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Review Article

Signaling lymphocyte activation molecule family in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease characterized by a breakdown in immune tolerance leading to the development of autoreactive lymphocytes and autoantibodies. Recent findings have provided new insight on the role of the signaling lymphocytic activation molecule family (SLAMF) receptors, a group of nine co-regulatory molecules involved in the activation of hematopoietic cells, and their downstream protein SLAM-associated protein (SAP), into the pathogenesis of SLE. This review summarizes the current knowledge on SLAMF in human SLE immunopathogenesis, and the importance of SLAMF molecules as new therapeutic targets.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex, multifactorial and potentially life threatening autoimmune disease of unknown etiology affecting mainly young women of reproductive age. A combination of hormonal, genetic, epigenetic and environmental factors are implicated in the break of tolerance to self-antigen which characterizes SLE [1]. In very rare cases, single-gene defects, the most common among them being deficiencies in early complement activation components (C2, C3, C1q) may be sufficient in driving the development of systemic autoimmunity [2,3]. However, SLE is a genetically complex disease with a variety of gene defects and/or polymorphisms that contribute to the overall genetic susceptibility.

T cells and B cells signaling abnormalities as well as dysregulated interactions between these two cell populations lead to aberrant immune cell function and eventually to the production of autoantibodies and organ damage [4–6]. Despite significant progress made over the past decades in understanding the molecular and biochemical events that lead to the abnormal activation of the immune system in lupus, management of SLE still relies on the use of corticosteroids and non-specific immunosuppressive agents, thus making the need to discover newer, safer and more effective treatments mandatory.

Activation, proliferation and differentiation of T cells are determined by tightly controlled interactions between antigen-presenting cells (APC) and T lymphocytes. Three different types of signals have been described to play major roles in the modulation of the T cell receptor (TCR) signaling and response: (i) antigen recognition, (ii) co-stimulation and co-inhibition (iii) effect of cytokines [7,8]. The best-characterized co-stimulation pathway involves the CD28 co-stimulatory receptor on T cells. After ligation by its natural ligands, B7-1 (CD80) or B7-2 (CD86) on APC, CD28 signaling enhances the T cell response. The activation of CD28 is counterbalanced by co-inhibitory molecules. Programmed death 1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) are two major, well characterized co-inhibitory molecules that are expressed on T cells following activation. These co-inhibitory molecules can be directly or indirectly targeted to modulate the immune response [9]. Many other costimulatory molecules have been described and shown to deliver co-stimulatory or co-inhibitory signals upon T or B cell activation, including SLAMF (signaling lymphocyte activation molecule family) [10]. SLAMF represents a complex family of surface co-receptors that is comprised of nine different members (SLAMF1-9) belonging to the CD2 superfamily of immunoglobulin domain-containing molecules. These members include SLAMF1 (CD150 or SLAM), SLAMF2 (CD48), SLAMF3 (CD229 or Ly9), SLAMF4 (CD244 or 2B4), SLAMF5 (CD84), SLAMF6 (CD352, NTBA or SF2000 in human or Ly108 in mice), SLAMF7 (CD319, CS1 or CRACC). The gene encoding SLAMF8 (CD353 or BLAME) and SLAMF9 (CD84-H1 or SF2001) are located in close proximity to the main SLAMF gene cluster [11]. SLAMF receptors are composed of an extracellular segment (with two to four Ig-like domains), a transmembrane domain and a cytoplasmic tail [10].

Abbreviations: APC, antigen-presenting cells; B, B cells; CD4, CD4+ T cells; CD8, CD8+ T cells; DN, double negative T cells; IFN, interferon; IL, interleukin; mAb, specific monoclonal antibody; NK, natural killer; pDC, plasmacytoid dendritic cells; TNF, tumor necrosis factor; Tregs, regulatory T cells

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The cytoplasmic domain of SLAMF members contains one to four intracellular switch motif amino acid sequences (ITSM). SLAMF2, SLAMF8 and SLAMF9 differ structurally compared to the rest of the SLAMF members in the sense that SLAMF2 is a glycophosphatidylinositol (GPI)-anchored protein with no transmembrane or cytoplasmic domain [12], whereas the cytoplasmic domains of SLAMF8 and SLAMF9 are short and do not contain ITSM sequences [13].

One of the most interesting and unique features of the SLAMF members is that they act as self ligands, interacting with one another in a homotypic manner, with exception of SLAMF2 whose ligand is SLAMF4 and CD2, albeit with lower affinity. Upon SLAMF engagement, the ITSM sequence recruits its adaptor molecules SLAM-associated protein (SAP) or Ewing's sarcoma's/FLI1-activated transcript 2 (EAT-2) to mediate downstream signaling [10,12].

Genome-wide analysis studies (GWAS) have identified at least 50 loci conferring to lupus susceptibility [14]. Studies using gene mapping methods conducted during the early 2000s [15,16] identified the 1q23 chromosomal region, which encodes for the SLAMF receptors, as a highly polymorphic region and as a susceptibility locus for SLE. Moreover, studies in different murine models of spontaneous autoimmunity (NZB/WF1, NZM, BXSB strains) showed a strong connection between the genomic 1H3 region, which in mice is the syntenic genomic region of human 1q23, and severe lupus manifestations [17–19]. In humans, single nucleotide polymorphisms and specific SLAMF variants have been associated with rheumatoid arthritis, neuropsychiatric SLE and lupus nephritis, thus further highlighting the importance of 1q23 region and potential involvement of SLAMF members in systemic autoimmunity [20–23].

To this date, only a limited number of studies have systematically addressed the expression of SLAMF receptors and/or the *in vitro* effect of specific anti-SLAMF monoclonal antibodies on SLE T and B cells [24–31]. In this review, we present current data and future directions on the role of SLAMF members in SLE (Table 1).

2. SLAMF1

T cells, B cells and dendritic cells express SLAMF1, while SLAMF1 is not expressed by monocytes and NK cells [32,33]. On T cells, and especially on CD4+ T cells, SLAMF1 expression increases with cell differentiation, displaying a low level of expression on naïve cells and higher levels of expression on effector and memory cells [24]. SLAMF1 is also upregulated following T and B cell activation, suggesting that the expression of this receptor may reflect the activation status of several leucocyte populations [32,34].

Increased SLAMF1 levels have been described in T cells, mostly on memory CD4+ T cells, from patients with SLE compared to healthy subjects [24,26]. Elevated SLAMF1 levels are also detected on lupus CD8+ T cells and B cells, especially B cells within the naïve cell compartment [24,26]. Data regarding the function of SLAMF1 on SLE T cells are limited. In a study by Linan-Rico et al., authors examined the role of SLAMF1 engagement on regulatory T cells (Tregs) and demonstrated that co-engagement of SLAMF1 with an anti-SLAMF1 monoclonal antibody increases SLE Tregs suppressive function [26].

Regarding B cells, it is worth noting that SLAMF1 engagement on healthy human B cells, using a recombinant form of soluble or membrane bound SLAMF1, promotes B cell proliferation and immunoglobulin production [34]. A recent paper suggests that a monoclonal antibody directed against SLAMF1 might play a role in inhibiting B-T cells interaction [35]. Indeed, authors have emphasized that, in the presence of an anti-SLAMF1 antibody, B cells are no longer able to form conjugates with T cells, thus inhibiting their role as APC. Moreover, ligation of SLAMF1 on B cells also has a direct co-inhibitory effect on IL-6 production, thus reducing the production of IL-6 by B-cells, a key cytokine involved in SLE inflammation and in T cells differentiation. According to these findings, monoclonal antibodies directed against SLAMF1 may represent an interesting target for SLE and other autoimmune diseases, where B-T cell interaction plays a pivotal role.

3. SLAMF2

From a structural point of view, SLAMF2 is unique compared to the rest of the SLAMF members in that it does not possess a cytoplasmic tail, yet upon interaction with SLAMF4 or CD2 it elicits downstream signaling in a mechanism that still remains unclear [36]. SLAMF2 is an integral component of the lipid rafts. Its co-engagement enhances early TCR-initiated responses by facilitating actin cytoskeleton reorganization and recruitment of associated lipid rafts to the TCR associated activation cap [37]. Moreover, studies from the early 2000s demonstrated that lipid rafts exist in a pre-aggregated form in lupus T cells, thus contributing to the rapid signaling responses and elevated calcium flux that characterize SLE T cells [38]. In patients with SLE, SLAMF2 expression is increased on naïve and on all differentiated subsets of CD4+ and CD8+ T cells [24]. In agreement with this, earlier studies documented increased SLAMF2 mRNA expression in CD4+ T cells isolated from patients with SLE [39]. Whether increased SLAMF2 levels in lupus T cells are involved in the pre-clustering of lipid rafts remains to be investigated. Another important function of SLAMF2 entails the stabilization of the SLAMF2/CD2 interaction and the maintenance of optimal distance between antigen presenting cells and T cells upon antigen presentation [40]. In addition, SLAMF2 serves as a survival molecule for DNA-activated human dendritic cells during their interaction with SLAMF4-expressing cells *in vitro*, thus prolonging the time frame of effective stimulation of T cells by antigen presenting cells [41].

Table 1
Expression and function of SLAMF receptors in human SLE.

SLAMF member	Expression levels in SLE compared to healthy controls	Effect of SLAMF receptor ligation with mAb	Ref
SLAMF1 (CD150, SLAM)	Increased expression on CD4 and B	Inhibits T-B cells interaction. Decreases IL-6 production by B cells. Increases Tregs suppressive function	[24,26,35]
SLAMF2 (CD48)	Increased expression on CD4 and CD8. Increased expression on CD56bright NK cells.	Potential role in the stabilization of the immunologic synapse between APC and T cells	[24,40,41,45]
SLAMF3 (CD229, Ly9)	Increased expression on naive CD4 and naive CD8. Decreased expression on NK cells.	Enhances CD4 cells IL-2 response, promotes Tregs differentiation and CD4 proliferation	[24,27,45]
SLAMF4 (CD244, 2B4)	Decreased expression on differentiated subsets of CD8, DN, NK, monocytes, platelets	Contradictory data on CD8 and NK activation and degranulation	[24,28,29]
SLAMF5 (CD84)	No significant difference observed on T and B. Decreased expression on pDC	Increases IFNγ production by T cells	[24,25,45,57]
SLAMF6 (CD352, NTBA, SF2000)	No significant difference observed	IL-17 (low mAb concentration) and/or IFNγ/TNFα (high mAb concentration) production by CD4	[24,25,30,31]
SLAMF7 (CD319, CS1, CRACC)	Decreased expression on differentiated subsets of CD8 and pDC. Increased expression on CD56bright NK cells	Enhances CD8 cytotoxicity in response to viral antigens	[24,25,45,55]
SLAMF8 (CD353, BLAME)	Unknown	Unknown	
SLAMF9 (CD84-H1, SF2001)	Unknown	Unknown	

4. SLAMF3

The extracellular segment of SLAMF3 is slightly different compared to other SLAMF members, being composed of four Ig-like domains (2 tandem repeats of V-like regions and C2-like regions) [12]. Recent data in humans have shown that SLAMF3 is expressed at a high level on CD4+, CD8+, double negative (DN) T cells, B cells and, at a lower level, on NK cells [24,27]. On CD4+ and CD8+ T cells, SLAMF3 expression has been observed on every differentiated CD4+ and CD8+ T cell subset from naïve to effector memory [24]. By contrast, SLAMF3 is not expressed on granulocytes, red cells and platelets [32,42].

Studies have suggested an involvement of SLAMF3 in the pathogenesis of SLE. SLAMF3 deficient mice develop spontaneous SLE-associated antibodies and show a decreased proliferation of T cells as well as a compromised antigen-driven IL-2 production [43,44]. More importantly, polymorphisms have been described in the SLAMF3 gene in SLE families [20,21]. At the protein level, there is a small difference in the expression of SLAMF3 on T cells isolated from SLE patients in comparison to healthy controls, with only a slight increased expression on the surface of naïve CD4+ T and naïve CD8+ T cells [24,27]. No difference in the expression of SLAMF3 was detected on memory or effector SLE T cells as compared to healthy subjects [24,27]. Despite low levels of expression on NK cells, a significant reduction of SLAMF3 expression was described on NK cells from SLE patients [45].

SLE is characterized by an impaired production of IL-2 by T cells, a crucial cytokine for the differentiation and function of Tregs. In lupus prone mice, low IL-2 availability is associated with a decreased number of Tregs while disease progresses [46]. In human SLE, currently available data on Tregs are conflicting, potentially due to lack of uniformed phenotypic markers of human Tregs and because some Tregs markers – such as CD25 and FoxP3 – can also be transiently expressed by activated conventional T cells (Tconv) [47]. Nevertheless, recent studies showed that Tregs function may be impaired in SLE, as expression of CD25 has been shown to be reduced in SLE and SLE first-degree relative [44]. Furthermore, it has been observed that upregulation of CD25 in response to naïve Tregs activation is impaired in SLE patients compared to controls [48]. Moreover, a recent study emphasized that not only IL-2 production but also IL-2 signaling pathway is defective in CD4+ T cells from SLE patients [49], as JAK3 and STAT5 phosphorylation in response to IL-2 are reduced in SLE.

Engagement of SLAMF3 with a monoclonal antibody can improve IL-2 sensitivity of CD4+ T cells in SLE [27]. More specifically, activation of SLAMF3 enhances the phosphorylation of the transcription factor Smad3, which in turn binds the promoter region of the IL-2 receptor subunit alpha (CD25) thus promoting its transcription. This process further promotes the activation of the IL-2/IL-2R/STAT5 pathway (Fig. 1). Additionally, activation of SLAMF3 on naïve CD4+ T cells plays a role in the balance of Tregs/Tconv differentiation. In fact, T cells that are differentiated in the presence of an anti-SLAMF3 monoclonal antibody develop a suppressive phenotype and phenotypic markers of induced Tregs (iTregs), while differentiation of Th1, Th2 and Th17 effector cells is inhibited [27].

Recently, low-dose IL-2 (1 to 3 × 10^6 IU per day) was reported to be beneficial for SLE clinical symptoms in the context of non-controlled small clinical studies [50–52]. Examination of the peripheral blood mononuclear cells (PBMC) from patients receiving low-dose IL-2 showed an increased number of Tregs and a decreased proportion of Th17, T follicular helper and DN T cells [52]. These data need to be confirmed in a controlled prospective study. In this setting, drugs that enhance SLAMF3 signaling, and especially monoclonal antibodies, could be beneficial in SLE and in other diseases where either IL-2 availability is impaired or IL-2R expression or IL-2 signaling are decreased.

5. SLAMF4

Compared to other SLAMF receptors, SLAMF4 does not interact through a homophilic interaction, but is activated after it binds SLAMF2, its natural ligand. SLAMF4 expression is mainly reported on cytotoxic cells. On CD8+ T cells, its expression is up-regulated while cells acquire a differentiated phenotype, with almost 100% of terminally differentiated effector memory cells expressing SLAMF4 [24,28]. To some extent, it follows the expression pattern of immune inhibitory receptors, such as PD-1, lymphocyte-activation gene 3 (LAG-3) and CTLA-4. CD8+ T cells that are positive for SLAMF4 display an effector phenotype, as they express cytolytic enzymes (granzyme B, perforin) and produce cytokines (TNFα, IFNγ, IL-2) in response to stimulation. In the context of SLE, most studies evaluating SLAMF4 described a decreased expression of the receptor compared to healthy controls. This reduced expression was observed on the surface of SLE-CD8+ T cells, DN T cells, NK cells, monocytes and platelets [24,28,29]. Furthermore, two different isoforms of SLAMF4 have been identified [53]. An analysis of total PBMC isolated from SLE patients has shown that the ratio of the two splice variants is altered in SLE patients compared to healthy controls, thus suggesting that splicing of SLAMF4 is regulated differentially in SLE patients [29].

At a functional level, initial experiments using monoclonal antibodies or membrane-bound forms of SLAMF4 suggested that it may function as a co-stimulatory molecule, promoting NK and CD8+ T cell proliferation, activation and degranulation. However, data also exist demonstrating an inhibitory role following SLAMF4 ligation on these same cell types. Although the mechanism of this dual function needs to be clarified, it may depend on the relative abundance of SAP family adaptors over SH2 domain inhibitory phosphatase in the cell cytoplasm (reviewed in [11]). Furthermore, the abundance of SLAMF2, the natural ligand of SLAMF4, on the target cell has also been proposed to play a role on the dual function of SLAMF4 [11].

Few studies have evaluated the function of SLAMF4 in SLE. Some studies focused on its role on cytotoxic CD8+ T cells, a T lymphocyte subset that has been invariably described as defective in SLE [54,55]. Compared to healthy controls, CD8+ T cells from SLE patient express lower amounts of SLAMF4, thus decreasing the ratio of SLAMF4+ *vs* SLAMF4- CD8+ T cells [24,28,29]. SLAMF4 negative cells display a poor cytotoxic capacity and impaired proliferation in response to viral antigen, thus contributing to the increased rate of infection observed in SLE patients, one of the leading causes of mortality [28]. Moreover, it is speculated that SLAMF4-CD8+ T cells will give rise to DN T cells, a T lymphocyte subset involved in SLE pathogenesis and organ damage [28]. The role of SLAMF4 in SLE requests further clarification and especially its role on the function of NK cells whose function is also impaired in SLE [56].

6. SLAMF5

SLAMF5 is expressed on all hematopoietic cells [12]. Data regarding the role of SLAMF5 in SLE are limited and mostly focused on its expression on cells of innate and adaptive immunity. T cells isolated from patients with biopsy-proven lupus nephritis displayed decreased expression of SLAMF3, SLAMF5 and SLAMF7 on the cell surface of CD8+ and DN in patients who were in remission compared to patients with active nephritis [25]. Decreased expression of SLAMF5 has also been reported on circulating plasmacytoid dendritic cells (pDC) from patients with SLE [45]. Yet, others did not find differences in the levels of SLAMF5 expression on T cells and B cells from SLE patients and healthy controls [24]. From a functional point of view, there are reports suggesting that ligation of SLAMF5 with monoclonal antibodies or SLAMF5-Ig fusion protein and CD3 enhances IFNγ secretion by human T cells [57] and thus functions as a survival factor for chronic lymphocytic leukemia cells [58]. It was also recently shown that SLAMF5 co-engagement with a monoclonal antibody on human monocyte-

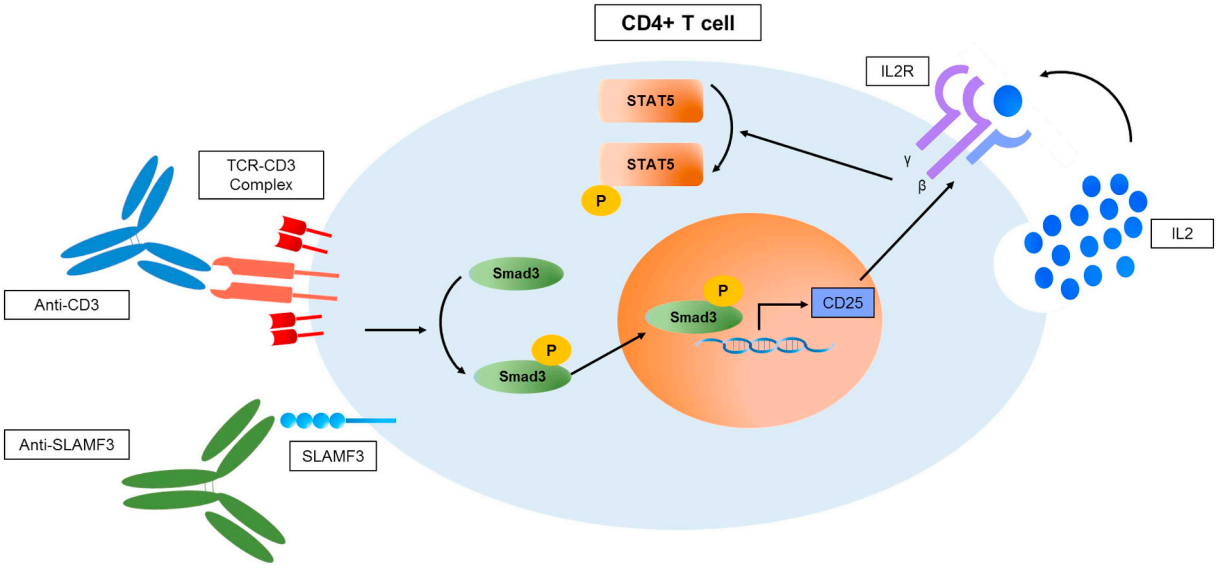

Fig. 1. SLAMF3 engagement on SLE CD4+ T cells restores IL-2 signaling.
Co-engagement of the TCR-CD3 complex together with the co-receptor SLAMF3 using a specific monoclonal antibody leads to the phosphorylation of the transcription factor Smad3. The phosphorylated Smad3 enters the nucleus and binds to the promoter region of CD25, thus increasing the expression of the IL-2 receptor alpha sub-unit on the cell surface. Binding of IL-2 to its receptor, in an autocrine fashion, allows STAT5 phosphorylation, which subsequently activates the downstream signaling pathway. Through this process, SLAMF3 restores the SLE CD4+ T cells sensitivity to IL-2 to normal levels.

derived dendritic cells enhances autophagy and regulates IL-1β, IL-23 and IL-12 production by inhibiting proteolytic degradation of interferon regulatory factor 8 (IRF8) [59].The potential pathophysiological significance of the above findings in SLE remains to be examined.

7. SLAMF6

Most studies evaluating expression levels of SLAMF6 on hematopoietic cells did not detect any significant differences between SLE and healthy donors. Moreover, few studies assessed its function in humans or SLE in particular [24,30]. In one study, which focused on a small cohort of SLE patients, an increased expression of SLAMF6 on T cells has been reported and co-engagement of SLAMF6 with a specific anti-SLAMF6 monoclonal antibody has been associated with increased TNFα, IFNγ and IL-17 cytokine production by normal and SLE T cells [30,31]. Further studies are warranted in order to draw definitive conclusions regarding potential implications of SLAMF6 in lupus.

8. SLAMF7

SLAMF7 is expressed on NK cells, NK T cells, CD8+ T cells, DN T cells, plasma cells, macrophages and dendritic cells [10,60]. On CD8+ T cells, SLAMF7 follows a similar pattern of expression to SLAMF4, which is a high expression level on effector memory and terminally differentiated effector memory cells, while its expression is low on naïve CD8+ T cells [24,61]. The frequency of SLAMF7 expressing CD4+ T is very low (less than 5%), whereas almost 100% of NK cells are positive for SLAMF7 [24,29,45,61]. As for SLAMF4, SLAMF7 is co-expressed on cells displaying cytotoxic effector capacity: SLAMF7 expressing cells also express cytolytic enzymes (granzyme A and B, perforin), produce cytokines (TNFα, IFNγ, IL-2) in response to stimulation and display a strong proliferative capacity [61]. On the contrary to SLAMF4, SLAMF7 is barely expressed by monocytes [24]. In addition to its exclusive pattern of expression, SLAMF7 has other features that distinguish it from other SLAMF receptors [62]. Firstly, SLAMF7 presents the unique feature of having only one ITSM in its intracellular domain. Secondly, two different isoforms of SLAMF7 have been identified and show different signaling properties and function. Finally, SLAMF7 binds to the adaptor protein EAT-2, but not to SAP.

Recent observations indicated that SLAMF7 could be a potential target for specific monoclonal antibodies at the onset of human diseases. Indeed, because of its high level of expression on plasma cells compared to other leucocytes, SLAMF7 was examined in patients suffering from multiple myeloma, a malignant hematologic disorder [63]. Malignant plasma cells were shown to express high levels of SLAMF7 and treatment of these patients with elotuzumab, a specific monoclonal antibody directed against SLAMF7 is an efficient therapeutic option in some patients [11]. The mechanism by which anti-SLAMF7 antibody kills malignant plasma cells is not completely understood. However, it seems that SLAMF7 promotes NK cells antibody-dependent cell-mediated cytotoxicity, as well as NK cells direct cytotoxicity against tumor cells [63,64]. Moreover, a potential contribution of CD8+ T cells activation by elotuzumab in the onset of multiple myeloma treatment has not been thoroughly assessed yet, but activation of these cells could play a role in the anti-tumoral immune response.

SLAMF7 expression is significantly reduced on CD8+ T cells isolated from SLE patients compared to healthy donors [24,61]. Ligation of SLAMF7 with a monoclonal antibody enhances degranulation and cytotoxic CD8+ T cells response against viral antigens in healthy controls and patients with SLE (Fig. 2) [61]. This finding is of interest as CD8+ T cell function is impaired in SLE patients and infections are the leading cause of morbidity and mortality in SLE. Finally, yet importantly, SLAMF7 signaling in CD8+ T cells requires further clarification. Indeed, SLAMF7 recruits the SH2 adaptor protein EAT-2 in NK cells to initiate the cytotoxic response, an adaptor molecule that is not expressed in CD8+ T cells [61]. How SLAMF7 mediates downstream signaling in CD8+ T cells remains to be elucidated.

Few data are currently available on the role of SLAMF7 in SLE NK cells. In one study, a decreased expression of SLAMF7 was shown on SLE CD56 bright NK cells compared to healthy controls, while no difference was observed on CD56dim NK cells [45]. As NK cells function is impaired in SLE [56], it would be of interest to further investigate this aspect. SLAMF7 expression has not been examined yet on SLE plasma cells, because of a limited access to secondary lymphoid organs in these patients. Nevertheless, expression levels of SLAMF7 on SLE B cells isolated from the periphery remains very low compared to other leucocytes types. In one paper, authors showed a higher level of SLAMF7 expression in SLE B cells as compared to healthy controls [29], a finding

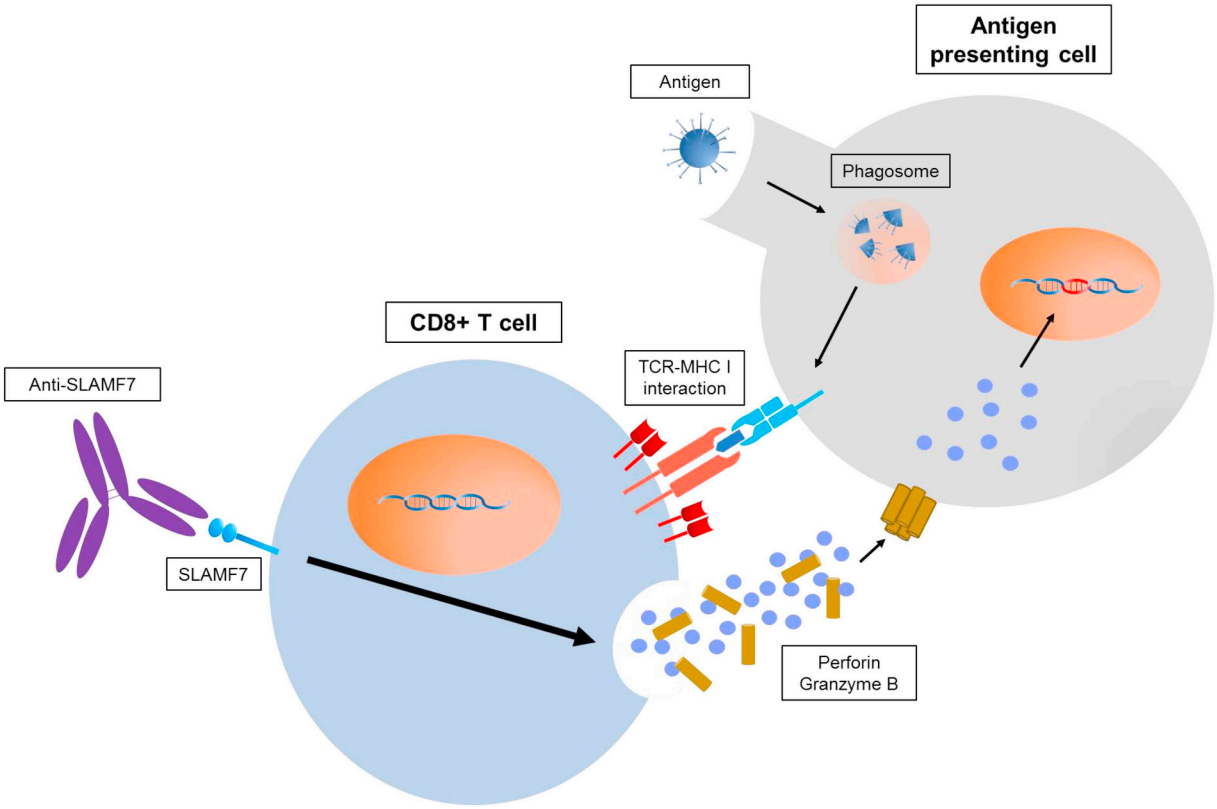

Fig. 2. SLAMF7 engagement on SLE CD8+ T cells restores the cytotoxic response.
Antigen presenting cell (APC) processes foreign protein (for instance viral antigen) to present an antigen, which is associated to class I MHC to CD8+ T cells. The simultaneous engagement of SLAMF7 with a specific monoclonal antibody enhances SLE CD8+ T cells impaired degranulation, thus allowing cytotoxic lysis of the infected cell.

that was not confirmed in other studies [24]. Moreover, an increased expression of SLAMF7 was observed on SLE pDC as compared to controls [45].

9. SAP

Upon engagement, SLAMF receptors interact with SAP (SLAM associated protein, SH2D1A), a highly conserved, non-polymorphic cytoplasmic SH2-domain-containing molecule [12]. It is predominantly expressed in T cells, NK cells, NKT cells, eosinophils and platelets.

Absence or loss-of-function mutations of SAP result in a rare primary immunodeficiency, known as XLP (X-linked lymphoproliferative disease) [12]. Fulminant infectious mononucleosis is the most common clinical presentation of XLP and is characterized by excessive proliferation of EBV-infected B cells and cytotoxic T cells, other patients develop secondary hemophagocytic lymphohistiocytosis. Patients who survive, display dysgammaglobulinemias, defective NK function and may develop lymphomas.

T cell lines from SAP-deficient patients display abnormal TCR-elicited responses characterized by increased tyrosine phosphorylation levels, elevated $[Ca^{2+}]i$ response and compromised IL-2 production [65,66], a pattern of response reminiscent of the one observed in SLE T cells [67,68]. A similar response was obtained when SAP was silenced in T cells isolated from healthy controls [69].

Aberrant expression of SAP levels has been described in patients with SLE, although results are conflicting. One study reported increased levels of SAP in CD4+ T cells in a cohort of Chinese patients with SLE [70]. In another study, reduced SAP protein and mRNA levels were observed in T cell subsets isolated from the peripheral blood of patients with SLE compared to healthy controls. Forced expression of SAP in lupus T cells resulted in correction of the hyper-responsive phenotype and restored production of IL-2 to normal levels [69]. In light of these data, further studies are warranted to clarify the potential involvement of SAP in autoimmunity in humans.

10. Conclusions

Members of the SLAM family of co-receptors appear to play an important role in immune regulation involved in autoimmune diseases and more specifically in SLE. Recent findings emphasize that SLAMF molecules may be implicated in the mechanisms involved in the proliferation, differentiation and maintenance of hematopoietic cells, especially lymphocytes, by playing a role as co-stimulatory or co-inhibitory molecules that regulate cell fate after activation. SLAMF is a complex and redundant system that encompasses at least 9 molecules. Most studies available focus on one specific SLAMF receptor at a time, thus not giving an exhaustive overview of this complex family of molecules at a single cell level. The SLAMF system is further elaborated by the presence of different adaptor molecules, whose expression differs from one hematopoietic cell type to another. These adaptor molecules play a major role in the SLAMF integrated activating or inhibitory signals delivered by SLAMF receptors. Recently, it has been demonstrated that each hematopoietic cell expresses three to five different SLAMF molecules simultaneously.

Assessing all different SLAMF molecules at single cell level was until recently not possible due technical limitations inherent to flow cytometry. New technologies allowing the examination of up to 40 parameters, using mass cytometry, should allow to counteract this problem.

More importantly, SLAMF receptors could represent a valuable therapeutic target in the onset of autoimmunity. From this point of view, a monoclonal antibody directed against SLAMF7, elotuzumab, has been successfully used in the onset of multiple myeloma and was

shown to be safe and well-tolerated. This emphasizes that SLAMF molecules can be targeted to treat human diseases. It would be of interest to further evaluate the potential role of SLAMF7 ligation in the onset of SLE, as CD8+ T cells, as well as NK cells, have been shown to have an impaired function in this disease. This might at the same time restore cytotoxic cell function and promote anti-microorganism adaptive immune response. More careful studies of SLAMF7 expression, as well as usage of anti-SLAMF7 monoclonal antibodies in autoimmunity animal models are warranted in order to move forward on this aspect.

Recent data on SLAMF3 are also of interest, as SLAMF3 has been shown to enhance IL-2 response of CD4+ T cells, thus favoring iTregs differentiation, while inhibiting Th1, Th2 and Th17 cell differentiation. If this phenomenon can be confirmed *in vivo*, engagement of SLAMF3 may become a novel therapeutic option in patients suffering from autoimmune diseases.

In this light, research on SLAMF receptors is a fascinating and promising field that deserves further characterization in the onset of autoimmune diseases and especially SLE, where a better understanding of the underlying pathophysiology, as well as development of less toxic and more efficient treatment are essential.

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