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REVIEW

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Hemophagocytic lymphohistiocytosis: current treatment advances, emerging targeted therapy and underlying mechanisms

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rapidly progressing, life-threatening syndrome characterized by excessive immune activation, often presenting as a complex cytokine storm. This hyperactive immune response can lead to multi-organ failure and systemic damage, resulting in an extremely short survival period if left untreated. Over the past decades, although HLH has garnered increasing attention from researchers, there have been few advancements in its treatment. The cytokine storm plays a crucial role in the treatment of HLH. Investigating the detailed mechanisms behind cytokine storms offers insights into targeted therapeutic approaches, potentially aiding in early intervention and improving the clinical outcome of HLH patients. To date, there is only one targeted therapy, emapalumab targeting interferon-γ, that has gained approval for primary HLH. This review aims to summarize the current treatment advances, emerging targeted therapeutics and underlying mechanisms of HLH, highlighting its newly discovered targets potentially involved in cytokine storms, which are expected to drive the development of novel treatments and offer fresh perspectives for future studies. Besides, multi-targeted combination therapy may be essential for disease control, but further trials are required to determine the optimal treatment mode for HLH.

Keywords Hemophagocytic lymphohistiocytosis, Cytokine storm, Pathogenic mechanisms, Targeted therapy, Emapalumab

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a fatal disease characterized by pathological immune activation and dysregulated inflammation that cause widespread tissue damage and multi-organ failure [1]. The first case related to HLH under the term "Histyocytic Medullary Reticulosis" was reported in 1939 by Scott and Robb-Smith in their seminal series of articles [2], and the inherited kind of HLH was then recognized in the mid-twentieth century with the name of familial hemophagocytic reticulosis [3] (Fig. 1). With the advancement of genetic technology, the subsequent identification of HLH-related gene mutations has enhanced the understanding of familial HLH and highlighted the importance of distinguishing between inherited (primary) and acquired (secondary) forms of the syndrome.

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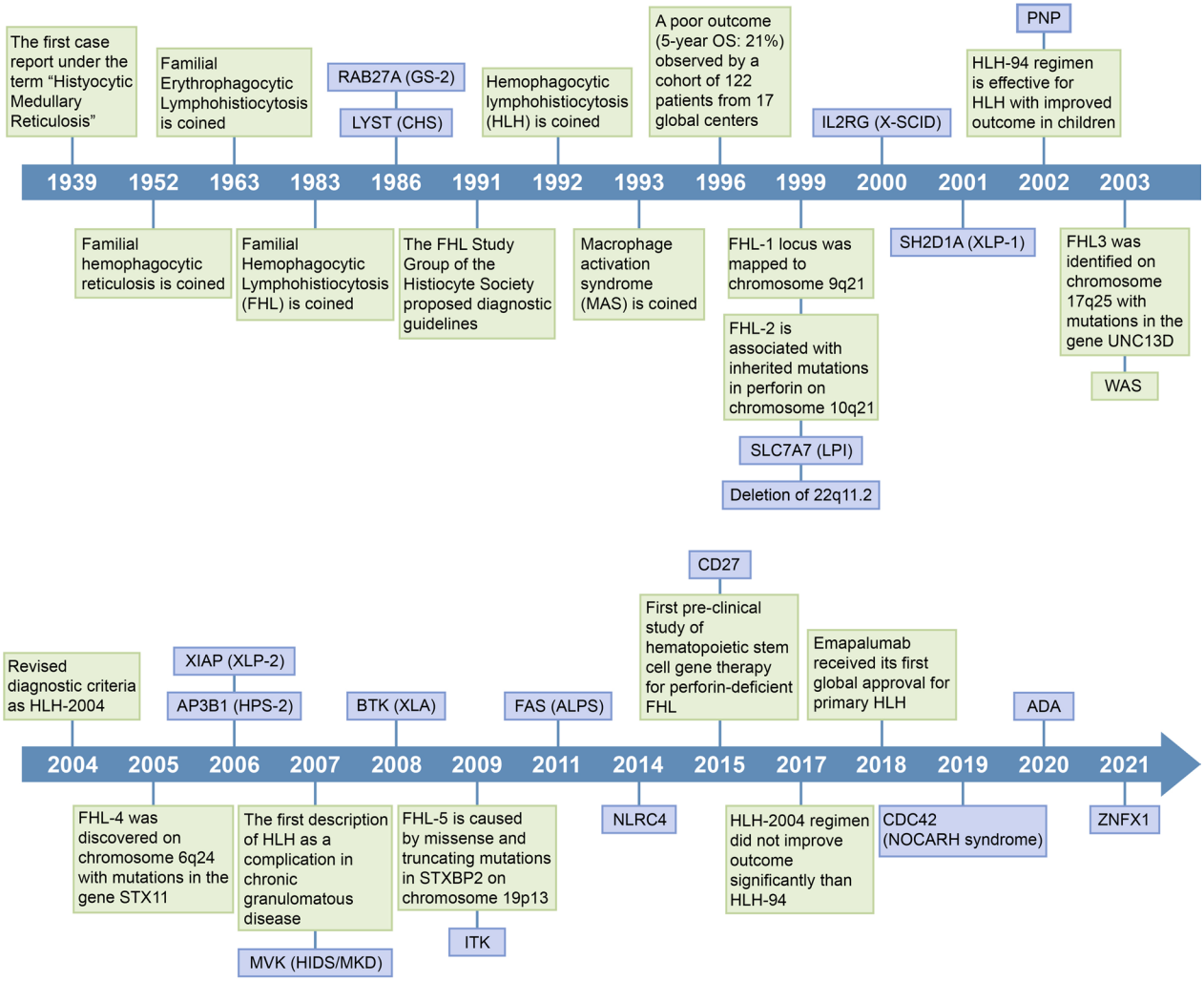

Fig. 1 Timeline of the history of hemophagocytic lymphohistiocytosis (HLH). The figure illustrates the key milestones in the discovery of HLH over the past 80 years. HLH was first described in 1939, and since then, various types of primary and secondary HLH have been defined gradually. Mutations in genes associated with HLH have also been progressively discovered. CHS chédiak-higashi syndrome, GS-2 griscelli syndrome type 2, LPI lysinuric protein intolerance, X-SCID X-linked severe combined immunodeficiency, XLP-1 X-linked lymphoproliferative sisease-1, HPS-2 hermansky–pudlak syndrome 2, XLP-2 X-linked lymphoproliferative disease-2, HIDS hyper-IgD syndrome, MKD mevalonate kinase deficiency, XLA X-linked agammaglobulinemia, ALPS autoimmune lymphoproliferative syndrome

The main clinical manifestations of HLH include fever, hepatosplenomegaly, lymphadenopathy, cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and multiorgan dysfunction, which may also lead to neurological symptoms [4]. HLH, diagnosed according to the HLH-2004 criteria and HScore, can be classified into primary HLH (pHLH) and secondary HLH (sHLH) based on the presence of underlying genetic defects (Fig. 2). Primary HLH is a rare but severe genetic immune system disorder, primarily caused by a group of genetic mutations associated with immune dysfunction such as *LYST*, *SH2D1A*, *PRF1*, etc [5–9]. Since allogeneic hematopoietic stem cell transplantation (HSCT) can effectively control the development of pHLH, early genetic testing to identify gene abnormalities for pHLH diagnosis is crucial for subsequent treatment and prognosis. On the other hand, patients with sHLH are believed to develop the syndrome as a complication triggered by various diseases, such as infection, malignancy, autoimmune disease, etc. Specifically, HLH secondary to rheumatic or autoinflammatory diseases is also referred to as macrophage activation syndrome (MAS), which is commonly seen in systemic juvenile idiopathic arthritis (sJIA), systemic lupus erythematosus (SLE), Kawasaki disease, and adult Still's disease (AOSD) [10–13].

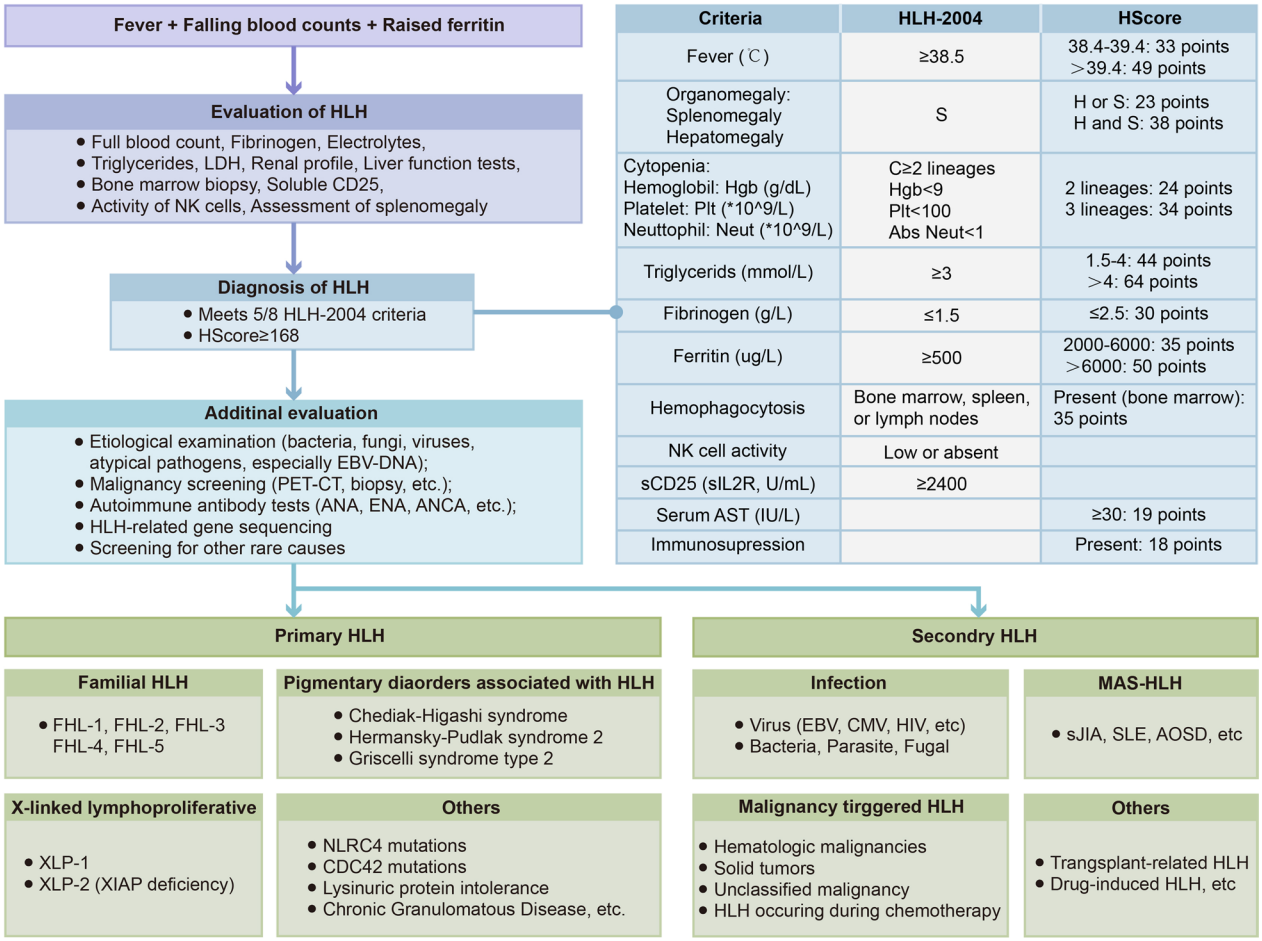

Fig. 2 Diagnostic process for hemophagocytic lymphohistiocytosis (HLH). This figure illustrates the diagnostic strategy for HLH, from initial clinical suspicion to differential diagnosis. One recent pHLH diagnostic guideline recommended incorporating functional testing of NK cells and cytotoxic T cells into the FHL diagnostic criteria, and proposed that the HLH-2004 criteria without testing NK cell function had a higher diagnostic accuracy for FHL at 99.0% (sensitivity 96.2%; specificity 99.5%) [464]. It is noteworthy that HLH can be the initial presentation of an undiagnosed malignancy, and malignancy-associated HLH typically indicates a poor prognosis [465]. The diagnosis of HLH still primarily relies on the HLH-2004 criteria, which often lack specificity in differentiating HLH from other hyperinflammatory disorders, especially in the context of malignancy. Therefore, the importance of imaging studies and biopsies should be emphasized, and all HLH patients may need to undergo tumor screening, and treating the primary malignancy is crucial for improving prognosis. MAS macrophage activation syndrome, LDH lactate dehydrogenase, EBV epstein-barr virus, PET-CT positron emission tomography-computed tomography, ANA Antinuclear Antibody, ENA extractable nuclear antigen, ANCA anti-neutrophil cytoplasmic antibody, FHL familial hemophagocytic lymphohistiocytosis, XLP X-linked lymphoproliferative disease, XIAP X-linked inhibitor of apoptosis protein, CMV cytomegalovirus, HIV human immunodeficiency virus, sJIA systemic juvenile idiopathic arthritis, SLE systemic lupus erythematosus, AOSD adult-onset still's disease, AST aspartate aminotransferase, Hgb hemoglobin, Plt platelet, Abs Neut absolute neutrophil count

Notably, it is a prerequisite for the diagnosis of sHLH to exclude any mutations in these known affected genes.

The reported 1-month mortality rate was 27.7% and the 1-year survival rate was 50% among HLH patients, underscoring the urgent need for the development of HLH treatment [14, 15]. The HLH-94 regimen remains to be the first-line treatment for controlling acute inflammation in HLH, but the therapeutic resistance and mortality rates are still clinically unacceptable [16, 17]. For pHLH patients with clear HLH-related genetic mutations or those with relapsed and refractory HLH, HSCT can be an option. However, progress in HLH treatment has been limited over the past decades, largely due to the unclear pathogenesis of HLH. For both primary and secondary HLH, the key treatment goal is to control the excessive secretion of inflammatory cytokines, including interleukin-2 (IL-2), IL-6, IL-18, interferon-γ (IFN-γ), etc. Therefore, targeting the inflammatory cytokines to inhibit the cytokine storm is one of the important treatment strategies for HLH. In 2018, the monoclonal antibody targeting

IFN-γ, emapalumab, has gained global approval for the treatment of HLH, marking the beginning of targeted therapies for HLH [18].

Hence, considering the delay in exploring HLH diagnosis and treatment, this review aims to provide a comprehensive overview of the preclinical and clinical advances in HLH therapy, highlighting potential innovative strategies targeting inflammatory cytokines and related key molecules. A deep understanding of potential therapeutic targets for HLH can further guide the design of clinical trials and help elucidate their roles in HLH development and disease control.

HLH pathogenesis

Regardless of whether HLH is the primary or secondary subtype, its pathogenesis and development involve a series of proinflammatory cytokines such as IFNγ, IL-1β, IL-6, IL-18, and TNF-α. T cells, NK cells and macrophages are predominantly responsible for the increased secretion of these inflammatory cytokines. However, despite having a hyperinflammatory storm similar to the cytokine release syndrome [19, 20], the specific pathogenic mechanisms of HLH remain not well understood. Nearly all types of HLH patients showed similar clinical manifestations, characterized by a systemic hyperinflammatory syndrome caused by a cytokine storm, leading to widespread tissue damage and multi-organ failure [21].

Under the normal condition, NK cells and cytotoxic T cells (CTLs) recognize target cells upon contact and form an immunological synapse, which then directionally release perforin and granzymes through exocytosis (Fig. 3) [22–25]. Perforin forms pores in the cell membrane, allowing granzymes to enter the target cell, triggering a series of enzymatic reactions that ultimately lead to apoptosis of the target cell [25]. However, in patients with pHLH, mutations in genes related to granule release function (such as *PRF1*, *UNC13D*, *STX11*, and *STXBP2*) prevent NK/cytotoxic T cells from effectively eliminating infected or abnormal cells, thereby prolonging the existence of the immunological synapse and leading to excessive production of inflammatory cytokines [26–28]. Simultaneously, the immune cells with impaired granule function fail to terminate the activation of antigen-presenting cells (macrophages, monocytes, and dendritic cells), resulting in sustained activation and proliferation of T cells, which further produce pro-inflammatory cytokines like IFNγ, thus forming a cytokine storm [29]. Although patients with sHLH do not usually have lymphocyte dysfunction caused by genetic abnormalities, the cytokine storm is usually triggered by external factors like infections, malignancies or autoimmune diseases that lead to excessive activation of macrophages (Fig. 3).

Currently reported HLH-related genes can be broadly classified into the following categories: Familial HLH genes (*PRF1* [5], *UNC13D* [30], *STX11* [31], *STXBP2* [32]), X-linked lymphoproliferative disease genes (*SH2D1A* [33], *XIAP* [34]), pigment abnormality genes (*LYST* [35], *RAB27A* [35], *AP3B1* [36]), immune deficiency genes (*IL2RG* [37], *WAS* [38], *CGD* [39], *BTK* [40], *ITK* [41], *FAS* [42], *NLRC4* [43], *CD27* [44], *CDC42* [45], *ZNFX1* [46], deletion of 22q11.2 [47]), and some inborn errors of metabolism genes (*SLC7A7* [48], *PNP* [49], *MVK* [50], *ADA* [51]). Genes affecting cellular degranulation include Familial HLH genes and pigment abnormality genes. Mechanisms of HLH caused by mutations in genes that do not affect degranulation mainly involve altering the function, proliferation and signal transduction of immune cells, rather than directly inhibiting the release of cytotoxic granules.

HLH therapy

Remission induction

The treatment of HLH is primarily divided into two phases: controlling excessive inflammation and replacing the defective immune system. The standard treatment for the first phase is based on chemotherapy with etoposide (HLH-94 treatment protocol), while the second phase typically involves achieving remission through allogenic HSCT (allo-HSCT) following myeloablative/reductive conditioning [52]. In the early 1990s, researchers from the International Histiocyte Society proposed a treatment regimen consisting of etoposide and corticosteroids (HLH-94), suggesting the use of etoposide (150 mg/m^2 intravenous injection, twice weekly during weeks 1–2, then weekly during weeks 3–8) in combination with dexamethasone [53]. This regimen significantly improved the survival rate of HLH patients [54], which has become the standard therapy for all types of HLH/MAS with lymphocytes and macrophages hyperactivated. Glucocorticoids can suppress the activation, differentiation and chemotaxis of inflammatory cytokines, thus controlling HLH characterized by excessive release of inflammatory cytokines. Etoposide is a widely used chemotherapeutic agent that inhibits topoisomerase II, and its mechanism for HLH treatment may involve effectively and selectively eliminating activated T cells and inhibiting the production of inflammatory cytokines [55, 56]. Subsequently, the HLH 2004 trial was conducted, suggesting that adding cyclosporine to the HLH-94 regimen did not help control acute immune activation [57]. The early response to etoposide could quite effectively predict the later mortality rate, but a small fraction of patients did not respond well [58, 59]. A potential

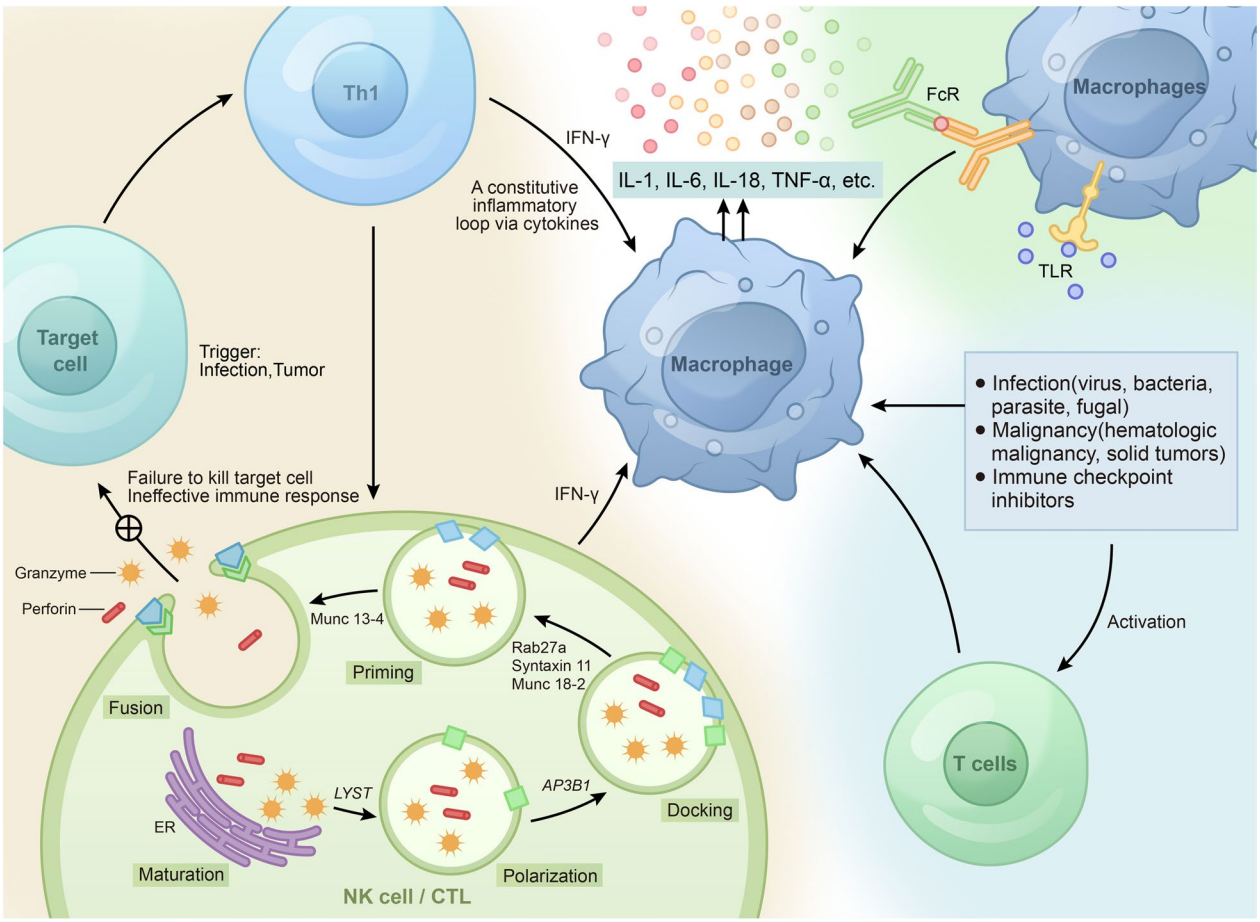

Fig. 3 Schematic diagram of the pathogenesis of hemophagocytic lymphohistiocytosis (HLH). The impaired ability of natural killer cells and cytotoxic T cells to secrete perforin and granzyme results in defective clearance of target cells, leading to sustained immune cell activation and excessive production of cytokines such as interleukin-1 (IL-1), IL-6, IL-18, and tumor necrosis factor-α (TNF-α). The intense pro-inflammatory response mediated by macrophages may also be due to increased production of autoantibodies and immune complexes, resulting in abnormal immune system activation and subsequently persistent inflammatory reactions. Infections, malignancies, and immune checkpoint inhibitors can also lead to excessive immune system activation, causing hyperactivity of macrophages and T cells, which release large amounts of pro-inflammatory cytokines, resulting in a cytokine storm

drawback of etoposide-based therapy is bone marrow suppression, with some patients experiencing invasive fungal or bacterial infections during treatment.

About 30% of HLH patients did not respond to the standard HLH-94 protocol, and lower than 60% of them achieved disease-free survival through this regimen [60]. Previous studies suggested that the L-DEP regimen (PEG-asparaginase combined with liposomal doxorubicin, etoposide, and methylprednisolone) showed some efficacy as salvage therapy for refractory Epstein-Barr virus (EBV)-related HLH, achieving an overall response rate (ORR) of approximately 80% and a significant reduction in EBV-DNA load [61–63]. However, a significant decrease in early EBV-DNA load did not predict better long-term outcomes; therefore, once complete remission is achieved, allo-HSCT should be promptly considered [61].

Allogeneic hematopoietic stem cell transplantation

Although chemotherapy based on the HLH 94/04 protocol can be used for initial treatment, allo-HSCT remains to be the only potentially curative treatment for HLH [64]. However, when transplantation is performed in patients with active disease, allo-HSCT appears to be associated with adverse outcomes. Lai et al. reported in 2018 that the survival rate was higher than 50% when patients underwent allo-HSCT after achieving remission; however, the survival rate was only 33% when patients had active HLH before allo-HSCT [65]. It was reported that a reduced-intensity

conditioning (RIC) regimen seemed to be more beneficial [66, 67]. Moreover, utilizing early alemtuzumab before RIC regimen had great tolerability and efficacy [66, 67].

However, it is important to be vigilant that HLH can also occur post allogeneic and autologous HSCT, especially associated with graft-versus-host disease (GVHD) in patients undergoing allo-HSCT [68, 69]. HLH typically occurs in the early phase, within 2–6 weeks post allo-HSCT [70]. Infections, particularly EBV and cytomegalovirus (CMV), can be triggering factors for HLH. Mortality rates were found obviously high in patients with HLH secondary to infections [71]. Multicenter studies reported an estimated incidence of HLH post allo-HSCT at 1.09%, significantly lower after autologous HSCT at 0.15% [72].

Gene therapy and adoptive T cell therapy

Gene therapy, utilizing virus vector-mediated gene transfer into autologous hematopoietic stem cells, has been demonstrated to cure various severe monogenic immunodeficiencies [73, 74]. One preclinical studies in $Prf^{-/-}$ mouse models suggested a significant correction of cytotoxic defects both in vitro and in vivo upon transplantation of *PRF1* gene-corrected hematopoietic stem cells and $CD8^+$ T cells [75, 76]. Jinx mice were used as a preclinical mouse model for familial HLH 3 (FHL3). Studies showed that transferring the lentiviral *UNC13D* gene into Jinx hematopoietic stem cells (HSCs) could restore T cell function in transplanted Jinx mice [77, 78]. Moreover, using lentivirus as a vector restored Munc13-4 expression and degranulation capacity in T cells from FHL3 patients and HSCs from FHL3 disease model mice [78]. The further research demonstrated that effective gene editing of Jinx mouse HSCs resulted in functional T cell responses with a diverse T cell receptor (TCR) repertoire, exhibiting rapid virus clearance and protection against HLH [74]. In X-linked lymphoproliferative disease (XLP)-1 mouse models, HSC gene correction was also able to improve the immunological manifestations of the disease and overcome HSCT-related complications [79].

Adoptive T cell therapy (ATCT) was found to be able to partially restore cellular cytolytic activity in HLH. Kristoffer et al. transferred functional virus-specific T cells into mice models of pHLH ($Prf^{-/-}$ mice and Jinx mice) [80]. The transferred T cells eliminated HLH-inducing viral triggers, silenced disease processes, cured excessive inflammation in Jinx mice and protected HLH mice from fatal HLH progression, without life-threatening side effects. The cured mice were able to avoid HLH recurrence in the long term [80].

Therapy for CNS-HLH

Primary HLH may present with isolated neurological symptoms, which can occur months before the appearance of systemic manifestations of HLH [81]. Therefore, performing a lumbar puncture for screening is necessary to differentiate the central nervous system involvement of HLH (CNS-HLH) from similar conditions such as demyelinating syndromes, chronic infections, malignancies and CNS vasculitis. For CNS-HLH patients, in addition to the systemic treatment, intrathecal injections of methotrexate and dexamethasone can be additionally performed. Receiving HSCT after the systemic treatment of HLH appears to be crucial for improving survival and neurological outcomes [82].

Emerging targeted therapy and mechanisms for HLH

In 20–30% of adult cases, HLH is refractory to first-line treatment or relapses after initial remission [83]. There is still lack of standardized treatment approach for relapsed/refractory pHLH patients, and cure is often achieved only through allo-HSCT, but approximately 20–25% of HLH patients died before transplantation [60, 84, 85]. It is worth mentioning that treatment delay was reported to be an independent poor prognostic factor for HLH, reflecting the importance of early selection of the appropriate treatment to break the cycle of immune dysregulation [86].

Due to the critical role of excessive immune activation and elevated cytokinemia in the pathogenesis of HLH, several targets have been proposed in recent years, including IFN-γ, Janus kinase-signal transducer and activator of transcription (JAK-STAT), IL-6, TNF-α, IL-1, IL-18, CD52, CD20 and programmed cell death protein 1 (PD-1) (Fig. 4). Preclinical studies and clinical investigations, including clinical trials and exploratory clinical studies, concerning the aforementioned targets were also compiled and summarized (Tables 1, 2, 3, 4).

Targeting IFN-γ

IFN-γ, belonging to type II interferons, is a soluble cytokine produced by T lymphocytes, macrophages, NK cells, and other immune cells [87]. The production of IFN-γ is mainly regulated by cytokine stimulation (such as IL-18), antigen stimulation, and other immune stimuli [88, 89]. IFN-γ can bind to the IFN-γ receptor (IFNGR), activate the JAK-STAT pathway and induce the expression of IFN-γ-stimulated genes, playing important roles in tissue homeostasis, immunity, inflammation and tumor immune surveillance [87, 90]. IFN-γ binds to its cell surface receptor IFNGR1 and induces IFNGR1 dimerization, then binding to two IFNGR2 to form a

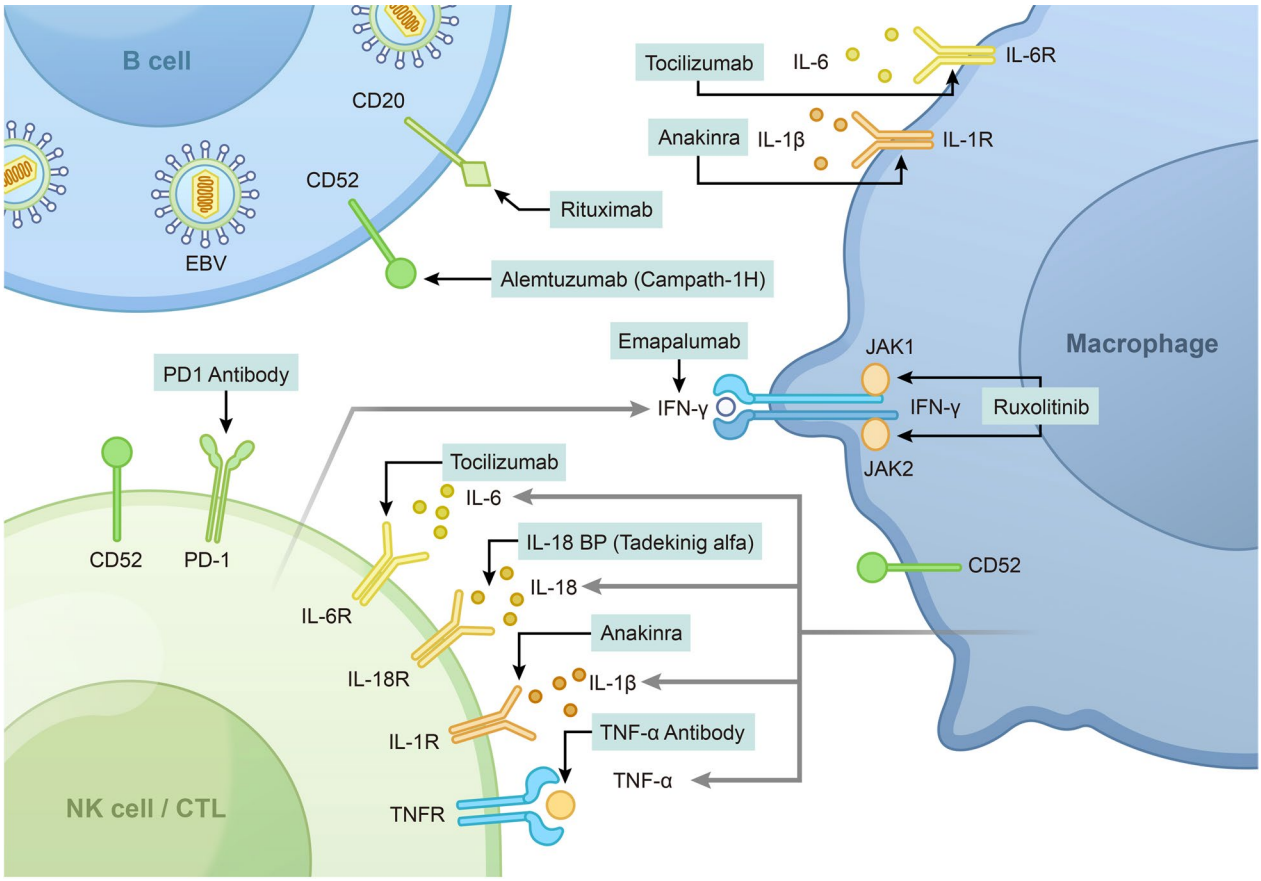

Fig. 4 Schematic representation of targeted therapy for hemophagocytic lymphohistiocytosis (HLH). HLH is a syndrome characterized by excessive immune activation. Therapeutic strategies to mitigate inflammatory responses involve the inhibition of key cytokines and signaling pathways. EBV epstein-barr virus

receptor complex. In this receptor complex, IFNGR1 activates the JAK1 kinase, while IFNGR2 activates the JAK2 kinase [91]. Activation of JAK1 and JAK2 can lead to receptor phosphorylation, recruiting and phosphorylating STAT1 [91, 92]. Phosphorylated STAT1 forms dimers and trans-locates to the nucleus, where it can bind to the Gamma-activated sequence (GAS) in the promoter region of target genes, thereby regulating the transcription of downstream genes [93]. Many genes regulated by the IFN-γ/STAT1 signaling pathway are transcription factors, thus the IFN-γ/STAT1 signaling pathway indirectly regulates the expression of more downstream genes [94]. Meanwhile, the IFN-γ/STAT1 signaling pathway can activate MAPK, PI3K-AKT, and NF-κB signaling pathways, enabling IFN-γ/STAT1 to participate in the regulation of the expression of more genes [95].

The loss of cytotoxic function in $CD8^+$ T cells can lead to immune imbalance, promoting abnormal and excessive production of IFN-γ [96]. IFN-γ is a classical activator of macrophages and mediates polarization of macrophages towards the M1 phenotype [87, 96]. M1 macrophages exhibit strong pro-inflammatory properties and release inflammatory mediators such as IL-1β, IL-6, TNF-α, etc [97, 98]. Peripheral levels of IFN-γ were elevated in both primary and secondary HLH patients, with its levels correlating with clinical status, being elevated in active HLH but lower than detection levels in remission patients and healthy controls [99, 100]. Furthermore, one research has shown that IFN-γ was associated with liver function damage and coagulation disorders, and could directly act on macrophages in vivo, altering phagocytic activity and stimulating blood cell uptake, leading to severe anemia [100–102].

In one pre-clinical study, the anti-IFN-γ antibody significantly improved bone marrow function and survival in perforin-deficient mice after lymphocytic choriomeningitis virus (LCMV) infection [103]. In a mouse model of CpG DNA induced sHLH, the development of HLH was also found to be IFN-γ dependent [104]. However, the efficacy of anti-IFN-γ antibody in secondary HLH murine models is limited, possibly due to the distinct biological mechanisms between pHLH and sHLH [105].

Table 1 Targeted therapy for hemophagocytic lymphohistiocytosis (HLH) in ongoing clinical trials

Target	NCT Number	HLH type	Interventions	Phase	No. Patient	Start Date	Study status
IFN-γ	NCT06038422	R/R HLH	GTP	3	15	2023/9/15	Not yet recruiting
IFN-γ	NCT05744063	Primary HLH	Emapalumab	4	13	2023/2/3	Active not recruiting
IFN-γ	NCT05001737	MAS	Emapalumab	3	41	2021/12/15	Recruiting
JAK1/2	NCT06244862	Severe HLH	Ruxolitinib	2	42	2024/2/1	Not yet recruiting
JAK1/2	NCT06160791	HLH	Ruxolitinib + ED	2	36	2024/2/1	Not yet recruiting
JAK1/2	NCT05762640	Primary HLH	Ruxolitinib	2	20	2024/3/1	Not yet recruiting
JAK1/2	NCT05491304	Pediatric HLH	Ruxolitinib + ED	4	400	2022/9/1	Recruiting
JAK1/2	NCT05137496	MAS	Ruxolitinib + methylprednisolone	3	40	2022/6/1	Not yet recruiting
JAK1/2	NCT04999878	Lymphoma-associated HLH	RUE-DDGP	4	30	2021/5/30	Recruiting
JAK1/2	NCT04551131	HLH	Ruxolitinib + ED	1/2	62	2021/7/13	Recruiting
JAK1/2	NCT04120090	R/R HLH	ruxolitinib	3	80	2019/7/1	Unknown
JAK1/2	NCT03795909	R/R HLH	Ruxolitinib + Dex	1/2	50	2017/3/1	Unknown
JAK1	NCT05063110	Non-severe HLH	Itacitinib	2	63	2022/5/1	Recruiting
JAK2	NCT04326348	HLH	TQ05105	1	40	2020/7/17	Unknown
IL-6	NCT02007239	HLH	Tocilizumab	2	NA	2013/12/1	Withdrawn
IL-1	NCT02780583	MAS	Anakinra	1	40	2016/5/15	Active not recruiting
IL-18	NCT03512314	NLRC4-MAS, XIAP Deficiency	Tadekinig alfa (IL-18BP)	3	10	2018/1/24	Active not recruiting
CD52	NCT01821781	HLH	Conditioning regimen before HSCT: Flu + Mel + Alem + thiotepa	2	20	2013/3/1	Recruiting
CD20	NCT05384743	EBV-HLH	Rituximab	3	30	2022/2/1	Unknown
CD20	NCT05258136	EBV-HLH	CD20 monoclonal antibody	NA	20	2021/6/1	Enrolling by invitation
PD-1	NCT05008666	ENKTL-HLH	Sintilimab + chidamide + azacitidine	2	37	2021/12/1	Unknown
PD-1	NCT05775705	HLH	PD-1 antibody + L-DEP	3	25	2023/8/1	Not yet recruiting
PD-1	NCT05315336	HLH	PD-1 antibody + L-DEP	3	50	2022/6/1	Not yet recruiting
PD-1	NCT05164978	HLH	PD-1 antibody + DEP	NA	20	2021/5/1	Unknown
PD-1	NCT05039580	HLH	PD-1 antibody + L-DEP	4	36	2021/5/15	Unknown
PD-1	NCT04084626	HLH	PD-1 antibody + lenalidomide	3	40	2019/9/15	Unknown
PD-1	NCT04944511	HLH after allo-HSCT	Toripalimab	NA	20	2021/7/1	Unknown
PD-1	NCT04690036	EBV-HLH after transplantation	Toripalimab	1	20	2021/7/1	Unknown
IL-18 + IL-1β	NCT04641442	NLRC4-GOF, XIAP Deficiency, CDC42 Mutations	MAS825 (anti-IL-1β/IL-18)	2	18	2020/12/18	Recruiting

IFN-γ interferon-γ; *JAK1/2* Janus kinase 1/2; *IL-1* interleukin-1; *IL-6* interleukin-6; *IL-18* interleukin-18; *PD-1* programmed death 1; *IL-1β* interleukin-1 beta; *R/R* relapsed/refractory; *MAS* macrophage activation syndrome; *Allo-HSCT* allogeneic hematopoietic stem cell transplant; *EBV* Epstein-Barr virus; *GTP* emapalumab + teniposide + methylprednisolone; *ED* etoposide + dexamethasone; *Dex* dexamethasone; *RUE-DDGP* Ruxolitinib + Etoposide + cisplatinum + Dexamethasone + Gemcitabine + Pegaspargase; *Flu* + *Mel* + *Alem* + *thiotepa* fludarabine + melphalan + alemtuzumab + thiotepa; *DEP* liposomal doxorubicin, etoposide, and methylprednisolone; *L-DEP* PEG-asparaginase combined with liposomal doxorubicin, etoposide, and methylprednisolone; *IL-18BP* IL-18 binding protein

Emapalumab is a fully human IgG1 monoclonal antibody targeting IFN-γ, capable of binding both free-form and receptor-bound IFN-γ (inhibiting receptor dimerization and IFN-γ signal transduction) and neutralizing its biological activity [106]. It is the first targeted therapy approved for HLH treatment, especially beneficial to patients unresponsive to conventional treatment [106, 107]. A phase 2–3, open-label, single-group study demonstrated that 27 relapsed/refractory (r/r) pHLH patients treated with a combination of emapalumab, dexamethasone and others achieved a remission rate of 63%, with a low incidence rate of adverse events [108]. Another potential advantage of IFN-γ blockade therapy for pHLH may be its ability to improve engraftment in allo-HSCT, preventing and treating graft failure [109–111]. In a prospective single-arm trial involving 14 patients with treatment-refractory HLH/ MAS who did not respond to high-dose corticosteroids (with or without anakinra), all clinical and laboratory parameters showed rapid improvement after treatment with anti-IFN-γ

Table 2 Targeted therapy and associated results for hemophagocytic lymphohistiocytosis (HLH) in completed clinical trials

Target	NCT number	HLH type	Interventions	Phase	No. patient	Start date	Last update posted	Outcome
IFN-γ	NCT01818492	Primary HLH	NI-0501 (Anti-IFNγ mAb) + glucocorticosteroid, HSCT	2/3	34	2013/7/1	2023/2/21	ORR 53%, CR 21%, PR 32%
IFN-γ	NCT02069899	Primary HLH	Emapalumab, HSCT	2/3	34	2014/8/4	2022/6/28	ORR 47%, CR 21%, PR 26%, 1-year OS 71%
IFN-γ	NCT03312751	Primary HLH	Emapalumab, HSCT	3	35	2019/2/6	2024/3/12	ORR 42.8%, CR 11.4%, PR 31.4%, 1.5-year OS 54.3%
IFN-γ	NCT03311854	MAS	Emapalumab	2	14	2018/2/20	2022/5/17	ORR 93%, 1-year OS 100%
IFN-γ	NCT03985423	HLH	Emapalumab	2/3	NA	2020/6/2	2023/10/6	NA
JAK1/2	NCT02400463	Secondary HLH	Ruxolitinib + Dex	2	5	2016/2/5	2021/1/25	ORR 100%, CR 60%, PR 40%, 2-mouth OS 100%
JAK1/2	NCT03533790	R/R HLH	Ruxolitinib-DEP	3	54	2018/6/1	2018/5/30	Excluding 12 patients who had previously received DEP: ORR 78%, CR 19.5%, PR 58.5% R/R HLH patients who had previously received DEP: PR 58.3%
IL-18	NCT03113760	NLRC4-MAS, XIAP Deficiency	Tadekinig alfa (IL-18BP)	3	NA	2017/7/21	2024/2/2	NA
CD52	NCT01998633	HLH	Conditioning regimen before HSCT: Flu + Mel + Alem	2	34	2013/12/1	2022/12/8	1.5-year OS 68%
CD52	NCT02472054	HLH	Alemtuzumab + MP + CSA	1/2	NA	2015/6/29	2021/4/15	NA
CD52	NCT00368355	HLH	Conditioning regimen before HSCT: Ara-C + CTX + Alem + TBI	2	NA	2000/4/1	2020/1/21	NA
CD52	NCT00176865	HLH	Conditioning regimen before HSCT: Flu + Mel + Alem/ATG	2	19	2002/8/1	2017/12/28	1-year OS 68.4%
IL-1/IL-6	NCT04339712	COVID-19-associated MAS	Anakinra or Tocilizumab	2	NA	2020/4/2	2021/1/11	NA
CD52/IL6	NCT02385110	HLH	Alemtuzumab/Tocilizumab + Etoposide + Dexamethasone	2	18	2015/9/23	2024/1/17	7-year OS 50%/42.75%
IL-1 + IL18	NCT06309823	XIAP Deficiency	MAS825	3	NA	2023/2/8	2024/3/13	NA

IFN-γ interferon-γ; *JAK1/2* Janus kinase 1/2; *IL-18* interleukin-18; *IL-1* interleukin-1; *IL-6* interleukin-6; *MAS* macrophage activation syndrome; *R/R* relapsed/refractory; *HSCT* hematopoietic stem cell transplant; *DEX* dexamethasone; *DEP* liposomal doxorubicin, etoposide, and methylprednisolone; *IL-18BP* IL-18 binding protein; *Flu + Mel + Alem* fludarabine + melphalan + alemtuzumab; *ATG* Anti-Thymocyte Globulin; *Ara-C* cytarabine; *CTX* cyclophosphamide; *TBI* Total Body Irradiation; *ORR* overall response rate; *CR* complete response; *PR* partial response; *OS* overall survival; *NA* not available

[112]. By week 8, 13 out of 14 patients achieved remission within a median time of 25 days [112]. Therefore, emapalumab may be an important additional treatment option for HLH, and patients often respond well to it, which is helpful in gradually discontinuing steroids [113]. When used in combination with etoposide, there is rarely a need for etoposide administration more frequently than once a week or every two weeks [113].

Patients with HLH often have concurrent infections. There have been case reports of refractory HLH patients with multiple severe and complicated infections that were treated with emapalumab and supportive antimicrobial therapy [114, 115]. Following this treatment regimen, all clinical symptoms and laboratory parameters gradually became normalized. Additionally, in patients with HLH complicated by severe infection, the inhibition

Table 3 Preclinical studies on targeted therapy for hemophagocytic lymphohistiocytosis (HLH)

Target	PMID	Authors	Year	Model	Treatment	Highlights
IFN-γ	20,049,711	Jana Pachlopnik Schmid et al	2009	Prf1-/- pHLH by LCMV; Rab27a-/- pHLH by LCMV	Anti-IFN-γ (0.5 mg, every third day)	Anti-IFN-γ therapy led to recovery from hemophagocytosis in genetic models, improving survival, correcting blood cytopenia, stabilizing body temperature, reducing cytokine levels, restoring splenic structure, and decreasing liver hemophagocytosis Anti-IFN-γ therapy protected the central nervous system in Rab27a-deficient mice
IL-18	22,891,066	Laura Chiossone et al	2012	Prf1-/- pHLH by MCMV;	IL-18BP (10 μg, qd)	IL-18BP reduced hemophagocytosis and repaired liver and spleen damage IL-18BP also lowered IFN-γ and TNF-α production in CD8 + T and NK cells and decreased Fas ligand expression on NK cells Antiviral drug and IL-18BP combination therapy prevents organ damage
JAK1/2	26,825,707	Rupali Das et al	2016	Prf1-/- pHLH by LCMV; sHLH by CpG	Ruxolitinib (90 mg/kg, bid);	Ruxolitinib ameliorates the hematologic manifestations, lowers serum cytokine levels and reduces tissue inflammation in CpG-treated mice Ruxolitinib lessens the manifestations, enhances survival and reduces T-cell expansion in LCMV-induced HLH Ruxolitinib lowers T-cell cytokine production without affecting degranulation or cytotoxicity in LCMV-induced HLH Ruxolitinib inhibits STAT1-dependent gene expression in T cells from infected Prf1-/- mice
JAK1/2, IFN-γ	27,222,478	Sophia Maschalidi et al	2016	Prf1-/- pHLH by LCMV; ab27a-/- pHLH by LCMV	Ruxolitinib (1 mg/kg, bid); Anti-INF-γ (1 mg, every third day)	Ruxolitinib therapy enhances survival in Prf1 − /− mice, improves clinical and biological signs of HLH, and reduces inflammatory macrophage infiltration in tissues Ruxolitinib significantly lessens central nervous system involvement in Rab27a(-/-) mice
JAK1/2, IFN-γ	31,015,190	Sabrin Albeituni et al	2019	Prf1-/- pHLH by LCMV; sHLH by CpG + αIL-10R	Ruxolitinib (90 mg/kg, bid); Anti-IFN-γ (0.5 mg, every third day)	Ruxolitinib and Anti-IFN-γ reduced inflammation-associated anemia in both models Ruxolitinib operates through IFN-γ-dependent and -independent mechanisms to dampen HLH by targeting the deleterious effects of T cells and neutrophils
JAK1/2	32,530,039	Lauren K Meyer et al	2020	Prf1-/- pHLH by LCMV	Dexamethasone (1.5 mg/kg/d); Ruxolitinib (60 mg/kg, bid)	JAK/STAT pathway inhibition enhances CD8 T cell sensitivity to dexamethasone-induced apoptosis during hyperinflammation Dexamethasone and Ruxolitinib synergistically reduce hyperinflammation in a murine HLH model

Table 3 (continued)

Target	PMID	Authors	Year	Model	Treatment	Highlights
JAK1/2, JAK1, IFN-γ	34,232,994	Vandana Chaturvedi et al	2021	Prf1-/- pHLH by LCMV	Ruxolitinib (1 mg/kg; 90 mg/kg, bid); JAK1 inhibitor AZD4205 (25 mg/kg bid); Anti-IFN-γ (40 mg/kg, every 3 to 4 days)	Continuous IFN-γ signaling blockade is essential for HLH control; JAK2 inhibition, unlike JAK1, is toxic in experimental HLH
TNF-α, IFN-γ	33,278,357	Rajendra Karki et al	2021	sHLH by Poly I:C + LPS	TNF-α and IFN-γ Antibodies	Treatment with TNF-α and IFN-γ blocking antibodies fully protected against lethality in an HLH model
IFN-γ, IL-6, IL-18, JAK1/2	35,973,477	Josée-Anne Joly et al	2023	Prf1-/- pHLH by LCMV	Anti-IFN-γ (0.2 mg, every 3 days); Anti-IL-6R (0.5 mg, every 3 days); Anti-IL-18 (0.2 mg, every 3 days); Ruxolitinib (4 mg/kg bid)	Anti-IFN-γ antibodies and ruxolitinib effectively control HLH; Combining IL-6 signaling inhibition with IFN-γ blockade does not enhance treatment response Anti-IL-18 with ruxolitinib or IFN-γ blockade is not more effective than monotherapies Ruxolitinib combined with anti-IFN-γ antibodies leads to rapid HLH resolution
JAK1/2, IFN-γ	37,228,616	Sabrin Albeituni et al	2023	Prf1-/- pHLH by LCMV;	Ruxolitinib (90 mg/kg, bid); Anti-IFN-γ (0.5 mg, every third day)	Anti-IFN-γ alone or with ruxolitinib effectively reverses anemia and lowers serum IFNg levels Combining ruxolitinib and anti-IFN-γ does not improve inflammation reduction compared to either drug alone
JAK1/2, JAK1, JAK2	38,446,698	Camille Keenan et al	2024	Prf1-/- pHLH by LCMV; sHLH by CpG + αIL-10R	JAK1 inhibitor itacitinib (120 mg/kg bid); JAK2 inhibitor fedratinib (60 mg/kg bid); JAK1/2 inhibitor ruxolitinib (90 mg/kg bid)	Selective JAK1 inhibition reduces disease manifestations in secondary HLH Combined JAK1 and JAK2 inhibition is needed for optimal improvement in both primary and secondary HLH
JAK1/2	38,621,611	Honglan Wang et al	2024	sHLH by CpG; sHLH by Poly I:C + LPS	M NP-R (Ruxolitinib was encapsulated into macrophage membrane-coated nanoparticles)	M NP-R significantly improved clinical and laboratory signs of HLH M NP-R greatly increased survival in lethal HLH mice

IFN-γ interferon-γ; *JAK1/2* Janus kinase 1/2; *IL-6* interleukin-6; *IL-18* interleukin-18; *TNF-α* tumor necrosis factor-α; *pHLH* primary HLH; *sHLH* secondary HLH; *LCMV* lymphocytic choriomeningitis virus; *MCMV* murine cytomegalovirus; *IL-18BP* IL-18 binding protein

Table 4 Exploratory clinical studies on targeted therapy for hemophagocytic lymphohistiocytosis (HLH)

Target	PMID	Authors	Year	HLH type	Age	No. Patient	Treatment	Outcome
JAK1/2	23,692,048	DeepakBabu Chellapandian	2013	Secondary HLH	6.75 (1.2–44)	42	Rituximab,etoposide, dexamethasone, cyclosporine A	ORR 43% Median OS 1120 d Significant reductions in EBV load
CD52	22,522,603	Rebecca A Marsh	2013	Refractory HLH	6 (0.1–24)	22	Alemtuzumab	2-week PR 64% Treatment with alemtuzumab allowed 77% of patients with refractory HLH to survive until HSCT
CD52	23,131,490	Rebecca A Marsh	2013	XIAP	3 (0.4–19)	19	RIC (alemtuzumab, fludarabine, busulfan) (n = 10); other conditioning regimens (MAC, etc.); HSCT	1-year OS RIC: 57%, MAC: 14% RIC and remission from HLH: 86%
CD52	24,035,782	Rebecca A Marsh	2013	Primary HLH	Proximal RIC: 3.9 (0.25–25.5) Intermediate RIC: 4 (0.41–24.3) Distal RIC: 6.1 (0.43–10.8)	71	Proximal/ Intermediate/ Distal RIC (alemtuzumab, fludarabine, busulfan); HSCT	1-year OS 80–91% The intermediate RIC regimen decreases the risk of mixed chimerism, carries a minimal risk of upfront acute GVHD, and reduces the need for additional hematopoietic cell products after HSCT
CD52	24,923,536	Rebecca A Marsh	2014	XLP1	6.1 (1.8–17.7)	16	RIC (alemtuzumab, fludarabine, busulfan) (n = 16); HSCT	1-year OS 80%
JAK1/2	30,061,947	Yu Chang	2018	LAHS	36 (4–76)	57	Rituximab and other chemotherapy regimens	Median OS 43 days The outcome of patients with B-cell LAHS may be significantly improved following treatment with rituximab
IL-1	28,631,531	Philipp Wohlfarth	2019	Severe HLH	38 (20–58)	8	Anakinra, Corticosteroid, IVIG	Hospital survival rate: 50%
JAK1/2	32,666,469	Ang Wei	2020	R/R HLH	1.7 (0.75–5)	9	Ruxolitinib, dexamethasone	D7: PR 33.3%, improvement 55.6%, death 11.1%
JAK1/2	32,690,141	Han Wang	2020	Secondary HLH	45 (24–52)	3	Ruxolitinib, etoposide, dexamethasone	All patients had rapid response to treatment without obvious adverse effects
JAK1/2	32,617,699	Lanlan Zhou	2020	Secondary HLH	NA	36	R-DED (ruxolitinib, doxorubicin, etoposide, dexamethasone);	2 weeks: ORR 83.3% median OS: 5mouths
JAK1/2	32,447,592	Nicholas J Gloude	2020	Refractory HLH	HLH + TMA: 1.5 (0.4–23) HLH: 1 (0.1–4)	23	HLH + TMA: emapalumab, eculizumab, HLH: emapalumab	All patients who received eculizumab and emapalumab had complete resolution of their TMA and survived
JAK1/2	31,515,353	Jingshi Wang	2020	R/R HLH	27.5 (2–70)	34	Ruxolitinib, dexamethasone	ORR 73.5%, CR 14.7%, PR 58.8%

Table 4 (continued)

Target	PMID	Authors	Year	HLH type	Age	No. Patient	Treatment	Outcome
IL-6	32,321,563	Etienne Dufranc	2020	Secondary HLH	54.5 (23, 66)	9	Tocilizumab, dexamethasone, etoposide, cyclophosphamide	ORR 88.9%
IL-1	31,513,353	Esraa M Eloseily	2020	Secondary HLH	10 (1–19)	44	Anakinra	Anakinra appears to be effective in treating pediatric patients with non-malignancy-associated secondary HLH/MAS
IL-1	32,725,881	Sakshi Bami	2020	Secondary HLH	1.8 (0.8–14.9)	6	Anakinra, dexamethasone	3-year OS 83%
PD-1	31,914,172	Pengpeng Liu	2020	R/R EBV-HLH	23 (15–36)	7	Nivolumab	CR 71.4%
JAK1/2	33,523,540	Sarah Hansen	2021	Secondary HLH	35.5 (20–56)	4	Ruxolitinib, etoposide, dexamethasone	All patients had rapid, sustained improvement in clinical status, inflammatory markers, and hematological cell counts followed by durable remission
JAK1/2	32,732,367	Qing Zhang	2021	Secondary HLH	4.7 (1.3–13.4)	12	Ruxolitinib	D28: ORR 83.3%, CR 66.7%, PR 8.3%, improvement 8.3%; 87.5% CR > 6 mouths EBV-HLH: CR 75%, PR 25%
JAK1/2	33,794,928	Ying Chi	2021	Secondary HLH	3.3 (1–6)	11	Ruxolitinib, etoposide, dexamethasone, cyclosporine A	Patients treated with ruxolitinib: The glucocorticoid dosage was significantly lower; The body temperature decreased to normal levels more rapidly;
JAK1/2	33,826,999	Guang-Qiang Meng	2021	EBV-HLH	37 (1–68)	15	R-DEP/HLH-94	2 weeks: ORR 93.3%, CR 26.7%, PR 66.7%, Median OS 318 days
CD20	33,303,420	Baihua Li	2021	Secondary HLH	57 (28–76)	31	HLH-04, R-CHOPE/CHOPE, R-CHOP/CHOP, R-DA-EPOCH	Median OS 1.5mouth Treatment regimens containing etoposide, anti-CD20 monoclonal antibodies, or anthracyclines improved patient prognosis
JAK1/2	35,344,583	Qing Zhang	2022	HLH	3.7 (0.1–14.4)	52	Fronrline: ruxolitinib; Intensive treatments: methylprednisolone, etoposide, cyclosporine A, liposomal doxorubicin and pegaspargase	D28 (ruxolitinib monotherapy): ORR 69.2, CR 42.3%, PR 17.3%, improvement 9.6% After intensive treatments: CR 73.1% 1-year OS 86.4%
IL-6	36,131,317	Ju Yeon Kim	2022	Secondary HLH	TCZ:47.3 ± 17.5 Control: 48.5 ± 19.7	64	Tocilizumab (n = 8) Control: HLH-2004 (n = 35), Chemotherapy (n = 7), Glucocorticoid (n = 8), other immunosuppressants (n = 6)	D14: tocilizumab: no PR or CR; Control: CR 8.9%, PR 35.7% 8 weeks OS: TCZ 12.5%; Control: 51.9%

Table 4 (continued)

Target	PMID	Authors	Year	HLH type	Age	No. Patient	Treatment	Outcome
IL-1	36,233,667	Clara Baverez	2022	Secondary HLH	45 (33–58)	21	Anakinra, corticosteroid, cyclosporine A, azacytidine	ORR 90.5% 10-mouth OS 85.7%
JAK1/2, IL-1	35,948,764	Leonard Naymagon	2022	Secondary HLH	40.5 (19–82)	16	Anakinra, corticosteroid, etoposide, ruxolitinib	Median OS 1.7 months (range 0.2–59)
JAK1/2	37,457,729	Yue Song	2023	Secondary HLH	46.5 (27–76)	8	Ruxolitinib, etoposide, dexamethasone, cyclosporine A	CR 100% 2-mouth OS 75%
JAK1/2	37,062,931	Qing Zhang	2023	Secondary HLH	10.5 (0.8–12.4)	6	Ruxolitinib, etoposide, dexamethasone/Methylprednisolone, cyclosporine A	CR 100%
IL-1	37,385,631	Benjamin J Lee	2023	Secondary HLH	45 (18–78)	30	Anakinra, etoposide, Steroids	Anakinra + steroids: (n = 6): D30 ORR 83.3%; 1-year PFS 63.6%, 1-year OS 77.8% HLH-94 (n = 10): D30 ORR 60%; 1-year PFS 30%, 1-year OS 33.3%
CD52	35,439,287	Mahasweta Gooptu	2023	HLH	45 (21–72)	21	RIC (alemtuzumab, fludarabine, busulfan/cyclophosphamide/ total body irradiation); HSCT	3-year OS 75%, 3-year PFS 71% RIC with early alemtuzumab preconditioning results in favorable outcomes in HLH following HCT
JAK1/2, PD-1	37,787,838	Ying Xu	2023	EBV-HLH	52 (22–68)	12	Ruxolitinib, Sintilimab, etoposide, dexamethasone/Methylprednisolone	1 mouth: CR 50%; 5-mouth OS 50%
IFN-γ	38,429,096	Shanmuganathan Chandrakasan	2024	Primary HLH	1 (0.3–21)	46	Emapalumab, corticosteroid, etoposide, HSCT	Forty-two (91.3%) patients were considered eligible for transplant Pre-transplant survival was 38/42 (90.5%) Thirty-one (73.8%) transplant-eligible patients proceeded to transplant and 23/31 (74.2%) of those transplanted were alive at the end of the follow-up period 12-month OS (n = 46) 73.1%
JAK1/2	37,470,145	Jian Ge	2024	Primary HLH	3.1 (0.13–15.03)	21	Ruxolitinib, etoposide, Methylprednisolone	8 weeks: CR 90.5%, PR 9.5% Relapsed after CR 42.1% HSCT 81.0%: CR 76.5%, PR 17.6%, Reactivation 5.9% 1-year OS 90.5% Eight (38.1%) patients received zero doses of etoposide

Table 4 (continued)

Target	PMID	Authors	Year	HLH type	Age	No. Patient	Treatment	Outcome
JAK1/2, IL-1	38,633,898	Benjamin J Lee	2024	HLH	48 ± 19	1204	Ruxolitinib, anakinra, etoposide	1-year OS: Ruxolitinib 54.5% Anakinra 65.6% Etoposide 44.3%

IFN-γ interferon-γ; *JAK1/2* Janus kinase 1/2; *IL-1* interleukin-1; *IL-6* interleukin-6; *PD-1* programmed death 1; *R/R* relapsed/refractory; *HSCT* hematopoietic stem cell transplant; *MAS* macrophage activation syndrome; *ORR* overall response rate; *CR* complete response; *PR* partial response; *OS* overall survival

of the inflammatory state by blocking IFN-γ allowed for discontinuation of conventional immunosuppressive therapy, aiding in infection control [115].

In terms of drug safety, emapalumab dosages can be gradually increased from 1 to 10 mg/kg twice weekly based on patient tolerance and clinical progress [116]. Prior to administering emapalumab infusions, latent tuberculosis infection should be excluded through interferon-γ release assays, and EBV and CMV infections should be monitored every two weeks [117]. Additionally, the adjunctive use of acyclovir and trimethoprim-sulfamethoxazole should be considered to prevent herpes zoster and pneumocystis jirovecii infections [117, 118].

However, LCMV infection in IFN-$\gamma^{-/-}$ and Prf1$^{-/-}$ mice still result in severe HLH-like state, suggesting that the driving cytokines for human HLH are not limited to IFN-γ [119]. Therapies targeting upstream activators of $CD8^+$ T cells, such as interleukin-33/ST2 signaling, can be considered [119]. Additionally, in previous reports, HLH patients often received combination therapy rather than IFN-γ monoclonal antibodies alone. It is conceivable that solely inhibiting IFN-γ may not be sufficient to control the disease in the majority of patients. Targeting multiple cytokines simultaneously may be considered, but further clinical trials are warranted for validation [120].

Targeting JAK-STAT

The classical JAK-STAT pathway transduces extracellular signals activated by cytokines to the nucleus, mediating gene expressions and playing indispensable roles in a range of cellular processes, particularly those with immunomodulatory functions [121, 122]. The JAK family comprises a group of tyrosine kinases associated with cell signal transduction, primarily consisting of four members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK1, JAK3 and TYK2 are responsible for immune system development and regulation, while JAK2 primarily participates in hematopoiesis, playing crucial roles in erythrocyte and platelet production [123–125]. The enzymatic function of JAK is activated by the binding of cytokines to their receptors. Cytokine-activated JAK phosphorylates tyrosine residues of each other and the intracellular tails of receptor subunits, thereby creating docking sites to recruit downstream signaling molecules [126]. A key subset of substrates binding to phosphorylated cytokine receptors is the STAT family of DNA-binding proteins. Receptor-bound STATs are phosphorylated by JAK, dimerize, and translocate to the nucleus, where they bind to DNA, activating gene transcription [121]. Mammals have seven STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [127]. Through selective binding to cytokine receptors, different cytokines have the ability to preferentially recruit different STATs [128, 129].

In HLH patients, the JAK-STAT signaling pathway can be aberrantly activated due to immune dysregulation. Elevated cytokines in HLH, such as IFN-γ, IL-2, IL-6, IL-10, IL-12 and granulocyte–macrophage colony-stimulating factor (GM-CSF), can all signal through the JAK-STAT pathway [129]. By inhibiting downstream signaling of many HLH-related cytokines, such as the JAK-STAT pathway we discussed here, it is possible to effectively alleviate the immune response associated with HLH. Several JAK inhibitors, such as ruxolitinib, tofacitinib, baricitinib and oclacitinib, have been used in the treatment of inflammatory diseases [130]. Preclinical study have indicated that the JAK1/2 inhibitor ruxolitinib was more effective in treating HLH compared to the JAK1 inhibitor itacitinib and the JAK2 inhibitor fedratinib [131].

Ruxolitinib is an orally administered, potent and highly bioavailable JAK1/2 inhibitor, approved by the Food and Drug Administration (FDA) for patients with myeloproliferative neoplasms and steroid-refractory GVHD [132, 133]. Some studies using ruxolitinib to treat Prf1$^{-/-}$ or Rab27a$^{-/-}$ mice infected with LCMV (pHLH model; Table 3), as well as wild-type mice exposed to repeated injections of CpG DNA (sHLH model), have demonstrated that monotherapy with ruxolitinib reversed a series of HLH manifestations and significantly prolonged survival [134–136]. Both Ruxolitinib and the anti-IFN-γ antibody improved hemoglobin levels, but only ruxolitinib significantly reduced the number and activation status of immune cells, thus decreasing the frequency and absolute numbers of infiltrating $CD8^+$ cells, monocytes and neutrophils [105]. Using the pHLH mouse model (Prf1$^{-/-}$ mice), the combination of ruxolitinib (4 mg/kg, twice a day) with low-dose anti-IFN-γ antibodies (200 μg per mouse, every 3 days) showed a synergistic effect, effectively alleviating HLH manifestations [137]. However, studies have also shown that higher doses of ruxolitinib (90 mg/kg, twice daily) combined with anti-IFN-γ antibodies (500 μg or 1 mg, administered once every 3–4 days) did not provide superior anti-inflammatory benefits compared to their individua use [138, 139]. Therefore, caution should be exercised when combining these two classes of drugs, especially when higher doses are used [138, 139]. Exploratory studies of combination therapy with dexamethasone and ruxolitinib have found that by blocking cytokine signaling, ruxolitinib can sensitize $CD8^+$ T cells to dexamethasone-induced apoptosis in vitro, effectively overcoming cytokine-induced dexamethasone resistance [136].

For patients with r/r HLH, ruxolitinib has shown promising efficacy in improving the inflammatory state. A study described the use of ruxolitinib in combination

with corticosteroids to treat 34 patients with r/r HLH (median age 27.5 years; 1 case of FHL2, 25 cases of EBV-HLH, 2 cases of HLH/MAS, 6 cases unclear) [140]. After two weeks of treatment, ferritin and sCD25 levels significantly decreased, indicating an improvement in the inflammatory state. The ORR was evaluated to be 73.5%, with complete response (CR) in 14.7% and partial response (PR) in 58.8% [140]. However, for patients with EBV-HLH, EBV-DNA levels remained unchanged, suggesting that ruxolitinib reduced inflammation without targeting the underlying cause of HLH, thereby still necessitating the need for allo-HSCT [140, 141]. Another study including 41 r/r HLH patients who had not previously received the DEP or L-DEP regimen showed an ORR of 78.0% with Ru-DEP (ruxolitinib-DEP) treatment [142]. A total of 8 cases (19.5%) achieved CR and 24 cases (58.5%) achieved PR. The CR rate with Ru-DEP was higher than with ruxolitinib monotherapy (14.7%) [142]. Although the response rate with the Ru-DEP regimen (76.2%) was similar to that observed in adult patients with refractory HLH treated with DEP in previous studies, 7 cases still achieved PR (58.3%) among the 12 HLH patients who had failed or relapsed after prior DEP or L-DEP treatment [142]. Some studies have also reported the efficacy of ruxolitinib in suppressing the inflammatory state in pHLH patients, potentially making it a safe bridge therapy for refractory HLH undergoing allo-HSCT [141, 143, 144].

For HLH patients with severe infections, ruxolitinib also demonstrated promising efficacy. Sostad et al. and Zandvakili et al. reported that two cases of sHLH with severe fungal infections showed clinical improvement after receiving ruxolitinib and antimicrobial agents as first-line treatment [145, 146]. Additionally, ruxolitinib also showed favorable outcomes in treating patients with malaria-, tuberculosis-, HIV-, SLE- and lymphoma-associated HLH [147–150]. There were also case reports of patients with central nervous system-involved r/r HLH achieving remission after receiving emapalumab combined ruxolitinib, followed by transplantation [151].

Overall, ruxolitinib is effective in inflammation control, but cannot eradicate the underlying cause. Nevertheless, allo-HSCT should still be considered the ultimate treatment following ruxolitinib. During drug administration, caution should be exercised regarding the side effects associated with JAK inhibitors, which may be related to off-target effects [152]. The use of JAK inhibitors increases the risk of severe and opportunistic infections, with reactivation of varicella-zoster virus being one of the most common infectious complications [152]. JAK inhibitor therapy further leads to anemia and decreased counts of lymphocytes, NK cells, neutrophils and platelets, possibly due to the inhibition of signaling pathways by cytokines such as JAK2 (e.g., erythropoietin, thrombopoietin) and other hematopoietic growth factors (e.g., IL-6 and IL-11) [139]. During usage, a balance between the therapeutic effects of the disease and the risks of side effects should be considered, ensuring that patients receive optimal treatment outcomes while minimizing adverse reactions.

Targeting IL-6

IL-6 is a core participant involved in acute inflammatory responses, which mediates the acute phase responses during the immune defense and induces the production of inflammation-related biomarkers such as C-reactive protein and procalcitonin [153, 154]. In addition, IL-6 can be used for diagnosis of early inflammation and provide an early warning for the occurrence of sepsis [155–157]. Upon encountering pathogen-associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs), a variety of innate immune cells such as macrophages and monocytes rapidly initiate the expression and release of IL-6 to eliminate infected cells or damaged tissue [158–160]. IL-6 is mainly activated by the signals of IL-1β and TNF-α, with positively regulating by a series of small molecules, including platelet-derived growth factor (PDGF), lipopolysaccharide (LPS), phorbol myristate acetate (PMA), etc. [161–166]. However, overproduction of IL-6 can also result in chronic inflammatory diseases, such as SLE, rheumatoid arthritis, etc., as well as fetal cytokine storm-related conditions of receiving chimeric antigen receptor-T cell therapy, suffering severe coronavirus disease 2019 (COVID-19) and HLH [29, 167–172]. In sJIA patients, the increased IL-6 levels were associated with disease activity, in accordance with the high risk of HLH/MAS in this population [173, 174]. However, IL-6 is not elevated in HLH as significantly as in sepsis [99], suggesting that other pro-inflammatory cytokines are also critical for HLH development.

IL-6 is typically present as a monomer, and includes one specific binding site for IL-6 receptor (IL-6R) and two gp130 (signal-transducing protein) binding sites, responsible for its complex and extensive functions [154, 175]. IL-6 downstream pathways can be classified into classical signaling, trans-signaling and trans-presentation, all of which require interactions between IL-6 and receptors through cytokine-binding domain, however, leading to distinct biological effects by different ligand-receptor binding modes [154, 175]. Although almost all stromal cells, macrophages, E-selectin mesangial cells, tumor cells, etc. can produce IL-6, IL-6R expression is more restricted and specifically found in immune cells and response-related cells, such as neutrophils, monocytes and hepatocytes, while gp130 is expressed within almost all cells [176–178]. Noteworthily, there are two

kinds of IL-6R forms, membrane-bound IL-6R (mIL-6R) and the circulating soluble IL-6R (sIL-6R) [179]. In the classical signal pathway, IL-6 binds to its receptor mIL-6R to form a protein complex, which then associates with the membrane protein gp130 to initiate intracellular signal transduction [154, 180]. Cells that express gp130 but do not express IL-6R cannot result in the downstream signals of mIL-6R that are mainly responsible for regeneration and protection. However, the trans-signaling pathway is mediated via binding of IL-6-sIL-6R complex to gp130 in almost all cells that express this signal transduction protein, leading to the formation of protein hexamer that activates JAK for the initiation and development of a series of biological events that include pro-inflammatory responses [181–184]. Summarily, JAK's autophosphorylation of tyrosine residues within its intracellular sequence, serving as recruitment sites for transcription factor STAT, feedback regulator SOCS3, adaptor protein and phosphatase SHP2, can activate multiple downstream signals, such as STAT3, MAPK, PKB/Akt and NF-κB pathways that are broadly involved in pathological conditions [181–192]. In the trans-presentation pathway, mIL-6R on dendritic cells binds to IL-6, which is then presented to T cells expressing gp130, playing a critical role for Th17 cells [193].

IL-6 is reported to drive the occurrence and development of diseases in human autoimmunity and inflammation [178]. Although IL-6 has been regarded one of molecules involved in the pathogenesis of HLH, its role and associated mechanisms remain unclear and require to be better studied. Current viewpoints suggest that the elevated IL-6 in patients with HLH may be derived from activated macrophages, which initiate its release synchronously with TNF-α and IL-1β during the early stage of inflammation [194–196]. One study involving liver tissue biopsies from five patients with MAS found a significant presence of activated macrophages producing IL-6 [195]. However, another study focusing on cytokine release syndrome (CRS) suggested that monocytes are the primary source of IL-1 and IL-6 [197]. In a transgenic mice model with IL-6 overexpression, prolonged exposure to IL-6 in vivo exacerbated the inflammatory responses to toll-like receptor (TLR) ligands, and these mice exhibited clinical manifestations similar to HLH [194]. Another study confirmed that IL-6 reduced the expression of perforin and granzymes by inhibiting the cytotoxic activity of NK cells, which may be one of the mechanisms underlying MAS in sJIA patients [198]. Based on the fact that pHLH is caused by genetic homozygous defects in genes encoding proteins involved in cellular cytotoxicity, including perforin, findings on IL-6's inhibition of NK cells further support the hypothesis that pHLH and sHLH may share similar pathogenic mechanisms [198–201]. Besides, sJIA patients who received IL-6 blockade therapy seemed to have a lower incidence of MAS and significantly less severe clinical presentation compared to the untreated patient group [202, 203]. However, inflammatory response-associated biomarkers could be well corrected via the IL-6 blockade therapy in patients with refractory AOSD [204]. Therefore, though these findings may indicate the amplifying effects of IL-6 on inflammatory responses and its relevance to HLH onset and development, the definitive role of IL-6 in HLH still requires more explorations.

IL-6 has been discovered as one of key cytokines involved in the dysregulation of many diseases, and thus targeting the IL-6 pathway has resulted in a series of novel therapeutics for rheumatic diseases, chimeric antigen receptor T (CAR-T) adoptive infusion and immune checkpoint blockade-related CRS, as well as COVID-19 pneumonia and HLH [1, 19, 205–210]. Based on the evidences supporting the use of IL-6 pathway inhibition in the treatment of COVID-19 pneumonia and CRS [19, 153, 206, 211], which are similar to HLH in clinical characteristics and surged cytokine profiles, the use of IL-6 antagonists, such as tocilizumab, has shown some efficacy in the treatment of HLH, despite the current limitations of retrospective study and case report [204, 208, 212]. By binding to IL-6R and inhibiting IL-6-mediated signaling, tocilizumab can serve as an alternative therapy for patients with HLH, especially in adults with sHLH or MAS, or as a salvage treatment for those with familial HLH who showed an inadequate response to etoposide and corticosteroid [204, 208, 212]. Still, there is a lack of clinical trials for assessing the safety and efficacy of IL-6 blockade therapy in HLH patients, except one nonrandomized, interventional, parallel phase II trial that focuses on the tocilizumab or alemtuzumab treatment for HLH adults when combining with etoposide and dexamethasone (NCT02385110).

Targeting TNF-α

TNF-α is a pivotal polymorphic cytokine extensively involved in pro-inflammatory responses, and drugs targeting TNF-α for neutralization have emerged as one of highly effective treatments for diseases of the human immune system [213–217]. During the course of HLH occurrence and progression, a significant increase in serum levels of TNF-α has been observed in patients [218, 219] and animal models [96, 218, 220]. However, TNF-α seemed not to be critical in the pathogenesis of HLH as IL-1β, IL-6 and IL-18, but may reflect the activation degree of inflammatory responses [219]. The specific mechanisms underlying the upregulation of TNF-α in HLH are not fully understood, but it may be driven by preliminarily-elevated TLR ligands such as endotoxin or

cytokines [218]. During the process, a large amount of TNF-α and chemokines was secreted by various cell types via binding and induction of mature IL-18 molecules [221–223] and targeting IL-18 blockade could effectively decrease production of TNF-α and reverse hemophagocytosis-caused outcomes in the preclinical study [218]. In addition, the combination of TNF-α and IFN-γ blocking antibodies has been shown to provide 100% lethal protection in sHLH mice models induced by poly I:C and LPS attack [224, 225]. Thus, we speculate that the increased level of TNF-α tends to be merely one of downstream or intermediate events in the development of HLH, further promoting the activation of inflammatory response and tissue damage through its involvement in the cytokine cascades.

TNF-α exhibits complex regulatory roles of inflammation in both physiological and pathological conditions, particularly in autoimmune diseases [226–230]. TNF-α is synthesized and released by multiple kinds of cells such as macrophages, mononuclear cells, dendritic cells or lymphocytes, especially myeloid cells and activated T cells in response to diverse inflammatory stimuli [222]. Two forms of TNF-α are discovered within humans: a membrane-bound form (mTNF-α) capable of acting as a ligand or receptor, and a soluble form (sTNF-α) that functions as a ligand [231–233]. The 26-kDa mTNF-α can be converted into the 17-kDa sTNF-α by TNF-α-converting Enzyme (TACE) [233], which can exert its effects throughout the whole human body after entering the systematic circulation [234–236]. Both mTNF-α and sTNF-α play crucial roles in the inflammatory response. However, mTNF-α primarily functions at the local cellular level, whereas sTNF-α exerts systemic effects.

TNF-α can activate numerous downstream signaling pathways upon binding to its two distinct receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), which share structural similarity but possess divergent biological functions. TNFR1, also called tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) and CD120a, can be responsible for initiating most of TNF-α's physical activities [237–241]. Upon binding of trimeric TNF-α to TNFR1, multiple intracellular signal cascades are activated by recruiting several death signaling proteins such as adaptor protein TNFR1-associated death domain (TRADD), Fas-associated death domain (FADD) and TNF receptor-associated factor 1 (TRAF1), leading to the activation of key transcription factors, such as NF-κB, to induce inflammation and cell apoptosis [229, 239, 242–245]. In HLH, the dysregulation of NF-κB signaling pathway contributes to the persistent activation of immune cells and the further production of pro-inflammatory cytokines as TNF-α, IL-1β, IL-6 and etc., promoting the formation of vicious inflammatory cycle that drives the HLH development [26, 209, 246–248]. Besides, with the increasing understanding of TNF signaling in recent years, researchers have found that TNF not only directly drives inflammatory responses by inducing the expression of inflammatory genes but also indirectly drives inflammation by inducing cell death, triggering immune responses and promoting disease development [249–252]. Cell death is one of the driving factors of inflammatory diseases, such as apoptosis, necrosis, and pyroptosis, which lead to the release of DAMPs and activate subsequent inflammatory cascades [253, 254]. In addition to activating the NF-κB signaling pathway to directly promote inflammatory responses, TNF, upon binding to TNFR1, can also indirectly promote inflammatory signaling by inducing cell death [255–259].

However, unlike TNFR1 that widely exists in various cell types, TNFR2 is specifically expressed in thymic T lymphocytes, endothelial cells, microglia, and oligodendrocytes [239, 260–263]. Only mTNF-α can tightly bind to TNFR2 and fully initiate the following cellular events by recruiting TRAF1 or TRAF2 adaptors to the receptor due to the lack of death domain [229, 242, 244, 245, 264, 265]. The resulting activated signals involve cIAP1/cIAP2 kinases, as well as the canonical and non-canonical NF-κB, JNK, and AKT pathways [229, 242, 244, 245, 264, 265]. In spite of its activations for cell survival and proliferation by upregulation of PI3K/AKT pathway [266], the interaction between mTNF-α and TNFR2 mainly have stimulated effects on regulatory T cells (Treg) [267–269] and myeloid-derived suppressive cells (MDSC) [270–272] for immune inhibition because of TNFR2's preferred expressions on their surfaces [265]. During inflammation responses, the excessive expression of mTNF-α is supposed to bind to TNFR2 for activating Treg cell to control the amplification of TNF-α's pro-inflammatory effects [267–269, 273, 274]]. However, in HLH, highly activated $CD8^+$ T lymphocytes disrupts IL-2 homeostasis, resulting in a shift away from Treg cell maintenance and toward promotion of a feed-toward inflammation preference [275]. Thus, the dysfunctional Tregs cannot response to the strong mTNF-α-TNFR2 interaction to mitigate the inflammation progression in patients with HLH.

Despite the potent pro-inflammatory effects of TNF-α through the activation of innate and adaptive immunity, it also exerts functional inhibitions on NK cell-like Treg cells [276, 277]. It is speculated that the mechanism involves TNF-α increasing the adhesion of NK cells to endothelial cells or exerting direct cytotoxicity on NK cells [277]. During the occurrence and progression of HLH, the activity of NK cells is suppressed, and impaired or deficient NK cell cytotoxic function can serve as one of the diagnostic criteria for HLH [278–281]. Therefore,

it is hypothesized that high levels of TNF-α may be one of the causes that contribute to the secondary functional defects of NK cells in HLH, leading to sustained activation of inflammatory signals and hindering the disease control.

In summary, as one of the inflammatory effector cytokines, TNF-α can firstly activate a series of immune cells and endothelial cells through binding to TNFR1, leading to the initiation of inflammatory signals and release of numerous inflammatory cytokines. Additionally, TNF-α also serves a function of inflammatory regulation via TNFR2, mainly by activating immunosuppressive cells expressing TNFR2, such as MDSCs and Tregs. In patients with HLH, the crucial regulatory function of Treg cells in controlling inflammation is impaired, thus unable to respond to TNF-α-TNFR2 interaction-mediated inflammatory regulatory signals. This may be one of the mechanisms of amplifying the inflammatory cycle in HLH. Although TNF-α elevation may not be the core mechanism leading to HLH, targeting the TNF-α signaling pathway to alleviate the cytokine storm and reduce tissue damage is worth further researches. TNF-α-blocking antibodies have been used to treat various rheumatic or autoimmune diseases [213–217], and blocking TNF-α seems to have a certain therapeutic effect in MAS [282–287]. However, conflicting results have been reported in multiple studies [96, 282–286, 288, 289], which may be associated with the discrepancy of TNF-α levels. For critically-ill patients with a sharp increase in TNF-α, the treatment with TNF-α-neutralizing antibodies may be an option [283]. Furthermore, there were also reports suggesting that TNF-α therapy could indirectly induce HLH or worsen inflammation [290, 291]. Therefore, the application value of targeting TNF-α-related signaling pathways remains to be further studied for treating HLH and requires careful consideration. The intervention timing and inflammation degree may be critical factors, especially for HLH patients secondary to autoimmune diseases.

Targeting IL-1β

The IL-1 family includes several cytokines and receptors, and most of them share similar functions in inflammation and immune regulation as TLR families [292, 293]. IL-1α and IL-1β are two different molecular forms of the IL-1 ligands, both of which belong to immune-stimulated cytokines that mainly initiate innate immune-related inflammatory responses but also have effects on adaptive immune, especially T and B cell activation [293]. A large amount of IL-1 can be released when these cells are activated by foreign antigens or mitogens, which can be regarded as one of innate defense mechanisms [293, 294]. IL-1α and IL-1β signals will exert similar biological functions upon binding to their receptors, IL-1RI and IL-1RII [295, 296].

IL-1β is one of the key pro-inflammatory cytokines involved in the pathogenesis of HLH [209]. Under normal physiological conditions, IL-1β is intracellularly stored as the precursor form known as pro-IL-1β with low biological activity [297, 298]. Upon activation by PAMPs or DAMPs, transcription of pro-IL-1β is obviously upregulated [299–304]. In addition, inflammatory cytokines such as IL-18, TNF-α, and IL-1β itself can also promote the production of pro-IL-1β [305–309]. IL-1β acts on the cell surface IL-1RI through autocrine, paracrine, or systemic secretion, mediating inflammation by promoting the release of other pro-inflammatory cytokines such as IL-6 and TNF-α, which plays a critical role in bridging innate and adaptive immunity via interaction with Th1 and Th17 cells [310–312]. Therefore, several levels can be regulated to control the inflammatory burst associated with pathologically-elevated IL-1β in the treatment of HLH.

IL-1β is highly associated with sJIA, which is one of the main causes of sHLH [313–316]. However, the exact role of IL-1β in the development of HLH remains unclear. HLH is characterized by elevated levels of various cytokines, and its clinical manifestations differ from diseases primarily mediated by the increased IL-1β level, such as sJIA, cryopyrin-associated periodic fever syndrome, and familial Mediterranean fever [219, 317]. Generally, these diseases demonstrated great responses to IL-1 blockade therapy, with rapidly reduced IL-1β levels observed after administration [219, 317–319]. However, the efficacy of targeting IL-1β in the treatment of HLH remains uncertain.

The competitive inhibitor for IL-1 ligands, Anakinra, is a recombinant soluble receptor antagonist for both IL-1β and IL-1α and has been widely used in the treatment of sJIA. However, previous studies showed its varied efficacy in MAS, and there were reports of Anakinra that might induce the occurrence of MAS [196, 205, 315, 320–326]. In a re-analysis of data from a phase III multicenter randomized clinical trial evaluating the use of anakinra in severe sepsis, it was found that anakinra reduced the mortality rate by 30% in patients with clinical signs of HLH [327]. Treatments with anakinra significantly alleviated patients' symptoms and decreased hemophagocytosis scores in HLH patients secondary to severe COVID-19 pneumonia, suggesting its potentials in lowering death risk for cytokine storm-related diseases [328]. Canakinumab is a high-affinity fully human monoclonal antibody against IL-1β that specifically neutralizes IL-1β [329]. Although MAS has been considered an adverse event in clinical trials of canakinumab for the treatment of sJIA, the incidence rate of MAS in these

trials does not seem to be higher than those reported in real-world data for sJIA patients [330], suggesting that canakinumab does not affect the occurrence risk of MAS [331, 332]. The efficacy of targeting IL-1β in HLH may be dose-dependent. In most studies reporting successful responses to anakinra in treating MAS, patients were administered at high doses up to 10 mg/kg [205], while lower doses around 1–2 mg/kg might be associated with higher risk of drug-induced MAS [325, 326], although clear conclusions still require further evaluation. The current dosages (< 4 mg/kg) used in canakinumab clinical trials may not be sufficient to neutralize the increased IL-1β levels in MAS [205], thus further exploration of its higher dosages is needed to assess its inflammation control efficacy in MAS.

The aforementioned studies indicate that IL-1β plays a certain role in the occurrence and development of HLH, especially MAS. The therapeutic effect of blocking IL-1β may not only be attributed to the direct reductions in the production and release of IL-1β, but also to the control of the persistently-elevated pro-inflammatory cytokines. However, targeted blockade of IL-1β with canakinumab in sJIA patients were found ineffective both in reducing MAS risk and in treating MAS, also suggesting the limited role of IL-1β in the pathogenesis of MAS. Additionally, the non-selective IL-1α/β inhibitor, anakinra, appears to have better prospects in controlling inflammation in patients suffering MAS. Moreover, the IL-1α/β competitive inhibitor, anakinra, has shown promising results as an adjuvant therapy in twelve pediatric MAS patients [324]. Therefore, further exploration of blocking IL-1α in HLH patients can be worth in the future. Overall, targeting a single blockade of IL-1 signaling may not be the key point for controlling HLH, as other cytokines induced by its resulted cascade responses are supposed to block at the same time.

Targeting IL-18

IL-18 is a pro-inflammatory cytokine that belongs to the IL-1 family, normally existing as an inactive 24 kDa precursor form [333]. Activation of NF-κB following TLR stimulation induces the transcription of Pro-IL-18, which is further cleaved by caspase-1 into one mature and biologically active 18 kDa molecule, then releasing into the extracellular environment [334, 335]. IL-18 is predominantly present in monocytes/macrophages, antigen-presenting cells and epithelial cells in healthy humans and mice [336]. Similar to IL-1, IL-18 induces the production of inflammatory mediators by activating the NF-κB signal [336]. After binding to IL-18 receptor alpha (IL-18Rα) and its following recruitment of IL-18 receptor beta (IL-18Rβ), mature IL-18 initiates TLR/ IL-1R-like pro-inflammatory signaling via the MyD-IRAK1/4-NF-κB axis and p38 MAPK [336–339].

IL-18 is an important cytokine involved in immune mechanisms of activating macrophages and Th1 cells, which are critical to HLH pathogenesis [340]. A synergistic action of IL-18 and IL-12 stimulates Th1-mediated immune reactions, inducing expressions of chemokines and cell adhesion molecules [341] and promoting the secretion of inflammatory cytokines such as IL-1, IFN-γ and TNF-α [338, 342–346]. Significantly elevated levels of IL-18 can be observed in both primary and secondary HLH patients [347–349]. Serum levels of IL-18 were positively correlated with disease activity in HLH [347, 350–355]. Specifically, IL-18 was previously referred to as the IFN-γ-inducing factor [356], while IFN-γ rapidly drives the immune activation that promotes HLH occurrence [357]. Moreover, the sustained stimulation of macrophages by IL-18 and their continued activation further promote the release of various inflammatory cytokines, such as IL-1, IL-6, IL-18, and TNF-α, leading to tissue impairment and hemophagocytosis by macrophages [96, 195].

There are other diseases associated with HLH in which IL-18 levels are often significantly elevated, though with distinct underlying mechanisms, such as MAS, X-linked inhibitor of apoptosis protein (XIAP) deficiency and the *NLRC4* mutation [205, 358, 359]. MAS is one of the most common secondary form of HLH and usually originates from rheumatic diseases or systemic autoinflammatory diseases (SAID) [360], including sJIA, AOSD, SLE, Kawasaki disease, systemic vasculitis, etc [219, 281, 334]. Actually, MAS can be a potentially life-threatening complication of rheumatic diseases, characterized by excessive activation and expansion of T lymphocytes/macrophages exhibiting hemophagocytic activity [281]. Compared to patients with EBV-HLH, patients with MAS exhibited more elevated levels of serum IL-18 [361], which might partly contribute to the occurrence of liver damage among them by inducing Fas ligands on NK cells [362]. Most patients with XIAP deficiency would experience recurrent HLH and exhibit a high level of serum IL-18 [353]. XIAP deficiency is a rare primary immunodeficiency caused by *BIRC4* mutations, also known as XLP-2 [359, 363]. Clinical features of XIAP deficiency include HLH and inflammatory bowel diseases due to defective nucleotide binding oligomerization domain containing 2 (NOD2) responses [79, 359], but the specific mechanism by which mutated XIAP leads to the presentation of HLH remains incompletely understood. Elevated levels of IL-18 may offer crucial insights into the pathogenesis of this disease. On the other hand, the NLRC4 inflammatory is part of the human innate immune system, and its activation can lead

to the cleavage of the pro-inflammatory cytokines IL-1β and IL-18, which also promotes inflammation [364]. The gain-of-function mutations in *NLRC4* lead to HLH and gastrointestinal pathology [26, 43, 365], resulting in spontaneous activation of NLRC4 inflammasomes that increased IL-18 levels [360, 366]. It was reported that one patient with refractory NLRC4-MAS exhibited a significant response after IL-18 blockade treatment (IL-18 binding protein, IL-18BP) [367].

IL-18BP is a constitutive protein that can bind to IL-18 with high affinity, forming a complex that prevents IL-18 from interacting with its cell surface receptors [339]. Therefore, IL-18BP acts as a natural inhibitor of IL-18, controlling excessive IL-18-mediated inflammatory responses [368–370]. Imbalance between IL-18 and IL-18BP may lead to the activation of T lymphocytes and macrophages in HLH [347]. IL-18BP can be induced by IFN-γ, considering that IL-18 signaling has a negative feedback loop [336, 350, 371]. In a pHLH mouse model, the IL-18BP treatment reduced hemophagocytic activity and reversed liver and spleen damage [218]. Meanwhile, it also decreased the production of IFN-γ and TNF-α by $CD8^+$ T cells and NK cells, as well as the expression of Fas ligand on the surface of NK cells. However, this therapeutic did not improve the survival outcome [218]. Some clinical studies reported that recombinant human IL-18BP successfully treated patients with severe inflammatory responses carrying the NLRC4 mutation [367]. Currently, some clinical trials (NCT03512314) are underway for IL-18BP (tadekinig alfa) in patients with *NLRC4* or *XIAP* mutations. Overall, IL18-BP holds great potentials of modulating the inflammatory response triggered by IL-18, thereby exerting a positive impact on HLH. However, further clinical research and assessment are required to determine the efficacy and safety of IL18-BP as a treatment for HLH.

Targeting CD52

CD52 is a glycoprotein consisting of 12 amino acids anchored to glycosylphosphatidylinositol (GPI) [372, 373]. It is a widely distributed antigen found on lymphocytes, monocytes, eosinophils and dendritic cells differentiated from monocytes in the hematopoietic system, with a high density on lymphocytes [374]. Some studies have suggested that CD52 is an important immunomodulatory factor in T cell activation [375]. However, the specific pathways and mechanisms require further elucidation.

Alemtuzumab, also known as Campath-1H (trade name in Europe: MabCampath), is a humanized monoclonal antibody targeting the cell surface CD52 antigen [374]. It has been approved for chronic lymphocytic leukemia, multiple sclerosis (MS), and is also utilized in some autoimmune diseases such as rheumatoid arthritis, solid organ transplantation and GVHD following bone marrow transplantation [376–382]. Alemtuzumab eliminates T and B lymphocytes through mechanisms such as inducing cell apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [383–385]. One study reported the usage of T-cell depletion agents like alemtuzumab as salvage therapy for refractory HLH [386]. The high levels of CD52 expression on T cells and tissue cells make alemtuzumab a rational alternative for disrupting the uncontrolled immune responses like HLH.

One study reported that among 22 patients with refractory HLH treated with alemtuzumab, 14 of them experienced an overall partial response with 77% of them surviving to undergo allo-HSCT [386]. In a case of recurrent atypical HLH refractory to multiple immunosuppressive agents, alemtuzumab induction resulted in remission, enabling successful allo-HSCT [387]. As for HLH/MAS, in a case of SLE-induced HLH, despite refusal of high-intensity immunosuppressive therapy, the patient's condition gradually improved after alemtuzumab treatment [388]. Additionally, RIC regimens typically including alemtuzumab improved survival outcome in HLH patients after allo-HSCT [66]. However, caution is warranted regarding viral reactivation when using alemtuzumab.

For patients with refractory HLH, alemtuzumab may be an effective salvage therapy. However, some previous studies have also indicated that alemtuzumab induced HLH in patients with hematologic malignancies [389]. Therefore, the use of alemtuzumab in HLH should be approached with extreme caution.

Targeting CD20

CD20 remains to be one of most important surface markers expressed on B lymphocytes since the late pre-B cell stage, and is lost in terminally differentiated plasma cells and plasmablasts [390]. CD20 is a 33–37 kDa non-glycosylated protein classified into the membrane-spanning 4-domains subfamily A (MS4A), encoded by MS4A1 [391, 392]. The biological function and physiological ligands of CD20 on B cells are still not fully understood. Some studies suggested that CD20 deficiency lead to the decreased circulating memory B cells, less immunoglobulin isotype switching and lower IgG levels [393]. CD20 is associated with several protein tyrosine kinases, including Lyn, Fyn, Lck, and p75/85 kinases, which can cause activation of phospholipase-C-gamma (PLC-γ) and the subsequent MAPK (JNK, ERK, and p38MAPK) signaling pathways [394]. PLC-γ can also hydrolyze PIP3, generating inositol trisphosphate and diacylglycerol, which are

signaling molecules involved in pathways highly similar to B cell receptor (BCR) signaling [395].

Patients with perforin-dependent cytotoxicity defects or genetic predisposition are susceptible to EBV-HLH [396, 397]. Some studies suggested that EBV encoding protein mimicked key signaling pathways within B cells [398–401]. For instance, LMP1 could simulate active CD40 receptor, and latent membrane protein 2A (LMP2A) could simulate or replace BCR signaling [398–401]. Furthermore, CD20 indirectly regulated calcium release dependent on the BCR pathway, and $CD20^+$ B cells that lack BCR were unable to initiate calcium-releasing signals [402]. Some studies also demonstrated that CD20 directly functioned as an ion channel, and overexpression and knockout of CD20 might increase or decrease calcium current in B cells, respectively [403].

EBV, also known as human herpesvirus 4, is a double-stranded DNA virus [404], mainly targeting B lymphocytes both in vitro and in vivo, which serves as the location site for virus preservation in healthy carriers [405]. Preferentially, EBV infects B lymphocytes by two strategies: (1) binding to the B-cell surface CD21 through viral envelope glycoprotein gp350; (2) binding to human leukocyte antigen through glycoprotein gp42 [406–408]. EBV infection drives the transformation of B lymphocytes [409]. Within these host B cells, EBV may primarily exist as the free form and replicate via host DNA polymerase, but its nucleotide sequences can be integrated into the host genome by the non-random pattern [410]. Within healthy individuals, transformed B lymphocytes will be rapidly eliminated by NK and cytotoxic $CD8^+$T cells, while target cell killing deficiencies in patients with familial or sHLH may trigger the dysregulation of systematic inflammatory responses that contribute to HLH occurrence [279, 411, 412].

Anti-CD20 monoclonal antibodies (mAbs) are targeted drugs against B cells by blocking CD20 molecules [413]. Based on different characteristics, anti-CD20 antibodies can be classified into type I (such as rituximab) and type II (such as obinutuzumab), depending on their ability to induce redistribution of CD20 into lipid rafts on the cell membrane [414]. Type I CD20 mAbs induce the recombination of CD20 molecules into lipid rafts and then effectively activate the classical pathway of complement system. Type II CD20 mAbs exhibit poorer abilities in complement activation, but perform better to induce cell death after directly binding to CD20 without cross-linking through secondary antibodies [393, 414–416]. Anti-CD20 mAbs exert their effects through CDC, ADCC and direct cytotoxicity, leading to the destruction of targeted B cells [417, 418]. Moreover, it can also interfere with BCR signaling and downregulate BCR expression [419–421]. Rituximab is a chimeric mouse/human mAb that can deplete $CD20^+$ cells within 48 h after administration, decreasing the incidence rate of EBV reactivation [422]. Rituximab is effective in treating various EBV-mediated diseases, such as EBV-induced post-transplant lymphoproliferative disorder (EBV-PTLD) [423–425]. EBV usually demonstrates a poor response to anti-viral drugs, and thus its presence within B lymphocytes allows for rapid depletion through the use of targeted mAbs [426, 427].

Rituximab-based chemotherapeutic regimens have been used for EBV-HLH. Chellapandian et al. retrospectively reported a clinical cohort involving 42 patients with EBV-HLH who received a regimen including rituximab with great tolerability, which effectively improved the physical status for 43% of patients with significant decreases in EBV load and serum ferritin levels [428]. There were also one report of two cases of central nervous system involvement in patients with EBV-HLH on which alleviated symptoms were rapidly observed with the use of rituximab as a monotherapy [429, 430]. Monocytes/macrophages play a crucial role in the depletion of B cells, and the activation of macrophages is commonly observed in HLH patients, which may facilitate the ADCC effects of anti-CD20 mAbs [431]. However, in some cases, EBV can also infect other kinds of cells, such as T cells and NK cells [432], which may not be eliminated by giving Rituximab [433, 434]. In a study analyzing EBV-DNA level in lymphocyte subpopulations of 15 HLH patients, it was found that EBV primarily infected T and NK cells in 5 patients, and only infected B cells in the remaining 10 patients [333]. After receiving a regimen including rituximab, the patients who had infected T and NK cells had no obvious changes in EBV viral load, while the other 10 patients showed the significantly decreased EBV levels [333]. In HLH cases whose B cell-depletion have been confirmed, the persistently high EBV-DNA level suggested the EBV infection into T/NK cells [333, 396]. Therefore, combining with etoposide and dexamethasone may help to eliminate infected T and NK cells for promotion of virus clearance [1, 398, 435].

The primary therapeutic principles for EBV-HLH include suppressing excessive inflammation, eliminating EBV and reversing impaired immune system function [333, 436]. Dampening EBV activation and cutting its virus burden were proved to have potentials of controlling clinical symptoms and improving survival outcome [333, 436]. During the active phase, the use of rituximab was able to limit immune responses by getting rid of EBV-infected B cells [428, 437]. However, patients previously treated with rituximab (often in combination with other medications) usually hace varying administration schedules and dosages, potentially leading to reporting biases and confounding factors. Overall, treatment regimens

including rituximab have demonstrated a promising outlook in reducing EBV load and alleviating hyperinflammation, which, nevertheless, should be further validated. In patients with EBV-HLH, monitoring of the response to rituximab can be performed using EBV blood polymerase chain reaction assays, which at the same time help reflect the increases in viral load and recovery of B cells after rituximab therapy [396, 428]. However, B cell-targeted therapies lead to a strong immune suppression, thus necessitating precautions such as effective isolation and antifungal prophylaxis. Besides, it is necessary to regularly monitor potential pathogens (CMV, adenovirus or aspergillus) to prevent infection or reactivation.

Anti-CD20 mAbs are expected to be primarily utilized for EBV-HLH. Since EBV tends to infect B cells, targeting EBV-infected B cells using anti-CD20 mAbs may effectively dampen the amplified inflammatory response, but infection monitoring is necessary due to the substantial impact of B cell clearance on the immune function of the body. Currently, the clinical evidence for the use of anti-CD20 mAbs in HLH is limited to case reports or small-sample retrospective studies. The definitive role of CD20 in HLH remains unclear, and further explorations through standardized clinical trials are required.

Targeting PD-1

PD-1, also known as CD279, is a prototypical immune inhibitory checkpoint predominantly found on the surface of T cells [438]. It regulates T cell effector function during various physiological responses, including acute and chronic infections, cancer, autoimmune diseases and immune homeostasis [439]. The cytoplasmic tail of PD-1 contains two tyrosine-based motifs: an Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM) and an Immunoreceptor Tyrosine-based Switch Motif (ITSM) [440, 441]. The PD-1 has two ligands, PD-L1 (CD274) and PD-L2 (CD273) [442]. PD-L1 is broadly expressed across various cell types, found in hematopoietic cells (including T cells, B cells, dendritic cells (DCs), and macrophages) as well as non-hematopoietic cells (including vascular and stromal endothelial cells) [439]. In contrast, PD-L2 expression is more restricted, primarily expressed by DCs, macrophages, and subsets of B cells [439]. Upon binding with its ligands, PD-1 is phosphorylated at these tyrosine residues, leading to the recruitment of protein tyrosine phosphatases (PTPs) such as SHP2 [443]. These PTPs can dephosphorylate kinases and counteract the positive signals generated through T cell receptor (TCR) and CD28, affecting downstream signaling pathways including those involving PI3K-AKT, RAS-ERK, and PLC-γ [439, 444]. The aforementioned interaction between PD-1 and its ligands can suppress T cell proliferation, activation, cytokine production and cytotoxic T lymphocyte killing function, thereby protecting the organism from autoimmune attacks [445]. Many malignant tumors express PD-L1, and thus high PD-L1 expression is associated with poor prognosis in diseases such as malignant melanoma, colon cancer, pancreatic cancer, hepatocellular carcinoma, and ovarian cancer [446]. Therefore, PD-1 inhibitors have been approved for the treatment of various malignant tumors. PD-1 blockade can significantly prolong the survival of patients with such diseases and provide long-term sustained remission. Additionally, some studies have suggested that inhibitors targeting the PD-1 pathway can rescue T cells from exhaustion, reactivate dysfunctional $CD8^+$ T cell populations and restore immune responses [447].

During certain chronic infections, persistent antigen exposure results in sustained PD-1 expression, which limits the clearance of immune-mediated pathogens or tumor cells [439]. It was reported that PD-1 inhibitors had been successfully used to treat the chronic viral infection [448]. In all kinds of HLH cases, infections are a common trigger. Several reports have demonstrated successful treatment of EBV-HLH and chronic active EBV infection (CAEBV) through PD-1 blockade [449–454]. A study involving seven r/r EBV-HLH patients treated with nivolumab as a monotherapy showed responses in six patients (85.7%), with five patients (71.4%) achieving clinical CR and a gradual reduction in plasma EBV-DNA copy numbers [452]. Single-cell sequencing revealed positive enrichment of multiple T cell activation pathways and degranulation pathways in $CD8^+$ T cells after nivolumab treatment, suggesting that nivolumab may restore the cytotoxicity function of $CD8^+$ T cells [452].

One study involved 12 EBV-HLH patients in the intensive care unit with sintilimab and ruxolitinib therapy, with six patients (50%) achieving CR within 1 month [455]. With a median follow-up time of 5 (4.4 to 14.7) months, six of them died, resulting in a mortality rate of 50% [455]. For EBV-HLH patients with post-transplant relapse, PD-1 blockade also showed promising effects. An EBV-HLH patient who relapsed after chemotherapy and allo-HSCT might benefit from the addition of sintilimab as salavage therapy, with normalization of fever, cell count, liver enzyme elevation, serum ferritin and sCD25 levels and negative EBV-DNA loads [456]. Therefore, PD-1 blockade therapy may be an option for r/r and critically ill EBV-HLH patients, though further validation is required.

However, stimulating the immune system is a double-edged sword, as sustained immune activation may also trigger HLH or exacerbate HLH symptoms [457]. Some reports have indicated cases of immune checkpoint inhibitor-related HLH in patients with various solid tumors [458–461]. There have even been studies

reporting HLH induction in two CAEBV patients following the treatment with sintilimab [462]. Additionally, one case report described the worsening of symptoms and CRS-related pulmonary injury in a 3-year-old girl with r/r EBV-HLH when treated with nivolumab during the acute phase of HLH disease [463]. Therefore, considering safety concerns, cautions should be exercised when using the PD-1 blockade strategy in HLH during the peak of inflammation.

Conclusions

In summary, HLH is a life-threatening hyperinflammatory syndrome characterized by excessive immune activation. HLH can be hereditary or sporadic, triggered by various events that disrupt immune homeostasis. HLH is typically treated with immunosuppressive therapy to induce remission. For patients with pHLH, allo-HSCT is considered once the high-inflammatory state is controlled. For patients with r/r HLH, cytokine-targeted therapy and immunotherapy can be a treatment option, including the addition of the L-DEP regimen, JAK1/2 inhibitors, anti-CD52 antibodies, anti-CD20 antibodies, and PD-1 blocking agents. The IL-6 antagonists, IL-1 receptor antagonists, TNF-α blocking antibodies and L-18BP may be considered for MAS patients. Besides, anti-the IFN-γ antibody, emapalumab, has been proved to have efficacy for pHLH. All the above-mentioned targeted therapeutics can be combined with the conventional treatments, which is worth looking forward to in the future studies. Specifically, HLH patients planned for allo-HSCT may consider receiving a RIC regimen with anti-CD52 antibodies that should be personalized based on the doctor's expertise and the patient's condition. Overall, further clinical cohort studies are required to explore the efficacy of single-agent and combination therapies with different targeted drugs in HLH.

Abbreviations

HLH	Hemophagocytic lymphohistiocytosis
HSCT	Hematopoietic stem cell transplantation
MAS	Macrophage activation syndrome
sJIA	Systemic juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
AOSD	Adult Still's disease
IL	Interleukin
IFN-γ	Interferon-γ
EBV	Epstein-barr virus
XLP	X-linked lymphoproliferative disease
XIAP	X-linked inhibitor of apoptosis protein
NOD2	Nucleotide binding oligomerization domain containing 2
CMV	Cytomegalovirus
CTLs	Cytotoxic T cells
ORR	Overall response rate
allo-HSCT	Allogenic HSCT
RIC	Reduced-intensity conditioning
GVHD	Graft-versus-host disease
HSCs	Hematopoietic stem cells
TCR	T cell receptor
ATCT	Adoptive T cell therapy
JAK-STAT	Janus kinase-signal transducer and activator of transcription
PD-1	Programmed cell death protein 1
IFNGR	IFN-γ receptor
GAS	Gamma-activated sequence
LCMV	Lymphocytic choriomeningitis virus
CNS	Central nervous system
TYK2	Tyrosine kinase 2
GM-CSF	Granulocyte-macrophage colony-stimulating factor
FDA	Food and Drug Administration
CR	Complete response
PR	Partial response
PAMPs	Pathogen-associated molecular patterns
DAMPs	Damage associated molecular patterns
PDGF	Platelet-derived growth factor
LPS	Lipopolysaccharide
PMA	Phorbol myristate acetate
mIL-6R	Membrane-bound IL-6R
sIL6R	Soluble IL-6R
TLR	Toll-like receptor
CAR-T	Chimeric antigen receptor T cell
CRS	Cytokine release syndrome
TACE	TNF-α-converting Enzyme
TNFR1	TNF receptor
TNFR2	TNF receptor 2
TNFRSF1A	Tumor necrosis factor receptor superfamily member 1A
TRADD	Adaptor protein TNFR1-associated death domain
FADD	Fas-associated death domain
TRAF1	TNF receptor-associated factor 1
Treg	Regulatory T cell
MDSC	Myeloid-derived suppressive cell
IL-18Rβ	IL-18 receptor beta
SAID	Systemic autoinflammatory diseases
IL-18BP	IL-18 binding protein
GPI	Glycosylphosphatidylinositol
MS	Multiple sclerosis
ADCC	Antibody-dependent cellmediated cytotoxicity
CDC	Complement-dependent cytotoxicity
PLC-γ	Phospholipase-C-gamma
BCR	B cell Receptor
LMP2A	Latent membrane protein 2A
mAbs	Monoclonal antibodies
EBV-PTLD	EBV-induced post-transplant lymphoproliferative
ITIM	Immunoreceptor Tyrosine-based Inhibitory Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
DCs	Dendritic cells
PTPs	Protein tyrosine phosphatases
CAEBV	Chronic active EBV infection
PBMCs	Peripheral blood mononuclear cells

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Availability of data and materials
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Declarations

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Not applicable.

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