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The role of the SLAM-SAP signaling pathway in the modulation of CD4+ T cell responses

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Abstract

The signaling lymphocytic activation molecule (SLAM), present on the surface of hematopoietic cells, can regulate some events of the immune responses. This modulatory action is associated with the capacity of SLAM to interact with an intracytoplasmic adapter, such as SLAM-associated protein (SAP). SLAM is constitutively expressed in most of these cells, is rapidly induced after antigenic or inflammatory stimuli, and participates in the immunological synapse. Defects in the function of the SLAM-SAP pathway contribute to immunological abnormalities, resulting in autoimmune diseases, tumors of the lymphoid tissues and inadequate responses to infectious agents. Initially, the role of SLAM was investigated using an anti-SLAM monoclonal antibody (α-SLAM mAb) identified as an agonist of the SLAM-SAP pathway, which could induce the production of interferon-γ and could redirect the immune response to a T helper 1 (Th1) cell profile. However, in this review we postulate that the SLAM-SAP pathway primarily induces a Th2 response and secondarily suppresses the Th1 response.

Key words: SLAM; SAP; IFN-γ; Immunoreceptor; Immunomodulation

Introduction

The response of the cells of the immune system is controlled by the equilibrium of signals received by a large number of cell surface receptors, among them the activation receptors, co-stimulatory molecules and inhibitory molecules (1,2). Binding of immunoreceptors by their ligands induces a tyrosine phosphorylation signal that is essential for cell activation. Although immunoreceptors such as the T cell receptor (TCR) and the B cell receptor have no intrinsic protein tyrosine kinase activity, they associate with subunits bearing immunoreceptor tyrosine-based activation motifs in their intracellular domain (3). Signaling through the immunoreceptors alone is not sufficient for the activation of gene transcription. The amplification of the signal is also necessary. Therefore, co-receptors and co-stimulatory molecules come into play. Evidence indicates that receptors of the signaling lymphocytic activation molecule (SLAM) family and a group of intracellular adapter proteins, chiefly SLAM-associated protein (SAP) among them, are involved in the modulation of the immune responses (2-5). Following the activation of T lymphocytes, the SLAM-SAP signaling pathway exerts an important function in inducing the expression of the T helper 2 (Th2) cytokine (6), in the production of antibodies, in the generation of memory B cells, in the activation as well as the inhibition of natural killer (NK) cells, and in the development of natural killer T (NKT) cells (3).

The family of receptors related to SLAM

The SLAM family of receptors is a subgroup of the immunoglobulin super family, which regulates the function of T cells, B lymphocytes, macrophages, and mature dendritic cells (2-7), thereby influencing both the innate and the adaptive immune responses. These families include nine receptors (3,4,6,8-11) (Table 1).

All members of the SLAM family have a structure uncommon in the extracellular region. It is characterized by a variable Ig-like N-terminal domain (V) and a constant

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type 2 Ig-like C-terminal domain (C2), except for CD229 (Ly-9), which has a V-C2 domain, a transmembrane region, and a cytoplasmic portion containing tyrosine-based motifs (8).

The action of the SLAM family of receptors results in the phosphorylation of these molecules by protein kinases of the Src family (12). These receptors also function as their own ligands, with the exception of 2B4, which is involved in homotypic and heterotypic cell-cell interactions (8,12). Each receptor initiates a signal whose end result will depend on the disposition of the tyrosine motifs in their cytoplasmic domain, their amino acid sequence and the types of amino acids they contain (13).

The genes encoding the receptors related to SLAM are located on chromosome 1, at the SLAM locus, in both humans and mice, with the exception of CD2, which is located on chromosome 3 (4,14). These receptors have been implicated in the physiopathology of autoimmunity. The Sle1b region confers a greater susceptibility to systemic lupus erytematosus in mice, and corresponds to the region of the gene of the SLAM family (15). Polymorphisms in this particular region have been associated with human systemic lupus erythematosus (16).

The signaling lymphocytic activation molecule

The SLAM was initially identified in human cells as IPO-3, a cell surface glycoprotein that was expressed in cells of the immune system (17,18) and was later cloned (A12) and named the SLAM (19). This receptor has a molecular mass of 70 kDa and is made up of 335 amino acids. Its structure includes an extracellular portion containing 202 amino acids, a transmembrane region with 22 amino acids and a cytoplasmic region with 77 amino acids. The cytoplasmic portion has a domain containing three motifs with tyrosine residues Y^{281}, Y^{307}, and Y^{327}. The motif that contains tyrosine residue Y^{281} shows a greater affinity for SAP (20). The tyrosine-based motifs are constituted by the consensus amino acid sequence TxYxxV/I, where

Table 1. Expression, ligands and effects of the signaling lymphocytic activation molecule (SLAM) family of receptors in hemopoietic cells.

SLAM family of receptors	Expression	Ligand(s)	Effects
SLAMF1 (SLAM, CD150, IPO-3)	Thymocytes, macrophages, monocytes, mature dendritic cells, platelets, B cells, T cells, hematopoietic stem cells	Self-ligand, measles virus	$CD4^+$ T cells: ↑ IL-4 secretion
			Macrophages: ↑ IL-12, TNF-α production
SLAMF2 (CD48)	B cells, T cells, monocytes	SLAMF4	T cells: ↓ IL-2, ↓ IFN-γ production and ↓ proliferation
SLAMF3 (CD229, Ly-9)	B cells, T cells, some thymocytes, NK cells, NKT cells	Self-ligand	T cells: ↓ IL-4 and ↓ proliferation
SLAMF4 (2B4, CD244)	NK cells, T cells, memory $CD8^+$ T cells, monocytes, basophils, eosinophils, mast cells	SLAMF2	NK cells: ↑ IFN-γ and cytotoxicity
			$CD8^+$ T cells: immune synapse formation, ↑ IFN-γ and ↑ IL-2
			Eosinophils: ↑ cytotoxicity, ↑ cytokines
SLAMF5 (CD84, Ly-9b)	Most thymocytes, B cells, T cells, NKT cells, mast cells, monocytes, macrophages, dendritic cells, neutrophils, basophils, eosinophils, platelets, human hematopoietic stem cells	Self-ligand	T cells: ↑ IFN-γ production and ↑ proliferation
			Platelet dispersion
SLAMF6 (NTB-A, SF2000)	B cells, T cells, NK cells	Self-ligand	Human NK cells: ↑ IFN-γ production and ↑ cytotoxicity
			$CD4^+$ T cells: ↓ IFN-γ
SLAMF7 (CRACC, CS1, 19A)	B cells, T cells, NK cells, mature dendritic cells	Self-ligand	NK cells: ↑ IFN-γ production and ↑ cytotoxicity
			T cell: ↑ IFN-γ production
SLAMF8 (BLAME)	Macrophages, dendritic cells	Unknown	Unknown
SLAMF9 (CD2F-10, SF2001)	B cells, T cells, macrophages, dendritic cells	Unknown	Unknown

NTB-A = natural killer, T and B cell antigen; CRACC = CD2-like receptor activating cytotoxic cells; BLAME = B lymphocyte activator macrophage expressed; NK cells = natural killer cells; NKT cells = natural killer T cells (3,4,6,8-11). ↑ = increase; ↓ = decrease.

T corresponds to threonine, Y to tyrosine, V to valine, I to isoleucine, and x to any other amino acid residue (8). SLAM has the capacity to interact in a homotypic way at the level of its extracellular domains, but with a low affinity (8,12), and functions through a bidirectional signaling after SLAM-SLAM binding (19,21).

Four SLAM isoforms have been identified thus far, all originating from the selective elimination of exons - splicing. Two of these are composed of 305 amino acids and correspond to the transmembrane extension and the other two are cytoplasmic, with one being soluble. The soluble form of SLAM is capable of interacting with SLAM expressed on the cell membrane surface, influencing the immune response (18).

The expression of SLAM is demonstrated in the cells of innate as well as adaptive immunity (1), such as thymocytes, monocytes, macrophages, dendritic cells, B and T lymphocytes, NK cells, granulocytes, and platelets, in both human and murine models (8,17,18). In the majority of these hematopoietic cells, the expression of SLAM occurs constitutively, being rapidly induced in T and B lymphocytes in viral infections, and in dendritic cells by antigenic (22) or inflammatory stimuli, such as lipopolysaccharide and interleukin-1β (IL-1β) (23), and in macrophages activated by LPS and interferon-γ (IFN-γ) (8,19,24). The expression of this molecule was also observed in hematopoietic cells of the bone marrow, liver of fetal mice (25), ganglia, spleen and tonsils, as well as in a particular subpopulation of endothelial cells (14).

SLAM has been considered to be the principal receptor of measles virus, contributing to the lymphotropic characteristic of this infectious agent, which induces lymphopenia (26) and immunosuppression (27). Other agents, such as morbilliviruses, also utilize this molecule as a receptor (14).

SLAM promotes the adhesion between T lymphocytes and antigen-presenting cells, participating in the formation of the immunological synapse, principally in the co-stimulation dependent on TCR (4,12,19). This co-stimulator also modulates the production of cytokines by $CD4^+$ T lymphocytes, macrophages and dendritic cells, where their actions differ depending on the type of stimulus (6). An increase in the expression of SLAM has been observed in autoimmune diseases such as experimental murine lupus (16) and human multiple sclerosis (28). Greater concentrations of soluble forms of SLAM have been detected in the synovial fluid of patients with rheumatoid arthritis (29). There is evidence that SLAM causes an amplification of the secretion of Th2 cytokines in allergic responses (30). Also, a study evaluating patients with tuberculosis showed that the activation of SLAM induces the phosphorylation of the transcription factor cAMP response element-binding protein (CREB) (31) and the production of IFN-γ (32).

The family of adapters related to SAP

The molecules of adapters related to SAP represents a family of cytoplasmic proteins composed of a single Src homology 2 (SH2) domain and a small carboxy-terminal region (33). It has been suggested that this carboxy-terminal region of SAP can be associated with the stability of this molecule (2). These proteins are involved in the pattern of intracellular signaling, principally in the regulation of the process of lymphocyte activation (11,34), and modulate the activity of various members of the family of SLAM receptors (20).

This family includes 3 members (3,6,9-11) (Table 2). In mice and humans, chromosome 1 harbors the genes encoding EAT-2 in the regions 1q22 and ERT, next to the SLAM locus, while the SAP gene is located on the long arm of chromosome X, in the Xq25 region (33,35).

The expression of SAP, or its mRNA, has been detected in thymocytes, T lymphocytes, NK cells, and NKT

Table 2. Expression of the signaling lymphocytic activation molecule (SLAM) family of receptors and effects of the SLAM-associated protein (SAP) family of adaptors on hemopoietic cells.

SAP family of adaptors	Expression	SLAM family of receptors associated	Effects
SAP	Human thymocytes, T cells, mature human and mouse NK cells, NKT cells, some B cells, eosinophils, platelets	SLAMF1, 3, 4, 5, and 6	↑ IL-4 secretion, GC formation
			Human NK cells activation
			NKT cell development
			$CD8^+$ T cell activation
EAT-2	Mature human NK cells, mouse NK, dendritic cells, T cells activated, human B cell lines, macrophages, platelets	SLAMF1, 3, 4, 5, 6, and 7	NK cells downregulation
ERT	Mature mouse NK cells (human pseudogene)	SLAMF4	NK cells downregulation

EAT-2 = Ewing's sarcoma-activated transcript-2; ERT = EAT-2-related transducer; NK cells = natural killer cells; NKT cells = natural killer T cells (3,6,9-11). ↑ = increase.

lymphocytes, as well as in platelets, eosinophils (36-38), and some B lymphocytes (36). Other reports have shown this expression in neuronal cells, proliferative nodules of chronic lymphocytic leukemia (39) and germinal centers of angioimmunoblastic T cell lymphoma (40).

The SLAM-associated protein

The SAP has a molecular mass of 15 kDa, is composed of 128 amino acids, with a single SH2 domain (34) and a carboxy-terminal region of 24 to 26 amino acids. The SH2 domain has two binding surfaces; one of the surfaces interacts with a tyrosine-based motif, i.e., immunoreceptor tyrosine-based switch motif (ITSM) (41) in the cytoplasmic portion of SLAM, via the region containing an arginine at position 32 (Arg32) (33,35), while the other, with arginine at position 78 (Arg78), binds to the SH3 domain of tyrosine phosphokinase (11,33).

The protein adapter related to SAP binds with high affinity, through its SH2 domains, to tyrosine-based motifs located in the cytoplasmic domains of the receptors of the SLAM family (21,42). SAP is involved in the transduction of intracellular signals, interacting with the cytoplasmic tail of SLAM through its SH2 domain and thereby blocking the binding of proteins with this region, independent of phosphorylation (2,4,5,43). In addition, SAP promotes the recruitment and enzymatic activation of protein tyrosine kinase Fyn T, inducing the phosphorylation of the cytoplasmic domain of SLAM and allowing the propagation of events of the signaling cascade (20,42). In neural cells, SAP exerts its role through the recruitment of protein kinases related to tropomyosin (39).

The engagement of SAP in the signaling pathway through SLAM influences the immune response, resulting in the production of IL-4, formation of germinal centers, activation of human NK cells, development of NKT lymphocytes, and activation of the regulator of $CD8^+$ T lymphocytes (6).

Mutations or deletions of the SH2D1A gene lead to an X-linked lymphoproliferative syndrome (4,33,35,44), a primary immunodeficiency characterized by an elevated susceptibility to infection by Epstein-Barr virus (33), with a high risk for the development of fulminant infectious mononucleosis, B cell lymphoma and dysgammaglobulinemia (4,24).

The deletion of the gene that encodes SAP, depending on the immune system cells involved, can result in a reduction of Th2 cytokines, the cytotoxicity of NK and $CD8^+$ cells, the formation of the germinal centers, and the production of T lymphocyte-dependent antibodies (5,6,36,45,46).

$SAP^{-/-}$ mice show a deficiency in antitumor immunity and immune responses to viral infection, and can even display a tendency towards hypogammaglobulinemia (5,47). These animals fail to adequately control infections due to the development of defects in cell-mediated immunity such as the increase in the proliferation of antigen-specific $CD4^+$ and $CD8^+$ lymphocytes. After a stimulus with lymphocytic choriomeningitis virus, *Leishmania major* or *Toxoplasma gondii*, these mice display a cytokine response of the Th1 phenotype. Despite surviving the acute infection by lymphocytic choriomeningitis virus, these animals show high mortality due to the lack of an intense and prolonged Th1 response, as is generally demonstrable in the spleen and liver cells of animals infected with these agents (48).

The SLAM-SAP signaling pathway

TCR activation induces SLAM expression on the membrane of immune response cells and SLAM amplifies the TCR signaling trigger (9).

The interaction between SLAM and SAP occurs through the SH2 domain of SAP centered on arginine 32 (Arg32), which binds to ITSM, present in the cytoplasmic portion of SLAM. This binding does not depend on the phosphorylation of Y281, suggesting that SAP is constitutively associated with SLAM. SAP acts as a natural inhibitor, competing with other proteins containing the SH2 domain, such as tyrosine phosphatase (SHP-2), by binding to the same ITSM in SLAM (33). After binding to SLAM, SAP undergoes a conformational change and then binds to and activates Fyn T (49) through another binding surface in the SH2 domain containing arginine at position 78 (Arg78), forming a multiprotein complex. Upon recruiting Fyn T for SLAM, SAP phosphorylates the cytoplasmic portion of SLAM-ITSM, initiating cytoplasmic signal transduction (7,42). Thus, the phosphorylated site in the SLAM serves as the base for the SH2 domain of inositol-containing phosphatase (SHIP), which then phosphorylates and binds to the adapters of docking protein (Dok)-1 and Dok-2. The phosphorylated Dok-2 binds to the SH2 domain of Ras GTPase activating protein (RasGAP) (20). The overall result of this pathway activation is the increasing production of IL-4 and suppression of IFN-γ production (6,9,21) (Figure 1).

The SLAM-SAP signaling pathway can also modulate the immune response through the TCR interaction, while SAP regulates the activation of protein kinase C-teta, B cell lymphoma 10, NF-κB, and GATA-3 (6,50) (Figure 1). The transcription factor GATA-3 acts as positive regulator of the genes of Th2 cytokines, increasing IL-4, IL-5 and IL-13 production. On the other hand, GATA-3 also suppresses IFN-γ genomic programs (51) and at the same time inhibits receptor IL-2 expression (6). Simultaneously, IL-13 inhibits the IL-12 receptor β'-chain synthesis (52). All of these events together impair the Th1 response. Contributing to this idea, a study with murine thymoma cells showed that the SLAM-SLAM interaction induced the reduction of IFN-γ production (21).

It must be emphasized that the result of the SLAM-SAP signaling pathway depends on various factors, such as: the antigen receptor, stimulus intensity, the SLAM redundancy, the mode of induction of expression of SLAM family of

receptors, the type and amount of α-SLAM antibody used, and the substrates involved in the downstream. Models of deficient mice in SLAM family of receptors (SLAM, Ly108 or Ly9) showed a reduction in the production of Th2 cytokines, but this alteration was not as marked as in SAP-deficient mice (53,54). The probable explanation for this phenomenon is the likelihood of a redundant expression of the SLAM family receptors in the same cell, which could contribute to overcome or mask the deficiency or absence of the receptor (3,6,31).

Initially, the role of SLAM was investigated using anti-SLAM monoclonal antibody (α-SLAM mAb). Several investigators observed that, the TCR stimulation in the presence of α-SLAM mAb induced an increase in IFN-γ production (17,19,21) and cytotoxicity of $CD8^+$ T lymphocytes (55). These findings led to the belief that the α-SLAM mAb was agonistic and that its activation regulated the differentiation of T cell, increasing the production of IFN-γ and redirecting the immune response toward a Th1 profile (17,19).

However, it is possible that the α-SLAM mAb may act by blocking the binding sites of SLAM in its extracellular portion, preventing the activation of the signaling pathway (3,6). Another possibility is that α-SLAM mAb was bound to SLAM soluble molecules or to be associated with TCR molecules due to electric charge affinity, leading to α-SLAM mAb functional sequestrum, implying in inactivation of SLAM-SAP signaling pathway (9). It was also shown that, in the *in vitro* sensitization of human lymphocytes with *Leishmania amazonensis*, the anti-SLAM antibody induced an important inhibition of IL-13 production, with a slight increase in the production of IFN-γ (56).

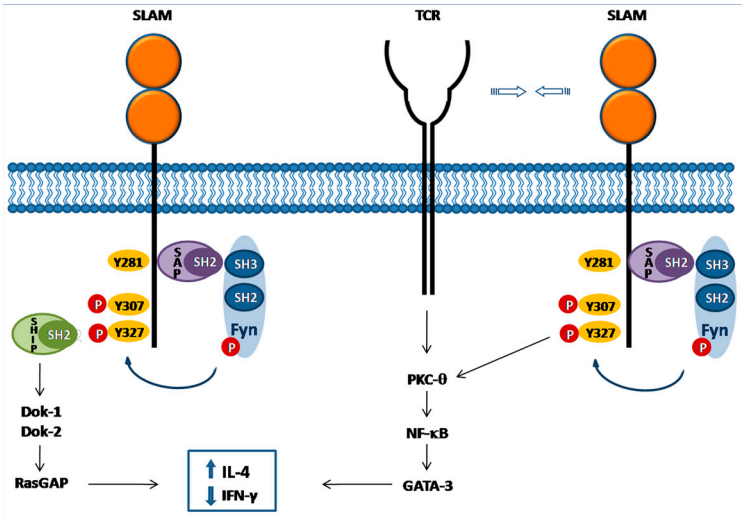

Figure 1. SLAM-SAP signaling pathway. After T cell receptor (TCR) activation, signaling lymphocytic activation molecule (SLAM) binds to SLAM-associated protein (SAP), which recruits and activates the protein tyrosine kinase Fyn T. Phosphorylated SLAM triggers the activation of substrates downstream, such as the SH2 domain of inositol-containing phosphatase (SHIP), Dok (docking protein)-1, Dok-2 and Ras GTPase activating protein (RasGAP). Still, the interaction between TCR and the SLAM-SAP signaling pathway leads the activation of substrates, such as protein kinase C-teta (PKC-θ), B cell lymphoma 10 (Bcl-10), nuclear factor-κB (NF-κB), and GATA-3. These signaling pathways increase Th2 cytokines such as IL-4.

These data strengthen the hypothesis that SLAM-SAP signaling pathway is not primarily involved in Th1 differentiation and that blocking this signaling pathway with the α-SLAM mAb directly undermines the Th2 response. Another important contribution to a better understanding of the SLAM-SAP signaling pathway came from studies with genetically modified mouse models, or human cells with mutations of SAP, as in X-linked lymphoproliferative disease.

It has been reported that $CD4^+$ T cells of mice deficient in SAP, when stimulated *in vitro*, show an increase in the production of IL-2 and IFN-γ, accompanied by a simultaneous reduction in the secretion of IL-4 and IL-13 (48,57,58), as well as the reduction in the expression of the transcription factor GATA-3 (57). Other studies have also demonstrated that $CD4^+$ T cells of mice deficient in SLAM show a reduction of IL-4 and IL-13 production, with mild increase in the production of IFN-γ (24,57). The same effect can be seen in Fyn $T^{-/-}$ mice stimulated with TCR, which show reduction in the phosphorylation of B cell lymphoma 10 and, as a consequence, a decrease in IL-4 production (50).

The blocking of the SLAM-SAP signaling pathway simulates the effects of the deficiency of both SLAM and SAP since the tyrosine phosphorylation cascade initiated by this pathway exerts its action only if SLAM and SAP are available (21). These results demonstrate the interdependence of SLAM and SAP receptors in this signaling pathway and their action in Th2 differentiation. These findings imply that SLAM is primarily involved in promoting Th2-cytokine secretion.

In summary, the SLAM receptor plays an important role in the immunological synapse, where it is detected in almost all cells of the immune system. Although the results of some studies suggest that SLAM is an inducer of IFN-γ, we agree with the interpretation that the SLAM-SAP interplay can be an important signaling pathway for inducing the synthesis of Th2 cytokines, and exerting a down-modulation of the Th1 immune response. Thus, the defects in the SLAM-SAP pathway could potentially contribute to the various immunological abnormalities observed both in humans and in murine models. In addition, advances in knowledge of this signaling pathway may lead to new strategies for the treatment and prevention of autoimmune, allergic, neoplastic, and infectious diseases.

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