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Hematopoietic stem cell state and fate in trained immunity

Weinian Liao[1], Xiaodong Zai[1], Jun Zhang[1] and Junjie Xu[1*]

Abstract
Trained immunity serves as a *de facto* memory for innate immune responses, resulting in long-term functional reprogramming of innate immune cells. It enhances resistance to pathogens and augments immunosurveillance under physiological conditions. Given that innate immune cells typically have a short lifespan and do not divide, persistent innate immune memory may be mediated by epigenetic and metabolic changes in long-lived hematopoietic stem cells (HSCs) in the bone marrow. HSCs fine-tune their state and fate in various training conditions, thereby generating functionally adapted progeny cells that orchestrate innate immune plasticity. Notably, both beneficial and maladaptive trained immunity processes can comprehensively influence HSC state and fate, leading to divergent hematopoiesis and immune outcomes. However, the underlying mechanisms are still not fully understood. In this review, we summarize recent advances regarding HSC state and fate in the context of trained immunity. By elucidating the stem cell-intrinsic and extrinsic regulatory network, we aim to refine current models of innate immune memory and provide actionable insights for developing targeted therapies against infectious diseases and chronic inflammation. Furthermore, we propose a conceptual framework for engineering precision-trained immunity through HSC-targeted interventions.

Keywords Hematopoietic stem cell, Trained immunity, Stem cell state, Cell fate decision, Innate immune cell

Introduction

The immune system is typically divided into two complementary parts: innate immunity and adaptive immunity. These two branches differ significantly in the types of immune cells involved, the speed of activation, the specificity of responses, and the capacity for immunological memory. Innate immunity rapidly recognizes and responds to pathogens or damage-associated molecular patterns (PAMPs or DAMPs) through pattern recognition receptors (PRRs), thereby providing immediate and effective host defense [1]. However, these responses are relatively non-specific, and traditional views suggest that they do not generate immune memory. In contrast, adaptive immunity develops more slowly, often taking days to weeks to fully engage, triggered by the recognition of specific antigens, ensuring a high degree of specificity against pathogens. The activation of the adaptive immune system is facilitated by specialized antigen-presenting cells from the innate immune system, leading to the formation of immunological memory that guarantees long-term protection [2]. Immune memory has been considered exclusive to the adaptive immune system in the past. More recently the concept of trained immunity has gained traction, demonstrating that the innate immune system can also establish long-lasting immune memory following infections and certain vaccinations, thus enhancing responsiveness upon re-encountering with the same or

*Correspondence:
Junjie Xu
xujunjie@sina.com
[1]Laboratory of Advanced Biotechnology, Beijing Institute of Biotechnology, Beijing 100071, China

even unrelated pathogens [3]. This concept is referred to as "trained immunity".

In contrast with adaptive immune memory which is based on specific antigens and relies on genetic rearrangement mechanisms as well as clonal expansion of adaptive immune cells, trained immunity is fundamentally linked to changes in cellular reprogramming of innate immune cells [4]. These alterations are intricately associated with metabolic reprogramming and epigenetic modifications that regulate the transcription of genes related to host defense upon reactivation. The functional reprogramming of innate immune cells leads to more effective antimicrobial responses, such as enhanced phagocytosis and cytokine secretion, increased production of reactive oxygen species (ROS), and more efficient pathogen clearance mechanisms [5]. Given the short lifespan and non-proliferative nature of innate immune cells, researchers have proposed that persistent innate immune memory may be mediated by state and fate adaptation in long-lived immune stem cells (hematopoietic stem cells, HSCs) [6]. HSC-mediated durable innate immune memory is termed "central trained immunity" [7].

HSCs are the common progenitor cells for all immune cells, which finely balance self-renewal state and multilineage differentiation fate to adapt to immune demands. Previous study demonstrated that HSCs directly participate in the primary response to both acute and chronic infections through increasing proliferation to replace depleted progeny pools [8–10]. In addition to the passive "pushed" effect that peripheral cell deficiencies may exert on HSCs, HSCs can also be active "pull" towards cell division and differentiation fate by directly sensing infection [11]. Typically, innate immune cells serve as the first line of defense in the organism, requiring widespread distribution or constant patrol within various peripheral tissues to recognize invading pathogens. HSCs residing in the bone marrow were previously considered to exhibit a delayed response to pathogen detection. However, recent research has revealed that when microbial invasion poses a severe threat to life, HSCs can directly recognize and respond to infections [12]. Infections activate downstream targets and reprogram HSC state and fate through both intrinsic and extrinsic immune signaling pathways, such as Toll-like receptors (TLRs), DNA/RNA sensors, and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), leading to hematopoietic-immune stress and the release of robust immune alert signals [13]. Concurrently, pathogen-derived compounds can trigger stress-induced hematopoiesis, characterized by HSC proliferation and enhanced myeloid differentiation [14]. Therefore, perturbation of HSC state and fate leads to systemic effects in immune responses.

Recent advances have demonstrated that, under certain circumstances, immune response can induce persistent innate immune memory in hematopoietic stem and progenitor cells (HSPCs), thereby enhancing broad resistance to secondary challenges [15–18]. These investigations elucidate the activation of cell proliferation and myeloid hematopoiesis pathways following immune challenges driven by microorganisms (such as Bacillus Calmette-Guérin, BCG and *Mycobacterium tuberculosis*, *Mtb*), microbial compounds (such as Lipopolysaccharide, LPS and β-glucans), viral mimetics (such as polyinosinic: polycytidylic acid, Poly: IC) and other factors (such as heme and Western diet) [19]. In these scenarios, the initial exposure to stimuli triggers long-term epigenetic and metabolic reprogramming of HSPCs. HSC state and fate in trained immunity are characterized by an increased quantity of myeloid cell production, enhanced non-specific antibacterial capabilities in HSC progeny cells, and heightened stress resistance of HSCs to secondary infections or chemotherapy-induced bone marrow suppression [16, 17]. Importantly, these phenomena have also been observed in human HSCs (hHSCs), with evident immune memory characteristics in HSCs and progeny cells following BCG vaccination [20, 21]. Otherwise, previously unrecognized inducer of trained immunity like labile heme could also confer long-term immunological regulation on hHSCs [22]. Western diet has been found to reprogram HSPCs, resulting in deleterious trained immunity and increasing the reactivity of innate immune cells [23]. Thus, HSCs *de facto* serve as the central hub of trained immunity, while the effects and mechanisms through which HSCs participate in the trained immune response, along with the alterations in their state and fate in both adaptive and maladaptive trained immunity, remain not fully understood.

In this review, we summarized the recent advances of HSC state and fate under homeostatic conditions, during acute and chronic infections, and in response to immune modulators, representing key areas of current trained immunity research. This review aims to deepen the understanding of the effects and mechanisms by which stem cell-level regulation influences trained immunity. Additionally, it may offer new strategies for the treatment of infectious and inflammatory diseases, as well as provide fresh perspectives for developing novel immune therapies.

Of note, in the context of trained immunity, changes in HSC "state" predominantly occur at the transcriptional, epigenetic, and metabolic levels, while alterations in HSC "fate" are reflected in self-renewal capacity, proliferative activity, differentiation potential and survival advantage. For clarity, this review adopts the following terminology: (1) HSC state encompasses molecular-level modifications (transcriptional, epigenetic, and metabolic); (2) HSC fate

refers to as functional changes in stem cell behavior (self-renewal, proliferation, differentiation and survival). Since current investigations into trained immunity predominantly rely on murine models, this review referenced herein employ these experimental systems unless explicitly stated.

HSC state and fate support immune functionality under homeostasis

To manage the state and fate under homeostasis, HSCs engage a delicate balance of pro-survival and stress-response mechanisms, ensuring a functional HSC compartment while adapting to the demands of immune cell production. In response to stress, HSCs activate survival mechanisms to safeguard HSC populations. For instance, HSCs display greater anti-apoptotic capacity compared to downstream progenitor cells under stress, evidenced by reduced pro-apoptotic gene expression and increased pro-survival gene expression [24], quiescence-mediated protection from the p53-dependent apoptotic program [25], and by survival advantages conferred by micro-environmental cells [26]. In addition, HSCs maintain self-renewal and regenerative potential via various stress-response pathways, including autophagy and mitophagy. Autophagy helps preserve HSC quiescence by degrading active mitochondria and inhibiting differentiation signals from oxidative phosphorylation (OXPHOS), thereby enabling a shift back to glycolytic metabolism upon cell cycle activation [27, 28]. Mitophagy, executed through peroxisome proliferator-activated receptors, further supports quiescence by removing damaged mitochondria [29]. HSC fitness also depends on tightly regulated protein synthesis rates, which protect HSCs from functional deficits induced by the accumulation of misfolded proteins [30]. By utilizing intrinsic mechanisms, HSCs maintain quiescence and protect against the effects of active metabolism in the hypoxic bone marrow. Quiescent HSCs primarily rely on glycolysis for energy, minimizing mitochondrial respiration and ROS production associated with OXPHOS [31]. Of note, fine-tuned metabolic activation of HSCs also undergoes epigenetic and transcriptional remodeling, which are crucial for HSC self-renewal and fate decision [32]. Thus, the enforcement of relatively quiescent state and stable fate in HSCs is a crucial characteristic, which protects the HSC pool integrity and lifelong immune cell production.

HSCs keep their state and fate during steady-state hematopoiesis, but play a crucial role in responding to stresses such as hemorrhage, infections, and chemotherapy or radiotherapy. The antiviral cytokines Type I interferon (IFNα) drives HSC proliferation by briefly relaxing quiescence-enforcing mechanisms in response to acute IFNα exposure [25]. Nevertheless, this proliferative response is transient, with HSCs quickly returning to a protective quiescent state. It has been demonstrated that IFNα could prime HSCs for apoptosis but induce direct cell death only upon active proliferation, thereby explaining their suppressive effects on HSC function [25]. The inflammatory cytokine tumor necrosis factor-alpha (TNF-α) shield HSCs from depletion during inflammation by activating the transcription factor PU.1, which inhibits excessive cell cycle progression and protein synthesis [33]. Overall, HSCs dynamically respond to inflammatory stress while maintaining their numbers and functions, thus preserving homeostasis in the hematopoietic-immune system throughout the lifespan. Despite such HSC responses can be beneficial in promoting the elimination of an acute infection, chronically sustained activation may impair HSC function, ultimately leading to HSC exhaustion and persistence of inflammatory pathologies. For instance, prolonged or repeated infections may disrupt this quiescent state, causing excessive proliferation or abnormal differentiation of HSCs, which can ultimately lead to premature exhaustion or depletion of the HSC pool [34]. Therefore, the state and fate of HSCs direct the production and function of their progeny immune cells, which in turn determines the overall immune functionality of the organism.

HSC state and fate in beneficial and maladaptive trained immunity

Trained immunity reshapes the transcriptomic, epigenetic, and metabolic states of HSCs

HSCs undergo continuous adaptations in transcription, epigenetics, and metabolism, which provides a foundation for the induction of trained immunity. Similar to observations in monocytes and macrophages, the establishment of immune memory in HSCs is closely linked to alterations in their transcriptomic landscape. Analysis following initial stimulation with β-glucan and BCG revealed evident activation of gene programs associated with the cell cycle and myeloid differentiation within HSC lineages [15–17]. Specifically, BCG reprograms HSCs through IFN-γ signaling, promoting their priming and expansion [15]. β-glucan induces HSC training through the IL-1β/GM-CSF axis with adaptations in glucose metabolism and cholesterol biosynthesis [16]. Trained immunity induced by *Listeria monocytogenes* is manifested by significant increased HSCs and multipotent progenitors (MPPs), including increased myeloid-biased MPP3 and lymphoid-biased MPP4, which contributes to the elevated leukocyte counts before and during infection [17]. Following LPS stimulation, HSCs displayed transient changes in their abundance, progeny, composition and gene expression. However, persistent alterations were observed in the C/EBPβ-dependent accessibility of specific myeloid lineage enhancers, which heightened the responsiveness of associated immune

genes to secondary stimulation [18]. It demonstrated that LPS-induced gene transcriptional changes, rather than epigenetic alterations, are not sustained, as HSCs quickly revert to transcriptional homeostasis [18]. In this context, epigenetic alterations facilitate the persistent presence of previously dormant open chromatin regions in innate immune genes, which are primed for reactivation upon secondary stimulation.

Trained immunity is influenced by a combination of metabolic and epigenetic adaptations, which are often functionally interconnected (Fig. 1). Following BCG vaccination, macrophages derived from BCG-trained HSCs exhibit accessible chromatin at interferon regulatory factor (IRF) and signal transducer and activator of transcription (STAT) binding sites, thereby establishing a long-lasting antimicrobial immune memory. These changes can persist for several weeks in the absence of BCG stimulation and are associated with stable modifications in activating histone marks, including mono- and trimethylation of H3K4 and acetylation of H3K27 [15]. In the β-glucan stimulation model, specific changes in gene programs regulating cellular metabolism were observed in HSCs. It was indicated that innate immune memory in HSCs is associated with a shift toward glycolytic metabolism and cholesterol biosynthesis, particularly through the mevalonate pathway, thereby mimicking key metabolic features related to monocyte/macrophage immune training [16]. In contrast, dysregulation of iron metabolism in HSCs following *Mtb* infection hinders myeloid differentiation and directly drives the development of a

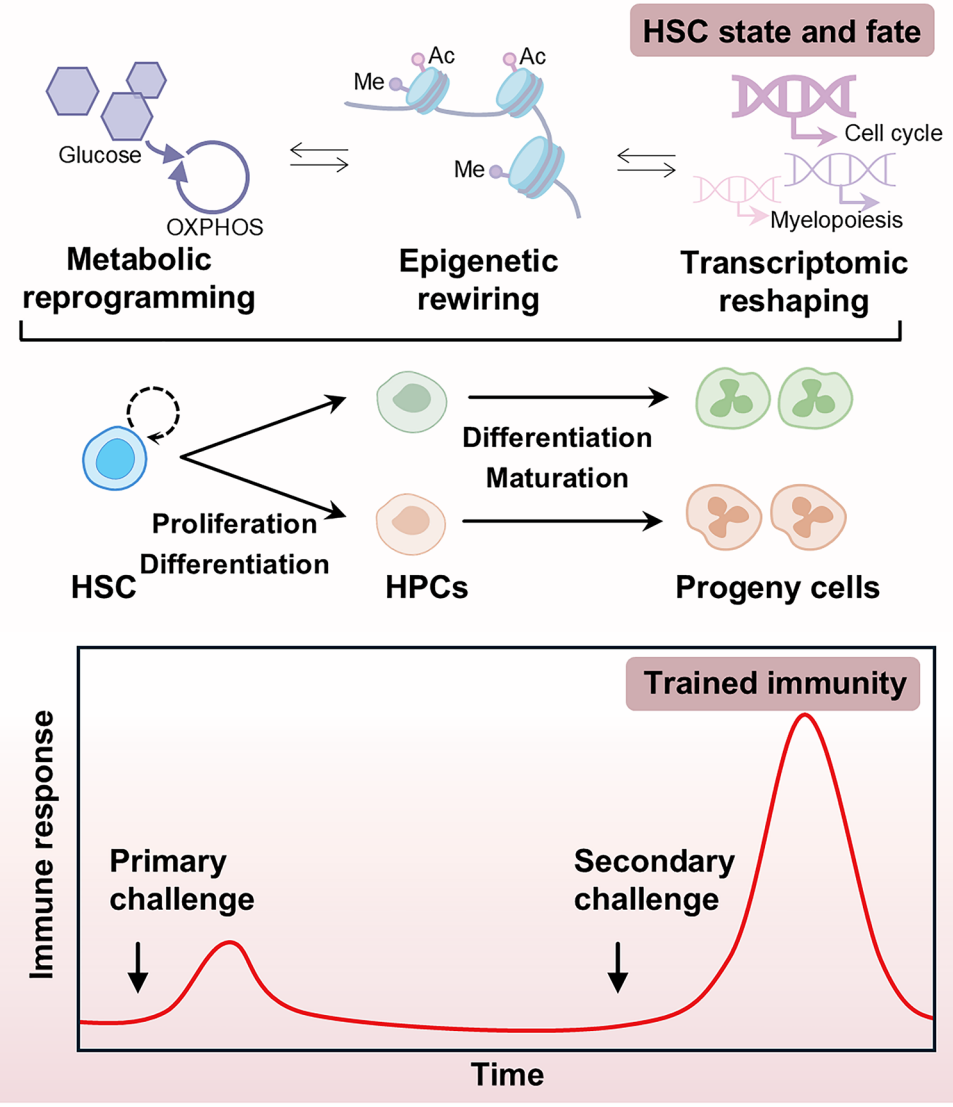

Fig. 1 Trained immunity reshapes the state and fate of HSCs. Trained immunity agonists stimulate long-term metabolic, epigenetic, and consequent transcriptional adaptations in HSC state and fate. The trained HSCs proliferate and preferentially give rise to trained progeny immune cells. The trained phenotype enables innate immune cells to respond faster and stronger to secondary challenges with the same or heterologous stimuli

tolerant phenotype [35]. Furthermore, cholesterol accumulation has been shown to promote myelopoiesis as a result of trained immunity in HSCs [16]. Intriguingly, BCG vaccination persistently alters gene expression in hHSCs. In contrast, it modulates chromatin accessibility in hematopoietic progenitor cells (HPCs), with the most prominent changes occurring at sites regulated by Kruppel-like factors (KLF) and early growth response (EGR) transcription factors, rather than affecting gene expression [21]. In this way, HSCs maintain a differentiation bias toward the myeloid lineage after 3 months post BCG vaccination [21]. This finding suggests that chromatin accessibility serves as an epigenetic memory in HSCs in trained immunity, which is subsequently imparted onto the progeny cells, even if many of the differential gene expression programs are silenced. Overall, adaptations in transcription, epigenetics, and metabolism in HSCs lay the groundwork for trained immunity induction.

Trained immunity profoundly impacts the fate of HSCs and their progeny cells

Persistent fate remodeling of HSPCs induced by trained immunity preferentially occurring in more primitive HSCs has been observed in both mouse models and human samples, which is characterized by HSC proliferation and myeloid differentiation (Table 1; Fig. 2) [15, 21]. This preference may be explained by heterogeneity of HSCs, as trained immunity predominantly induces selective expansion of myeloid-biased HSCs, leading to their clonal advantage [16]. On the contrary, *Mtb* infection exclusively induced cell death in myeloid lineage HSPCs, which impaired trained immunity against subsequent *Mtb* infection [35]. Trained immunity also educates a subset of HSCs that have always existed but were recently discovered. For instance, *Mycobacterium avium* (*M. avium*) induced trained immunity in HSCs and directed the expansion of a distinct HSC subpopulation with an infection-activated phenotype [36], a concept that might prove true across species [37]. This HSC subpopulation expressed not only classical HSC markers but also upregulated markers associated with activated immune responses to infection and those related to B cells [36]. Future studies, incorporating advanced single-cell tracing and clonal analysis techniques, may determine whether the long-term impact of trained immunity is initiated at the level of cell fate decision in primitive HSCs and lineage-committed subpopulations.

One of the outstanding questions in trained immunity is the longevity of imprinting in trained immune cells. The concept of trained immunity being initiated at the stem cell-level is further supported by analyses of HSC responses in healthy volunteers vaccinated with BCG [20]. BCG vaccination induced a sustained myeloid bias in the transcriptome of hHSCs, accompanied by a lasting (post 3 months) enhancement in the responsiveness of peripheral innate immune cells to heterologous stimuli [20]. Transplantation experiments confirmed that BCG-exposed HSCs displayed enhanced myeloid hematopoiesis even 12 weeks post transplantation [16]. A more recent study utilizing single-cell RNA sequencing and bone marrow transplantation experiments demonstrated that the imprinting of HSCs by BCG and *Mtb* contributes to protective or failed trained immunity for at least 1 year, respectively, and can be transmitted to progeny cells [35]. Additionally, competitive bone marrow transplantation experiments indicated that BCG-trained HSCs exhibit superior engraftment compared with control or *Mtb*-exposed HSCs, indicating that BCG reprograms HSCs to enhance their engraftment capacity [35]. Nevertheless, transplantation of *M. avium* -trained HSC alone did not result in improved immunity, suggesting that the protective trained immune response is probably dependent on other HSPC-compartment cells [36]. These results suggest that various HSPC components may play distinct roles in mechanisms that could be complementary in trained immunity. Additionally, an intergenerational and transgenerational transmission of *C. albicans* induced trained immunity in HSPCs was observed across two generations [38]. Strikingly, the progeny of *C. albicans*-exposed mice inherited an epigenetic signature from the HSPC populations of their parents, resulting in improved myeloid cell output and activation as well as increased survival following *Escherichia coli* infection [38].

Importantly, trained immunity not only enhances the responsiveness of HSCs themselves to subsequent challenges but also improved the quality and function of their progeny immune cells [6, 11]. Recent advances have further revealed that BCG alters gene expression and chromatin accessibility in hHSCs which predicts cytokine secretion in paired peripheral blood mononuclear cells (PBMCs) [20, 21]. Macrophages derived from *M. avium*-trained HSPCs exhibited enhanced bacterial killing and metabolism [36]. These studies suggest that the immune memory characteristics and functional properties of HSCs can be conveyed to their progeny immune cells through hierarchical differentiation. However, the specific molecular mechanisms underlying this process remain to be elucidated.

Otherwise, the significance of the observed alterations of HSC fate in various memory-inducing factors in these studies still requires further confirmation. The complex interplay among the type, intensity, and duration of the initial stimulus determines the acquisition of memory and its characteristics, influencing either the enhancement (pre-activation) or suppression (tolerance) of subsequent immune responses. For instance, exposure to low and high doses of LPS can respectively induce pre-activation or tolerance in macrophages during

Table 1 HSC state and fate in trained immunity

Training factors	State and fate of HSCs)	Effects and outcomes of trained immunity	Species	Reference
In beneficial trained immunity				
BCG vaccination	Induced cell cycle and myeloid-biased differentiation gene signature in HSPCs	Enhanced protection against *Mtb* infection	Mouse	[15]
β-glucan treatment	Increased expression of genes involved in myeloid-skewing, immune functions and metabolism in HSCs	Enhanced production of more myeloid cells, and less B cells	Mouse	[16]
β-glucan treatment	Stimulated myelopoiesis of HSPCs	Increased blood antimicrobial activity	Mouse	[17]
LPS vaccination	Induced transient changes in HSC abundance, composition, progeny, and gene expression	Enhanced production of more myeloid cells and improved innate immunity responses	Mouse	[18]
BCG vaccination	Imprinted a persistent transcriptomic myeloid bias on HSPCs	Transcriptomic remodeling of HSPCs conveyed to peripheral $CD14^+$ monocytes	Human	[20]
BCG vaccination	Altered gene expression in HSCs, while changing chromatin accessibility in HPCs	Induced myeloid-biased differentiation of HSCs and cytokine secretion of peripheral immune cells	Human	[21]
Heme	Induced transcriptomic activation in HSCs and expanded myeloid-primed HSCs	Promoted resistance to sepsis	Mouse	[22]
M. avium infection	Activated gene expression in HSPCs and expanded a distinct HSC subpopulation with an infection-activated phenotype	Enhanced bacterial killing and metabolism in macrophages derived from trained HSPCs	Mouse	[36]
C. albicans infection	Increased expression of genes involved in myeloid-skewing and immune functions in HSPCs	*C. albicans*-exposed mice inherited signature of trained immunity in HSPCs from their parents	Mouse	[38]
β-glucan treatment	Promoted granulopoiesis of HSCs and generation of a distinct neutrophil subset	Enhanced disease tolerance and maintained lung tissue homeostasis during viral infection	Mouse	[40]
β-glucan treatment	Induced expansion and myelopoiesis of HSPCs	Enhanced production of proinflammatory cytokines upon secondary *Mtb* challenge	Mouse	[41]
β-glucan treatment and *C. albicans* infection	Induced differentiation of HSPCs through a dectin-1- and MyD88-dependent pathway	Activated HSPCs and induced their differentiation to trained macrophages	Mouse	[42]
In maladaptive trained immunity				
Western diet	Induced transcriptomic and epigenomic reprogramming of HSPCs	Increased proliferation and enhanced innate immune responses	Mouse	[23]
Mtb infection	Reprogramed HSCs via an IFNα response that dysregulates iron metabolism and induced cell death specifically in myeloid lineage	Hindered myeloid differentiation of HSCs and lead to a tolerant phenotype	Mouse	[35]
Rheumatoid arthritis	Enhanced proliferation of the HSPCs in the bone marrow and the spleen	Increased circulating myeloid cells and impaired atherosclerotic lesion regression	Mouse	[45]
Periodontitis	Epigenetic rewiring of HSPCs	Sustained enhancement of production of myeloid cells with increased inflammatory preparedness	Mouse	[46]
Cardiovascular disease	Skewed towards myelopoiesis and enrichment of neutrophil- and monocyte-related pathways in HSPCs	Enhanced cytokine production capacity of mature immune cells was higher in patients with atherosclerosis	Human	[47]
CHIP	Increased clonal expansion of HSPCs into both myeloid and lymphoid lineages	Aggravated experimentally induced periodontitis and arthritis	Human, mouse	[49]

subsequent challenges [39]. In vivo high-dose LPS stimulation exerts dual effects on HSCs, promoting robust secondary innate immune responses and simultaneously limiting certain potentially harmful inflammatory signals [18]. β-Glucan treatment also promotes granulopoiesis of HSCs in a IFNα-dependent manner, leading to the generation of a distinct neutrophil subset endowed with regulatory properties. These specialized neutrophils are essential for establishing disease tolerance and maintaining lung tissue homeostasis during viral infection [40]. Consistent with this notion, the acquisition of memory and its outcomes are linked to the activation of specific cytokine pathways. For example, IL-1, GM-CSF, and type II interferon (IFNγ) are associated with protective phenotypes following β-glucan or BCG stimulation [15, 16, 41, 42]. Conversely, IFNα activity is related to acquired tolerance induced by *Mtb* infection [35]. The intricate rules connecting the initial inducers, target cells, and cell-fate outcomes following secondary stimulation remain to be clarified.

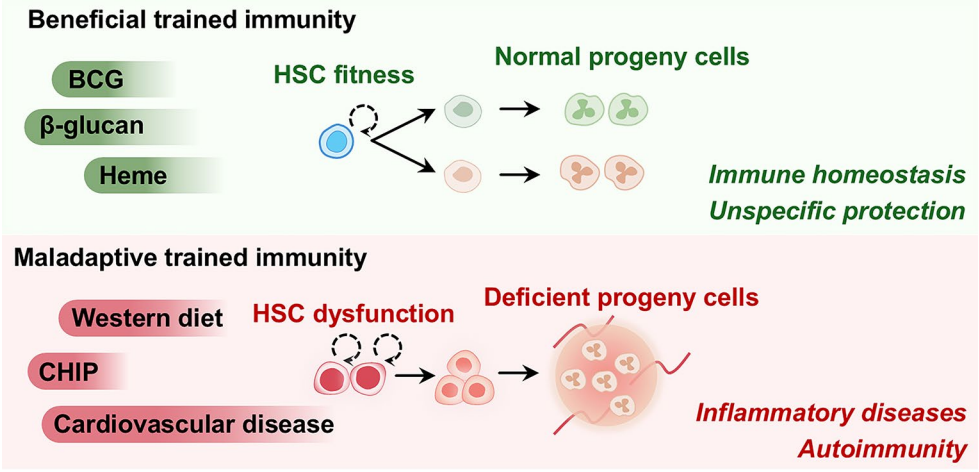

Fig. 2 Overview of HSC state and fate in beneficial and maladaptive trained immunity. Current studies suggest that trained immunity can have both beneficial and detrimental effects. BCG vaccination and β-glucan administration are known to induce a long-lasting reprograming of myeloid cells, resulting in the unspecific protection against different pathogens. Otherwise, previously unrecognized inducer of trained immunity like labile heme could also confer long-term immunological regulation on HSCs. On the other side, western diet was found to reprogram bone marrow granulocyte progenitors, increasing the inflammatory reactivity of innate immune cells. Similarly, maladaptive trained immunity was suggested to be involved in the pathological hyperinflammation affecting patients suffering from CHIP and cardiovascular diseases. A healthy trained immunity response that is essential for immune homeostasis provides the unspecific protection against pathogens. However, maladaptive trained immunity can lead to a variety of inflammatory and autoimmune diseases

Maladaptive trained immunity induced dysregulation of HSC state and fate

Trained immunity provides broad protection against reinfection and plays a vital role in other disease contexts, such as reinforcing anti-tumor effects [43]. However, maladaptive trained immunity can also promote dysregulated immune responses, exacerbating chronic inflammation and metabolic diseases, including atherosclerosis and primary hyperaldosteronism, where myeloid cells are pivotal to the pathogenesis [11]. Maladaptive trained immunity can be induced by various inflammatory stimuli, which results in a persistent inflammatory state through the increased production of myeloid cells with remarkably proinflammatory potential (Table 1; Fig. 2). These observations were consistent with transcriptomic alteration in HSCs, which demonstrated that the enrichment of innate immune-related pathways at the expense of pathways was related to lymphocyte hematopoiesis and function [16]. A preclinical study demonstrated that abnormal trained immunity following Western-type diet (WD) in HSPCs and its pathological consequences by simulating inflammation due to metabolic syndrome [23]. Specifically, when low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) mice were fed a high-calorie WD, IL-1-dependent HSPCs transcriptomic and epigenetic reprogramming were observed, leading to the generation of myeloid cells with enhanced proinflammatory potential. Consistent with the long-term effects of trained immunity, this maladaptive HSPCs reprogramming persisted even after the mice reverted to a normal diet [23]. Since there is always the potential for HSCs to acquire maladaptive innate immune memory and respond to inflammatory stimuli, which may have detrimental effects on chronic inflammatory diseases. The adaptation to signals from ongoing conditions, such as cardio-metabolic diseases, promoted myelopoiesis and increased the production of inflammatory myeloid cells, further amplifying inflammation, which not only exacerbates the disease but also perpetuates HSPC-driven myelopoiesis [11]. Consequently, a feed-forward loop is established between maladaptive trained HSPCs and the inflammatory disorder, potentially perpetuating disease chronicity.

Moreover, maladaptive training of HSPCs may provide a basis for understanding the mechanisms of autoimmune diseases and inflammatory comorbidities, such as increased cardiovascular risk in patients with periodontitis, rheumatoid arthritis or atherosclerosis [44]. In this regard, systemic inflammation associated with experimental arthritis in mice leads to increased membrane cholesterol in HSPCs, promoting myeloid cell generation. The abundance of myeloid cells in circulation is associated with an increased macrophage burden in atherosclerotic lesions in arthritis mice [45]. In another maladaptive training axis, systemic inflammation induced by experimental periodontitis in mice caused epigenetic reprogramming of HSPCs, resulting in a sustained increase in the production of myeloid cells with heightened inflammatory preparedness [46]. Recent clinical research indicated that peripheral blood monocytes from patients with atherosclerosis exhibit a higher capacity for cytokine production upon in vitro stimulation when compared to

healthy controls. Furthermore, transcriptome analysis of HSPCs in the bone marrow of atherosclerotic patients revealed an enrichment of neutrophil and monocyte-related pathways [47], suggesting a bias towards myeloid differentiation of trained HSPCs. Otherwise, maladaptive trained immunity does not necessarily involve aberrant activation of inflammatory responses. Research has shown that myocardial infarction in mice epigenetically reprograms Ly6C^{high} monocytes in the bone marrow, driving them towards an immunosuppressive phenotype. These cells are subsequently recruited to breast tumors, promoting tumor growth [48]. Consistent with this finding, cardiovascular events (such as myocardial infarction or stroke) following cancer diagnosis in early-stage breast cancer patients are associated with an increased risk of cancer recurrence and cancer-specific mortality [48]. In addition, an epigenetic state reshaped by clonal hematopoiesis of indeterminate potential (CHIP) mutations on HSCs and their progeny cells directed a permanent state of maladaptive inflammation thereby mimicking a "fixed" type of maladaptive trained immunity [49]. Therefore, further research of pathophysiology, particularly focusing on innate immunity memory imprinting of HSC state and fate that sustains trained myelopoiesis, may uncover previously unrecognized factors driving maladaptive trained immunity in comorbidities.

Translational implications

Assessment of trained immunity based on HSC state and fate in distinct pathophysiological contexts

Innate immunity serves as the first line of defense against pathogens during the early stage of disease, making trained immunity an important new target for expanding host-directed therapies. Nevertheless, dysregulation of trained immunity may exacerbate autoimmune and inflammatory diseases. Therefore, future research should develop precise and dynamic methods for assessing the state of trained immunity function. While HSC responses can be beneficial for promoting the elimination of infections, chronic activation of HSCs may impair their function, ultimately resulting in HSC exhaustion and persistence of inflammatory pathologies [19]. Although recent studies have proposed trained immunity evaluation models for specific types of HSC progeny cells or cell lines [50–53], their widespread application remains somewhat limited. Most importantly, there is still a lack of integrated models and methods for accurately assessing the trained immunity of HSCs and their various progeny cells—models that evaluate both peripheral and central trained immunity simultaneously. Developing more complex models of immune training, such as sequential memory inducers, single-cell analyses of initial HSCs, and clonal studies of their output after secondary challenges, could help elucidate the functional characteristics of HSC immune memory.

However, the precise mechanisms underlying HSCs-mediated immune regulation under different circumstances, particularly how they sense and respond to infections and orchestrate various aspects of the immune system, remain poorly understood. Although HSCs are deeply embedded in the complex structure of the bone marrow, they can directly participate in immune responses upon acute infection or chronic inflammatory conditions. Owing to the expression of various receptors for microbial products, such as the TLRs, DNA/RNA sensors, and receptors for inflammatory cytokines and growth factors, HSCs exhibit a sensitivity to external stimuli similar to that of their progeny immune cells [13]. The abundance of these receptors gradually increases after systemic infection, thus enabling HSCs to detect infection signals and initiate appropriate immune responses [11]. However, the precise mechanisms by which HSCs respond to infections and regulate immune cell production following trained immunity are still unresolved. Therefore, it is crucial to develop new high-throughput and convenient methods for analyzing HSC state and fate, such as PBMCs analysis with progenitor input enrichment (PIE) single-nuclei RNA sequencing which enables HSC enrichment within peripheral blood analysis [54]. To meet the growing need for interdisciplinary integration in trained immunity research, our team also introduce "Flag Biology" which uses advanced technologies to distill complex biological processes into a quantifiable and characteristic framework [55], enabling precise assessments of trained immunity from the HSC perspective across various physiological and pathological contexts.

Epidemiological studies have consistently shown that autoimmune diseases (such as lupus and rheumatoid arthritis) are more prevalent in women [56]. Recent studies have shown that the regulatory factors of HSCs in females significantly differ from those in males in terms of expression and function [57, 58]. Additionally, HSCs exhibit sex-specific cellular responses to inflammatory stimuli, which are reflected in differences in the expression of pathways regulating metabolism, hypoxia, and inflammation [59]. These differences shape distinct hematopoietic processes during both homeostasis and regeneration. The marked biological sex gender disparity underscores the importance of further investigating the role of sex differences in immune regulation and disease pathogenesis. Existing evidence suggests that sex chromosomes, hormonal fluctuations, and gender-specific environmental exposures likely converge to influence this immunological dichotomy [60]. However, most preclinical studies still predominantly use male animal models, creating a significant knowledge gap in understanding

female-specific pathophysiology. Future research should prioritize comparative analyses of immune cell function, cytokine profiles, and microbiome interactions across genders, with a balanced experimental design. Addressing these research gaps will catalyze the development of sex-specific therapeutic strategies, inform global health policies through sex-stratified vaccine design, and contribute to establish precision medicine frameworks capable of predicting individualized treatment responses based on sex-hormone-responsive biomarkers.

Maintenance of beneficial trained immunity based on HSC fitness

The hematopoietic-immune system exhibits unique plasticity and adaptability, as environmental factors dynamically shape HSC state and fate over time, thereby influencing their long-term myeloid output and responsiveness to stress [61]. Analogously, maladaptive training of the immune system is likely to result in abnormal myeloid output from HSCs and a decline in stem cell functionality. Thus, maintaining an appropriate dimension of HSC state and fate is crucial for preserving HSC quantity and functionality, representing as a vital strategy for sustaining beneficial trained immunity while preventing maladaptive responses. Interestingly, aging also causes gradual deterioration in HSC function, impairing memory immune generation and maintenance as well as weakening the immune response to infectious and inflammatory diseases [62, 63]. This age-related shift from HSCs with myeloid-biased output (my-HSCs) to HSCs with balanced output of lymphoid and myeloid cells (bal-HSCs), decreases lymphopoiesis and increases myelopoiesis, thereby impairing both trained and adaptive immunity and contributing to numerous pathologies in aged individuals [64]. Depleting my-HSCs effectively rescued the diminished trained and adaptive immunity in aged mice [64], which further highlights the importance of HSC fitness in trained immunity. Therefore, understanding the specific mechanisms of HSC dysfunction under various pathophysiological states, including its role in immune decline and strategies for restoring normal HSC function, remains a key focus in current immunological research.

The mechanisms underlying the establishment and maintenance of innate immune memory are delicately balanced with the preservation of long-term HSCs, while the precise nature of this balance remains to be determined. In recent years, the phenotypic and functional diversity of HSC subpopulations has been well demonstrated. Single-cell analyses have revealed considerable heterogeneity in HSCs regarding their self-renewal capabilities and differentiation potential [65]. HSCs may exhibit early lineage-specific traits and appear to have a bias toward generating certain blood lineages. For instance, $CD41^+$ HSC subpopulations with myeloid-megakaryocyte bias during the memory induction process [16]. Meanwhile, HSCs with higher expression of major histocompatibility complex II (MHC II) seem to display stronger interactions with both the innate and adaptive immune system [26, 66]. Classical models depict long-term hematopoietic stem cells (LT-HSCs) as quiescent stem cells that maintain homeostasis, while short-term HSCs (ST-HSCs), and MPPs are considered stress-responsive progenitors [67]. However, single-cell studies have shown that both LT-HSC differentiation bias and the expansion of ST-HSC/MPP contribute to stress responses [68]. Since the expansion of ST-HSC/MPP occurs downstream of LT-HSC fate commitment, effectively limiting this expansion could provide a sufficient means to control myeloid bias during early hematopoiesis. This challenges traditional boundaries, as surface markers (such as CD34, CD135 and c-Kit) fail to accurately distinguish "primed" LT-HSCs from ST-HSCs with overlapping transcriptional profiles [69]. Discrepancies in inflammatory signaling-mediated hematopoietic activation, where some studies directly implicate LT-HSCs [70, 71], while others attribute emergency hematopoiesis to ST-HSC/MPPs [72, 73], likely arise from model-specific variables, such as cytokine gradients and microenvironmental dynamics. These inconsistencies highlight the limitations of static transplantation assays and underscore the pressing need for dynamic fate-tracking systems that preserve native cellular interactions. Therefore, leveraging the "memory" and "forgetting" characteristics of specific HSC subpopulations, we hope to develop more precise strategies to regulate the persistence and responsiveness of both established and newly formed immune memories.

Optimizing central trained immunity based on HSC state and fate

Adjuvants are components of vaccines that act as immune stimulants, enhancing the intensity and persistence of the immune response. They are crucial for optimizing antigen-specific immune responses, in part by activating innate immune receptors and associated pathways to boost the immunogenicity of the vaccine [74]. Leveraging the regulatory effects of vaccine adjuvants on HSC state and fate, we can design and optimize inducers of trained immunity for preventive application. Various trained immunity inducers activate innate immune cells and significantly enhance the immune response by secreting cytokines such as IL-1β and IFN, further amplifying both peripheral and central trained immunity [15, 16]. Increasing evidence from experimental animal models suggested that molecules with adjuvant capabilities can provide heterologous protection against secondary infections via modulation of HSC state and fate. For instance, the

fungal cell wall component β-glucan induces long-term functional changes in mononuclear phagocytes by activating HSCs [16], thereby enhancing the ability to combat acute infections against various pathogens, including *Leishmania*, *Mtb*, and *Leptospira* [41, 75, 76]. Meanwhile, recent studies indicated that several vaccine adjuvants are associated with trained immunity characteristics. For example, administration of the influenza vaccine with the oil-in-water emulsion adjuvant AS03, triggers epigenetic changes in myeloid cells, leading to an antiviral state and enhanced resistance against unrelated viruses, such as Zika and Dengue, in vitro [77]. This epigenetic remodeling reveals a new role for AS03 as an inducer of trained immunity. Interestingly, the recombinant zoster vaccine (RZV), which contains the liposomal adjuvant AS01, has recently been shown to provide non-specific immunity against COVID-19 [78]. Furthermore, the TLR7/8 agonist 3 M-052 exhibits long-term transcriptomic and epigenomic activation in murine myeloid cells [79]. Notably, enhanced innate immune responses have been observed following the second dose of COVID-19 vaccine Comirnaty, manifesting epigenomic reprogramming characteristic of trained immunity, which confers augmented cytokine responsiveness to heterologous challenges subsequent vaccine exposures [80]. Lipid nanoparticle (LNP) carriers used in COVID-19 mRNA vaccines also serve as potent adjuvants [81]. This phenomenon may originate from vaccine-elicited lymphoid-myeloid crosstalk. Future research will be critical for optimizing cross-protective immunity and overcoming antigenic imprinting in sequential vaccination, based on HSC-intrinsic trained immunity mechanisms. Intriguingly, inflammatory cytokine IFNγ-induced trained immunity can protect against antigenically unrelated pathogens affecting distant organ systems [36]. Determining the ideal combination of cytokines and other signaling factors could allow for HSPC training in the absence of an infectious pathogen in vivo or ex vivo. This strategy could serve as a translational platform to protect vulnerable patients like bone marrow transplant recipients from life-threatening infections. Of note, response heterogeneity within the HSPC pool was not correlated with IFNγ receptor expression [36], indicating that heterogeneity in responses may be due to local differences in pathogen or cytokine exposure within bone marrow niches. This functional diversification implies the existence of transcriptionally primed HSPC subsets with preprogrammed epigenetic landscapes that encode diverse responses to a variety of pathogens challenges. Therefore, the specific effects of diverse adjuvants on HSC state and fate, as well as their impact on central trained immunity are outstanding research fields in the future.

Besides, the hyperreactivity induced by trained immunity, characterized by the secretion of cytokines and activation of innate immune cells, can enhance the immunogenicity of certain vaccines. Currently, vaccines known to induce trained immunity are primarily designed to protect against specific pathogens rather than providing broad heterologous protection. Next-generation vaccines that incorporate trained immunity stimulators may provide non-specific protection against a range of infections, including emerging pathogens. By manipulating the metabolic and epigenomic features of HSCs, trained immunity adjuvants can effectively boost innate immune responses and prolong their duration, ideally improving adaptive immune responses as well. Overall, live attenuated vaccines, such as BCG, measles vaccine, and oral polio vaccine, appear to be most effective at inducing trained immunity, although some adjuvanted vaccines (such as influenza vaccine) may also elicit this response [77]. Different vaccines inducing trained immunity trigger distinct programs. For example, influenza or SARS-CoV-2 vaccines generate antiviral interferon-related trained immunity responses, while BCG primarily induces a trained immunity response geared toward bacterial defense [77]. Further studies are needed to explore the variations of these innate immune memory programs and clarify their roles in regulating HSC state and fate, which will help the identification of vaccine candidates offering superior and more applicable protection against specific types of pathogens. Additionally, refining administration routes and optimizing delivery systems can facilitate targeted regulation of HSCs and central trained immunity, thus providing robust heterologous protection.

Conclusions

In conclusion, this review underscores the pivotal role of HSCs in trained immunity, highlighting how their state and fate reprogramming can influence both innate immune responses and overall hematopoiesis. As HSCs adapt their state and fate to meet the demands of trained immunity, they not only enhance resistance to pathogens but also present challenges that can lead to maladaptive immune outcomes. This dualistic role positions HSCs as both the bedrock of immunological memory and a vulnerability in dysregulated immune states. The mechanistic insights gleaned from murine models reveal striking disparities between murine and human HSC biology. Key disparities include species-specific HSC surface marker expression, divergent cytokine sensitivity, and unique epigenetic landscapes. These discrepancies underscore the urgent need for cross-species validation frameworks, such as humanized mouse models and induced pluripotent stem cell-derived HSC platforms, to bridge the bench-to-bedside gap. By integrating cutting-edge technologies, including single-cell multi-omics, spatial transcriptomics, and AI-driven predictive modeling,

we aim to unravel the molecular logic governing HSC-trained immunity crosstalk. A deeper understanding of these processes could lead to developing novel immune therapies, including advanced vaccine formulations and targeted stem cell treatments, ultimately contributing to enhanced health outcomes.

Abbreviations

BCG	Bacillus Calmette-Guérin
CHIP	Clonal hematopoiesis of indeterminate potential
DAMPs	Damage-associated molecular patterns
HPCs	Hematopoietic progenitor cells
HSPCs	Hematopoietic stem and progenitor cells
HSCs	Hematopoietic stem cells
IFN	Interferon
LPS	Lipopolysaccharide
MHC II	Major histocompatibility complex II
M. avium	Mycobacterium avium
Mtb	Mycobacterium tuberculosis
OXPHOS	Oxidative phosphorylation
PAMPs	Pathogen-associated molecular pattern
PBMCs	Peripheral blood mononuclear cells
Poly	IC: polyinosinic: polycytidylic acid
PRRs	Pattern recognition receptors
RLRs	Retinoic acid-inducible gene I-like receptors
ROS	Reactive oxygen species
TLRs	Toll-like receptors
WD	Western-type diet

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Data availability
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Declarations

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