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Review

XIAP deficiency syndrome in humans

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ABSTRACT

The X-linked inhibitor of apoptosis (XIAP) deficiency, also known as the X-linked lymphoproliferative syndrome type 2 (XLP-2), is a rare primary immunodeficiency. XIAP deficiency is characterized by a key triad of clinical manisfestations, which consist of a high susceptibility to develop hemophagocytic lymphohistiocytosis (HLH) frequently triggered by Epstein–Barr virus (EBV) infection, recurrent splenomegaly and inflammatory bowel disease (IBD) with the features of a Crohn's disease. XIAP deficiency can be considered as one of the genetic causes for inherited IBD. XIAP is an anti-apoptotic molecule, but it is also involved in many other pathways. Recent findings demonstrate the role of XIAP in innate immunity and in the negative regulation of inflammation. In this review, we focus on the clinical aspects, the molecular etiology and the immunopathogenesis of XIAP deficiency. We also discuss recent progress in the understanding of XIAP function in relation to the pathophysiology of XLP-2.

Contents

1. Introduction

1.1. Discovery of the XLP-2 syndrome

In 2006, 12 boys of three non-related families were identified as carriers of deleterious mutations in *XIAP* leading to loss of XIAP protein expression and function. These boys all suffered from immunodeficiency and most of them had developed hemophagocytic lymphohistiocytosis (HLH) subsequently to Epstein–Barr Virus infection (also termed virus-associated hemophagocytic

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syndrome (VAHS)) [1]. Some boys had also hypogammaglobulinemia and two developed inflammatory bowel disease (IBD). The susceptibility to EBV infection that triggers HLH, and the hypogammaglobulinemia, were reminiscent of the clinical phenotypes associated with the X-linked lymphoproliferative (XLP) syndrome caused by mutations in the gene *SH2D1A* (also named SAP deficiency) [2]. Based on these clinical similarities, XIAP deficiency was defined as a second genetic cause of XLP and denoted as XLP type 2 (XLP-2), while SAP deficiency was termed XLP-1. Furthermore and interestingly enough, *SH2D1A* and *XIAP* are both localized in Xq25 in the same vicinity and are only separated by a region of 2 Mb containing a single gene. At that time, it was tempting to hypothetize that *SH2D1A* and *XIAP* could form a functional cluster. Since then, however, a growing body of evidence has suggested that XLP-1 and XLP-2 are non-functionally related diseases, even if they share some striking similarities at first sight. The most convincing common feature is HLH, also known as macrophage activation syndrome (MAS). HLH is a life-threatening immunodeficiency characterized by hyperinflammation caused by an uncontrolled and ineffective immune response, in which activated T lymphocytes and macrophages accumulate in organs, and produce massive amounts of pro-inflammatory cytokines, such as IFN-γ, TNF-α and IL-6, resulting in tissue damage and organ failure [3,4]. HLH is triggered in most cases by infectious pathogens, in particular viruses.

2. Functions of XIAP

XIAP belongs to the Inhibitor of Apoptosis Protein (IAP) gene family and shares important functional and structural features with two other cellular IAPs, cIAP-1 and cIAP-2. It is composed of 3 BIR domains (Baculovirus Inhibitor of apoptosis Repeats), an Ubiquitin-associated domain (UBA), and a C-terminal RING domain which has E3 ubiquitin ligase activity. XIAP is ubiquitously expressed and its expression is significantly increased in cancer cells. Originally, the first function ascribed to XIAP was an anti-apoptotic activity. In fact, XIAP is a potent inhibitor of programmed cell death/apoptosis by its capacity to directly block the activated forms of the effector caspases 3, 7 and 9 via its BIR2 and 3 domains, in contrast to cIAP-1 and cIAP-2 that are not direct inhibitors of caspases [5]. In addition to its anti-apoptotic function, XIAP has been also shown to be involved in a large variety of signaling pathways and/or cellular responses [6,7]. Most of these additional functions of XIAP rely on its capacity to promote protein ubiquitylation via its RING domain and to activate the canonical NFκB and the MAPK pathways for example. Activation of NFκB and the MAPKs by XIAP is dependent on its BIR1 domain that recruits the TAB1/TAK1 complex. The TGF-β-activated kinase 1 (TAK1) is a ubiquitin-dependent MAP kinase kinase kinase (MAPK3) that directly phosphorylates and activates the IκB kinase complex (IKK) and the MAPKs, including JNK, p38 and ERK [8]. The UBA domain of XIAP is also involved in the activation of NFκB by its capacity to bind to polyubiquitylated NEMO of the IKK complex [9].

Among the ancillary functions, a major breakthrough came in 2009 with the discovery that XIAP (as well as cIAP-1 and cIAP-2) is required for the signal transduction and function of Nod-like receptors (NLRs) NOD 1 and 2 [10]. NOD1 and 2 receptors are intracellular pattern recognition receptors that sense degradation products of the peptidoglycan from the bacterial cell wall [11]. In addition, there is accumulating evidence that NODs can be activated by viral products [12,13]. When activated by their ligands, NOD1/NOD2 play an important role in innate immunity by their ability to activate NFκB and to produce cytokines (including pro-inflammatory, but also anti-inflammatory cytokines such as IL-10), chemokines and antimicrobial peptides [11]. NOD1 is expressed in epithelial cells, while NOD2 is more restricted to myeloid cells, and Paneth cells in the gut.

At a molecular level, XIAP contributes to the signal transduction of NOD1/2 by its ability to promote ubiquitylation of the receptor-interacting protein kinase 2 (RIPK2), an inducer of NFkB activation. In response to NOD1/2 ligands, RIPK2 is polybiquitylated and plays the role of a scaffold for the binding of the TAB/TAK1 complex, which results in the activation of the MAPK and NFκB pathways [14,15]. It was shown that XIAP binds to RIPK2 via its BIR2 domain, and ubiquitylation of RIPK2 by XIAP upon NOD1/2 stimulation promotes the recruitment of the linear ubiquitin chain assembly complex (LUBAC), which in turn activates NFκB and cytokine production [16–18]. It is not clear whether the TAB/TAK1 complex is directly implicated in this XIAP-dependent activation of NFkB cascade. TAB/TAK1 complex could be recruited via the BIR1 domain of XIAP and/or via a cIAP-1- and/or cIAP-2-dependent mechanism, since cIAP-1 and cIAP-2 are also required for NOD1/2 signaling by promoting RIPK2 ubiquitylation [10]. In mouse and humans models, the absence of XIAP leads to defective secretion of pro-inflammatory cytokines after stimulation with NOD ligands [16–18].

More recently, the role of XIAP in innate immunity was extended by the finding that XIAP is involved in the function of Dectin-1, a pattern recognition receptor implicated in the control of fungal infections by its capacity to recognize β-glucan from fungi [19]. In this model, XIAP was shown to be necessary for NFκB and MAPK activation, cytokine production and phagocytosis, following Dectin-1 activation by its ligands. This effect arises from the capacity of XIAP to bind and to ubiquitylate BCL10, an important activator of the canonical NFκB pathway, which was recently reported to be also involved in Rac1-dependent phagocytosis. BCL10 is known to be required for Dectin-1-induced NFkB activation. Interestingly, other pathways that required BCL10 to activate NFκB, such as the T-cell receptor (TCR) seem also dependent to some extent of XIAP to activate NFκB [19].

Another important advance was the recent demonstration that cIAP-1, cIAP-2 and XIAP, are regulators of TNF receptor 1 signaling by their ability to dampen and inhibit receptor-interacting protein kinase 1 (RIPK1)- and RIPK3-dependent downstream signaling [20]. RIPK1 is known to be involved in TNFR1 signaling as a scaffold necessary for cIAP-1/2-dependent NFkB activation [21] and RIPK3 has been shown to be implicated in TNF-α-mediated necroptosis, a inflammatory type of cell-death that arises in the absence of caspase-8 activation [22]. In particular, XIAP (as well as cIAP-1 and cIAP-2) in myeloid cells was shown to limit RIPK1- and RIPK3-dependent TNF-α-induced pro-inflammatory cytokine and chemokine secretion and cell death [23–25]. Intriguingly, this abnormal signaling through RIPK1 and RIPK3 when XIAP is lacking, results in the activation of the classical caspase-1/NLRP3 inflammasome complex and increased cell death [23,24]. However, the exact role of XIAP in this inhibitory mechanism remains to be elucidated. Besides, the implication of XIAP in inflammasome complexes was previously suggested in two studies showing the association of XIAP with the NLRP1/NALP1 inflammasome complex when activated, although the role of XIAP in this complex was not examined [26,27].

3. Mouse models of XIAP deficiency

Xiap-deficient mouse models have been developed, and the first characterization of these models did not reveal any obvious phenotype or abnormalities, in particular regarding apoptosis [28,29]. However, the following recent studies reveal that Xiap-deficient mice have compromised immunity leading to decreased survival when infected with certain pathogens. Those include intracellular

gram-negative and -positive bacteria, such as *Listeria monocytogenes* [30], *Chlamydophilia pneumonia* [31] and *Shigella flexneri* [32], and the fungus *Candida albicans* [19]. The control of viral infections appears to be also altered in Xiap-deficient mice, as they displayed abnormal high viral loads when infected with MHV-68, a murine γ-herpes virus [23]. However, this sensitivity to infections seems not to be general; for instance Xiap-deficient mice are not particularly susceptible to infection by *Salmonella typhimurium*, a gram-negative intracellular bacteria [31]. Under infectious conditions with *L. monocytogenes*, *S. flexneri* and *C. albicans*, the early NFκB activation and cytokine production post infection were significantly reduced, which is suggestive of defective innate immunity. Interestingly, Xiap-deficient mice infected with MHV-68 or *C. albicans* developed splenomegaly several days post infection, with increased cellularity of mononuclear cells including myeloid cells [19,23]. In *C. albicans* infection, the splenomegaly was concomitant with increased levels of pro-inflammatory cytokines, and in MHV-68 infection splenomegaly was driven by TNF-α and was dependent on RIPK3 [23]. Thus, in these models splenomegaly appears to occur secondarily to the innate defect, and could be dependent of abnormal levels of inflammation caused by the persistence of pathogens.

Compromised innate immunity to *L. monocytogenes* and *C. albicans* was associated with defects in NOD2- and Dectin-1-mediated cytokine production by XIAP-deficient myeloid cells, respectively [19,30]. Strikingly, Dectin-1-mediated phagocytosis of *C. albicans* by macrophages was found to be abolished in absence of XIAP, and restoration of phagocytosis by Resolvin D, an anti-inflammatory lipid mediator rescued *C. albicans* clearance and resolved the inflammation [19]. Similarly, the susceptibility of Xiap-deficient mice to infection by *S. flexneri* is likely caused by impaired NOD1 function, as clearance of *S. flexneri* is known to depend on NOD1 [33]. The alteration of the NOD1/2 pathway in Xiap-deficient mice was confirmed in additional studies that also demonstrated the importance of the RING and the BIR2 domains of XIAP in NOD1/2 function [17,18,30]. In comparison, responses to ligands (pathogen- or danger-associated or molecular pattern molecules/PAMPs or DAMPs) for Toll-like receptors (TLR) (including TLR2, TLR3, TLR4, TLR5, TLR7/8 and TLR9) were found to be normal and not dependent of XIAP [19,23,24,30], with the exception of the infectious model with *C. pneumonia*, in which the authors reported abnormal TLR4 responses to LPS and decreased susceptibility to endotoxin shock to LPS [31]. The reason of this discrepancy is not known.

The function of XIAP together with those of cIAP-1 and cIAP-2 (simply referred to as IAPs later on in the text) was also evaluated in single, double or triple IAP-deficient mice, and sometimes in combination with treatment of these mice with SMAC mimetics that deplete IAP protein expression by inducing their proteosomal degradation [34]. These experiments demonstrated an important overlap and redundancy in the functions of XIAP, cIAP-1 and cIAP-2 [20,24,25,35]. Notably, it was shown that deletion of both XIAP and cIAP-1 impaired anti-viral adaptive immunity during lymphocytic choriomeningitis virus (LCMV) infection, due to increased apoptosis of virus-specific CD8 T cells that did not properly expand [35]. A similar defect might account for the compromised immunity to the MHV-68 virus in Xiap-deficient mice [23]. Other studies revealed a crucial role for the IAPs in the limitation of pro-inflammatory cytokine production by myeloid cells [24,25]. In one report, deletion of IAPs in the myeloid lineage led to hyper-inflammation, granulocytosis and splenomegaly, driven by over production of pro-inflammatory cytokines [25]. This process was initially mediated by TNF-α and TNFR1 signaling and was shown to be dependent of RIPK1 and RIPK3. In another study, deletion IAPs in dendritic cells and macrophages resulted in inflammasome activation and subsequent production of active IL-1β, after priming of the cells by TLR ligands, but was shown to be independent of TNF-α and TNFR1 signaling [24]. Interestingly, the cleavage of the IL-1β precursor was mediated not only by the classical NLRP3-caspase-1 inflammasome, but also by activated caspase-8. Activation of caspases in this setting was dependent of RIPK3 and reactive oxygen species production by RIPK3, but not of RIPK1. Importantly, in a third study, deletion of XIAP alone was sufficient to induce IL-1β production by dendritic cells and macrophages by a similar mechanism, but in contrast to the above study it was fully dependent of TNF-α/TNFR1 and independent of cIAP-1 and cIAP-2 [23]. Remarkably, treatment of Xiap-deficient mice by Alum crystals, an activator of NLRP3, led to exacerbated inflammation and splenomegaly characterized by infiltration of neutrophils, macrophages, eosinophils and lymphocytes. In all these studies, the production of inflammatory cytokines was associated with increased cell death of myeloid cells, which was dependent on RIPK3 and RIPK1.

4. XIAP deficiency in humans

4.1. Clinical features

Since its original discovery, more than 70 male patients from different countries have been diagnosed with an XLP-2/XIAP deficiency [1,36–40]. XIAP deficiency is mostly a pediatric disease and boys can be affected very early in their life (during the first months) with symptoms which are especially severe – the younger the patient is. The most frequent clinical manifestations are HLH (54%), recurrent splenomegaly (57%) and IBD (26%). EBV is very often the trigger of HLH (in more than 60% of cases), but HLH can develop in the course of cytomegalovirus (CMV) or human herpesvirus 6 (HHV-6) viral infection, or in the absence of a documented infectious agent. Importantly, all the symptoms can occur independently from each other. HLH is often severe and can be fatal in young boys presenting with fulminant infectious mononucleosis associated with primary EBV infection. Episodes of splenomegaly occur in the absence of systemic HLH and are usually associated with fever and cytopenia. They likely represent minimal forms of HLH, and hemophagocytosis, which is a key feature of HLH was observed histologically in the spleen after splenectomy [36]. Splenomegaly is the initial clinical presentation of the disease in many cases [1,36,40]. Interestingly, several patients had inflammatory liver diseases that might also correspond to incomplete forms of HLH [36,40,41].

IBD is generally severe and drug-resistant with a lethal outcome in 10% of cases. In 2011, Wortley et al. reported the first description by exome sequencing of an inactivating XIAP mutation in a young boy, who presented at 15 months with an intractable inflammatory bowel disease evoking Crohn's disease, and no other symptoms [42]. Based on the molecular diagnosis of XIAP deficiency, the patient underwent hematopoietic stem cell transplant (HSCT) and recovered from IBD. The predominant role of XIAP mutations in the occurrence of pediatric IBD, was later confirmed by two independent studies that analyzed cohorts of 96 and 83 male patients with pediatric or early onset IBD as an unique clinical trait. They respectively identified 4 and 3 boys to be carriers of inactivating XIAP mutations, which is a compelling prevalence (approximately 4%) [43,44]. Interestingly, in the study by Zeissig et al., cohorts of patients with adult onset-Crohn's disease and -IBD were also analyzed and no mutations were detected [44]. From these observations, XIAP deficiency is considered now as one of the mendelian causes of inheritance for IBD in infancy [45]. IBD in XIAP deficiency shares most of the biological and histology features of Crohn's disease, which is one of the most frequent IBD forms in adults [43,44]. These features include focal inflammatory lesions affecting all digestive segments with ulcerations, crypt abscesses, granulomas, and polymorphic cellular infiltrates. Some XLP-2 patients (7% of patients) also experienced other inflammatory

manifestations, including arthritis, cutaneous abscesses, erythema nodosum, uveitis and nephritis (Aguilar and Latour, unpublished observations) [40,43]. Hypogammaglobulinemia is reported in 16% of patients and it is rarely a severe and persistent symptom.

4.2. Mutations and genetics

The incidence of mutations in *XIAP* leading to XLP-2 is estimated to be 1–2 cases per million of live births, making it a rare inherited X-linked immunodeficiency. Today, more than 50 different deleterious mutations in *XIAP* have been identified [36–40,43,44,46–49]. They are distributed along all coding exons and include missense and nonsense mutations, deletions and insertions [50]. A majority of the mutations are amorphic or null mutations leading to complete loss of protein expression. However, several hypomorphic missense and nonsense mutations have been reported. These mutations preserve some residual expression of full-length or truncated proteins. Interestingly, missense mutations form two hotspots that target either the BIR2 domain or the RING domain, highlighting the importance of these two domains in XIAP function [18,50]. However, a few missense mutations are found in the BIR1 (G39C) and the BIR3 domains (K297T and A321G) as well. In any case, these mutations behave as loss of function or inactivating mutations, and carriers of hypomorphic mutations develop manifestations as severe as patients carrying null mutations. In a same family the symptoms can be quite different (HLH versus IBD) and very variable in term of severity (asymptomatic to death) from one patient to another. This individual variability is likely explained by additional genetic and/or environmental factors that may influence the outcome of the disease, including the emergence of rare phenotypes. Along these lines, a modifier gene was identified in a large family carrier of a hypomorphic *XIAP* mutation (G466X), leading to a weak expression of a truncated protein [41]. In this family, the range of the symptoms and the severity was broad (from asymptomatic to death). In addition to the mutation in *XIAP*, symptomatic individuals were carriers of a hypomorphic missense mutation in *CD40LG*, which deficiency is known to cause X-linked hyperIgM syndrome (XHIGM). Both mutations were proven to have functional effects in vitro, and carriers of a single mutation were asymptomatic, strongly suggesting that the association of *XIAP* and *CD40L* mutations in this family is necessary for the clinical expression of the disease. Furthermore, this genetic association might account for the progressive hypogammaglobulinemia seen in all symptomatic individuals of this family [41].

In disorders with a X-linked recessive inheritance, female carriers who have only one copy of the mutated allele are usually asymptomatic. In accordance, female heterozygous carriers of *XIAP* mutations were originally reported as healthy [1]. Interestingly, in these women, the X chromosome inactivation of their peripheral blood leukocytes (PBL) is not as random as expected, but shifted toward the X chromosome carrying the mutated allele [1,51]. This indicates that PBL with an active wild-type allele (in which the mutated allele is inactive) have a selective survival advantage in contrast to cells with an active mutated allele, and thus cells (in PBL) with the active normal wild-type allele typically accumulated in these women. These observations stress the role of XIAP in the cell survival, which likely depends of its anti-apoptotic activity. It would be interesting to know if this abnormal X chromosome inactivation could occur in other tissues such as epithelial cells. Remarkably, three female carriers of *XIAP* mutations (from three different families) were recently reported to be symptomatic [43] (Aguilar and Latour, unpublished observations). Two suffered from IBD and one had an episode of EBV-triggered HLH. Notably, leukocytes of these female symptomatic subjects showed a random X inactivation or slightly shifted toward the wild-type allele, indicating that cells with an active mutated allele normally survived and expanded, in contrast to what is seen in healthy female carriers [43]. This very likely explains why these women develop symptoms. The mechanism underlying this abnormal X inactivation is not known.

4.3. Outcomes and treatments

XIAP deficiency is associated to date (2006–2014) with a lethal outcome in more than 20% of cases (22 deaths out of 100 known patients) (Aguilar and Latour, personal communication). In fact, 12 patients died during allogenic hematopoietic stem cell transplantation (HSCT), 4 of HLH, 4 of IBD, 1 of pneumonia and 1 of liver failure. HLH and IBD symptoms are treated with classical immunosuppressive drugs including etoposide, corticosteroids and cyclosporine for HLH [52] and corticosteroids, azathioprine, mesalazine and anti-TNF-α for IBD [40,43,44]. Hypersplenism can require splenectomy (in 3 patients) and several patients with IBD had colectomy (7 patients). The only curative treatment is a hematopoetic stem cell transplant. Nevertheless, HSCT in XIAP deficiency has been associated initially with a bad prognosis. A retrospective international survey of 19 XIAP-deficient patients demonstrated a high transplant mortality with 12 deaths [53]. In this study, the use of chemotherapy with full dose conditioning/myeloablative regimen and the HLH at time of treatment were identified as factors accounting for this harmful outcome. It was proposed that chemotherapy in the absence of XIAP possibly results in excessive apoptosis of hepatocytes and/or other cell types and increased cytotoxicity [54]. Corroborating that minimal chemotherapy can improve the outcome, successful HSCT following reduced intensity conditioning has been recently reported [54,55], although in another study reduced conditioning was associated with complications of HLH [56]. Interestingly, of 6 XIAP-deficient patients with severe IBD who received HSCT [40,42,43] 1 patient died, but the treatment allowed remission of the disease in 5 patients, with a follow up of 3 years for the first transplanted patient [43], arguing for a hematopoietic cell origin of IBD in XIAP deficiency.

4.4. Immunological parameters and defects

No gross abnormalities in the classical immunological parameters have been reported in asymptomatic or stable XIAP-deficient patients. However, several defects associated with XIAP deficiency have been demonstrated in vitro or upon challenge. XIAP-deficient T lymphocytes (from patients) are characterized by a high susceptibility to apoptosis in vitro in response to stimulation of the cell-death receptors FAS/CD95, TRAIL-R or when activated by the T-cell antigen receptor (TCR), which results in activation-induced cell death [1,37,40]. Activation-induced cell death in T lymphocytes, that is dependent on CD95, is known to be important to shut down T cell responses [57]. Consequently, the expansion of activated XIAP-deficient T cells in vitro is compromised and is rescued by expression of wild-type XIAP [1]. In proliferating T cells, XIAP interacts with caspases-3/-7, thereby blocking their full activation and subsequent cell death induction [58]. This exagerated sensitivity to apoptosis of activated T lymphocytes in vitro has no influence on circulating blood lymphocytes populations in patients, whose cell numbers and proportions are apparently normal, with the exception of innate-like T cell populations.

XIAP-deficient patients often exhibit decreased numbers of circulating innate-like T lymphocyte populations, iNKT cells and MAIT cells [1,51,59]. Deficiency in iNKT cells likely results from their depletion secondary to EBV infection or/and the high inflammatory environment associated with HLH and IBD. Indeed, some patients with normal iNKT cell numbers have not encountered EBV, and patients with HLH not related to XIAP deficiency can also have low numbers of iNKT cells [51,59]. iNKT and MAIT cells are in

fact characterized by a pro-apoptotic propensity, and so are likely more dependent on XIAP for their survival than other populations of T cells [59].

Recently, several studies showed that monocytes from PBMC of XIAP-deficient patients have compromised cytokine production, including TNF-α and IL-8, in response to NOD2 ligands, while the response to TLR-2, -4 receptor stimulation is normal [42–44]. In one study, it was shown that this defect can be used as a reliable and easy cell-based functional test for diagnosis of XIAP deficiency, which clearly discriminates with other immunodeficiencies sharing similar clinical hallmarks [47].

Pro-inflammatory cytokines in the serum of 10 XIAP-deficient patients who presented with HLH have been analyzed. IL-18 levels were found to be markedly high in these patients. IL-6, TNF-α and IFN-γ were also found to be elevated but their levels were comparable to those in patients with XLP-1 and FLH. Interestingly, IL-18 concentrations remained elevated and stable in XIAP-deficient patients that recovered from HLH, in contrast to levels of IL-6, TNF-α and IFN-γ that declined [48]. IL-18 is mainly produced by cells of myeloid lineage and is synthetized as pro-IL-18, an inactive precursor that needs to cleaved through caspase-1/inflammasome activation to be active, similarly as IL-1β [60]. It would be important to test whether IL-18 levels are also elevated in patients that never experience HLH.

After the discovery of the XLP-2 syndrome, studies of XIAP-deficient humans and mice have looked for defects similar to those associated with the SAP deficiency (XLP-1 syndrome), because of the apparent clinical similarities of the two diseases. The immunopathogenesis of XLP-1 is quite well understood and multiple defects have been documented in SAP-deficient humans and mice. Those include a complete block of iNKT cell development, altered antibody production associated with low numbers of switched memory B cells and loss of germinal center formation, and defective $CD8^+$ T and NK cell-cytotoxicity against EBV-infected B cells [2]. In XIAP-deficient patients, the T and NK cell-cytotoxicity responses are normal, including those specific for EBV and did not display a defect in the numbers of switched memory B cells [1,37,61]. These observations contribute to the notion that XLP-1 and XLP-2 are different and non-related immune disorders (see Section 1).

4.5. Pathophysiology of XIAP deficiency

The recent advances revealing a key role for XIAP in innate immunity and in the regulation of inflammation, now offer new and important clues in the understanding of the pathogenesis of XLP-2, which can help to explain the different clinical phenotypes.

4.5.1. Susceptibility to EBV

The susceptibility to EBV (and also CMV) infection in XIAP deficiency could be explained in part by defects in adaptive immunity, affecting T lymphocyte responses that are particularly important during viral infections. Of note, immune response against EBV and CMV in immunocompetent individuals depends on a massive expansion of $CD8^+$ T cells, which can be associated with an important inflammatory response resulting in infectious mononucleosis, a self limiting lymphoproliferative disorder. In XIAP-deficient patients, the excessive susceptibility to FAS-mediated apoptosis of activated T cells seen in vitro, may compromise in vivo the expansion and proliferation of virus-specific T cells during EBV infection. Supporting this assumption, studies in mice have shown that XIAP and cIAP-1 are required for the survival and the expansion of virus-specific T cells, when mice are infected with the LCMV virus [35]. Of note, EBV is not infectious in mice. In these studies, the defective expansion results from increased apoptosis of virus-specific T cells, which is partially dependent on TNF-α/TNF-R1, and presumably on others cell-death receptors such as FAS and TRAIL-R. Hence, in humans, exacerbated inflammation during EBV infection may contribute to cell-death of T cells (including iNKT and MAIT cells) and other cell types, in addition to FAS- and TRAIL-mediated apoptosis. Along these lines, hypogammaglobulinemia could be thus a consequence of transient exhaustion of B lymphocytes in the context of elevated inflammation.

The deficiency of iNKT cells (which are highly susceptible to apoptosis in the absence of XIAP) might also contribute to the susceptibility of EBV infection [62]. iNKT cells are known to be rapidly activated in the early phases of immune responses including viral responses [63], and there are some indications that EBV-infected cells can directly activate IFN-γ production and cytotoxicity by iNKT cells [64]. Furthermore, defects in iNKT cells occur in several other primary immunodeficiencies characterized by a peculiar susceptibility to EBV and EBV-associated pathologies [65]. Defects in NOD2 might also contribute to the susceptibility to EBV in accordance with recent findings showing that NOD2 can also sense viral products including those from a herpes virus [12,13].

4.5.2. HLH

Several genetic defects causing familial HLH (FHL), including XLP-1 have been identified, and all defects resulted in the impairment of cytotoxic responses of $CD8^+$ T lymphocytes and NK cells [3,4]. In this context, infected cells are not eliminated and persist, leading to exaggerated cytokine production by activated T and NK cells, that subsequently activates macrophages. Production of IFN-γ by activated T and NK cells plays an essential role in these inherited forms of HLH, as pathology can be reversed by anti-IFN-γ antibodies. In contrast to FHL and XLP-1, HLH triggered by EBV in XIAP deficiency is not associated with defects in the cytotoxicity responses of NK and $CD8^+$ T cells, which are apparently normal [1,37,61]. These observations tend toward different pathophysiological mechanisms at work in the manifestation of HLH in the absence of XIAP.

The recent observations in mice showing that XIAP is a potent negative regulator of the NLRP3 inflammasome and pro-inflammatory cytokine production provide a reliable explanation for this specific emergence of HLH in XIAP-deficient patients [23–25]. Although, we do not know if XIAP in humans is also an inhibitor of NLRP3 (and/or other inflammasomes), like it is in mice. Impairment of this control might represent a key pathological mechanism, leading to hyperinflammation in the context of viral infections or persistent infections (Fig. 1). This could account not only for HLH, but also for the episodes of splenomegaly, which may be reflective on the infectious status of the patient. This is exemplified by the splenomegaly that develops in Xiap-deficient mice few days after being infected by the fungus *C. albicans* in association with high levels of inflammatory cytokines [19]. Direct evidence for a role of NLRP3 in splenomegaly is provided by the observation that Xiap-deficient mice exhibit TNF-α- and RIPK3-dependent splenomegaly, when mice are treated with Alum, an activator of NLRP3 [23]. Splenomegaly is also seen when mice are infected with the MHV-68 virus, and it is RIPK3-dependent, strongly suggesting that NLRP3 is actually activated during MHV-68 infection [23]. However, MHV-68 and LCMV infections have not been reported to trigger full-blown HLH in Xiap-deficient mice, possibly due to the redundancy with the other IAPs in mice.

Interestingly, the importance of inflammasome activation in HLH has been recently highlighted by the identification of two dominant activating mutations in the NLRC4 inflammasome in humans suffering from recurrent HLH and autoinflammation [66,67]. These mutations result in the spontaneous formation and activation of

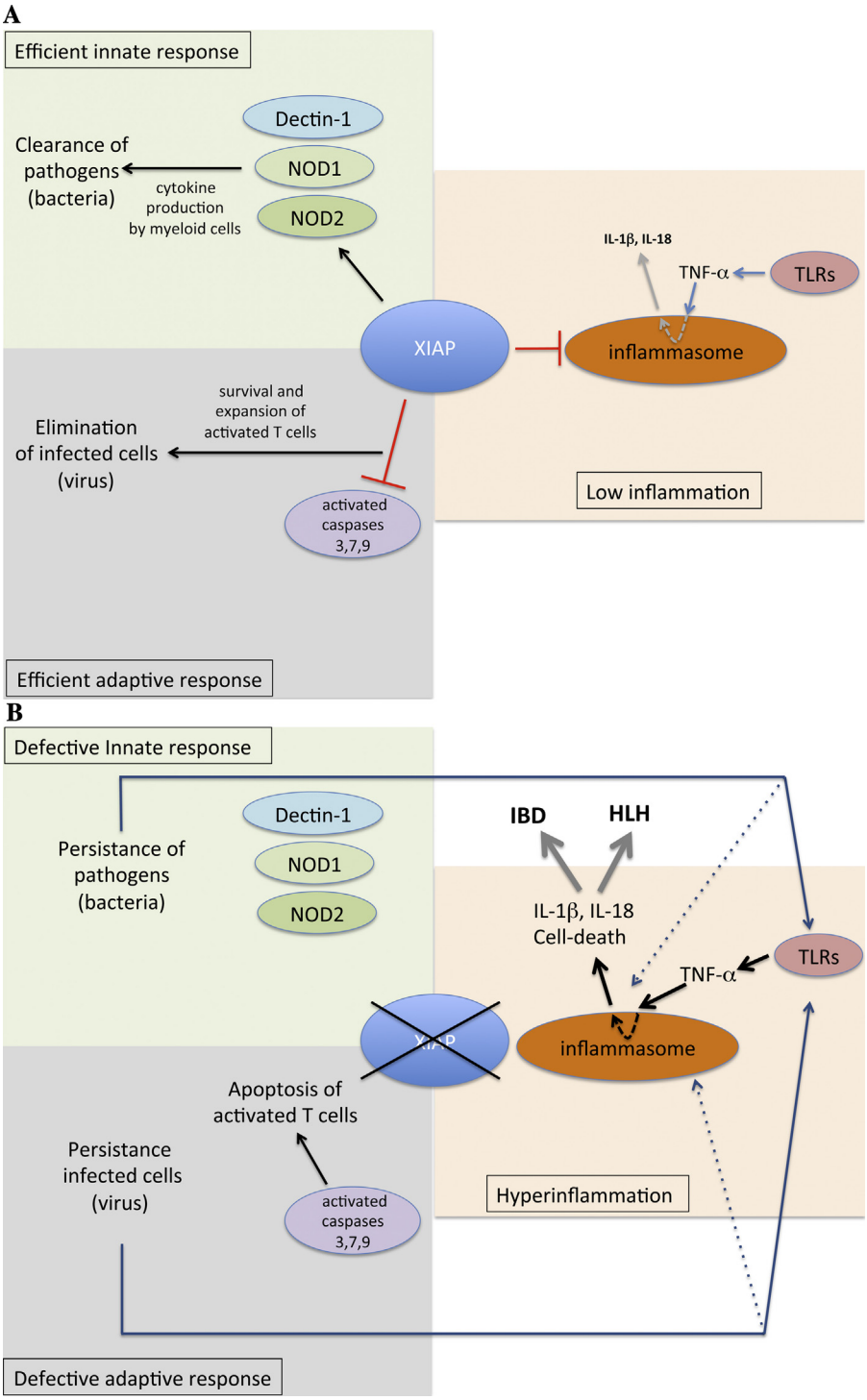

Fig. 1. Model for the pathogenesis of HLH and IBD in XIAP deficiency. (A) In healthy individuals, innate and adaptive responses are efficient. On one hand, XIAP inhibits caspases in activated T cells allowing their survival and expansion, in particular for virus-specific $CD8^+$ T cells that kills infected cells. On the other hand, XIAP participates in innate immunity for the signaling and function of the pattern-recognition receptors (NOD1/2 and Dectin-1), which are sensors of derived products from bacteria and fungi, respectively. When NOD1/2 and Dectin-1 are activated by their ligands during infection, they promote cytokine production by myeloid cells, resulting in acute inflammation necessary to clear the infectious pathogens, in part by recruiting neutrophils and phagocytes. Moreover, XIAP is involved in the inhibitory signaling of inflammasomes (NLRP3 in mice) and limits its TNF-α-dependent or independent activation by various pathogen-associated molecular patterns (PAMPS), which can activate TNF-α production via Toll-like receptors (TLRs). In this context, local acute inflammation is rapidly resolved and general inflammation is low. (B) In XIAP-deficient patients, innate and adaptive responses are compromised, leading to accumulation of infectious pathogens (and the associated PAMPS) and subsequent uncontrolled activation of the inflammasomes, which is not properly regulated in the absence of XIAP. In this context, there is accumulation of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-18, and increased cell-death of lymphocytes, myeloid cells and possibly other cell types. This results in a high chronic inflammatory environment leading to splenomegaly, IBD and HLH.

the NLRC4 inflammasome, leading to constitutive secretion of IL-18 by myeloid cells. Increased IL-1β was also observed, but only in response to stimuli that activate NLRC4. Importantly, patient carriers of these mutations had elevated IL-18 serum levels, like it is reported for XIAP-deficient patients [48], and hence it is plausible that IL-18 may play an important and specific role in the pathogenesis of HLH associated with abnormal inflammasome activation.

As discussed above, it is not known whether NLRP3 is regulated by XIAP in humans, but dominant gain mutations in NLRP3 in humans cause rare inherited dominant autoinflammatory disorders named Cryopyrin-associated periodic syndromes (CAPS) [68]. Even though the clinical expression of NLRP3 mutations has a wide spectrum, IBD and HLH have not been reported to be associated with NLRP3 mutations. This could suggest that XIAP is not implicated in NLRP3 regulation in humans, but rather in other inflammasomes such as NLRC4.

4.5.3. IBD

Monocytes from XIAP-deficient patients displayed a defective capacity to secrete cytokines and chemokines including TNF-α, IL-10, IL-8 and MCP-1, in response to stimulation with NOD2 ligands [42–44]. Similarly, production of IL-8 and IL-6 by XIAP-deficient fibroblasts from patients had diminished responses to NOD1 ligands [43]. Notably, *NOD2* is the strongest genetic factor associated with Crohn's disease in adults, for which it contributes to 2.5–5% of the total genetic variance [69–71]. The *NOD2* risk alleles are known to alter the ligand recognition capacity and the function of NOD2 [72]. Thus, the pathological mechanisms underlying IBD in XIAP deficiency are, in all likelihood, very close to those of Crohn's disease associated with NOD2 risk alleles. Many studies suggest a pivotal role of NOD2 in immune innate host defense in the gut. Remarkably, IL-8 and MCP-1 that are among the most predominant cytokines secreted in response to NOD2 activation, are important chemokines for the recruitment of neutrophils. Furthermore, IL-10 is a crucial anti-inflammatory cytokine involved in intestinal homeostasis, and defects in the IL-10 pathway cause very early onset IBD (VEO-IBD) [73]. Therefore, NOD2-impaired secretion of these cytokines may disturb intestinal homeostasis in XIAP-deficient patients. Impaired IL-8 and MCP-1 production could compromise neutrophil influx, a defect which has been documented in patients with Crohn's disease [74–76]. A key role of neutrophils and myeloid cells in the pathogenesis of IBD is also supported by the observation that 40% of patients with chronic granulomatous disease (CGD) – a primary immunodeficiency due to mutations affecting the oxidative respiratory burst of phagocytes – develop IBD indistinguishable from Crohn's disease [77]. In XIAP deficiency, the predominant contribution of a myeloid defect to IBD is further underlined by the findings of low level of XIAP and defective NOD2 response in monocytes of a symptomatic female (carrier of a deleterious XIAP mutation), who developed IBD without other symptoms, while expression of XIAP was almost normal in her lymphocytes [43]. Taken together, these observations point to a model, in which compromised cytokine production in response to NOD2 would impair bactericidal response of neutrophils and macrophages, leading to defective clearance of pathogenic bacteria or agents in the gut. This could also account for gut microbiota imbalance or dysbiosis, that have been well documented in Crohn's disease patients. Along these lines, the immune response to *S. flexneri*, an invasive enteropathogenic bacteria, involves NOD1 activation in intestinal epithelial cells [33], and which depends on XIAP in mice [32]. Moreover, *S. flexneri* infection is known to provoke severe inflammatory colitis [78].

Accumulation of pathogenic bacteria might secondarily trigger progressive inflammation, which could not be properly control in the absence of XIAP leading to the NLRP3 inflammasome activation and increased cell death via a LPS-, TNF-α- and RIPK3-dependent pathway (Fig. 1) [23]. In support for a role of this pathway in IBD, is the high level of RIPK3 expression in association with increased necroptosis that has been observed in Paneth cells of patients with Crohn's disease [79]. Additional mechanisms may also contribute to IBD, including defective NOD1 functions (in epithelial cells) and increased cell death of T lymphocytes populations in the gut, in particular MAIT and iNKT cells that are highly dependent of XIAP for their survival [59]. MAIT and iNKT cells are characterized by their tropism for mucosal tissues and their rapid activation by bacteria, and they have been recently implicated in the homeostasis and the defense of the gut [80–83]. These additionnal defects might account for the early onset and the higher severity and penetrance of IBD in XIAP-deficient patients compared to carriers of NOD2 risk alleles. Finally, it should be pointed out that Xiap-deficient mice have not been yet reported to be prone to develop colitis like their human counterparts.

Based on mouse and human studies, a potential model for the immunopathogenesis of the inflammatory manifestations in the XIAP deficiency is depicted in Fig. 1.

5. Conclusion and perspectives

The recent findings revealing that XIAP (as well as cIAP-1 and cIAP-2) is an important player in innate immunity and in the negative regulation of inflammation provide new insights into the immunopathogenesis of XIAP deficiency in humans. These studies also open novel perspectives for the treatment of the XIAP deficiency or related diseases. TNF-α and IL-18 appear to be important cytokines associated with the disease, thus they may represent potential therapeutic targets for inflammation inhibition. Furthermore, there are still remaining important and interesting questions, and many more to come, emanating from these novel observations. Some of them that would come to mind are listed below. There are convincing indications that adaptive responses are compromised in the absence of XIAP. How do these defects contribute to the pathogenesis of the XIAP deficiency? The absence of XIAP clearly results in increased cell death from apoptosis and necroptosis. It is not clear what are the XIAP-dependent pathways and/or mechanisms involved in each type of cell death, and under what circumstances they occur? More importantly, it is not known, what is the contribution of this increased cell death to the pathogenesis of XLP2. Is it an amplification mechanism of inflammation? Do cell death and/or dead cells directly or indirectly activate inflammation? Other fundamental issues also emerge from these observations. What is the exact contribution of each IAP in innate immune responses and in the regulation of inflammation? Is the redundancy of IAPs observed in mice any different and/or less important than in humans? What are the exact mechanisms by which XIAP and cIAP1-2 limit inflammasome activation? Is XIAP involved in innate receptors/pathways and inflammasomes other than NOD1/2, Dectin-1 and NLRP3? The answers to many of these questions will undoubtedly provide a better understanding of immunodeficiencies associated with inflammatory disorders, and hopefully suggest potential therapies.

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