bjh review

X-linked lymphoproliferative syndrome: a genetic condition typified by the triad of infection, immunodeficiency and lymphoma

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Summary

X-linked lymphoproliferative disease (XLP) is an inherited immunodeficiency characterized by the clinical triad of increased susceptibility to primary Epstein–Barr virus (EBV) infection, dysgammaglobulinaemia and lymphoma. Most cases are caused by germline mutations in the *SH2D1A* gene, which encodes the adaptor molecule Signalling Lymphocytic Activation Molecule (SLAM)-associated protein (SAP). Recently, a subset of patients with an XLP-like phenotype was found to carry mutations in *XIAP*, the gene encoding the X-linked inhibitor of apoptosis protein (XIAP). Studies of XLP patients and *Sap*−/− mice reveal that loss of SAP expression impairs immune cell activities, such as natural killer and CD8+ T cell cytotoxicity, T cell cytokine production, activation-induced cell death, germinal centre formation and natural killer T cell development. Efforts to dissect the diverse roles of SAP and XIAP are enhancing our understanding of immune cell biology and defining how genetic defects in these molecules predispose to EBV-specific as well as more general cellular and humoral immune dysfunction. These studies are also highlighting critical signalling pathways that might be amenable to pharmacological targeting to improve the treatment of XLP and other disorders associated with impaired antiviral and antitumour immunity.

Keywords: immunodeficiency, infection, malignancy, X-linked lymphoproliferative syndrome, SLAM-associated protein.

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X-linked lymphoproliferative disease (XLP) is a rare primary immunodeficiency characterized by three dominant clinical features, including fulminant infectious mononucleosis (FIM), dysgammaglobulinaemia and lymphoma (Table I) (Seemayer *et al*, 1995). Since its initial description in the mid-1970's, XLP has been notable for the unique propensity of affected males to develop progressive lymphoproliferation, hepatosplenomegaly, cytopenias and erythrophagocytosis following Epstein–Barr virus (EBV) infection (Bar *et al*, 1974; Provisor *et al*, 1975; Purtilo *et al*, 1975). Originally named X-linked recessive progressive combined variable immunodeficiency, or Duncan's disease in recognition of a well-studied kindred (Purtilo *et al*, 1975), the condition is now referred to as XLP. In 2006, a second genetically distinct X-linked disorder associated with the development EBV-induced immune dysregulation was reported (Rigaud *et al*, 2006). In this review, we discuss the clinical and molecular features typifying these two disorders and where possible, explain how recent scientific advances have increased our understanding of the complex pathogenesis of these immunodysregulatory conditions.

Clinical manifestations

In patients with XLP, disease onset is usually at the age of 2·5 years and is triggered by EBV infection in many cases (Lim & Elenitoba-Johnson, 2004; Speckmann *et al*, 2008). Interestingly, most patients appear healthy prior to contracting EBV (Speckmann *et al*, 2008); however, following infection, patients often develop T and B cell lymphoproliferation and secondary haemophagocytic lymphohistiocytosis (HLH) (Mroczek *et al*, 1987; Nelson & Terhorst, 2000; Schimmer *et al*, 2006; Seemayer *et al*, 1995; Speckmann *et al*, 2008). Dysgammaglobulinaemia and lymphoma are two other common manifestations, which occur in EBV-positive as well as EBV-negative patients. (Brandau *et al*, 1999; Strahm *et al*, 2000; Sumegi *et al*, 2000). XLP patients may exhibit rarer clinical features, including aplastic anaemia, lymphoid vasculitis, pulmonary lymphoid granulomatosis and autoimmune

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Table I. Features of SAP *versus* XIAP deficiency.

Feature	SAP deficiency (XLP)	XIAP deficiency
Clinical manifestations		
HLH	Yes	Yes
Hypogammaglobulinaemia	Yes	Yes
Lymphoma	Yes	No
Aplastic anaemia	Yes	No
Vasculitis	Yes	No
Genetics		
Causative gene	*SH2D1A*	*XIAP*
Genetic locus	Xq25	Xq25
Encoded protein	SAP	XIAP
Effect of mutation	Reduced, absent protein expression	Reduced, absent or truncated protein
Immune cell functions		
NK cytotoxicity/degranulation	Reduced	Normal
NKT cell number (blood)	Absent	Variable
Restimulation-induced death	Reduced	Increased
Memory B cell numbers	Reduced	Not reported
Treatment options		
HLH	Immunosuppression and/or chemotherapy (etoposide) Consideration of Rituximab	Immunosuppression and/or chemotherapy (etoposide Consider Rituximab for EBV+ cases
Humoral deficiency	Intravenous IgG infusions	Intravenous IgG infusions
Lymphoma	Standard chemotherapy	
Curative therapy	Stem cell transplantation	Stem cell transplantation

HLH, haemophagocytic lymphohistiocytosis.

features such as colitis and psoriasis (Dutz *et al*, 2001; Purtilo *et al*, 1991; Schuster & Kreth, 2000; Seemayer *et al*, 1995; Talaat *et al*, 2009; Nichols, unpublished observations). Prior reports indicate that the prognosis for XLP is poor, with 70% of patients dying before the age of 10 years (Seemayer *et al*, 1995) and mortality nearing 96% for those with a history of EBV infection (Seemayer *et al*, 1995). Fortunately, the outcome for XLP patients may be improving due to increased awareness and enhanced ability to diagnose this condition, as well as application of newer approaches to the management of EBV infection (Milone *et al*, 2005; Booth *et al*, 2010). The only curative option for XLP is myeloablative or reduced intensity haematopoietic stem cell transplantation (SCT) [see below and (Cooper *et al*, 2008; Gross *et al*, 1996; Lankester *et al*, 2005)].

Genetic defect

The first gene defective in XLP was identified in 1998 (Coffey *et al*, 1998; Nichols *et al*, 1998; Sayos *et al*, 1998) and termed the Src Homology 2 (SH2)-Domain Containing Gene 1A (*SH2D1A*, OMIM*300490), which encodes the Signalling Lymphocytic Activation Molecule (SLAM)-associated protein (SAP). To date, over 70 *SH2D1A* alterations have been reported (Filipovich *et al*, 2010; Piirilä *et al*, 2006; Vihinen & Notarangelo, 2008), including missense, nonsense and deletion mutations. Most mutations result in diminished or absent SAP protein expression (Nichols *et al*, 2005a) and there is no apparent correlation between type of *SH2D1A* mutation and severity of disease (Brandau *et al*, 1999; Nelson & Terhorst, 2000; Sumegi *et al*, 2000).

The SAP protein consists of 128 amino acids and includes an SH2 domain and a short tail at the carboxyl-terminal region (Fig 1) (Sayos *et al*, 1998). SAP is expressed in T cells, natural killer (NK) cells and natural killer T (NKT) cells, but is not expressed in most normal human or murine B cells (Veillette *et al*, 2008; Ma *et al*, 2006). SAP is present, however, in some malignant B cells (Nagy *et al*, 2000, 2002). SAP modulates intracellular signal transduction via its association with receptors belonging to the SLAM family (Latour & Veillette, 2003) and possibly other receptors, including CD22 (Ostrakhovitch *et al*, 2009) and FcγRIIB (Li *et al*, 2008).

In 2006, the X-linked Inhibitor of Apoptosis gene *(XIAP*, formerly *BIRC4*, OMIM*300079) was identified as mutated in 12 patients with an XLP-like disease from three families lacking *SH2D1A* mutations (Rigaud *et al*, 2006). Remarkably, *XIAP* is located at Xq25 in close vicinity to *SH2D1A* (Rigaud *et al*, 2006). As with *SH2D1A*, mutations in *XIAP* are primarily 'loss of function' and associated with diminished or absent protein expression or less commonly, expression of a truncated protein (Marsh *et al*, 2009a; Rigaud *et al*, 2006). *XIAP* encodes the X-linked Inhibitor of Apoptosis Protein (XIAP), a member of 'Inhibitor of Apoptosis' (IAP) family of molecules. This protein consists of three Baculovirus IAP Repeat domains that participate in interactions of XIAP with caspases, as well as a

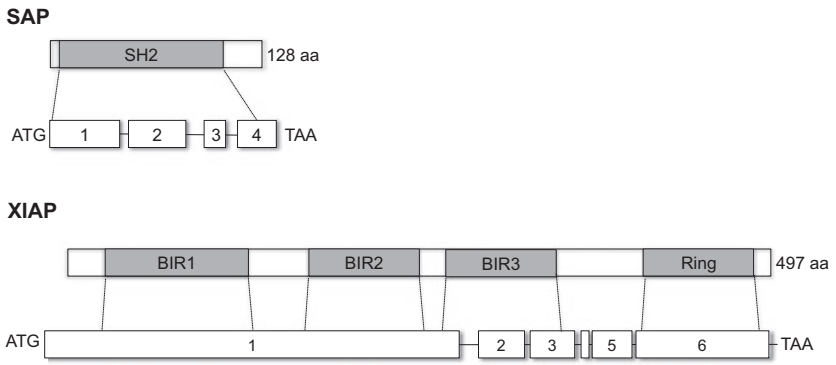

Fig 1. Protein and gene structures of SAP and XIAP. The human SAP protein is 128 amino acids in length and comprised of a single SH2 domain and a short carboxyl-terminal tail. SAP is encoded by the *SH2D1A* gene, which has four coding exons and is located at Xq25. Human XIAP is a protein of 497 amino acids that contains three Baculovirus IAP Repeat (BIR) domains that participate in interactions of XIAP with caspases and a C-terminal ring domain having potential E3 ubiquitin ligase activity. This protein is encoded by the *XIAP* (previously *BIRC4*) gene, also at Xq25.

C-terminal ring domain having E3 ubiquitin ligase activity (Fig 1). XIAP is expressed broadly within immune cells, where it is present in T, NK, NKT, B and myeloid cells (Marsh *et al*, 2009a; Rigaud *et al*, 2006). Although the loss of SAP and XIAP both cause EBV-associated HLH, it appears that the clinical features associated with XIAP deficiency do not completely overlap with those of XLP [see below and (Filipovich *et al*, 2010; Marsh, 2010)].

Mechanisms of SAP signalling

SAP was initially identified as a protein capable of binding to the cytoplasmic domain of the SLAM receptor (Sayos *et al*, 1998). Based on this observation, it was suspected that SAP might regulate the intracellular signals initiated by this receptor. Since this original finding, it has become clear that SAP, as well as the homologous proteins Ewing sarcoma-associated transctipt-2 (EAT-2) and the EAT-2-related transducer (ERT) (Veillette *et al*, 2009), are each capable of interacting with and regulating the activity of SLAM and the structurally similar 'SLAM family' receptors, including 2B4 (CD244; SLAMF4), NK- T- and B cell antigen (NTB-A; Ly108 in the mouse, SLAMF6), CD2-like receptor activating cytotoxic cells (CRACC, CD319; SLAMF7), CD84 (SLAMF5) and Ly9 (CD229; SLAMF3) (Bottino *et al*, 2001; Bouchon *et al*, 2001; Cocks *et al*, 1995; de la Fuente *et al*, 1997, 2001; Martin *et al*, 2001; Mathew *et al*, 1993; Romero *et al*, 2005; Tangye *et al*, 2000a). These receptors each consist of an extracellular portion containing two immunoglobulin (Ig)-like domains (except for Ly-9, which contains four Ig-like domains) (Latour & Veillette, 2003), a transmembrane domain and a cytoplasmic tail containing at least two tyrosine residues embedded in 'immunotyrosine switch motifs (ITSM)'. These ITSM conform to the sequence TxYxxV/I (where T stands for threonine, Y – tyrosine, V – valine, I – isoleucine and x – any other residue) and interact with SAP as well as other SH2 domain containing molecules. With the exception of 2B4, which binds to CD48 as its ligand (Brown *et al*, 1998; Latchman *et al*, 1998), the SLAM receptors bind to themselves with low affinity (Falco *et al*, 2004; Martin *et al*, 2001; Mavaddat *et al*, 2000; Romero *et al*, 2005). Thus, these receptors mediate homotypic and heterotypic interactions among cells of the haematopoietic and immune systems. Given that XLP patients lack functional SAP, it is currently proposed that the phenotypes of disease result from perturbed signalling downstream of one or more of these receptors.

Numerous studies have focused on dissecting the biochemical mechanisms utilized by SAP during immune cell activation. As SAP contains an SH2 domain and no other obvious functional regions, it was originally put forth that SAP might serve to block the recruitment of SH2-domain containing molecules to the cytoplasmic tail of the SLAM family receptors (Fig 2A). This model was based on observations that SAP competitively interfered with the binding of the SH2 domain-containing protein tyrosine phosphatase (PTPN11; SHP-2) to the phosphorylated cytoplasmic tail of SLAM (Sayos *et al*, 1998), Ly9 (Sayos *et al*, 2001), CD84 (Sayos *et al*, 2001) and 2B4 (Tangye *et al*, 1999) or the association of the SHP-1 phosphtatase (PTPN6) to phosophorylated CD84 (Lewis *et al*, 2001). By blocking the binding of inhibitory phosphatases, it was believed that SAP might influence intracellular signalling by further enhancing the phosphorylation of the SLAM receptors and/or other SLAM-associating signalling proteins. While this mechanism of signalling has been principally observed in *in vitro* studies where tagged molecules were introduced into heterologous cells, there are some data to suggest that it might also hold true in primary human T cells (Snow *et al*, 2009) as well as NK cells (Parolini *et al*, 2000).

An alternative model reveals that SAP functions not as an inhibitor of protein–protein interactions, but rather as an adaptor that supports the generation of SLAM receptor-associated signalling complexes (Fig 2B). This model is based on the observation that a unique portion of the SAP SH2 domain binds to the Src Homology 3 (SH3) domain of the Src family tyrosine kinase FynT (Chan *et al*, 2003; Latour *et al*, 2001, 2003). In so doing, SAP promotes FynT activation and

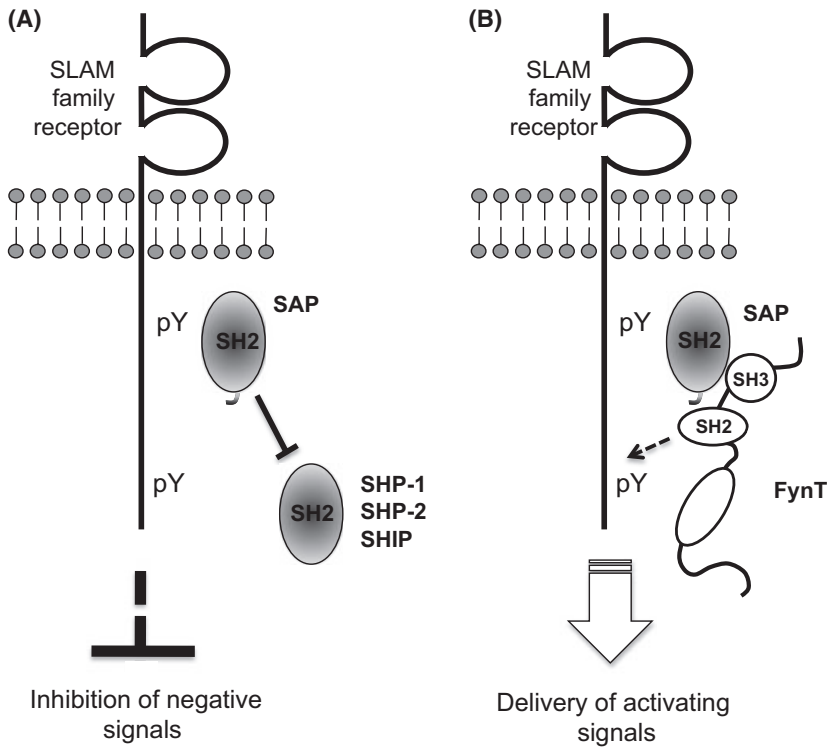

Fig 2. SAP signals via at least two distinct mechanisms. In (A), the SAP SH2 domain binds to phosphorylated tyrosine residues contained within the cytoplasmic tails of the SLAM family receptors. In so doing, SAP interferes with the binding of other SH2 domain-containing molecules, such as the inhibitory phosphatases SHP-1, SHP-2 and SHIP. (B) Alternatively, the SAP SH2 domain binds via arginine 78 to the SH3 domain of the Fyn T tyrosine kinase. SAP recruits FynT to the SLAM receptor tail, where FynT then phosphorylates additional tyrosines within the SLAM receptor tail as well as other associated signalling molecules.

recruits it to the cytoplasmic domain of SLAM. Active FynT then phosphorylates tyrosine residues within the SLAM receptor, which form docking sites for other signalling proteins, leading to the generation of a multi-protein SAP- and FynT-dependent tyrosine phosphorylation signal.

Molecular and cellular pathogenesis of XLP

Since the mechanisms and outcomes of SAP signalling have been most extensively studied in the context of SLAM, 2B4 and NTB-A, these pathways will be discussed further here. For information on the SAP-associated signals induced by other SLAM family receptors, we refer the readers to other excellent recent reviews (Ma *et al*, 2007; Veillette *et al*, 2009).

SLAM

The interaction of SAP with SLAM is unique when compared to its interaction with other SLAM family members in that SAP binds to the SLAM cytoplasmic tail in the absence of receptor tyrosine phosphorylation. Despite the constitutive nature of the SLAM-SAP association, interaction of the SLAM-SAP complex with FynT is absolutely dependent upon SLAM engagement. Recent studies suggest that engagement of SLAM may allow for changes in the structure of the SAP SH2 domain, thereby exposing arginine 78 and facilitating its interaction with the SH3 domain of FynT (Chen *et al*, 2006). The association of SAP with FynT increases the kinase activity of FynT, leading to the phosphorylation of SLAM, as well as other proteins recruited to the SLAM tail, such as the SH2 domain containing inositol phosphatase (SHIP-1), the adapters Docking protein-1 (Dok-1) and -2 (Dok-2), the Src homology/collagen adaptor (Shc) and the Ras-GTPase-activating protein (Ras-GAP) (Latour *et al*, 2001). Activation of FynT by SLAM and SAP also initiates the nuclear factor kβ (NFkβ) pathway via its effects on protein kinase C theta (PKCθ) and BcL10 (Cannons *et al*, 2004) (Table II). Importantly, if SAP or FynT are absent, or if the SAP-Fyn interaction is disrupted, SLAM engagement fails to generate these tyrosine phosphorylation signals. Thus, SAP and FynT are critical for proper SLAM receptor functions.

SLAM is present on the surface of T cells, B cells, dendritic cells (DCs) and macrophages (Bleharski *et al*, 2001; Castro *et al*, 1999; Cocks *et al*, 1995; Howie *et al*, 2002; Kruse *et al*, 2001; Punnonen *et al*, 1997) and its expression is increased by various stimuli, such as antigen receptor-induced B and T cell activation (Castro *et al*, 1999; Cocks *et al*, 1995; Punnonen *et al*, 1997), activation of macrophages with lipopolysacharide (LPS) and interferon (IFN)-γ (Howie *et al*, 2002) and activation of DCs and B cells through CD40 or in response

Table II. SAP-dependent functions of the SLAM family receptors.

Receptor	Signalling proteins	SAP-dependent functions	Fyn dependence
SLAM	SAP	↑ CD4 T cell Th2-type cytokines	Yes
	SHIP1	activation of PKCθ	
	Dok1	activation of NFkβ	
	Dok2	upregulation of GATA-3	
	SHC		
	Ras-GAP	NKT cell ontogeny (with Ly108)	Yes
2B4	SAP	NK cell cytotoxicity	Not reported
	Vav-1		
	c-Cbl	CD8+ T cell cytotoxicity	Not reported
	SHP-1, 2	formation of lytic synapse	
	Csk	polarization of perforin	
NTB-A, Ly108	SAP	↑ CD4 T cell Th2-type cytokines	Not reported
	SHP-1, 2	NK cell cytotoxicity	Not reported
	Vav-1	NKT cell ontogeny (with SLAM)	Yes
	c-Cbl	Reactivation induced cell death	No
		Germinal centre formation (with CD84)	No

to inflammatory molecules [e.g. LPS or interleukin (IL)-1β] (Bleharski *et al*, 2001; Kruse *et al*, 2001). While it is probable that SLAM modulates many aspects of immune cell function, here we discuss its role in T and NKT cells, as these lineages express SAP and are therefore relevant to our understanding of XLP.

Insights into the role of SLAM in CD4+ T cells have been provided by the use of anti-SLAM antibodies and examination of mice genetically deficient for SLAM expression. Engagement of SLAM with antibodies results in increased proliferation and induction of IFN-γ by previously activated T cells (Aversa *et al*, 1997; Carballido *et al*, 1997; Cocks *et al*, 1995), but no change or even a decrease in amount of T helper (T_H) 2-type cytokines (e.g. IL-4). Based on these observations, it was originally proposed that SLAM functioned as a co-stimulatory receptor to enhance T cell receptor (TCR)-induced proliferation of T cells and production of T_H1-type cytokines. Ironically, subsequent examination of CD4+ T cells from *Slam*−/− mice also revealed an increase, albeit mild, in the production of IFN-γ in response to TCR ligation (Wang *et al*, 2004). More striking however, was the marked reduction in TCR-induced IL-4 production by *Slam*−/− cells (Wang *et al*, 2004). The conflicting results between the *in vitro* and *in vivo* assays are believed to result from the fact that the anti-SLAM antibodies used in the initial studies were not agonistic, but rather had a blocking effect on SLAM function. Thus, SLAM modulates cytokine production in CD4+ T cells by inhibiting TCR-induced IFN-γ secretion and supporting optimal IL-4 production (Table II).

The pattern of altered cytokine production by *Slam*−/− CD4+ T cells resembles that observed in TCR-stimulated *Sap*−/− cells, which demonstrate variable increases in IFN-γ secretion and impaired IL-4 production (Czar *et al*, 2001; Wu *et al*, 2001). Together with prior biochemical data, these findings suggest that SAP and SLAM participate in a common signalling pathway promoting TCR-induced IL-4 production. Consistent with this possibility, CD4+ T cells from *Slam*−/−, *Sap*−/− and *Fyn*−/− mice, as well as mice harbouring a germline mutation in arginine 78 of SAP that abrogates Fyn binding (Sap^{R78A}) each exhibit impairments in TCR-induced activation of NF-kB and upregulation of GATA-3, critical transcription factors required for optimal IL-4 production (Cannons *et al*, 2004; Davidson *et al*, 2004).

XLP patients and *Sap*−/− mice lack invariant NKT cells, a lineage of innate type T lymphocytes with numerous functions including protection from specific cancers and pathogens, prevention of autoimmunity and promotion of tolerance (Chung *et al*, 2005; Nichols *et al*, 2005b; Pasquier *et al*, 2005). Recently, this block in NKT cell development was identified as occurring early in ontogeny, just at or after positive selection in the thymus (Griewank *et al*, 2007). Given its known association with SLAM, it was hypothesized that SAP might interact with this or other SLAM receptors in immature progenitors to promote NKT cell ontogeny. In support of this notion, interference with Ly108 and SLAM signalling profoundly limits NKT cell development in mice (Griewank *et al*, 2007). As the NKT cell phenotypes of *Sap*−/−, *Fyn*−/− and Sap^{R78A} mice are similar, it is probable that SLAM and Ly108 require SAP and Fyn to promote the generation of signals required for development of the NKT cell lineage (Nunez-Cruz *et al*, 2008) (Table II).

2B4

2B4 is expressed broadly on immune cells including NK cells, NKT cells, monocytes, eosinophils, basophils, memory CD8+ T cells, γδT cells and mouse bone marrow-derived mast cells (Garni-Wagner *et al*, 1993; Mathew *et al*, 1993; Nakajima *et al*, 2000; Romero *et al*, 2004; Speiser *et al*, 2001; Tangye *et al*, 1999, 2000b; Valiante & Trinchieri, 1993) and interacts with CD48, a

glycosylphosphatidylinositol-linked receptor, as its physiological ligand (Brown *et al*, 1998; Latchman *et al*, 1998). 2B4 has a cytoplasmic tail with multiple tyrosines, at least two of which are embedded in ITSMs and therefore capable of binding to SAP (Eissmann *et al*, 2005; Latour & Veillette, 2003). Unlike the SLAM-SAP interaction, which is constitutive, the interaction of 2B4 with SAP is negligible at baseline and increases following 2B4 ligation (Chen *et al*, 2004). As with SLAM, 2B4 ligation leads to generation of a SAP- and Fyn-dependent signal; however, this signal is slower and lesser in magnitude, and involves different molecules compared to those participating downstream of SLAM. For example, there is no evidence that Dok-1, Dok-2 or Shc are involved. Instead, 2B4 ligation leads to tyrosine phosphoryation of the guanine nucleotide exchange factor Vav-1, the ubiquitin ligase c-Cbl (Chen *et al*, 2004) and possibly SHP-1, SHP-2 and the c-src tyrosine kinase Csk (Eissmann *et al*, 2005) (Table II). The disparity in phosphorylation of substrates following 2B4 or SLAM ligation may result from the different cell types being examined (NK cells *versus* T cells), as well as the selective binding of specific molecules to unique sequences present within the cytoplasmic tails of 2B4 *versus* SLAM (Chen *et al*, 2004).

Detailed studies of 2B4 function have been completed using NK cells, where studies of human cells indicate that this receptor directly enhances or co-stimulates NK cell activation. Exposure of human NK cells to anti-2B4 antibodies or ligation of 2B4 in redirected cytotoxicity assays or following contact with CD48-bearing target cells triggers NK cytotoxicity and IFN-γ secretion (Brown *et al*, 1998; Garni-Wagner *et al*, 1993; Latchman *et al*, 1998; Moretta *et al*, 2001; Nakajima *et al*, 1999; Tangye *et al*, 2000b; Valiante & Trinchieri, 1993). Consistent with a stimulatory role, microscopy studies show that 2B4 and SAP rapidly localize to the contact site between NK and target cells in a region of active signalling (Roda-Navarro *et al*, 2004). Interestingly, NK cells from XLP patients are not able to efficiently kill target cells when specifically activated through 2B4 (Benoit *et al*, 2000; Nakajima *et al*, 2000; Parolini *et al*, 2000; Tangye *et al*, 2000b), yet they kill targets normally when stimulated via activating receptors that do not associate with SAP, such as CD16, NKp46, NKp30 and NKp44. Paradoxically, co-engagement of 2B4 and one or more of these activating receptors on SAP-deficient cells leads to marked inhibition of target cell killing (Parolini *et al*, 2000). Although the mechanisms of inhibition are not yet well understood, there are several possible explanations for this finding. First, it is possible that in the absence of SAP, 2B4 interacts with inhibitory phosphatases (such as SHP-1 or -2) that negatively influence the generation of activating signals normally induced by 2B4 or other receptors residing in close vicinity (Parolini *et al*, 2000). Second, it is possible that the SAP-related adaptor EAT-2, which has inhibitory properties in mice (Roncagalli *et al*, 2005) binds to 2B4 and leads to the generation of a unique signal that inhibits NK cell activation.

2B4 also functions as an activating receptor on human CD8+ T cells. 2B4 engagement augments TCR-induced CD8+ T cell proliferation and killing of target cells, including autologous and allogeneic EBV-transformed B cells (Dupre *et al*, 2005; Sharifi *et al*, 2004). Again, SAP-deficient cells exhibit impaired IFNγ secretion and target cell killing, with the latter finding associated with defective polarization of 2B4 and perforin at the site of contact of CD8+ cells with target cells (Dupre *et al*, 2005). Retroviral expression of SAP in XLP CD8+ T cells restores defects in cytokine production and killing, supporting a critical role for SAP in these CD8+ T cell functions (Sharifi *et al*, 2004). Given that loss of SAP impairs lytic synapse formation in CD8+ T cells, it remains possible that a similar disorganization of the lytic synapse occurs in SAP-deficient NK cells. Thus, mislocalization of 2B4 and other activating NK cell receptors could impair target cell lysis following co-engagement of 2B4 and these other activating receptors.

In contrast to human cells, studies of murine NK cells have revealed dichotomous roles for 2B4. On the one hand, 2B4 functions as an inhibitory, not an activating, receptor. This property is most notable when NK cells are stimulated by target cells bearing the 2B4 ligand CD48. For example, exposure of wild-type NK cells to CD48+ targets results in reduced target cell lysis compared to exposure to CD48-negative cells (Lee *et al*, 2004; Mooney *et al*, 2004). The reduced target cell killing can be reversed by addition of 'blocking' 2B4 or CD48-specific antibodies (Lee *et al*, 2004; Mooney *et al*, 2004). Further support for an inhibitory role for 2B4–CD48 interactions comes from the study of *2b4*−/− mice, whose NK cells exhibit enhanced cytotoxicity and increased IFNγ secretion following exposure to CD48-positive targets (Lee *et al*, 2004; Mooney *et al*, 2004).

On the other hand, 2B4–CD48 interactions play a positive role in promoting crosstalk between neighbouring NK cells or T cells. Abrogation of the 2B4–CD48 interaction using anti-2B4 or -CD48 antibodies or cells lacking expression of these molecules negatively influences IL-2 driven CD8+ T cell proliferation (Kambayashi *et al*, 2001) and cytotoxicity (Lee *et al*, 2003), as well as NK cell-induced TCR-dependent T cell proliferation (Assarsson *et al*, 2004). In addition, 2B4–CD48 interactions are important for supporting the expansion and functional maturation of murine NK cells in response to cytokines, such as IL-2, or exposure to tumour cells (Lee *et al*, 2006a). Thus, 2B4 has dual functions in mice, where it inhibits the cytotoxic responses of NK cells towards CD48-bearing targets, yet enhances the proliferative responses and acquisition of cytokine-induced effector functions of 2B4- and CD48-expressing NK, CD4+ and CD8+ T cells.

The mechanisms underlying 2B4's dual functions in mice could be explained in a number of ways. First, murine NK cells express a 'long' and a 'short' isoform of 2B4, which differ in their ability to bind SAP and modulate NK cell functions (Schatzle *et al*, 1999; Stepp *et al*, 1999). Thus it is possible that the outcome of 2B4 signalling could vary depending on the relative abundance of 2B4 proteins encoded by the long and short isoforms. Second, NK might cells express different

amounts of activating or inhibitory 2B4-associated signalling molecules (such as SAP, EAT-2, ERT) depending on their degree of maturation or functional activation. Therefore, the levels of these proteins within an NK cell could direct 2B4 signals in either an activating or inhibitory direction. Supporting this possibility, engagement of 2B4 on wild-type mouse NK cells by CD48+ melanoma cells leads to induction of target cell lysis, while similar stimulation of NK cells lacking SAP, EAT-2 and ERT results in the inhibition of target cell killing (Dong *et al*, 2009). In NK cells lacking SAP, EAT-2 and ERT, engagement of 2B4 enhances the tyrosine phosphorylation and activation of SHIP-1, leading to inhibition of its downstream targets Erk and Akt (Dong *et al*, 2009). Thus, in SAP adaptor deficient cells, 2B4-mediated inhibition of NK functions could be due in part to enhanced activation of the SHIP-1 phosphatase.

NTB-A

Like other members of the SLAM family, NTB-A (Ly108 in the mouse) contains multiple tyrosines within its cytoplasmic portion, two of which are found within canonical ITSMs. Biochemical studies of human NK cells reveal that phosphorylated NTB-A associates with SAP, as well as SHP-1 and SHP-2 (Bottino *et al*, 2001). T cell studies reveal variable results, where some reports indicate that phospho-NTB-A can interact with SHP-1 (Snow *et al*, 2009), yet others suggest that it may not (Valdez *et al*, 2004). The discrepancy between these reports could reflect differences in the methods used for T cell stimulation. In IL-2-activated human NK cells, phospho-NTB-A associates with EAT-2 as well as SAP (Eissmann & Watzl, 2006). Studies using a murine T cell line reveal that engagement of Ly108 leads to a SAP- and Fyn dependent tyrosine phosphorylation signal involving Ly108 itself, Vav-1 and c-Cbl (Zhong & Veillette, 2008) (Table II). In this study, it was not noted whether EAT-2, SHP-1 or -2 are involved in Ly108 signalling.

NTB-A is expressed on almost all human B, T and NK cells (Bottino *et al*, 2001; Fraser *et al*, 2002; Peck & Ruley, 2000; Valdez *et al*, 2004). In the mouse, Ly108 expression is similar except that it is present on only a subset of NK cells (Dong *et al*, 2009). NTB-A functions in a homotypic manner to enhance NK cell cytotoxicity (Bottino *et al*, 2001; Falco *et al*, 2004; Flaig *et al*, 2004; Stark & Watzl, 2006), IFNγ secretion (Eissmann & Watzl, 2006; Falco *et al*, 2004; Flaig *et al*, 2004) and perhaps proliferation (Flaig *et al*, 2004). Similar to 2B4, engagement of NTB-A on SAP-deficient human NK cells is associated with impaired target cell killing and inhibition of killing induced by other stimulatory receptors (Bottino *et al*, 2001). Thus, NTB-A is an activating receptor on human NK cells, whose function depends upon the presence of SAP.

Initial studies of NTB-A function in T cells demonstrated that triggering of NTB-A using monoclonal antibodies leads to enhanced TCR-induced T cell proliferation, expression of activation markers and secretion of IFNγ (Valdez *et al*, 2004). Use of an Ly108-Fc fusion to block Ly108-mediated intercellular interactions in a mouse model of experimental encephalitis led to a slowed kinetics of disease onset and prevention of pathology in a subset of animals (Valdez *et al*, 2004). These data led to the conclusion that NTB-A functions in T cells to co-stimulate T cell activation and promote T_H1-type cytokine responses. However, later studies using CD4+ T cells from *Ly108*$^{\Delta 2+3}$ mice in which exons 2 and 3 of the *Slamf6* (*Ly108*) gene are deleted, demonstrated that these cells produce less IL-4 than wild-type cells in response to TCR stimulation or cutaneous infection with *Leishmania mexicana* (Howie *et al*, 2005). Although it is not understood why the results among these studies vary, the similar phenotypes of *Ly108*$^{\Delta 2+3}$, *Slam*−/− and *Sap*−/− mice suggest that these molecules participate in a similar signalling pathway, controlling the production of T_H1 and T_H2-type cytokines by activated CD4+ T cells (Table II).

Recent data also implicate NTB-A in a process known as restimulation-induced cell death (RICD) (Snow *et al*, 2009). Programmed cell death via apoptosis is essential to eliminate activated T cells during a productive immune response. At the peak of the response, when antigen and survival cytokines such as IL-2 are abundant, restimulation through the TCR deletes activated effector T cells. This regulatory mechanism is postulated to control the immune response, thereby preventing lymphoproliferation and T cell-mediated tissue damage. Recently, A. L. Snow *et al* (2009) demonstrated that XLP patient T cells exhibit defective RICD and impaired expression of the death promoting proteins Fas ligand (FasL) and Bcl-2-interacting mediator of cell death (BIM). Similar results were obtained when SAP was silenced in primary human T cells, indicating that SAP is critical signalling molecule required to promote RICD.

NTB-A is the most abundant SLAM family receptor expressed on TCR re-stimulated T cells and silencing of NTB-A, but not other SLAM receptors, reduced expression of FasL and BIM and decreased the sensitivity of wild-type T cells to RICD. In re-stimulated wild-type T cells, NTB-A associated with SAP and co-localized with the TCR (Snow *et al*, 2009). In contrast, re-stimulated SAP-deficient T cells exhibited less NTB-A co-localization with the TCR, TCR clusters appeared less ordered and there was prolonged contact between NTB-A and SHP-1. Thus, when bound to NTB-A, SAP facilitates formation of TCR clusters, which augment TCR signal strength in favour of RICD. In the absence of SAP, NTB-A-mediated recruitment of SHP-1 to TCR clusters could inhibit TCR signalling, leading to RICD resistance. Consistent with this notion, siRNA-mediated knockdown of NTB-A or SHP-1 restored the sensitivity of SAP-deficient T cells to RICD.

Impaired SLAM-SAP signalling and the phenotypes of XLP

While questions remain regarding the functions of the SLAM receptors and the dependence of these functions on the presence of SAP and/or FynT, it is now generally accepted that

SLAM-SAP interactions regulate important aspects of immune cell activation and ontogeny. Thus, in XLP patients who lack functional SAP, impaired SLAM receptor signals lead to aberrant cellular responses, which, in all likelihood, contribute to the complex phenotypes of this immune deficiency. Here, we describe the more common manifestations of XLP and attempt to explain the pathogenesis of these manifestations in the context of the cellular deficiencies described above.

Susceptibility to EBV infection

Epstein, Achong and Barr first discovered EBV, a member of the human γ-herpes virus family, by electron microscopy of cells cultured from Burkitt lymphoma tissue (Cohen, 2000; Epstein *et al*, 1964). EBV is a ubiquitous virus that infects most individuals during infancy and childhood (Kanegane *et al*, 1997). In immunocompetent individuals, primary infection during childhood is usually asymptomatic, while infection during adolescence and adult years may lead to signs and symptoms related to transient EBV-induced lymphoproliferation, a condition known as infectious mononucleosis (IM) (Cohen, 2000; Luzuriaga & Sullivan, 2010). In patients with cellular immunodeficiency, EBV can elicit a more fulminant form of IM marked by the dysregulated proliferation of EBV-infected B cells, reactive CD8+ T cells and macrophages. Immunodeficient individuals are also prone to develop chronic active EBV infection, EBV-induced lymphoproliferative disorders and malignant B cell lymphomas (Cohen, 2000; Cohen *et al*, 2008; Thorley-Lawson & Gross, 2004). In XLP patients, EBV infection can progress to hepatitis, bone marrow aplasia and HLH (Mroczek *et al*, 1987). Patients developing these manifestations exhibit B, CD8+ T cell and macrophage infiltration into affected tissues, including liver, lymphoid organs, bone marrow and central nervous system. Although XLP was first described based on the increased susceptibility of affected males to develop fatal EBV infection, recent studies suggest that primary infection does not always result in fulminant IM (Sumegi *et al*, 2000).

EBV infects epithelial cells and resting B cells in the oropharynx (Miyawaki, 2004). EBV-infected B cells are induced to proliferate, produce virus and express viral proteins (Cohen, 2000). EBV-infected B cells elicit an immune response that probably involves NK cells, which produce IFNγ and inhibit outgrowth of virus-infected target cells *in vitro* (Hislop *et al*, 2007). Subsequently, antigen-specific CD4+ and CD8+ T cells emerge and facilitate the production of neutralizing antibodies and elimination of the majority of EBV-infected B cells (Hislop *et al*, 2007). Nonetheless, a small proportion of memory B cells remain infected lifelong (Babcock *et al*, 1998) and serve as a reservoir of virus that can become reactivated when T cell immunity is suppressed.

XLP-associated fulminant IM probably occurs due to cumulative defects in the functions of several immune lineages. For example, it is probable that 2B4-associated defects in NK and CD8+ T cell function are central to the development of this condition. Indeed, CD48, the natural ligand for 2B4, was initially identified as a molecule upregulated on B cells following their infection with EBV (Thorley-Lawson *et al*, 1982). In healthy individuals, 2B4 might direct NK and CD8+ T cell lytic activity to CD48+ EBV-infected B cells. In XLP patients, the diminished ability of NK and CD8+ T cells to kill through 2B4, and possibly other receptor-mediated pathways, could allow for the persistence of EBV-infected B cells, which would further stimulate NK and CD8+ T cells and result in the excess secretion of pro-inflammatory cytokines. This excess CD8+ T cell expansion might be exacerbated by defects in RICD, which could lead to further accumulation of activated CD8+ T in the tissues of EBV-infected patients. Last, it is possible that the lack of NKT cells in XLP patients contributes to impaired clearance of EBV or defective regulation of the immune response induced by the virus. Indeed, NKT cells have been implicated in the control of numerous virus infections in mice, including Herpes simplex virus (Types 1 and 2), Lymphocytic choriomeningitis virus, murine cytomegalovirus and others (Diana & Lehuen, 2009).

A recent report describes two female siblings from a consanguineous Turkish family who developed chronic active EBV infection in early childhood, followed by a fatal EBV-associated lymphoproliferation later in life (Huck *et al*, 2009). Both siblings harboured a homozygous mutation in the gene encoding the Interleukin-2 inducible T cell kinase (*ITK*, OMIM*186973), which destabilized the expression of ITK and was associated with a reduction in the number of peripheral blood NKT cells. Interestingly, ITK-deficient mice also exhibit impairments in NKT cell development and altered T cell functions (Atherly *et al*, 2006; Broussard *et al*, 2006; Felices & Berg, 2008; Liao & Littman, 1995). Although it is not understood why these girls developed an EBV-driven disease, it is possible that their T and NKT cell defects contributed to impaired viral clearance and subsequent development of immune-mediated pathology. Based on the emerging role of NKT cells in anti-viral immunity, we propose that these cells may be important regulators of the anti-EBV immune response in humans. While their regulatory functions may be less critical in immunocompetent individuals, NKT cells may play a more dominant role in the setting of NK, CD4+ and CD8+ T cell dysfunction, as occurs in patients with ITK or SAP deficiency.

Dysgammaglobulinaemia

Patients with XLP exhibit abnormal humoral immune responses, ranging from specific subclass deficiencies or elevated levels of IgM (Grierson *et al*, 1991) to generalized hypogammaglobulinaemia. While defects in antibody production are most notable in patients who survive EBV infection, these manifestations may also occur in patients who are EBV-naïve. As the result of humoral immune defects, patients may present with sinopulmonary infections (Seemayer *et al*, 1995) and less commonly cutaneous, gastrointestinal or

systemic infections. These manifestations can make it difficult to distinguish between XLP and common variable immunodeficiency (CVID) (Aghamohammadi *et al*, 2003; Eastwood *et al*, 2004; Gilmour *et al*, 2000; Hugle *et al*, 2004; Morra *et al*, 2001; Nistala *et al*, 2001; Soresina *et al*, 2002).

Investigations into the humoral defect in XLP demonstrate that circulating B cell numbers are usually normal (Lindsten *et al*, 1982; Ma *et al*, 2005); however, there is a marked reduction in CD27+ memory B cells (Ma *et al*, 2005; Malbran *et al*, 2004). Furthermore, the majority of residual memory cells express IgM and not IgG, suggesting a defect in naïve B cell differentiation *in vivo* (Ma *et al*, 2006). Consistent with this finding, the spleens of XLP patients (Ma *et al*, 2006) and *Sap*−/− mice (Crotty *et al*, 2003) have reduced numbers of germinal centres (GC), lymphoid structures critical for the generation of long-lasting isotype switched B cell responses.

Many lines of evidence point to the fact that SAP expression in CD4+ T cells, not B cells, is essential for promoting productive GC responses. First, *Sap*−/− mice produce antibodies in a manner comparable to wild type mice following immunization with T cell-independent antigens (Cannons *et al*, 2006; Kamperschroer *et al*, 2006; Morra *et al*, 2005). Similarly, human XLP B cells proliferate and produce antibodies normally when stimulated *in vitro* with T-independent antigens (Ma *et al*, 2005, 2006). These data indicate that B cell function is generally normal in the absence of SAP and that the reduced immunoglobulin levels in SAP-deficient hosts are due to aberrations in other cell types. Second, adoptive transfer of SAP-expressing but not SAP-deficient CD4+ T cells with SAP-deficient B cells into irradiated or immunodeficient mice improves defects in GC formation and antigen-specific antibody responses (Crotty *et al*, 2003; Kamperschroer *et al*, 2006). Third, targeted deletion of SAP in T cells, not B cells, leads to GC defects recapitulating those observed in *Sap*−/− mice (Veillette *et al*, 2008). Collectively, these findings lead to the conclusion that SAP is required in CD4+ T cells to promote the full differentiation of B cells *in vivo* into antibody secreting plasma cells.

Early investigations into the defect in T cell help to B cells revealed that SAP-deficient CD4+ T cells exhibit reduced and/or delayed expression of the inducible costimulator (ICOS) following TCR ligation (Cannons *et al*, 2006; Ma *et al*, 2005). Interestingly, there are many features common to SAP-deficient and ICOS/ICOS-ligand-deficient humans and mice, including absence of GC, defective immunoglobulin isotype switching, reduced memory B cells and decreased IL-10 and IL-4 production by CD4+ T cells (Crotty *et al*, 2003; Czar *et al*, 2001; Grimbacher *et al*, 2003; Wu *et al*, 2001; Warnatz *et al*, 2006). These data suggest that SAP might function in part by inducing regulated ICOS expression, thereby allowing for optimal GC responses.

More recently, it was demonstrated that loss of SAP expression in mice is associated with a possible decrease in the number of T follicular helper (T_{FH}) cells, antigen-activated CD4+ T cells that acquire expression of CXCR5 and relocate from the T cell zone to the B cell follicle to induce and maintain GC formation (Kamperschroer *et al*, 2008; Qi *et al*, 2008; Cannons *et al*, 2010; Linterman *et al*, 2009). More importantly, SAP-deficient murine CD4+ T cells do not form stable contacts with B cells or efficiently enter and remain within GC (Qi *et al*, 2008). Thus, SAP may be required for the differentiation, as well as the function and/or persistence of T_{FH} within lymphoid tissues and for expression of specific adhesive molecules that facilitate stable T cell:B cell interactions. In a recently published report, Cannons *et al* (2010) generated and examined a strain of *CD84*−/− mice, which also exhibited modest reductions in the number of T_{FH} cells and diminished GC responses, albeit not to the same extent as *Sap*−/− animals. Using adoptive transfer approaches, these investigators also show that the co-operative function of CD84 and Ly108, the SLAM receptors most highly expressed on T_{FH} cells, are required to sustain stable T cell:B cell contacts and promote optimal GC and humoral responses.

It is also possible that the lack of NKT cells, which comprise a subset of CD4+ T cells, plays a role in the humoral immune defect in XLP. Human NKT cells promote the proliferation of autologous naive and memory B cells *in vitro* and induce immunoglobulin production (Galli *et al*, 2003). Activation of NKT cells *in vivo* enhances protection against infection and elicits higher frequencies of memory B cells (Galli *et al*, 2007). Interestingly, vaccination with proteins and the NKT cell specific agonist alpha-galactosyl ceramide, elicits antibody responses in major histocompatibility complex (MHC) class II-deficient mice in which conventional CD4+ T cell functions are impaired (Galli *et al*, 2007). Conversely, mice lacking NKT cells exhibit a time-dependent loss of specific antibodies following immunization. Together, these data suggest that, like conventional CD4+ T cells, NKT cells promote and sustain antigen-specific antibody responses.

Lymphoma

About 30% of XLP patients present with lymphoma as the initial manifestation of disease (Seemayer *et al*, 1995; Speckmann *et al*, 2008). While many patients develop lymphoma as the result of malignant transformation of EBV-infected B cells, some patients demonstrate no evidence of a prior EBV infection (Brandau *et al*, 1999; Sumegi *et al*, 2000). Lymphomas usually manifest earlier in EBV-infected (*c.* 5 years) *versus* non-infected (*c.* 8 years) patients (Latour & Veillette, 2003; Seemayer *et al*, 1995; Sumegi *et al*, 2000). As expected, the majority of lymphomas are of B cell origin with 50% having a Burkitt-type (small non-cleaved) histology. The remaining lymphomas exhibit a variety of histologies, including immunoblastic (18%), large non-cleaved (12%), as well as small cleaved, mixed and unclassified (Egeler *et al*, 1992; Gaspar *et al*, 2002; Harrington *et al*, 1987). Extranodal lymphomas may involve the central nervous system, liver and kidneys (Harrington *et al*, 1987).

It is not yet well understood how *SH2D1A* mutations lead to the increased rate of lymphomas in XLP patients, but it is possible that the loss of a pro-apoptotic function of SAP in T and possibly B cells, could lead to the development of lymphomas (Nagy & Klein, 2010; Nagy *et al*, 2009). In addition, defects in NK and CD8+ T cell cytotoxicity might result in impaired anti-tumour surveillance against EBV-infected or non-infected B cells. Indeed, this notion is supported by studies revealing that SAP, 2B4, Ly108 and SLAM are each required for promoting optimal clearance of tumour cells *in vitro* and *in vivo* (Bloch-Queyrat *et al*, 2005; Dong *et al*, 2009; Mehrle *et al*, 2008; Vaidya *et al*, 2005). It is also conceivable that the impaired surveillance against tumour cells is due in part to the lack of invariant NKT cells that occurs in affected patients. NKT cells exhibit direct lytic activity against tumour cells and tumour-associated macrophages and enhance the cytotoxic activities of NK and CD8+ T cells (Berzofsky & Terabe, 2009; Song *et al*, 2009). Consistent with their protective anti-tumour functions, many studies document a paucity of NKT cells in the peripheral blood or tissues of patients with advanced forms of cancer (Dhodapkar *et al*, 2003; Gulubova *et al*, 2009; Lynch *et al*, 2009; Yuling *et al*, 2009). In mice heterozygous for the tumour suppressor p53, loss of type 1 NKT cells enhances susceptibility to tumours, including sarcomas, carcinomas and hematopoietic tumours (Swann *et al*, 2009). Recent studies also show that NKT cells protect against B cell lymphomas in mice (Renukaradhya *et al*, 2008). Interestingly, infection of humanized mice with EBV promotes the generation of cytotoxic NKT cells, which produce IFNγ and enhance T-cell killing of EBV-positive tumour cells (Yuling *et al*, 2009). Collectively, these data reveal an important role for NKT cells in anti-tumour immune surveillance and it remains possible that expansion and activation of these cells could help to prevent or treat EBV-related cancers in XLP patients in the future.

Clinical features of XIAP deficiency

Inactivating mutations in *XIAP* occur in a subset of male patients with features similar to XLP (Marsh, 2010; Marsh *et al*, 2009a,b; Rigaud *et al*, 2006). In the original report of XIAP-deficient patients, Rigaud *et al* (2006) described 12 affected boys of whom 11 (92%) developed EBV-induced HLH and 4 (33%) hypogammaglobulinaemia. More recently, Marsh (2010) described an additional 10 patients, with 9 (90%) developing HLH. In many of these latter patients HLH was recurrent, yet in only 3 (30%) was it associated with EBV infection. The difference in incidence of EBV-induced disease between these two studies might reflect the fact that patients in the original cohort were selected based on their XLP-like phenotype (classically defined by an increased sensitivity to EBV). In the study by Marsh, hypogammaglobulinaemia was identified in two of nine patients examined; however, this manifestation was felt to be secondary to therapy because several patients exhibited normal immunoglobulin levels prior to receiving any treatment. No XIAP-deficient patients have yet been reported to develop lymphoma. Laboratory studies of XIAP-deficient patients reveal variable NKT cell defects, hyperinflammation and haemophagocytosis consistent with other hereditary or acquired HLH syndromes and paradoxically, normal NK cell function (Table I). Together, these investigations suggest that, despite their potential similarities, XLP and XIAP-deficiency are not mirrors of one another and instead are likely to represent distinct disorders.

Pathogenesis of XIAP-associated disease

Although unproven, a number of possibilities exist to explain why mutations in the *XIAP* gene lead to the development of an HLH-like disease. First, XIAP is a ubiquitin ligase that binds to and inhibits the activity of caspases 3, 7 and 9 (Deveraux *et al*, 1997). Therefore, XIAP may function to prevent HLH by inhibiting the apoptosis of cells that mediate the clearance of pathogens. In support of this possibility, T cell blasts from EBV-positive XIAP-deficient patients exhibit increased apoptosis (Marsh, 2010; Rigaud *et al*, 2006), as do macrophages from *Chlamydia pneumonia*-infected *Xiap*−/− mice (Prakash *et al*, 2010). Second, loss of XIAP may contribute to immunopathology in the setting of infection by promoting the apoptosis of regulatory T cell populations, such as NKT or CD4+ Treg cells, which would otherwise downregulate pathogen-induced immune cell responses. Currently, there are conflicting data as to whether NKT cell populations are reduced in XIAP-deficient humans and there are no published data on the number of Tregs at baseline or in response to specific infections. Third, the loss of XIAP might lead to disease via a completely different mechanism. Specifically, the preferential death of XIAP-deficient target cells might not allow for stable infection by viruses or other pathogens, which would favour dissemination of pathogen and potentially the development of an exaggerated immune response. Interestingly, *Xiap*−/− murine fibroblasts die more readily than wild-type cells and release more live virus following infection with murine γ-herpesvirus-68, a viral strain commonly used to model EBV infection (Rumble *et al*, 2009). Last, it is conceivable that the loss of XIAP influences immune cell activation based on other functions of the protein, such as its participation in the transforming growth factor (TGF)-β, notch, c-Jun N terminal kinase (JNK) and/or NF-κβ pathways (Rumble *et al*, 2009). Recent studies in mice have provided evidence in support of this possibility. For example, XIAP regulates innate immunity to *Listeria monocytogenes* by modulating JNK and NF-kB signalling and promoting production of proinflammatory cytokines (Bauler *et al*, 2008). Deficiency of XIAP in mice also leads to increased sensitivity to infection with *Chlamydia pneumonia* that is associated with dysregulated production of TNFα and defects in macrophage and CD8+T cell functions (Prakash *et al*, 2010). Collectively, these observations suggest that the loss of XIAP expression and/or function contribute to disease via a

number of mechanisms that favour the persistence of pathogen and impair the host immune response.

Establishing a diagnosis of SAP or XIAP deficiency

SAP or XIAP-deficiency should be included in the differential diagnosis for any male patient who presents with fatal or near fatal EBV infection, HLH in childhood or adolescence, or hypogammaglobulinaemia, particularly when patients have a positive family history for maternally-related males with similar features. As XIAP-deficient patients seem not to develop lymphoma, male patients with lymphoma should be evaluated for SAP, but not XIAP deficiency. While several laboratory abnormalities are suggestive of SAP-deficiency, such as a reduced number of CD27+ B memory cells (Chung *et al*, 2005; Ma *et al*, 2006; Malbran *et al*, 2004), lack of NKT cells (Chung *et al*, 2005; Ma *et al*, 2006; Malbran *et al*, 2004; Nichols *et al*, 2005b; Pasquier *et al*, 2005), and variably impaired NK cell lytic function (Benoit *et al*, 2000; Dupre *et al*, 2005; Latour & Veillette, 2003; Parolini *et al*, 2000), perhaps the most efficeint way to determine whether a patient might have one of these conditions is to evaluate for SAP or XIAP protein expression by flow cytometry. Fortunately, flow cytometric assessment of SAP or XIAP protein expression requires a minimal amount of blood, has a rapid turnaround time and is clinically available (Marsh *et al*, 2009a; Tabata *et al*, 2005). Thus, for male patients with appropriate clinical features, the identification of reduced or absent protein expression should prompt genetic counselling and analysis for the presence of a germline *SH2D1A* or *XIAP* mutation.

Treatment of SAP or XIAP deficiency

The treatment of SAP or XIAP deficiency is often tailored to address the specific needs of individual patients. Immunoglobulin replacement therapy is suggested for patients with humoral immune defects (Speckmann *et al*, 2008) and while such treatment may prevent bacterial infections, it may not be effective in the prevention of primary EBV-infection and/or lymphoma (Okano *et al*, 1991). Patients with lymphoma should be treated according to standard chemotherapy regimens, but monitored closely for the development of hypogammaglobulinaemia and infection. Unfortunately, relapses are often common (Speckmann *et al*, 2008). Finally, for patients with HLH, regardless of the trigger, good responses have been documented following institution of specific HLH-directed protocols (Trottestam *et al*, 2009).

As for EBV infection, it is important that primary infection be diagnosed promptly, prior to the onset of a dysregulated immune response. However, it is often not possible to know whether an individual has SAP or XIAP deficiency in the absence of a positive family history. Thus, it is often difficult to use a 'preventative' strategy. Fortunately, the diagnosis of IM is readily suggested based on the triad of fever, pharyngitis and lymphadenopathy, with other manifestations including malaise, anorexia, hepatosplenomegaly and liver dysfunction (Ebell, 2004; Hurt & Tammaro, 2007; Luzuriaga & Sullivan, 2010). In patients with these features, EBV infection can be confirmed by polymerase chain reaction to detect the presence of viral genome in the blood or other tissues. Serological testing is generally not useful as SAP or XIAP-deficient patients may have existing dysgammaglobulinaemia and SAP-deficient patients are known to exhibit defects in the production of anti-EBV antibodies (Seemayer *et al*, 1995). For patients with EBV infection, strong consideration should be given to use of anti-CD20 antibodies, such as rituximab to eliminate mature B cells, which serve as the reservoir for EBV. Indeed, rituximab has been used to prevent or to treat HLH in a limited number of EBV+ patients when used with steroids and/or chemotherapy to curtail T cell and macrophage activation (Balamuth *et al*, 2007; Milone *et al*, 2005; Lee *et al*, 2006b; Mischler *et al*, 2007). Given that the use of Rituximab can lead to reactivation of hepatitis B, patients should be tested for the presence of this virus prior to initiation of therapy (Ram & Raanani, 2009). Rituximab can also be used prophylactically to prevent EBV disease prior to stem cell transplantation in EBV-naïve patients (Nichols, unpublished observations).

At present, SAP-deficiency can only be cured by allogeneic SCT. In the literature, 15 XLP patients have been described as undergoing myeloablative SCT. These patients were treated with a variety of conditioning regimens and 12 of the 15 are reported to be alive (Gross *et al*, 1996; Lankester *et al*, 2005). Reduced intensity conditioning SCT has been used to treat a limited number of patients with SAP deficiency (Amrolia *et al*, 2000; Cooper *et al*, 2006; Slatter *et al*, 2005); however, the efficacy of this approach remains to be determined. Currently, there is little in the literature describing the use of SCT as a therapy for XIAP deficiency. Nonetheless, given the propensity of patients to develop recurrent bouts of HLH, it seems reasonable that these patients be approached regarding SCT when an appropriately matched unaffected donor is available. Gene therapy could also be considered as a possible future therapeutic option for SAP or XIAP deficiency (Sharifi *et al*, 2004), but this technology has not yet been fully developed for these conditions (Blaese, 2007).

Conclusions

A little over a decade has passed since the identification of the first gene responsible for XLP. In this time, we have learned much about this intriguing immunodeficiency and we are beginning to understand its relationship to the more recently described condition caused by deficiency of XIAP. Advances in our understanding of the clinical and laboratory features associated with XLP and XIAP deficiency and improvements in our ability to detect SAP and XIAP expression by intracellular staining have made it possible to diagnose these conditions more readily. Rapid detection is critical, as it allows for confirmatory genetic testing and monitoring of affected

individuals for the development of disease onset before significant morbidity has occurred.

Laboratory studies probing SAP and XIAP function reveal that these molecules regulate a wide array of responses within the immune system. We must now translate these findings into new and improved therapies. Exemplifying the successful application of scientific knowledge to the clinical management of XLP patients is the use of B cell-deleting antibodies to treat EBV infection to prevent the onset of HLH. Future efforts should aim to refine the timing and application of SCT or gene therapy and establish whether the adoptive transfer of NKT or other immune cells, or correction of apoptotic defects, will further improve the outcome for affected individuals.

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