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REVIEW

Role of SLAM-Associated Protein in the Pathogenesis of Autoimmune Diseases and Immunological Disorders

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Abstract Signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) is an adaptor molecule containing a Src homology 2 (SH2) domain. SAP is expressed in T cells and natural killer (NK) cells and binds to the cytoplasmic domains of SLAM family receptors, resulting in the subsequent recruitment of Fyn. The *SAP* (*SH2D1A*) gene is located on the X chromosome and is responsible for X-linked lymphoproliferative disease, characterized by higher susceptibility to Epstein-Barr virus infection. The SAP-mediated signal is not only essential for the development of NKT cells, i.e. unconventional CD1d-restricted T cells with invariant Vα14 T cell receptors, but also for the regulation of the function of NK cells and conventional T cells. The role of SAP-mediated signaling in the induction of autoimmune diseases has been analyzed using animal models such as lupus, hepatitis, and graft-versus-host disease and is considered important in their pathogenesis in humans. In this review we highlight the current findings on SAP-mediated signaling in hematopoietic cells and discuss its importance in autoimmune diseases and immunological disorders.

Keywords SLAM · SAP · Autoimmune diseases

Abbreviations

SLAM	Signaling lymphocytic activation molecule
SAP	SLAM-associated protein
XLP	X-linked lymphoproliferative disease
NK	Natural killer
EBV	Epstein-Barr virus
GVHD	Graft-versus-host disease
Ig	Immunoglobulin
ITSM	Immunoreceptor tyrosine-based switching motif
DC	Dendritic cell
SNP	Single-nucleotide polymorphism
SH2	Src homology 2
EAT-2	Ewing's sarcoma-activated transcript-2
ERT	EAT-2-related transducer
AICD	Activation-induced cell death
MR-1	MHC-related 1
MAIT	Mucosal-associated invariant T
XIAP	X-linked inhibitor of apoptosis
SLE	Systemic lupus erythematosus
RA	Rheumatoid arthritis
FasL	Fas ligand
ConA	Concanavalin A
MHC	Major histocompatibility complex
mHC	Minor histocompatibility complex
BMT	Bone marrow transplantation

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Introduction

The intercellular interactions of co-stimulatory molecules and their ligands, such as CD28 and B7, CTLA-4 and B7, PD-1 and PDL-1, and CD40 and CD40L, play important roles in immune regulation and in the development of autoimmune conditions and immunological disorders. Signaling lymphocytic activation molecule (SLAM) family receptors are type I transmembrane proteins with co-stimulatory functions mediated by SLAM-associated protein (SAP). The SLAM–SAP signaling pathway in hematopoietic cells is important in the development of autoimmune diseases and immunological disorders. Here we review the biological features of SLAM and SAP in in vitro and in vivo.

SAP and Slam Family Receptors

SLAM family receptors belong to the immunoglobulin (Ig) superfamily, possessing two or four Ig domains in the extracellular part of the molecule, and include SLAM (CD150), 2B4 (CD244), Ly9 (CD229, 4Ig domains), CD84, Ly108 (NTB-A), CD48, CS1 (CRACC, CD319), BLAME, and CD84-H1 (Fig. 1) (Engel et al. 2003). SLAM, 2B4, Ly9, CD84, and Ly108 are expressed in hematopoietic cells, contain one or more immunoreceptor tyrosine-based switching motifs (ITSMs, TI/VYXXV/I) in their cytoplasmic tails, and bind to a SAP molecule. Human CS1 molecule binds to a SAP molecule, but mouse CS1 molecule does not. SLAM is expressed in activated T cells, B cells, and dendritic cells (DCs), but not in natural killer (NK) cells. 2B4 is expressed in NK cells and in subpopulations of T cells, DCs, and mast cells. Ly9, CD84, and CD48 are expressed in almost all lymphocytes. The ligands of SLAM, CD84, Ly108, and Ly9 are, respectively, the same molecules, i.e. there is homotypic receptor recognition. However, the ligand of 2B4 is CD48, a glycosylphosphatidylinositol anchored molecule without an ITSM (Latchman et al. 1998). Some SLAM family receptor genes are highly polymorphic, with many non-synonymous single-nucleotide polymorphisms (SNPs) in the exon regions (Fig. 1). These SLAM family receptor genes are located on chromosome 1 in humans (Ch.1q23.3) and mouse (Ch.1H3), forming a gene cluster. This locus overlaps with the lupus-sensitive loci *Sle1*, *Nba2*, *Lbw7*, and *Swrl-1*, as described in previous studies (Nguyen et al. 2002).

SAP is an adaptor molecule containing a Src homology 2 (SH2) domain and a short C-terminal tail (Engel et al. 2003; Veillette et al. 2007). It is expressed in T, NK, and NKT cells. Binding with SAP SH2 domains occurs via ITSMs in the cytoplasmic domains of SLAM family receptors. The binding of SAP with SLAM in T cells results in the subsequent recruitment of the Src family kinase Fyn (Latour et al. 2003). The recruited Fyn

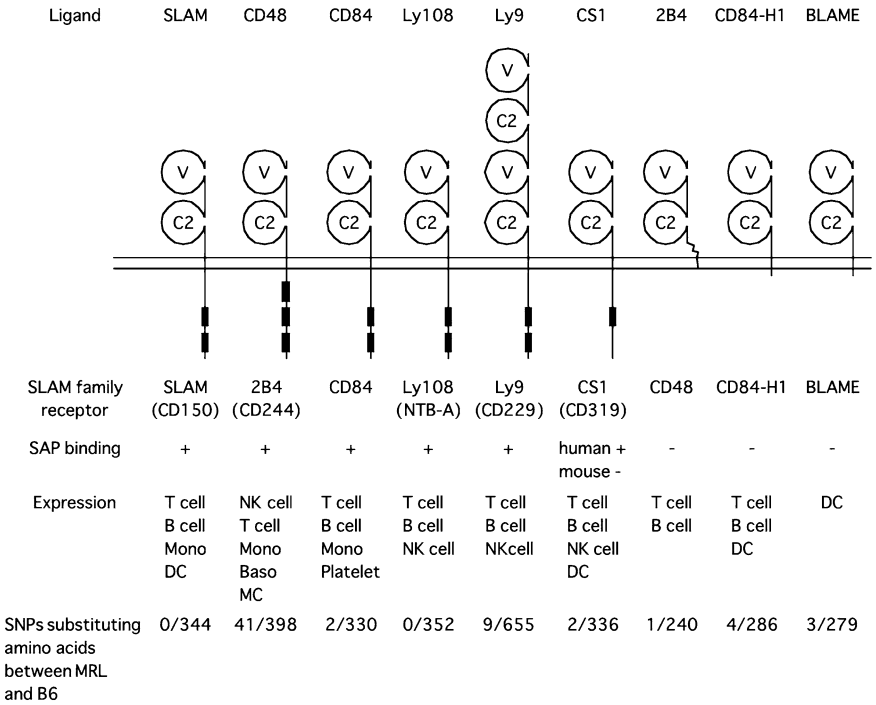

Fig. 1 SLAM family receptor members. SLAM family receptors are members of the immunoglobulin superfamily and are mainly expressed in hematopoietic cells. Some members contain one or more immunoreceptor tyrosine-based switching motifs (ITSMs, TI/VYXXV/I) in their cytoplasmic tails and bind to the SAP molecule. With the exception of 2B4 and CD48, SLAM family receptors themselves act as their own ligands in a homotypic manner. SLAM family receptors are highly polymorphic, including many non-synonymous SNPs. Abbreviations: *NK* natural killer, *Mono* monocyte and macrophage, *DC* dendritic cell, *Baso* basophil; *MC* mast cell. *Reproduced* from the reference (Furukawa and Ono 2005)

phosphorylates tyrosines in the ITSMs of SLAM family receptors and transduces signals through PKCΘ and Bcl-10, leading to the activation of NF-κB, resulting in IL-4 production and Th2 responses (Cannons et al. 2004; Veillette 2006). Ewing's sarcoma-activated transcript-2 (EAT-2) and EAT-2-related transducer (ERT) are also adaptor molecules containing an SH2 domain and a short C-terminal tail. They also bind to the cytoplasmic domains of SLAM family receptors via SH2 domains and ITSMs (Ma et al. 2007; Morra et al. 2001; Veillette 2006). EAT-2 is expressed in NK cells, DCs, and monocytes, while ERT is expressed in NK cells. EAT-2 and ERT were believed to act as analogues of SAP and attenuate the signals mediated by SAP molecules. However, the signals mediated by EAT-2 and ERT have still not been identified. The SAP gene (in humans *SH2D1A*, in mouse *Sh2d1a*) is located on the X chromosome in humans (Xq25) and mouse (XA4), whereas the genes for EAT-2 (in humans *SH2D1B*, in mouse *Sh2d1b1*) and ERT (*Sh2d1b2,* only in rodents) are also both located on chromosome 1 in humans (1q23.3) and mouse (1H3), very close to the loci of SLAM family receptors (Veillette 2006).

The SAP-deficient mouse exhibits altered B-cell responses to viruses and parasites resulting in the reduced production of specific antibodies because of $CD4^+$ T-cell dysfunction (Crotty et al. 2003; Czar et al. 2001; Wu et al. 2001; Yin et al. 2003). It was speculated that several SLAM family members are involved in the regulation of $CD4^+$ T-cell function. In the SAP-deficient mouse, $CD8^+$ T-cell proliferation and cytokine secretion are enhanced and activation-induced cell death (AICD) inhibited (Chen et al. 2007). The roles of SAP in B cells in antibody production and isotype switching are still unclear. Studies using SAP-deficient mice showed that SAP-mediated signals augmented and EAT-2-mediated signals inhibited the natural cytotoxicity and cytokine secretion activity of NK cells (Roncagalli et al. 2005). These SAP-mediated signals are essential for the development of Vα14 NKT cells (Vα24 NKT cells in humans), i.e. unconventional T cells with invariant T-cell receptors restricted by an major histocompatibility complex (MHC) class Ib molecule, CD1d (Furukawa et al. 2009; Nichols et al. 2005). These Vα14 or Vα24 NKT cells are absent in SAP-deficient mice and humans, respectively, as well as in Fyn-deficient mice (Eberl et al. 1999). Vα14 NKT cells recognize glycolipid antigens on CD1d molecules, such as α-galactosylceramide, originally derived from a marine sponge, or endogenous isoglobotrihexosyl ceramide, and they secrete large amounts of IL-4 and IFN-γ (Matsuda and Gapin 2005; Yu and Porcelli 2005). NKT cells play important roles in the development of autoimmune diseases and tumor rejection. SLAM and Ly108 are believed to mediate signals important for the development of NKT cells through association with SAP and Fyn. In addition, the *Nkt1* locus is partially responsible for the decreased number of NKT cells in non-obese diabetic mice and was later shown to be identical to the *Slam* locus (Jordan et al. 2007). In contrast, SAP-mediated signaling is not essential for the development of Vα19 NKT cells, i.e. unconventional MHC-related 1 (MR-1)-restricted T cells with invariant Vα19 T cell receptors in mice or Vα7.2 T cell receptors in humans. These Vα19 NKT cells are also called MR-1-restricted mucosal-associated invariant T (MAIT) cells, as can be observed in the intestine of SAP-deficient patients (Veillette et al. 2007). MAIT cells may express other adaptors, such as EAT-2 or ERT. Thus, SAP-mediated signaling plays important roles in the function and development of different populations of lymphocytes.

SAP in X-Linked Lymphoproliferative Disease

A hemizygous defect in the *SH2D1A* gene, which encodes the SAP molecule in humans, is responsible for X-linked lymphoproliferative disease (XLP) in males (Sayos et al. 1998). XLP patients are highly susceptible to Epstein-Barr virus (EBV) infection and suffer from fulminant infectious mononucleosis with hemophagocytic syndrome, malignant lymphoma, and hyper- or hypogammaglobulinemia. In XLP patients with *SH2D1A*-deficiency, the cytotoxic functions of $CD8^+$ T and NK cells are reduced, the functions of $CD4^+$ T cells are altered, antibody production is reduced, and Vα24 NKT cells are almost absent (Latour and Veillette 2003; Nichols et al. 2005). Defects in the gene encoding the X-linked inhibitor of apoptosis (XIAP), a member of the inhibitor-of-apoptosis protein family, also causes XLP (Rigaud et al. 2006; Vaux and Silke 2005). The *XIAP* gene (Xq25) is located close to the *SH2D1A* gene (Xq25) on the X chromosome. Phenotypes of XLP in XIAP-deficient patients are quite similar to those of SAP-deficient patients except that the former is associated with splenomegaly instead of lymphoma. In XLP patients with a hemizygous defect of the *XIAP* gene, the cytotoxic functions of $CD8^+$ T cells and NK cells are not altered, but the number of Vα24 NKT cells is markedly reduced. These findings suggest that defects of Vα24 NKT cells are responsible for the main phenotype of XLP, the severe lymphoproliferative disorder induced by EBV infection. In a mouse study it was found that SAP-deficient animals had defects in their Vα14 NKT cells because of the lack of SLAM-, SAP-, and Fyn-mediated signaling (Eberl et al. 1999; Jordan et al. 2007; Nichols et al. 2005), whereas XIAP-deficient mice had normal numbers of Vα14 NKT cells. This hypothesis could be proven by experimental infection of XIAP-deficient mice. Although it is still unclear why the number of Vα24 NKT cells is reduced in

XLP patients with *XIAP*-deficiency, the higher sensitivity of peripheral lymphocytes to AICD may be causally implicated in this state.

SAP-Mediated Signals in Lupus

MRL/Mp-$Fas^{lpr/lpr}$ (MRL/lpr) is a lupus-prone strain of mice derived from crosses between the LG, AKR, C3H, and C57BL/6 strains. MRL/lpr mice show severe lymphadenopathy and splenomegaly due to the abnormal expansion of *lpr*-T cells, namely $CD4^{-}CD8^{-}B220^{+}Thy1.2^{+}$ $\alpha\beta$T cells (Andrews et al. 1978). MRL/lpr mice also exhibit vasculitis and autoantibody production. This mouse model mimics human systemic lupus erythematosus (SLE) quite well. This abnormality was induced by the *lpr* gene, a mutant *Fas* gene characterized by integration of an early transposon into the wild-type *Fas* gene (Adachi et al. 1993; Chu et al. 1993; Watanabe-Fukunaga et al. 1992). The Fas antigen is a member of the tumor necrosis factor receptor superfamily and mediates apoptotic signals. The generalized lymphoproliferative disease gene *gld* is a mutant developed in C3H/He mice (Davidson et al. 1986; Roths et al. 1984). These mice also show severe lymphadenopathy and splenomegaly due to the abnormal expansion of $CD4^{-}CD8^{-}B220^{+}Thy1.2^{+}$ $\alpha\beta$T cells; this expansion was indistinguishable from that induced by the *lpr* gene. This phenomenon is associated with a Fas ligand (FasL) defect in which an amino-acid substitution resulted in a loss of function (Takahashi et al. 1994). The MRL/Mp-$Fasl^{gld/gld}$ (MRL/gld) mice, i.e. the *gld*-congenic MRL strain of mice, exhibit traits similar to those of the MRL/lpr mice (Ito et al. 1997).

We found spontaneous mutants in the MRL/lpr strain. The long-living mutant MRL/lpr/rpl mice displayed minimal autoimmune phenotypes, including lymphadenopathy, splenomegaly, glomerulonephritis, vasculitis, and autoantibody production (Komori et al. 2006). In the spleen and lymph nodes of the MRL/lpr/rpl mice, the number of *lpr*-T cells was reduced, thereby diminishing splenomegaly and lymphadenopathy. This abnormality is induced by the regression of phenotype associated with the lpr gene, or *rpl*. A positional cloning study using (MRL/lpr/rpl X C3H/lpr)F_2 mice revealed that the *rpl* gene, a mutation of the *Sap* gene in the MRL/lpr/rpl (MRL/Mp-$Fas^{lpr/lpr} \cdot Sap^{rpl/-}$) mice, abrogated autoimmune traits. The insertion of one adenine base at the 68th base position from the start codon in exon 1 of the *Sap* gene caused a frame shift and a subsequent premature stop codon. The SAP protein was not detected in the thymus of MRL/lpr/rpl mice, probably because of its degradation. In addition, Fyn-deficient MRL/lpr mice lost the lupus phenotypes similarly to MRL/lpr/rpl mice (Takahashi et al. 1997). These data indicate that the SLAM family receptor and SAP-mediated signals are essential for the induction of lupus.

The MRL/gld/rpl (MRL/Mp-$Fasl^{gld/gld} \cdot Sap^{rpl/-}$) mice were generated by intercrossing F_1 mice (MRL/lpr/rpl × MRL/gld). They lived longer than MRL/gld mice and, like MRL/lpr/rpl mice, they lacked lupus-like phenotypes (Table 1). The number of *lpr*-T cells was also reduced in the spleen and lymph nodes of the MRL/gld/rpl mice, thereby diminishing splenomegaly and lymphadenopathy. These data indicate that the mechanism causing lupus-like traits in MRL/gld mice similarly depends on SAP-mediated signals, as in MRL/lpr mice.

It was also reported that SAP-deficient mice of the 129 background were resistant to lupus experimentally induced with pristane (2,6,10,14-tetramethylpentadecane, an isoprenoid alkane obtained from shark liver oil), even though wild-type 129 mice were susceptible (Hron et al. 2004). This pristane-induced lupus model also has similar characteristics to SLE in humans. The degree of resistance of SAP-deficient mice was evaluated by assessing serum immunoglobulins, autoantibodies, renal immune deposits, and glomerulonephritis. These mouse model studies using

Table 1 Phenotypes of MRL/gld/rpl

	MRL/gld mice	MRL/gld/rpl mice	*P* value
Mean survival time (weeks)[a]			
Males	31.0 ($n = 14$)	32.9 ($n = 14$)	0.6300
Females	26.1 ($n = 15$)	31.5 ($n = 18$)	0.0044
Mean spleen weight (g)[b]			
Males	0.277 ± 0.050 ($n = 10$)	0.132 ± 0.020 ($n = 8$)	0.0008
Females	0.581 ± 0.204 ($n = 9$)	0.331 ± 0.147 ($n = 8$)	0.0179
Mean axillary lymph node weight (g)[b]			
Males	0.351 ± 0.122 ($n = 10$)	0.058 ± 0.021 ($n = 8$)	0.0008
Females	0.828 ± 0.460 ($n = 9$)	0.046 ± 0.033 ($n = 8$)	0.0017
Mean body weight (g)[b]			
Males	41.8 ± 3.3 ($n = 10$)	41.9 ± 4.0 ($n = 8$)	0.3682
Females	40.3 ± 4.1 ($n = 9$)	37.6 ± 2.8 ($n = 8$)	0.0251

[a] Survival of the mice were followed until 34 weeks of age and log rank test was used

[b] Autopsy was performed at 22 weeks of age. Data were presented as mean ± SD. Mann–Whitney U-test was used

SAP-deficient animals suggest that SAP-mediated signals are essential for the pathogenesis of human SLE due to the production of Abs resulting from the collaboration of T and B cells.

Genetic studies using the lupus-prone mice (NZB × NZW)F_1 and their susceptible recombinant congenic relatives, NZM2410 mice, identified a lupus susceptibility locus, *Sle1b*, which overlapped with the loci of SLAM family receptors (Wandstrat et al. 2004). One of these SLAM family receptor genes, *Ly108*, was recently shown to be causative for lupus (Chan et al. 2006; Kumar et al. 2006). A polymorphic *z* allele of *Sle1b* from the NZW strain altered the expression pattern of two splicing variants of *Ly108* (Ly108.1, a shorter isoform with two ITSMs, and Ly108.2, a longer isoform with three ITSMs) and increased susceptibility to lupus. The Ly108.1 variant, which was highly expressed in immature B cells from *Sle1b*^{z}-bearing mice, impaired B-cell anergy induction. In addition, the congenic mice B6.*Sle1b*, that comprise *Sle1b*^{z} allele on the C57BL/6 background, were generated and analyzed in SAP-deficient condition to elucidate the roles of SLAM family receptors and SAP-mediated signals in lupus (Jennings et al. 2008). In this model, the production of autoantibodies was reduced in the SAP-deficient condition, suggesting that the SAP-mediated signals play important roles in the induction of lupus. NK cells may play an important role in the production of autoantibodies in the model.

The roles of SAP have been analyzed in some lupus models with SAP deficiency. Since the development of some cell populations was altered in SAP-deficient mice, it was difficult to distinguish whether the phenotype of disease was altered by the reduced signals in some cell populations, reduced cell numbers of other cell populations, or both of these. For example, the numbers of Va14 NKT and *lpr*-T cells were reduced in MRL/lpr/rpl mice although the other conventional cell populations, such as T, B, or NK cells, seemed intact, but may have had some functional or developmental defects. It was suggested that the SAP deficiency in MRL/lpr causes the reduced T-cell signaling in the pathogenic T-cell population and that reduced numbers of Va14 NKT and *lpr*-T cells do not simply diminish the lupus phenotypes in MRL/lpr/rpl (Komori et al. 2006). The SAP deficiency may similarly cause the reduced T-cell signaling in pathogenic T-cell populations in the other lupus models. However, only cell transfer experiments of the pathogenic cell populations can reveal this, even though the pathogenic cell populations are still unknown. Further studies on SAP-deficient mice can help for a better understanding of the discussion.

In genetic studies on SLE patients it was suggested that SNPs in the *LY9* gene are associated with SLE susceptibility in Caucasians (Cunninghame Graham et al. 2008) and that the *SH2D1A* polymorphism was associated with early-onset SLE in Japanese (Furukawa et al., unpublished data). It was recently reported that SNPs in *2B4* were associated with disease in Japanese rheumatoid arthritis (RA) and SLE patients (Suzuki et al. 2008). In addition, the expression of SAP was reduced in peripheral T cells from RA patients (Chan et al. 2006; Sawada and Takei 2005; Takei et al. 2001), whereas the expression of SLAM was increased in peripheral B cells from these patients (Isomaki et al. 1997). Thus the SLAM family-SAP signaling pathway is important for the development of lupus traits and other autoimmune diseases.

SAP-Mediated Signals in Hepatitis

Concanavalin A (ConA)-induced hepatitis is a murine experimental model of autoimmune hepatitis. ConA is a plant lectin derived from the Jack bean, *Canavalia ensiformis*, and specifically binds to the α-mannose and α-galactose residues of sugars. In in vitro cultures in the presence of ConA, T cells proliferate and produce cytokines and NK cells show augmented cytotoxicity against a broader spectrum of targets. Systemic injection of ConA causes hemagglutination, activation of lymphocytes, secretion of cytokines such as TNF-α, IL-6, IFN-γ, and IL-4, and subsequent hepatocyte injury (Tiegs et al. 1992). Mice with severe combined immunodeficiency and athymic mice are less sensitive to ConA-induced hepatitis, indicating the involvement of T cells. Mice lacking Vα14 NKT cells as well as MRL/lpr and MRL/gld mice were all resistant to hepatitis in this model (Kaneko et al. 2000; Tagawa et al. 1998; Takeda et al. 2000). Several studies have reported the involvement of P-selectin, LIGHT, osteopontin, IL-4, IFN-γ, and CD1d in ConA-induced hepatitis (Anand et al. 2006; Diao et al. 2004; Kaneko et al. 2000; Massaguer et al. 2002; Tagawa et al. 1998; Takeda et al. 2000; Toyabe et al. 1997).

We reported that MRL/lpr/rpl mice lack Vα14 NKT cells and are deficient in Fas antigen but sensitive to ConA-induced hepatitis (Furukawa et al. 2009). On the other hand, MRL/Mp-*Sap*$^{rpl/-}$ (MRL/+/rpl) mice also lack Vα14 NKT cells but have intact Fas antigen and are resistant to ConA-induced hepatitis. It was found that $CD4^+$ and $CD8^+$ T cells were the effector cells in this system and that blockade of 2B4, one of the SLAM family receptors, by 2B4-Fc fusion protein inhibited the induction of hepatitis in MRL/lpr/rpl mice. These data suggest that 2B4 signals mediated by molecules other than SAP in T cells play important roles in the induction of hepatitis in MRL/lpr/rpl mice. A good candidate could be EAT-2 because this molecule is expressed in T cells of MRL/lpr/rpl mice.

Vα14 NKT cells are known to be essential for the induction of hepatitis. Because Vα14 NKT cells were absent in MRL/lpr/rpl mice, ConA-induced hepatitis in this model is clearly independent of Vα14 NKT cells. Instead, MR-1-restricted Vα19 NKT cells, recently described as unconventional NKT cells (Kawachi et al. 2006), are candidates for the $2B4^+$ T cells responsible for hepatitis induction. This is consistent with reports of expansion of MR-1-restricted Vα19 NKT cells in Vα14 NKT-deficient mice (Croxford et al. 2006). Thus paradoxical ConA-induced hepatitis in MRL/lpr/rpl mice is independent of Vα14 NKT cells.

Interestingly, the susceptibility to lupus and hepatitis in MRL/lpr/rpl and MRL/lpr mice is reciprocal; thus MRL/lpr/rpl mice are resistant to lupus and susceptible to hepatitis, but the opposite is true for MRL/lpr mice. This differential susceptibility and resistance pattern suggests the existence of immunological mechanisms common to lupus and hepatitis which act reciprocally on the phenotypes of these autoimmune diseases.

SAP-Mediated Signals in Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) is one of the major complications of bone marrow transplantation (BMT) and blood transfusion. Although disparity in the major or minor histocompatibility complexes (MHC and mHC, respectively) between donor and recipient is associated with the pathogenesis of allogeneic GVHD, autologous and syngeneic GVHD have also been reported in the absence of such disparity in some cases of recipients of identical twin transplants or autologous BMT therapies (Adams et al. 2004; Latif et al. 2003). In animal models, short-term treatment of rodents with cyclosporine A after syngeneic BMT resulted in the development of chronic GVHD (Glazier et al. 1983; Hess et al. 1985). Another murine model of autologous chronic GVHD is *lpr*-GVHD (Allen et al. 1990b; Theofilopoulos et al. 1985). On transfer of bone marrow cells or splenocytes from MRL/lpr mice lacking Fas antigen to irradiated MRL/Mp-$Fas^{+/+}$ (MRL/+) recipients bearing intact Fas, the latter develop a wasting syndrome with skin rash and diarrhea similar to that of chronic GVHD, rather than the lupus-like autoimmune syndrome occurring in MRL/lpr mice (Allen et al. 1990a, b; Mosbach-Ozmen and Loor 1987; Piguet et al. 1987). Because MRL/+ bone marrow cells were accepted by the irradiated MRL/lpr recipients and no in vitro mixed lymphocytic reaction was observed between these two strains, differences in MHC or mHC between donors and recipients were not associated with this phenomenon (Fujiwara and Kariyone 1984; Perkins et al. 1987). *lpr*-GVHD was believed to be caused by the strong expression of FasL in lymphocytes of the MRL/lpr mice (Chu et al. 1995), but it was still unclear which population of lymphocytes, including the *lpr*-T-cell population, played a pathogenic role in the induction of *lpr*-GVHD. We found that a deficiency in FasL in the recipients accelerated *lpr*-GVHD and that MRL/lpr-$CD8^+$ T cells were the effector cells in this response (Table 2), even though FasL was highly expressed only in *lpr*-T cells. Furthermore, we found that a SAP deficiency in the donor promoted this process and therefore suggest that FasL in recipients provides protection from *lpr*-GVHD and that SAP-mediated signals in donor $CD8^+$ effector T cells inhibit *lpr*-GVHD induction.

SAP-mediated signals in $CD8^+$ T cells appeared to decrease the severity of *lpr*-GVHD. It was previously reported that the proliferation of SAP-deficient $CD8^+$ T cells was augmented and that AICD was impaired (Chen et al. 2007). In the case of lymphopenia-induced homeostatic proliferation in *lpr*-GVHD, autoreactive $CD8^+$ T cells without Fas and SAP can also survive longer and cause more severe *lpr*-GVHD. The mechanism behind this phenomenon involved reduced induction of p73, a key mediator of TCR-induced apoptosis through the mitochondrial pathway (Chen et al. 2007). Defects in SAP-mediated signaling result in longer-lived $CD8^+$ T cells due to decreased apoptosis, but make *lpr*-T and lupus-pathogenic T cells die. Thus these contrasting findings explain the opposite phenotypes of more severe *lpr*-GVHD caused by donor cells from MRL/lpr/rpl mice but alleviation of lupus traits in MRL/lpr/rpl mice (Komori et al. 2006). Interestingly, a rare manifestation of the SAP defect is autoimmune disorders such as vasculitis, colitis, and psoriasis. These clinical features of SAP-deficient XLP patients can be partially explained by over-activated $CD8^+$ T cells without SAP molecules, as shown in autologous *lpr*-GVHD models.

Table 2 Survival of lpr-GVHD

Donor	Recipient	GVHD grade
MRL/lpr	MRL/lpr	−
MRL/lpr	MRL/+	+
MRL/lpr	MRL/gld	++
MRL/lpr/rpl	MRL/gld	+++
MRL/lpr	MRL/gld/rpl	−
MRL/lpr/rpl	MRL/gld/rpl	−
MRL/lpr $CD4^+$ T cell	MRL/gld	+
MRL/lpr $CD8^+$ T cell	MRL/gld	+++
MRL/lpr/rpl $CD4^+$ T cell	MRL/gld	+
MRL/lpr/rpl $CD8^+$ T cell	MRL/gld	++++

Survival of the mice were followed until 9 weeks after the transfer

Conclusion

The roles of SAP have been analyzed in other animal models. SAP-deficient mice are also susceptible to experimental autoimmune encephalomyelitis (Hron et al. 2004) and experimental colitis induced by dextran sodium sulfate (unpublished data), as are wild-type mice. Future studies on the differential impact of SAP deficiency in autoimmune disease models will shed further light on the pathogenic mechanisms of these diseases. Because the SAP gene was originally identified by positional cloning of the XLP susceptibility gene, its role in the pathogenesis of immunological disorders was obviously predictable. Recent studies of SAP-deficient mice and humans have elucidated the pathophysiological roles of SAP-mediated signaling in autoimmune diseases. Vα24 NKT cells play a central role in the elimination of EBV and the induction of lupus and hepatitis, raising the possibility of interactions between virus infection and autoimmune diseases, i.e. the induction of autoimmune diseases by the incomplete elimination of viruses and inappropriate immunological reaction against viruses.

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