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REVIEW

Cytokine storm and targeted therapy in hemophagocytic lymphohistiocytosis

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic hyperinflammatory syndrome. The central pathogenesis is an explosive cytokine storm characterized by a significant increase in proinflammatory cytokines, including IL-1β, IL-6, IL-18, IFN-γ, and TNF-α. Meanwhile, negative regulatory factors, such as IL-10 and TGF-β, are also related to the production of HLH. Exploring the specific mechanism of cytokine storms could provide ideas regarding targeted therapy, which could be helpful for early treatment to reduce the mortality of HLH. Although some research has focused on the advantages of targeted therapies, there is still a lack of a comprehensive discourse. This article attempts to summarize the mechanisms of action of various cytokines and provide a therapeutic overview of the current targeted therapies for HLH.

Keywords Hemophagocytic lymphohistiocytosis · Cytokine storm · IFN-γ · Targeted therapy · Cytokine inhibitor

Introduction

Scott and Robb-Smith first reported hemophagocytic lymphohistiocytosis (HLH) in 1939 [1]. The hereditary form of HLH was first described in 1952 as familial hemophagocytosis [2]. HLH is a hyperinflammatory syndrome caused by cytokine storms due to the overactivation of cytotoxic T cells (CTLs), natural killer (NK) cells, and macrophages. The main clinical symptoms of HLH are fever, splenomegaly, blood cell reduction, frequent jaundice, skin abnormalities, and laboratory abnormalities [3]. Blood cell reduction includes hemoglobin, platelets, and neutropenia, and the skin abnormalities include panniculitis, measles-like erythema, maculopapular rash, and systemic purpura [3]. The laboratory abnormalities include hyperferritinemia, hypertriglyceridemia, hypofibrinemia, low NK-cell activity, and elevated sCD25. Clinical observations suggest that in the emergency department, HLH should be considered in critically ill patients with fever, splenomegaly, low hemoglobin, and a low platelet count [4]. Furthermore, 30–73% of HLH patients have central nervous system symptoms, including seizures, focal defects, meningitis, and changes in the level of consciousness [5]. The central nervous system is affected and predicts a worse prognosis.

In epidemiological surveys in China, statistical results concerning the HLH incidence are lacking. Nonetheless, studies in Sweden and the UK have shown that the annual incidence of pHLH in children is approximately 0.12/100,000 [6]. Moreover, the prevalence of HLH in children in Texas is 1/100,000 [7]. In general, the incidence of HLH in Japan and China is higher than the average worldwide.

The case fatality rate of HLH is very high; the course of the disease is usually 7 days to 5 years, and the average survival time is 4 weeks. Drug therapy, bone marrow transplantation, and hematopoietic stem cell transplantation can

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significantly prolong survival. The 5-year progression-free survival rate was increased to 54–62% after treatment compared with less than 5% in untreated patients [8]. Early and timely intervention for HLH is an effective way to prevent its progression. Currently, HLH-1994 and HLH-2004 revised by the Histocyte Society are the commonly used initial treatment regimens for HLH [9].

Pathogenesis and classification of HLH

The HLH can be divided into primary and secondary types [10, 11]. Primary HLH is mainly caused by mutations in the perforin-dependent pathway, resulting in damage to the cytotoxic function of NK cells and CTLs, which usually occurs in the juvenile phase [11]. Primary HLH includes monogenic disorders classified into familial HLH, immune correlation HLH, and Epstein–Barr virus (EBV)–associated HLH (EBV-HLH) [12]. Secondary HLH is due to various underlying conditions that lead to immune disorders, including infection, autoimmune diseases, and malignancies, especially infection [13]. Furthermore, secondary HLH is more common than primary HLH in adults generally without a family history or known inherited genetic defect [14, 15]. Primarily, macrophage activation syndrome (MAS) as a form of secondary HLH (or acquired HLH) is studied in this paper [16]. MAS occurs most frequently in patients with systemic juvenile idiopathic arthritis (sJIA) and systemic lupus erythematosus in rheumatology [16]. Due to the particularity of EBV-HLH, it includes both primary and secondary HLH [17, 18]. Primary HLH in EBV-HLH has X-linked lymphoproliferative syndrome (XPL-1, XLP-2) [17–21]. Regarding secondary HLH, the most common type in childhood HLH is virus-associated HLH, especially EBV-HLH [12, 20, 22].

Regarding the pathogenesis, $CD1^+$ macrophages can phagocytose free Hgb through CD1 and then produce IL-10 and haem oxygenase-1 (HO-1). HO-1 can decompose haem into CO and Fe^{2+}. Fe^{2+} is oxidized to Fe^{3+} under heavy ferritin chain (FHC) ferrous oxidase, further producing ferritin [23]. This regulation of ferritin is a compensatory mechanism of organisms that can chelate Fe_{2+} to initiate cytoprotective pathways, reduce oxidative stress-mediated apoptosis, and inhibit microvascular stasis. Ferritin can chelate Fe^{2+} to initiate cytoprotective pathways, reduce oxidative stress-mediated apoptosis [24], and inhibit microvascular stasis [23]. In addition, macrophages secrete the plasminogen activator after activation, leading to high plasmin levels and hyperfibrinolysis [25]. Severe hypofibrinogenemia causes HLH complicated by fibrinolytic wasting coagulopathy with a poor prognosis [26]. As mentioned earlier, TNF-α maintains high levels in HLH.

Treatment

The current initial treatment for HLH aims to suppress the excessive activation of the immune system and treat the cytokine storm [12]. According to the HLH-2004 treatment plan, chemoimmunotherapy includes the initial use of etoposide, dexamethasone, cyclosporine A, methotrexate, and cortisol in selected patients. Cortisol (CS) is a first-line treatment. After excluding lymphoma-related HLH, dexamethasone or methylprednisolone can be used [12]. The dose of dexamethasone (DEX) is 10 mg/m^2/day, and the dose of methylprednisolone (mPSL) pulse therapy is 20–30 mg/kg/day (3 consecutive days, maximum 1 g/day) [12]. If cortisol is ineffective, the parenteral administration of cyclosporine A (CSA) can be used. CSA can quickly control symptoms and reduce cortisol usage. The dose of CSA is generally 2–7 mg/kg/day [27]. Etoposide can play a role in treatments when cortisol and cyclosporine A are not effective. However, etoposide has potential toxicity and can cause bone marrow suppression and numerous infections during treatment [28, 29]. Antithymocyte globulin (ATG) may be a substitute for etoposide [30]. Familial, persistent, or recurrent HLH requires allogeneic hematopoietic stem cell transplantation [9]. The indications include (1) persistent NK-cell dysfunction; (2) proven familial or genetic diseases; (3) relapsed or refractory HLH; and (4) HLH with central nervous system involvement [31]. For patients with relapsed and refractory HLH, the initial treatment is not ideal for 25–50% of patients, resulting in a poor prognosis and a high mortality rate. For these patients with relapsed and refractory HLH, new targeted drug therapy may be the best choice [31].

The cytokine storm in HLH

Regardless of the causes of HLH, the exact pathophysiological mechanisms lead to cytokine storms. Several cytokines have been studied in detail, including IL-1β, IL-6, IL-18, IFNγ, and macrophage colony-stimulating factor (M-CSF). These cytokines are divided into positive and negative regulators according to their roles in HLH (Fig. 1). Below, we discuss several cytokines that play an essential role in an HLH cytokine storm and summarize their mechanisms of action and clinical findings.

Positive regulators

IL-1β

IL-1β is a proinflammatory cytokine produced mainly by activated mononuclear macrophages, causing the activation

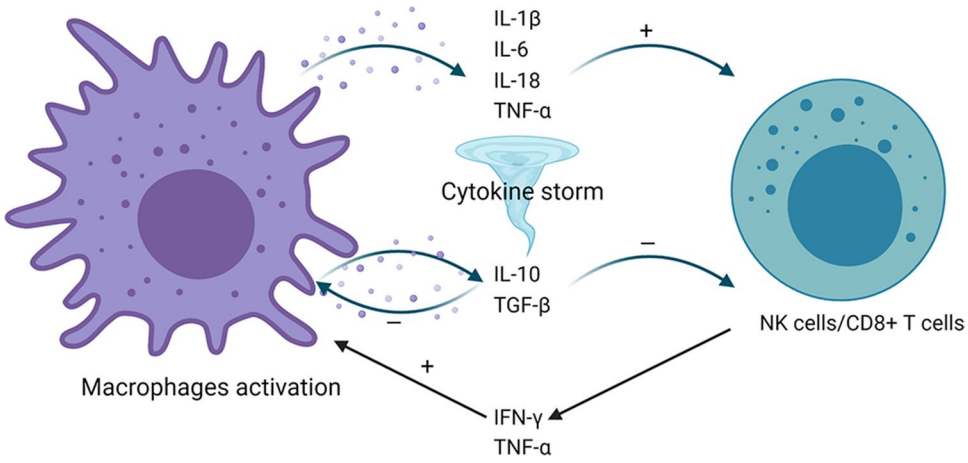

Fig. 1 Regulation of various cytokines on immune-related cells in HLH-induced cytokine storm

of white blood cells and endothelial cells and effective production of other inflammatory cytokines, including IL-6 [27]. IL-1β exists in an inactive form in vivo (proIL-1β) and accumulates persistently in the cytosol [32]. The activated processing of proIL-1β is closely bound to the nucleotide-binding domain and leucine-rich repeat pyrin–containing protein-3 (NLRP3) and the proinflammatory protease caspase-1 [32]. Caspase-1 is activated by a variety of typical inflammasomes belonging to the following three gene families: AIM2-like receptors (ALRs), Nod-like receptors (NLRs), and tripartite motif family (TRIM) [33]. When exogenous ATP activates cells via the P2X7 receptor, procaspase-1 is activated by recruiting the NLRP3 inflammasome, which causes activated caspase-1 to convert proIL-1β into a biologically active form, and mature IL-1β is secreted out of the cell [27, 34, 35]. IL-1β has been highly correlated with systemic juvenile idiopathic arthritis (sJIA), the primary disease triggering HLH [36]. Therefore, the inhibition of IL-1β can control the occurrence and development of HLH during treatment [27].

IL-6

IL-6 is a multifunctional cytokine produced by macrophages that is commonly secreted with TNF-α and IL-1β during the early stage of inflammation [27, 37]. IL-6 can play proinflammatory and anti-inflammatory roles under certain conditions, which is critical in a cytokine storm.

The binding of IL-6 to IL-6R initiates an IL-6 signaling cascade mediated by the ubiquitous transmembrane protein gp130 as an IL-6 signal transducer [38].

After the activation of IL-6R signaling, two major downstream signaling pathways are activated, including the Janus kinase (JAK) signal transducer and activator of transcription 3 (STAT3) pathway and the JAK-SH2 domain tyrosine phosphatase 2 (SHP2)–mitogen-activated protein (MAP) kinase pathway [38]. In the JAK-STAT3 pathway, STAT3 is phosphorylated by JAK kinase to form a homologous dimer that is transferred to the nucleus for transcriptional activity [39]. Additionally, STAT3-dependent IL-6R signaling induces the expression of suppressors of cytokine signaling 1 (SOCS1) and SOCS3, which play an anti-inflammatory role. [38, 40]. On the one hand, the binding of SOCS1 to JAK directly reduces its activity [40]. On the other hand, SOC3 binds GP130 to block the induction of the IL-6 signaling cascade and terminate JAK activation [38].

To date, the role of IL-6 in the pathogenesis of MAS has still not been comprehensively investigated. In a study of transgenic mice overexpressing IL-6, the results indicate that long-term exposure to IL-6 leads to an increased inflammatory response to Toll-like receptor (TLR) ligands [37]. This finding suggests that the increased IL-6 in HLH may be related to an amplified inflammatory response that causes a cytokine storm [27]. In addition, IL-6 has an inhibitory effect on the cytotoxicity of NK cells by decreasing the expression of perforin and granzyme B based on observations using IL-6-Tg mouse models [41]. The results of the above research may contribute to a deeper understanding of the pathogenesis of HLH.

IFN-γ

In recent studies, IFN-γ has been shown to play an important role in the cytokine storm of HLH. IFN-γ is a type II interferon secreted by T lymphocytes and NK cells during the Th1-mediated immune response process. IFN-γ plays an influential regulatory role in regulating the immune system and is an indispensable component required for the body to play its immune function and remove pathogens from the body [42]. In an inflammatory environment, IFN-γ triggers immune responses and stimulates the elimination of pathogens [43, 44]. It also prevents the excessive activation of the immune system and tissue damage. However, the mechanism of this reaction is not yet understood [43, 44]. IFN-γ plays a

role in activating monocytes and macrophages. Macrophages activated by IFN-γ have a typical proinflammatory phenotype manifested by an enhanced response to TLR ligands and antigen processing and upregulation. These activated macrophages can produce multiple cytokines in turn, including IL-6 and IL-12, leading to a more severe inflammatory response [27, 45–47]. Meanwhile, the blood level of the downstream effector chemokine C-X-C motif ligand nine is increased along with IFN-γ [48].

Thus far, several studies have demonstrated the central role of IFN-γ in the pathogenesis of FHLH [49]. IFN-γ showed a significantly elevated trend in the corresponding animal models [50, 51]. In initial mouse experiments, it was demonstrated that hyperactive CTLs and high levels of IFN-γ cause severe HLH [50]. In another experiment, after using antibodies to exhaust IFN-γ in HLH model mice, survival was significantly improved compared with that following the neutralization of other factors in the same model [50]. Similarly, in relevant human studies, IFN-γ was disproportionately increased in HLH patients compared to other cytokines and was significantly decreased following treatment with effective drugs. This result also provides new ideas concerning the treatment of HLH using IFN-γ blockers to achieve therapeutic effects [52, 53].

IL-18

IL-18 is a proinflammatory cytokine in the IL-1 family produced by activated macrophages [54, 55]. It induced IFN-γ production in NK and T cells and was initially described as an IFN-γ-inducing factor isolated from serum [27, 55]. IL-18 can also induce the release of other proinflammatory cytokines, such as TNFα and chemokines [27]. Diagnostically, IL-18 can help distinguish the type of HLH and determine the susceptibility of patients who have hyperferritinemia or autoinflammatory diseases to MAS [56]. It is possible that because IL-18 belongs to the same family of cytokines as IL-1β, it is similar to IL-1β in several ways [55]. IL-18 is an inactive precursor in macrophages, monocytes, and dendritic cells and is processed into the mature form by activated caspase-1 in cells [55].

Although the binding receptor is different, the downstream effector pathway of IL-18 is similar to that of IL-1β [55]. IL-18 first binds the ligand-binding chain IL-18Rα with low affinity and then recruits the coreceptor IL-18Rβ to initiate TLR/IL-1R-like proinflammatory signaling through the MyD-IRAK1/4-NF-κB axis and p38 mitogen-activated protein (MAP) kinase [57, 58]. However, there are differences in signal transduction between IL-18 and IL-1β. IL-18 must be activated, requiring stimulants that increase the number of IL-18 receptors on immunoreactive cells, such as IL-12, which is essential for IL-18 to induce IFN-γ production [55, 58]. Moreover, IL-18 requires a high concentration of 10–20 ng/ml to be activated. In contrast, IL-1β activates a wide range of cells at low concentrations without stimulants, often in the picograms or less per milliliter range [59].

TNFα

TNFα is a polymorphic pro-inflammatory cytokine produced mainly by macrophages and monocytes and can drive the polarization of macrophages with an M1 phenotype [26, 27].

A study on the effect of rhTNF on the activity of peripheral blood NK cells in patients showed that after receiving NK cell treatment, the specific lysis value of NK cells isolated from peripheral blood mononuclear leukocytes decreased [60]. This experiment provides evidence that TNF-α has a negative regulatory effect on the activity of NK cells. The speculated mechanism is that TNF-α can increase the adhesion of vascular endothelial cells to NK cells or has a direct toxic effect on NK cells. The activity of NK cells is inhibited in the progress of HLH, and its functional defect is an integral part of HLH [61]. When NK cells are inhibited, it will cause a prolonged inflammatory response, which is not suitable for HLH healing [62].

Although TNF-α levels are significantly elevated in animal models of HLH, it does not appear to be the core cytokine responsible for HLH [27, 51].

Negative regulators

IL-10

IL-10 is expressed by various immune cells, one of the three major subgroups of the IL-10 cytokine family, and has a variety of immune mediator functions [63]. IL-10 mainly sends signals through the JAK-STAT pathway, acts on various cells of the immune system, and exerts a powerful anti-inflammatory function [64]. IL-10 mainly interferes with the function of antigen-presenting cells (APC) and the expression of major histocompatibility complex-2 (MHC-II) leading to the dysfunction of antigen presentation [65]. Furthermore, IL-10 inhibits cytokines required for the differentiation of CD4 + T cells, such as IL-12 and IL-23, and directly acts on T cells to inhibit T-cell proliferation and the secretion of cytokines [66], and induce anergy [67]. Regarding $CD8^+$ T cells, IL-10 impairs secondary responses [68]. In addition, IL-10 can similarly inhibit the production of inflammatory mediators by neutrophils [69].

The essence of HLH is inflammatory response overload, and IL-10 can slow the occurrence of HLH to a certain extent. Existing experiments have shown that MAS model mice injected with CpG continuously exhibit IL-10 blockade, which induces and worsens explosive MAS [70]. The protective mechanism of IL-10 on immune cells is as follows. Macrophages phagocytose and clear free hemoglobin

(Hgb) mediated by the surface CD163 receptor and producing IL-10 and haem oxygenase (HO-1) [24]. IL-10 upregulates the expression of CD163 on macrophages [71]. HO-1 mediates the decomposition of haem to produce carbon monoxide (CO) and ferrous ions (Fe^{2+}), which have an anti-inflammatory effect [26]. By inhibiting the overall immune system, IL-10 has an important negative regulatory effect on HLH.

TGF-β

According to the human genome, the 32 members of the TGF-β ligand superfamily are mainly divided into two subfamilies, TGF-β and BMP [72]. The TGF-β subfamily is the most important member of the immune regulation of the TGF-β superfamily. TGF-β binds TβRII with high affinity, recruits TβR1 with the assistance of TβRIII [73], and activates the Smad protein family through phosphorylation [74]. Phosphorylated Smad2, Smad3, and Smad4 form heteromeric complexes that regulate the interaction between the nucleus and various transcription factors, leading to cellular responses [75].

TGF-β plays an important role in regulating the normal function of the immune system, especially the regulation of T-cell types, suggesting that TGF-β may play an essential role in inhibiting the process of HLH. TGF-β can inhibit the proliferation of CD4 + T cells by inhibiting the production of autocrine IL-2 [76]. TGF-β can activate the Smad protein family, cooperating with ATF1 to inhibit CTL cells from secreting IFN-γ, perforin, granzyme, and Fas ligand [77]. The Smad2 protein activated by TGF-β and the activated STAT5 signal and NFAT signal cooperate to induce the expression of Foxp3 to promote the differentiation of Treg cells [78]. Furthermore, TGF-β inhibits the differentiation of Th1 cells by inhibiting the T-bet transcription factor and inhibits the differentiation of Th2 cells by inhibiting the expression of MSC and SOX4 [79–81]. The above processes are all caused by activating the Smad protein. In addition, TGF-β can inhibit NK-cell function in many ways [82].

In summary, TGF-β can negatively regulate the functions of various immune cells, and promote the proliferation and differentiation of Treg cells. Through the regulation of T cells and NK cells, the progression of HLH may be slowed.

Treg-IL-2 homeostasis network

Regulatory T cells (Tregs) play a critical negative regulatory role in the immune response. In maintaining immune homeostasis and self-tolerance, Tregs can suppress excessive or misleading immune responses to their normal tissue cells [83]. The Treg population mainly refers to CD4 + CD25 + T cells, which explicitly express forkhead box protein 3 (Foxp3) [84]. Foxp3, as a specific protein, plays a negative regulatory role mainly through the transcription of silencing T-cell effector genes and the activation of molecular genes encoding inhibitory functions [83].

T cells with adverse regulatory effects may substantially affect the entire HLH process, but these cells suffer a series of destruction during HLH. In an experiment in which LCMV infection activated the immune system of wild-type mice and perforin-deficient (Prf1 -/-) mice, the Prf1 − / − mice had the same genetic defect characteristics as patients with familial hematopoietic lymphohistiocytosis (FHL) [85]. The experiment revealed that after 10 days of LCMV infection, the number of Tregs in the wild-type mice was reduced by 40%, while the number of Tregs in the Prf1 − / − mice was reduced by 90%. Further study of the phenotype showed that compared with the wild-type mice, the expression of Foxp3 and CD103 on the Treg cells in the Prf1 − / − mice was reduced, indicating that its function was impaired. This finding is related to damage to the homeostatic network of Treg-IL-2. After infection, CD25 receptors on the surface of Tregs are reduced, CD8 + T cells consume too much IL-2, and IL-2 signals cannot be transmitted, resulting in a decrease in downstream Mcl1 expression and providing a potential mechanism for the death of Tregs.

TNF-α

TNF-α is a cytokine that plays a positive role in the progression of HLH, which was described above.

There are cases in which TNF-α inhibitors indirectly induce HLH, which is inconsistent with the discussion of TNF-α as a positive regulator of HLH. In a literature review by Rahaf Baker et al., there were 10 reports of MAS associated with etanercept, infliximab, or adalimumab [86]. The report showed that the occurrence of MAS was time-correlated with the use of TNF-α inhibitors, and patients developed adalimumab-related MAS 2.5 months after the use of adalimumab. The possible mechanisms of TNF-α inhibitor-related MAS include infection and immune system disorders. Four of the reported cases developed infections after the use of adalimumab, including visceral leishmaniasis, disseminated histoplasmosis, liver abscess, and primary EBV. Furthermore, TNF-α rarely leads to a paradoxical effect of the immune response, i.e., compensatory immune system activation following a suppressive effect on the immune system [87], which can lead to an imbalance in the immune system, which can cause MAS. TNF-α inhibitors may be related to the occurrence of HLH, but they cannot confirm the negative regulatory effect of TNF-α, and the related mechanism still needs to be explored.

Target therapy

HLH is divided into primary and secondary. Regarding HLH caused by gene mutations (PRF1, UNC13D, STX11, and STXBP2), the current primary method is to provide symptomatic treatment (using steroids and chemotherapy) to extend life, including the HLH-94 and HLH-2004 programs [25]. The only cure is allogeneic hematopoietic stem cell transplantation (HSCT) [88]. Regarding secondary HLH caused by multiple factors, etiological treatment is given based on the cause, such as infection, cancer, and autoimmune disease. Furthermore, measures are taken to counter the excessive immune response [88].

The overall goal of treatment in children with HLH is to suppress and control excessive inflammation and hypercytokinemia and eliminate activated and infected cells [89]. However, a large proportion of pediatric patients with HLH are genetically related; thus, the effect of using conventional drugs is not ideal. Once the genetic form of HLH is diagnosed, HLA typing is required immediately. For PRF1, UNC13D, STX11, STXBP2, RAB27A, LYST, SH2D1A, and some XIAP-deficient pediatric patients, HSCT is effective under suitable donor conditions [10].

Regarding HPS, currently, experience in the clinical use of targeted therapy drugs, such as anakinra (recombinant IL-1 receptor antagonist) and emapalumab (anti-IFN-γ monoclonal antibody), is limited. In a trial of 44 pediatric HLH patients treated with anakinra [90], the cohort's overall mortality rate was 27%. Anakinra was associated with decreased mortality ($P = 0.046$), and the serum ferritin levels were decreased by 57%. In another trial involving 34 pediatric HLH patients using emalumab [91], 65% of the emapalumab group showed efficacy, and 71% of the emapalumab group survived in the last observation. Anakinra and emapalumab have been proven to be effective against HPS in clinical trials, and more targeted therapies will be used to treat HPS in the future.

In summary, cytokine-related targeted therapies have become more attractive recently, and next, we introduce the mechanism and research status of the currently popular targeted drugs (Figs. 2 and 3).

IL-1β inhibitors

Canakinumab is a high-affinity monoclonal antibody targeting the IL-1β cytokine, a common therapeutic target for sJIA [16, 26]. Canakinumab can combine with IL-1β in humans

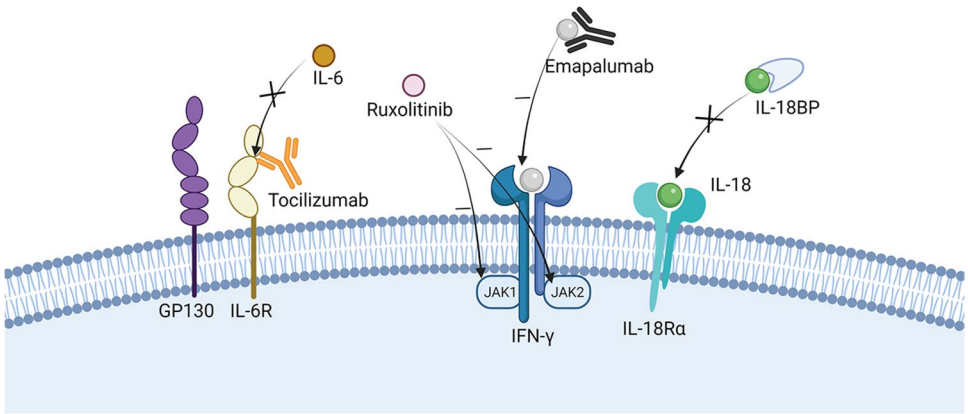

Fig. 2 Mechanism of action of various cytokine antagonists in the HLH target therapy

Target	Example	Therapeutic mechanism	Identifier	Phase I	Phase II	Phase III
IL-1β	Canakinumab	IL-1 receptor antagonist	NCT00886769			
IL-1α,IL-1β	Anakinra		NCT04443881			
IL-6	Tocilizumab	IL-6 receptor inhibitor	NCT04445272			
IFN-γ	Emapalumab	IFN-γ inhibitor	NCT03312751			
	Ruxotinib	JAK1 and JAK2 inhibitor	NCT03795909			
IL-18	tadekinig alfa	IL-18 inhibitor	NCT03113760			

Fig. 3 Comparison of clinical trial stages of various cytokine targeting inhibitors

to reduce the increased IL-1β content. Nevertheless, studies have shown that canakinumab has no significant effect on the MAS incidence, although it effectively controls the symptoms of sJIA effectively [92].

Anaconda is a recombinant IL-1Rα antagonist that competitively inhibits the activity of IL-1α and IL-1β [26, 93]. It has been reported that anaconda used as an auxiliary in clinical treatment could play an effective role in 12 pediatric MAS patients [94]. In general, the incidence of MAS in patients with sJIA is ambiguous, suggesting the need for further clinical research.

IL-6 inhibitor: tocilizumab

Tocilizumab (TCZ) is a humanized monoclonal antibody against the IL-6 receptor [16, 95], and is effective in treating rheumatoid arthritis [96]. In cytokine-release syndrome, TCZ can entirely reverse cytokine disorders and multiple-organ failure, which is significant for treating cytokine storms in severe HLH. TCZ inhibits IL-6-mediated signaling by combining with IL-6R and can be an alternative therapy for patients with HLH [16, 95]. In a phase III clinical trial of SJIA in Japan, MAS occurred in approximately 1.5% of SJIA patients after TCZ treatment [96]. Although TCZ can treat sJIA effectively, it does not reduce the incidence of MAS complications and even changes the clinical symptoms and laboratory results of MAS [96, 97]. It was reported that the C-reactive protein (CRP) levels remained in the normal range in some patients who received TCZ and that the elevated levels of ferritin were lower than before [97–99]. Therefore, the role of TCZ in the treatment of HLH-induced cytokine storms may be limited.

IL-18 inhibitor: rhIL-18BP

The activity of IL-18 is regulated by the high-affinity binding protein in the human body, called IL-18-binding protein (IL-18BP) [7]. IL-18BP is a constituent-secreted protein, and the serum concentration in healthy people is a 20-fold molar excess of IL-18, which forms a natural balance [28, 31]. In addition, increased IFN-γ can enhance the gene expression of IL-18BP, resulting in a negative feedback loop of the inflammatory response [31]. Once the balance between IL-18 and IL-18BP is broken, it may activate T lymphocytes and macrophages, inducing the production of large amounts of IFN-γ and TNF-α and then causing HLH [8, 28]. One study showed that patients with XIAP deficiency had significantly and persistently elevated serum IL-18 levels, resulting in a much higher than average susceptibility to HLH [3, 33]. Therefore, maintaining the level of IL-18 in the human body through the artificial regulation of IL-18BP to treat HLH may be an effective cytokine targeted therapy [34].

In animal studies of perforin-deficient mice, synthetic IL-18BP improved liver damage but had a limited effect on the cytokine storm, suggesting that further work is needed to characterize the effects of IL-18BP [100]. Moreover, recombinant human IL-18BP (rhIL-18BP) was successfully applied in combination with anaconda to treat severe refractory NLRC4-MAS infants [101]. This report suggests that IL-18 inhibition may be an effective strategy for HLH, at least in the genetic background of NLRC4 mutations [55]. To date, it has been proven to be a promising biological drug.

IFN-γ inhibitor

The HLH-94 protocol is commonly used for the treatment of HLH, and HLH treatment in adults and children inhibits life-threatening inflammation of the disease [102, 103]. The mortality rate remains high despite HLH treatment. As cytokine-targeting drugs are increasingly identified, the targeted drugs for IFN-γ are emapalumab and ruxolitinib until now. Emapalumab is an IFN-γ antagonist, and ruxolitinib not only antagonizes IFN-γ but also treats HLH by inhibiting the JAK-STAT pathway [103–105].

Emapalumab is the first approved cytokine-targeted treatment for HLH [102]. Emapalumab has been approved for refractory patients with primary HLH, recurrence, or progressive HLH in adults or children with intolerance to conventional treatment [102]. It is a complete human immunoglobulin G1 monoclonal antibody with the noncompetitive inhibition of IFN-γ and has a high affinity ($K(d) = 1.4$ pM) binding to free IFN-γ and IFN-γ bound to its receptor [102]. An experiment used a model of perforin-null (Prf1 −/−) mice. Then, the mice developed HLH-like pathology after stimulation with lymphocytic choriomeningitis virus. After adequate treatment with antibodies, CD8 + T cells and IFN-γ were consumed, improving the survival rate of the mice [50].

A study investigated the safety and efficacy of emapalumab in children affected by HLH (NCT01818492) [91]. Thirty-four pediatric patients with primary HLH participated in the trial, with a median age of 1 year. Twenty-five (74%) patients harbored germline mutations affecting the pHLH genes. Of the 34 patients, 27 were previously treated for HLH, and 7 were treatment naïve. All 34 patients received emapalumab at an initial dose of 1 mg/kg every three days with a possible escalation up to 10 mg/kg for at least 4 weeks, with dexamethasone throughout. Of the 27 previously treated patients, 26% achieved a complete response (CR), 30% achieved a partial response (PR), and 7% achieved "disease improvement." Of the seven treatment-naive patients, there was 0% CR, 43% PR, 29% disease improvements, and two patients without a response (29%).

The outcome does not rival the 69% CR rate among the HLH patients in the HLH-94 study; thus, the therapy method

of single emapalumab does not satisfy the demand for curing HLH contemporarily [106]. Multiple cytokines play a role in the high inflammatory cytokine storms in HLH; thus, targeting single cytokines may not be sufficient to improve the tissue inflammation and organ disorder that accompany the disease [70, 107]. Notably, the inhibition of single cytokines may not appear to be the future development direction of HLH and related inflammation control. In clinical practice, HLH patients are often complicated by other diseases, and sometimes, primary and secondary HLH cannot be distinguished. Therefore, even if emapalumab has a certain control effect on patients with secondary HLH, etoposide and dexamethasone are still the main treatment options at this stage. Furthermore, we need to focus on the idea of multi cytokine inhibition, such as ruxolitinib.

Ruxolitinib is a selective kinase inhibitor that inhibits Janus-related kinase (Janus-associated kinases, JAKs) JAK1 and JAK2 and blocks the JAK signaling and transcription activator (signal transducer and activator of transcription, STAT) pathway. Janus kinase (JAK) signal transducer and activator of transcription (STAT) is the common path of many cytokines (IFN-γ, IL-2, IL-6, IL-10, IL-12, and GM-CSF) in the signal transmission of the pathogenesis of HLH [108]. Ruxolitinib inhibits JAK1 and JAK2, but not IFN-γ [109, 110], which plays a role downstream of multiple cytokines [109, 110]. However, whether the beneficial role of ruxolitinib stems solely from targeting the IFN-γ signaling pathway or targeting other cytokine signaling pathways remains unclear [104]. Studies have shown that the discontinuity treatment with ruxolitinib is expected to improve survival in patients with HLH [111]. As of 2021, 18 studies reported 115 HLH patients receiving ruxolitinib [88]. The method of administration was twice a day, and the dose range is 2.5–25 mg. The results showed that within 24–48 h of medication, the clinical symptoms were improved, and the levels of ferritin, soluble CD25, IFN-γ, IL-18, and MIP-1-α in the plasma were reduced until they returned to normal [88]. Recently, new studies showed that ruxolitinib has more evident advantages in reducing cytokine levels and organ enlargement than simply applying IFN-γ antagonists. Ruxolitinib can significantly reduce the frequency and/or absolute number of invasive organ CD8 + cells, monocyte cells, and neutrophils and reduce the activation of T cells and neutrophils [104]. The most critical mechanism may sensitize $CD8^+$ T cells to dexamethasone-induced apoptosis. This finding also provides a new research direction and idea for the prognosis of HLH.

Conclusion

As a refractory hyperinflammatory syndrome, HLH has not been fully analyzed thus far, and the effects of treatment options are uneven. However, the common pathways of the cytokine storm of primary and secondary HLH provide targeted therapy ideas.

The positive regulatory media mainly include IL-1β, IL-6, IFN-γ, and IL-18. The proIL-1β of mononuclear macrophages is activated to IL-1β under the stimulation of exogenous ATP [35] and causes the activation of white blood cells and endothelial cells out of the cell [27]. The ideal inhibitors of IL-1 include canakinumab and anakinra. IL-6 produced by macrophages exerts an anti-inflammatory effect through the JAK-STAT signaling pathway [38, 39], and exerts a proinflammatory effect through the Toll-like receptor pathway [38, 40] while inhibiting the cytotoxicity of NK cells [41]. The ideal inhibitor of IL-6 is tocilizumab. CTLs produce a large amount of IFN-γ after being out of control [53], and IFN-γ exerts a proinflammatory effect by activating macrophages to produce more cytokines [112]. The ideal inhibitor of IFN-γ is emapalumab. IL-18 is mainly produced by activated macrophages [54, 55]. The action of costimulatory factors activates TLR/IL-1R-like proinflammatory signaling [55, 57, 58], thereby activating T cells and macrophages, and inducing the release of other proinflammatory cytokines [55]. The ideal inhibitor of IL-18 is rhIL-18BP.

The negative regulatory media mainly include IL-10, TGF-β, and Tregs. IL-10 produced by a variety of immune cells can weaken cellular immunity and enhance humoral immunity through the JAK-STAT signaling pathway [64], while simultaneously triggering the protective mechanism of immune cells [71]; thus, it can reduce HLH to a certain extent. TGF-β directly inhibits the secretion of IL-2 [76] and can also activate the Smad protein family to negatively regulate Th cells, CTL cells, and NK cells [79–82]. However, TGF-β promotes the proliferation and differentiation of Treg cells [78]. TGF-β may slow the HLH process. As an important immune regulatory cell, Tregs can play a negative regulatory role through transcription of silencing T cell effector genes and activation of molecular genes encoding inhibitory functions [83]. During the HLH period, Tregs are depleted, and the Treg-IL-2 homeostasis network is damaged [85]. Therefore, restoring the Treg-IL-2 homeostasis network may achieve a therapeutic effect [85]. Currently, the ideal therapeutic drug for negative regulation media is recombinant cytokines to enhance the inhibitory effect. However, the negative regulation media have not been fully studied, and are currently in the theoretical stage.

In summary, the cytokine regulation mechanism in the complex pathogenesis of HLH is still important, and further understanding of the target treatment options of various mediators could greatly increase the cure rate of HLH.

Abbreviations HLH: Hemophagocytic lymphohistiocytosis; CTL: Cytotoxic T-cells; NK: Natural killer; EBV: Epstein–Barr virus; MAS: Macrophage activation syndrome; sJIA: Systemic juvenile

idiopathic arthritis; XLP: X-linked lymphoproliferative; HO-1: Heme oxygenase-1; FHC: Ferritin heavy chain; CS: Cortisols; DEX: Dexamethasone; mPSL: Methylprednisolone; CSA: Cyclosporine A; ATG : Antithymocyte globulin; ALRs: AIM2-like receptors; NLRs: Nod-like receptors; TRIM: Tripartite motif family; JAK: Janus kinase; STAT3: Signal transducer and activator of transcription 3; MAP: Mitogen-activated protein; SOCS: Signaling induces the expression of suppressor of cytokine signaling; APC: Antigen-presenting cells; MHC: Major histocompatibility complex; Treg: Regulatory T cells; PCR: Polymerase chain reaction; TCZ: Tocilizumab; Hgb: Hemoglobin

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Declarations

Conflict of interest The authors declare no competing interests.

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