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Review

Host-directed therapies modulating innate immunity against infection in hematologic malignancies

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ABSTRACT

Patients with hematologic malignancies (HM) are highly susceptible to bloodstream infection (BSI), particularly those undergoing treatments such as chemotherapy. A common and debilitating side effect of chemotherapy is oral and intestinal mucositis. These Patients are also at high risk of developing sepsis, which can arise from mucosal barrier injuries and significantly increases mortality in these patients. While conventional antibiotics are effective, their use can lead to antimicrobial resistance (AMR) and disrupt the gut microbiota (dysbiosis). In this review, we discuss utilizing host defense peptides (HDPs), key components of the innate immune system, and immune system inducers (ISIs) to maintain mucosal barrier integrity against infection, an underexplored host-directed therapy (HDT) approach to prevent BSI and sepsis. We advocate for the discovery of potent and safe ISIs for clinical use and call for further research into the mechanisms by which these ISIs induce HDPs and strengthen mucosal barriers.

1. Bloodstream infection and sepsis in hematologic malignancies

Infectious diseases have become increasingly problematic globally in the modern era due to rapid population growth, changes in social interaction, and impacts of climate change [1]. Hematologic malignancies (HM), including leukemia, lymphoma, multiple myeloma, and polycythemia, are common cancer types worldwide. Patients with HM are particularly vulnerable to many different types of bacterial-, viral-, and fungal infections due to their compromised immune system. These patients are predisposed to infections during treatments with chemotherapy and hematopoietic stem cell transplant (HSCT), along with potential nosocomial infections.

1.1. Bloodstream Infection

Patients with HM undergoing anti-cancer therapy or HSCT, as well as those who develop neutropenia, are highly susceptible to bloodstream infections (BSI) caused by a variety of pathogens, including antibiotic-resistant strains. Gram-negative bacteria, such as *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumoniae,* along with opportunistic fungi are common culprits, significantly contributing to increased morbidity and mortality in these vulnerable patients [2,3]. Notably, bacteria that produce robust biofilms, especially those with resistant phenotypes, can markedly increase the risk of developing end-organ diseases [4]. The mismatch between donor and recipient increases the risk of graft versus host disease (GvHD) during HSCT, which further elevates the risks of inflammation, intestinal barrier disruption, and microbial infections [5]. Common complications of HM patients with BSI are pneumonia, sepsis, invasive fungal diseases, cystitis, urinary tract infection, perianal infection, and ulcers. The identification of risk factors and accurate biomarkers for early BSI diagnostics is critical. It has been shown that HM patients with complications, low albumin concentration, high glucose level, escalated number of platelets, or increased levels of interleukin-6 (IL-6) or d-dimer (a protein fragment that is produced when a blood clot dissolves in the body; elevated levels can indicate clotting problems) are at higher risk of developing bacteremia and BSI [6].

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Nosocomial infections associated with central venous catheters (CRBSI) are a significant concern for hemato-oncological patients. Mucosal Barrier Injury-Laboratory-Confirmed Bloodstream Infection (MBI-LCBI), which often occurs in patients with severe mucosal barrier injury caused by chemotherapy and radiotherapy, also poses a great threat. Multinational Association for Supportive Care in Cancer (MASCC) risk index score is a scoring system to identify low-risk patients for complications of febrile neutropenia. A prospective observational study reported that adult HM patients with febrile neutropenia are prone to MBI-LCBI, particularly when they have low MASCC scores and a prior colonization with the fungus *Pichia kudriavzevii* (formerly *Candida krusei*) [7]. Citrulline is an amino acid secreted by enterocytes and recognized for its stability in healthy individuals. Citrulline levels drop in chemotherapy when the enterocytes collapse and after the epithelial barrier is disrupted (hypocitrullinemia). An association was also noted between hypocitrullinemia and candidemia in adult patients with HM at fever onset [7], which could indicate a barrier breach of pathogens in these patients. Successful standardized clinical interventions are needed to mitigate MBI-LCBI in HM patients [8]. Both CRBSI and MBI-LCBI require vigilant monitoring through rigorous surveillance systems [9]. A Brazilian study demonstrated that applying MBI-LCBI criteria could significantly reduce the reported incidence of central-line–associated bloodstream infection (CLABSI). Furthermore, many cases initially classified as MBI-LCBI were later identified as CRBSI [10].

1.2. Sepsis

One of the life-threatening complications of infection in patients with HM is sepsis, an overactive host response against pathogens. It arises when the body's response to an infection causes extensive deleterious inflammation, leading to tissue damage and organ dysfunction. Sepsis contains an initial hyperinflammatory phase and a prolonged immunosuppressive phase. It may trigger considerable immune defects in patients, including severely impaired cytokine production, apoptosis and depletion of immune cells, such as lymphopenia, T-cell exhaustion, and increased numbers of myeloid-derived suppressor cells, all of which will predispose patients to recurrent infections and increase mortality [11]. Interestingly, a combination of sepsis markers, including C-reactive protein (CRP), procalcitonin, and presepsin, may be utilized to predict invasive fungal infections in HM patients [12].

Sepsis is a leading cause of mortality in HM patients, especially during neutropenic episodes. Systematic analyses of the prevalence and mortality of severe sepsis or septic shock in hospitalized cancer patients in the United States reveal that severe sepsis occurs at higher rates among hematologic cancers compared to solid tumors, particularly in patients with lymphocytic leukemia. Mortality rates from severe sepsis are also notably higher in hematologic cancer patients [13,14]. Although there have been substantial improvements in survival rates for HM patients with sepsis over the last two decades, their 90-day survival remains poor, and the mortality rate of sepsis in patients with HM remains higher than in other septic patients in the intensive care units (ICUs) [15,16]. The growing issue of antimicrobial resistance (AMR) further exacerbates the challenge. It is crucial to carefully develop, refine, and efficiently share supportive care protocols together with diagnostic and therapeutic strategies across both developed- and developing countries to successfully manage sepsis [17–20].

1.3. Challenges associated with antibiotic use

Antibiotics are the most prevalent and effective treatment for bacterial infections. However, their use is not without problems, highlighted by the development of bacterial strains with AMR and triggering dysbiosis. AMR is an escalating global crisis that demands urgent attention. As AMR advances, common infections may become life-threatening (e.g., development of sepsis), and routine medical procedures, such as surgeries, organ transplants, cancer treatments, and the care of immunosuppressed patients, could become markedly more perilous. According to the World Health Organization, infectious diseases are a leading cause of death worldwide, which could be exacerbated by the rising threat of AMR. Despite the serious implications for global public health, pharmaceutical companies have largely abandoned the development of new antibiotics, primarily due to their limited profitability [21]. β-lactam antibiotics, cefepime and piperacillin-tazobactam, have remained as effective empirical treatment for high-risk patients with febrile neutropenia in some institutions [22]. However, the effectiveness of these antibiotics can vary widely between institutions due to differences in local microbial ecology. Inappropriate empirical antibiotic treatment of *Pseudomonas aeruginosa* with β-lactam antibiotics, resulting from adherence to international guideline recommendations without considering microbial environment of the area, has become increasingly problematic [2]. Thorough understanding of the local microbial environment and early initiation of appropriate combination antimicrobial therapy with broad-spectrum coverage are critical for achieving better clinical outcomes [3]. The disruption of gut microbiota by antibiotics has been proposed to be responsible for the incidences of antibiotic use associated oncogenic progression of different HM [23]. Recently, it was reported that the prevalence of HM in European countries was associated with the consumption patterns of antibiotics [23]. There was a significant positive correlation between the incidence of Hodgkin lymphoma and the consumption of tetracycline. Non-Hodgkin lymphoma was positively correlated with the use of narrow spectrum, beta-lactamase resistant penicillin. Multiple myeloma and the application of tetracycline or penicillin were also positively correlated, while a strong negative correlation between non-Hodgkin lymphoma and cephalosporin was observed [23]. These challenges necessitate enhanced research support and a reorganization of research efforts for the development of innovative therapeutic strategies and new treatment modalities to effectively combat infections in patients with HM. For instance, a novel synthetic approach was recently developed, involving the conjugation of the antileukemic agent cell-penetrating peptide transportan 10 (TP10) with fluoroquinolone antibiotics. The strategy aims to increase therapeutic efficacy while simultaneously reducing microbial infections in leukemic patients undergoing HSCT [24].

2. Host-directed therapies: an alternative to conventional antibiotics

Host-directed therapies (HDTs) are interventions to modify intracellular, innate, and adaptive host immune responses against pathogenic infections and inflammation. They function either by augmenting host immunity to eradicate intruders or by ameliorating immunopathology to protect hosts from tissue/organ damages [25], exemplified by the success of therapeutic vaccination and cancer immunotherapy. The concept of enhancing the body's natural ability to fight infections is not new. As early as the late nineteenth century, scientists had attempted to inoculate cancer patients to leverage their immune system to fight cancer. The remarkable success of HDT strategy in cancer immunotherapy in recent years, especially through the development of immune checkpoint inhibitors, has supported the application of HDTs to strengthen host innate immune defenses to oppose infections [26]. A major distinction between HDT and conventional antibiotics lies in the mechanism of action. HDT modulates host immune responses and host-pathogen interactions. It interferes with the pathways that pathogens use for immune evasion and replication. In contrast, antibiotics directly target pathogens for killing or inhibiting growth. For infections where few direct antimicrobial drugs are available against the pathogen (e.g., hepatitis B and AMR bacterial infection), HDT presents a promising alternative. In addition, HDT may improve the effectiveness of existing treatments when administered adjunctively. In most clinical trials conducted for treating *Mycobacterium tuberculosis* (*Mtb*) infection, candidates for HDT were tested as adjuvants to antibiotics [25]. Beyond the systematic immunological host responses triggered by HDTs [25], the

cellular processes exploited by pathogens and targeted by HDTs, such as phagosome acidification and trafficking, autophagy, cell cycle, and cell signaling, are also imperative [27].

There are several advantages of HDTs which support the development of applying HDTs in the clinic to attenuate infections. First, molecules developed as HDT hold cross-species activities and have a broad spectrum of effects against pathogens. Second, these therapeutics should remain effective against drug-resistant pathogens, because they circumvent the mechanisms through which pathogens develop resistance by targeting host cellular machinery rather than directly attacking pathogen components. Third, there may be cooperative effects between HDTs and antibiotics, paving the way for combination therapy. Lastly, HDTs may help prevent or reduce the development of AMR. The likelihood of resistance to HDTs is generally considered as low, particularly for therapies that target multiple cellular mechanisms [27]. Since sepsis is a heterogeneous disease with significant variability in host responses, leading to different outcomes from similar therapeutic interventions, HDTs, with dual functions of antimicrobial activity and immunomodulation, might be advantageous. For example, low levels of cytokine Metrnl/Interleukin-41 ($\leq$ 274.40 pg/mL) are associated with higher mortality rates in septic patients with impaired immunity, and administering recombinant Metrnl in mouse models of sepsis has been shown to reduce inflammation and enhance immune defenses, highlighting its potential as HDT for sepsis [28].

HDTs encompass a diverse range of modalities, such as small molecules [27], recombinant cytokines, cell-based therapies, and repurposed drugs, all of which are explored in the context of HDT-mediated tuberculosis (TB) treatment [25,29]. There is substantial support for the efficacy of HDTs against intracellular human pathogens, evidenced by studies using small molecules as genuine HDTs, which have been thoroughly reviewed [27]. Cytokine-based therapies, particularly those leveraging the immunomodulatory properties of interleukin-2 (IL-2) and interferon-gamma (IFN-γ), have been extensively investigated [25]. Immune cell- and stem cell therapies exhibit considerate immunomodulatory and anti-inflammatory benefits, which contribute to their indirect antimicrobial effects [29]. Immunotherapy involving the expression of chimeric antigen receptors (CARs) in T cells, natural killer (NK) cells, or macrophages represents a promising, personalized, and adaptable strategy for the treatment of chronic and persistent infections [29,30]. As manifested by their diverse functions, repurposed drugs hold significant promise as adjunctive agents in the HDT-mediated treatment of infections. Type 2 diabetes mellitus (T2DM) poses an increased risk of mortality for patients on TB treatment. Concurrent use of Metformin, one of the most widely prescribed medications for T2DM, has been shown to be effective in decreasing the odds of mortality for TB patients who had developed DM [31]. Metformin promotes phagolysosome fusion, enhances production of mitochondrial reactive oxygen species (ROS), and induces expression of adenosine monophosphate-activated protein kinase (AMPK), leading to modulation of autophagy in macrophages followed by elimination of *Mtb* [29,31]. In search for remedies for co-infection of HIV and *Mtb*, the antiretroviral protease inhibitor Saquinavir, has been found to be repurposed for controlling TB, as it enhances intracellular killing of *Mtb*, improves the expression of human leukocyte antigen (HLA) class II antigen presentation in infected macrophages, and increases T cell priming and proliferation [32].

In a randomized controlled trial that our group collaborated on, adjunctive therapy with phenylbutyrate (PBA) and vitamin D3 was shown effective for the clinical recovery of TB patients [33]. PBA and vitamin D3 work as immune system inducers (ISIs) to induce the expression of host defense peptides (HDPs) and boost host defenses in TB patients. In the study, 219 TB patients were treated with either a placebo, PBA, vitamin D3, or a combination of both. By week 4, 71 % of patients receiving the PBA and vitamin D3 combination therapy were sputum culture-negative for *Mtb*, compared to 43.7 % in the placebo group. Additionally, LL-37 levels were significantly elevated in peripheral blood mononuclear cells (PBMCs) and monocyte-derived macrophages (MDMs) in these patients. The approach of modulating innate immunity as a HDT to combat problematic infections is underappreciated in the field, and more attention is needed on the clinical issue of damage to host barrier integrity, particularly in the intestinal mucosa. In this review, we present novel perspectives on HDTs, focusing on the induction of HDPs, a component of the host immune barrier and a pivotal part of the innate immune defense, the strengthening of host barrier integrity, and the potential to develop therapeutic agents that target the gut-immune axis, with the aim to alleviate infections in patients with HM, mainly blood cancer **(**Fig. 1**)**.

3. Introduction on host defense peptides

HDPs, also known as antimicrobial peptides (AMPs), are naturally occurring cationic peptides that are typically amphipathic. They are natural endogenous broad-spectrum antimicrobials against bacteria, viruses, fungi, biofilms, and parasites that are expressed across a wide range of kingdoms of life, including vertebrate and invertebrate animals, plants, and fungi [34]. Induction of HDPs is part of the HDT scheme against infections. Cathelicidins and defensins are the two major classes of HDPs that exist in humans. LL-37 is the main antimicrobial peptide encoded by the sole human cathelicidin gene and generated by cleavage of hCAP18—the uncleaved proprotein of human cathelicidins, also referred to as pro-LL-37—and is stored in neutrophil-specific granules. In contrast, humans have two classes of defensins, namely α-defensins and β-defensins, where both have multiple genes and active peptides. α-defensins are the main types of HDPs in the granules of human neutrophils and were first detected and categorized almost 40 years ago [35]. The human β-defensin-I (HBD1) was first isolated and identified from human hemofiltrate, with 3 mg of HBD1 being isolated from nearly five thousand liters of hemofiltrate [36]. The development and identification of HDPs have advanced significantly over the past few decades. Nowadays, the database of HDPs is growing continuously [37], and scientists are exploring the vast repertoire of HDPs to develop novel therapeutic peptides and peptidomimetics against infections and inflammation, in hope of solving the problems with AMR. To facilitate the discovery of antibiotics against AMR, AMPSphere, an open-access database of next to 1 million non-redundant candidate HDPs, was created. It employs a machining-learning based approach where publicly available metagenomes and microbial genomes were computationally investigated [38]. HDPs are integral components of the innate immune system with antimicrobial- and immunomodulatory effects. Dysregulation of HDPs has been linked to a variety of diseases and infection risks, such as cancer, atopic dermatitis, psoriasis, Crohn's disease, colitis, and diabetic wound healing [39]. The exploitation, development, and application of HDPs, along with their antimicrobial- and immunomodulatory characteristics have been extensively reviewed and well-documented in the scientific literature [34,39–43].

3.1. The antimicrobial functions of host defense peptides

The antibiotic functions of HDPs were implied in a case-control study nested within a cohort of individuals initiating chronic hemodialysis, where patients with low baseline levels of hCAP18 were found to be at a higher risk of infection-related mortality [44]. The exact antimicrobial mechanism of action of HDPs in vivo is not yet fully elucidated. Different HDPs are co-expressed and may work synergistically in vivo. The antibacterial efficacy of HDPs is influenced by both the specific peptide and the type of pathogen, which is primarily attributed to the cationic and amphipathic nature of HDPs. These properties enable HDPs to disrupt bacterial membranes by inserting into the lipid bilayer, leading to membrane destabilization and dysfunction. Notably, human β-defensin 3 (HBD3) has also been shown to interfere with the biosynthesis of the bacterial cell wall by binding to the cell wall precursor lipid II, leading to lesions and subsequent osmotic ruptures of cells [45]. Intriguingly, human α-defensin 6 (HD6), which is highly expressed by Paneth cells in

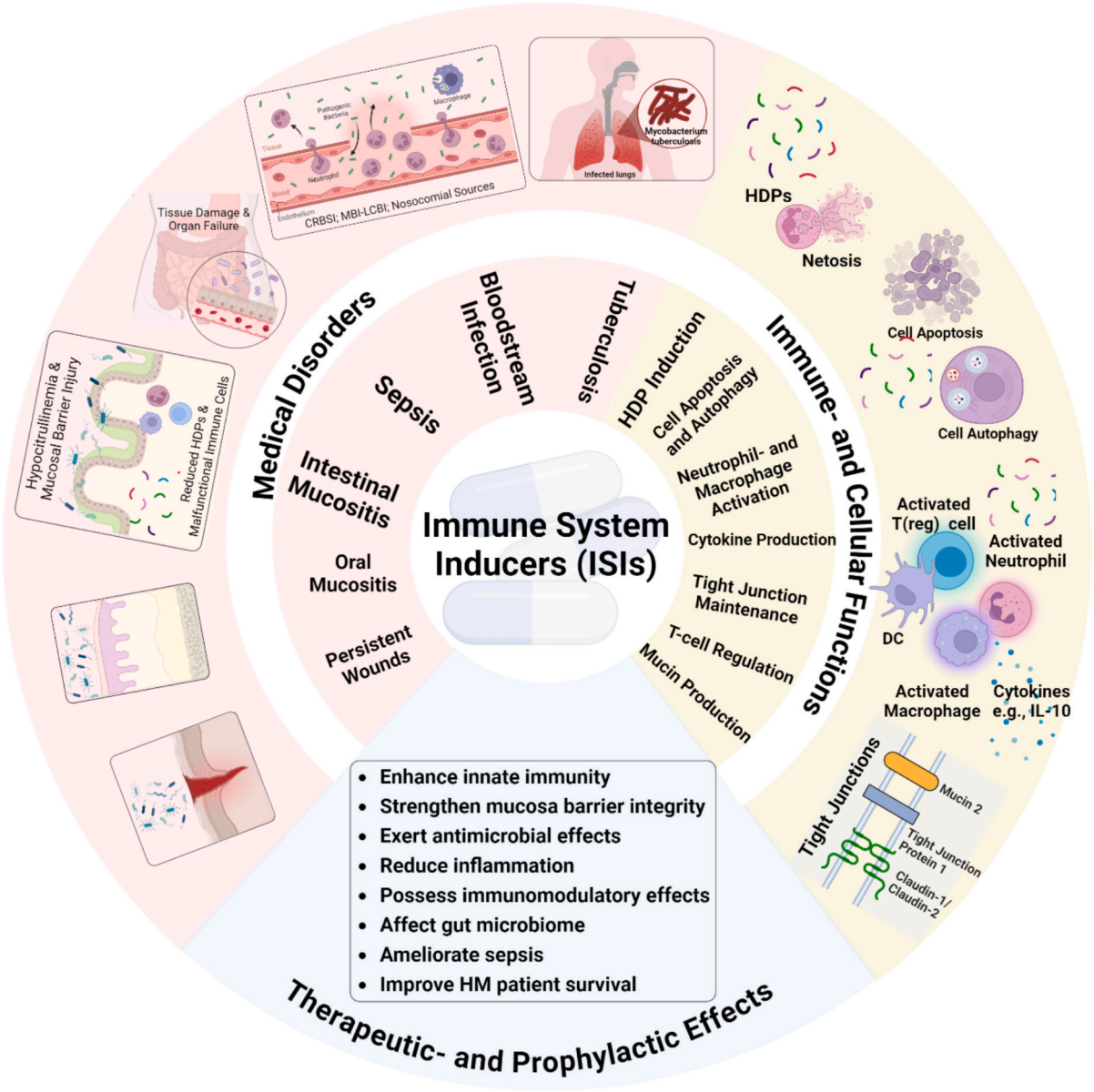

Fig. 1. ISIs as a novel HDT to target the gut-immune axis against infections. Patients with HM are immune compromised and highly vulnerable to various infectious complications, a condition worsened by treatments such as chemotherapy and HSCT. ISIs, exemplified by vitamin D3, microbial metabolites (mainly SCFAs such as butyrate), phenylbutyrate, synthetic HDACi (such as Entinostat, also known as APD based on its chemical structure), hold promise as therapeutic- and/or prophylactic agents to alleviate infections in HM patients. For instance, vitamin D3 and phenylbutyrate have demonstrated beneficial effects in patients with TB. As a novel HDT, ISIs modulate the immune system holistically. They notably enhance the production of HDPs (e.g., cathelicidins and defensins), key components of the innate immune defense which interacts with immune cells and a variety of cellular functions. ISIs may boost immune defenses directly or indirectly through the upregulation of HDPs, contributing to enhanced resistance to infections and reduced complications. APD: aroylated phenylenediamines; CRBSI: central venous catheters; DC: dendritic cell; HDACi: histone deacetylase inhibitors; HDP: host defense peptide; HM: hematologic malignancies; HSCT: hematopoietic stem cell transplant; HDT: host-directed therapy; ISI: immune system inducer; MBI-LCBI: mucosal barrier injury-laboratory-confirmed bloodstream infection; NET: neutrophil extracellular traps; SCFA: short chain fatty acid; TB: tuberculosis. Created in BioRender. Gudmundsson, G. (2024) BioRender.com/m28e411

the small intestine and distinct from other defensins, exhibits net-forming activity. Upon encountering enteric bacteria, HD6 self-assembles into fibrils and nanonets, entrapping the bacteria and preventing them from invading the intestinal lining [46]. Additionally, a few HDPs can penetrate bacterial cells and interfere with internal processes, contributing further to their antimicrobial effects. It is noteworthy that HDPs can affect the composition of gut microbiome in vivo [47,48], and compared to conventional antibiotics, HDPs may protect the host against dysbiosis [34]. HDPs show antiviral effects by targeting the viral envelope, inhibiting viral replication, and preventing viral invasion. Defensins, however, have been reported to promote some viral infections in certain contexts [49]. The antifungal effects of HDPs are thought to involve several mechanisms, including inhibition of β-glucan synthase or chitin biosynthesis in the fungal cell wall, membrane disruption or thinning, induction of DNA damage or interference with replication, and inhibition of RNA or protein synthesis [50]. HDPs show promise as antifungal agents. With the rising demand for antifungal treatments, further research is needed to better understand their mechanisms of action [51]. Unfortunately, pathogens may develop resistance against the direct killing actions of HDPs [34,41,52]. HDPs function as antimicrobial agents when their local concentrations exceed certain thresholds. The physiological concentration of naturally

occurring HDPs in vivo has been claimed inadequate for direct antimicrobial activity, suggesting that HDPs may primarily modulate host immune defenses indirectly [34]. There is also potential for synergistic interactions among various defense peptides and proteins in vivo, enhancing their effectiveness in direct microbial killing. Several antimicrobial proteins in humans function as host immune defense against pathogens, including Hepcidin, Histatins, Dermcidins, Adrenomedulin, Psoriasin, Secretory leukocyte protease inhibitors (SLPI), Lysozyme, RNases, Lipocalin, Azurocidin, Calprotectin, Bactericidal/permeability-increasing protein (BPI), and Lactoferrin [53]. They target pathogens through diverse and specific mechanisms, and together with HDPs, they create a robust defense system with versatile activities, making it difficult for pathogens to evade.

3.2. Cell types that produce host defense peptides

HDPs are expressed and secreted by various cells throughout the body as innate immune effectors and exert their effects on various immune cells. Epithelial cells located at the interface of external environment and internal tissues in the skin, lungs, and intestinal tract are capable of producing HDPs [52]. Blood cells, mainly the phagocytic cells - neutrophils and macrophages [35,54], as well as specific populations of lymphocytes, such as B cells and NK cells, are other sources of these peptides. The expression of α-defensins is more restricted than that of cathelicidins, being found predominantly in certain leukocyte populations [55]. In a human myeloid leukemia cell line, HL-60, where different granulocytic differentiation stages were simulated, defensin mRNA transcription was found to be restricted to the promyelocyte, myelocyte, and early metamyelocyte stages of granulocytic differentiation [56]. Similarly, hCAP18 is synthesized in myelocytes and metamyelocytes when secondary or specific granules are produced in the bone marrow in myelopoiesis [57]. Since the neutrophil is one of the main sources of cathelicidins in blood plasma, the plasma level of cathelicidins may serve as a good marker for neutropenia. Acting on this perspective, a study was conducted in neutropenic patients with different etiologies and found that the plasma level of hCAP18 can be used as a diagnostic marker for chronic neutropenia with severity, discriminating benign from chronic neutropenia [58]. Interestingly, phagocytosis of apoptotic neutrophils and their granule content by macrophages can enhance the antimicrobial activity of macrophages, facilitating the elimination of intracellular *Mtb* [59]. Cathelicidins mediate a wide range of interactions with different cell types [39]. They have been shown to induce platelet activation, promote platelet secretion, and interact with neutrophils, thereby playing a key role in thrombo-inflammation [60]. There are strong connections and interactions between HDPs and the innate and adaptive immune cells, immune effectors, such as, cytokines and chemokines, and inflammatory factors, which have been extensively studied and summarized [34,40,41].

3.3. Host defense peptides and extracellular traps

HDPs also work synergistically with neutrophil extracellular traps (NETs) for host immune defenses. NETs, released by neutrophils, are part of the neutrophilic arsenal in combating pathogenic microbes. They constitute a network of neutrophil granule proteins rich in HDPs and extracellular DNA derived from the nucleus and mitochondria of neutrophils during NETosis. The embedded HDPs within NETs contribute to pathogen clearance, and LL-37 can also translocate to the nucleus and mediate nuclear membrane disruption, facilitating the formation of NETs [61]. The formation and clearance of NETs are regulated by a complex and intricate regulatory network that remains unraveled. Under physiological conditions, NETs play a significant role in trapping and killing pathogens, where HDPs is of central importance, constituting an inseparable part in host defenses. However, NETs have also been implicated in the pathogenesis of various diseases, including cancer, autoimmune diseases, thrombosis, and chronic inflammatory conditions [62,63]. NETs play a dual role in HM; on one hand, they defend against infections by trapping and neutralizing pathogens, while on the other hand, they contribute to the pathogenesis of HM [64]. Depending on the context, NETs can either inhibit tumor growth by enhancing anti-tumor immune responses or promote tumor progression and metastasis by fostering a pro-inflammatory and immunosuppressive environment [64]. Furthermore, LL-37 has been shown to bind the inert self-DNA or RNA and enter plasmacytoid dendritic cells (pDCs) for activation, which induces interferon IFN-α and drives autoimmunity in the inflammatory skin disease, psoriasis [65,66]. Polymorphonuclear neutrophils may sense RNA-LL-37 complexes, instead of the conventional DNA-LL-37 complexes, triggering the release of NETs, after which, the NET-associated RNA and LL-37 complexes may further deteriorate the chronic inflammation in psoriasis [67]. The role of LL-37-mediated NET functions in HM remains unclear and warrants further investigation, but undoubtedly, maintaining a balance between the protective and pathological functions of NETs is critical for improving host defenses in patients with HM against infections.

3.4. Host defense peptides in cancer

HDPs may be involved in cancer, and dysregulation of HDPs reflects aberrant host defense responses in cancer patients. The role of cathelicidin in cancer progression is tissue specific, and depending on the biological features of tumors, it can be pro- or anti-tumorigenic [68]. The peptide LL-37 can induce apoptosis in leukemia cells and enhances the anticancer effectiveness of tumor-associated macrophages (TAM) [69]. The role of defensins in cancer progression varies, depending on the specific subfamilies of defensins and the types of cancer. HBD3 can recruit TAM, aiding tumor progression [49]. Higher serum levels of defensins (HBD1 and human β-defensin 2 (HBD2)) were found in lung cancer patients, especially in early-stages, compared to both healthy individuals and patients with pneumonia [70]. The serum concentration of both hCAP18 and HBD2 are elevated in patients with basal cell carcinoma (BCC) with high specificity, and the risk of developing BCC significantly increases when the concentrations of hCAP18 and HBD2 exceed certain thresholds [71]. On the other hand, HBD2 demonstrated significant anti-tumor effects on breast cancer by modulating macrophages and enhancing their anti-tumor functions [72]. Cathelicidins and defensins may directly inhibit tumor growth by modulating cell proliferation and promoting apoptosis and autophagy. While their pro-inflammatory activities can sometimes favor tumor development, they also interact with the tumor microenvironment—including immune cells (e.g., dendritic cells and T cells), mesenchymal stromal/stem cells (MSCs), and tumor-associated fibroblasts—potentially either promoting or inhibiting tumor progression. Additionally, these peptides influence cytokine production and serve as ligands to activate downstream signaling pathways such as EGFR and MAPK [68,73]. Several review papers have discussed the role of HDPs in cancer development [34,39], and more studies are needed to unravel the complexity for complete comprehension.

3.5. Host defense peptides in wound healing

A common chemotherapy-mediated complication in cancer patients is impaired wound healing [74]. The regulation of mouse cathelicidins and defensins is linked to functions of the permeability barrier in epidermis, and mouse cathelicidins are key components in maintaining the homeostasis of permeability barrier [75], suggesting the potential of HDPs in facilitating cutaneous wound healing. This is supported by a recent systematic review linking hyperglycemia in T2DM to reduced expression of cathelicidins and defensins, which subsequently lead to enhanced inflammation, increased vulnerability to infections, and impaired diabetic wound closure [76]. Indeed, both human and mouse cathelicidins have been shown to be induced after skin injury and are a

highly active antimicrobial agent against group A streptococcus (GAS), which are responsible for various human skin infections [77]. In addition to its direct antimicrobial activities, upon wounding, LL-37/hCAP18 are generated in the epidermal keratinocytes in the wound edges to facilitate re-epithelialization and wound closure, which could not be observed in impaired, inflammatory, and chronic wounds [78]. Furthermore, a recent study has shown that LL-37 can facilitate the nuclear import of transcriptional factor, TFEB, to activate autophagy, leading to keratinocyte migration and diabetic wound healing [79]. Application of HDPs on open wounds may facilitate wound healing, which has been confirmed in a randomized double-blind controlled trial, where the cream form of LL-37 could effectively accelerate wound healing in diabetic foot ulcers [80]. Conversely, during the pathogenic progression of acute lung injury (ALI), α-defensin released by activated neutrophils at high concentrations may contribute to the loss of alveolar barrier function [81]. Similarly, both human and mouse cathelicidins may also be involved in promoting pulmonary injury and inflammation, potentially via mediating platelet and neutrophil activation and platelet-neutrophil interactions [60].

3.6. Host defense peptides in hematologic malignancies

HDPs play important roles in the development and alleviation of HM. For example, LL-37 (human cathelicidin HDP) is often found to be deficient in neutrophils of patients with acute myeloid leukemia (AML), especially during infection [82]. LL-37 (or hCAP18, the pro-LL-37) levels are also low in serum of children with impaired myelopoiesis, such as those with acute leukemia, aplastic anemia, and myelodysplastic syndrome. In contrast, children with chronic myeloid leukemia (CML) exhibit elevated circulating levels of LL-37, likely due to the high number of myeloid cells at various stages of differentiation [83]. Interestingly, children with acute leukemia are predisposed to oral mucositis, which is associated with the low plasma levels of LL-37 [84]. A positive correlation has been observed between the plasma concentrations of lipocalin-2 (LCN2), an innate immune defense protein induced by microbiota, and the severities of GvHD following HSCT, including both acute and chronic forms [85]. LCN2 was also markedly increased in septic patients, and during the acute phase of infection in patients with BSI, both hepcidin and LCN2 were elevated significantly [86]. Hepcidin is a human peptide hormone with antimicrobial activities that plays a key role in iron homeostasis. In HM patients undergoing allogeneic HSCT, pretransplant serum levels of hepcidin may be used to predict the risks of BSI post-transplant [87]. The antimicrobial function of LCN2 is via binding and inhibiting siderophores, which are small, high-affinity iron-chelating compounds secreted by microorganisms to accumulate iron. During the acute phase of a BSI, iron deficiency in the blood induced by increased hepcidin can reduce iron accessibility for certain pathogens, and increased levels of LCN2 further inhibit pathogen iron acquisition by binding to siderophores, enhancing antimicrobial defense [86]. MSC-derived exosomes exhibit anti-inflammatory, anti-apoptotic, and tissue regenerative properties, and they have been shown to facilitate bacterial clearance in sepsis models [88]. MSCs are known to express HDPs, which may help to explain their immunomodulatory- and antimicrobial effects in sepsis. Indeed, a recent study found that significantly lower levels of LL-37 and regulatory T cells (Treg) may be reliable biomarkers for the onset of late-onset sepsis (LOS) in preterm infants, and autologous cord blood mononuclear cell infusion—rich in stem and precursor cells—could increase the levels of LL-37 and Treg and reduce LOS [89]. Recently, mouse cathelicidin was shown to protect against peritonitis-induced polymicrobial sepsis in a mouse model of cecal-ligation and puncture (CLP)-induced sepsis. In cathelicidin knockout mice, both mucin production and tight junctions of intestinal epithelial cells were reduced following CLP-induced sepsis, compared to the wild type. The absence of endogenous cathelicidin led to increased apoptosis of intestinal epithelial cells and higher levels of neutrophils and M1 macrophages in the septic mice, underscoring the crucial roles of cathelicidin in preserving intestinal barrier integrity and modulating immune cell infiltration during sepsis [90].

4. Host barrier integrity: focus on the gut barriers

Enhancing host defenses involves multiple strategies, including the induction of HDPs and the strengthening of tight junctions, the physical components of epithelial barriers. Applying HDTs to eliminate infections may require fortifying the host's epithelial barriers in the gut, lungs, skin, mammary glands and epididymis, which are potential sources of BSI (bacteremia). Disruption of the intestinal epithelial barriers by chemotherapy may facilitate bacterial translocation, leading to systematic infection, such as sepsis. In return, sepsis may induce disturbances of vasculature and perfusion in the intestines, coagulopathy, increased apoptotic events, and release of proteases. It contributes to further destruction of the intestinal mucosa, highlighting the therapeutic potential of targeting the gut in patients undergoing sepsis in the clinic [91]. Due to the immunocompromised condition, hematological cancer patients are particularly susceptible to life-threatening infections, hence, it is paramount to lower the risk of infection in those patients. Blijlevens and de Mooij conducted a comprehensive review of mucosal barrier injuries and infections, thoroughly examining the interplay between the microbiome, antimicrobial treatments, and mucositis. They emphasize the crucial role of the gut-immune axis in the context of HM [92]. Interestingly, the same group performed a retrospective analysis of various HM treatment regimens to unravel the relationship between the occurrence of BSI and the degree of intestinal mucositis. They observed a strong correlation between BSI and the duration of hypocitrullinemia [93]. Depending on the depth and duration of hypocitrullinemia, the severity of intestinal injury can be classified, and the risk for BSI can be predicted. This has challenged the view that neutropenia is the most reliable marker for the onset of BSI. The risk of BSIs has been reported to strongly correlate with hypocitrullinemia in patients undergoing intensive cancer treatments or HSCT and in children with acute lymphoblastic leukemia (ALL) [92–94], highlighting citrulline as a functional marker of intact gastrointestinal epithelium and intestinal mucositis. Since HDPs are critical components of the intestinal epithelial barrier, correlating citrulline levels with induced HDP expression is therefore of interest.

The gastrointestinal (GI) tract is a complex and intricate organ, where ileum of the small intestine has divergent cell composition, with enterocytes, stem cells, Paneth cells, tuft cells, and goblet cells that are affected in small bowel infectious and inflammatory diseases. The GI tract is composed of complex epithelial structures, including villi, crypts, and microvilli, with diverse structural-, functional-, and immune-associated cells that orchestrate and maintain the homeostasis of the intestinal mucosal barrier. Paneth cells within the crypts are a major source of HDPs in the small intestine. Intestinal barrier disruption is both a cause and consequence of sepsis. Sepsis triggers overwhelming inflammatory responses and affects significantly the intestinal mucosa which is an inseparable part of the innate immune defense. Novel therapeutic interventions that address the complex dysregulations of sepsis are needed. These should incorporate HDPs, immune modulators, and unconventional ideas of fecal microbiota transplant (FMT), synbiotics, and probiotics to effectively target the condition [91]. HM patients are particularly susceptible to the disruption of intestinal barrier [95]. More severe intestinal mucositis, characterized by largely decreased plasma citrulline levels and elevated CCL20 which functions as both an inflammatory and homeostatic chemokine, is associated with the occurrence of BSI in children treated for ALL, suggesting chemotherapy-induced intestinal epithelial cell loss and mucosal inflammation are potential risk factors of infectious complications. Accurate quantification and close monitoring of mucositis severity are critical for the prognosis of BSI in these patients [94]. Apart from intestinal mucositis, the microbial profile of blood in patients who develop BSI after allogenic HSCT has been detected to closely resemble that of

oral microorganisms, implying the necessity of monitoring the oral microbe in BSI cases [96]. Both supersaturated calcium phosphate rinse (SCPR), an anti-mucositis and analgesic oral rinse, and Palifermin, a truncated human recombinant keratinocyte growth factor, are FDA-approved medications for oral mucositis. In HSCT patients receiving radiotherapy-based myeloabative conditioning, Palifermin has shown superior effectiveness in reducing the severity of oral mucositis [97]. For HM patients with mild mucositis who can tolerate oral intake, ciprofloxacin has been recommended as prophylaxis against Gram-negative infections [98], but this can lead to selection of AMR strains and disruption of the endogenous microbiota.

5. Microbiota health: a vital component of antimicrobial therapy

HDP-based antimicrobial therapy helps preserve microbiota, which is disrupted by conventional antibiotics. There is a complex relationship among the human gut microbiome, microbial metabolites, host immunity, cancer therapies, and hematological cancers, which has been observed in diverse HM types, including multiple myeloma, ALL, non-Hodgkin lymphoma, AML, and myeloproliferative neoplasms (MPN) [99–101]. The composition and diversity of gut microbiota are significantly altered in AML [102]. The JAK2V617F genetic mutation in MPN patients has been found to drive gut dysbiosis, where patients possess a low relative abundance of specific SCFA-producing bacteria [101]. Gut dysbiosis in HM patients can compromise epithelial barrier integrity, trigger inflammation, and weaken both innate- and adaptive immune defenses. This disruption can lead to increased susceptibility to infections, diminished therapeutic efficacy, and exacerbated side effects [103,104]. Gut microbiota influences the effectiveness of cutting-edge treatments for HM patients, such as the chimeric antigen receptor T cell (CAR-T) therapy [104], where the characteristics of gut flora differ among patients, and there are dynamic changes in the gut microbiome during treatment. Alteration in gut microbiota in these patients is associated with severe cytokine release syndrome, and there is a significant correlation between gut microbiota functions and the therapeutic outcome [99].

GI tract is the major source of bacteremia in immunocompromised patients. The presence of intestinal domination and the occurrence of BSI are connected in some types of HM, for instance, allogeneic HSCT [105]. However, this association has not been observed in patients with AML [106]. Disruption of the gut commensal microbiota is essential for both the onset and worsening of sepsis, leading to the selection of pathogenic microbes, inflammation, and decreased production of beneficial SCFAs, followed by end-organ dysfunction [107]. Modulating microbiota offers promising therapeutic potential for sepsis treatment [108]. Current microbiome-based therapies, such as probiotics and FMT, may be advantageous for reducing morbidity and mortality in certain groups of patients. However, these novel approaches are still in the early stages and require further validation and more mechanistic insights [107,108]. Patients may develop intestinal dysbiosis after HSCT [109]. Research has shown that gut flora can influence the pathogenic progression of acute GvHD by evaluating four fecal biomarkers —calprotectin, soluble CD8 (sCD8), soluble intracellular adhesion molecule 1 (sICAM-1), and β-defensin 2—as indicators of gut mucosal immunity defects in pediatric allogeneic HSCT recipients [110].

Interestingly, skin dysbiosis and imbalanced cutaneous immune responses may be correlated with the disease progression and severity of acute skin GvHD following HSCT [109]. Since non-enteric pathogens, such as *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, are also present in the flora of HM patients, both oral and stool samples need to be genetically analyzed to monitor the presence of pathogens and AMR strains and accurately access the probability of BSI. In which case, digital droplet PCR (ddPCR) offers a more precise surveillance tool compared to conventional 16S rRNA sequencing. This approach highlights the potential for personalized therapeutic strategies and targeted antibiotic treatments in ameliorating patients with bacteremia [106]. It is important to note that antibiotic treatment worsens intestinal dysbiosis and accelerates HM cancer progression [102]. Therefore, utilizing ISIs to modulate the innate immune system, enhance HDP expression, and strengthen the epithelial barrier, is of significant interest.

6. Immune system inducers as novel HDT strategy to treat infection

6.1. Natural immune system inducer - vitamin D3

Previous research on vitamin D3 in the treatment of TB suggests that employing natural or synthetic inducers to enhance the host's immune defenses in a holistic manner holds promise for effectively combating infections. This approach underscores strengthening the host's immune system as a key strategy in managing and treating infections from a host-oriented perspective [111,112]. In 1903, a Faroese scientist and medical doctor Niels Ryberg Finsen was awarded the Nobel Prize for the invention of Finsen Lamp which was used as light therapy to treat a type of TB, lupus vulgaris. Today, it is known that the light facilitates the synthesis of vitamin D (Fig. 2), and the presence of vitamin D, specifically its active form 1,25-dihydroxyvitamin D (1,25(OH)$_2$D, which is typically used in in vitro experiments), mediates bacterial elimination and modulates immune cells, such as the antigen-presenting macrophages and dendritic cells and various lymphocytes. 1,25(OH)$_2$D exercises its antimicrobial function via its nuclear receptor VDR, partially under control of the Toll-like receptor (TLR) pathway, involving the NF-κB signaling pathway and inflammatory modulators. TLRs detect pathogen-associated signals, leading to the induction of 1-α-hydroxylase (CYP27B1) expression. This upregulation of CYP27B1 increases local production of 1,25(OH)$_2$D. NF-κB may work in conjunction with VDR to regulate the expression of cathelicidin and defensin. Both TLR and NF-κB enhance host defenses and support innate immunity [111]. In humans, 1,25(OH)$_2$D can directly induce cathelicidins and, to a much lesser extent, defensins, whose promoters contain sequences that are consensus with the vitamin D response elements [34,39,41,113]. The induction can be observed in myeloid leukemia cell lines, human bone marrow cells, macrophages, immortalized keratinocyte, and colon cancer cell lines [114]. Induction of cathelicidins by 1,25(OH)$_2$D is substantiated by the observed correlation between the plasma level of hCAP18 and serum level of 25(OH)D ($\leq$ 32 ng/mL, the circulating form of vitamin D3) in healthy middle-aged adults [115]. The increased production of cathelicidins in human macrophages by 1,25(OH)$_2$D via TLRs is essential for eradicating *Mtb* in TB patients, and past research shows that individuals with low serum levels of 25(OH)D and inefficient production of cathelicidins are more susceptible to TB [116]. In various clinical forms of TB, hypovitaminosis D (vitamin D deficiency) and low local expression of LL-37 (coupled with elevated systemic levels of LL-37) are associated with active pulmonary TB [117]. Evidently, vitamin D contributes to combating infections, partly by inducing HDPs. A recent epidemiological study shows that vitamin D deficiency has been prevalent worldwide over the past twenty years, indicating that patients with HM are also likely to be deficient in vitamin D, leading to increased susceptibility to infections [118].

Vitamin D3 supplementation may improve survival in cancer patients, warranting further clinical studies with robust designs [119]. Chemotherapy-induced immunosuppression poses a significant challenge in cancer treatment, while vitamin D3 stimulates the immune system and predominantly regulates immune defense genes in the leukocytes of healthy individuals and in the bone marrow blasts of patients with HM. As a result, vitamin D3 has been proposed as a supportive therapeutic immune modulator for patients not suitable for aggressive chemotherapy [120]. Allogenic HSCT primarily exerts its efficacy through the graft-vs.-leukemia (GvL) effect, wherein activated donor immune cells combat malignant cells in the host. However, complications such as GvHD after HSCT often hinder the effectiveness of GvL,

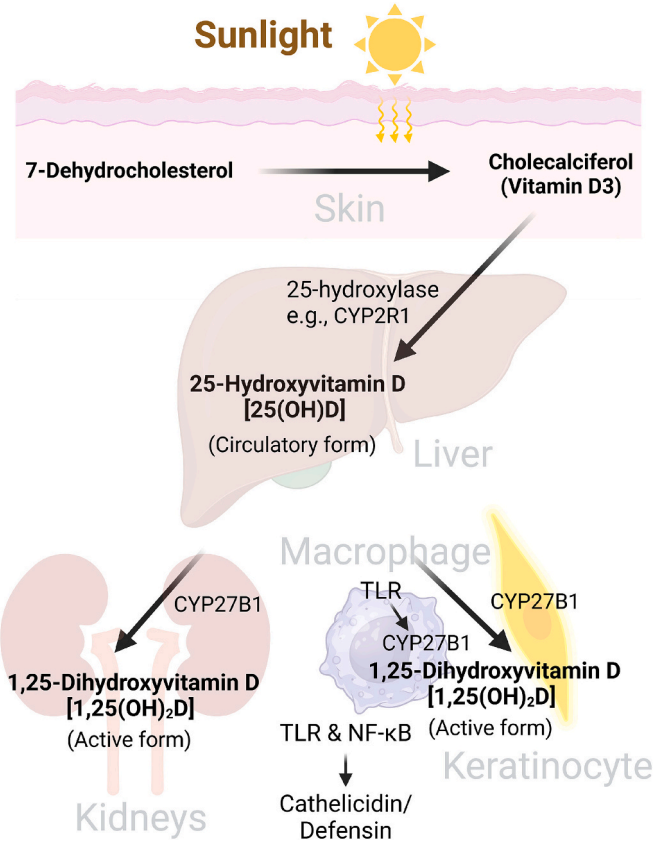

Fig. 2. Overview of the vitamin D metabolic pathway. Sunlight (UVB radiation) triggers the conversion of 7-dehydrocholesterol into vitamin D (cholecalciferol) in the skin. However, vitamin D itself is inactive and must undergo modifications for biological functions. The first step is conversion to 25-hydroxyvitamin D [25(OH)D], the main circulating form, which occurs primarily in the liver and is facilitated by 25-hydroxylase enzymes, with CYP2R1 being the most significant. Next, 25(OH)D is converted to the active hormonal form, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], by the enzyme 1-α-hydroxylase (CYP27B1). This transformation occurs mainly in the kidneys, though it can also take place in extrarenal tissues, as epithelial and immune cells express CYP27B1. Notably, CYP27B1 regulation differs by tissue: in the kidneys, it is regulated by hormones like parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and 1,25(OH)$_2$D itself, while in macrophages and keratinocytes, it is regulated by cytokines and toll-like receptor (TLR) signaling. The expression of cathelicidin and defensin may be regulated by both TLR and NF-κB signaling pathways. Once 1,25(OH)$_2$D is formed, it mediates antimicrobial functions and immune modulation. Created in BioRender. Gudmundsson, G. (2024) https://BioRender.com/l01s391

highlighting the need for immune modulation strategies. Vitamin D3 modulates both innate and adaptive immunity through T cells and dendritic cells, fostering an anti-inflammatory immune environment by reducing T cell activation, dendritic cell maturation, and pro-inflammatory cytokine production. It enhances phagocytic- and tumoricidal activity of immune cells and maintains the beneficial GvL effects via cell- and antibody-dependent cellular cytotoxicity. Additionally, vitamin D3 alleviates GvHD by creating an immunosuppressive environment by promoting Treg, strengthens antimicrobial defenses, and preserves the intestinal barrier integrity in HM patients with allogenic HSCT [121]. A randomized clinical trial has shown that Calcitriol (1,25(OH)$_2$D), the active form of vitamin D3, can improve both absolute neutrophil counts and relapse-free survival in HM patients post-HSCT [122]. Vitamin D3 deficiency has been linked to increased risks of sepsis. Supplementation of vitamin D3 can upregulate the expression of cathelicidin in the ileum of septic mice and increase the production of mucin, holding the potential as a prophylactic- and therapeutic agent for sepsis. Both inactive and active forms of vitamin D3 can be used as prophylaxis to decrease sepsis-associated mortality and severe symptoms. It is worth noting that after the onset of sepsis, only the active form, 1,25(OH)$_2$D, was effective when administered to treat sepsis [90].

Vitamin D is widely supported for immune stimulation, but its use is limited by potential toxicity at high doses, particularly hypercalcemia, where elevated blood calcium can lead to tissue calcification. To address this, numerous low-calcemic vitamin D analogs have been developed to retain efficacy with minimal calcemic effects [123]. While some analogs reduce the risk of hypercalcemia by reducing calcium absorption in the intestinal epithelium, their capacity for HDP induction in the intestine may also be compromised. Therefore, the analogs must be carefully evaluated for their potential to induce HDP and reduce infection risk.

6.2. *Therapeutic- and prophylactic potentials of a novel class of immune system inducers – histone deacetylase inhibitors*

HDP induction by 1,25(OH)$_2$D can be synergistically enhanced by lipopolysaccharides (LPS), short-chain fatty acids (SCFAs), and secondary bile acids (sBAs) produced by gut microbiota [113,124,125]. Reversely, an adequate and stable amount of HDPs needs to be presented in the gut to regulate the host-microbiota interaction and maintain homeostasis [52]. SCFAs, such as butyrate, propionate, and acetate, are microbial metabolites with HDACi activity (especially butyrate). They are produced by the gut microbiome and influenced by diet, microbiota composition, and antibiotic use. SCFAs support gastrointestinal health and enhance both mucosal- and systemic immunity, helping to mitigate the progression of inflammatory bowel disease (IBD). Albeit being produced in the gut, they function at extra-intestinal sites, such as the liver, lungs, brain, and reproductive system, where they play a role in various diseases including asthma, neuroinflammation, and cancer. SCFAs mediate a broad range of cellular signaling pathways and modulate histone acetylation. Butyrate can affect intestinal epithelial cells, promote immune cells, and exert anti-inflammatory effects, aiding the maintenance of the integrity of mucosal barriers [126]. Notably, a randomized, double-blind, placebo-controlled trial demonstrated that a synbiotic strategy of oral treatment of *Lactobacillus plantarum* and fructo-oligosaccharide, which the bacteria use to produce SCFAs, showed promising results in preventing sepsis in early infancy. The study observed a significant reduction in sepsis and respiratory tract infections among the enrolled infants [127]. The fecal butyrate levels in AML patients are rapidly reduced, and feeding butyrate to AML mice can delay cancer advancement. In murine models of AML, antibiotic-induced gut dysbiosis led to a marked reduction in intestinal butyrate levels, further aggravating the disease. In addition, the integrity of the intestinal barrier was compromised, resulting in increased leakage of LPS into the bloodstream, which in turn exacerbated leukemia progression. Notably, butyrate gavage was shown to repair the damaged intestinal barrier and alleviate AML severity. It suggests that targeting the microbiota-butyrate-barrier axis could be a promising strategy to slow AML progression [102].

Butyrate and its synthetic derivative, PBA are HDP inducers that have been shown to combat *Shigella* and ameliorate shigellosis, where LL-37 peptides are decreased in the rectal and lung epithelia [124]. The roles and mechanisms of microbiota-derived SCFAs in inducing HDPs are beyond the scope of this review and have been extensively covered in recent literature [128]. Sodium phenylbutyrate is an FDA-approved drug to treat urea cycle disorder. To pave the way for the application of PBA in TB patients, a dose finding study was conducted in healthy volunteers. Results show that there is a synergistic effect of PBA and vitamin D3 on LL-37 production in monocyte-derived macrophages and lymphocytes, and macrophages conditioned with PBA and vitamin D3 exert enhanced intracellular killing activity of *Mtb* ex vivo [129]. These pieces of evidence highlight the potential of the ISI-instigated HDT in treating infections and inflammation. Motivated by the concept, our research group conducted a compound screening study to identify

natural or synthetic ISIs, the potency of which was indicated by the induction capacity of cathelicidin [130]. A novel class of ISI, aroylated phenylenediamines (APDs), was uncovered, and Entinostat, a class I histone deacetylases inhibitor (HDACi), showed the most promise. Entinostat at 2.5 μM induced cathelicidin gene expression to a level approximately 9 times higher than the reference compound PBA at 2 mM. Using a reporter cell line-based high-throughput screening assay—similar to our approach—where the induction of the HBD1 gene serves as a reliable marker for enhanced innate immunity, benzamide-containing HDACi were identified as potent human HDP inducers. These HDACi may also play a role in maintaining intestinal barrier integrity by regulating key proteins, such as claudin-1, claudin-2, tight junction protein 1, and mucin 2 [131].

The pro- and anti-inflammatory phenotypes of immune cells are tightly regulated by epigenetic regulations, encompassing acetylation and deacetylation of histones where HDACs are crucial in repressing gene transcription. In sepsis, the expression of genes related to inflammation is disordered, causing massive hyper- and hypo-inflammation. Applying HDACi may help restore gene expression profiles and delay the progression of sepsis [132]. HDACi affects various cellular processes in cancer cells, including the cell cycle, apoptosis, DNA damage repair, and cell metabolism [133]. They are an important pharmacological class for HM treatment both as monotherapy and as adjuvant agents [133] and have been shown to ameliorate GvHD due to their immunomodulatory and anti-inflammatory properties [134,135]. Notably, HDACi also act as potent HDP inducers [130,131,136] and play a pivotal role in regulating immune cell activity, inflammation, cytokine production, and microbial makeup [137]. Entinostat can attenuate the inflammatory responses in macrophages by affecting the NF-κB pathway and the anti-inflammatory cytokine, IL-10. The anti-inflammation potential of Entinostat in the clinic was evaluated in a cigarette smoke-induced neutrophilic airway inflammation mouse model [138]. One of the obstacles to adopting HDACi as therapeutics has been linked to the lack of selectivity for different HDAC isoforms. Efforts are needed to explore the structure-activity relationships of various HDACis to design novel and potent HDACi for anti-infection and inflammation therapies [139]. Interleukin-15 (IL-15) is a well-known and efficient immune cell modulator, promoting the activation and expansion of NK cells, T cells, and B cells, which provides a possible strategy for cancer immunotherapy. The combination of IL-15 and different HDACis, a class of widely studied anticancer drugs (e.g., valproic acid (VPA), sodium butyrate, Romidepsin, trichostatin A (TSA), and suberoylanilide hydroxamic acid (SAHA)), have been proposed as a promising approach to treat HM. IL-15 may synergize with HDACi to activate NK and CD8+ T cells and enhance innate immune anti-tumor responses [140]. During macrophage differentiation by IL-15, the presence of $1,25(OH)_2D$ has been confirmed to be critical for human cathelicidin expression and the subsequent antimicrobial responses against invading pathogens like *Mycobacterium leprae* [141]. Therefore, adjunctive administration of vitamin D3 to hematological cancer patients undergoing treatment with HDACi and/or IL-15 may serve as a prophylactic measure to reduce the incidence of infections.

7. Conclusions and future considerations

BSI, sepsis, and the associated complications are common and can be life-threatening in patients with HM. Given the well-known challenges of antibiotic use, HDTs, which target the host rather than pathogens, have gained prominence due to their broad-spectrum effects and lower risk of developing resistance. The beneficial effects of HDTs have been demonstrated in conditions such as TB and sepsis, where current HDT candidates like vitamin D3 are often used as adjuvants. There are various approaches to applying HDTs to mitigate infections, and based on previous work from our group, natural- and synthetic ISIs that target the gut-immune axis are promising candidates [130,142]. Vitamin D3, microbial metabolites like butyrate, and certain HDACi are all potent ISIs and epigenetic regulators identified to date. These ISIs work through two main mechanisms: inducing HDPs, such as cathelicidins and defensins, and fortifying the intestinal and epidermal mucosal barriers, both of which enhance defenses against infections. Cathelicidins and defensins have been extensively studied for their antimicrobial activity in infectious diseases. In addition to their direct antimicrobial effects, HDPs interact with various cellular processes related to infection, such as NETs. A strong correlation has been observed between BSI occurrence and hypocitrullinemia, a marker of mucositis. These findings suggest that upregulating HDP expression and reinforcing mucosal barrier integrity, while maintaining a healthy microbiota, could be crucial in managing infections in HM patients.

The therapeutic- and prophylactic potential of ISIs, as a novel HDT approach to enhance innate immunity and combat infections in HM patients and beyond, warrants further exploration. Epigenetic regulation plays a crucial role in the control of innate immunity and has been extensively studied in this context [143]. Since many ISIs function as epigenetic regulators—primarily influencing histone and protein acetylation—there is a growing need for further research into how these epigenetic modifications contribute to ISI-induced enhancement of immune defenses. Intestinal cells are heterogenous and organized into different neighborhoods that form different communities, with cells in different regions having different compositions [144]. The cell type composition in the intestine differs when reacting to different bacterial infections [145]. Notably, intestinal stem cells can stimulate regulatory T cells in the gut to produce IL-10 for their renewal [146], and inflammation can induce changes in intestinal stem cells to alter gut mucosal tissues [147]. Single cell sequencing of the human intestinal tract has been increasingly studied and is well-documented on GutCellAtlas.org [147]. Understanding the epigenetic effects of ISIs at the single cell level could significantly enhance our knowledge of the detailed mechanisms by which ISIs modulate immune responses in the gut. It will be key to optimizing ISI-based therapies for immune-related conditions. Furthermore, the discovery of more potent and safer ISIs is crucial for the future, with the goal of developing approved drugs that are readily available to patients in need.

8. Practice points

1. HM patients with febrile neutropenia are at risk of MBI-LCBI, and an association was also noted between low citrulline levels and candidemia in adult patients with HM at fever onset.
2. The mortality rate of sepsis in patients with HM remains higher than in other septic patients.
3. HDT may improve the effectiveness of existing treatments (e.g., antibiotics) when administered adjunctively.
4. Adjunctive therapy with PBA and vitamin D3 as ISIs can induce the expression of HDPs and boost innate host defenses.
5. HDPs are natural broad-spectrum antibiotics linked to various diseases and infection risks. Cathelicidins and defensins are the two major classes of HDPs that exist in humans, where neutrophils and epithelial cells are the two main cell types producing HDPs.
6. HDPs are dysregulated in HM patients, and enhancing the expression of HDPs may protect patients from sepsis. For example, cathelicidins may preserve intestinal barrier integrity and modulate immune cell infiltration during sepsis.
7. Patients with HM are prone to and vulnerable to mucosal barrier injuries. The GI tract is composed of diverse cell types, forming a complex and intricate intestinal architecture where HDPs and ISIs play a protective role in preventing microbial invasions and strengthening the barrier.
8. The depth and duration of hypocitrullinemia, an indicator for severe intestinal mucositis, can predict the risk for BSI and classify the severity of intestinal injury.

9. Vitamin D3, butyrate produced by microbiota, FDA-approved drug phenylbutyrate, and certain HDACi are recognized as ISIs and have antimicrobial-, anti-inflammatory-, and immune-modulating properties.
10. There is a synergistic effect between vitamin D3 and other ISIs in immune modulation.
11. A novel class of ISIs, known as APDs, defined based on their chemical structure, was recently introduced, with benzamide-containing Entinostat as an example.
12. ISIs can induce HDPs and strengthen mucosal barriers, which have been shown in sepsis and HSCT.

9. Research agenda

1. Identify natural ISIs and develop synthetic approaches to create more potent, drug-like ISIs with improved efficacy and safety profiles for infection and mucositis
2. Explore the mechanisms of action of ISIs in ex vivo systems and animal infection models, such as the CLP-induced murine sepsis model, with a focus on epigenetic regulation. Special attention should be given to elucidating the synergistic interactions between Vitamin D3 and HDACi.
3. Assess the significance of HDACi in the observed effects on host immune defense and identify the specific or class of HDACi responsible; specifically, understand the structure-activity relationship (SAR) between APD compounds and their effects on innate immunity.
4. Apply comprehensive Omics technologies to systematically study the mechanisms and induced phenotypes of ISIs, both ex vivo and in animal models. This should include analysis of downstream gene/protein expression, as well as post-translational modifications such as protein acetylation and phosphorylation, to uncover key regulatory pathways.
5. Utilize single cell sequencing techniques to analyze the cellular dynamics within the intestine, offering detailed insights into the distinct changes induced by ISIs across various cell types.

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Declaration of competing interest

Egill Másson, Peter Bergman, Guðmundur Hrafn Guðmundsson have shares in Akthelia Pharmaceuticals developing ISIs as drugs against infections.

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