

X-linked Inhibitor of Apoptosis Protein Deficiency: More than an X-linked Lymphoproliferative Syndrome

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Received: 19 November 2014 / Accepted: 9 February 2015 / Published online: 4 March 2015
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Abstract X-linked inhibitor of apoptosis (XIAP) deficiency (also known as X-linked lymphoproliferative syndrome type 2, XLP-2) is a rare primary immunodeficiency. Since the disease was first described in 2006, more than 70 patients suffering from XIAP-deficiency have been reported, thus extending the clinical presentations of the disease. The main clinical features of XLP-2 are (i) elevated susceptibility to hemophagocytic lymphohistiocytosis (HLH, frequently in response to infection with Epstein-Barr virus (EBV)), (ii) recurrent splenomegaly and (iii) inflammatory bowel disease (IBD) with the characteristics of Crohn's disease. XIAP deficiency is now considered to be one of the genetic causes of IBD in infancy. Although XIAP is an anti-apoptotic molecule, it is also involved in many other pathways, including the regulation of innate immunity and inflammation. XIAP is required for signaling through the Nod-like receptors NOD1 and 2, which are intracellular sensors of bacterial infection. XIAP-deficient T cells (including innate natural killer T cells and mucosal-associated invariant T cells) are overly sensitive to apoptosis. NOD2 function is impaired in XIAP-deficient monocytes. However, the physiopathological mechanisms underlying the clinical phenotypes in XIAP deficiency, notably

the HLH and the EBV susceptibility, are not well understood. Here, we review the clinical aspects, molecular etiology and physiopathology of XIAP deficiency.

Keywords X-linked lymphoproliferative syndrome · hemophagocytic lymphohistiocytosis · inflammatory bowel disease · crohn's disease · susceptibility to EBV infection

History of the Condition

X-linked lymphoproliferative disease (XLP) is a rare, inherited immunodeficiency with an incidence of 1–2 cases per million males. The disease was first described by David Purtilo in 1974 [1, 2]. XLP is characterized by a key triad of symptoms including (i) an extreme susceptibility to EBV infection (leading to fulminant infectious mononucleosis with the features of hemophagocytic lymphohistiocytosis (HLH)), (ii) dysgammaglobulinemia and (iii) lymphoma [3]. In 1998, inactivating mutations in *SH2D1A* were identified as a cause of XLP [4–6]. In 2006, we reported on 12 boys (from three families) who developed HLH following EBV infection [7]. Some of the boys also displayed hypogammaglobulinemia, and two developed inflammatory bowel disease (IBD). An X-linked condition was suspected in the three families, prompting us to hypothesize that these boys were suffering from an XLP-like syndrome. The boys were tested for XLP deficiency but were found not to be carrying mutations in *SH2D1A*. Further genetic linkage analysis identified a unique 2 Mb region on the X chromosome that co-segregated with the disease in the three families. Strikingly, this region was located in Xq25 and included *SH2D1A* and several other genes. At that time, the occurrence of intronic mutations within regulatory regions of *SH2D1A* could not be formally ruled out. However, sequencing of the region's genes revealed the presence of hemizygous mutations in the gene for X-linked

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inhibitor of apoptosis (XIAP, also known as BIRC4) in all boys tested. The three families each carried distinct null mutations. Following this original report, *SH2D1A* and *XIAP* deficiencies were respectively referred to as XLP-1 and XLP-2 (based on their clinical similarities).

More patients were diagnosed after this seminal study, and it became possible to examine the similarities and differences between the respective symptoms of XLP-1 and XLP-2 [8]. Although EBV-triggered HLH is the most frequent, severe symptom in both diseases, XLP-1 and XLP-2 differ in terms of several clinical features. In contrast to XLP-1 patients, XLP-2 patients never develop lymphoma. Although recurrent splenomegaly and IBD occur frequently in XLP-2 patients, these symptoms are absent (or very rare) in XLP-1 patients. Hypogammaglobulinemia is common to XLP-1 and XLP-2, however, while the condition is severe and stable in XLP-1, this is often transient in XLP-2. A few XLP-2 patients have developed variable, auto-inflammatory-like symptoms not shared by XLP-1 patients. Recently, young boys with early-onset IBD as the only clinical trait were reported to be carriers of inactivating *XIAP* mutations - thus confirming the predominant role of XIAP deficiency in the occurrence of IBD [9–11]. Hence, XIAP deficiency should be now considered as one of the Mendelian determinants of inherited IBD in infancy [12]. In fact, these observations revealed that the spectrum of XLP-2 associated phenotypes was much broader than had been originally reported.

Functions

XIAP is a member of the inhibitor of apoptosis protein (IAP) family. It is composed of 3 Baculovirus inhibitor of apoptosis protein repeat (BIR) domains, a ubiquitin binding domain (UBA), and a C-terminal RING domain with E3 ubiquitin ligase activity [13]. The BIR domains mediate protein-protein interactions by binding to a specific peptide sequence (the IAP-binding motif/IBM). The expression of XIAP is ubiquitous and is significantly elevated in cancer cells [14]. XIAP has been implicated in a variety of pathways; however, as indicated by its name, the first function ascribed to this protein was an anti-apoptotic activity. XIAP inhibits programmed cell death by directly binding to (via its BIR2 and 3 domains) and blocking activated forms of the effector caspases 3, 7 and 9 [15, 13]. In addition to its anti-apoptotic role, XIAP has been found to be involved in many other signaling pathways and/or cellular responses via its ubiquitin ligase activity [16]. For example, XIAP is involved in NF κ B activation (via the TAB1/TAK1 pathway) [17], TGF- β receptor signaling [18], activation of the MAPK pathway [19], copper metabolism [20] and autophagy [21]. Importantly, recent findings also indicated that XIAP has a direct role in innate immunity and the negative regulation of inflammation. XIAP

is required for signal transduction and function of the nucleotide oligomerization domain receptor (NOD)-like pattern recognition receptors (NLRs) NOD 1 and 2 [22]. Studies in mice show that XIAP is a negative regulator of TNFR1-dependent pro-inflammatory cytokine production and NLRP3 inflammasome activation in myeloid cells [23, 24]. In TNFR1 signaling, XIAP is required in order to limit the activity of the scaffold proteins RIPK1 and RIPK3, the abnormal activation of which is associated with cell-death and inflammasome activation [25].

In view of the clinical similarities between XLP-1 and XLP-2 (at least at first sight) and *SAP* and *XIAP* neighboring positions (within 2 Mb of each other on the X chromosome), it was hypothesized that the two deficiencies could be functionally related. SAP is a small adapter protein containing a single SH2 domain. SAP is a key component of the signaling pathways involving SLAM family receptors [3]. However, there is currently no evidence to suggest that SAP and XIAP form a functional cluster or even that they interact together.

Clinical Features

Worldwide, more than 70 XIAP-deficient patients have been reported in the literature [9, 11, 8, 7, 26–29]. Over the last few years, we have identified additional patients and have been made aware of yet other patients by our collaborators (Aguilar and Latour, unpublished observations). Table 1 summarizes the clinical data on the 100 patients with known XIAP deficiency. On this basis, HLH and recurrent splenomegaly appear to be the most frequent clinical traits (54 and 57 %, respectively). EBV is the major trigger for HLH, although several patients experienced HLH in the course of cytomegalovirus (CMV) and human herpes virus 6 (HHV6) infections or in the absence of a documented infectious agent. HLH is often severe and can even be fatal in young boys presenting fulminant infectious mononucleosis triggered by EBV. Episodes of splenomegaly are frequent (56 %) and often occur in the absence of systemic HLH. They are usually associated with fever and cytopenia, and probably represent a minimal form of HLH [8]. In fact, splenomegaly is often the first clinical sign of the disease to be noticed. IBD is also a prevalent phenotype and affecting 25–30 % of patients. IBD can occur before HLH and may be the first and the only symptom of the disease [9, 8, 11, 10]. The age at onset of IBD varies greatly from 3 months to 41 years [9]. The clinical presentation and the biological and histological features are very similar to those observed in adult patients with Crohn's disease [9, 10]. In fact, the IBD can be very severe and is often resistant to various treatments. The outcome is fatal in 10 % of cases. Hypogammaglobulinemia affects 16 % of patients but is generally transient. XIAP-deficient patients can also develop other inflammatory phenotypes, including arthritis, skin abscesses, erythema nodosum,

Table 1 Clinical manifestations in patients with XIAP deficiency

Country	Patients (n)	HLH (n)	EBV ^a (n)	IBD (n)	Hypog. ^b (n)	Splenomegaly (n)	Skin abscesses and other inflammatory manifestations (n)	References
France	35	25	20	8	4	18	2	7, 8 and & ^c
England	9	1	1	3	3	6	3	7, 8, and & ^c
Germany	33	12	8	10	5	19	2	9, 10, 28, 29
USA	11	9	3	1	2	10	ND	11, 26
Japan	12	7	4	4	2	4	ND	9, 27
TOTAL	100	54	36	26	16	57	7	

^a EBV as trigger of HLH or patients with severe infectious mononucleosis at onset

^b Hypogammaglobulinemia

^c Aguilar and Latour, unpublished observations

uveitis and nephritis (Aguilar and Latour, unpublished observations) [9, 29]. These manifestations are rather rare, since they affect only 7 % of patients. Importantly, all the above-mentioned phenotypes can be observed independently of each other. In most cases, patients develop at least two symptoms.

Genetics

XIAP comprises six exons. To date, more than 50 different XLP-2-causing mutations have been identified (covering all exons), including missense mutations, nonsense mutations, deletions and insertions. Both null mutations (leading to the complete loss of protein expression) and hypomorphic mutations (leading to residual protein expression or the expression of truncated forms) have been described. All the mutations behave as loss-of-function or inactivating mutations. Interestingly, several *XIAP* missense mutations form clusters within the BIR2 and RING domains - highlighting the roles of these domains in XIAP-deficiency, as the mutations preserve some degree of XIAP expression [30]. However, patients carrying hypomorphic mutations can develop manifestations as severe as those observed in patients carrying null mutations. Within a given family, the phenotype may be highly variable - ranging from poorly symptomatic individuals to patients with very severe IBD and/or HLH. This variability is presumably due to a combination of additional genetic and/or environmental factors that directly influence the disease outcome. This type of genetic influence has been reported in a large family with a hypomorphic *XIAP* mutation [7]; affected individuals also carried a rare polymorphism in *CD40LG* (coding CD40L), which decreased the capacity of CD40L to bind to CD40. CD40LG deficiency is known to cause X-linked hyperIgM syndrome. In this particular family, the combination of these two genetic variants appears to be necessary for the clinical expression of XIAP deficiency because carriers of a single variation/mutation are asymptomatic. Interestingly, all patients

also developed progressive hypogammaglobulinemia, which is not a common feature of XIAP deficiency. This observation emphasizes that variable and/or rare clinical phenotypes in XIAP deficiency can result from the interplay between several genetic determinants.

Although most of the female heterozygous carriers of XIAP mutations are healthy and asymptomatic, some are symptomatic. Recently, two heterozygous female carriers with IBD and one with EBV-triggered HLH have been identified [9] (Aguilar and Latour, unpublished observations). In affected women, the X chromosome inactivation pattern was shown to be random or shifted towards the wild-type allele. This contrasts with the inactivation pattern seen in healthy carriers, which is shifted towards the mutated allele - indicating that cells containing an active wild-type allele have a selective advantage.

Defects and Immunopathogenesis

Cytotoxicity

After XIAP-deficiency was identified, cellular defects similar to as those associated with *SH2D1A* (*SAP*) deficiency have been examined. The physiopathology of XLP-1 is well understood, and multiple defects have been characterized in SAP-deficient humans and mice, including a complete block of iNKT cell development, altered antibody production associated with low switched memory B cell counts and the loss of germinal center formation, and defects in the CD8+ T and NK cell-cytotoxic response against EBV-infected B cells [3]. These defects explain most of the clinical phenotypes of XLP-1 and result from dysfunction of the SLAM family receptors, in which signal transduction depends on SAP. Importantly, the impaired cytotoxicity of SAP-deficient CD8+ T cells and NK cells against EBV-infected B cells (via SLAM receptor interactions) has an essential role in the susceptibility to EBV

infection observed in XLP-1. In XIAP-deficient patients, T and NK cell cytotoxic responses are normal (regardless of whether or not they depend on SLAM receptors), indicating that the mechanisms underlying EBV-driven HLH in XLP-2 differ from those in XLP-1 and familial lymphohistiocytosis (FHL) [31].

Excessive Apoptosis

In vitro, XIAP-deficient T lymphocytes from patients are excessively prone to apoptosis in response to various stimuli by the cell-death receptors FAS/CD95 and TRAIL-R or the T-cell antigen receptor (TCR) [26, 7, 29]. This heightened susceptibility to apoptosis upon TCR activation (also termed activation-induced cell death) results in impaired proliferation and expansion of activated XIAP-deficient T cells (which can be corrected by the expression of wild-type XIAP) [7]. In proliferating T cells, XIAP interacts with caspases-3/-7 - thereby blocking full activation of the latter and thus cell death [32]. In XIAP-deficient patients, excessive cell death might compromise the expansion and proliferation of activated T cells that normally occur during responses of the adaptive immune system. In immunocompetent individuals, an efficient immune response against EBV depends on a massive expansion of CD8+ T cells. In the setting of XIAP deficiency, accumulation of apoptotic cells and persistence of EBV-infected cells could trigger abnormal inflammation and thus contribute to HLH. Cell types other than T cells might be also subjected to increased cell death sustained by the inflammatory context. This hypothesis is supported by the recent observation that loss of XIAP in mice results in excessive cell death of dendritic cells, inflammasome activation and aberrant IL1- β secretion dependent on TNFR1 complex and RIPK3 [25].

Hypogammaglobulinemia might also be a consequence of exacerbated B cell death in a context of systemic, sustained inflammation. Indeed, hypogammaglobulinemia in XIAP deficiency is variable and transient. Furthermore, XIAP-deficient patients have normal Ig-switched memory B cell counts.

Although total circulating T cell counts are normal in XIAP-deficient patients, counts of blood innate-like T cell populations, iNKT cells and MAIT cells are abnormally low [7, 33]. In fact, iNKT and MAIT cells are more sensitive to apoptosis than conventional T cells, and so are more dependent on XIAP for survival [33]. The low iNKT cell counts in XIAP-deficient patients appear to result from the depletion of iNKT cells caused by EBV infection, since some patients with normal iNKT cell counts have not encountered EBV [33, 34]. EBV-infected cells may also directly trigger activation-induced apoptosis of iNKT cells - an event that is exacerbated in the absence of XIAP. This hypothesis is supported by the recent demonstration that EBV-infected cells directly activate

IFN- γ production and cytotoxicity by iNKT cells and depletion of iNKT cells increased both viral titers and the frequency of EBV-infected B cells in vitro [35]. Importantly, defects in iNKT cells are also observed in several primary immunodeficiencies (caused by mutations in *SH2D1A*, *CD27*, *ITK*, *CORO1A* and *CTPS1*) characterized by a high susceptibility to EBV and EBV-associated pathologies [36]. Taken as a whole, these observations suggest that iNKT cells might be important players in the early phase of the immune response against EBV through their innate-like functions and hence, their defect might contribute to the altered immune response to EBV infection.

Lastly, many reports show that depletion of XIAP sensitizes tumor cells to cell death, and so inhibitors of XIAP are currently tested in clinical trials for cancer treatment [37, 38]. These observations might explain why XIAP-deficient patients are not prone to the development of lymphoma in contrast to SAP-deficient patients.

Defects in NOD Signaling

The NOD1/2 receptors are intracellular pattern recognition receptors that are activated by the recognition of peptidoglycan degradation products derived from the bacterial cell wall. Once activated, these receptors play an important role in innate immunity through their ability to activate NF κ B and release of cytokines (mainly pro-inflammatory cytokines but also anti-inflammatory cytokines, such as IL-10), chemokines and antimicrobial peptides [39]. NOD1 is expressed in epithelial cells, whereas NOD2 is more restricted to myeloid cells and Paneth cells. XIAP participates in NOD1/2 signaling by its capacity to interact with the receptor-interacting kinase 2 (RIPK2) (via its BIR2 domain) and to catalyze ubiquitylation of the latter [22, 40, 30]. NOD1/2 receptors are directly coupled to RIPK2 and ubiquitylation of RIPK2 by XIAP promotes the recruitment of the linear ubiquitin chain assembly complex (LUBAC), which in turns activates NF κ B signaling and cytokine production [22, 40, 30]. We and others have reported that XIAP-deficient monocytes from patients display an impaired production of cytokines and chemokines (including TNF- α , IL-10, IL-8 and MCP-1) in response to stimulation with NOD2 ligands [9–11]. Furthermore, fibroblasts from XIAP-deficient patients also show defective production of IL-8 and IL-6 in response to NOD1 activation [9].

Importantly, the strongest genetic factor associated with Crohn's disease is *NOD2*, which accounts for 2.5 to 5 % of the total associated genetic variance [41–43]. The risk alleles affect the ligand recognition and function of NOD2 [44]. Hence, these observations strongly suggest that the pathophysiological mechanisms of IBD in XIAP-deficient patients are probably quite similar to those that are associated with NOD2 risk alleles in Crohn's disease. Many studies have suggested that NOD2 has pivotal role in innate host defenses in

the gut [45]. IL-8 and MCP-1 are important chemokines for neutrophil recruitment, whereas IL-10 is a key anti-inflammatory cytokine involved in intestinal homeostasis (defects in the IL-10 pathway are known to be responsible for very early onset IBD [46]). Consequently, defective secretion of IL-8, MCP-1 and IL-10 in response to NOD1/2 signaling may alter intestinal homeostasis in XIAP-deficient patients. In particular, impaired neutrophil recruitment might be compromised (due to the defects in IL-8 and MCP-1 secretion), as has indeed been reported in patients with Crohn's disease [47–49]. On the same lines, 40 % of patients with chronic granulomatous disease (a primary immunodeficiency caused by mutations affecting the oxidative respiratory burst of phagocytes) develop IBD that is very similar to Crohn's disease - further highlighting the role of neutrophils and myeloid cells in gut homeostasis [50]. One proposed model is that defects in neutrophils and macrophages impair the clearance of pathogenic bacteria in the gut and thus lead to progressive inflammation. In this context, unleashed activation of inflammasomes (by pathogenic bacteria) resulting from the absence of XIAP might further sustain inflammation, leading to chronic inflammation. The importance of a myeloid defect in the pathogenesis of IBD in XIAP deficiency is also directly suggested by the observation of a symptomatic female carrier with low levels of XIAP and a compromised response to NOD2 in her monocytes, whereas XIAP expression by her lymphocytes [9]. Importantly, the deficiency of monocytes argues in favor of a hematopoietic origin for the IBD and lends support that the latter can be treated by allogeneic hematopoietic stem cell transplantation (HSCT). Other mechanisms may also account for the IBD. Particularly, gut defenses and homeostasis could be weakened by defective NOD1 functions and excessive cell death of lymphocyte populations (such as MAIT and iNKT cells, given their tropism for mucosal tissues and their rapid activation by bacteria). Accordingly, two recent studies have shown that iNKT cells are involved in gut homeostasis in the mouse [51, 52].

Diagnosis

A diagnosis of XIAP deficiency must always be considered in boys presenting with HLH in the course of viral infection not only with EBV but also with CMV, other herpes viruses or even in the absence of an identified viral infection [26, 29]. XIAP deficiency must also be considered in boys with severe IBD - especially when the latter is combined with splenomegaly, HLH and/or a family history of IBD. It is noteworthy that we recently found XIAP mutations in a relatively high proportion (4 %) of a pediatric cohort of 83 boys with IBD [9]. A fairly similar prevalence was also observed in a German pediatric cohort of patients with IBD [10]. Diagnosis of a

XIAP mutation must prompt the analysis of family members and thus the identification of male and female carriers. This is important because female carriers can receive genetic counseling if they are of child-bearing age. Furthermore, female carriers are not always asymptomatic and can develop clinical signs.

The only way to definitely diagnose XIAP deficiency is to sequence the gene itself. XIAP expression can be also reliably evaluated by Western blotting of lysates of T-cell blasts or peripheral blood mononuclear cells (PBMCs). Detection of XIAP by flow cytometry may also work but this technique cannot dependably identify mutations that maintain some degree of protein expression [29, 53]. Analyses of iNKT and MAIT cells cannot be used to diagnose XIAP deficiency, since low or null iNKT cell counts are also seen in immunodeficiencies such as Wiskott Aldrich syndrome [54] and STXBP2 deficiency,[55] for example. Moreover, the significance of these low iNKT cell counts must be interpreted with caution, in view of the high variability in healthy individuals. Functional assays can be performed: assaying for activation-induced cell death specifically reveals excessive apoptosis. However, this technique is too cumbersome to be used routinely. Recently, an easy, reliable way of screening patients has emerged by looking at intracellular TNF- α production by PBMCs in response to MDP (the ligand of NOD2) [56], which is abolished when XIAP is defective. Lastly, analysis of the X chromosome inactivation profile may be of value in female carriers with symptoms of XLP-2.

Prognosis and Treatment

Of more than 70 patients reported to date, 22 have died. Twelve deaths occurred following allogeneic HSCT. The other deaths were variously due to HLH ($n=4$), IBD ($n=4$), pneumonia ($n=1$) and liver failure ($n=1$). HLH is treated with conventional drugs, including etoposide, corticosteroids and cyclosporine [57]. IBD often requires several immunosuppressive treatments (corticosteroids, azathioprine, anti-TNF α ...). The only curative treatment is HSCT. However, HSCT in the context of XIAP deficiency is associated with a poor prognosis. In a retrospective international survey of 19 XIAP-deficient patients having undergone HSCT, the mortality rate was high (63 %) [58]. Factors associated with this unfavorable outcome were (i) the use of a full-dose conditioning/myeloablative regimen and (ii) ongoing HLH at time of transplantation. It was suggested that this particular sensitivity to chemotherapy was due to excessive apoptosis in hepatocytes and/or other cell types (caused by the absence of XIAP). Fortunately, it has been confirmed

that a low-intensity conditioning regimen can improve the outcome in patients with XIAP deficiency; successful HSCT after antibody-based conditioning has been reported in a patient with refractory HLH [59]. In another study, low-intensity conditioning resulted in the reappearance of HLH symptoms, which were successfully treated with donor lymphocyte infusions [60]. Recently, 6 patients with severe IBD underwent HSCT (including low-intensity conditioning) [61, 11, 9, 29]. One patient died but disease remission was observed in the other five patients, with a follow-up of up to 3 years. Nevertheless, HSCT remains to be evaluated as a general treatment for XIAP deficiency, since some patients can be asymptomatic for a long time.

Conclusion and Perspectives

XIAP deficiency was initially described as the second most frequent cause of XLP syndrome. It now appears that the phenotype is broader and differs from the conventional phenotype associated with XLP-1/SAP-deficiency in some important respects. XIAP deficiency can cause Crohn's disease and perhaps other inflammatory disorders. The physiopathology of IBD is probably related to the defect of NOD2 in monocytes/macrophages, but the exact disease mechanisms leading to HLH and EBV susceptibility are still not clearly understood today and remain to be elucidated. One interesting line of enquiry stems from the fact that defects in NOD1/2 pathways and other related innate immune pathways also have a role in these clinical manifestations. Notably, the recent reports showing that XIAP can interact with inflammasomes and downregulate their activity provide novel insights into the disease mechanisms underlying excessive inflammation in XIAP deficiency. Another issue concerns the role of excessive apoptosis; it is still not entirely clear that the latter is important in the physiopathology of XIAP deficiency. However, one general model is emerging from these observations. Defects in innate (compromised NOD1/2-dependent cytokines production) and adaptive (excessive apoptosis of activated T cells) immune responses in the absence of XIAP might secondarily result in a high inflammatory environment due to excessive and uncontrolled activation of inflammasomes by accumulation pathogens.

Acknowledgments We thank our collaborators for sharing their clinical observations.

S.L. is a senior scientist at the Centre National de la Recherche Scientifique (France) and C.A. received a fellowship from the Fondation ARC pour la Recherche sur le Cancer (France).

This work was funded by grants from INSERM, the Agence Nationale de la Recherche (ANR) (ANR-08-MIEN-012-01, ANR-2010-MIDI-005-02 and ANR-10-IAHU-01), the Fondation ARC pour la Recherche sur le Cancer (France), the European Research Council (ERC-2009-AdG_

20090506 n°FP7-249816), the Rare Diseases Foundation (France) and the François Aupetit Association (France).

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