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Signaling Lymphocytic Activation Molecule Is Expressed on CD40 Ligand-Activated Dendritic Cells and Directly Augments Production of Inflammatory Cytokines

Joshua R. Bleharski,*† Kayvan R. Niazi,*† Peter A. Sieling,*§ Genhong Cheng,‡¶ and Robert L. Modlin2*†§

Dendritic cells (DC) contribute by several mechanisms to the generation of an effective immune response against foreign Ags. As part of the innate immune system, DC express various pattern recognition receptors that can be triggered upon recognition of microbial ligands (1, 2), bacterial CpG DNA (3), and viral RNA (4) to induce the release of proinflammatory cytokines that can influence the nature of the adaptive T cell response (5). Additionally, DC are the most potent of the professional APCs, providing a pathway for the direct activation of specific T cell populations during the adaptive immune response (6, 7).

In order for DC to carry out their duties during an adaptive immune response, they must first be activated to begin the maturation process. When an appropriate maturation cue is received, DC are signaled to undergo rapid morphological and physiological changes that facilitate the initiation and development of immune responses (8). Among these are the up-regulation of molecules involved in Ag presentation; production of proinflammatory cytokines, including IL-12, key to the generation of Th1 responses; and secretion of chemokines that help to drive differentiation, expansion, and migration of surrounding naive Th cells (7, 9, 10). Collectively, these up-regulated molecules facilitate the ability of DC to coordinate the activation and effector function of other surrounding lymphocytes that ultimately provide protection for the host. Although the process of DC maturation is commonly associated with events that lead to the generation of adaptive immunity, many stimuli derived from the innate branch of the immune system are also capable of activating DC to initiate this process. In this manner, DC provide a link between the two branches of the immune response, in which their initial activation during the innate response can influence both the nature and magnitude of the ensuing adaptive response (11).

Several independent pathways have been characterized that induce DC maturation, all of which enhance the ability of DC to initiate and direct the immune response. One such pathway involves the interaction between CD40 on the surface of the DC, and CD40 ligand (CD40L) expressed on activated Th cells (12). The importance of CD40 signaling in the context of the development and establishment of an immune response has been clearly documented. Previous studies using CD40−/− and CD40L−/− mice have demonstrated that these mice are more susceptible to Leishmania major infection and have severe defects in the production of inflammatory cytokines, including IL-12, TNF-α, and IFN-γ, compared with wild-type mice (13–17). These mice also appear to have impaired T cell proliferative responses, as well as decreased primary and secondary humoral responses (17, 18). In humans, CD40-activated DC are known to be endowed with an enhanced ability to stimulate CD4+ T cells, primarily by up-regulating Ag presentation and costimulatory molecules and by the release of proinflammatory cytokines (19). Because of the importance of CD40-CD40L signaling events in the establishment of inflammatory immune responses, we investigated genes that are up-regulated during DC maturation that contribute to their effector function. In this study, we used a subtractive hybridization technique to identify genes induced in CD40L-matured DC. Through this analysis, we have identified signaling lymphocytic activation molecule (SLAM; also known as...
CDw150, IPO-3), an unusual costimulatory molecule previously characterized on T and B cells (20, 21). SLAM belongs to the Ig superfamily of receptors, and has been shown to enhance cellular proliferation, production of inflammatory cytokines, and Ig secretion. In T cells, engagement of SLAM was shown to augment production of IFN-γ from cells of the Th1 lineage. Interestingly, committed Th2 cells appeared to be reprogrammed to become Th1/Th0-like following SLAM engagement, down-regulating their production of IL-4 in favor of IFN-γ. In this study, we show that transcripts encoding both membrane-bound and secreted isoforms of SLAM were detected in DC treated with CD40L. SLAM protein was also found to be highly expressed on the surface of DC activated by CD40L, LPS, or poly(I:C), a synthetic dsRNA molecule.

SLAM receptor engagement on DC augmented the production of proinflammatory cytokines, including IL-12, pivotal in the differentiation of T cell responses toward the Th1 pattern, but had no effect on production of IL-10, a cytokine involved in the down-regulation of Th1 responses. Together, our data suggest that the expression of SLAM on DC facilitates the generation of proinflammatory Th1 responses.

Materials and Methods
Preparation, maturation, and stimulation of DC
Peripheral blood taken from healthy donors was enriched for CD14+ cells using the RosetteSep monocyte enrichment kit (StemCell Technologies, Vancouver, British Columbia, Canada). Blood was then centrifuged over a Ficoll gradient (Amersham Pharmacia, Uppsala, Sweden) to isolate PBMC. Adherent cells were isolated by culturing in complete medium (RPMI 1640, 0.1 mM sodium pyruvate, 2 mM penicillin, 50 µg/ml streptomycin; Life Technologies, Grand Island, NY) supplemented with 1% FCS (Omega Scientific, Tarzana, CA) for 2 h. Remaining nonadherent cells were removed by washing with 1× PBS. To generate immature DC, adherent cells were cultured in a CO2 incubator at 37°C for 7 days in complete medium containing 10% FCS, 800 U/ml GM-CSF (Genetics Institute, Cambridge, MA), and 1000 U/ml IL-4 (Schering-Plough, Madison, NJ) as previously described (22). These cells were nonadherent, displaying typical DC morphology. Purify of the DC was typically >95%, as determined by flow cytometry.

For DC maturation, cells were harvested from flasks after 7 days using PBS-EDTA (1 mM), and washed twice in complete medium. Cells were counted and plated at a concentration of 2.5–5 × 10^5 DC/ml in either T75 or T25 tissue culture flasks or 96-well tissue culture plates (Corning Glass Works, Corning, NY). DC were treated with 1 µg/ml soluble CD40L trimer (generously provided by Immunix, Seattle, WA) for 24 h to induce maturation. Other maturation stimuli/cytokines used in this study were the following: purified Salmonella minnesota-derived LPS (10 ng/ml) and poly(I:C) (20 µg/ml), both purchased from Sigma (St. Louis, MO); recombinant IL-12 (5 ng/ml) and IL-18 (1 ng/ml), both purchased from R&D Systems (Minneapolis, MN); and M13 reverse, CAGGAAACAGCTATGAC. Reactions were run on agarose gels and visualized by ethidium bromide staining.

RT-PCR
RT-PCR was performed on total RNA isolated from the subtraction, reverse transcribed using Superscript II RT (Life Technologies) to generate cDNA for use in RT-PCR. Reactions were performed for a total of 35 cycles, consisting of a denaturation at 94°C for 30 s and annealing/extension at 65°C for 1 min. RT-PCR typically contained 2.5 mM MgCl2, 0.2 mM dNTP, 2 U Taq polymerase, and 20 pm 5′ and 3′ oligonucleotide primers (Life Technologies). The sequences of the primer pairs used, 5′ and 3′, were the following: 5′-actgagtgtgcagctgggctccggggg-3′ and 5′-gagggggcgtagcagttcctcctccct-3′ for SLAM; 5′-actgagtgtgcagctgggctccggggg-3′ and 5′-gagggggcgtagcagttcctcctccct-3′ for LPS; and 5′-gagggggcgtagcagttcctcctccct-3′ and 5′-gagggggcgtagcagttcctcctccct-3′ for IL-12. Reaction products were then gel purified using a Qiaex II kit (Qiagen, Valencia, CA) and radiolabeled by random priming. After incubation with probes, blots were washed and visualized by autoradiography.

Flow cytometry
To assess the cell surface expression of SLAM, standard flow cytometric analysis was performed. Cells were harvested and blocked with normal serum for 1 min at 25°C to reduce nonspecific FcR binding. Cells were then stained with an unconjugated anti-SLAM mAb (IPO-3; IgG2a; Kamiya Biomedical, Seattle, WA). All other Abs used were purchased from Caltag Laboratories (South San Francisco, CA). PE CD1a (Vii 6b, IgG1), CD3 (S4.1, IgG2a), or BD Pharmingen (San Diego, CA), PE CD80 (L307.4, IgG1), PE CD86 (2331, IgG1), PE HLA-DR (G46-6, IgG2a). Appropriate isotype control Abs (mouse PE IgG1, PE IgG2a, or unconjugated IgG2a) were used in all experiments. A FITC-conjugated goat anti-mouse IgG secondary was used to detect all unconjugated mAb used. After staining, cells were washed and fixed in 1% paraformaldehyde, and analyzed on a BD Biosciences (Mountain View, CA) FACSscan flow cytometer. For all data acquisition, live cells were gated on and 5000 gated events were collected from each sample. All data analysis was conducted using WinMDI 2.8 (J. Trotter, The Scripps Research Institute, San Diego, CA).

In vitro stimulation of DC
DC were harvested on day 7 and plated in six-well tissue culture plates in 2 ml of complete medium. All cells were stimulated with CD40L trimer (1 µg/ml) for 24 h to induce SLAM expression. Cells were then washed thoroughly with complete medium, and fresh medium containing a sterile anti-SLAM mAb (IPO-3), an isotype-matched control, or LPS (10 ng/ml) were added. Abs used for tissue culture did not contain azide and contained <1 ng/ml LPS contamination, as determined by a Limulus-amoeboocyte assay (BioWhittaker, Walkersville, MD). Following cell stimulation, supernatants were harvested at various time points and analyzed for the presence of IL-12, IL-10, and IL-8 cytokines using a standardized sandwich ELISA. Abs and protein standards used for IL-12 and IL-10 ELISA were purchased from BioSource International (Camarillo, CA). IL-8 ELISA reagents were purchased from BD Pharmingen.
Results
Identification of CD40L-inducible genes in DC by subtractive hybridization

It has previously been shown that CD40L is one of many stimuli capable of inducing DC maturation and subsequent expression of genes involved in directing the adaptive T cell response toward the Th1 lineage (10, 25). To better understand the role of DC in inflammatory responses, we used subtractive hybridization to identify genes up-regulated by CD40L in DC. To this end, DC from healthy donors were cultured in the presence or absence of soluble CD40L, and total RNA was isolated for use in subtractive hybridization. Activation of the DC by CD40L was confirmed by assaying for up-regulation of IL-12 p40 by RT-PCR and ELISA (data not shown).

We performed three separate subtractive hybridization experiments and isolated a total of 2300 cDNA fragments from the CD40L-stimulated DC. A portion of these cDNA fragments was sequenced and identified using the BLASTN database at the National Center for Biotechnology Information. A partial list of the genes identified is shown in Table I, organized into five general categories based on either cellular location or proposed function.

Some of the genes identified, such as IL-1β, IL-12, and macrophage-derived chemokine, are known to be up-regulated in mature DC (26, 27), providing an internal control for the reliability of this technique. Of particular interest to us were known or novel genes having immunological relevance, specifically those that may participate in regulating Th1 responses. One such gene was SLAM, which encodes a protein that has been previously characterized in regulating Th1 responses. Another such gene was the variable or cytoplasmic domain, and a cytoplasmic SLAM isoform with a 30-aa transmembrane domain, a variable SLAM isoform with a truncated cytoplasmic domain, and a cytoplasmic SLAM isoform lacking the leader sequence have also been described. Although both the membrane-bound and secreted isoforms of SLAM have been demonstrated to have physiological effects on studies using T and B cells, no function has been assigned to the variable or cytoplasmic isoforms of SLAM. To determine which isoforms of SLAM mRNA were induced in DC by CD40L, we performed RT-PCR using SLAM isoform-specific oligonucleotide primers. The cDNA template was diluted up to 50-fold to ensure results were not due to nonlinear amplification, and all reactions were normalized to β-actin mRNA levels. As shown in Fig. 2, mRNA encoding both the membrane-bound and secreted isoforms of SLAM was strongly up-regulated in DC in response to CD40L. No message encoding the variable or cytoplasmic SLAM isoforms was detected (data not shown).

To determine whether SLAM protein was expressed on CD40L-activated DC, cells were labeled with anti-SLAM mAbs and analyzed by flow cytometry. Fig. 3A shows that CD40L induced the expression of SLAM protein, as well as the expression of CD1a, CD80, CD86, and HLA-DR molecules, known to be up-regulated and untreated DC. Cells were stimulated in the presence or absence of soluble CD40L trimer, and total RNA was isolated. RNA was transferred to nylon membranes and hybridized with radiolabeled gene-specific probes. Fig. 1 shows that SLAM mRNA is significantly up-regulated in CD40L-stimulated DC. Similar results were obtained for the characteristic Th1 cytokine IL-12 and for the chemokines, macrophage-derived chemokine and monokine induced by IFN-γ, used as positive controls. All blots were normalized to β-actin to ensure equal RNA loading. These data corroborate the results obtained by subtractive hybridization, indicating the up-regulation of SLAM in CD40L-activated DC.

Table I. Differentially expressed genes in CD40L-activated DC

<table>
<thead>
<tr>
<th>Cytokines/chemokines</th>
<th>Cell growth/apoptosis</th>
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<tr>
<td>IL-1β</td>
<td>G9 (sialidase)</td>
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<tr>
<td>IL-12 (p40) (NKS, CTLMF)</td>
<td>Glutamate transporter-1</td>
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<tr>
<td>Macrophage-derived chemokine</td>
<td>EF-1α</td>
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<tr>
<td>Macrophage-inflammatory protein 3α</td>
<td>Cholesterol acetyl transferase</td>
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<tr>
<td>Monokine induced by IFN-γ</td>
<td>Cyclin G2</td>
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<tr>
<td>Membrane receptors</td>
<td>Ferritin L chain</td>
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<tr>
<td>SLAM (CDw 150, IPO-3)</td>
<td>Manganese superoxide dismutase</td>
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<td>β2-microglobulin</td>
<td>Spermine synthase</td>
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<tr>
<td>Fas (Apo-1)</td>
<td>JKTBP</td>
</tr>
<tr>
<td>Leptin-related receptor</td>
<td>MHC-1 (TNFR/TRAF associated protein)</td>
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<tr>
<td>IL-10R</td>
<td>cIAP-2</td>
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<tr>
<td>CD83 (BL11)</td>
<td>CCR7 (EBI-1)</td>
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<tr>
<td>TMP-21</td>
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<tr>
<td>Cytoplastic/structural</td>
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<tr>
<td>Fibroblast tropomyosin</td>
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<td>α-Centrin</td>
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<td>TM30</td>
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<td>Vimentin</td>
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<td>ARC21</td>
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<td>GBP-2</td>
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<td>RACK1</td>
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<tr>
<td>Secretory granule core peptide</td>
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<tr>
<td>Monocyte/neutrophil elastase inhibitor</td>
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<td>71-kDa heat shock protein</td>
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<tr>
<td>90-kDa heat shock protein</td>
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<tr>
<td>Synexin (annexin VII)</td>
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<td>LAMP</td>
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in mature DC. To confirm that SLAM was expressed on DC and not a contaminating subpopulation, cells were labeled with anti-SLAM and anti-CD1a mAbs conjugated with either FITC or PE dye and analyzed by two-color flow cytometry. As shown in Fig. 3B, 74% of the CD1a+ DC cell population was also positive for SLAM expression following maturation with CD40L. These levels are relatively high when compared with the expression levels observed in previous studies using both activated T and B cells, which seem to be between 25 and 50% positive (20, 21). Fetal thymocytes, however, express SLAM at levels comparable with DC, approaching 80% positive. Finally, to ensure that the SLAM protein detected was not the result of a DC/T cell aggregate, cells were then labeled with mAbs to CD1a and CD3 conjugated with either FITC or PE dye. Only 7.4% of the CD1a+ population was also CD3+, suggesting that SLAM expression on DC was not a result of T cell contamination.

To examine the kinetics of SLAM induction on DC, cells were treated with CD40L and assayed for cell surface expression at various time points. As shown in Fig. 3C, SLAM is first detectable on the surface of DC as early as 12 h poststimulation with CD40L. SLAM expression observed at this time appears to approach maximal levels, as no significant increase in expression could be detected even after 2 days. Four days after the initial stimulation with CD40L, SLAM expression begins to diminish and ultimately reaches baseline levels on day 6. These kinetics appear to closely mirror those observed in B cells, in which SLAM expression is observed as early as 6 h and reaches maximal levels 24–48 h following stimulation (21, 24). Thus, SLAM expression appears to be rapidly up-regulated on DC during the maturation process.

SLAM expression is up-regulated in response to other known DC maturation stimuli

In addition to CD40L, other stimuli have been shown to have the ability to drive DC activation and maturation. Several microbial ligands are believed to be potent mediators of DC maturation, LPS being one of the best characterized. Recently, it has also been shown that the 19-kDa lipoprotein from Mycobacterium tuberculosis mediates DC maturation via Toll-like receptor 2 (TLR) (28), a determination made based on changes in cell surface protein expression, uptake and presentation of Ag, and secretion of proinflammatory cytokines such as IL-12 that characterize this process.

Another stimulus having the ability to drive DC maturation is poly(I:C) (29), a synthetic molecule originally designed to induce production of type I IFNs important for the control of viral infections (30, 31). Much like CD40L and LPS, poly(I:C) is also capable of inducing DC to secrete high levels of proinflammatory cytokines such as IL-12; however, its receptor has not yet been identified.

To determine whether these ligands also induce SLAM expression in DC, immature DC were cultured in the presence of different maturation stimuli and assayed for cell surface expression of SLAM by flow cytometry. Fig. 4A shows that both CD40L and poly(I:C) up-regulated SLAM expression on DC to similar levels. Of the microbial ligands we tested, only LPS was capable of inducing expression of SLAM on DC, whereas the 19-kDa lipoprotein from M. tuberculosis (19 kDa), the OspA lipoprotein from Borrelia burgdorferi (OspA), and the 47-kDa lipoprotein from Treponema pallidum (Tp47) had no effect. However, all the microbial stimuli added to immature DC cultures were able to induce high levels of IL-12 production (Fig. 4B), suggesting that the lack of SLAM expression observed under some conditions was not due to DC unresponsiveness. Additionally, cytokines typically secreted by DC during maturation, such as IL-12 and IL-18, had no effect on SLAM expression when added alone or in combination. Minimal up-regulation of SLAM was observed on DC in response to TNF-α; however, this effect was inconsistent and never equivalent to the levels observed following stimulation with CD40L, LPS, or poly(I:C). Collectively, our data suggest that SLAM is up-regulated by DC during their maturation with CD40L, poly(I:C), or LPS, and is not the result of secondary events, such as cytokine release, that occur during the maturation process.

Engagement of SLAM on DC augments secretion of Th1-inducing, but not Th2-inducing cytokines in vitro

Previous studies describing SLAM expression on activated T and B cells have shown that this molecule exhibits a number of co-stimulatory properties, including the ability to enhance cellular proliferation and inflammatory cytokine release (20, 21, 24, 32). Evidence also exists to suggest that SLAM serves as its own ligand, exhibiting weak homophilic binding properties in vitro (33). It is therefore possible that interacting DC and T cells expressing SLAM could be activated simultaneously through this molecule.
Given the ability of SLAM engagement to affect T cell function, we wanted to determine whether SLAM receptor ligation had an effect on DC function. To this end, DC were treated with soluble CD40L trimer to induce expression of SLAM and thoroughly washed before restimulation with agonistic anti-SLAM mAbs. As a positive control for the ability to restimulate DC after their initial exposure to CD40L, LPS was added to some samples. Supernatants from these cultures were collected and analyzed for cytokine release by ELISA. As shown in Fig. 5, retreatment of SLAM-expressing DC with anti-SLAM mAbs, but not an isotype control mAb, augmented the amount of IL-12 produced by these cells. Similar results were obtained for IL-8 production, albeit to a lesser degree. The increase in IL-12 produced in response to SLAM engagement appeared to peak at 12 h, tapering off at the 24-h point. The kinetics of IL-8 production were somewhat different, with levels still increasing after 24 h and beginning to diminish 48–72 h poststimulation (data not shown). These changes in cytokine production were dose dependent, as lower concentrations of the anti-SLAM Ab had more modest, yet still significant, effects. The amount of IL-10 produced by these cells was not affected by the anti-SLAM or isotype control mAbs, although LPS was able to induce low levels of IL-10. These results suggest that the engagement of SLAM enhances the ability of DC to secrete proinflammatory cytokines and chemokines that contribute to the development of the Th1 response.

Discussion
The activation and maturation of DC provide a key pathway by which the innate immune response influences the nature and magnitude of the adaptive immune response. A number of receptors on the surface of DC are known to mediate their maturation, including CD40 (19), the receptor for CD40L expressed on T cells. To better understand the role of mature DC in the establishment of adaptive immune responses, we investigated genes that are up-regulated in CD40L-activated DC. Using subtractive hybridization, we identified SLAM, a molecule previously identified on activated T and B cells and shown to have costimulatory properties for Th1 cytokine responses (20). Flow cytometry confirmed that SLAM was expressed on CD40L-activated DC. Other stimuli known to induce the maturation of DC, including LPS and poly(I:C), were also able to induce SLAM expression, but not microbial lipoproteins such as the M. tuberculosis 19-kDa lipoprotein. The induction of SLAM
appears to be a direct effect of the maturation stimuli, as cytokines such as IL-12, IL-18, and TNF-α that are secreted during DC activation and maturation had no effect on SLAM expression. Functionally, SLAM receptor engagement on DC augmented production of IL-12 and IL-8, but not IL-10. These data suggest that SLAM expression on mature DC may play a role in facilitating the ability of DC to initiate inflammatory immune responses by increasing local cytokine concentrations that impact the nature and magnitude of the adaptive T cell response.

During the course of maturation, DC are transformed into highly specialized immune cells with an enhanced ability to affect the activation and differentiation of surrounding lymphocytes (6, 7, 10). This ability of mature DC may play a role in facilitating the ability of DC to initiate inflammatory immune responses by increasing local cytokine concentrations that impact the nature and magnitude of the adaptive T cell response.

In addition to their ability to receive signals from activated T cells during the adaptive immune response, DC are also integrally involved in innate immunity to microbial pathogens. We found that two microbial ligands that have been shown to drive DC maturation, namely the TLR4 ligand LPS and poly(I:C), a synthetic dsRNA molecule used to mimic viral RNA, up-regulated SLAM expression on DC. Interestingly, microbial lipoproteins, TLR2 ligands, were unable to induce SLAM expression in DC, despite the fact that 19 kDa has recently been shown to drive DC maturation (28). Given our current understanding that LPS mediates signaling via TLR4 (34) and lipoproteins via TLR2 (35), it is tempting to speculate that TLR4, but not TLR2, selectively mediates the up-regulation of SLAM expression on DC during maturation. Alternatively, it is possible that LPS-mediated induction of SLAM expression on DC occurs through a TLR-independent pathway (36, 37). Collectively, these data suggest that SLAM may also be expressed on DC that undergo maturation in response to bacterial and viral pathogens during the innate immune response.

One of the most influential roles of DC in establishing protective immunity is to help drive the expansion and commitment of surrounding T cells toward either the Th1 or Th2 lineage (7). The mechanisms surrounding these events are believed to be partially dependent on the pattern of cytokines secreted by DC into the local environment, which has been shown to be modulated by SLAM expression on DC.
microenvironment (5). Activation of SLAM on DC using an agonist mAb augmented the release of the Th1 cytokine IL-12, but not IL-10, a Th2-inducing cytokine. SLAM engagement also enhanced DC production of IL-8, a chemotactic cytokine for neutrophils and T cells (38). The effects resulting from SLAM receptor engagement on DC may contribute to their ability to initiate Th1 responses.

Previous studies have described that SLAM engagement on activated T cells leads to the generation of a Th1 cytokine response. In one study, SLAM was shown to augment the production of IFN-γ from cells of the Th1 lineage (20). Given that homophilic SLAM-SLAM interactions have been shown to occur in binding assays (33), it is tempting to speculate that DC and T cells, or any other pair of SLAM-expressing cells, may interact via SLAM-SLAM interactions. An interaction of this sort could lead to the bidirectional activation of these cells, synergizing in the generation of a Th1 response. We suspect that SLAM is one part of a matrix of receptors expressed on activated DC that can be engaged upon interaction with a T cell to aid in potentiating immune responses. Alternatively, the existence of a secreted isoform of SLAM suggests that receptor engagement does not necessarily involve direct cell-to-cell contact, and may be mediated instead through an indirect mechanism (24, 39).

Developing our overall understanding of SLAM function may also have clinical benefits, in light of several studies that have correlated its expression with human disease. First, in patients affected with acute multiple sclerosis, a neurological disorder believed to result in part from the unchecked activation of cell-mediated immunity, SLAM expression on CD4+ T cells was higher compared with patients with stable multiple sclerosis and healthy controls (40). Second, a recently discovered gene that maps to the same chromosome locus for X-linked lymphoproliferative disease controls (40). Second, a recently discovered gene that maps to the same chromosome locus for X-linked lymphoproliferative disease.

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