Review

Innate Immunity

Innate Immunity
Volume 31: 1–15

DOI: 10.1177/17534259251326700
journals.sagepub.com/home/ini

Sage

Emerging roles of SLAMF7 in immune cells and related diseases

Zheng Zhang[1], Ying Zhang[2], Zeyu Chen[1] and Lin Xia[1,3]

Abstract

Immune cells are heterogeneous and perform different functions in different microenvironment, thus playing different roles in different stages of diseases. Studies have shown that immune cells are involved in the pathogenesis of many diseases, and there is a causal association of immune cells with disease states. Signaling Lymphocyte Activation Molecule family (SLAMF) members are a newly appreciated group of specific receptors that are mainly expressed in immune cells and whose role is to regulate the function of immune cells. SLAMF7, also known as CD319, has been widely reported in multiple myeloma, and in recent years, more and more studies have shown that SLAMF7 is widely involved in the function of immune cells and the progression of breast cancer, acquired immune deficiency syndrome, systemic lupus erythematosus and other immune cells-related diseases. However, the mechanisms underlying the regulatory role of SLAMF7 on immune cells, and the impact on the progression of immune cells-related diseases remain poorly elucidated. In this review, we summarize current knowledge about the role of SLAMF7 in immune cells and related diseases such as cancer, infectious disease, autoimmune disease and atherosclerosis, and the therapeutic strategy targeting SLAMF7 is also described. By better understanding the role and regulation of SLAMF7, we hope to provide new insights and directions for improving the diagnosis and treatment of inflammation.

Keywords

SLAMF7, immune cells, immune cells-related diseases, immunomodulatory

Date received: 1 October 2024; revised: 21 December 2024; accepted: 21 February 2025

Introduction

The Signaling lymphocyte Activation Molecule Family (SLAMF) members, including SLAMF1-9, which are consistently expressed on the surface of hematopoietic cells, are a newly appreciated group of specific receptors that are expressed primarily in immune cells.[1] SLAMF members play significant roles in the functional and phenotypic regulation of various immune cells and have been demonstrated to be crucial in the regulation of both adaptive and innate immunity.[2,3] The functionality of SLAMF1, 3, 5, 6, 7, 8, 9 are achieved through homotypic interactions.[4–6] Among these molecules, SLAMF7 is well known due to the high expression in multiple myeloma (MM) and the regulation of toxic function in natural killer (NK) cells. However, with the deepening of research, SLAMF7 has been found to have a non-negligible regulatory effect on the function of a variety of other immune cells. In NK cells, SLAMF7 promotes NK cytotoxicity by recruiting EWS-FLI1-activated transcrip-2 (EAT-2) to activate the extracellular signal-regulated kinase (ERK) pathway.[7] SLAMF7 stimulates the proliferation of naïve and memory B cells by activating B cells to secrete lymphotoxin A (LTA), tumor necrosis factor-alpha (TNF-α), and flt3 ligands (flt3L).[8] Besides, the upregulation of SLAMF7 induced by nuclear factor kappa B (NF-κB) and phosphoinositide 3-kinase (PI3 K) pathways leads to a decrease in the production of TNF-α and interleukin (IL)-12p70 in monocytes.[9] These studies indicate that SLAMF7 is involved in the regulation of immune cell function.

To date, monoclonal antibodies targeting SLAMF7 for the treatment of MM, such as elotuzumab, have been developed.[10,11] It is worth noting that SLAMF7 is a heterophilic receptor, implying that SLAMF7 on MM cells can also interact with SLAMF7 present on the surface of other immune cells. However, the extent to which elotuzumab can elicit anti-tumor effects by influencing immune cells

[1]Department of Laboratory Medicine, Affiliated Hospital of Jiangsu University, Zhenjiang, China
[2]Department of Biochemistry and Molecular Biology, School of Medicine, Jiangsu University, Zhenjiang, China
[3]Institute of Hematological Disease, Jiangsu University, Zhenjiang, China

Corresponding author:
Lin Xia, Department of Laboratory Medicine, Affiliated Hospital of Jiangsu University, No. 438 Jiefang Road, Zhenjiang, 212001, China.
Email: xialinfzdx@126.com

such as T cells, B cells, and macrophages remains uncertain. In addition to MM, SLAMF7 has also been reported in other immune cells-related diseases such as sepsis and systemic sclerosis (SSc). For example, in sepsis, the rise of SLAMF7 inhibits the production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α in macrophages, which have an inhibitory effect on the macrophage inflammatory response.[12] However, the specific mechanism and whether SLAMF7 also has an inhibitory effect on the inflammatory response of macrophages in other diseases are not very certain. Furthermore, SLAMF7 is implicated in the cytotoxic elimination of $CD4^+$ T cells in SSc, and the release of granular toxic contents by SLAMF7 is likely contribute to the pathology of SSc.[13,14] Based on the role of SLAMF7 in the cytotoxic function of NK cells and T cells, SLAMF7 may be associated with cell killing. There are many preliminary studies about SLAMF7 regulation of immune cells involved in immune cells-related diseases, but the mechanism is unclear. Given that other members of SLAMF receptors, such as SLAMF4 and SLAMF6, have been widely reported to be involved in the progression of diseases such as X-linked lymphoproliferative disease (XLP), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE),[6,15] the impact of SLAMF7 on human diseases urgently needs to be clarified. Therefore, we summarize the effect of SLAMF7 on immune cells and related diseases, and the therapeutic strategy targeting SLAMF7 is also described, which could contribute to clinical treatment and drug development.

Characteristics and functions of SLAMF7

Gene expression and regulation

The SLAMF7 gene is located on the long arm of human chromosome 1 and contains seven exons.[16,17] The −750 to −746 region of its promoter contains a zinc finger transcriptional repressor Blimp-1 (PRDM1) binding site (GAAAG), which activates human SLAMF7 transcription when bound to Blimp-1.[18] SLAMF7 is also expressed in cells that do not express Blimp-1, suggesting that SLAMF7 is also regulated by other transcription factor. There is a Yin-yang 1 (YY1) binding site between promoter p-707 and p-527, and after deletion of this site, the activity of SLAMF7 promoter in mice is increased, indicating that YY1 can inhibit the transcription of SLAMF7.[19]

SLAMF7 expression on different cells is regulated by different molecules. In lipopolysaccharide (LPS)-activated monocytes, SLAMF7 is induced through the NF-κB and PI3 K pathways.[9] In macrophages, interferon-gamma (IFN-γ) induces SLAMF7 expression via the JAK1 and JAK2 signaling pathways.[20] Cytokines IFN-β, IL-1β, and TNF-α, as well as Toll-like receptor (TLR) agonists Pam3, CSK4, and LPS, also increase the expression of SLAMF7 in macrophages, but at lower levels than IFN-γ.[20] The TLRs/myeloid differentiation Primary Response 88 (MyD88)/NF-κB signaling pathway promotes the expression of SLAMF7 in monocytes and macrophages, and the SLAMF7 promoter region contains multiple potential NF-κB and activator protein 1 (AP-1) binding sites.[12] These results suggest that NF-κB and AP-1 may induce SLAMF7 expression by regulating the transcription of SLAMF7. The expression of SLAMF7 in B cells is regulated by IL-21 and IFN-γ.[21] IFN-α and IL-12/IL-18 can up-regulate SLAMF7 on $CD56^{dim}$ NK cells.[22] In non-immune cells such as breast cancer (BC) cells, STT3A catalyzes the N-glycosylation of SLAMF7, thereby stabilizing the expression of SLAMF7, enhancing the "don't eat me" signaling of tumor cells, and inhibiting the phagocytosis of macrophages.[23]

Protein structure

SLAMF7 is a transmembrane protein, which consists of three parts: extracellular domain, transmembrane domain and cytoplasmic domain.[24] The extracellular domain of SLAMF7 consists of a proximal immunoglobulin (Ig) like constant (C2) domain and a distal Ig like variable (V) domain responsible for recognizing ligands.[25] And there are seven glycosylation consensus motifs (N56, N98, N142, N148, N172, N176 and N204), of which N98, N142 and N148 are highly conserved motifs.[23] The cytoplasmic domain of SLAMF7 contains the immune receptor tyrosine switch motif (ITSM)-TxYxxI/V, which has strong affinity for EAT-2 and SLAMF-associated protein (SAP).[26] According to the presence or absence of ITSM in the cytoplasmic domain, SLAMF7 is divided into SLAMF7-L and SLAMF7-S.[16] Human NK cells have both SLAMF7-L and SLAMF-S, SLAMF7-L has ITSM and plays an active role, while SLAMF-S does not show any effect, and its function needs to be further explored.[16]

Function in immune cells

SLAMF7 is constitutively expressed on the surface of hematopoietic cells[2] and plays an important role in regulating the function of a variety of immune cells such as NK cells, T cells and macrophages.[7] The mechanism by which SLAMF7 regulates immune cells is shown in Figure 1.

Nk cells. SLAMF7 is expressed on the surface of all NK cells, with the $CD56^+$ $CD16^+$ NK cell subset exhibiting the highest expression levels.[27] Upon activation, SLAMF7 interacts with EAT-2 within NK cells, leading to phosphorylation mediated by Src kinase. Subsequently SLAMF7 contributes to the degranulation of NK cells through phospholipase C-gamma (PLC-γ), inducing phenotypic changes of NK cells, regulating the cytolytic activity, and enhancing target cell killing.[28,29] In the absence of EAT-2, the activation of SLAMF7 results in the binding

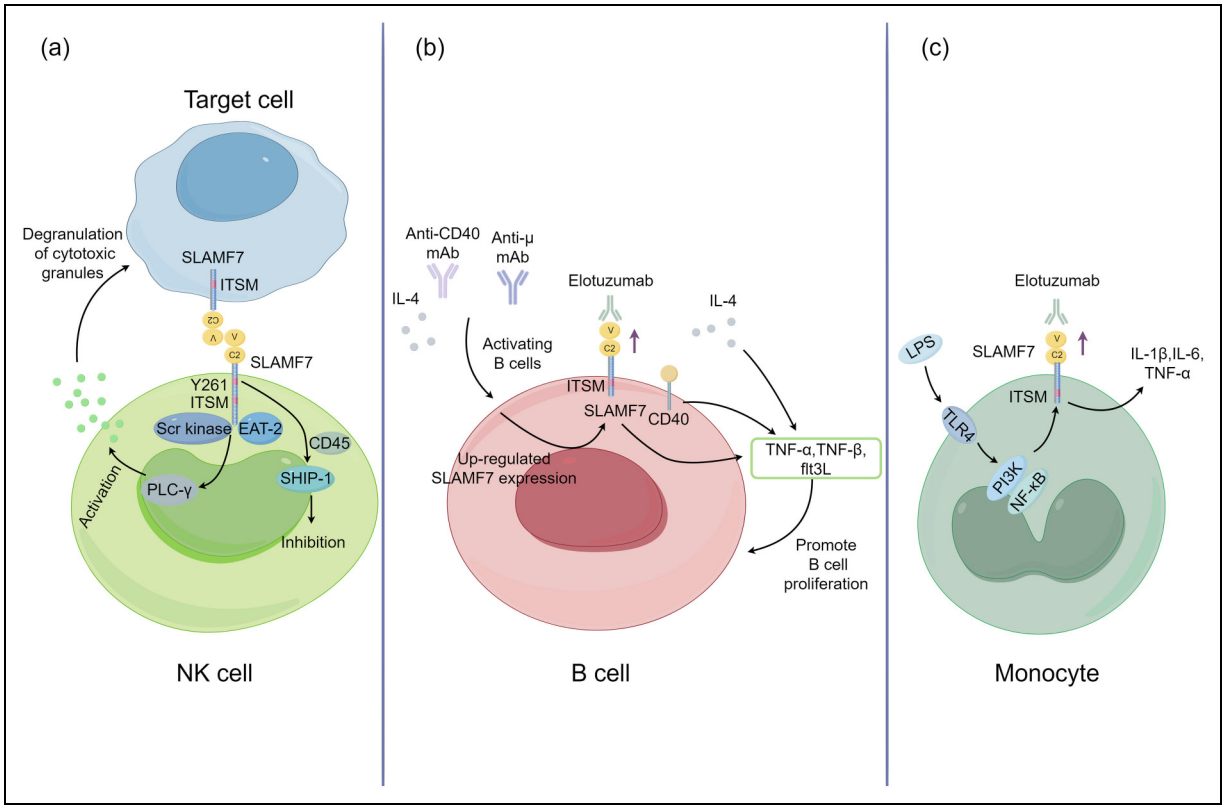

Figure 1. SLAMF7 affects NK cell, B cell and monocyte function. (a) SLAMF7 activates the degranulation function of NK cells by binding with EAT-2 to enhance the killing ability, and SLAMF7 mediates SHIP1 inhibition when EAT-2 is absent in NK cells. (b) The promotion of B cell proliferation is facilitated by the presence of CD40 and IL-4, in conjunction with the action of SLAMF7. (c) LPS stimulates the up-regulation of SLAMF7 expression in monocytes, and the activation of SLAMF7 increases the expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α.

of tyrosine 261 (Y261) in the cytoplasmic domain to inositol phosphatase 1 (SHIP1) mediated by Src kinase, thereby inhibiting the function of NK cells.[30] The presence of Src kinase is crucial for the inhibitory signaling induced by SLAMF7. The protein tyrosine phosphatase CD45 is an essential phosphatase for the activation of Src kinase,[30] and in the absence of CD45, SLAMF7 fails to trigger tyrosine phosphorylation of SHIP1 or initiate the inhibitory signal.[30] The function of SLAMF7 is achieved through homophilic interaction, and SLAMF7-SLAMF7 binding between NK cells and neighboring immune cells does not lead to fratricide. This is because the immune cells expressing SLAMF7 can recognize major histocompatibility complex class I (MHC-I) molecules, which specifically recognizes "self" and "non-self", blocking the killing of adjacent immune cells after SLAMF7 activation, and effectively protecting the maintenance of the normal physiological state of the immune system.[31]

T and B cells. T cells are the principal cellular subsets involved in the adaptive immune response. $CD4^+$ T cells mainly play the auxiliary function, and $CD8^+$ T cells mainly play the cytotoxic function. It has found that some $CD4^+$ T cells show cytolytic activity,[32] while some $CD8^+$ T cells lack cytotoxic characteristics and play auxiliary functions.[33] In comparing the differential markers of cytotoxic T cells with helper T cells, it has observed that all helper T cells are highly expressive of the IL-6 receptor (IL-6R), while all cytotoxic T cells are highly expressive of SLAMF7.[34] T cells with a high expression of SLAMF7 secrete elevated levels of granase and perforin B.[34] Additionally, SLAMF7 is highly expressed in other cell populations that demonstrate cytotoxic characteristics, such as $CD56^+$ NK cells, natural killer T (NKT) cells, and type 1 innate lymphoid cell (ILC1).[34] Therefore, SLAMF7 could serve as a potential marker for identifying the cytotoxic function of immune cells. Similarly, B cells, which are integral components of the adaptive immune response, also possess SLAMF7 expression. It is worth noting that the expression of SLAMF7 is significantly upregulated after activation of B cells by anti-CD40 monoclonal antibodies, IL-4 and anti-μ monoclonal antibodies.[8] When SLAMF7 is activated, along with CD40 and IL-4, it enhances the ability of B cells to produce cytokines such as LTA, TNF-α, and flt3L,[8] which serve as regulators of autocrine growth and differentiation factors. LTA, also

referred to as TNF-β, and TNF-α, are capable of stimulating B cell proliferation,[35,36] while flt3L is crucial for the differentiation and proliferation of B cell progenitors, as well as the maturation of B cells.[37,38] These findings indicate that SLAMF7 plays a significant role in the developmental processes of B cells.

Monocytes and macrophages. The identification of SLAMF7, CD120b, and TLR2 as novel cell surface markers for pro-inflammatory macrophages.[39] lPS, Flagellin, Pam2CSK4 and Pam3CSK4 stimulate TLR4, TLR5, TLR2/6 and TLR1/2, respectively, and significantly induce SLAMF7 expression in monocytes and macrophages.[40] Activation of SLAMF7, in collaboration with TLRs, leads to increased expression levels of IL-1β, IL-6, and TNF-α.[40] However, SLAMF7 itself does not directly induce cytokine production.[40] Hence, SLAMF7 appears to play an auxiliary role in the inflammatory response of monocyte/macrophage, regulating the shift towards pro-inflammatory phenotype. Furthermore, the interaction between SLAMF7 and TLRs may be mediated by CD14, as knockdown of CD14 inhibits the secretion of LPS-mediated inflammatory factors.[40] Additional studies have demonstrated that the expression of SLAMF7 in monocytes activated by LPS is contingent upon the NF-κB pathway and involves the PI3 K pathway.[9] Furthermore, the activation of SLAMF7 on the surface of LPS-activated monocytes inhibits the expression of TNF-α and IL-12p70, potentially due to the insufficiency of EAT-2 in monocytes post-activation.[9] This finding contradicts the notion that SLAMF7 facilitates the expression of pro-inflammatory factors in monocytes. Hence, it is imperative to conduct further investigation into the regulatory mechanism of SLAMF7 in relation to the inflammatory response expressed by monocyte/macrophage.

The significance of SLAMF7 in neoplastic tissue

Cancers are the main cause of death worldwide, and immune cells are deeply involved in the process of cancers, and also provide new ideas for clinical treatment of cancers. Immunotherapy expresses superior efficacy and prolonged tumor cell elimination compared to conventional therapies, while also minimizing deleterious side effects. Immunotherapy is able to "wake up" immune cells and enhance the interaction between immune cells and tumor cells, thereby altering tumor outcomes. However, because of its high specificity, it is particularly important to identify suitable biomarkers in immunotherapy. SLAMF7 is expressed on a variety of immune cells and has become a therapeutic target marker in MM. Given the role of SLAMF7 in immune cells, it has the potential to become a novel immune intervention target.

Hematological neoplasms

Multiple myeloma. MM is a prevalent hematologic malignancy characterized by a malignant tumor originating from terminally differentiated plasma cells. Multiple studies have substantiated the substantial expression of SLAMF7 on nearly all MM cells, thereby establishing its significant involvement in the pathogenesis of MM, which are reviewed by previous studies.[41,42] In humanized immunocompromised NOD SCID Il2rg$^{-/-}$ (NSG) mouse myeloma xenotransplantation model, αSLAMF7 Bispecific T cell engaging antibodies (BiTE) binding CD3^{+} T cells significantly inhibits MM cell growth, and SLAMF7 can be used as a target for MM cells.[41] In addition to the surface of MM cells containing SLAMF7, the serum of MM patients also contains soluble SLAMF7 (sSLAMF7).[43] sSLAMF7 has the ability to bind to SLAMF7 on MM cell surfaces, and then stimulate MM cell proliferation by activating the protein Src homology 2 domain-containing protein tyrosine phosphatase (SHP) 2 and ERK signaling pathways.[43] Clinical trials have demonstrated that compared to patients lacking sSLAMF7, patients with detectable levels of sSLAMF7 express higher International Staging System (ISS) and Revised International Staging System (R-ISS) scores, as well as shorter progression-free survival (PFS) durations.[44] Moreover, the anti-SLAMF7 monoclonal antibody elotuzumab blocks the growth-promoting function of sSLAMF7 and is currently approved for clinical use.[43,45–47] It follows that sSLAMF7 is deeply involved in the progression of MM and may be a useful indicator of the disease progression.

Immune cells are integral components of the bone marrow and play a crucial role in the pathogenesis and progression of MM. Through single-cell RNA sequencing, the immunospectrum of MM patient tissue is detected, and it has found that ZNF683^{+} NK cells are significantly enriched, with reduced cytotoxicity and exhaustion phenotype, and the intracellular SH2D1B expression is downregulated.[48] SH2D1B encodes EAT-2, a crucial functional molecule responsible for the activation of NK cells via SLAMF7. The transcription factor ZNF683 not only contributes to the depletion of NK cells and the reduction of cytotoxicity, but also directly binds to the SH2D1B promoter to significantly induce the downregulation of SH2D1B,[48] which might prevent SLAMF7 from activating NK cells and the cytotoxic functions. The absence of EAT-2 hinders the effective activation of a subset of NK cells by SLAMF7, thereby compromising the killing ability of immune cells to some extent and facilitating the progression of MM. Moreover, SLAMF7 is highly expressed on immunosuppressive CD8^{+} CD28^{-} CD57^{+} regulatory T cells (Tregs) in MM patients, and co-expresses with programmed cell death 1 (PD-1), T cell immunoreceptor with Ig and ITIM domains (TIGIT), lymphocyte activation

gene 3 (LAG-3), and other inhibitory receptors.[49] SLAMF7^{+} CD8^{+} T cells display an exhausted phenotype and express significantly reduced cytotoxicity compared to SLAMF7^{-} CD8^{+} T cells.[49] This suggests that SLAMF7 is involved in the regulation of CD8^{+} T cell phenotype transition to exhaustion. According to the above findings, targeting sSLAMF7 in the serum of patients with antagonistic MM, activating immune cells, especially NK cells may contribute to the treatment of MM.

Other hematologic neoplasm diseases. Furthermore, apart from its association with MM, SLAMF7 has been identified as intricately connected to the advancement of other hematological malignancies. Tumor cells employ diverse mechanisms to evade immune surveillance, with one such mechanism involving the utilization of the SIRPα-CD47 axis to impede macrophage phagocytosis. The therapeutic intervention of blocking the SIRPα-CD47 axis expedites the elimination of cancer cells.[50,51] Research has demonstrated that in hematological tumors, the presence of SLAMF7 on both macrophages and tumor cells plays a crucial role in augmenting phagocytosis subsequent to the inhibition of the SIRPα-CD47 axis.[52] The specific mechanism is that after inhibition of the SIRPα-CD47 axis, SLAMF7 on macrophages interacts with SLAMF7 on human B-cell lymphoma cells, resulting in SLAMF7 in macrophages binding to DAP12 and FcRγ containing immunoreceptor tyrosine-based activation motifs (ITAMs) via the integrin Mac-1 receptor.[52] This binding causes Src, Syk, and Btk kinases to trigger the activation of macrophages, thereby enhancing phagocytosis (Figure 2).[52] This finding indicates that the presence of SLAMF7 on the surface of macrophages and tumor cells is essential for macrophage phagocytosis after the SIRPα-CD47 axis is blocked. However, alternative perspectives have been put forth by certain scholars. Some studies show that the expression of SLAMF7 on hematopoietic cancer cells is not necessary for the enhanced phagocytosis of macrophages caused by the SIRP-α-CD47 axis.[53,54] Although only OCI-ly3 cells express SLAMF7 in seven diffuse large B-cell lymphoma (DLBCL) cell lines tested, there is no significant effect on macrophage phagocytic function,[53] which suggests that the presence of SLAMF7 in hematopoietic cancer cells does not impact the phagocytic capacity of macrophages following the inhibition of the SIRPα-CD47 axis. When SLAMF7 is knocked out on macrophages, CD47-targeted phagocytosis disappears, so the expression of SLAMF7 on the surface of macrophages is the key to affecting phagocytosis.[52] Notably, SLAMF7 has previously been identified as a novel surface marker of pro-inflammatory macrophages.[39,55] Therefore, it would be expected that pro-inflammatory macrophages would express heightened phagocytic activity following the blockade of the SIRPα-CD47 axis. However, the experimental findings indicate that the phagocytic response of anti-

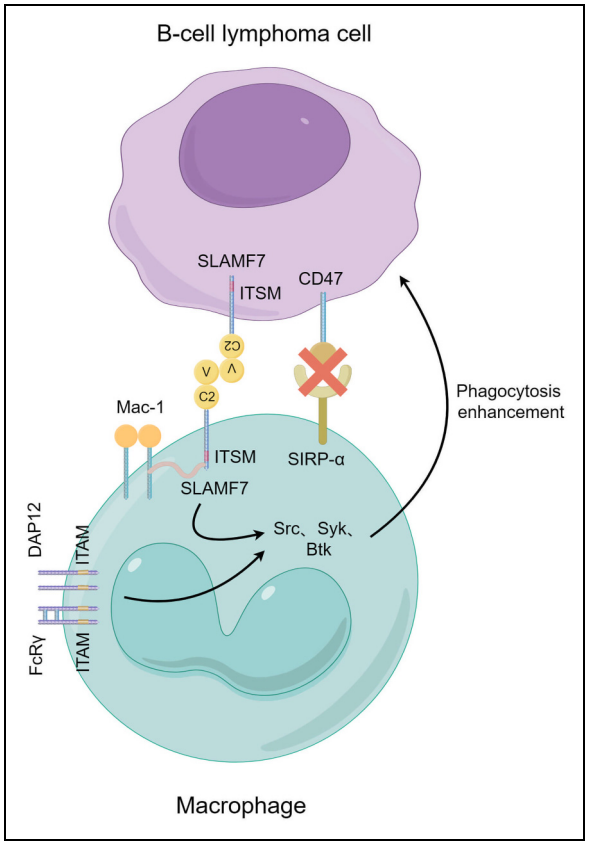

Figure 2. After CD47-SIRP-α blockade, SLAMF7 enhances the ability of macrophages to phagocytic tumor cells. In hematologic tumors, after CD47-SIRPα is blocked, SLAMF7 binds DAP12 and FcRγ via Mac-1, and then relies on Src, Syk, and Btk kinases to enhance macrophage phagocytosis.

inflammatory macrophages following CD47 targeting does not exhibit a significant disparity compared to that of pro-inflammatory macrophages, or potentially even surpasses it.[53] Consequently, it is imperative to conduct further comprehensive investigations to ascertain whether the variation in SLAMF7 expression among distinct macrophage phenotypes will indeed influence phagocytosis. On the whole, in hematological malignancies, SLAMF7 enhances the phagocytic function of macrophages and further interferes with the progression of the disease.

Non-hematological neoplasms

Despite the extensive research on the involvement of SLAMF7 in hematological tumors, it is noteworthy that SLAMF7 is associated with the progression of various other tumor diseases, including BC, renal cell carcinoma, and ovarian cancer. Studies have demonstrated that the expression level of SLAMF7 is significantly higher in BC tissues compared to normal tissues and the presence of high SLAMF7 levels is strongly correlated with the prognosis of BC.[23] One Study has shown that BC patients who

overexpress SLAMF7 have longer survival and lower recurrence rates.[56] Another study has reached the opposite conclusion, that high expression of SLAMF7 is associated with poor prognosis.[23] In addition, SLAMF7 can also participate in the process of BC by regulating immune cells. SLAMF7 is expressed in macrophages of BC patients, and the combined use of anti-SLAMF7 antibody and N-linked glycosylation inhibiter-1 (NGI-1) can not only enhance the phagocytosis ability of macrophages, but also effectively inhibit the glycosylation process of SLAMF7 in BC cells, and further strengthen the antibody affinity of SLAMF7.[23] Hence, the combination of anti-glycosylation and anti-SLAMF7 drugs is expected to enhance the cytotoxicity of immune effector cells to BC cells.

In clear cell renal cell carcinoma (ccRCC), elevated SLAMF7 expression correlates with the exhausted phenotype of $CD8^+$ T cells and is associated with diminished survival rates of patients.[57] ccRCC is characterized by a substantial population of $CD8^+$ T cells, although a majority of these T cells express impaired functionality.[58] In co-culture models of tumor-associated macrophages (TAM)-T cells derived from mice, the interactions between $SLAMF7^{high}$ $CD38^{high}$ TAM and $CD8^+$ T cells, specifically through SLAMF7-SLAMF7 interaction, lead to the upregulation of inhibitory receptors such as LAG-3 and PD-1 on T cells, ultimately resulting in T cell dysfunction.[57] Compared with wild-type mice, $SLAMF7^{-/-}$ mice show significantly reduced tumor growth and significantly fewer exhausted $CD8^+$ T cells.[57] Although the involvement of other cell types in inducing T cell exhaustion remains uncertain, targeting $SLAMF7^{high}$ $CD38^{high}$ TAM could potentially serve as an effective strategy to attenuate the progression of ccRCC. Inhibition SLAMF7 activity in ccRCC will help reduce the adverse effects caused by $CD8^+$ T cell failure.

Furthermore, SLAMF7 expresses significant upregulation in ovarian cancer and is closely linked to unfavorable prognoses among patients.[59] Alongside GNAS, TBX2-AS1, and LY6/PLAUR domain-containing 6 (LYPD6), SLAMF7 is recognized as a surface marker for anti-inflammatory TAM in ovarian cancer, which inversely correlates with patients survival rates.[60] Apart from TAM, SLAMF7 exhibits significant upregulation in ovarian cancer cells, thereby enhancing their viability and facilitating the migration, invasion, and epithelial-mesenchymal transition (EMT).[60] Moreover, elevated SLAMF7 levels are associated with cisplatin resistance in ovarian cancer cells.[60] Although the mechanism of SLAMF7 in ovarian cancer is still unclear, its identification provides a new way to further study ovarian cancer, and the functional antagonism of SLAMF7 will provide new ideas for the treatment of ovarian cancer. In the aforementioned cancers, whether blood system cancer or ovarian cancer, ccRCC, or BC, SLAMF7 seems to have a positive relationship with tumor growth. Instead, in high-risk neuroblastoma cases, elevated levels of SLAMF7 are associated with a more favorable prognosis for patients.[61] $SLAMF7^+$ tumor cells may have isotype interactions with surrounding immune effector cells, resulting in immune cell activation to kill the tumor cells.[61] Subsequently, effective activation of SLAMF7, enhancing the link between tumor cells and immune cells, could expand the advantages of disease treatment.

The significance of SLAMF7 in infectious diseases

Pathogenic microorganisms such as bacteria, viruses and parasites are the common pathogenic factors of clinical diseases at present. On the one hand, immune cells such as T cells, neutrophils, macrophages kill pathogenic microorganisms by secreting cytokines or directly binding with pathogens. On the other hand, an overactivated immune system damages body tissues. In sepsis, keratitis, and acquired immune deficiency syndrome (AIDS), SLAMF7 alleviates excessive inflammation by regulating immune cells function and inhibiting the inflammatory response.[12,62,63] The regulation of SLAMF7 for the inflammatory response of immune cells enables the immune system to target various pathogens more appropriately and scientifically, which contributes to the control and treatment of infectious diseases.

Diseases associated with infections

Sepsis, a syndrome characterized by a systemic inflammatory response, arises from the invasion of the body by pathogenic microorganisms, and stands as a prominent cause of mortality within hospital settings.[64] Recent research has demonstrated that SLAMF7 is prominently expressed on monocytes/macrophages in sepsis patients, inhibits the pro-inflammatory function of macrophages, and is associated with a positive prognosis.[12] The TLRs/MyD88/NF-κB signaling pathway enhances the expression of SLAMF7 in monocytes and macrophages. Once activated, SLAMF7 interacts with SHIP1 to hinder the activation of NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways in macrophages by the inhibition of TNF receptor associated factor 6 (TRAF6) self-ubiquitination, leading to the decrease in the secretion of inflammatory cytokines such as IL-6, IL-1β, and TNF-α.[12] In SLAMF7-KO mice, sepsis-induced lung structural damage is greater, and levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are significantly elevated.[12] Activation of SLAMF7 with recombinant mouse SLAMF7 (rmSLAMF7) protein can significantly reduce lung injury and inflammatory cell infiltration in sepsis mice, significantly reduce the expression of TNF-α, IL-1β and IL-6, and improve the survival rate of sepsis mice.[12] Hence, macrophages with

elevated levels of SLAMF7 expression constitute a significant immunosuppressive inflammatory subset in sepsis.

Furthermore, in the corneas of mice infected with *pseudomonas aeruginosa*, the expression of SLAMF7 on macrophages increases in a time-dependent manner.[62] The absence of SLAMF7 results in an up-regulation of inflammatory factors such as IL-1β, inducible nitric oxide synthase (iNOS), and transforming growth factor beta (TGF-β) secretion, while down-regulating the expression of the anti-inflammatory macrophage marker CD206 on the cell surface.[62] Treatment with rmSLAMF7 in mice infected with *Pseudomonas aeruginosa* show reduced inflammatory cell infiltration in the infected cornea, down-regulated mRNA levels of pro-inflammatory cytokines including TNF-α and IL-1β, upregulated anti-inflammatory cytokines such as TGF-β and IL-10, and marked remission of the disease symptoms.[62] As expected, constructing an infection model in SLAMF7-KO mice produces the exact opposite result.[62] Hence, SLAMF7 regulates the polarization of macrophages towards an anti-inflammatory phenotype, thereby alleviating inflammation, which is mediated by the activation of Signal Transducer and Activator of Transcription 6 (STAT6) phosphorylation.[62] Significant expressions of SLAMF7 and STAT6 are also found in corneal tissues of *acanthamoeba* keratitis (AK) patients, along with a large concentration of anti-inflammatory macrophages,[65] suggesting that SLAMF7 could inhibit inflammation by regulating the phosphorylation of STAT6, which may affect the immunocompetence and tissue repair. Based on these studies, we infer that SLAMF7 may inhibit the inflammatory response of monocyte/macrophage, especially in the case of bacterial or parasitic infections. However, the potential similarity or divergence of SLAMF7 function on immune cells remains uncertain, necessitating further investigation.

Acquired immune deficiency syndrome

AIDS is a chronic systemic disease characterized by immune activation and dysfunction, resulting from infection with the human immunodeficiency virus (HIV).[66] Research findings indicate that the presence of SLAMF7 on monocytes of individuals with HIV is elevated and can be enhanced through IFN-α stimulation. On the one hand, the activation of SLAMF7 on monocytes of HIV-infected persons can reduce the susceptibility of monocytes to HIV-1 infection by the inhibition of CC chemokine receptor 5 (CCR5) and the increase in the expression of CC chemokine ligand 3 like-1 (CCL3L1), and on the other hand, the activation of SLAMF7 can inhibit the expression of monocyte pro-inflammatory marker CD16.[63] Moreover, SLAMF7 activation obstructs IFN-α-mediated production of C-X-C primitive chemokine ligand (CXCL) 10, but this has only been observed in the blood of a subset of HIV-infected patients.[63] The mechanism of selective inhibition after SLAMF7 activation remains unclear, but it has been established that it is independent of the expression levels of SLAMF7 and EAT-2, and is not affected by SHP1, SHP2, SHIP1, and CD45.[63] Further investigation is required to elucidate the specific factors contributing to the discrepancy. In addition to IFN-α, LPS levels are elevated in the blood of HIV-infected patients,[67] and SLAMF7 has been shown to suppress the expression of TNF-α and IL-12p70 in LPS-stimulated monocytes.[9] These studies suggest that SLAMF7 can effectively inhibit the inflammatory response of monocytes in HIV infection, providing a promising avenue for targeted intervention in the management of AIDS. The anti-inflammatory effect of SLAMF7 on monocytes broadens the current research on the mechanism of action of immune cells in HIV-infected patients.

The association between SLAMF7 and autoimmune disease

Autoimmune disease (AID) is a pathological condition characterized by the disruption of immune tolerance towards autoantigens, resulting in an aberrant immune response by the body towards these self-antigens. In the autoimmune diseases, SLAMF7 influences various immune cell populations, such as T cells, macrophages, and dendritic cells (DCs). For instance, research has demonstrated that SLAMF7 enhances the cytotoxicity and killing capacity of $CD4^+$ T/$CD8^+$ T cells, thereby exacerbating disease progression. Additionally, the activation of SLAMF7 on macrophages also contributes to the advancement of RA. Although the coverage of SLAMF7 in AID has been quite extensive, there are still many unknown aspects. For example, the influence of SLAMF7 on DCs in SLE remains uncertain. Additionally, the mechanism of the escalation of $SALMF7^+$ $CD4^+$ T cells in SSc remains unidentified. Thus, further research is needed on the potential role of SLAMF7 in AID.

IgG4-associated disease

IgG4-related disease (IgG4-RD) is a disease mediated by the immune system, characterized by the presence of swollen lesions, frequent elevation of serum IgG4 levels, and tissue fibrosis.[68] The main inflammatory cell groups involved in IgG4-RD are $CD4^+$ T cells, B cells, and plasma blast cells.[69] $CD4^+$ T cells have a significant role in facilitating B cells in the production of IgG4.[70] In addition, abnormal clonal expansion of $CD4^+$ cytotoxic T lymphocyte (CTL) populations is accumulated in IgG4-RD tissues.[71,72] Among the various subsets, T helper type 1 (Th1), activated circulating follicular T helper (cTfh) 1, and activated cTfh2 express a significant increase in IgG4-RD patients.[21] SLAMF7 is predominantly expressed on Th1 and cTfh1 in IgG4-RD patients, and the activation of SLAMF7 on cTfh1 leads to the increase in the production of IL-10 and IL-21,[21] which play a crucial

role in the differentiation of plasma cells.[73,74] These studies suggest that SLAMF7 may induce B cells to generate IgG4 by modulating cytokine production, thereby driving the progression of the disease. Additionally, follicular T helper 1 (Tfh1)-related cytokines, such as IL-21 and IFN-γ, can augment the expression of SLAMF7 on B cells.[21] Hence, it is hypothesized that the binding of SLAMF7-SLAMF7 may enhance the association and interaction between B cells and T cells in IgG4-RD tissue, leading to the increased production of IgG4 by B cells, thereby exacerbating IgG4-RD.

$CD4^+$ CTLs serve as the principal pathological driver of IgG4-RD,[71,72] which has been identified as SLAMF7 expressing cells with cytotoxic capacity comparable to $CD8^+$ T cells.[71,75] Studies have shown a significant increase in circulating $SLAMF7^+$ $CD4^+$ cytotoxic effector/memory T (TEM) cells in IgG4-RD patients.[76] Glucocorticoids are the preferred treatment for IgG4-RD, and the proportion of circulating $SLAMF7^+$ $CD4^+$ TEM cells decreases significantly after six months of glucocorticoid therapy.[76] And $CD8\alpha^-$ $SLAMF7^+$ $CD4^+$ TEM cells, one of the $SLAMF7^+$ $CD4^+$ TEM cells subgroups, even drop to levels comparable to those of healthy individuals.[76] These data suggest that $SLAMF7^+$ $CD4^+$ TEM cells may be involved in the progression of IgG4-RD, and high levels of SLAMF7 on $CD4^+$ T cells accelerate IgG4-RD progression, so further exploration the mechanism will be more valuable.

Systemic lupus erythematosus

SLE is a complex AID affecting multiple systems. Current treatments for SLE are still limited to corticosteroids and immunosuppressants that non-specifically target immune cells. In SLE patients, there is a deficiency in cytotoxic $CD8^+$ T cell activity,[77] which is associated with an increased susceptibility to infections.[78] Therefore, enhancing cytotoxic $CD8^+$ T cell function may hold promise as a therapeutic approach for SLE. The proportion and the SLAMF7 expression of effector memory (EM) $CD8^+$ T cells and end-differentiation effector memory (TDEM) $CD8^+$ T cells decrease in SLE patients compared with healthy controls, and in both healthy controls and SLE patients, the expression of SLAMF7 is higher on both EM and TDEM $CD8^+$ T cells than naïve $CD8^+$ T cells.[79] It has been confirmed that the activation of SLAMF7 on EM $CD8^+$ T cells and TDEM $CD8^+$ T cells augment the degranulation capability and cytolytic activity in response to viral antigenic peptides in *vitro* and *vivo* experiments in SLE patients.[79] This finding suggests that SLAMF7 has the potential to enhance the cytotoxicity of $CD8^+$ T cells in SLE patients and regulate their functional changes, thereby participating in disease progression.

Furthermore, alongside $CD8^+$ T cells, SLAMF7 is observed to be present on plasma cell-like dendritic cells (pDCs) and $CD56^{dim}$ NK cells in individuals with SLE.[22] pDCs have the capability to continuously release IFN-α when stimulated by immune complexes (IC), which serves as the primary factor contributing to the activation of the type I interferon system in SLE patients.[80] pDCs and $CD56^{dim}$ NK cells isolated from humans are stimulated by IC to increase the expression of SLAMF7 through TLRs and Fcgamma receptor (FcγR), respectively. SLAMF7 on $CD56^{dim}$ NK cells can be directly induced by IC, while SLAMF7 on pDCs requires IC in combination with NK cells or cytokines such as granulocytic-macrophage colony-stimulating factor (GM-CSF), IL-3, and IFN-α,[22] suggesting that the regulatory mechanism of SLAMF7 on pDCs is intricate. In addition, NK cell activators, IL-12/IL-18 can up-regulate SLAMF7 on $CD56^{dim}$ NK cells.[22,81] Therefore, SLAMF7 may be one mechanism by which IL-12/IL-18 increase NK cell toxicity. pDCs can produce IFN-α to participate in the inflammatory response, and pDCs with high secretion of IFN-α also express high expression of SLAMF7.[22] Hence, it is reasonable that SLAMF7 plays a role in modulating the inflammatory response of pDCs. Further studies show that the expression of SAP and EAT-2 can hardly be detected in pDCs of SLE patients, but the expression of SHIP1, SHP1, SHP2 and CSK can be detected.[22] In the absence of an activating ligand, these molecules are believed to interact with the SLAMF receptor and convey inhibitory signals.[82] Hence, it is reasonable to assert that SLAMF7 serves as the inhibitory receptor on pDCs in SLE. Moreover, there is a significant increase in the proportion of $SLAMF7^+$ B cells among SLE patients, and a positive linear correlation is observed between the proportion of $SLAMF7^+$ B cells and the disease severity.[83] Considering these evidences, it can be deduced that SLAMF7 plays a multifaceted role in regulating immune cell function in SLE. The activation of SLAMF7 on distinct immune cells exerts differential impacts on the disease and targeted activation or inhibition of SLAMF7 on certain immune cells could delay the progression of SLE.

Systemic sclerosis and multiple sclerosis

SSc is an uncommon chronic ailment characterized by the presence of autoantibodies and a substantial accumulation of T cells in the affected organ.[84] In patients with early diffuse cutaneous SSc (dcSSc), the proportion of $SALMF7^+$ $CD4^+$ T cells significantly rises, constituting 20–60% of the total $CD4^+$ T cells population, whereas $SALMF7^+$ $CD4^+$ T cells are virtually absent in healthy individuals.[84] SLAMF7 mediates the cytotoxic effects of $CD4^+$ T cells, and $SLAMF7^+$ $CD4^+$ T cells are capable of releasing cytotoxic granular components, including perforin and granzyme.[34] Within the skin of individuals with SSc, $SLAMF7^+$ $CD4^+$ T cells predominantly aggregate around the microvasculature, and compared to total $CD4^+$ T cells, they exhibit higher levels of IL-4, IL-17, and IFN-γ expression, and significant cytotoxicity,[14,84] which

may be involved in the pathogenesis of SSc. From this perspective, it is more beneficial to reduce SLAMF7$^+$ CD4$^+$ T cells or to reduce SLAMF7 expression.

Multiple sclerosis (MS) is a representative example of immune-mediated demyelinating disease, affecting the central nervous system (CNS) in humans.[85] Through genome-wide association studies involving a substantial number of MS patients and controls, it has been observed that the rs983494 single nucleotide polymorphism (SNP) located in the promoter region of the SLAMF7 gene expresses a significant association with susceptibility to MS.[86] The mechanism through which SNPs modulate the expression of SLAMF7 remains uncertain; however, it is evident that SLAMF7 is intricately linked to the progression of MS. In order to elucidate the role of SLAMF7 in the pathogenesis of MS, experimental autoimmune encephalomyelitis (EAE) model is established in wild-type mice and SLAMF7-deficient mice (SLAMF7$^{-/-}$), respectively. The results show that SLAMF7$^{-/-}$ mice produce higher levels of soluble inflammatory mediators (granulocyte colony-stimulating factor (G-CSF), GM-CSF, IFN-γ, IL-9, and CCL3) during EAE than wild-type mice, and SLAMF7$^{-/-}$ mice are also more likely to induce EAE,[87] suggesting that SLAMF7 exerts a protective influence on the autoimmunity targeting the central nervous system. During the construction of CNS immune landscape during EAE, the expression of SLAMF7 on B cells is reduced, and the activation of SLAMF7 on mouse B cells can inhibit the production of Eotaxin, IL-17, TNF-α and CCL5.[87] These suggest that SLAMF7 may have an inhibitory effect on B cells involved in central nervous system inflammation. Moreover, SLAMF7 may inhibit the activation of B cells by the inhibition of major histocompatibility complex class II (MHC-II), programmed death ligand 1 (PD-L1), CD80, and SLAMF7-SLAMF7 interactions between B cells and CD8$^+$ T cells, thereby inhibiting the activation of CD8$^+$ T cells, and ultimately reducing the severity of EAE.[87] The involvement of SLAMF7 in the regulation of immune responses within the CNS and the function of B cells establishes a connection between SLAMF7 and the susceptibility to MS, and SLAMF7 could play a beneficial role in MS. Additionally, this association offers a mechanistic rationale for the genetic correlation between the rs983494 SNP and MS. Given the above, activation of SLAMF7 could be a treatment strategy for MS.

Rheumatoid arthritis

RA is a prevalent chronic inflammatory ailment, distinguished by the infiltration of synovium by macrophages, accompanied by a substantial presence of lymphocytes and activated stromal cells.[88–90] The RNA-seq data obtained from synovial macrophages of RA patients reveals that SLAMF7 is closely linked to the superactivated state of macrophages in RA.[20] Initially expressed at minimal levels on quiescent macrophages,[82] the heightened expression of SLAMF7 may be associated with the pro-inflammatory properties of macrophages. Subsequent investigation into the mechanism reveals that IFN-γ plays a pivotal role as the key regulatory factor governing SLAMF7 expression in human macrophages.[20] After activation, SLAMF7 binds to FcγR through intracellular ITSM to activate downstream ERK, NF-κB P65, AKT and MAPK P38 pathways, resulting in a large release of macrophage pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α, which contributes to the inflammatory response of RA.[20] Notably, besides RA, high levels of SLAMF7 have also been detected in macrophages of individuals with Crohn's disease (IBD) and COVID-19 pneumonia.[20] These observations suggest that SLAMF7 is capable of regulating the transformation of macrophages into pro-inflammatory phenotypes in RA, and the inhibition of SLAMF7 activation on macrophages may play a non-negligible role in the treatment of RA.

The involvement of SLAMF7 in the pathogenesis of atherosclerosis

Atherosclerosis (AS), serves as the primary etiology for numerous cardiovascular ailments, encompassing myocardial infarctions and cerebrovascular accidents. Research findings have demonstrated that SLAMF7 plays a pivotal role in the progression of AS in the carotid artery.[91] Persistent inflammation contributes to plaque formation in the arteries, and the absence of vascular smooth muscle cells (VSMC) promotes plaque rupture and the formation of blood clots.[92] The absence of SLAMF7 in human arterial plaque derived macrophages, not only inhibits the expression of pro-inflammatory cytokines IL-6, IL-8, IL-12 and TNF-α via protein kinase B (PKB) and Phospholipase C gamma1 (PLCγ1), but also inhibits the proliferation of VSMC.[91] Therefore, SLAMF7 is associated with the pro-inflammatory function of macrophages in arterial plaque. SLAMF7 has been identified as a novel surface marker for pro-inflammatory macrophages,[39] and pro-inflammatory macrophages are implicated in the rupture of arterial plaques.[93] In comparison to stable and unstable plaques in patients, the expression of SLAMF7 is notably higher in unstable plaques, particularly in CD68$^+$ macrophages.[91] Hence, it is hypothesized that SLAMF7 on macrophages in AS not only contributes to the exacerbation of the inflammatory response, but also involves in the lysis of plaques. Macrophages have a strong phagocytosis function, and macrophages in AS will become foam cells after phagocytosis of lipids, assisting the development of AS.[94] In diabetic AS, the presence of SLAMF7 correlates with the phagocytic activity of macrophages.[95] Intermedin (IMD) can impede the expression of SLAMF7 by the lncRNA Dnm3os/miR-27b-3p/SLAMF7 axis, therefore inhibiting macrophage phagocytosis and

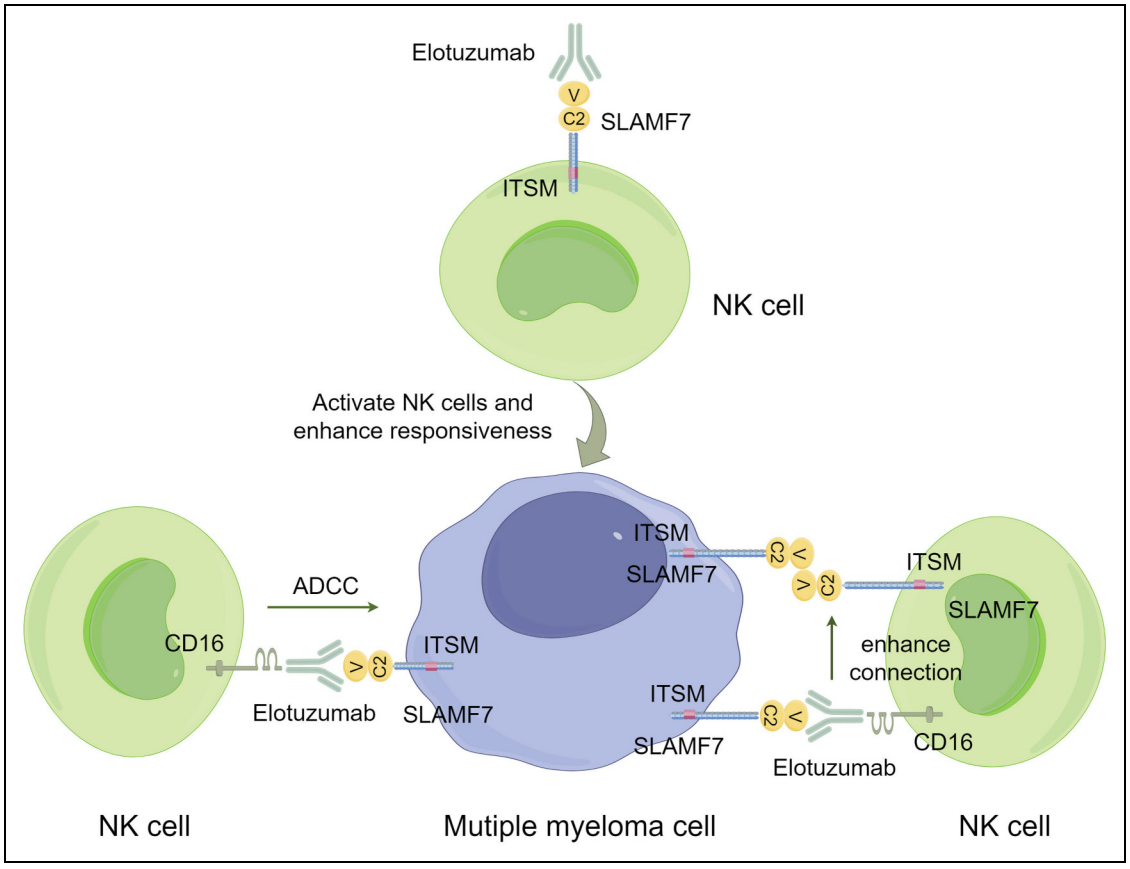

Figure 3. The anti-SLAMF7 antibody elotuzumab activates NK cells and kills MM cells. By connecting CD16 on the surface of NK cells with SLAMF7 on the surface of MM cells, elotuzumab can not only further strengthen the SLAMF7-SLAMF7 interactions between NK cells and MM cells, but also promote the ADCC of NK cells. Elotuzumab can also directly activate NK cells and improve NK cell reactivity.

alleviating AS in diabetic patients.[95] This evidence highlights the multifunctionality of SLAMF7 in macrophages and its crucial role in both macrophage biology and AS. Therefore, targeted inhibition of SLAMF7 as a therapeutic approach has significant potential to attenuate AS.

Therapeutic interventions aimed at SLAMF7

Elotuzumab, a humanized IgG1 immunostimulating monoclonal antibody, has been developed to specifically target SLAMF7 and is primarily indicated for the treatment of patients with MM.[11] Clinical studies have demonstrated that elotuzumab, either as a monotherapy or in combination with lenalidomide and dexamethasone, effectively reduces the mortality risk in MM patients, thus representing a potent treatment modality for MM.[47,96] The mechanisms encompass the following aspects (Figure 3). (i) MM cells are partially eliminated by NK cell-mediated antibody dependent cell-mediated cytotoxicity (ADCC) in the presence of effective Fc-CD16 interactions and NK cells in the body.[11,97,98] (ii) The direct interaction of soluble elotuzumab with SLAMF7 on NK cells, which can induce a calcium signaling response by co-stimulating the binding of NKp46 and NKG2D polymers, independent of CD16. This co-stimulation has the potential to decrease the activation threshold for the binding of other NK cell receptors to their ligands on the surface of myeloma target cells, thereby potentially enhancing the reactivity of NK cells in patients.[99] This process necessitates the presence of SLAMF7 on both NK cells and target cells.[100] (iii) Elotuzumab has the potential to facilitate the physical bridging between SLAMF7 on myeloma cells and SLAMF7 on NK cells, thereby promoting adhesion and co-stimulating NK cell-mediated cleavage.[98] Furthermore, SLAMF7 is expressed on various immune cell types including B cells, T cells, monocytes, and NK cells, thereby rendering elotuzumab a potential therapeutic approach for primary effusion lymphoma (PEL),[27] plasmoblastic lymphoma (PBL)[101] and myeloid proliferative tumors (MPN).[102] By virtue of the affinity for SLAMF7, elotuzumab facilitates the activation of immune cells, enabling them to effectively eliminate tumor cells and combat microbial pathogens such as bacteria and viruses.

In addition to the utilization of monoclonal antibodies, the application of SLAMF7-chimeric antigen receptor (CAR) binding to immune cells, such as T cells and NK

cells, has proven to be an efficacious therapeutic approach in targeting SLAMF7. The administration of SLAMF7-CAR-T (HuLuc63-SLAMF7-CAR-T), which specifically targets the C2 domain located at the proximal end of SALMF7, has demonstrated significant anti-myeloma activity in mouse models.[103,104] However, it selectively induces cell death in SLAMF7$^{+/high}$ NK cells, CD4$^+$ T cells, CD8$^+$ T cells, and B cells, while preserving SLAMF7$^{-/low}$ NK cells and functional lymphocytes, including virus-specific T cells.[103] SLAMF7-CAR-T (Luc90-SLAMF7-CAR-T), which targets the distal V domain of SLAMF7, demonstrates effective tumor-killing ability in MM mouse models. However, CD8$^+$ T cells are cannibalized during the production process, so the SLAMF7-deficient Luc90-SLAMF7-CAR-T is designed to protect CD8$^+$ T cells without affecting the efficacy.[105] In addition to the evaluation of the extracellular domain of SLAMF7, the inclusion of the costimulatory domain of CAR is also a crucial factor to consider. The majority of clinically employ CARs utilize CD28 or 4-1BB as their co-stimulatory domain.[106] It has been observed that Luc90-SLAMF7-CAR-T exhibits a more effective tumor-killing ability when CD28 acts as a co-stimulatory domain of CAR.[107] BiTE acts in a similar way to CAR-T by linking the CD3ϵ of the TCR complex to tumor-associated antigen (TAA) to activate T cells.[108] SLAMF7, as a high level and universally expressed TAA on MM cells, binds to BiTE and inhibits MM growth.[41] These methods of targeting SLAMF7 are mainly applied to tumor-related diseases. In non-tumor diseases, SLAMF7 on immune cells can be activated by rmSLAMF7 protein, or SLAMF7 on immune cells can be knocked out, and immune cell function can be changed, thus regulating the direction of disease progression.[12,57,62,87] The current methods related to SLAMF7 activation may be feasible in clinical applications, but the lack of a practical and clear strategy to inhibit SLAMF7. Targeting EAT-2 or Mac-1, the downstream of SLAMF7, which can inhibit the transmission of activation signals to immune cells could be potential clinical strategies. Another viable option is to block the interaction between SLAMF7 molecules, reducing the activation effect. With the continuous deepening of research, SLAMF7 is expected to become a new intervention target for immune cells-related diseases.

Conclusion

SLAMF7 is an important regulatory molecule on the surface of immune cells, which is of great significance for the maintenance of normal physiological state of immune cells. A large number of studies have confirmed that SLAMF7 regulates the functions of a variety of immune cells. SLAMF7 enhances the cytotoxicity of NK cells, participates in the proliferation of B cells, and is associated with the cytotoxicity of T cells and the inflammatory response of monocyte/macrophage. SLAMF7 can not only affect tumor growth, but also inhibit the excessive inflammatory response of mononuclear macrophages in infected tissues, and SLAMF7 in different autoimmune diseases plays a role in immunosuppression or immune activation. However, apart from the mechanism in NK cells, the mechanism of SLAMF7 in immune cells remains unclear. An increasing number of studies have shown that SLAMF7, like other members of the SLAMF, has a non-negligible role in regulating immune cell function, and targeting SLAMF7 will potentially ameliorate the disease. In the future, we hope to further explore the effect of SLAMF7 on immune cells and the molecular mechanism, and we believe that the development and application of SLAMF7 targeting antibodies and chimeric antibodies will bring new hope to the treatment of immune cells-related diseases.

Author contributions

ZZ: investigation, writing—original draft, visualization. **ZY:** conceptualization, writing—reviewing and editing. **CZ:** investigation, visualization. **XL:** conceptualization, supervision, writing—reviewing and editing. All authors read and approved the final manuscript.

Data availability

No data was used for the research described in the article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This work was supported by the Chinese Postdoctoral Science Foundation (2019M660106) and the Postdoctoral Research Foundation of Jiangsu Province (2021K209B).

ORCID iDs

Zheng Zhang https://orcid.org/0009-0002-6311-2221
Ying Zhang https://orcid.org/0000-0002-6505-4822
Zeyu Chen https://orcid.org/0009-0007-3555-1522
Lin Xia https://orcid.org/0000-0002-5214-3615

References

1. Kloc D, Kurhajec S, Huniadi M, et al. SLAM Family receptors in B cell chronic lymphoproliferative disorders. *Int J Mol Sci* 2024; 25: 4014.
2. Kiel MJ, Yilmaz OH, Iwashita T, et al. SLAM Family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. *Cell* 2005; 121: 1109–1121.
3. Cannons JL, Tangye SG and Schwartzberg PL. SLAM Family receptors and SAP adaptors in immunity. *Annu Rev Immunol* 2011; 29: 665–705.

4. Li D, Xiong W, Wang Y, et al. SLAMF3 And SLAMF4 are immune checkpoints that constrain macrophage phagocytosis of hematopoietic tumors. *Sci Immunol* 2022; 7: eabj5501.
5. Gartshteyn Y, Askanase AD and Mor A. SLAM Associated protein signaling in T cells: tilting the balance toward autoimmunity. *Front Immunol* 2021; 12: 654839.
6. Dragovich MA and Mor A. The SLAM family receptors: potential therapeutic targets for inflammatory and autoimmune diseases. *Autoimmun Rev* 2018; 17: 674–682.
7. Bouchon A, Cella M, Grierson HL, et al. Activation of NK cell-mediated cytotoxicity by a SAP-independent receptor of the CD2 family. *J Immunol* 2001; 167: 5517–5521.
8. Lee JK, Mathew SO, Vaidya SV, et al. CS1 (CRACC, CD319) induces proliferation and autocrine cytokine expression on human B lymphocytes. *J Immunol* 2007; 179: 4672–4678.
9. Kim JR, Horton NC, Mathew SO, et al. CS1 (SLAMF7) inhibits production of proinflammatory cytokines by activated monocytes. *Inflamm Res* 2013; 62: 765–772.
10. Friend R, Bhutani M, Voorhees PM, et al. Clinical potential of SLAMF7 antibodies - focus on elotuzumab in multiple myeloma. *Drug Des Devel Ther* 2017; 11: 893–900.
11. Tai YT, Dillon M, Song W, et al. Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. *Blood* 2008; 112: 1329–1337.
12. Wu Y, Wang Q, Li M, et al. SLAMF7 Regulates the inflammatory response in macrophages during polymicrobial sepsis. *J Clin Invest* 2023; 133: e150224.
13. Fox DA, Lundy SK, Whitfield ML, et al. Correction to: lymphocyte subset abnormalities in early diffuse cutaneous systemic sclerosis. *Arthritis Res Ther* 2021; 23: 73.
14. Maehara T, Kaneko N, Perugino CA, et al. Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis. *J Clin Invest* 2020; 130: 2451–2464.
15. Wu N and Veillette A. SLAM Family receptors in normal immunity and immune pathologies. *Curr Opin Immunol* 2016; 38: 45–51.
16. Lee JK, Boles KS and Mathew PA. Molecular and functional characterization of a CS1 (CRACC) splice variant expressed in human NK cells that does not contain immunoreceptor tyrosine-based switch motifs. *Eur J Immunol* 2004; 34: 2791–2799.
17. Buller CW, Mathew PA and Mathew SO. Roles of NK cell receptors 2B4 (CD244), CS1 (CD319), and LLT1 (CLEC2D) in cancer. *Cancers (Basel)* 2020; 12: 1755.
18. Kim JR, Mathew SO and Mathew PA. Blimp-1/PRDM1 regulates the transcription of human CS1 (SLAMF7) gene in NK and B cells. *Immunobiology* 2016; 221: 31–39.
19. Dongre P, Mathew S, Akopova I, et al. YY1 And a unique DNA repeat element regulates the transcription of mouse CS1 (CD319, SLAMF7) gene. *Mol Immunol* 2013; 54: 254–263.
20. Simmons DP, Nguyen HN, Gomez-Rivas E, et al. SLAMF7 Engagement superactivates macrophages in acute and chronic inflammation. *Sci Immunol* 2022; 7: eabf2846.
21. Higashioka K, Ota Y, Maehara T, et al. Association of circulating SLAMF7(+)Tfh1 cells with IgG4 levels in patients with IgG4-related disease. *BMC Immunol* 2020; 21: 31.
22. Hagberg N, Theorell J, Schlums H, et al. Systemic lupus erythematosus immune complexes increase the expression of SLAM family members CD319 (CRACC) and CD229 (LY-9) on plasmacytoid dendritic cells and CD319 on CD56(dim) NK cells. *J Immunol* 2013; 191: 2989–2998.
23. Wang SH, Chou WC, Huang HC, et al. Deglycosylation of SLAMF7 in breast cancers enhances phagocytosis. *Am J Cancer Res* 2022; 12: 4721–4736.
24. Boles KS, Stepp SE, Bennett M, et al. 2B4 (CD244) and CS1: novel members of the CD2 subset of the immunoglobulin superfamily molecules expressed on natural killer cells and other leukocytes. *Immunol Rev* 2001; 181: 234–249.
25. Davis SJ and van der Merwe PA. The structure and ligand interactions of CD2: implications for T-cell function. *Immunol Today* 1996; 17: 177–187.
26. Campbell KS, Cohen AD and Pazina T. Mechanisms of NK cell activation and clinical activity of the therapeutic SLAMF7 antibody, elotuzumab in multiple myeloma. *Front Immunol* 2018; 9: 2551.
27. Panaampon J, Kariya R and Okada S. Elotuzumab, a potential therapeutic humanized anti-SLAMF7 monoclonal antibody, enhances natural killer cell-mediated killing of primary effusion lymphoma cells. *Cancer Immunol Immunother* 2022; 71: 2497–2509.
28. Tassi I and Colonna M. The cytotoxicity receptor CRACC (CS-1) recruits EAT-2 and activates the PI3 K and phospholipase cgamma signaling pathways in human NK cells. *J Immunol* 2005; 175: 7996–8002.
29. Gutierrez-Guerrero A, Mancilla-Herrera I, Maravillas-Montero JL, et al. SLAMF7 Selectively favors degranulation to promote cytotoxicity in human NK cells. *Eur J Immunol* 2022; 52: 62–74.
30. Guo H, Cruz-Munoz ME, Wu N, et al. Immune cell inhibition by SLAMF7 is mediated by a mechanism requiring src kinases, CD45, and SHIP-1 that is defective in multiple myeloma cells. *Mol Cell Biol* 2015; 35: 41–51.
31. Stark S and Watzl C. 2B4 (CD244), NTB-A and CRACC (CS1) stimulate cytotoxicity but no proliferation in human NK cells. *Int Immunol* 2006; 18: 241–247.
32. Mucida D, Husain MM, Muroi S, et al. Transcriptional reprogramming of mature CD4(+) helper T cells generates distinct MHC class II-restricted cytotoxic T lymphocytes. *Nat Immunol* 2013; 14: 281–289.
33. Frentsch M, Stark R, Matzmohr N, et al. CD40L Expression permits CD8+ T cells to execute immunologic helper functions. *Blood* 2013; 122: 405–412.
34. Loyal L, Warth S, Jurchott K, et al. SLAMF7 And IL-6R define distinct cytotoxic versus helper memory CD8(+) T cells. *Nat Commun* 2020; 11: 6357.
35. Worm M, Ebermayer K and Henz B. Lymphotoxin-alpha is an important autocrine factor for CD40 + interleukin-4-mediated B-cell activation in normal and atopic donors. *Immunology* 1998; 94: 395–402.
36. Boussiotis VA, Nadler LM, Strominger JL, et al. Tumor necrosis factor alpha is an autocrine growth factor for normal human B cells. *Proc Natl Acad Sci U S A* 1994; 91: 7007–7011.
37. Lin J, Chavin KD, Qin L, et al. Anti-CD2 monoclonal antibody-induced receptor changes. II. Interaction of CD2 and CD3. *Cell Immunol* 1996; 167: 249–258.

38. Sitnicka E, Brakebusch C, Martensson IL, et al. Complementary signaling through flt3 and interleukin-7 receptor alpha is indispensable for fetal and adult B cell genesis. *J Exp Med* 2003; 198: 1495–1506.
39. Beyer M, Mallmann MR, Xue J, et al. High-resolution transcriptome of human macrophages. *PLoS One* 2012; 7: e45466.
40. Choe U, Pham Q, Kim YS, et al. Identification and elucidation of cross talk between SLAM family member 7 (SLAMF7) and toll-like receptor (TLR) pathways in monocytes and macrophages. *Sci Rep* 2023; 13: 11007.
41. Geis M, Nowotny B, Bohn MD, et al. Combinatorial targeting of multiple myeloma by complementing T cell engaging antibody fragments. *Commun Biol* 2021; 4: 44.
42. Muccio VE, Saraci E, Gilestro M, et al. Multiple myeloma: new surface antigens for the characterization of plasma cells in the era of novel agents. *Cytometry B Clin Cytom* 2016; 90: 81–90.
43. Kikuchi J, Hori M, Iha H, et al. Soluble SLAMF7 promotes the growth of myeloma cells via homophilic interaction with surface SLAMF7. *Leukemia* 2020; 34: 180–195.
44. Ishibashi M, Soeda S, Sasaki M, et al. Clinical impact of serum soluble SLAMF7 in multiple myeloma. *Oncotarget* 2018; 9: 34784–34793.
45. Iida S, Nagai H, Kinoshita G, et al. Elotuzumab with lenalidomide and dexamethasone for Japanese patients with relapsed/refractory multiple myeloma: phase 1 study. *Int J Hematol* 2017; 105: 326–334.
46. Jakubowiak A, Offidani M, Pegourie B, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. *Blood* 2016; 127: 2833–2840.
47. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015; 373: 621–631.
48. Li X, Chen M, Wan Y, et al. Single-cell transcriptome profiling reveals the key role of ZNF683 in natural killer cell exhaustion in multiple myeloma. *Clin Transl Med* 2022; 12: e1065.
49. Awwad MHS, Mahmoud A, Bruns H, et al. Selective elimination of immunosuppressive T cells in patients with multiple myeloma. *Leukemia* 2021; 35: 2602–2615.
50. Chao MP, Alizadeh AA, Tang C, et al. Anti-CD47 antibody synergizes with rituximab to promote phagocytosis and eradicate non-Hodgkin lymphoma. *Cell* 2010; 142: 699–713.
51. Theocharides AP, Jin L, Cheng PY, et al. Disruption of SIRPalpha signaling in macrophages eliminates human acute myeloid leukemia stem cells in xenografts. *J Exp Med* 2012; 209: 1883–1899.
52. Chen J, Zhong MC, Guo H, et al. SLAMF7 Is critical for phagocytosis of haematopoietic tumour cells via Mac-1 integrin. *Nature* 2017; 544: 493–497.
53. He Y, Bouwstra R, Wiersma VR, et al. Cancer cell-expressed SLAMF7 is not required for CD47-mediated phagocytosis. *Nat Commun* 2019; 10: 533.
54. Bouwstra R, van Meerten T and Bremer E. Does cancer cell-expressed SLAMF7 impact on CD47-mediated phagocytosis? *Mol Cell Oncol* 2019; 6: 1600349.
55. Williams H, Suda S, Dervish S, et al. Monocyte M1/M2 profile is altered in paediatric burn patients with hypertrophic scarring. *Wound Repair Regen* 2021; 29: 996–1005.
56. Assidi M. Strong prognostic value of SLAMF7 protein expression in patients with lymph node-positive breast cancer. *Oncol Lett* 2022; 24: 433.
57. O'Connell P, Hyslop S, Blake MK, et al. SLAMF7 Signaling reprograms T cells toward exhaustion in the tumor microenvironment. *J Immunol* 2021; 206: 193–205.
58. Jiang P, Gu S, Pan D, et al. Signatures of T cell dysfunction and exclusion predict cancer immunotherapy response. *Nat Med* 2018; 24: 1550–1558.
59. Zhang W, Liu T, Jiang L, et al. Immunogenic cell death-related gene landscape predicts the overall survival and immune infiltration status of ovarian cancer. *Front Genet* 2022; 13: 1001239.
60. Liu C, Zhang Y, Li X, et al. Ovarian cancer-specific dysregulated genes with prognostic significance: scRNA-Seq with bulk RNA-Seq data and experimental validation. *Ann N Y Acad Sci* 2022; 1512: 154–173.
61. Tang XX, Shimada H and Ikegaki N. Macrophage-mediated anti-tumor immunity against high-risk neuroblastoma. *Genes Immun* 2022; 23: 129–140.
62. Zhu S, Chen Y, Lao J, et al. Signaling lymphocytic activation molecule family-7 alleviates corneal inflammation by promoting M2 polarization. *J Infect Dis* 2021; 223: 854–865.
63. O'Connell P, Pepelyayeva Y, Blake MK, et al. SLAMF7 Is a critical negative regulator of IFN-alpha-mediated CXCL10 production in chronic HIV infection. *J Immunol* 2019; 202: 228–238.
64. Angus DC and van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013; 369: 840–851.
65. Wei Z, Zhang Y, Chen Q, et al. SLAMF7/STAT6 Pathway inhibits innate immune response in late-stage human acanthamoeba keratitis: a comparative transcriptome analysis. *Microorganisms* 2023; 11: 365.
66. Paiardini M and Muller-Trutwin M. HIV-associated chronic immune activation. *Immunol Rev* 2013; 254: 78–101.
67. Hong S and Banks WA. Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. *Brain Behav Immun* 2015; 45: 1–12.
68. Della-Torre E, Lanzillotta M and Doglioni C. Immunology of IgG4-related disease. *Clin Exp Immunol* 2015; 181: 191–206.
69. Maritati F, Peyronel F and Vaglio A. IgG4-related disease: a clinical perspective. *Rheumatology (Oxford)* 2020; 59: iii123–iiii31.
70. Kamekura R, Takahashi H and Ichimiya S. New insights into IgG4-related disease: emerging new CD4+ T-cell subsets. *Curr Opin Rheumatol* 2019; 31: 9–15.
71. Mattoo H, Mahajan VS, Maehara T, et al. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. *J Allergy Clin Immunol* 2016; 138: 825–838.
72. Maehara T, Mattoo H, Ohta M, et al. Lesional CD4+ IFN-gamma+ cytotoxic T lymphocytes in IgG4-related dacryoadenitis and sialoadenitis. *Ann Rheum Dis* 2017; 76: 377–385.
73. Recher M, Berglund LJ, Avery DT, et al. IL-21 is the primary common gamma chain-binding cytokine required

for human B-cell differentiation in vivo. *Blood* 2011; 118: 6824–6835.
74. Rousset F, Garcia E, Defrance T, et al. Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes. *Proc Natl Acad Sci U S A* 1992; 89: 1890–1893.
75. Hildemann SK, Eberlein J, Davenport B, et al. High efficiency of antiviral CD4(+) killer T cells. *PLoS One* 2013; 8: e60420.
76. Della-Torre E, Bozzalla-Cassione E, Sciorati C, et al. A CD8alpha- subset of CD4 + SLAMF7+ cytotoxic T cells is expanded in patients with IgG4-related disease and decreases following glucocorticoid treatment. *Arthritis Rheumatol* 2018; 70: 1133–1143.
77. Stohl W. Impaired polyclonal T cell cytolytic activity. A possible risk factor for systemic lupus erythematosus. *Arthritis Rheum* 1995; 38: 506–516.
78. Kis-Toth K, Comte D, Karampetsou MP, et al. Selective loss of signaling lymphocytic activation molecule family member 4-positive CD8+ T cells contributes to the decreased cytotoxic cell activity in systemic lupus erythematosus. *Arthritis Rheumatol* 2016; 68: 164–173.
79. Comte D, Karampetsou MP, Yoshida N, et al. Signaling lymphocytic activation molecule family member 7 engagement restores defective effector CD8+ T cell function in systemic lupus erythematosus. *Arthritis Rheumatol* 2017; 69: 1035–1044.
80. Ronnblom L, Eloranta ML and Alm GV. The type I interferon system in systemic lupus erythematosus. *Arthritis Rheum* 2006; 54: 408–420.
81. Fehniger TA, Shah MH, Turner MJ, et al. Differential cytokine and chemokine gene expression by human NK cells following activation with IL-18 or IL-15 in combination with IL-12: implications for the innate immune response. *J Immunol* 1999; 162: 4511–4520.
82. Veillette A. SLAM-family receptors: immune regulators with or without SAP-family adaptors. *Cold Spring Harb Perspect Biol* 2010; 2: a002469.
83. Kim JR, Mathew SO, Patel RK, et al. Altered expression of signalling lymphocyte activation molecule (SLAM) family receptors CS1 (CD319) and 2B4 (CD244) in patients with systemic lupus erythematosus. *Clin Exp Immunol* 2010; 160: 348–358.
84. Fox DA, Lundy SK, Whitfield ML, et al. Lymphocyte subset abnormalities in early diffuse cutaneous systemic sclerosis. *Arthritis Res Ther* 2021; 23: 10.
85. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. *N Engl J Med* 2000; 343: 938–952.
86. International Multiple Sclerosis Genetics C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science* 2019; 365: eaav7188.
87. O'Connell P, Blake MK, Godbehere S, et al. SLAMF7 Modulates B cells and adaptive immunity to regulate susceptibility to CNS autoimmunity. *J Neuroinflammation* 2022; 19: 241.
88. Zhang F, Wei K, Slowikowski K, et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. *Nat Immunol* 2019; 20: 928–942.
89. Rao DA, Gurish MF, Marshall JL, et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature* 2017; 542: 110–114.
90. Kuo D, Ding J, Cohn IS, et al. HBEGF(+) macrophages in rheumatoid arthritis induce fibroblast invasiveness. *Sci Transl Med* 2019; 11: eaau8587.
91. Xia Z, Gu M, Jia X, et al. Integrated DNA methylation and gene expression analysis identifies SLAMF7 as a key regulator of atherosclerosis. *Aging (Albany NY)* 2018; 10: 1324–1337.
92. Bennett MR, Sinha S and Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res* 2016; 118: 692–702.
93. Stoger JL, Gijbels MJ, van der Velden S, et al. Distribution of macrophage polarization markers in human atherosclerosis. *Atherosclerosis* 2012; 225: 461–468.
94. Chistiakov DA, Melnichenko AA, Myasoedova VA, et al. Mechanisms of foam cell formation in atherosclerosis. *J Mol Med (Berl)* 2017; 95: 1153–1165.
95. Su Y, Guan P, Li D, et al. Intermedin attenuates macrophage phagocytosis via regulation of the long noncoding RNA Dnm3os/miR-27b-3p/SLAMF7 axis in a mouse model of atherosclerosis in diabetes. *Biochem Biophys Res Commun* 2021; 583: 35–42.
96. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med* 2018; 379: 1811–1822.
97. Hsi ED, Steinle R, Balasa B, et al. CS1, A potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res* 2008; 14: 2775–2784.
98. Collins SM, Bakan CE, Swartzel GD, et al. Elotuzumab directly enhances NK cell cytotoxicity against myeloma via CS1 ligation: evidence for augmented NK cell function complementing ADCC. *Cancer Immunol Immunother* 2013; 62: 1841–1849.
99. Pazina T, James AM, MacFarlane A, et al. The anti-SLAMF7 antibody elotuzumab mediates NK cell activation through both CD16-dependent and -independent mechanisms. *Oncoimmunology* 2017; 6: e1339853.
100. Pazina T, James AM, Colby KB, et al. Enhanced SLAMF7 homotypic interactions by elotuzumab improves NK cell killing of multiple myeloma. *Cancer Immunol Res* 2019; 7: 1633–1646.
101. Shi J, Bodo J, Zhao X, et al. SLAMF7 (CD319/CS1) is expressed in plasmablastic lymphoma and is a potential diagnostic marker and therapeutic target. *Br J Haematol* 2019; 185: 145–147.
102. Maekawa T, Kato S, Kawamura T, et al. Increased SLAMF7(high) monocytes in myelofibrosis patients harboring JAK2V617F provide a therapeutic target of elotuzumab. *Blood* 2019; 134: 814–825.
103. Gogishvili T, Danhof S, Prommersberger S, et al. SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7(+) normal lymphocytes. *Blood* 2017; 130: 2838–2847.
104. Wang X, Walter M, Urak R, et al. Lenalidomide enhances the function of CS1 chimeric antigen receptor-redirected T cells against multiple myeloma. *Clin Cancer Res* 2018; 24: 106–119.
105. O'Neal J, Ritchey JK, Cooper ML, et al. CS1 CAR-T targeting the distal domain of CS1 (SLAMF7) shows efficacy in high

tumor burden myeloma model despite fratricide of CD8 + CS1 expressing CAR-T cells. *Leukemia* 2022; 36: 1625–1634.
106. Weinkove R, George P, Dasyam N, et al. Selecting costimulatory domains for chimeric antigen receptors: functional and clinical considerations. *Clin Transl Immunology* 2019; 8: e1049.
107. Amatya C, Pegues MA, Lam N, et al. Development of CAR T cells expressing a suicide gene plus a chimeric antigen receptor targeting signaling lymphocytic-activation molecule F7. *Mol Ther* 2021; 29: 702–717.
108. Goebeler ME and Bargou RC. T cell-engaging therapies - BiTEs and beyond. *Nat Rev Clin Oncol* 2020; 17: 418–434.