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REVIEW

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Inflammasomes: potential therapeutic targets in hematopoietic stem cell transplantation

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Abstract

The realm of hematopoietic stem cell transplantation (HSCT) has witnessed remarkable advancements in elevating the cure and survival rates for patients with both malignant and non-malignant hematologic diseases. Nevertheless, a considerable number of patients continue to face challenges, including transplant-related complications, infection, graft failure, and mortality. Inflammasomes, the multi-protein complexes of the innate immune system, respond to various danger signals by releasing inflammatory cytokines and even mediating cell death. While moderate activation of inflammasomes is essential for immune defense and homeostasis maintenance, excessive activation precipitates inflammatory damage. The intricate interplay between HSCT and inflammasomes arises from their pivotal roles in immune responses and inflammation. This review examines the molecular architecture and composition of various types of inflammasomes, highlighting their activation and effector mechanisms within the context of the HSCT process and its associated complications. Additionally, we summarize the therapeutic implications of targeting inflammasomes and related factors in HSCT.

Keywords Hematopoietic stem cell transplantation (HSCT), Graft-versus-host disease (GVHD), Inflammasomes, NLRP3, Pyroptosis

Introduction

Hematopoietic stem cell transplantation (HSCT) entails the intravenous infusion of hematopoietic stem and progenitor cells (HSPCs) after conditioning regimens like high-dose chemotherapy and/or radiotherapy. The primary objective is to eradicate residual tumour cells via graft-versus-leukemia (GVL) effects, while simultaneously replacing damaged or dysfunctional HSPCs to rejuvenate both the hematopoietic and immune systems [1]. Since the pioneering efforts of Gatti, Good [2], and Thomas [3] in the late 1960s, who initially employed HSCT to address human immunodeficiency disorders and aplastic anemia, this technology has been widely adopted for treating benign and malignant hematopoietic diseases. As a curative approach, HSCT has significantly improved clinical outcomes. From 1957 to 2019, over 1.5 million HSCT procedures were performed worldwide, with an annual growth rate exceeding 10% [4]. Despite recent significant advancements in HSCT, such as expanded indications, improved management of complications, and better integration with targeted therapies and immunotherapies [5]. HSCT still poses substantial risks for graft failure, relapse, and severe transplant-related complications, which are closely

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linked to immune tolerance and reconstruction [6, 7]. Therefore, elucidating the mechanisms underlying these adverse outcomes and identifying novel therapeutic targets are crucial.

The innate immune system acts as the body's initial defense mechanism against invasion and endogenous threats, playing a critical role in eliminating infections and damaged cells [8]. The central mechanism of this immune response is triggered by cytoplasmic protein complexes called inflammasomes [9]. Inflammasomes possess a remarkable capacity to swiftly discern pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Their activation subsequently triggers innate immune responses by facilitating the release of pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18), initiating an inflammatory cascade [10]. Proper inflammasome activation can swiftly eliminate damaged cells and strengthen immune defense. However, prolonged activation causes severe tissue damage in the body and may induce pyroptosis, a highly inflammatory form of cell death characterized by cellular lysis and destruction [11]. More than ten types of inflammasomes have been identified currently, each intricately intertwined in the pathogenesis of inflammatory and metabolic diseases, including cancer, diabetes, and infections [12, 13]. The intense reactivity of inflammasomes to various danger signals broadens their association with other diseases. Emerging evidence supports that inflammasomes are widely expressed in the hematopoietic system and have participated in several critical stages of HSCT. NLRP1, NLRP2, and NLRP3 have demonstrated significant prognostic implications for overall survival, relapse, and non-relapse mortality rates in HSCT [14]. Thus, meticulous modulation of inflammasome activation and tempering their excessive response are beneficial for post-HSCT outcomes.

In this paper, we present an overview of the individuality and commonality among different inflammasomes, focusing on their composition, activation, and effector functions. We systematically address the key roles of inflammasomes in coordinating mobilization, hematopoietic reconstitution, and associated complications, with particular emphasis on acute graft-versus-host disease (aGVHD). Finally, we assess the potential benefits of targeting inflammasomes in the treatment of HSCT.

Inflammasomes

Classification and composition of inflammasomes

The concept of inflammasomes, first described by Martinon et al. (2002), refers to multiprotein complexes and immune regulators that respond to pathogenic or physiological stimuli [10]. To date, more than ten types of inflammasomes have been identified, distinguished primarily by their components, activation mechanisms, and biological functions. Inflammasomes are categorized into three types according to their constituent proteins: the NLR family, the ALR family, and the Pyrin [15]. This section introduces several common inflammasomes.

The NLR family

The NLR family is the most well-characterized, consisting primarily of NLRP1, NLRP3, NLRP6, and NLRC4 [16]. These inflammasomes feature three functionally distinct domains. The C-terminal leucine-rich repeat (LRR) domain acts as the "sensor", recognizing and binding ligands due to its unique three-dimensional structure [17]. These ligands include exogenous PAMPs and endogenous DAMPs, differing in their molecular origins. The innate immune system rapidly recognizes and responds to signals from invading pathogens or damaged self-cells by distinguishing between self and non-self components [8]. The nucleotide-binding domain (NBD), also referred to as NACHT, is shared by other NLR members and facilitates LRR oligomerization by binding adenosine triphosphate (ATP). This interaction relieves the autoinhibition of LRR and promotes immune signal transduction [18]. Due to the sensitivity of the NBD to mutations, functional changes are commonly observed [19]. It is worth mentioning that NLRP1 exerts its function independently of the ATPase activity of the NBD. It features a unique FIIND domain non-covalently linked to the N-terminus to self-cleavage, separating the N-terminal and C-terminal domains of NLRP1 and leading to its activation [20]. Another significant protein domain is the variable N-terminal domain containing the pyrin domain (PYD), caspase recruitment domain (CARD) as well as baculovirus inhibitor of apoptosis repeat (BIR) domain. These domains interact with the adaptor protein ASC through PYD-PYD or CARD-CARD linkages, ultimately resulting in the activation of pro-caspase-1 [21]. NLRs are categorized into four subfamilies based on their divergent N-terminal domains: CIITA with an acidic transactivation domain, BIR domain, NLRPs with an N-terminal Pyrin domain and NLRCs with an N-terminal CARD domain [16].

The ALR family

The ALR family includes AIM2 and IFI16, both of which structurally contain the C-terminal oligonucleotide DNA-binding HIN-200 domain and an N-terminal domain composed solely of PYD [22]. These domains facilitate the nonspecific recognition of DNA through electrostatic interactions, where positively charged consecutive oligonucleotide/oligosaccharide-binding residues in the HIN domain interacts with the negatively

charged sugar-phosphate backbone of double-stranded DNA (dsDNA). This electrostatic interaction enables the HIN domain to recognize aberrant endogenous or exogenous DNA structures [23]. Subsequently, the signal is relayed to the N-terminal PYD, which exhibits a pronounced tendency for self-oligomerization. Binding of dsDNA induces conformational changes in the HIN domain, exposing the PYD and initiating signal transduction [24]. The exposed PYD interacts with ASC, promoting oligomerization and recruiting caspase-1 via CARD-CARD interactions [25]. Unlike AIM2, the IFI16 protein can localize to both the nucleus and the cytoplasm. IFI16 contains two HIN-200 domains, which are separated by a linker region rich in serine, threonine, and proline residues [26]. In addition to its role in classical inflammasome activation, the PYD of IFI16 indirectly activates the stimulator of interferon genes (STING) pathway through oligomerization, leading to the induction of type I interferon production [26].

The pyrin

Pyrin, named after the Greek word for "fever", contains an N-terminal PYD, a B-box domain, a coiled-coil domain, and a C-terminal B30.2/SPRY domain [27]. The B30.2/SPRY domain in Pyrin detects alterations in the cytoskeleton and transmits danger signals, typically triggered by pathogen infections (Fig. 1B) [28]. The PYD interacts with ASC through signal transduction, participating in the activation of the classical inflammasome.

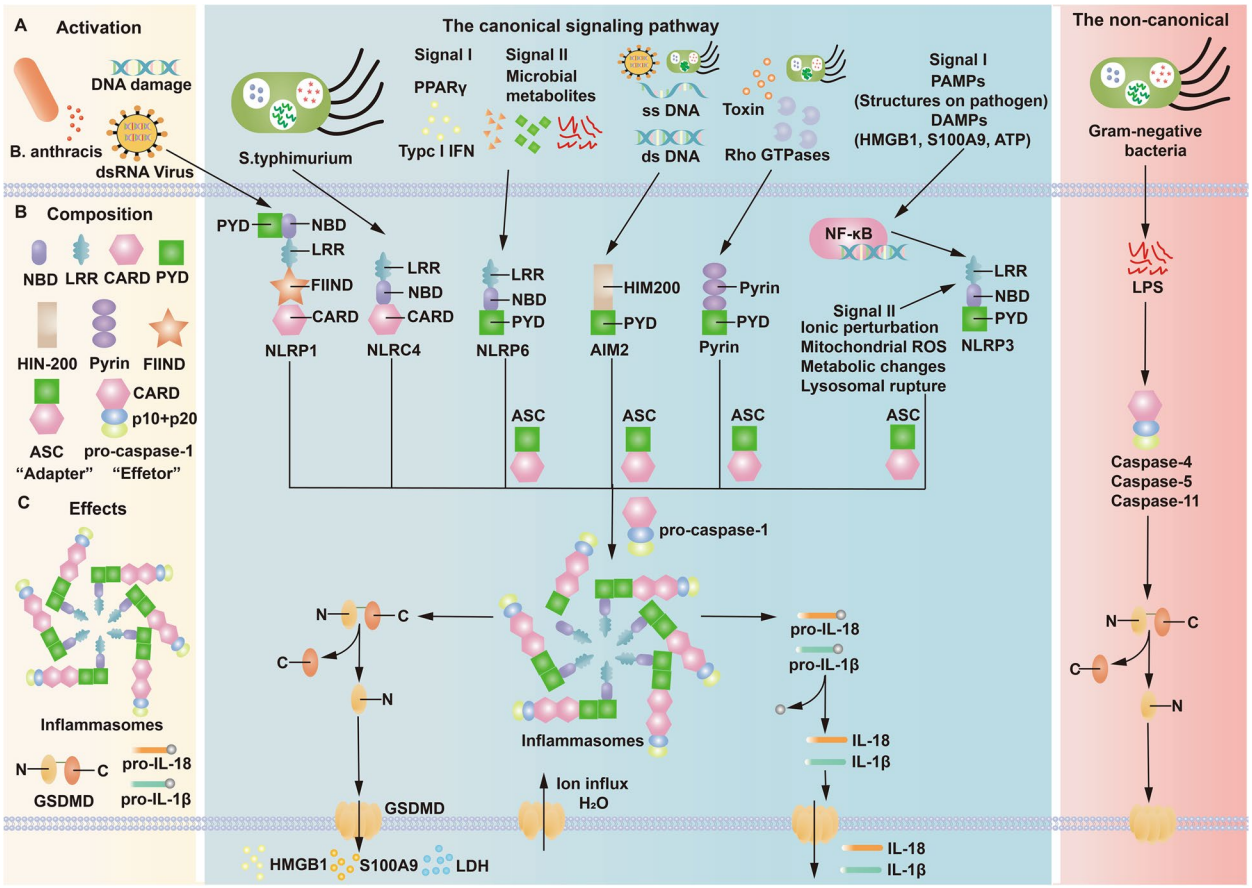

Fig. 1 Inflammasomes are multiprotein complexes composed of several domains with distinct functions. They are activated upon detecting various danger signals, such as pathogen toxins, nucleic acids, secretion systems, changes in cellular structures, metabolic alterations, ionic disturbances, and organelle damage. The PYD domain of inflammasomes interacts with the adaptor protein ASC, facilitating the assembly of the inflammasome complex. Subsequently, the CARD domain of ASC recruits pro-caspase-1 to form the complex. In the canonical signaling pathway, inflammasome activation results in the self-cleavage and activation of caspase-1. Activated caspase-1 then cleaves pro-IL-1β and pro-IL-18 into their mature, biologically active forms. Additionally, it cleaves GSDMD, generating its active N-terminal domain, which oligomerizes to form stable pores in the plasma membrane. This pore formation induces cell swelling and rupture, leading to inflammatory cell death and the release of intracellular substances such as IL-1β, IL-18, HMGB1, and LDH. In the non-canonical signaling pathway, LPS directly binds to the CARD domain of caspase-4/5/11, resulting in the cleavage of GSDMD. However, GSDMD requires NLRP3 activation to cleave pro-IL-1β and pro-IL-18

The remaining domains contribute to signal transmission and maintaining structural stability [27].

Activation of inflammasomes

The differentiation between priming and activating signals in inflammasomes minimizes redundancy, thereby effectively regulating the immune protective functions of these complexes and mitigating tissue damage under various conditions.

NLRP3, the most extensively studied inflammasome, is activated by a wide range of irritants and pathogens. Its activation requires a dual-signal mechanism to ensure stringent regulation. The first signal, priming, is elicited by both PAMPs and DAMPs. PAMPs encompass conserved structures found on pathogens, such as lipopolysaccharide (LPS) derived from gram-negative bacteria, components of cell walls and viral nucleic acids [29]. DAMPs are endogenous molecules released in response to cellular stress or injury within the host. These include high mobility group box 1 (HMGB1), S100 calcium-binding protein, heat shock proteins, ATP, and uric acid [30]. Both PAMPs and DAMPs are recognized by cell surface receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), including NOD1 and NOD2 as well as cytokine receptors like the IL-1 receptor and tumor necrosis factor-alpha receptor (TNF-α). The activation of these receptors triggers signaling molecules myeloid differentiation primary response 88 (MyD88), which subsequently lead to the transcriptional activation of NF-κB and the upregulation of NLRP3 [31, 32]. The priming step is regulated by both the transcriptional control of inflammasome components, which modulates the quantity of inflammasome subunits, and post-translational modifications, such as ubiquitination, phosphorylation, and succinylation [33]. Subsequently, the activation signal directly induces the assembly of NLRP3 oligomers, ASC, and pro-caspase-1 into the inflammasome protein complex. This signal is associated with various cellular disturbances, including alterations in ion channels, such as potassium ion (K^+) efflux and calcium ion (Ca^{2+}) influx, as well as the generation of reactive oxygen species (ROS) resulting from oxidative stress, mitochondrial dysfunction, lysosomal rupture, and metabolic changes [34]. Collectively, these closely related, multi-layered signals regulate and determine NLRP3 activation.

Anthrax lethal toxin (LeTx) enters the cytoplasm by oligomerizing protective antigen on the host cell membrane. The lethal toxin protease subunit subsequently cleaves the N-terminus of murine NLRP1, thereby exposing its CARD domain and activating the NLRP1 inflammasome [35]. Similar effects are observed with viral proteases that cleave human NLRP1 [36]. Additionally, viral proteases [37], phosphorylation modifications due to viral infection [38], and intracellular DNA damage [39] can alter the conformation of NLRP1. NLRP6 is primarily expressed in the intestines, lungs, and liver, and it plays a crucial role in the host's defense against microbial infections. Similarly, full activation of the NLRP6 inflammasome requires both priming and activation signals. Priming signals encompass microbial signals (interferon signaling) [40] and metabolic pathways (peroxisome proliferator-activated receptor gamma, PPAR-γ) [41], which promote the transcription and expression of NLRP6 [42]. Once NLRP6 has accumulated sufficiently, activation signals, including microbe-associated molecular patterns (MAMPs), become effective. These MAMPs consist of microbial components and metabolic products, such as lipoteichoic acid (LTA) from gram-positive bacteria [43], LPS and ATP from gram-negative bacteria [44], as well as certain microbial metabolites like taurine, histamine, and spermidine [45]. Additionally, NLRC4 primarily responds to bacterial flagellin and the type III or type IV secretion systems (T3SS or T4SS) of gram-negative bacteria [46]. AIM2 and IFI16 primarily recognize intracellular dsDNA through electrostatic interactions mediated by HIN-200 domain [47]. AIM2 is predominantly activated by pathogen-derived dsDNA, thereby protecting the host from microbial invasion, a phenomenon frequently observed during viral infections [48]. In the non-classical activation pathway, low concentrations of bacterial DNA stimulate type I interferon production via the cyclic GMP-AMP synthase (cGAS) pathway, which serves as a sensor for cytosolic dsDNA. This signaling cascade results in the transcription of interferon-inducible genes, including GTPases, which promote bacteriolysis and facilitate the release of bacterial DNA into the cytoplasm. The released bacterial DNA is subsequently detected and recognized by the AIM2 inflammasome, leading to its activation [49, 50]. IFI16 senses both dsDNA and ssDNA, recruiting the endoplasmic reticulum protein STING. This interaction subsequently activates interferon-gamma (INF-γ) and pro-inflammatory cytokines through the TBK1-IRF3 and NF-κB signaling pathways, thereby exerting significant antiviral effects (Fig. 1A) [51].

Effects of inflammasomes

Despite variations in composition and signaling pathways, inflammasomes exhibit structural similarities that align with their extensive functional overlap. Inflammasomes primarily recruit and activate pro-caspase-1, which then promotes the maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18, and induces cell death through pyroptosis, apoptosis, and PANoptosis [52]. Specifically, inflammasomes begin to assemble upon receiving priming and activation signals, with ASC functioning as an "adapter" or "bridge". ASC contains

PYD and CARD domains, which facilitate interactions through homotypic PYD–PYD and CARD–CARD associations with pro-caspase-1 [53]. Notably, ASC amplifies the inflammasome signaling [54] and is essential for the assembly of most characterized inflammasomes including NLRP3, AIM2, IFI16, and Pyrin. Conversely, NLRP1 and NLRC4, endowed with inherent CARD domains, can interact autonomously with pro-caspase-1 independent of ASC [55].

The assembly of this complex facilitates the proteolytic self-cleavage of pro-caspase-1 at Gly315, resulting in the generation of the active caspase-1 subunits, referred to as p20 and p10 subunits [56]. Once activated, caspase-1 cleaves the downstream effector molecules pro-IL-1β and pro-IL-18, thereby releasing their active forms (IL-1β and IL-18) extracellularly, which initiate a robust inflammatory response to combat the invasion of exogenous pathogens [57]. Additionally, caspase proteins activated by inflammasomes trigger pyroptosis, a distinct programmed cell death pathway characterized by rapid plasma membrane rupture due to the cleavage of pore-forming effector proteins from the gasdermin family [58, 59]. Pyroptosis is further classified into the caspase-1-mediated canonical signaling pathway and the caspase-4/5/11-mediated non-canonical signaling pathway. In the classical pathway, the gasdermin protein, typically GSDMD, is cleaved by caspase-1 at a flexible linker, which releases the self-inhibitory N-terminal pore-forming domain and the C-terminal repressor domain [60]. The N-terminus of specific proteins can bind to particular lipids, such as phosphatidylinositol found in eukaryotic cell membranes and cardiolipin present in prokaryotic or mitochondrial membranes. In certain instances, these interactions may result in oligomerization and the formation of pore structures within the membrane [61].

The influx and efflux of K^+, sodium ions (Na^+), and water through stable pores initiate various GSDMD-dependent processes, including cell swelling, rapid plasma membrane rupture, and the modulation of pro-inflammatory components such as the cytokines IL-1β and IL-18, intracellular components (antigens or DAMPs), and intracellular hydrolases [62]. Pyroptosis leads to rapid cell failure and creates a potent inflammatory environment, which aids in the defense against infection or malignant transformation. The non-canonical signaling pathway operates independently of inflammasome signaling cascades to activate caspases. Instead, the CARD domains of caspase-4/5/11 directly detect lipopolysaccharides (LPS) within host cells, facilitating the cleavage of GSDMD [63]. Although these caspases can induce pyroptosis, they cannot directly cleave pro-IL-1β or pro-IL-18, necessitating the synergistic activation of canonical inflammasomes to amplify the inflammatory response [64]. Furthermore, there exists a complex interplay between inflammasomes and apoptosis, which includes the cell fate switch among apoptosis, necroptosis, and pyroptosis, as well as the activation or inhibition of inflammasomes by apoptotic pathways [65, 66]. This interplay may also encompass PANoptosis, a composite form of cell death that integrates features from multiple death pathways [67]. A comprehensive discussion of this area exceeds the scope of this study. These multilayered regulatory issues will not be explored in detail here (Fig. 1C).

Given the diversity of inflammasomes and their complex activation and regulatory mechanisms, it is of great importance to delineate the boundaries between moderate activation and excessive activation. The boundaries are dynamically continuous and closely related to the outcomes following activation [68]. Firstly, different activation products influence the nature of inflammasome activation. Generally, PAMPs are regarded as lower-risk and more defensible threats, while cytoplasmic DAMPs can trigger cell death and pose a higher risk [69]. For example, inflammasomes can swiftly detect exogenous bacterial or viral infections and subsequently secrete IL-1β and IL-18 to alert neighboring cells, thereby limiting the spread of infection. Concurrently, inflammasomes can induce pyroptosis, releasing pathogens and destroying their replication niche, which enables neutrophils to rapidly engulf and eliminate the pathogens [70]. This transient and rapidly diminishing immune defense is often advantageous to the host, as it not only clears harmful stimuli but also initiates the healing process to repair tissue damage. However, the relationship between host defense and uncontrolled inflammation is intricate and multifaceted [71]. Excessive activation of inflammasomes can lead to acute inflammatory damage or be exploited by pathogens for immune evasion, but such occurrences are relatively rare [72]. In contrast, the safety window for inflammasome activation in response to DAMPs is narrower, and even a slight imbalance can result in sustained pathological damage. This phenomenon has been found to be closely associated with modern lifestyle factors, including smoking, obesity, and psychological stress, all of which are directly or indirectly linked to the production of DAMPs. These factors may be one of the causes behind the development of various chronic diseases, such as type 2 diabetes and atherosclerosis [69]. Additionally, the activation of inflammasomes in various diseases demonstrates a dual-edged sword effect [73]. On one hand, inflammasome activation facilitates the clearance of pathogens and mitigates infection-induced damage. On the other hand, in autoimmune or metabolic diseases, chronic inflammasome activation may exacerbate disease progression, resulting in fibrosis and sclerosis [70].

In tumors characterized by high heterogeneity, these effects are particularly pronounced. It enhances antitumor immunity and slows tumor progression by activating pyroptosis and regulating the activity of natural killer (NK) cells and T cells. However, IL-1β and IL-18 can promote tumor signaling, thereby inducing tumor proliferation, invasion, and angiogenesis [74, 75]. The dual nature of this property is significantly influenced by the interplay of genetic background, tumor microenvironment, tissue type, and downstream molecules. Currently, the boundary between moderate activation and excessive activation remains ambiguous. Research has indicated that epigenetic regulation such as DNA methylation, histone modifications and post-translational modifications, may offer multi-layered insights into the intricate regulation of inflammasomes [76]. Nevertheless, critical issues such as the levels, spatial ranges, intensities, and synergies of inflammatory factors require further investigation. This is particularly important for conducting layered research utilizing cell fate maps, in vivo imaging technology, and organoid models to comprehensively analyze the regulatory network of the inflammasomes.

Role of inflammasomes in hematopoietic stem cell transplantation

Participation in mobilization, homing, and engraftment

Mobilization and homing are critical yet contrasting stages essential for successful HPSCs migration, particularly in the contexts of bone marrow adhesion and chemotaxis [77]. Previous studies have underscored the paramount importance of inflammasomes, especially NLRP3, in maintaining the delicate equilibrium between these processes.

Mobilization can be divided into three distinct phases: initiation, amplification, and effector. The initiation phase is driven by various pro-inflammatory mediators that accumulate through positive feedback mechanisms. Granulocyte-colony stimulating factor (G-CSF) and AMD3100, which are complementary mobilizing agents, are commonly employed to stimulate the production of DAMPs that induce sterile inflammation. These DAMPs activate innate immune cells, primarily neutrophils and monocytes in the microenvironment. Upon tissue damage, these cells release additional DAMPs, such as ATP and ROS [78]. Prior to this cascade, innate immune cells have already recapitulated the initial signal of the NLRP3 inflammasome through the gut-derived LPS from gram-negative bacteria by binding to TLR4 [79, 80]. Subsequently, ATP emerges as the most critical second signal, released extracellularly through the pannexin-1 membrane channel, which serves as an essential transmembrane pathway connecting the intracellular and extracellular environments [81]. Studies showed that inhibition of the pannexin-1 channel by 10Panx impaired the mobilization of HSPCs and negatively affected the engraftment of white blood cells and platelets [82]. In the extracellular space, extracellular ATP (eATP) serves as an activating ligand for several ionotropic P2X and metabotropic P2Y purinergic receptors [83, 84]. Specifically, eATP interacts with purinergic receptors P2X7, P2X4, and P2X1, which are highly expressed in HSPCs, facilitating Ca^{2+} influx as an activation signal for NLRP3 [85]. Notably, eATP is also processed by cell surface ectonucleotidases CD39 and CD73 into its metabolites: ADP and AMP (produced by CD39), and adenosine (produced by CD73) [86]. Conversely, adenosine exerts an inhibitory effect during mobilization through heme oxygenase 1 (HO-1) [87] and inducible nitric oxide synthase (iNOS) [88], suppressing NLRP3 activation and reducing adhesion capacity, ultimately inhibiting the migration of HSPCs [89]. The release of mature and biologically active IL-1β and IL-18 is contingent upon the inflammasome-mediated activation of caspase-1, which facilitates communication among innate immune cells via autocrine and paracrine pathways. This process further stimulates the release of additional DAMPs, such as HMGB1 and S100A9 [90]. It is plausible that NLRP1, AIM2, and NLRP12 inflammasomes may also exert similar effects in response to eATP and other DAMPs; however, the specific mechanisms underlying these interactions remain to be elucidated [91]. Moreover, supplementation with IL-1β or IL-18 demonstrated limited mobilization in NLRP3-deficient and caspase-1-deficient models, a deficiency that could be corrected by the injection of a DAMP mixture (eATP + HMGB1 + S100A9) [92]. These factors appeared to establish a positive feedback loop that enhances sustained ATP release and NLRP3 activation, ultimately leading to optimal mobilization outcomes (Fig. 2A).

During the amplification phase, these DAMPs activate the complement cascade (ComC) through three main pathways: C1q (classical pathway), mannose-binding lectin (MBL) and Factor B (via the alternative pathway) [93]. Notably, DAMPs primarily exert their effects by activating the MBL pathway [94]. The DAMPs-MBL complex subsequently triggers mannose-binding lectin-associated serine proteases (MASPs), which cleave and activate complement 3 (C3) and prothrombin, thereby inducing the activation of ComC and the coagulation cascade (CoaC) [93, 95]. Furthermore, the study found that Factor B deficiency inhibited NLRP3 and the activation of the alternative pathway, leading to poor cell homing and engraftment [96]. Furthermore, the study found that Factor B deficiency inhibited NLRP3 and the activation of the alternative pathway, leading to poor cell homing and engraftment [92]. These pathways converge in a shared

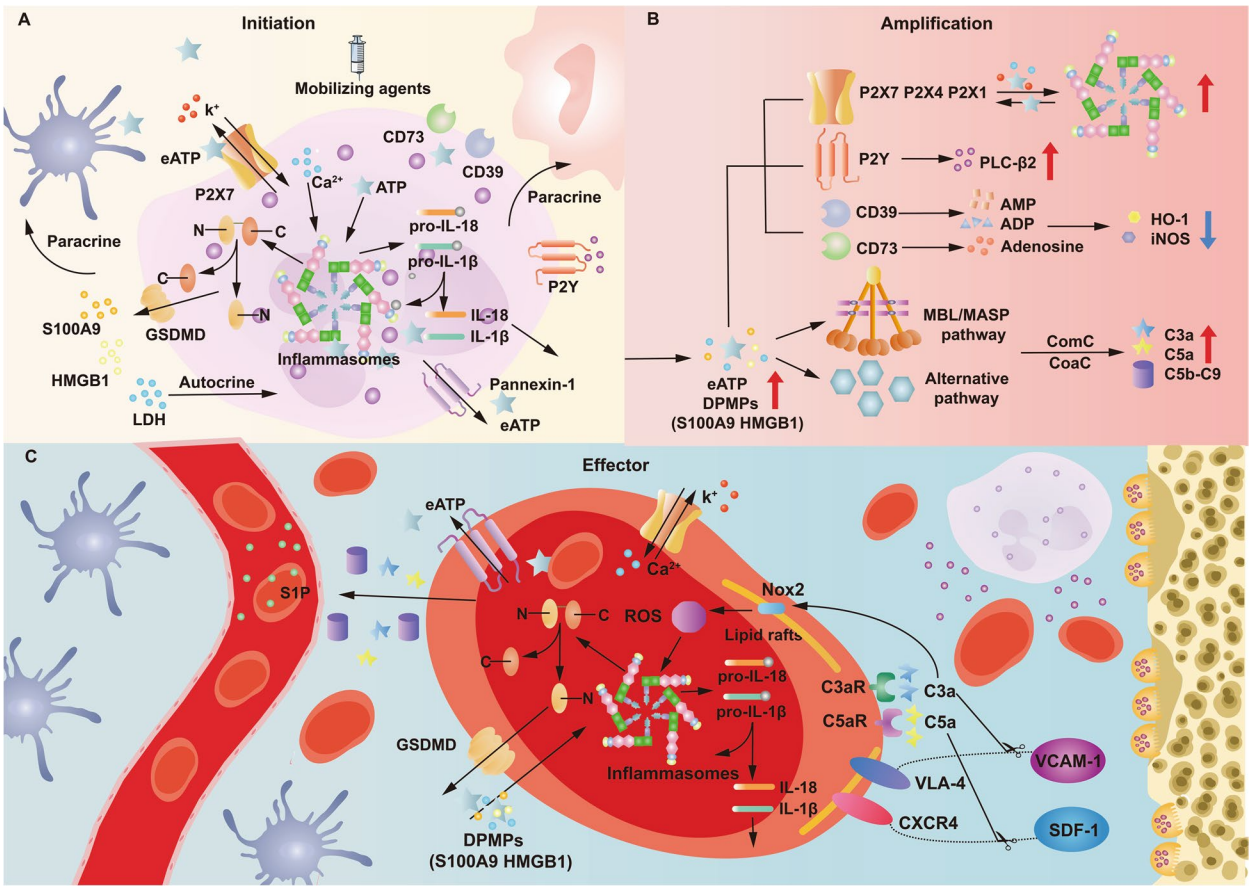

Fig. 2 Role of inflammasomes in the three stages of HSCT Mobilization. **A** In the initiation phase, mobilizing agents stimulate the transmembrane protein pannexin-1 in innate immune cells, leading to the release of eATP. eATP subsequently binds to P2X ion channels (P2X1, P2X4, P2X7), causing an influx of K^+ and an efflux of Ca^{2+}, which triggers the activation of inflammasomes and caspase-1. This process also results in the release of various DAMPs, such as IL-1β, IL-18, HMGB1, and S100A9 through GSDMD, thereby creating a positive feedback loop that amplifies inflammation. **B** During the amplification phase, DAMPs modulate the MBL/MASPs pathway and the alternative complement pathway, triggering the activation of the ComC and CoaC. This results in the production of C3a, C5a, desArgC5a, and the C5b-C9 complex. At this stage, eATP is converted into adenosine by CD39 and CD73, which inhibits mobilization by upregulating HO-1 and iNOS. Pathways promoting mobilization are indicated by red arrows, while the inhibitory pathways associated with adenosine are marked by blue arrows. **C** In the effector phase, C5a initiates NLRP3 activation in HSPCs, further escalating the inflammatory response. Additionally, these complement molecules enhance granulocyte degranulation, leading to the secretion of hydrolases that weaken the CXCR4-SDF-1 and VLA-4-VCAM-1 axis. S1P is released by the MAC to chemotax HSPCs into peripheral blood vessels. Moreover, lipid rafts are stimulated by increased membrane assembly via the Nox2/ROS/NLRP3 pathway. This process facilitates the integration of CXCR4 and VLA-4 on the plasma membrane, enhancing HSPCs' sensitivity to environmental signals, thereby promoting their mobilization, homing, and engraftment

terminal response, resulting in the formation of C5a, C3a, and C5b-9 (membrane attack complex, MAC) as potent inflammatory effector molecules, which connect complement, coagulation, and fibrinolysis proteolytic cascades [97, 98] (Fig. 2B).

In the effector phase, the migration of HSPCs is dependent on ligand-receptor interactions between stromal cell-derived factor 1 (SDF-1) and its receptor, C-X-C chemokine receptor type 4 (CXCR4) [99], as well as very late antigen-4 (VLA-4) and its receptor vascular cell adhesion molecule 1 (VCAM-1) [100, 101]. Upon binding to their respective receptors, these agents activate HSPCs and enhance their proliferation. NLRP3 was activated by C5a, desArgC5a, and MAC, maintaining a sterile inflammatory state in the bone marrow microenvironment. These fragments and anaphylatoxins facilitate granulocyte degranulation, leading to the release of hydrolases or lipases, thereby compromising the bone marrow niche associated with the SDF-1/CXCR4 and VLA-4-VCAM-1 axis. Simultaneously, innate immune cells migrate between the bone marrow endothelium and the periphery in response to chemotactic signals [102, 103]. Additionally, a sphingosine-1 phosphate (S1P) gradient transition between bone marrow and peripheral

blood induces HSPCs to cross the vascular endothelium and enter peripheral blood. S1P is released by red blood cells upon MAC induction in peripheral blood to facilitate optimal HSPC mobilization [104]. C3a maintains the retention of HSPCs rather than mobilization by enhancing their responsiveness to SDF-1 in the bone marrow to prevent an uncontrolled release of HSPCs [105].

Lipid rafts, which are membrane microdomains enriched in glycosphingolipids and protein receptors, enhance the efficiency of signal transduction and prolong the surface residency of receptors such as CXCR4 and VLA-4. This augmentation increases the sensitivity and responsiveness of HSPCs to microenvironmental signals [106]. The Nox2-ROS-NLRP3 inflammasome axis played a crucial role in regulating lipid raft assembly and the expression of lipid-synthesizing enzymes [97, 107]. eATP and inflammasomes facilitated the incorporation of the homing receptor CXCR4 into lipid rafts, thereby strengthening the response to the SDF-1 gradient and promoting the migration and engraftment of HSPCs (Fig. 2C) [108].

Disruption of hematopoiesis and post-transplant hematopoietic reconstruction

Hematopoietic reconstruction is a meticulously orchestrated process wherein transplanted HSPCs engraft, proliferate, and differentiate into various blood cells within the recipients. Successful HSC engraftment is characterized by the clinical recovery of myeloid (neutrophils), erythroid cells and megakaryocyte (platelet) lineages. Recovery standards include meeting hematologic criteria for engraftment and confirming that the hematopoietic cells originate from the donor, a process that typically spans several weeks [109]. In this context, we elucidate the impact of inflammasomes on hematopoiesis and post-transplant hematopoietic reconstruction using the model of "soil (bone marrow microenvironment), environment (external interventions), and seed (HSPCs)" [110].

The bone marrow microenvironment comprises various stromal cells, extracellular matrix components, reticular cells, other connective tissues, and multiple hematopoietic regulatory factors [111]. Bone marrow mesenchymal stem cells (BMSCs) function as self-renewing precursor cells of the microenvironment, and are capable of differentiating into diverse stromal cells. They play dual roles in signal transduction and transcriptional regulation supporting and repairing the microenvironment [112]. Research in NLRP1 knockout mouse transplant models revealed that the multi-lineage differentiation capacity of BMSCs was impaired, with reduced lipid droplets and osteogenic mineralization areas observed microscopically. Meanwhile, the reconstruction of HSPCs was found to be enhanced, particularly within erythroid lineages [113]. Adipogenesis adversely impacts the hematopoietic niche by compressing the hematopoietic space and suppressing hematopoietic signals [114]. While osteogenesis promotes the growth of hematopoietic cells, it may also lead to excessive differentiation, thereby inhibiting long-term hematopoiesis [112]. Another study revealed that Caspase-3 and NLRP3 share similarities in regulating the balance of BMSCs in hematopoiesis. Deficiencies in either Caspase-3 or NLRP3 result in myeloid hematopoiesis characterized by the expansion of myeloid cells ($CD11b^{+}Gr\text{-}1^{+}$ cells), ultimately distorting the normal composition of hematopoietic cells. This phenomenon was associated with a diminished secretion of hematopoietic maintenance factors, such as stem cell factor (SCF) and chemokine C–X–C motif chemokine 12 (CXCL12), which propelled HSPCs towards myeloid differentiation from their quiescent state. Interestingly, Caspase-3-deficient models indirectly influenced the hematopoietic microenvironment by reducing NLRP3 expression with dysregulated release of SCF and CXCL12, rather than directly interfering inflammatory pathways [115]. Smoking has been identified as a detrimental factor in hematopoiesis. Cigarette extracts induced ROS production in MSCs, activating the NLRP3 pathway. Concurrently, gene expression profiles were modified, resulting in the upregulation of inflammation and oxidative stress-related genes and downregulation of genes supportive of hematopoiesis. Collectively, these factors compromised hematopoietic support, as evidenced by the restricted expansion of $CD34^{+}CD90^{+}$ HSPCs and their diminished multipotency. This detrimental effect was alleviated by the application of ROS and NLRP3 inhibitors, which restored hematopoietic cell engraftment [116]. In the bone marrow microenvironment, a class of substances known as neuropeptides, including substance P (SP) and neurokinin A (NK-A), participate in the "neuro-immune-hematopoietic" communication network [117]. These neuropeptides exhibit antagonistic effects, influencing the expression of HMGB1 and thereby regulating hematopoietic balance. Specifically, SP promoted hematopoiesis by inhibiting HMGB1, while NK-A exerted an opposing effect. HMGB1 had dual roles in hematopoiesis, as it regulated the proliferation of hematopoietic progenitor cells while also preventing excessive proliferation and depletion of HSCs, thus maintaining a balance in long-term hematopoietic and immune functions. Furthermore, the effects of HMGB1 appeared to be lineage-dependent; its blockade enhances T cell subsets and NK cells while simultaneously reducing B cell differentiation [118].

HSPCs, as the foundational elements of hematopoiesis, possess the ability for self-renewal and exhibit

multi-directional differentiation potential [119]. Inflammasomes function as regulators of HSPC quantity and differentiation pathways. In NLRP1 knockout mice, a reduction in the expression of pro-inflammatory cytokines IL-18 and IL-1β was noted, alongside decreased inflammatory infiltration in the bone marrow and an increase in hematopoietic cells, particularly red blood cells and platelets. Furthermore, the secretion of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin was elevated, thereby further promoting HSPC proliferation, differentiation, and engraftment [113]. The knockout or inhibition of T-cell protein tyrosine phosphatase (TC-PTP), a widely expressed molecule across various hematopoietic lineages, enhances HSC numbers in both the bone marrow and peripheral blood by modulating the expression of immune factors through dephosphorylation [120]. Notably, TC-PTP deficiency activated the IL-18/IL-18 bp signaling axis, which triggered the production of IL-12 and IFN-γ, thereby promoting rapid expansion of HSPCs [121]. However, another study indicated that elevated IL-18 levels were associated with an increased risk of non-relapse mortality following transplantation [122]. In terms of differentiation potential, inflammasomes initiated the effector protein caspase-1, which cleaved and degraded GATA binding protein 1 (GATA-1), thereby impeding the development of erythroid progenitors and ultimately reducing erythropoiesis. This suggests that artificially regulating inflammasome activity may present a therapeutic avenue for addressing rare hematopoietic imbalance disorders [123]. Similarly, Caspase-3/7/8 exhibited comparable phenomena in this context [124]. NLRP1 also regulated erythroid-myeloid lineage decisions in HSPCs through the phosphorylation and activation of the ZAKα/P38 axis, with inhibition of NLRP1 promoting erythroid differentiation [125]. Moreover, inflammasomes regulated cell fate through metabolic pathways that are essential for the formation of embryonic HSPCs [126]. Glucose metabolism in macrophages produced ROS and hypoxia-inducible factor 1-alpha (HIF1α), which initiated inflammasome activation and sustained IL-1β production. Stimulation of the inflammasome increased the number of multilineage hematopoietic colony-forming units and T-cell progenitors in zebrafish embryos. Additionally, NLRP3 suppressed erythroid differentiation during the embryonic stage while promoting a bias towards lymphoid and myeloid lineages, effectively counteracting embryonic hypoxia [127].

External factors, inclusive of conditioning, immune suppression, infections, and inflammation, primarily exert indirect effects by modulating of HSPCs and the bone marrow microenvironment. Conditioning regimes can deteriorate the bone marrow microenvironment, concomitantly increasing inflammatory infiltration. Following total body irradiation (TBI) preconditioning, there was an upregulation of various inflammasome components, containing NLRP1 and NLRP6, with IL-1β and IL-18 functioning as key mediators of inflammatory damage. Caspase-1 inhibitors demonstrated efficacy in reducing inflammation and promoting the reconstruction of megakaryocytes and other hematopoietic cells [128]. AIM2 detected radiation-induced dsDNA breaks, subsequently recruited ASC domains, and induced caspase-1-dependent pyroptosis in response to ionizing radiation-induced damage [129]. Similarly, ionizing radiation activated the NLRP3/caspase-1 axis in macrophages, resulting in the release of lactate dehydrogenase (LDH) and inflammatory mediators from membrane rupture [130]. NLRP12 played a beneficial role independent of inflammasomes by suppressing TNF and NF-κB signaling during radiation exposure and heat-induced emergency hematopoiesis. This suppression diminished apoptosis in hematopoietic progenitor cells, bolstered the reconstruction of myeloid hematopoietic cells and peripheral immune function, mitigating lung dysfunction resulting from bacterial infections. Throughout this process, the key components of the inflammasome (caspase-1, ASC, IL-1R) remained unchanged [131]. GSDME, an alternative executor of pyroptosis, mediated HSPC swelling, blebbing, and membrane permeabilization in the presence of cisplatin. GSDME deficiency also heightened sensitivity to apoptosis. These findings underscored the role of GSDME in influencing the hematopoietic function of lymphoid and myeloid cells by regulating the balance between apoptosis and pyroptosis under adverse conditions [132].

The dual role of inflammasomes in GVHD

GVHD is the main complication and a leading contributor of non-relapse and transplant-related mortality in allogeneic HSCT, with an incidence of approximately 50% [133]. High-dose corticosteroids, which serve as the first-line therapy for aGVHD, are associated with limited efficacy and considerable toxicity, potentially affecting post-transplant relapse rates and immune reconstitution. Notably, around half of patients with aGVHD demonstrate a lack of response to steroid therapy, leading to poor outcomes and underscoring the urgent need for novel biomarkers and therapeutic strategies [134]. The pathophysiology of aGVHD can be delineated into three stages: the initiation phase, T-cell activation, and effector stages [135].

The initial stage involves tissue damage induced by conditioning regimes, which acts as a catalyst for widespread tissue damage by releasing DAMPs, PAMPs, numerous inflammatory and chemotactic factors [136]. These

signals upregulate the expression of major histocompatibility complex (MHC) antigens, adhesion receptors, and other molecules on host antigen-presenting cells (APCs), thereby amplifying the responses of alloreactive donor T cells. Additionally, these danger signals can enter the circulatory system, resulting in systemic GVHD [137]. Subsequently, T cells expressing tissue-specific adhesion molecules and chemotactic receptors migrate towards and infiltrate targeted organs. The second stage is initiated after activation of donor T cells by host APCs [138]. In response to various cytokines and environmental factors, $CD4^+$ T cells can differentiate into specialized effector subtypes, including T helper types 1/2/17, and regulatory T cells [139]. Th1 cells enhance the function of cytotoxic T cells by secreting IFN-γ and TNF-α, and they are recognized as the primary subtype promoting GVHD. Th17 cells, which secrete IL-17, IL-21, and IL-22, primarily target extracellular pathogens and contribute to the tissue damage associated with GVHD. In contrast, Th2 cells regulate humoral immune responses through the secretion of IL-4, IL-5, and IL-13, typically playing a protective role that mitigates GVHD. Overall, Th2 and regulatory T cells (Tregs) are associated with the attenuation of GVHD, while Th1 and Th17 cells are linked to the acceleration of its development and progression [140]. Altering the Th cell landscape helps the immune system prevent inappropriate activation. Cytotoxic effects and inflammatory cytokines drive the progression to the third stage of GVHD. Effector cells, including $CD4^+$ T cells, $CD8^+$ T cells, and NK cells, can exhibit cytotoxic effects through Fas-FasL, perforin/granzyme, and TNF pathways [141]. During this stage, various types of Th cells also release inflammatory cytokines, further contributing to the disease process.

Initiation

PAMPs, DAMPs and cytokines activate APCs, releasing additional alarm signals that sustain and amplify GVHD [137]. Koehn et al. [142] demonstrated that ATP release induced by conditioning regimens activated NLRP3 through binding to the P2X7 receptor. The subsequent release of the inflammatory cytokine IL-1β led to dysfunction of myeloid-derived suppressor cells (MDSCs), compromising their anti-inflammatory efficacy in the microenvironment. The study also revealed that, compared to localized ATP control or selective inhibition of P2X7 receptor and NLRP3 activity (via gene knockout or co-infusion of regulatory T cells to suppress MDSC inflammasome activity), the use of NLRP3 small molecule inhibitors combined with MDSC infusion in mice did not yield the anticipated results. This outcome may be attributed to the systemic inhibition of NLRP3 inflammasomes affecting other immune functions. Another study indicated that NLRP3 activation established a highly inflammatory environment, whereas NLRP3 knockout reduced levels of IL-1β and TNF-α, decreased ATP release, and lowered P2X7 receptor expression [143]. Given the significance of P2X7 in HSCT, 16 SNPs in the P2X7 gene were analyzed in DNA samples from 453 allo-HSCT donors and recipients, revealing correlations between these polymorphisms and clinical outcomes. The study identified that two loss-of-function P2X7 SNPs (Ile568Asn and Glu496Ala) were associated with higher aGVHD incidence and lower aGVHD risk, respectively, thus contributing to the development of personalized clinical prevention strategies [144]. After conditioning with TBI, busulfan/cyclophosphamide (BU/CY), or fludarabine/cyclophosphamide (FLU/CY) regimens, significantly elevated uric acid levels released by damaged cells were observed in the peritoneal cavity, which induced NLRP3 activation and IL-1β production. IL-1β further amplified inflammatory damage and promoted Th17 cell differentiation to exacerbate GVHD. In the early stages, uricase-mediated degradation of uric acid mitigated NLRP3 activation and the inflammatory response [145]. S100A8, S100A7, and S100A9 have been pinpointed as inflammasome-activating molecules, specifically expressed in the saliva of GVHD patients. These proteins might act as endogenous TLR4 ligands, enhancing inflammasome activation while increasing neutrophil binding affinity and leukocyte extravasation [146]. At this stage, inflammasomes complete the establishment of an inflammatory and damaging environment, facilitating the activation and migration of APCs to lymph nodes, where they further activate donor T cells (Fig. 3A).

Activation

The highly inflammatory environment established during the initiation phase lays foundation for subsequent T-cell activation. Host APCs present processed antigen fragments on their surfaces via HLA molecules. When these fragments interact with the T-cell receptor (TCR) domains of donor naive T cells, they rapidly stimulate T-cell proliferation, polarization, and the release of additional cytokines [147]. Inflammasomes play a role in modulating the behavior of APCs. For instance, dendritic cells (DCs) showed potently impaired migration towards inflammatory environments when lacking microRNA-155 in the presence of LPS and ATP chemotaxis. This impairment reduced inflammasome activation, subsequently inhibiting inflammatory events such as ERK, Caspase-1, and IL-1β activation, thereby mitigating the pathological manifestations of GVHD [148]. At this stage, inflammasomes were primarily involved in the differentiation of activated T cells and the subsequent propagation of inflammation. Caspase-11 directly

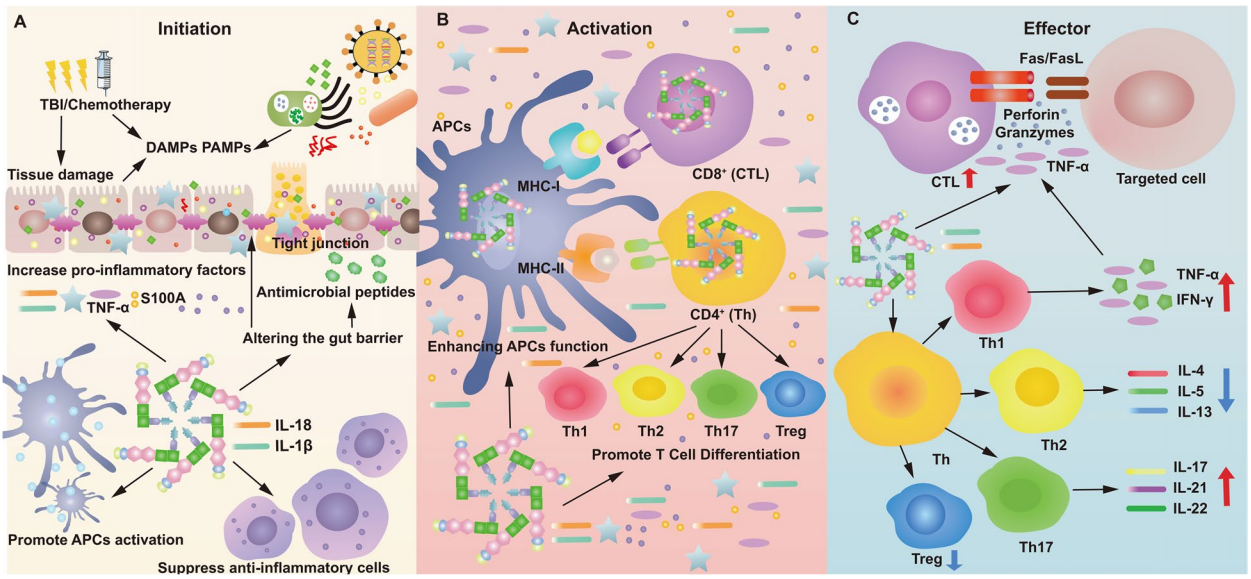

Fig. 3 Correlation between inflammasomes and HSCT. **A** Initially, conditioning regimens lead to extensive tissue damage throughout the body, triggering substantial PAMPs and DAMPs. These molecules activate inflammasomes in APCs and other cell types, amplifying inflammatory signals by enhancing the function of APCs. Additionally, they suppress anti-inflammatory cells and release further DAMPs. Inflammasomes also impact the structural integrity of intestinal cells and regulate the secretion of antimicrobial peptides. **B** In the second phase, donor T cells are activated after interacting with APCs. Inflammasomes affect the migration and antigen-presenting abilities of APCs. They also regulate T cell responses by promoting the maturation of $CD8^+$ T cells and driving $CD4^+$ T cells towards a pro-inflammatory phenotype, accelerating the progression of GVHD. **C** During the third phase, effector cells execute their functions through various molecular mechanisms. $CD8^+$ T cells induce cell damage via Fas-Fas ligand (FasL), perforin/granzyme, and TNF pathways. The cytotoxic effect of $CD8^+$ T cells is further enhanced by inflammasomes. Moreover, inflammasomes influence the proliferation and differentiation of $CD4^+$ T cells and regulate the secretion of pro-inflammatory cytokines, contributing to the development of GVHD

bound to LPS released by microbes, triggering a non-canonical pyroptosis pathway, leading to cell rupture and the release of pro-inflammatory cytokine IL-1α. This cytokine recruited neutrophils and amplified T-cell proliferation. The polarization of Th1 and Th17 cells, along with the production of IFN-γ were also associated with Caspase-11 activation, collectively accelerating the inflammatory response [149]. Elevated levels of HMGB1 have been detected in the serum of patients with aGVHD post-transplant [150]. HMGB1 reduced DNA methylation of the signal transducer and activator of transcription 3 (STAT3) in $CD4^+$ T cells to increase STAT3 mRNA levels in aGVHD patients. This process promoted the induction of promoting Th17 lymphocyte induction and inhibited Treg cell differentiation [151]. The choline metabolite trimethylamine N-oxide (TMAO) activated the NLRP3 inflammasome through initiation signals (NF-κB) and activation signals (mitochondrial ROS), promoting M1 macrophage polarization. These macrophages exhibited higher levels of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) and enhanced antigen-presenting capacity, further driving Th1 and Th17 cell polarization, culminating in intensified inflammatory responses and tissue damage. The NLRP3 inhibitor CY-09 significantly attenuated this phenomenon [152]. Furthermore, $CD4^+$ and $CD8^+$ T cells exhibiting elevated levels of active caspase-1 demonstrated pronounced inflammatory transcriptional characteristics and a metabolic phenotype resembling that of myeloid immune cells. This phenotype was marked by the upregulation of pro-inflammatory cytokines and a metabolic shift from oxidative phosphorylation to aerobic glycolysis. Such metabolic reprogramming typically resulted in enhanced metabolic activation, similar to what was in tumor cells, to meet increased energy demands [153]. During this process, these cells also contributed to mitochondrial dysfunction and the release of ROS and mitochondrial DNA, which further activated inflammasomes and intensified the vicious cycle of inflammation (Fig. 3B) [154].

Effector

In the third stage, the ongoing recruitment of both innate and adaptive immune cells, coupled with cytokine stimulation, prompts T cells to exert their effects. The ASC protein, a component of the inflammasomes, serves as a crucial link between the "sensor" and caspase-1 [53]. Cheong et al. [155] have demonstrated that ASC harbored substantial therapeutic potential in GVHD,

independent of inflammasome presence or the microbiome. ASC deficiency reduced granzyme B secretion and degranulation in CD8 + T cells. This lowered cytotoxicity and apoptosis, ultimately suppressing GVHD. ASC deficiency impaired GVL function but enough to provide antiviral protection. Inflammasomes amplified the function of effector cells, which in turn, activate them through unique mechanisms. Studies found that CTLs secreted perforin to create transient pores in the APC membrane, leading to granzyme release and ion perturbations, including K^+ efflux and Ca^{2+} influx. These disturbances facilitated the maturation of NLRP3 and IL-1β, which activated $CD4^+$ T cells and CTLs. The study elucidated a positive feedback loop between CTLs and APCs in GVHD and detailed the mechanisms by which adaptive immunity bolstered innate immunity [156]. Moreover, IL-18, a downstream effector of inflammasomes, enhanced the function of effector cells. Notably, in 60% of aGVHD patients, IL-18 and sIL-2R levels culminated on day 10 post-transplant, preceding the clinical manifestation of GVHD (averaging day 15 post-HSCT). This suggested that serum IL-18 levels were valuable indicators of aGVHD, potentially related to its enhancement of Th1 immune responses and CTL induction [157]. The IL-18Rα-neutralizing monoclonal antibody reduced inflammation by interfering with the IL-18/IL-18R interaction, affecting Th1, Th2, and Th17 subpopulations in the peripheral blood of aGVHD animal models. It also inhibited mitogen-activated protein kinase (MAPK) p38 activity and Fas/FasL expression to reduce apoptosis and ameliorate the GVHD response [158].

Mucosa-associated invariant T cells (MAIT cells), innate T cells with specialized antimicrobial functions, are abundant in the gut [159]. During intestinal GVHD, MAIT cells recognized gut bacterial metabolites (e.g., riboflavin) presented by MHC class I-related protein 1 via their TCR and rapidly migrated to the damaged area. Upon activation, MAIT cells proliferated in response to gut flora through the MR1/TCR-dependent pathway involving CD3/CD28, as well as through cytokines via the non-TCR-dependent pathway, including IL-12 and IL-18. Under TCR signaling, MAIT cells secreted more IL-17 to inhibit inflammation and limit $CD4^+$ T cell proliferation. This phenotype shift under IL-12/IL-18 stimulation leads to the secretion of higher amounts of granzyme B, TNF-α, and IFN-γ. This change promotes the expression of additional cytotoxic factors in mature subsets, thereby balancing the GVHD promotion with GVL effects (Fig. 3C) [160].

Double-edged sword

The gastrointestinal tract is one of the most prevalent and lethal sites afflicted by aGVHD [161]. NLRP6 plays a double-edged sword role in maintaining gut homeostasis. On the positive side, it effectively sustains the balance and diversity of the intestinal flora, thereby preserving intestinal integrity through the regulation of inflammatory pathways. By negatively regulating ZAP-70 signaling in donor T cells, NLRP6 alleviated the severity of GVHD. ZAP-70, an essential cytoplasmic tyrosine kinase, promotes T cell proliferation and differentiation through phosphorylation after binding with the TCR [162]. In mouse models, the absence of NLRP6 increased $CD4^+$ T cell proliferation, inhibited apoptosis and promoted pro-inflammatory Th1 cell differentiation by enhancing ZAP-70 phosphorylation. In contrast to the wild-type cells, NLRP6 deficiency did not influence $CD8^+$ T cell cytotoxicity or Treg suppression, indicating that NLRP6 reduces the severity of GVHD while preserving effective GVL responses [163]. NLRP6 played a protective role in the early stages following HSCT. Its absence promoted caspase-3-mediated apoptosis, leading to intestinal epithelial cell death, reduced expression of the tight junction protein occludin, loss of goblet cells, and decreased levels of antimicrobial peptides Reg3γ and Pla2g2a. NLRP6 deficiency also exacerbated inflammation, as evidenced by elevated inflammatory markers, including CD11b and myeloperoxidase, as well as an increased infiltration of inflammatory cells, such as macrophages, DCs, and neutrophils, within the intestinal [164]. Intriguingly, a recent study offered a new perspective, suggesting that NLRP6 deficiency also triggered compensatory inflammasome activity by activating NLRP3 and other inflammatory pathways. The loss of NLRP6 negatively regulated both the NF-κB and MAPK p38 signaling pathways. In NLRP6-deficient mice, significant increases in the expression levels of NLRP3, pro-caspase-1, p20, IL-1β, and IL-18, accompanied by more severe liver damage, inflammatory cell infiltration, and liver fibrosis. It was hypothesized that while NLRP6 activation resulted in the release of moderate levels of IL-1β to eliminate pathogens, NLRP6 deficiency led to excessive NLRP3 activation, thereby causing liver damage due to an intensified inflammatory response [165]. Paradoxically, some studies have reported opposing findings, indicating that NLRP6 deficiency in non-hematopoietic tissues mitigated the severity of aGVHD, particularly in the gastrointestinal tract, leading to reduced tissue damage and improved survival rates. This effect might be attributed to the expression of specific pro-inflammatory factors, activation of immune cells, and the regulation of the gut barrier (e.g., goblet cells, mucin-2, and tight junction proteins) which operated independently of microbiome regulation [166, 167].

Additionally, NLRP3, previously regarded as a positive regulator of GVHD, has been found to have a

protective role in non-hematopoietic tissues, particularly in intestinal epithelial cells. G protein-coupled receptors (GPR109A, GPR43, and GPR41) serve as microbial sensors that are essential for maintaining gut homeostasis and safeguarding gut barrier function [168]. Short-chain fatty acids (SCFAs), the bacterial metabolites, acted as ligands for these receptors and moderately activate NLRP3 in non-hematopoietic tissues through extracellular signal-regulated kinase (ERK) phosphorylation. This activation increased the secretion of the gut-protective factor IL-18, thereby supporting epithelial stability [169]. Moreover, SCFAs promoted the production of Tregs, contributing to regulatory and immunosuppressive effects. Nonetheless, this protective mechanism was disrupted when gut symbiotic bacteria were inhibited by the administration of broad-spectrum antibiotics [170].

Exacerbation of other post-transplant complications

Infection ranks as one of the leading causes of death following HSCT, primarily due to the severe immunodeficiency [171]. Immunosuppression or immune deficiency renders patients susceptible to pathogenic infections [172]. During the pre-engraftment phase, which spans from conditioning until 30 days post-HSCT, patients experience severe immunosuppression characterized by neutropenia, mucosal damage, and catheter-related risks. The most common pathogens during this period are bacteria, particularly those causing sepsis from gram-positive bacteria, as well as fungal infections (e.g., *Candida* and *Aspergillus*) and viral infections (e.g., herpes simplex virus). The early post-engraftment stage, occurring between 30 and 100 days post-transplant, is primarily marked by cellular immune deficiency. Common infections during this phase include those caused by bacterial pathogens (notably gram-negative bacteria), viral infections (such as Cytomegalovirus), and fungal infections (e.g., *Aspergillus*). In the late post-engraftment stage, which extends beyond 100 days, the immune system gradually recovers, but the main infection risks include invasive fungal infections (e.g., *Cryptococcus*), viral reactivation (e.g., cytomegalovirus, varicella-zoster virus), and Epstein-Barr virus-associated lymphoproliferative disorders [173, 174]. Despite the limited research on the interplay between infectious factors and inflammasomes during HSCT, it is plausible that inflammasomes, as sentinels of innate immunity, play a crucial role at different stages of transplantation [12]. Pathogens, including bacteria, fungi, viruses, and parasites, are recognized by host cells through their cell wall components, DNA, and metabolic products, which then activate inflammasomes. The extent of activation varies based on the environment and infectious agents involved. For instance, human dsDNA viruses, such as cytomegalovirus, activated the AIM2 inflammasome, associated with higher cell death rates due to the release of IL-18 and IL-1β. AIM2 also interferes with the transcription of early and late viral genes (UL54 and UL83), inhibiting viral replication and promoting cell death to curb viral spread [175]. Studies have demonstrated that virulent strains of HSV-1 increased the expression of NLRP3, NLRP12, and IFI16 inflammasomes. More virulent HSV-1 strains elicited activation of inflammasomes, resulting in a significant accumulation of inflammatory monocytes and neutrophils, which exacerbated disease severity. Notably, this phenomenon was exclusively observed in HSV-positive cells [176]. In HSV-1-infected microglial cells, the NLRP3 inflammasome triggered Gasdermin D-dependent pyroptosis, where the formation of membrane pores promoted the release of cellular contents and exacerbated tissue damage [177]. Among fungal infections, *Candida albicans* is recognized as one of the most commonly invasive species in HSCT. The transition of yeast cells to the hyphal form was a critical trigger for NLRP3 inflammasome activation. The hyphal form secreted Candidalysin, which damaged the cell membrane and directly activated the NLRP3 inflammasome, leading to the maturation of IL-1β and potentially limiting the invasion of Candida albicans in the host, possibly by disrupting K^+ balance [178]. In a model of acute lung injury mediated by *Pseudomonas aeruginosa* in HSCT, elevated levels of prostaglandin E2 (PGE2) led to increased IL-1β, which depends on the activation of cAMP response element-binding protein (CREB) transcription factor through cAMP mediated by EP2 and EP4 signaling [179]. The production of IL-1β was associated with the activation of caspase-1 in the canonical pathway and caspase-8 in the alternative pathway. Additionally, PGE2 inhibited the activation of autophagosomes LC3 and p62. The combined effect of IL-1β production and limited autophagic protection collaborated to inflict lung damage after infection, which was mitigated by the PGE2 inhibitor indomethacin [180]. Some pathogens have evolved mechanisms to evade host detection [181]. The pathogenic yeast *Candida albicans* evaded macrophages by inducing NLRP3 inflammasome-dependent pyroptosis, which caused candida lysin-dependent membrane perforation or hyphal membrane piercing. The GSDMD inhibitor Necrosulfonamide effectively mitigated the escape of *Candida albicans* and alleviated infection symptoms without interfering with caspase-1 cleavage activity [182]. In summary, moderate inflammasome activation can restrict pathogen infection, whereas excessive activation may initiate an inflammatory cascade that clears pathogens while simultaneously causing tissue damage.

In addition to GVHD and infections, inflammasomes also contribute to other post-transplant complications.

Pre-transplant conditioning regimens can lead to severe hepatic complications. A cohort study involving pediatric patients who underwent allogeneic HSCT found a significant association between the donor's IL-1β−511 TT genotype and the cumulative incidence of grade III-IV hepatic veno-occlusive disease (VOD) within three months post-transplant, with rates of 25 ± 13.1% for the TT genotype compared to 2.9 ± 2.9% and 3.6 ± 3.6% for the CT and CC genotypes, respectively ($P = 0.024$) [183]. Increased expression of NLRP3 in the liver was observed in hepatitis following Bu/Cy treatment, resulting in heightened inflammatory infiltration. Pharmacological NLRP3 inhibitors, such as BAN11-7082, showed potential in reversing this damage and restoring liver function [184]. Disseminated intravascular coagulation (DIC) following transplantation is a relatively rare complication. In a study of 12 patients administered with recombinant human soluble thrombomodulin (rhTM), rhTM was found to reduce levels of fibrinogen degradation products, C-reactive protein, and HMGB1. The mechanism might involve rhTM binding to HMGB1 DNA-binding proteins via its N-terminal lectin-like domain, which inhibited the release of HMGB1, thereby preventing the inflammatory cascade and protecting vascular endothelial cells [185]. Engraftment syndrome (ES) is a clinical syndrome that arises during neutrophil recovery [186]. A comparison of plasma samples from 56 pediatric patients across three groups, including ES, aGVHD, and a combination of both, revealed that those with isolated ES exhibited significantly elevated levels of pro-inflammatory cytokines (IL-1β, IL-6, and IL-12). Notably, the levels of IL-1β and IL-12 were significantly increased, with IL-1β showing a more pronounced rise compared to those with aGVHD [187]. However, discordant findings from another study [188] highlighted the necessity for cautious interpretation of these results.

Therapeutic targeting of inflammasomes in the transplantation process

Given the significance of inflammasomes in HSCT and their intricate molecular mechanisms for detecting and countering danger signals through precise and coordinated assembly, various strategies targeting inflammasomes have shown considerable therapeutic potential in animal models [189]. These strategies are especially promising for preventing GVHD while preserving GVL effects (Table 1).

Numerous studies have focused on targeting the NLRP3 inflammasome through its dual-signal pathway. In a liver injury model induced by BU/CY conditioning, the administration of the NLRP3 inhibitor BAN11-7082 after HSCT selectively inhibited IκB-α phosphorylation and blocked NF-κB release, consequently reducing levels of IL-1β, IL-18, and neutrophil infiltration in liver tissue and ultimately protecting liver function [184]. Berberine, a traditional Chinese medicine utilized for gastrointestinal diseases, has been shown to inhibit the TLR4 signaling pathway and suppress the transmission of the priming signal of NLRP3, effectively reducing the severity of GVHD in the lungs, liver, and colon. Notably, it reversed the impairment of tight junction proteins in the mouse colon and augmented the abundance of beneficial bacteria [190]. The P2X7 receptor, a ligand-gated ion channel that responds to ATP stimulation, facilitates K^+ efflux, thereby activating the second signal of NLRP3 [191]. Brilliant Blue G, a P2X7 receptor inhibitor, inhibited NLRP3 activation and reduced macrophage and neutrophil infiltration, with inflammatory mediators such as CXCL8 and CCL2 in peripheral blood decreased, thereby improving liver function compared to untreated mice [192]. Antagomir-155, an inhibitor of microRNA-155, regulates multiple aspects of both innate and adaptive immune responses [193]. Inhibition of miR-155 was reported to decrease the expression of purinergic receptors in DCs, which reduced sensitivity to LPS and ATP stimulation, weakened ERK activation, and decreased inflammatory tendencies of DCs, further inhibiting NLRP3 activation [148].

In addition to the broad-spectrum inhibition of NLRP3, targeting its downstream activator protein, caspase-1, provides greater specificity. The caspase-1 specific inhibitor Ac-YVAD-cmk effectively suppressed the infiltration of macrophages and neutrophils, as well as the production of chemokines. Furthermore, it facilitated hematopoietic reconstruction, leading to an increase in megakaryocytes and platelets observed in post-transplant models [128]. Another study demonstrated that Ac-YVAD-cmk mitigated pathological damage and inflammation in the liver, lungs, and colon by modulating the Th1/Th17/Treg balance and reducing their characteristic pro-inflammatory states. Specifically, it inhibited Th1/Th17 differentiation and promoted Tregs, thereby alleviating damage caused by T cells activation in GVHD [194].

Regulating the expression of downstream inflammatory effectors presents significant therapeutic potential. Antibodies that target IL-18Rα inhibited the interaction between IL-18 and its receptor, thereby affecting the levels of Th1, Th2, and Th17 subpopulations. Specifically, this intervention reduces Th1 and Th17 cell expression while enhancing anti-inflammatory effects. Additionally, these antibodies decreased the expression levels of apoptosis-related molecules such as Fas and FasL, as well as the phosphorylation of MAPK p38, which collectively reduced apoptosis and contributed to the preservation of organ function [158]. Although IL-18 might exert more

Table 1 Mechanisms of targeting inflammasomes in HSCT

Targets	Agents	HSCT Model	Mechanism	Ref.
NLRP3	MCC950	Human HSPCs	1. Decreased the expression of NLRP3, IL-1β, and caspase-1 2. Restored the HSPC-supporting ability of MSCs	[116]
NLRP3	BAN11-7082	BU/CY-treated mice	1. Attenuated infiltration of neutrophils and macrophages 2. Decreased the expression of IL-1β, IL-18, and caspase-1	[184]
NLRP3	Antagomir-155	aGVHD mice	1. Reduced the expression of P2X7, ERK, NLRP3, caspase-1, IL-1β 2. Weakened the migration ability of DCs	[148]
NLRP3	Brilliant blue G	aGVHD mice	1. Attenuated infiltration of neutrophils and macrophages 2. Reduced levels of CXCL8 and CCL2 3. Reduced the expression of IL-1β, IL-18, caspase-1, NLRP3 and P2X7	[192]
NLRP3	Berberine	aGVHD mice	1. Suppressed the expression of TLR4, NLRP3, IL-1β, IL-18, IFN-γ, TNF-α, MCP-1 and IL-6 2. Reversed the colonic tight junction proteins reduction and colonic barrier degradation 3. Renovated the abundances of genus Adlercreutzia, Dorea, Sutterella and Plesiomonas and increased the abundances of Lactobacillus	[190]
NLRP3	CY-09	aGVHD mice	1. Suppressed the expression of NLRP3, caspase-1 2. Attenuated mRNA expression of M1 signature cytokines or chemokines including IL-1β, IL-6, TNF-α, CXCL9 and CXCL10	[152]
Caspase-1	AcYVAD-cmk	TBI-treated mice	1. Attenuated infiltration of neutrophils and macrophages 2. Reduced levels of CXCL8 and CCL2 3. Accelerated hematopoietic reconstitution of platelets	[128]
Caspase-1	AcYVAD-cmk	aGVHD mice	1. Inhibited the differentiation of Th1 and Th17 cells and promoted the differentiation of Treg cells 2. Decreased the expression of IL-1β, IL-18, and HMGB1	[194]
IL-18	Anti-IL-18Rα mAb	aGVHD mice	1. Interfered Th1, Th2 and Th17 subsets 2. Decreased IL-18, apoptosis-associated molecules (Fas and FasL) and phosphorylation levels of MAPK p38	[158]
IL-18	IL-12/18- and IL-12/15/18-preactivated NK cells	aGVHD mice	1. Mediated stronger GVL effect 2. Mitigated cytotoxicity of NK cells 3. Reduced $CD4^+$ and $CD8^+$ T cells, as well as Th1 and Tc1 cells	[195, 196]
IL-1β	Anakinra	aGVHD mice	1. Suppressed Th17 polarization	[145]
HMGB1	NecroX-7	aGVHD mice	1. Decreased the infiltration of lymphocyte 2. Inhibited the HMGB1–induced allogeneic T cell proliferation 3. Inhibited HMGB1 secretion by suppressing the mitochondrial ROS and PKC pathways	[198]
IRAK4	PF-06650833	aGVHD mice	1. Suppressed T-cell production of IFN-γ 2. Impaired differentiation toward Th1, Tc1, and Th17	[199]

adverse effects in GVHD treatment, its combination with other cytokines to pre-activate NK cells in vitro prior to in vivo administration demonstrated remarkable therapeutic potential. This cytokine cocktail therapy encompassed two strategies: the IL-12/15/18 and the IL-12/18 methods, both of which pre-activated and matured NK cells with persistent memory retention. NK cells did not directly kill activated T cells or inhibit APCs, instead, they produced IFN-γ and other anti-inflammatory factors, effectively preserving GVL effects. Compared to the IL-12/15/18 method, the IL-12/18 approach offered greater advantages in cell activation, proliferation, and retention. Additionally, IL-12/18 demonstrated sustained beneficial effects in mild aGVHD, indicating enhanced safety [195, 196]. The study revealed that IL-1β, originated from the activation of NLRP3 in intestinal cells, acted on the IL-1 receptors of DCs, $CD4^+$ T cells, and $CD8^+$ T cells. Anakinra, an IL-1 receptor antagonist (IL-1Ra) inhibitor, influenced the polarization of Th17 cells, ultimately improving the survival rate of mice in the early stages of aGVHD [145]. However, a randomized clinical trial displayed that blockade of IL-1 using IL-1Ra during conditioning was not sufficient to reduce GVHD or to improve survival [197].

Other classic upstream inflammasome mediators, including HMGB1 and MyD88, also exhibit excellent inhibitory potential. NecroX-7 inhibited HMGB1 secretion and TLR4 expression in a dose-dependent manner by suppressing mitochondrial ROS and protein kinase C (PKC) pathways, which further modulated the Th1/Treg ratio, reducing inflammatory responses [198]. MyD88, a critical adapter in innate immune signal transduction, transmits signals from TLR and IL-1R family receptors by recruiting interleukin-1 receptor-associated kinase 4

(IRAK4) to activate the NF-κB pathway and inflammasomes. The IRAK4 inhibitor PF-06650833 suppressed MyD88's function, inhibiting the differentiation of pro-inflammatory cells (Th1, Th17, and Tc1) in GVHD, while sparing the differentiation of anti-inflammatory cells (Th2 and Tregs) [199].

Remarkably, despite the promising anti-GVHD potential of targeting NLRP3 and its downstream proteins, NLRP3 remains essential for HSC mobilization and homing. Current mobilization protocols still encounter a 40% non-responsiveness rate, and the side effects of mobilizing agents emphasize the urgency for gentler and more effective alternatives [200]. Similar to adjuvant function, strategies such as the combination of ATP with G-CSF or AMD3100 [201], or activating P2X4 and P2X7 receptors to elicit sufficient ATP for initiating NLRP3 activation signals [202, 203], presenting potential avenues. Additionally, the utilization of potent NLRP3 activators like Nigericin to rapidly alter the ionic environment of cells to activate NLRP3 [95], or inhibiting adenosine and its effectors (e.g., HO-1 and iNOS) to eliminate their inhibitory effects on NLRP3, are also viable strategies [87]. However, it has been found that reducing HO-1 expression increased the motility and migration of leukemia cells [204], further underlining the intricate and multifaceted nature of inflammasome regulation.

Conclusion and perspective

The multifaceted regulation of inflammasomes plays a pivotal role in innate immunity and inflammatory responses, making them promising therapeutic targets in HSCT. Inflammasomes are intricately involved in the mobilization, hematopoietic function, and complications related to transplantation, highlighting their significant potential in HSCT treatment.

However, numerous challenging issues remain to be addressed. For instance, the interplay between microbiota, their metabolites, and inflammasome signaling in GVHD warrants further exploration. In the context of chronic inflammation, sustained and recurrent activation of inflammasomes can lead to long-term tissue damage and fibrosis, highlighting the importance of analyzing their role in chronic graft-versus-host disease (cGVHD). Furthermore, immune reconstitution, infection, relapse, and human leukocyte antigen (HLA) matching are critical areas that require additional investigation, particularly concerning the unresolved challenges associated with infections. Relapse continues to be a prominent cause of HSCT failure, influenced by factors such as the regrowth of minimal residual disease, clonal evolution, and immune evasion [205]. Notably, specific NLRP3 activation features in MDSCs have been identified as potential early indicators of relapse [206]. Continued research into the mechanisms of relapse, aimed at developing clinical biomarkers, represents a promising direction. However, most current studies are limited to in vivo or in vitro experiments, with a notable lack of epidemiological cohort studies to validate findings in human populations, thereby limiting their persuasiveness.

Over the forthcoming decade, the pharmacological and genetic modulation of inflammasome activation or inhibition for preventive and therapeutic purposes are poised to become a key focus of research [189]. In the domain of HSCT research, many drugs remain experimental, with limited studies on dosage optimization, drug structure refinement, and side effects. Consequently, multicenter, large-scale, prospective, randomized controlled trials are imperative. Limited awareness of the diversity of therapeutic agents hampers the application of rich molecular scaffolds. Given the safety and broad biological activity of phytochemicals, future research may yield valuable insights into these potential drugs [207]. Moreover, the dual-targeting nature of inflammasomes must be considered seriously, particularly regarding the optimal timing and method of administration.

In summary, exploring the intricate interplay between HSCT and inflammasome activation will enhance our understanding of HSCT mechanisms and facilitate the development of improved therapeutic and management strategies.

Abbreviations

HSCT	Hematopoietic stem cell transplantation
HSPCs	Hematopoietic stem and progenitor cells
GVL	Graft-versus-leukemia
PAMPs	Pathogen-associated molecular patterns
DAMPs	Danger-associated molecular patterns
IL-1β	Interleukin-1β
IL-18	Interleukin-18
aGVHD	Acute graft-versus-host disease
NBD	Nucleotide-binding domain
LRR	Leucine-rich repeat
PYD	Pyrin domain
CARD	Caspase recruitment domain
BIR	Baculovirus inhibitor of apoptosis repeat
dsDNA	Double-stranded DNA
LPS	Lipopolysaccharide
HMGB1	High mobility group box 1
ATP	Adenosine triphosphate
TLRs	Toll-like receptors
NLRs	NOD-like receptors
TNF-α	Tumor necrosis factor-alpha receptor
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
K^+	Potassium ion
Ca^{2+}	Calcium ion
ROS	Reactive oxygen species
LeTx	Anthrax lethal toxin
PPAR-γ	Peroxisome proliferator-activated receptor gamma
MAMPs	Microbe-associated molecular patterns
LTA	Lipoteichoic acid
T3SS	Type III secretion system
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
Na^+	Sodium ions
eATP	Extracellular ATP

HO-1	Heme oxygenase 1
iNOS	Inducible nitric oxide synthase
MBL	Mannose-binding lectin
MASPs	Mannose-binding lectin-associated serine proteases
ComC	Complement cascade
C3	Complement 3
CoaC	Coagulation cascade
MAC	Membrane attack complex
SDF-1	Stromal cell-derived factor 1
CXCR4	C-X-C chemokine receptor type 4
VLA-4	Very late antigen-4
VCAM-1	Vascular cell adhesion molecule 1
S1P	Sphingosine-1 phosphate
SCF	Stem cell factor
CXCL12	Chemokine C–X–C motif chemokine 12
PGE2	Prostaglandin E2
SP	Substance P
NK-A	Neurokinin A
NK	Natural killer
TC-PTP	T-cell protein tyrosine phosphatase
GATA-1	GATA binding protein 1
HIF1α	Hypoxia-inducible factor 1-alpha
TBI	Total body irradiation
LDH	Lactate dehydrogenase
MHC	Major histocompatibility complex
APCs	Host antigen-presenting cells
Tregs	Regulatory T cells
MDSCs	Myeloid-derived suppressor cells
IRAK4	Interleukin-1 receptor-associated kinase 4
MUC2	Mucin 2
cGVHD	Chronic graft-versus-host disease

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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The authors declare no competing interests.

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