab and chemotherapy in patients with advanced non-small cell lung cancer, Invest. New. Drugs 35 (3) (2017) 345–358.
[217] G. Redelman-Sidi, M.S. Glickman, B.H. Bochner, The mechanism of action of BCG therapy for bladder cancer–a current perspective, Nat. Rev. Urol. 11 (3) (2014) 153–162.
[218] J. Kleinnijenhuis, et al., BCG-induced trained immunity in NK cells: Role for non-specific protection to infection, Clin. Immunol. 155 (2) (2014) 213–219.
[219] R. Pichler, et al., Intravesical BCG in bladder cancer induces innate immune responses against SARS-CoV-2, Front. Immunol. 14 (2023) 1202157.
[220] G.N. Thalmann, et al., Urinary Interleukin-8 and 18 predict the response of superficial bladder cancer to intravesical therapy with bacillus Calmette-Guerin, J. Urol. 164 (6) (2000) 2129–2133.
[221] E.C. De Boer, et al., Induction of urinary interleukin-1 (IL-1), IL-2, IL-6, and tumour necrosis factor during intravesical immunotherapy with bacillus Calmette-Guerin in superficial bladder cancer, Cancer Immunol. Immunother. 34 (5) (1992) 306–312.
[222] P. Conti, et al., Bacillus Calmette-Guerin potentiates monocyte responses to lipopolysaccharide-induced tumor necrosis factor and interleukin-1, but not interleukin-6 in bladder cancer patients, Cancer Immunol. Immunother. 38 (6) (1994) 365–371.
[223] K. Taniguchi, et al., Systemic immune response after intravesical instillation of bacille Calmette-Guerin (BCG) for superficial bladder cancer, Clin. Exp. Immunol. 115 (1) (1999) 131–135.
[224] S.R.J. Hofstraat, et al., Nature-inspired platform nanotechnology for RNA delivery to myeloid cells and their bone marrow progenitors, Nat. Nanotechnol. 20 (4) (2025) 532–542.
[225] D. Shi, S. Toyonaga, D.G. Anderson, Vivo RNA Delivery to Hematopoietic Stem and Progenitor Cells via Targeted Lipid Nanoparticles, Nano Lett. 23 (7) (2023) 2938–2944.
[226] J. Lennartsson, L. Ronnstrand, Stem cell factor receptor/c-Kit: from basic science to clinical implications, Physiol. Rev. 92 (4) (2012) 1619–1649.
[227] C. Chakraborty, et al., Therapeutic miRNA and siRNA: Moving from Bench to Clinic as Next Generation Medicine, Mol. Ther. Nucleic Acids 8 (2017) 132–143.
[228] K.F. Ortved, et al., RNA Interference Mediated Interleukin-1beta Silencing in Inflamed Chondrocytes Decreases Target and Downstream Catabolic Responses, Arthritis 2016 (2016) 3484961.