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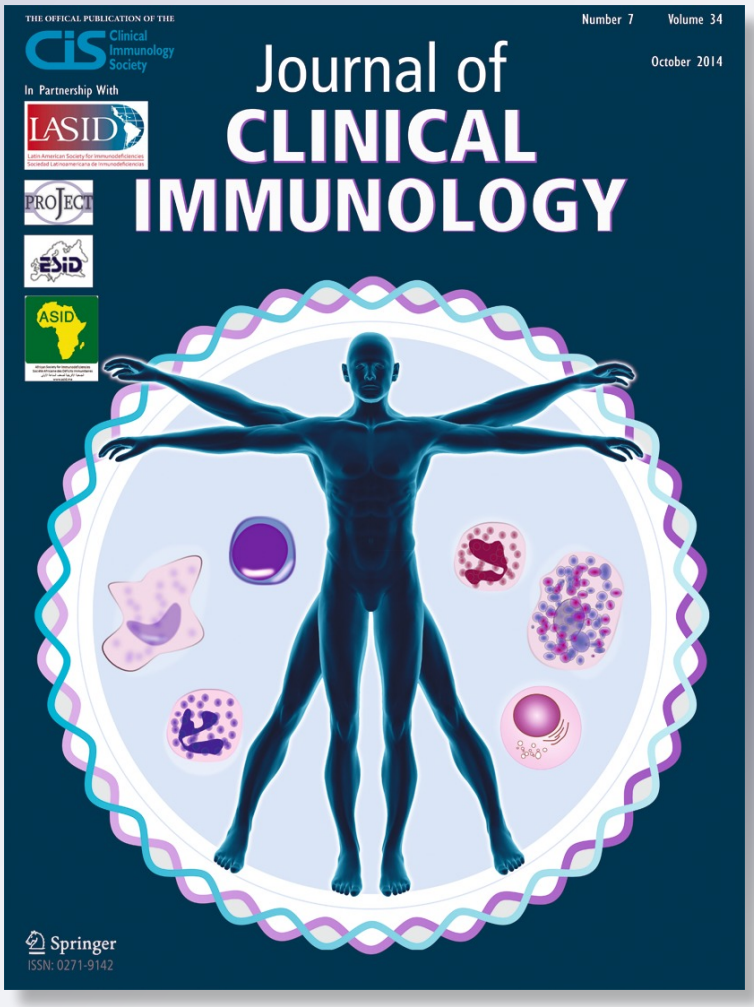

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KEY REVIEW ARTICLE

XLP: Clinical Features and Molecular Etiology due to Mutations in *SH2D1A* Encoding SAP

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Abstract X-linked lymphoproliferative disease (XLP) is a rare primary immunodeficiency affecting approximately 1–2 per 1 million males. A key feature of XLP is the exquisite sensitivity of affected individuals to disease induced following EBV infection. However, patients can also develop hypogammaglobulinemia and B-cell lymphoma independently of exposure to EBV. XLP is caused by loss-of function mutations in *SH2D1A*, which encodes the intracellular adaptor molecule SAP. SAP is predominantly expressed in T cells and NK cells, and functions to regulate signal transduction pathways downstream of the SLAM family of surface receptors to control CD4+ T cell (and by extension B cells), CD8+ T cell and NK cell function, as well as the development of NKT cells. The study of XLP had shed substantial light on the requirements for lymphocyte differentiation and immune regulation, which in turn have the potential to be translated into novel treatments for not only XLP patients but individuals affected by EBV-induced disease, impaired humoral immunity and malignancy.

Keywords XLP · SAP · EBV · hypogammaglobulinemia · infectious mononucleosis · lymphoma · PID

Introduction

In a seminal paper published in 1975, David Purtilo and colleagues described 6 related males, of a total of 18 in a single generation, from the Duncan kindred who were otherwise healthy but developed a fatal immune deficient condition characterised by *"benign or malignant proliferation of lymphocytes, histiocytosis and alterations in concentrations of serum immunoglobulin"*[1]. These features were accompanied by lymphoid infiltrates into non-immune tissues, and B-cell lymphoma in some affected patients. Strikingly, EBV infection and subsequent fulminant infectious mononucleosis (FIM) was observed in 3 patients, which led the authors to conclude that this represented a novel and rare immune defect triggered by exposure to EBV. As the affected males were all maternally related, and there were no affected females, it was concluded that this was a novel X-linked condition and thus was termed "X-linked recessive progressive combined variable immunodeficiency (Duncan's disease)"[1]. Although this is often considered the first description of this condition, it is worth appreciating that both Bar et al. and Provisor et al. described in 1974 and 1975, respectively, overlapping clinical features associated with EBV infection in seven other males, all of whom were related in each of these studies [2, 3]. Remarkably these patients had normal responses to infections with other childhood viruses including varicella zoster and CMV. These three studies detailed the classic features of what is now known as X-linked lymphoproliferative disease (XLP). The XLP discussed here is also known as XLP type 1 (XLP-1), to distinguish it from another form of XLP – XLP type 2 (XLP-2) – which has some clinical similarities but is caused by mutations in *BIRC4*, encoding XIAP) [4, 5]. Bar et al. presciently concluded that *"a genetically determined defect in host response to the virus is a likely explanation"* for the ability of EBV to induce the clinical sequelae of XLP [2]. Thus, XLP represents a primary immunodeficiency (PID) whereby affected males are exquisitely sensitive to disease caused by infection with a single pathogen – EBV – which usually runs a fairly benign course in most healthy individuals.

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Clinical Features of XLP

XLP has an incidence of ~1–2 per million males. It is typified by the triad of severe EBV-induced FIM and haemophagocytic lymphohistiocytosis (HLH), B-cell lymphoma and dysgammaglobulinaemia [6–16]. It is likely that exposure of XLP patients to EBV induces a vigorous and uncontrolled immune response involving activated lymphocytes and monocytes. Despite such immune activation, XLP patients fail to control EBV infection, resulting in FIM [11, 17]. Consequently, EBV infection can cause lymphadenopathy, hepatosplenomegaly and extensive tissue damage – especially to the liver and bone marrow - due to lymphocytic infiltration, subsequent HLH-like disease, often resulting in organ failure. Early reviews of the literature indicated that FIM occurred in ~60–75 % of cases, with >90 % mortality [6]. However, more recent studies indicate that while FIM still occurs in 30–40 % of patients, the subsequent mortality is reduced (~65 %) [14]. Despite these improvements in disease management over time, death still occurred very rapidly—within 2 months-in patients presenting with EBV-induced FIM/HLH [14].

Lymphoma and hypogammaglobulinemia affect ~25 % and 50 % of affected individuals, respectively, while aplastic anaemia, vasculitis and lymphoid granulomatosis have been reported in a small proportion of XLP patients. While FIM is clearly dependent on exposure to EBV, other features of XLP—lymphoma, hypogammaglobulinemia – develop in EBV seronegative patients, indicating that exposure to EBV is not required for all clinical features of this condition. Indeed, retrospective analysis of large cohorts of XLP patients revealed no significant difference in the incidence of lymphoma and hypogammaglobulinemia in EBV^- and EBV^+ patients [9, 14]. Remarkably, there is also no significant difference in the median age of presentation, median age of death or mortality rate between EBV^- and EBV^+ patients [6, 8–16].

Identification of the Genetic Lesion Underlying XLP

Although XLP was described as an immune deficient condition in the mid 1970's [1–3], and the disease-causing region of the X-chromosome was refined to Xq25 [16, 18–20], the molecular cause of this disease was not discovered until 1998, when 3 groups simultaneously identified a novel gene that is now known as *SH2D1A* [21–23]. The groups led by Alison Coffey [22] and Kim Nichols [23] were attempting to identify the causative gene by positional cloning. While these teams successfully identified loss-of function mutations in *SH2D1A* as the genetic cause of XLP, they were unable to provide a mechanism for how such mutations would manifest as a PID. Serendipitously, Cox Terhorst and colleagues were examining the biochemistry of the cell surface receptor SLAM (signaling lymphocytic activation molecule), and their discovery that the protein encoded by *SH2D1A* – named SAP (SLAM-associating protein) – associated with SLAM provided clues to how SAP functioned and how mutations in *SH2D1A* could potentially contribute to disease [21].

Structure and Function of SAP

SH2D1A comprises 4 exons that encode a 128 amino acid (aa) protein comprised of a 5 aa N-terminal domain, a central SH2 domain (~100 aa), and ~20 aa C-terminal region [21–23]. SAP is highly conserved across many species, and is essentially nonpolymorphic [21–23]. Consequently, most missense mutations abolish SAP expression. SAP associates with the cytoplasmic domain of SLAM via a conserved immunoreceptor tyrosine-based switch motif (ITSM; TxYxxI/V [where "x" is any aa]) [21]. This feature, along with the fact that SAP was largely comprised of an SH2 domain predicted that SAP would function in the SLAM signaling pathway. However, this was confounded by the absence of any additional functional domains. The seminal study by Sayos and colleagues, however, critically demonstrated that SAP was capable of competing with another SH2-domain containing protein—the phosphatase SHP-2—for binding to SLAM, thereby limiting recruitment of SHP-2 to this receptor [21]. Specifically, the arginine residue at position 32 in SAP (R32) was critical for the interaction between SAP and SLAM [21].

SLAM exhibits homology to several other surface receptors belonging to the Ig superfamily; these include 2B4 (CD244), CD84, Ly9 (CD229), NTBA and CRACC that are expressed on a variety of haematopoietic cells [11, 12, 24, 25]. With the exception of 2B4, which recognises CD48, all of these receptors are homotypic self-ligands. Since these receptors also contain one or more ITSMs in their cytoplasmic domains it was perhaps not surprising that all of these receptors could interact with SAP via the R32 residue, and this binding also prevented recruitment of SH2-domain containing phosphatases [11, 12, 24, 25]. Interestingly, recruitment of SAP to SLAM did not require phosphorylation of the tyrosine residue within the ITSM, which is unusual for SH2-domain containing proteins. However, tyrosine phosphorylation did enhance and stabilize this interaction. In contrast to SLAM, recruitment of SAP to other SLAM-related receptors was strictly dependent on tyrosine phosphorylation [11, 12, 24, 25]. These findings led to a model whereby SAP functioned to regulate signaling downstream of SLAM-related receptors by controlling interactions between these receptors and phosphatases. Several elegant studies have indeed confirmed that SAP dramatically alters the function of SLAM receptors on lymphocytes inasmuch that SAP-deficiency renders them inhibitory, rather than activating, via the recruitment and/or activation of phosphatases [26–31].

Despite this model, SAP does not simply act by preventing the delivery of a potential negative signal mediated by a phosphatase. Indeed, SAP also functions as an adaptor molecule by interacting with the protein tyrosine kinase Fyn. Notably, the interaction between SAP and Fyn involves R78 in SAP—distinct from R32 required for SLAM/SAP associations-binding to a proline residue in the SH3 domain of Fyn. This, therefore, allows SAP to simultaneously bind both SLAM and Fyn to form a ternary SLAM/SAP/Fyn complex [32–34]. Fyn promotes further phosphorylation of the SLAM receptors, recruitment of various signaling intermediates and activation of downstream signaling pathways critical for some functions of SLAM receptors [29, 32, 35, 36]. In contrast, other functions of SAP do not require Fyn [37]; however these signaling pathways that are Fyn-independent remain to be fully elucidated.

Functions of SLAM Family Receptors

Even before SAP was discovered, the function of some SLAM family receptors had been investigated. Historically, 2B4 was the first identified SLAM receptor, having been cloned as a molecule expressed by murine NK cells that, when cross-linked, increased NK cell cytotoxicity in a non-MHC restricted manner [38, 39]. In the same year, a study by Valiante and Trinchieri described a novel cell surface molecule on human NK cells and a subset of CD8+ T cells [40]. Akin to murine 2B4, cross-linking of this novel receptor with a specific mAb induced NK cell cytotoxicity in a non-MHC restricted manner [40]. It was not until 1999 (six years later), when the human homologue of murine 2B4 was cloned [27, 41], that it became appreciated that Valiante and Trinchieri were actually characterizing human 2B4 [40].

SLAM was cloned in 1995 [42] and its main function was found to regulate cytokine production by polarized CD4+ T cell subsets [42, 43]. Several other SAP-associating receptors—NTB-A, CRACC—were identified subsequent to the cloning of SAP [26, 44]. Similar to 2B4, ligation of NTB-A or CRACC on NK cells increased their cytotoxic function [26, 44]. 2B4 and NTB-A also have important functions on CD8+ T cells [28, 40, 45] (discussed further below). Although CD84 and CD229 have been studied for their ability to recruit SAP (reviewed in [12, 24, 25]), the physiological function of these receptors, and whether such functions are regulated by SAP, remain to be thoroughly investigated.

Cellular Defects in XLP as an Explanation of Clinical Features of this Disease

Ex vivo analysis of lymphocyte subsets and function in XLP patients has revealed numerous cellular defects. These include impaired effector functions of NK cells, $CD8^+$ T cells and $CD4^+$ T cells, a complete lack of NKT cells, and reduced frequencies of memory B cells. These findings point to critical functions of SAP in these processes, thereby providing mechanistic explanations for some of the clinical features of XLP.

Defects in Cytotoxic Lymphocytes

Sullivan et al. reported the first functional defects in lymphocytes from XLP patients as being impaired NK cell cytotoxicity [46], and this result was quickly confirmed in other studies [47]. These observations pre-dated the discovery of SAP by nearly 2 decades; thus the molecular defect underlying this perturbed function was unknown. However, subsequent studies in 2000 and 2001 found that the ability of 2B4 or NTB-A engagement to enhance NK cell cytotoxicity was abolished in SAP-deficient NK cells [26, 27, 48, 49]. Furthermore, the absence of SAP actually resulted in reduced killing of target cells by 2B4 or NTB-A-stimulated NK cells [26, 27]. These findings indicated that the ability of 2B4 and NTB-A to promote NK cell effector function was strictly SAP dependent, and were the first to propose the possibility that SAP deficiency converted these from activating to inhibitory receptors. Interestingly, although CRACC could also associate with SAP and promote lymphocyte cytotoxicity, XLP NK cells were still capable of responding to CRACC engagement [44], demonstrating that this receptor functions independently of SAP. NK cells from XLP patients could also respond normally to stimuli that did not require SAP, such as ligation of CD2 or CD16, establishing that NK cell function in general was not abolished by SAP deficiency [26, 27, 48, 49].

Early studies of CD8+ T cells from XLP patients also revealed them to have defects in responding to EBV-transformed B cells [47, 50]. Later studies of XLP patients, as well as heterozygous female carriers of XLP, revealed that SAP-deficient CD8+ T cells are also impaired in their responses to some stimuli, but not others. For instance, when peptides from different viruses were presented by B cells, SAP-deficient CD8+ T cells exhibited significantly reduced cytokine and cytotoxic responses compared to SAP-sufficient CD8+ T cells in response to the same Ag. However, responses by SAP-deficient and SAP-sufficient CD8+ T cells were comparable when the same peptides were presented by non-B cell Ag-presenting cells (DCs, monocytes, fibroblasts) [28, 45]. Thus, SAP-deficient CD8+ T cells have a selective impairment in responding to B cells. Consistent with prominent expression of 2B4 and NTB-A on CD8+ T cells, blocking mAbs against these receptors enhanced effector function of SAP-deficient CD8+ T cells in response to B cell APCs, consistent with the ability of these receptors to deliver inhibitory signals to CD8+ T cells in the absence of SAP [28, 45]. Thus, in the context of Ag presentation by B cells, successful engagement of specific CD8+ T cells by cognate B cells fundamentally requires interactions between SLAM family

receptors and subsequent SAP-dependent signaling in responding CD8+ T cells. Interestingly, a similar explanation underlies impaired development of NKT cells in XLP, inasmuch that cognate interactions between NKT cell precursors and CD1d-expressing cortical thymocytes are required for the selection of mature NKT cells and this process is mediated by SAP/Fyn signaling downstream of SLAM and Ly108 (NTB-A in humans) [51, 52].

The findings from SAP-deficient NK cells and CD8+ T cells, as well as the near-absence of NKT cells, provide mechanistic insight not only into the characteristic heightened susceptibility of XLP patients to EBV infection and disease but also the frequent development of B-lymphoma in these individuals. First, humans who lack NK cells or have profound functional NK cell defects, are often susceptible to infection with herpes viruses such as CMV, varicella zoster and EBV [53]. Thus, it is possible that the defective response of SAP-deficient NK cells following engagement of 2B4 or NTB-A by ligands expressed on EBV-infected B cells contributes to EBV-induced disease in XLP. A contribution of NK cells to controlling EBV infection is evidenced by the ability of a subset of tonsillar NK cells to potently suppress EBV-induced transformation of infected B cells in vitro [54, 55]. This is supported by recent work showing that in vivo depletion of NK cells in a humanized mouse model of EBV infection enhanced FIM-like symptoms as well as the development of B-cell lymphoma [56]. Interestingly, CD48 was initially characterized as a surface Ag "super-induced" on B cells following exposure to EBV [57]. Thus, engagement of 2B4 on NK cells by B-cell expressed CD48 may represent an early mechanism of NK-cell mediated control of viral infection, which would be impaired in XLP patients. Second, since EBV infects and resides in B cells during latent infection, the inability of SAP-deficient CD8+ T cells to respond to B cell APCs [28, 45] would render XLP patients exquisitely vulnerable to EBV infection. In contrast to these scenarios, residual NK function endowed by intact signaling through numerous other receptors, together with the ability of SAP-deficient CD8+ T cells to respond to Ag presented by non B-cells would ensure intact immune responses against infection with viruses other than EBV. Indeed, analysis of virus-specific CD8+ T cells in XLP carriers revealed that while >95 % of EBV-specific CD8+ T cells expressed SAP, those CD8+ T cells specific for influenza or CMV were detected in both the CD8+ SAP+and SAP-compartments [28]. Thus, these studies finally answered one of the original questions posed following the initial identification and characterization of XLP patients—why EBV? They revealed that EBV susceptibility was more to do with the exclusivity of EBV infecting B cells and the inability of SAP-deficient CD8+ T cells to respond to B cells than to the nature of EBV itself. This would predict that XLP patients would also be susceptible to viruses that utilize B cells as their host. However, there seems to be no other viruses with these features. Indeed, while the related virus Kaposi's sarcoma herpes virus can infect B cells, it has also been detected in endothelial cells as well as monocytes that can activate KSHV-specific CD8+ T cells [58]. The poor responsiveness of SAP-deficient CD8+ T cells against B cells would also explain the heightened incidence of B-cell lymphoma in XLP patients, and lack of correlation between EBV infection and lymphoma development. It is possible that the deficiency in NKT cells also contributes to compromised immunity against EBV infection and/or B-cell lymphoma in XLP patients [12, 11, 24, 25]. Interestingly, some individuals with other immunodeficiencies characterised either by susceptibility to EBV infection or B-cell lymphoproliferation – due to mutations in *CD27*, *ITK*, *BIRC4* (encoding XIAP) or *CORO1* (encoding coronin 1A)—also have a reduction in NKT cell numbers (reviewed in [5]). While these observations are correlative, they do lend support for a possible role of NKT cells in immunity against EBV infection.

Impaired Humoral Immunity due to CD4+ T cell Intrinsic Defects

Early studies established that although hypogammaglobulinemia and/or poor production of Ag-specific Abs was a common feature of XLP patients [1, 8, 59–61], B cells or B-cell lines from these individuals exhibited normal function [62–65]. This suggested that defects in humoral immunity were secondary to impaired function of CD4+ T cells, which is consistent with the lack of expression of SAP in normal mature B cells. It was found that XLP CD4+ T cells have several defects, such as impaired IL-10 production, reduced ICOS expression and a compromised ability to provide "help" for the in vitro differentiation of co-cultured B cells [64], that were consistent with compromised generation of T follicular helper (Tfh) cells. Tfh cells are the specialized subset of CD4+ T cells responsible for T-cell dependent differentiation of naïve B cells into long-lived, high affinity memory and plasma cells [66–68]. This has since been confirmed from the analysis of SAP-deficient mice, who exhibited marked impediment in generating Tfh cells following immunization with protein Ag or infection with various pathogens (reviewed in [66–68]). This diminution in Tfh cells led to very poor formation of germinal centers (GCs), which are required for the generation of these B cell subsets. The requirement for SAP in Tfh formation appears to reflect a role for SLAM-related receptors—specifically CD84 and NTB-A (Ly108 in mice)—in the formation of conjugates between activated cognate CD4+ T cells and B cells that underpin the dynamic 2-way delivery of signals that guide the differentiation of Tfh and GC B cells [30, 69, 70]. Strikingly though, initial priming of SAP-deficient CD4+ T cells by DCs is intact [70]. Studies of SAP-and SLAM-deficient mice have complemented these observations by revealing a critical role for SLAM/SLAM interactions and SAP signaling in inducing IL-4 production

by Tfh cells [71]. These findings explain the paucity of memory B cells in XLP patients and the accompanying hypogammaglobulinemia and/or impaired generation of Ag-specific Ab responses [64, 65]; they are also consistent with the original description of XLP by David Purtilo who observed a lack of GCs in lymphoid tissues of most of these patients [1].

Collectively, these intrinsic defects in SAP-deficientcytotoxic lymphocytes, NKT cells and CD4+ T cells provide explanations for the major clinical features of XLP, these being susceptibility to EBV infection and subsequent HLH, B-cell dysfunction resulting in hypogammaglobulinemia and poor serological memory, and predisposition to developing B-lymphoma. The fact that defects in SAP-deficient Tfh cells and CD8+ T cells, in terms of recognizing B cells as APCs or target cells, is independent of EBV also explains why hypogammaglobulinemia and B-lymphoma occur with similar frequencies in EBV-seronegative and seropostive XLP patients [9, 14]. Indeed, the fact that hypogammaglobulinemia and B-lymphoma can occur in EBV naïve XLP patients lead to the discovery of several male patients who presented with these features of XLP but had not been exposed to EBV, and were actually diagnosed with different conditions [72, 73].

Investigation of lymphocyte responses in XLP patients, as well as SAP-deficient mice, have revealed parallels between the generation of requisite effector functions by CD4+ T cells, CD8+ T cells and NK cells, as well as NKT cell development, inasmuch that they all involve interactions between lymphocytes and are dependent on SAP signaling. On the other hand, functionality of these immune cells towards non-lymphocyte populations (eg DC priming of CD4+ T cells; recognition by CD8+ T cells of Ag presented by non-B cells; selection of conventional T cells on thymic epithelium) is SAP-independent and thus proceed normally in XLP patients [24]. [25]. Interestingly, SAP has also been found to be expressed in cells beyond NK and T cells, including eosinophils and platelets [25]. Thus, it is possible that defects in these cells also contribute to the pathophysiology of XLP. However, this requires further investigation.

Somatic Reversion

While early studies indicated a dire outcome for XLP patients, with mortality approaching ~100 % by 10 years of age [16], some patients do indeed live well beyond this expected time frame [9, 14]. In other immune deficiencies, patients presenting with a milder-than-expected phenotype have been found to have cells that have undergone somatic reversion, with the resulting reverted cells persisting due to a selective survival advantage conferred by the revertant mutation [74]. This is reminiscent of skewed inactivation of the X-chromosome carrying the mutant gene in B cells and T cells in female carriers of XLA and X-SCID, respectively [75, 76]. Although no correlation has been reported between genotype and phenotype in XLP [9], we examined XLP patients for somatic reversion in the *SH2D1A* gene. To our surprise, we found that a small but detectable population of lymphocytes in most patients with missense mutations expressed SAP [77]. Detailed analysis of these SAP+cells revealed them to be mostly effector memory CD8+ T cells. Reverted cells were not detected in the CD4-lineage, nor in naïve CD8+ T cells, and only in NK cells from 1 patient. Strikingly, reversion was only detected in EBV+patients, and reverted SAP+CD8+ T cells were not only specific for EBV Ags but also were capable of responding to EBV Ags presented by autologous B cells [77]. This suggests that EBV exerts a selective pressure on CD8+ T cells, facilitating the expansion (and detection) of revertant cells to a functional level such that they will be capable of having a physiological effect on EBV infection in some XLP patients. Thus, it is likely that the presence of this small population of EBV-specific revertant-SAP+CD8+ T cells can adequately control EBV viral loads, thereby minimizing subsequent disease and resulting in greater longevity of some patients. However, as reversion was not detected in CD4+ T cells, humoral immune defects are likely to persist in these XLP patients. Despite this, since the greatest threat to survival of XLP patients is EBV infection, somatic reversion in XLP predicts that patients with missense mutations in *SH2D1A* may have a better long-term outcome than those with mutations that involve deletion of entire exons or large regions of Xq25.

Clinical Management of XLP Patients

Like many primary immunodeficiencies, haematopoietic stem cell transplant (HSCT) has been considered to be the only means of curing XLP [78]. The most recent comprehensive survey of the outcomes of HSCT indicated 81 % survival, compared to 62.5 % for untransplanted patients [14]. The major risk factor for successful HSCT was whether or not the patients had experienced previous episodes of HLH, with survival of those patients that had been affected by HLH being reduced by 50 % post-HSCT. Indeed, all patients who did not survive HSCT had HLH before or during the transplant, compared to ~20 % of those who did survive. Thus, transplanting XLP patients prior to the development of EBV-induced HLH would offer the greatest chance of survival and curing XLP.

XLP has also been treated with conventional anti-viral and immunosuppressive drugs, Ig replacement therapy, and chemotherapeutics for lymphoma [13, 16]. However, a novel approach has been the use of Rituximab to reduce EBV loads by eliminating B cells during primary EBV infection [79]. Although the number of patients tested is small, the outcomes were substantial, with marked reductions in EBV load and rapid recovery from the symptoms of FIM; consequently the

patients did not develop HLH [79]. A more recent development was a proof-of principle assessment of the utility of gene therapy in a mouse model of XLP. Here, HSCs from SAP-deficient mice were transduced with lentiviral vectors encoding human SAP and used to reconstitute lethally irradiated SAP-deficient mice [80]. Although only ~50 % of lymphoid cells expressed transduced SAP, this was sufficient to restore basal serum Ig levels and NK cell cytotoxicity to those observed in wild-type (WT) mice. Furthermore, the generation of GCs and Ag-specific Ig in response to T-dependent Ags was also improved, approximating 50 % of the response of WT mice. In contrast, although lentiviral transduction of human SAP into SAP-deficient HSC yielded some NKT cells on transfer into SAP-deficient mice, the overall numbers corresponded to only ~15 % of those observed in WT mice. Despite this, these results are encouraging as they predict that introduction of SAP into only a proportion of lymphocytes will be sufficient to restore function in CD4+ T cells (and by extension B cells), NK cells and presumably CD8+ T cells [80]. This is reminiscent of the finding that expression of reverted SAP in <10 % of total CD8+ T cells in XLP patients appeared to be sufficient to provide some protection against chronic infection with EBV [77], raising the prospect that transduction of the WT gene into only a low frequency of HSCs could have significant benefit on the clinical course of XLP patients who undergo gene therapy.

Conclusion

The discovery of novel PIDs and the underlying genetic cause provides great opportunities to advance our knowledge not only with respect to molecular etiology of this condition but also the fundamental requirements for a functional immune system. XLP is a great example – its initial discovery as a disease entity nearly 40 years ago immediately informed us that whatever caused XLP was absolutely critical for normal host protection against EBV infection. The subsequent identification of *SH2D1A* as the molecular lesion responsible for XLP, together with refined studies of lymphocyte function in these patients, and the generation of gene-targeted mice, has illuminated our understanding of novel signaling pathways utilized by lymphocytes for their development and function, as well as revealed surface receptors and molecular interactions that are indispensible for anti-EBV and anti-tumour immunity as well as robust and long-lived humoral immune responses. These discoveries have improved therapies and outcomes for XLP patients and, by exploiting the SLAM/SAP signaling pathway(s), also raised the prospect for developing vaccines against EBV and enhancing immune mechanisms that restrain lymphomagenesis. Thus, while the incidence of XLP is rare, the clinical implications of these developments will potentially benefit many people suffering from EBV-induced disease, haematological malignancies and dysfunctional Ab responses. This highlights the power of these rare PIDs as models for understanding immunobiology and advancing clinical management of often life-threatening conditions.

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