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# T-ing up the storm: pathogenic cycling lymphocytes in the biology of macrophage activation syndrome

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## Abstract

**Background** Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are potentially fatal cytokine storm syndromes with clinical features including fever, pancytopenia, hepatosplenomegaly, coagulopathy, and progressive multiorgan system dysfunction. Mechanistically, HLH / MAS are driven by persistent activation of lymphoid and myeloid cells, but our understanding of the pathogenic cell populations remains incomplete.

**Main body** In this Perspectives article, we provide an overview of the biology of HLH / MAS and the critical role of interferon-g in disease pathogenesis. We discuss the recent discovery of cycling lymphocytes in HLH / MAS marked by expression of CD38 and HLA-DR, which are primary producers of IFN-γ. The expansion of cycling lymphocytes correlates with disease activity and helps to distinguish HLH / MAS from clinical mimics. We demonstrate an approach to quantify $CD38^{+}HLA\text{-}DR^{+}$ cycling lymphocytes and evaluate their utility as a diagnostic biomarker for HLH / MAS. Lastly, we discuss the treatment of MAS, including potential therapeutic options to target these pathogenic lymphocytes.

**Conclusion** Understanding of biology of cycling lymphocytes in HLH / MAS will facilitate the development of novel therapeutic approaches to overcome these fatal hyperinflammatory disorders.

**Keywords** Macrophage activation syndrome, Hemophagocytic lymphohistiocytosis, T lymphocytes

## Background

Inflammation is central to the sequential activation of innate and adaptive immune responses against microbial pathogens. Detection of pathogen-associated molecular patterns by innate sensors such as Toll-like receptors (TLR) coordinates the production of cytokines and chemokines to recruit immune cells [1]. Antigen presenting cells (APCs) then license the activation of the adaptive immune system to generate antigen-specific humoral and cytotoxic responses. Once the infection is contained, downregulation of the immune response is necessary to resolve inflammation and restore homeostasis [2].

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To prevent collateral tissue damage from excessive inflammation, multiple regulatory mechanisms are in place to restrain and remove activated lymphocytes. When these mechanisms are breached, persistence of activated immune cells results in unremitting release of cytokines and chemokines, leading to a vicious cycle of hyperinflammation [3]. Familial hemophagocytic lymphohistiocytosis (fHLH) caused by genetic defects that impair cytotoxic cell function is a classic illustration of this pathologic process [4]. In rheumatology, the term macrophage activation syndrome (MAS; a form of secondary HLH) is used to describe a similar hyperinflammatory process that accompanies inflammatory diseases [5].

MAS and HLH are along a spectrum of hyperinflammatory disease known as cytokine storm syndromes [3]. Clinically, MAS and HLH share many clinical manifestations as well as laboratory derangements. Persistent activation of myeloid cells and lymphocytes leading to the production of interferon (IFN)-γ is a key driver of pathologic inflammation [6, 7]. Recent data point to cycling lymphocytes with surface expression of CD38 and HLA-DR as a hallmark of HLH / MAS that also constitute the major source of IFN-γ production [8–11].

In this Perspectives article, we review the biology of MAS and highlight recent findings on $CD38^{+}HLA\text{-}DR^{+}$ cycling lymphocytes. We discuss the utility of these cells as a biomarker for diagnostic evaluation of MAS and their role in disease pathogenesis. Lastly, we discuss the management of MAS including potential approaches to target these pathogenic lymphocytes.

## MAS: A cytokine storm associated with inflammatory diseases

MAS refers to a hyperinflammatory state characterized by systemic inflammation, cytopenia, lymphadenopathy, hepatosplenomegaly, and coagulopathy in rheumatology [3]. The connection between Still's disease (encompassing both systemic juvenile idiopathic arthritis and adult-onset Still's disease) and MAS is well established; 10–30% of patients with Still's disease experience MAS at disease onset and/or with subsequent flares [12, 13]. The dysregulated production of IL-1 and IL-18 in Still's disease may be responsible for propensity to develop MAS [14]. IL-18 is an excellent biomarker of Still's disease and even higher levels are observed in patients with MAS [14, 15].

Other inflammatory contexts can also trigger this hyperinflammatory cascade as MAS is linked to rheumatologic diseases including systemic lupus erythematosus (SLE), dermatomyositis, and Kawasaki disease. Infection is a common trigger of HLH in otherwise healthy individuals. Certain pathogens, such as Epstein-Barr virus (EBV), are especially adept in causing HLH [16]. Although identification of underlying etiology is important, prompt recognition of HLH / MAS and treatment initiation are paramount as the dysregulated inflammatory response can rapidly spiral towards multi-organ system failure and death [17].

Because of the clinical overlaps between HLH and MAS, the HLH diagnostic criteria are often considered for evaluation of MAS. The HLH-2004 criteria include fever, hepatosplenomegaly, cytopenia, defective NK cell cytotoxicity, evidence of hemophagocytosis, and elevated triglyceride, ferritin and soluble IL-2R/CD25 levels [18]. Recognizing that these criteria were validated for HLH, a set of classification criteria dedicated to the evaluation MAS associated with Still's disease was developed in 2016 [19]. These criteria established by the American College of Rheumatology (ACR) / European Alliance of Associations for Rheumatology (EULAR) utilize fever and hyperferritinemia as entry criteria as well as a combination of supplemental criteria including thrombocytopenia, hypertriglyceridemia, AST elevation, and fibrinogen consumption. These criteria have not been validated for MAS associated with other rheumatologic diseases.

Beyond inflammatory diseases, secondary HLH can occur as a complication of malignancies and drug reactions, although the nomenclature may differ depending on the context. Cytokine release syndrome, for example, refers to a group of pathologic processes associated with immunotherapies for cancers, including checkpoint inhibitors, bispecific T-cell engagers, and chimeric antigen receptor T (CAR-T) cells [20, 21]. For example, immune effector cell-associated neurotoxicity syndrome is an encephalopathy that presents with neurological and psychiatric manifestations after treatment with CAR-T and other cellular immunotherapies [22]. The underlying mechanism has not been fully elucidated but potentially involves interactions between CAR-T cells and myeloid cells, leading to aberrant release of cytokines that disrupt the blood brain barrier. On the other hand, immune effector cell-associated HLH describes persistent CAR-T cell activation and cytokine production upon tumor antigen engagement [23].

### Interplay of immune cells in the pathogenesis of MAS

In this section, we summarize key advances that have shaped our current understanding of MAS. HLH and MAS are discussed together as they are generally viewed as a disease spectrum and many studies do not distinguish these entities. Detailed historical overviews and in-depth reviews of HLH / MAS are available [3, 4, 16, 24].

HLH was first described in 1939 by Scott and Robb-Smith. The term "histiocytic medullary reticulosis" was used to describe several patients with the constellation of relapsing fever, anemia, thrombocytopenia, lymphadenopathy, splenomegaly [25]. Post-mortem spleen

and bone marrow microscopy revealed an abundance of activated lymphocytes and histiocytes with evidence of erythrophagocytosis. The observation of similar hemophagocytes resembling activated macrophages led to the descriptor of "MAS" in the context of rheumatic diseases [26].

While hemophagocytosis became a pathognomonic finding of HLH / MAS, an important role of T lymphocytes and NK cells emerged. In 1996, Egeler et al. demonstrated that impaired cytotoxicity of T and NK cells is a common feature of HLH [27]. This insightful observation built a foundation to understand the mechanistic basis of genetic susceptibilities for HLH. Starting with the discovery of Perforin (*PRF1*) variants, genes responsible for fHLH are found to regulate cytotoxic lymphocyte function [28]. The contribution of host genetics is not limited to HLH, as a substantial portion of patients with Still's disease-associated MAS possess heterozygous pathogenic variants in these genes [29, 30]. Ineffective cytolysis permits the proliferation and expansion of activated T lymphocytes, which perpetuates the inflammatory response by producing IFN-γ and other proinflammatory mediators [31]. Evidence of overt T cell activation is confirmed by the extraordinarily high levels of soluble IL-2R in patients with HLH relative to other inflammatory conditions [32]. IL-2 consumption by activated $CD8^+$T cells further augments immune dysregulation by disrupting the expansion of regulatory T cells [33].

The creation of the first murine model of HLH in 2004 was a major advance in defining pathogenic cells and cytokines. Jordan and colleagues showed that perforin-deficient mice challenged with lymphocytic choriomeningitis virus (LCMV) develop lethal HLH with hepatosplenomegaly, cytopenia, cytokine storm, and hemophagocytosis [6]. Importantly, they unequivocally demonstrated that $CD8^+$ T lymphocytes, IFN-γ, and APCs are essential for disease development [6, 34]. Activation of myeloid cells by IFN-γ leads to production of chemokines to recruit other immune cells and cytokines that further amplify the inflammatory cascade, including inducers of IFN-γ production (i.e. IL-12, IL-15, and IL-18). These observations support the paradigm of HLH / MAS as a cytokine storm driven by reciprocal activation of lymphocytes and myeloid cells, with susceptibility determined by a combination of host genetics, infectious and non-infectious triggers, and underlying inflammatory conditions (Fig. 1).

MAS is also a feature of two autoinflammatory syndromes characterized by aberrant inflammasome activation. Gain-of-function (GOF) variants in *NLRC4* cause enterocolitis and MAS while a GOF C-terminal variant in *CDC42* causes HLH, neonatal-onset cytopenia, painful

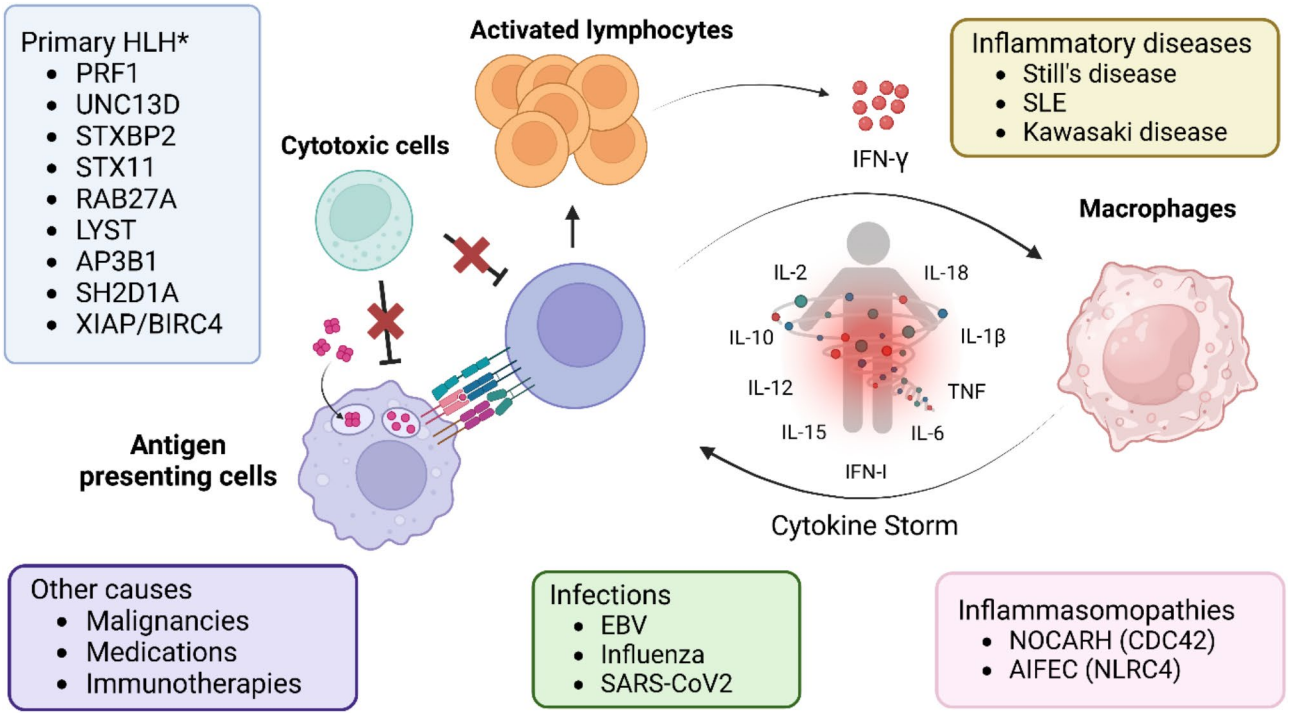


**Fig. 1** Schematic illustrating the causes of HLH / MAS and the role of various immune cell subsets in driving the cytokine storm. Infections, malignancies, medications, genetic defects in cytolysis, and inflammatory diseases are known triggers of HLH / MAS that lead to immune hyperactivation and cytokine storm. Critical immune cells include lymphocytes, macrophages, and antigen-presenting cells interact to drive the activation and expansion of pathogenic lymphocytes that produce IFN-γ. IFN-γ activates macrophages to produce other cytokines and chemokines to amplify the inflammatory cascade. *SH2D1A and XIAP/BIRC4 are associated with primary HLH but these genes are not directly involved in the cytolytic pathway

rash, myelofibrosis and enterocolitis [35–37]. Dysregulated production of IL-18 in these conditions likely contributes to the hyperinflammatory process. However, some genes associated with HLH are not directly linked to cytolytic functions (i.e. XIAP and SH2D1A) [38]. As illustrated by rare cases of HLH associated with T cell deficiency and IFN-γ signaling defects, there are additional ways to incite HLH pathology, but these mechanisms have not been characterized [39–41]. In line with this view, the murine model of MAS driven by repeated stimulation of TLR9 by CpG DNA is largely independent of lymphocytes and only partially requires IFN-γ [42, 43].

### Expansion of CD38$^+$HLA-DR$^+$ lymphocytes in HLH / MAS

While features of lymphocyte activation including the expression of HLA-DR and production of sIL-2R are known in HLH / MAS [44–46], several recent studies noted the characteristic expansion of T lymphocytes. Marked by surface expression of CD38 and HLA-DR, this lymphocyte subset appears to be a useful biomarker for diagnostic evaluation of HLH / MAS [8–11]. Accumulating evidence suggests that these cells are also primary producers of IFN-γ in driving the cytokine storm (Fig. 2).

CD38 is a surface glycoprotein with multiple immune functions including modulation of cellular metabolism by catalysis of nicotinamide adenine dinucleotide, facilitation of cell migration, and cytokine production [47]. HLA-DR is typically expressed by APCs but expression is also induced in proliferating T cells [48]. The expansion of CD38$^+$HLA-DR$^+$ T cells as a specific feature of HLH was first described by Chaturvedi in 2021 in an effort to distinguish HLH from early sepsis [8]. HLH was defined by the HLH-2004 criteria and included patients with primary HLH and infection-associated HLH, but excluded MAS and malignancy-associated HLH. The authors noted that >7% of CD38$^+$HLA-DR$^+$ cells among CD8$^+$ T cells is the optimal cut-off in separating HLH cases from early sepsis and healthy controls. The proportion of CD38$^+$HLA-DR$^+$CD8$^+$ T cells was even more striking in bone marrow aspirates and cerebral spinal fluid (CSF). Notably, the CSF profile was associated with evidence of HLH affecting the central nervous system manifesting as seizures, focal neurologic deficits, and abnormal findings on brain imaging.

De Matteis et al. found that CD38$^+$HLA-DR$^+$CD8$^+$ T cells are also expanded in MAS associated with Still's disease among other secondary causes [9]. The proportion of CD38$^+$HLA-DR$^+$ cells among CD8$^+$ T lymphocytes with low expression of CD4 can effectively distinguish patients with MAS from those with active Still's disease without MAS. This study and recent data from Nguyen et al. demonstrated a strong correlation between

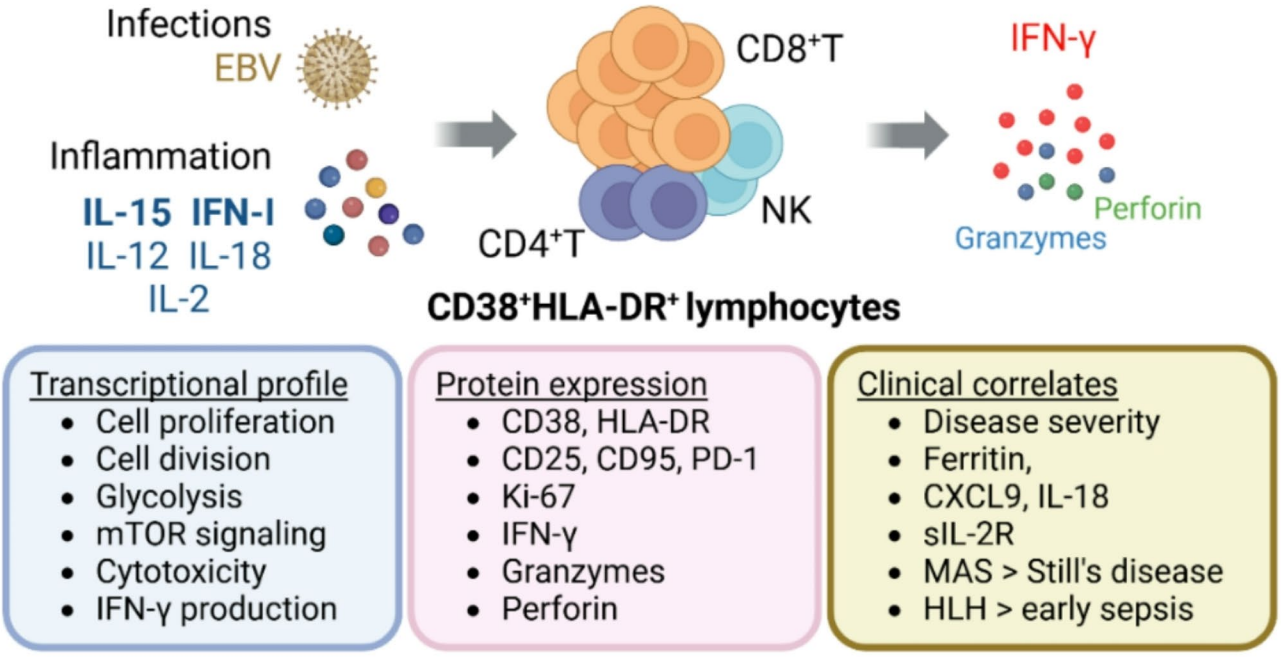


**Fig. 2** Schematic summarizing the recent studies on CD38$^+$ HLA-DR$^+$ cycling lymphocytes in HLH / MAS. [8–11] HLH / MAS is associated with a prominent expansion of CD38$^+$HLA-DR$^+$CD8$^+$ T cells and milder increase of CD4$^+$ T lymphocytes and NK cells with similar characteristics. CD38$^+$HLA-DR$^+$ cycling T cells are highly proliferative and metabolically active based on transcriptomic analysis and they are also prolific producers of IFN-γ, perforin and granzymes. The expansion of these cells correlates with clinical laboratory findings seen in patients with HLH/MAS. IL-15 and IFN-I in combination can induce the differentiation of CD38$^+$HLA-DR$^+$ lymphocytes in vitro [11]. Other cytokines including IL-2, IL-12, and IL-18 may elicit synergist effects on IFN-γ production. EBV infection can also induce the expansion of CD38$^+$HLA-DR$^+$ T cells with or without MAS [50, 51].

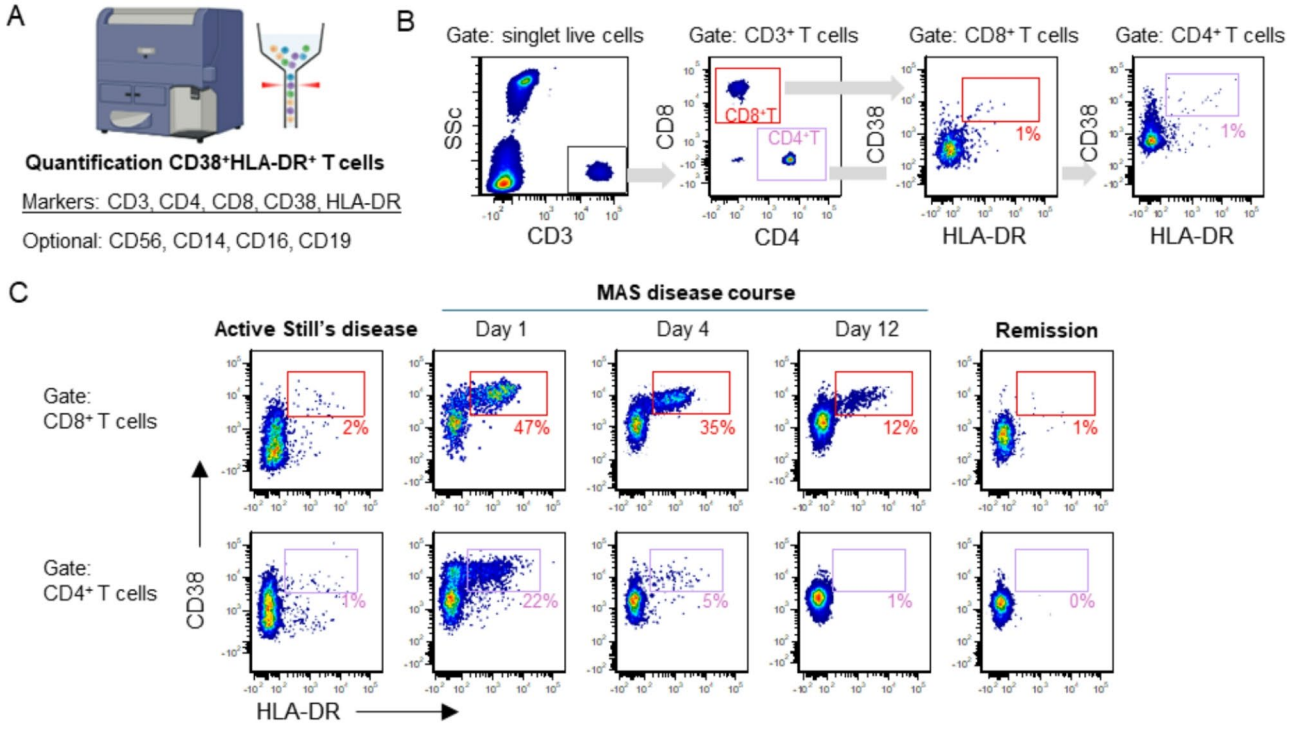


**Fig. 3** Identification and quantification of CD38$^+$HLA-DR$^+$T cells by flow cytometry. **(A)** Required and optional antibodies for the detection of CD38$^+$HLA-DR$^+$ T cells by flow cytometry. Optional antibodies are used to exclude other leukocyte subsets including NK cells (CD56), monocytes (CD14), neutrophils (CD16) and B lymphocytes (CD19). **(B)** Illustration of gating strategy for CD38$^+$HLA-DR$^+$ T lymphocytes and typical results from a healthy individual. The percentage of positive cells is shown in boxes. **(C)** Example of CD38$^+$HLA-DR$^+$ T cell quantification performed serially in a patient with Still's disease complicated by MAS

CD38$^+$HLA-DR$^+$CD8$^+$ T cell expansion with biomarkers of MAS including sIL-2R, CXCL9, IL-18 and serum ferritin (Fig. 2) [9, 10]. CXCL9 is a chemokine induced by IFN-γ that is clinically used as a surrogate marker of IFN-γ levels [7].

### Cycling lymphocytes as primary producers of IFN-g

Our group identified CD38$^+$HLA-DR$^+$ lymphocytes as a key feature of MAS associated with Still's disease by unbiased single cell RNA sequencing (scRNA-seq) and mass cytometry analysis of peripheral blood mononuclear cells [11]. A subset of lymphocytes that strongly express CD38, HLA-DR, and Ki-67 (at both transcript and protein levels) was observed in patients with MAS but not in those with active Still's disease (without MAS) or healthy controls. This population was termed "cycling lymphocytes" based on the prominent expression of numerous cell proliferation marker and annotation by a previous scRNA-seq study [49]. These cycling lymphocytes were comprised of predominantly CD8$^+$ T cells, but NK cells and CD4$^+$ T cells were also found [11].

scRNA-seq revealed that CD38$^+$HLA-DR$^+$Ki-67$^+$ T and NK cells are marked by expression of genes that govern cell division, proliferation, mTOR (mechanistic target of rapamycin) signaling, glycolysis, and cytolytic function (Fig. 2) [11]. Analysis of intercellular communication networks projected cycling lymphocytes as the primary producers of IFN-γ in MAS while monocytes serve as receivers of IFN-γ. Supporting this view, cycling T lymphocytes displayed the highest levels of *IFNG* transcript among all PBMC subsets. IFNG expression was higher in CD8$^+$ and CD4$^+$ T cells than NK cells among the cycling lymphocyte subpopulations.

Production of IFN-γ by cycling lymphocytes corroborates the correlation between the expansion of these cells and plasma CXCL9 levels noted by earlier studies [9, 10]. Resolution of MAS is associated with a significant reduction of these cells in the circulation. Given the importance of IFN-γ in HLH / MAS, these data collectively suggest that CD38$^+$HLA-DR$^+$ cycling lymphocytes are pathogenic cells with a central role in propagating the cytokine storm.

### Cycling lymphocytes as a diagnostic biomarker of HLH / MAS

Enumeration of CD38$^+$HLA-DR$^+$ cycling lymphocytes is straightforward and can be implemented in clinical laboratories with the capacity to perform flow cytometry (Fig. 3A). CD38$^+$HLA-DR$^+$ cells constitute less than 3% of the CD4$^+$ and CD8$^+$ T lymphocyte population in healthy

individuals (Fig. 3B). A cut-off of greater than 7–10% appears to be effective in distinguishing HLH from sepsis and MAS from active Still's disease [8–11]. As noted previously, the expansion of $CD8^+$ cycling T cells correlates with disease severity (Fig. 3C). A similar pattern is seen with $CD4^+$ cycling T cells but the degree of expansion in MAS is milder. This profile of T cell activation is specific for MAS in the context of pediatric rheumatologic diseases and was not observed in patients with non-systemic JIA, SLE, juvenile dermatomyositis, and Kawasaki disease [11]. Multisystem inflammatory syndrome in children, a hyperinflammatory syndrome associated with coronavirus disease 2019 infection with some clinical overlap compared to MAS, exhibits a mild expansion both $CD8^+$ and $CD4^+$ cycling T cells. $CD38^+HLA\text{-}DR^+$ NK cells are also expanded in MAS but their increase is also observed in other diseases [11].

However, quantification of $CD38^+HLA\text{-}DR^+$ lymphocytes cannot be used in isolation as a screening test for HLH / MAS. Recent studies have shown that acute EBV infection and leishmaniasis are associated with marked expansion of $CD38^+HLA\text{-}DR^+CD8^+$ T cells in the peripheral blood above a 7–10% threshold seen in patients without HLH / MAS [50, 51]. Although these data argue against specificity of cycling T cells for HLH / MAS, both EBV and leishmania are known to trigger a strong IFN-γ response that may be explained by the presence of IFN-γ-producing T cells [52, 53]. Unlike other common pediatric infections, EBV infection in otherwise healthy individuals is associated with significant production of IFN-γ and CXCL9, with levels comparable to those observed in MAS patients [51]. Intrinsic regulatory mechanisms to contain the T cell response from entering a vicious cycle of immune cell activation likely prevents full-blown HLH, although impairment of this process may explain why EBV is a common HLH trigger. Prolonged expansion of $CD38^+HLA\text{-}DR^+$ $CD8^+$ T cells is also associated with severe influenza infection as a predictor of fatality [54]. Although not specified in the study, these severe cases may be associated with hyperinflammation as features of HLH and associated genetic variants are linked to mortality in influenza infection [55].

In our view, the expansion of $CD38^+HLA\text{-}DR^+$ cycling lymphocytes is suggestive of an inflammatory process with abundant IFN-γ production. Enumeration of cycling T cells is validated in the context of delineating HLH from sepsis and MAS from active Still's disease, but we caution its use as a singular screening and diagnostic test for HLH / MAS. As with most clinical tests in rheumatology, the context of the patient's condition and other laboratory metrics are needed for interpretation. Nevertheless, the absence of cycling lymphocyte expansion and its associated IFN-γ signature argues against the diagnosis of MAS. Future comparative studies are needed to understand the antigen specificity and unique functional differences of $CD38^+HLA\text{-}DR^+$ lymphocyte associated with HLH / MAS vs. infectious causes.

### Approaches for the management of MAS

Management of MAS is focused on rapidly negating the hyperinflammatory state using immunosuppressive agents such as corticosteroids, calcineurin inhibitors, cytokine antagonists (i.e. anakinra). We will not discuss traditional treatment approaches as this topic has been extensively reviewed [12, 56–58].

Therapeutics that target IFN-γ and downstream signaling are gaining traction for the management of refractory disease. Supporting the mounting evidence for IFN-γ as a key mediator of disease, emapalumab (humanized monoclonal antibody against IFN-γ) was shown to be effective for refractory, recurrent, or progressive HLH [59]. In a small open-label trial for refractory MAS associated with Still's disease, emapalumab treatment achieved significant improvement of laboratory parameters and clinical remission in 13/14 patients [60]. A recent retrospective chart review study of emapalumab treatment in the real-world setting (REAL-HLH) for both HLH and MAS demonstrated similar efficacy [61, 62].

Janus kinase (JAK) inhibitors are another approach to counter the effects of IFN-γ as the receptor complex for IFN-γ mediates downstream signaling by activating JAK1 and JAK2 [63]. JAK inhibitors disrupt IFN-γ signaling and may elicit additional anti-inflammatory effects by blocking other JAK-dependent cytokines including IL2, IL-6, IL-12, IL-15, IFN-I, and granulocyte colony stimulating factor. Ruxolitinib, an orally available JAK1/2 inhibitor approved for myeloproliferative neoplasms and graft-versus-host disease, has shown promise for refractory MAS in case series [64–66]. A recent trial found ruxolitinib to be beneficial as first-line therapy in pediatric patients with MAS and EBV-HLH [67].

Etoposide is a standard treatment for HLH that inhibits the proliferation of activated T cells by forming a complex with topoisomerase II to block DNA synthesis [68]. The addition of etoposide significantly reduced mortality while bridging HLH patients to allogeneic hematopoietic stem cell transplant (HSCT) [69]. Etoposide and HSCT not commonly used for MAS associated with rheumatologic diseases but may be indicated in severe cases that are refractory to other options [70].

### $CD38^+HLA\text{-}DR^+$ cycling lymphocytes as potential therapeutic targets

The identification of cycling lymphocytes offers opportunities to target this population for the treatment of MAS. Conceptually, controlling the IFN-γ-producing cells that drive the hyperinflammatory response would abort the vicious cycle of inflammation while avoiding the adverse

effects of broad immunosuppression. While some of the agents discussed below are clinically available for other indications, preclinical studies are needed to evaluate their therapeutic potential for MAS.

*mTOR inhibitors.* mTOR is a metabolic hub that regulates cellular metabolism and immune cell function [71]. In T cells, glycolysis and mTOR complex 1 (mTORC1) signaling are important drivers of effector cell proliferation and function while blocking mTOR favors the development of regulatory T cells [72]. Therefore, mTOR inhibitors such as rapamycin can conceivably suppress the highly activated $CD38^+HLA\text{-}DR^+$ lymphocytes and also reverse the regulatory T cell defect in HLH / MAS. Persistent mTORC1 activation and efficacy of rapamycin treatment was demonstrated in murine models of Still's disease and MAS, although a similar approach was ineffective in the perforin-deficiency model of HLH [73, 74]. ScRNA-seq data from MAS patients illustrated specific enrichment of genes involved in mTORC1 and glycolysis in cycling lymphocytes [11]. Rapamycin and its derivatives are used for prophylaxis of graft rejection after organ transplant. While more data are needed to understand whether mTOR inhibitors can dampen the lymphocyte response in MAS, two case reports have shown beneficial effects of rapamycin in refractory Still's disease with or without MAS [75, 76].

*CD38 antagonists* CD38 is highly expressed by cycling lymphocytes as well as plasma cells and NK cells. Monoclonal antibodies to CD38 (daratumumab and isatuximab) are approved for the treatment of multiple myeloma [77]. Binding of the therapeutic antibodies to myeloma cells triggers antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, direct apoptosis, and complement-dependent cytotoxicity [78]. CD38 can also be targeted by engineering NK cells with a CD38-CAR using isatuximab-based single-chain variable fragments; CD38-CAR-NK cells have shown efficacy against $CD38^+$ hematologic malignancies [79]. Restoration of NK cell cytolytic function against activated T cells may correct the underlying mechanistic defect in HLH. Because NK cells also intrinsically express CD38, disruption of CD38 expression by gene editing is necessary to prevent CD38-CAR-NK cells from targeting one another [79]. It would be interesting to test whether these approaches are effective in depleting CD38 + HLA-DR + lymphocytes in HLH / MAS.

*IL-15 and type I IFN (IFN-I) antagonists* IL-15 is an inducer of IFN-g and also promotes the development of cytotoxic lymphocytes, NK cells, and type 1 innate lymphoid cell (ILC1), whereas IFN-I is critical to the antiviral response [80, 81]. In screening for immune mediators that promote the pathogenic T cell profile in MAS, we found that the combination of IL-15 and IFN-I was effective in generating $CD38^+HLA\text{-}DR^+$ T cells (and NK cells) from healthy PBMC in vitro [11]. The majority of these cells were $CD8^+$ T cells, consistent with the profile found in patients with MAS. Elevated levels of IL-15 and a transcriptional signature of IFN-I are present in the peripheral blood of MAS patients [11, 82]. Since both cytokines signal via JAK, JAK inhibitors may exert their benefits in part by modulating these pathways. A potentiating role of IFN-I may in part explain the risk of MAS associated with viral infections and autoimmune diseases with excess IFN-I production. Anifrolumab, a monoclonal antibody against the IFN-I receptor, is already in clinical use for the treatment of SLE [83]. IL-15 antagonists are not yet available clinically, although a neutralizing antibody against IL-15 was shown to be beneficial for patients with rheumatoid arthritis in a small trial [84]. Future studies are needed to address whether antagonists of IL-15 and IFN-I, alone or in combination, are promising options for MAS.

*IL-18 inhibitors* As noted earlier, IL-18 levels are extremely elevated in patients with MAS. Beyond its role as a biomarker, IL-18 is a potent inducer of IFN-γ production and the pathogenic roles of IL-18 in HLH / MAS are comprehensively discussed in a recent review [85]. IL-18 also functions in synergy with IFN-I as well as other IFN-γ inducers including IL-12 and IL-15 [86, 87]. It is unclear whether IL-18 directly participates in the generation of cycling lymphocytes as patients with active Still's disease (without MAS) do not exhibit significant expansion of these cells despite the chronically elevated IL-18 levels. Approaches to neutralize IL-18 including a bispecific antibody that targets IL-18 and IL-1β (MAS-825), and recombinant IL-18 binding protein (tadekinig alfa) have both shown beneficial effects for MAS in case reports [88, 89]. The latter is also currently being tested in a clinical trial for NLRC4-MAS and XIAP deficiency (NCT03512314). Additional studies are needed to understand the impact of IL-18 inhibition on the development and function of cycling lymphocytes in MAS.

## Conclusion and future perspectives

Advances in immune profiling have brought clarity to the pathologic mechanisms of complex inflammatory diseases but many questions remain regarding the biology of cycling lymphocytes in HLH / MAS. Factors that facilitate the expansion of these pathogenic cells are not well understood; it is likely that multiple pathways lead to their development, since MAS can occur in a variety of clinical contexts. The in vitro effects of IL-15 and IFN-I illustrated that proinflammatory mediators may act synergistically to drive the expansion of cycling T and NK cells [11], paving the way for future investigation of cytokine combinations and interactions therein that underpin

each disease associated with MAS. The clonality and antigen specificity of $CD38^+HLA\text{-}DR^+$ T cells in HLH / MAS has not been resolved, although a common trigger of T cell activation and hyperinflammation across HLH, rheumatologic diseases, infections and malignancies seems unlikely. De Matteis and colleagues did not find skewing of TCR usage in $CD3^+$ T cells in Still's disease-associated MAS but $CD38^+HLA\text{-}DR^+$ T cells were not separately analyzed. In patients with recurrent episodes of MAS, whether the same clones participate in each episode needs to be assessed through longitudinal studies.

The predominance of $CD8^+$ T cells among cycling lymphocytes in both HLH and MAS is consistent with the observations in the perforin-deficiency model of HLH, in which depletion of $CD8^+$ T cells profoundly reduced IFN-g production. ScRNA-seq data from human MAS illustrated that $CD38^+HLA\text{-}DR^+$ $CD4^+$ T cells and NK cells also express IFN-γ; [11] how these populations differentially contribute to the pathogenesis of MAS requires further investigation. A comprehensive understanding of cycling lymphocytes and their interactions will facilitate the development of treatment options for MAS and help extinguish the cytokine storm from multiple angles.

**Abbreviations**

| | |
|---|---|
| APC | Antigen presenting cell |
| CAR | Chimeric Antigen Receptor |
| CDC42 | Cell division cycle 42 |
| CSF | Cerebral Spinal Fluid |
| CXCL9 | Chemokine (C-X-C motif) ligand 9 |
| EBV | Epstein Barr Virus |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GOF | Gain of Function |
| HLA-DR | Human Leukocyte Antigen– DR isotype |
| HLH | Hemophagocytic lymphohistiocytosis |
| HSCT | Hematopoietic Stem Cell Transplantation |
| IFN-γ | Interferon gamma |
| IFN-I | Type I interferon |
| JAK | Janus kinase |
| JIA | Juvenile Idiopathic Arthritis |
| LCMV | Lymphocytic choriomeningitis virus |
| MAS | Macrophage activation syndrome |
| mTORC1 | Mechanistic Target of Rapamycin Complex 1 |
| NK | Natural Killer |
| NLRC4 | NLR family CARD domain-containing protein 4 |
| PBMC | Peripheral Blood Mononuclear Cell |
| SLE | Systemic Lupus Erythematosus |
| TLR | Toll like Receptor |

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

## Declarations

**Ethics approval and consent to participate**
not applicable.

**Consent for publication**
not applicable.

**Competing interests**
The authors declare no competing interests.

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