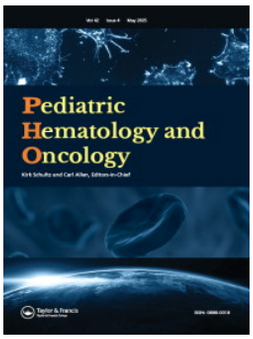

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LETTER TO THE EDITOR

The novel *XIAP* Lys396Ter variant alters mitochondrial membrane potential and endoplasmic reticulum intensity in monocytes of two XIAP-deficient patients

Benedetta Elena Di Majo[a,b], Fabiola Guerra[a,b], Mario Mauri[b], Maria Luisa Coniglio[c], Elena Sieni[c], Silvia Parolini[d], Giovanna Tabellini[d], Cristina Bugarin[e], Fabiola Dell'Acqua[a], Giovanna Lucchini[a], Sonia Bonanomi[a], Adriana Cristina Balduzzi[a,b], Jasmin Mann[f], Stephan Ehl[f], Andrea Biondi[e] and Francesco Saettini[a,e]

[a]Pediatric Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [b]Department of Medicine and Surgery, Milan-Bicocca University, Italy; [c]Hematology-Oncology Department, Meyer Children's Hospital IRCCS, Florence, Italy; [d]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; [e]Centro Tettamanti, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; [f]Institute for Immunodeficiency, Center for Chronic Immunodeficiency, University Medical Center Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

To the editor:

X-linking inhibitor of apoptosis protein (*XIAP*), also known as *baculoviral IAP repeat-containing protein 4* (*BIRC4*) is an endogenous regulator of cell death that primarily inhibits caspases.[1] Beyond its well-established role in apoptosis through caspase-3, -7 and -9 inhibition, XIAP is also involved in NOD1/2-induced nuclear factor-kB activation, TNF-receptor signaling and NOD-like receptor (NLRP3) inflammasome activity.[2]

XIAP deficiency, first described in 2006,[3] is a rare X-linked inborn error of immunity (IEI) affecting approximately 1–2 in a million males.[4] Also known as X-linked lymphoproliferative disease type 2 (XLP2), it presents with severe immune dysregulation, including hemophagocytic lymphohistiocytosis (HLH), inflammatory bowel disease (IBD), autoinflammatory phenomena but also hypogammaglobulinemia, susceptibility to infections, splenomegaly, and cytopenia.[5]

While standard immunological tests often reveal no major abnormalities beyond hypogammaglobulinemia, persistently elevated pro-inflammatory cytokines, particularly IL-18, are detectable even in remission. During HLH episodes, levels of IL-6, IL-2, IFNγ, TNFα are markedly increased.[6]

Currently, hematopoietic stem cell transplantation (HSCT) is the only curative treatment for patients with HLH or severe IBD. However, conservative management with immunosuppressants and immunoregulatory therapies remains challenging and often refractory.[2,6] Emerging therapeutic strategies, including targeted cytokine inhibition (eg anti-IL-18 drugs like MAS825) and autologous HSC gene therapy, are under investigation.[7,8]

CONTACT Francesco Saettini f.saettini@gmail.com Centro Tettamanti, Fondazione IRCCS San Gerardo dei Tintori, Via GB Pergolesi 33, Monza, MB, Italy

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Here, we describe a novel *XIAP* mutation and investigate the cellular mechanisms underlying XIAP deficiency, contributing to a deeper understanding of its pathophysiology.

Material and methods are detailed in the Supplemental online material. Two affected siblings (Patient 1 [II.1] and Patient 2 [II.4]) were compared to one heterozygous carrier (II.2) and healthy donors (HD).

II.1 was referred to our Pediatric hematology Outpatient Clinic at the age of 11. He was the first of four children born to non-consanguineous parents of Egyptian ancestry (Figure 1A). A liver biopsy performed for neonatal hepatosplenomegaly was unremarkable. A bone marrow (BM) smear showed erythroid, myeloid and megakaryocytic hypercellularity. His medical history included a single febrile episode at age 7, associated with otitis and lasting seven days. Laboratory tests at that time revealed iron-deficient microcytic anemia (Hb 11.2 g/dL; serum iron 18 ug/dL, n.v. 3–193) while ferritin, HbA2, lactate dehydrogenase (LDH), bilirubin, lymphocyte subsets and immunoglobulins (IgA 264 mg/dl, IgM 74 mg/dl, IgG 1,328 mg/dl) within age-matched normal range. NK-cell activity and soluble-CD25 were not assessed. Abdominal ultrasound (US) showed hepatomegaly (15 cm) and splenomegaly (13 cm). He was lost to follow-up until age 9, when anemia was reassessed, and oral iron therapy was initiated.

At age 11, he was admitted due to a 3-day history of persisting fever and vomiting. Blood tests showed microcytic anemia (9.2 g/dL, MCV 63.5 fL), neutropenia (0.48×10^9/L), hyperferritinemia (10,625 ng/mL, n.v. 30–400), hypertriglyceridemia (338 mg/dl, n.v. < 150), hypofibrinogenemia (103 mg/dl, n.v. 175–400) and elevated EBV-DNA (18,600 copies/mL). A BM smear showed no hemophagocytosis. Imaging (US, CT, PET and MRI) confirmed hepatosplenomegaly with diffuse lymphadenopathy. He met five of eight HLH-2004 criteria,[9] leading to a diagnosis of EBV-related HLH (Supplementary Table 1). Treatment was initiated according to the 2022 EULAR guidelines[10] with IVIG (1.5 g/kg) and methylprednisolone (30 mg/kg/d). The fever resolved within 24 h. On day three, steroids were tapered to 2 mg/kg/d. However, on day six, disease reactivation occurred, leading to the administration of 2 mg/kg/d cyclosporine (CSA), which resulted in a good clinical and laboratory response. He was discharged on oral prednisone and CSA, both tapered and discontinued after 6 and 7 months, without HLH reactivation.

Screening for primary HLH, including perforin expression, CD107a degranulation assay,[11] and NK-cell activity was within normal limits (Supplementary Table 1). Genetic testing identified a hemizygous *BIRC4* variant (NM_001167, c.1186A > T; p.Lys396Ter), predicted to result in a premature stop codon. Sanger sequencing confirmed the variant in both male siblings (II.1 and II.4), inherited from their mother. The older sister was heterozygous, while the younger sister was wild-type (Figure 1A,B). This variant was absent in public databases and predicted to be pathogenic (MutationTaster: disease-causing; CADD score: 37). Immunological evaluation at age 12 showed normal lymphocyte subsets and slightly reduced IgM levels (Supplementary Table 2).

II.4 had a history of inverse psoriasis, atopic dermatitis, and a previous skin infection with *S.Aureus* and *C.Werkmanii*. At age three, he was admitted for a 10-day history of persistent fever. Laboratory findings included hyperferritinemia (2,988 mg/dl, n.v. 30–400), hypofibrinogenemia (170 mg/dl, n.v. 175–400), hypertrigliceridemia (461 mg/dl, n.v. < 150) and elevated liver enzymes. EBV testing revealed active infection

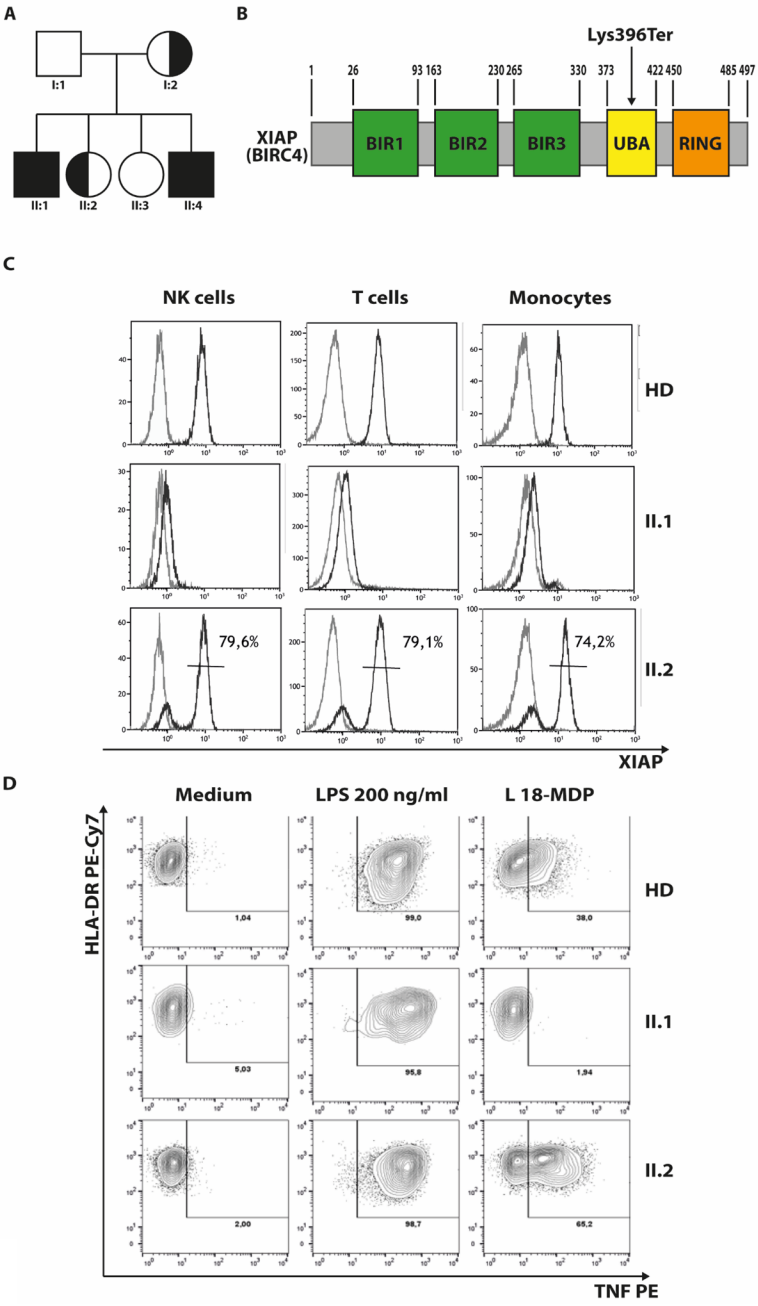

Figure 1. Identification and validation of the novel Lys396Ter variant. (A) Pedigree of the family showing segregation of the XIAP mutation. (B) Protein structure with the highlighted position of the Lys396Ter mutation. (C) Staining with anti-X-linked inhibitor of apoptosis (XIAP) and an iso-type control antibody, gated on NK cells, $CD3^+$ T lymphocytes and monocytes in one healthy donor, one XIAP-deficient patient and one asymptomatic XIAP carrier. (D) TNF-producing monocytes from one healthy donor, one XIAP-deficient patient and one asymptomatic XIAP carrier cultured in the presence of medium alone, 200 ng/mL L18-MDP or 200 ng/mL lipopolysaccharide (LPS). The percentages indicate the percentage of TNF-positive cells of all $HLA\text{-}DR^+CD14^+$ monocytes.

(EBV-DNA 29,713 copies/mL; EBV-IgM VCA >160.00 U/mL). Imaging showed hepatomegaly and multiple adenopathies. BM smear did not reveal hemophagocytosis. Although he did not fully meet the HLH-2004 criteria, genetic confirmation supported an HLH diagnosis (Supplementary Table 1). Treatment according to HLH-2004 protocol was initiated, including 8 wk of dexamethasone (10 mg/mq/day, tapered to 1.25 mg/mq/d) and etoposide (150 mg/mq/week), resulting in clinical response. Two doses of rituximab cleared EBV-DNA. HLA-typing did not identify a matched unrelated or familial donor. Continuation therapy per HLH-2004 protocol included dexamethasone pulses (10 mg/mq for three days every two weeks) and etoposide (150 mg/mq every two weeks) from week 9 to week 30. Subsequently, a conservative approach with CSA maintenance was adopted.

XIAP protein expression was severely reduced in the monocytes and lymphocytes of II.1. In one heterozygous carrier, a mild reduction of XIAP expression (74% compared to HD) was observed (Figure 1C, gating strategy shown in Supplementary Figure S1A). As previously described,[12] we evaluated TNFα production in monocytes stimulated with L 18-MDP. After L 18-MDP stimulation, TNFα production was absent in II.1, while it was normal in one heterozygous carrier (Figure 1D, gating strategy shown in Supplementary Figure S1B). Although patient II.2 had an absolute monocyte count comparable to those of the healthy donor and I.2 (see Supplementary Figure S2), monocyte enrichment following overnight plate adhesion was not observed in II.2 samples. As a result, the total number of cells available for analysis in the TNFα-producing monocyte assay was reduced. XIAP expression and TNFα production were performed only on patient II.1, as both siblings carry the same hemizygous *BIRC4* variant and presented with similar clinical manifestations.

We investigated the functional consequences of the novel Lys396Ter variant in monocytes and assessed whether these alterations were modified by the treatment II.4 was receiving. Although the total number of mitochondria was not different, XIAP-deficient patients showed a significantly reduced mitochondrial membrane potential (Figure 2A, Supplementary Figures S3A and S4), compared to HD, with II.4 exhibiting a significantly reduced membrane potential compared to II.1. Next, we stained monocytes with ER-tracker Red and examined endoplasmic reticulum (ER) intensity by confocal microscopy. We observed altered ER intensity and, overall, a significant decrease in ER-Tracker intensity (Figure 2B and Supplementary Figure S3B). Analysis of actin structure showed similar actin distribution in patients and HD (Figure 2D and Supplementary Figure S3C). The novel Lys396Ter variant was associated with increased LC3 signal in monocytes, which did not further accumulate upon chloroquine treatment (Supplementary Figures S3C and S5). While this may suggest impaired autophagosome degradation, the use of total LC3 intensity alone limits the definitive interpretation of autophagy flux.

XIAP deficiency presents with significant variability in presentation and disease progression. HLH is managed using established protocols (HLH-94 and HLH-2004) that include corticosteroids and etoposide, with Rituximab recommended for EBV-associated HLH. In the case of other clinical manifestations, treatment has to be tailored to individual clinical presentation. Splenomegaly typically does not require treatment, while hypogammaglobulinemia may necessitate immunoglobulin replacement therapy. IBD is managed with immunosuppressive agents.[6]

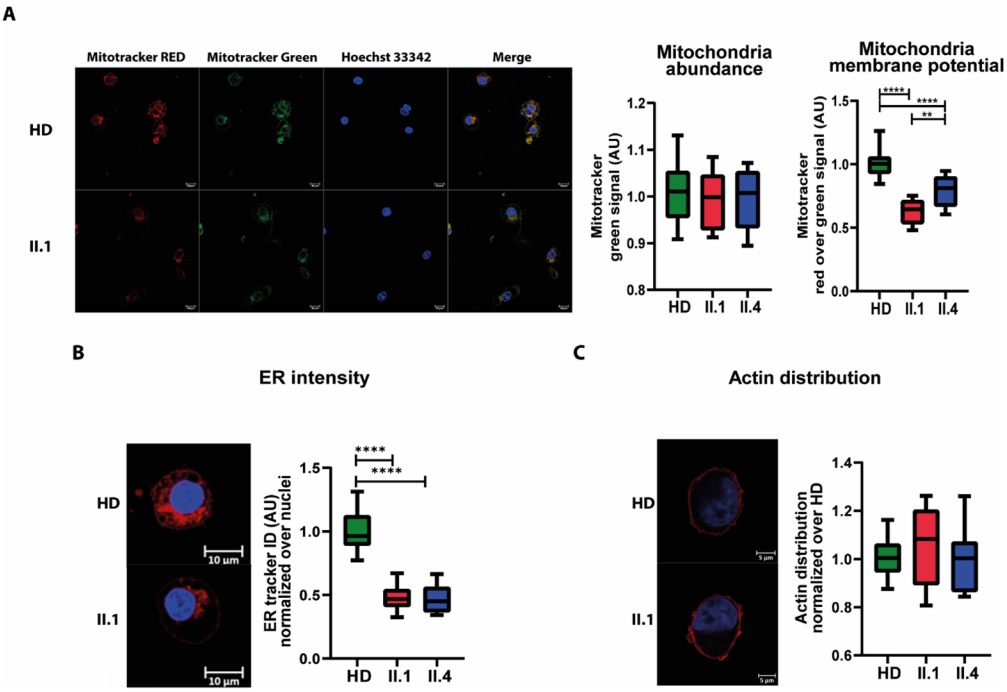

Figure 2. The novel XIAP Lys396Ter variant alters mitochondrial membrane potential and endoplasmic reticulum intensity in monocytes of XIAP-deficient patients. (A) Mitotracker showing impaired mitochondrial potential membrane. Quantification of total mitochondrial abundance (mitotracker green signal) and mitochondrial membrane potential (mitotracker red over green signal). (B) ER tracker showing altered ER intensity. (C) Confocal microscopy studies of cytoskeletal F-actin showing no differences in actin distribution. For each experiment, a minimum of 100,000 cells were collected. Image-based analyses were performed on at least ten fields per sample, with a minimum of 80 cells per field evaluated. In all graphs, *$p < .05$, **$p < .01$ and ***$p < .001$ and ****$p < .0001$ [AU = arbitrary units; ER = endoplasmic reticulum; HD = healthy donors].

Currently, the only curative treatment for XIAP deficiency is represented by allo-HSCT, indicated for patients with severe disease manifestations such as HLH or severe refractory IBD.[6] Early outcomes for HSCT were poor, with survival rates below 50%, particularly when myeloablative conditioning regimens were used. These regimens were associated with severe toxicities, including pulmonary hemorrhage and hepatic veno-occlusive disease. However, improved outcomes with reduced-intensity conditioning (RIC) approaches, with a 2-year overall survival rate of up to 74%, has been documented.[13] Despite these advances, graft-versus-host disease (GvHD) remains a significant risk factor for mortality. This risk remains particularly exacerbated by the XIAP-deficient tissue environment, which is prone to chronic inflammasome activation and inflammatory responses.[13]

Given these ongoing challenges in therapeutic management, there is a pressing need for targeted treatments that address the underlying immune dysregulation in XIAP deficiency. Therapies such as anti-IL18 drugs offer promises by directly tackling the inflammatory pathway involvement.[14] To develop novel targeted approaches, a deeper understanding of the molecular and cellular mechanisms of XIAP deficiency is essential.

Here, we identified and validated a novel pathogenic XIAP variant in two siblings, contributing to the understanding of the molecular basis of XIAP deficiency. The Lys396Ter variant in complete loss of XIAP protein expression in both monocytes and lymphocytes, indicating the loss of functional domains, including UBA and RING, and supporting the relevance of our findings across immune compartments. Our focus on monocytes reflects their pivotal contribution to the inflammatory phenotype observed in XIAP deficiency. XIAP-deficient monocytes are known to exhibit enhanced inflammasome activation and altered cytokine secretion, which contribute to the systemic hyperinflammation and HLH episodes seen in affected individuals.[15] XIAP-deficient monocytes from our patients fail to produce TNFα after MDP stimulation. The two patients presented the same variant and, although some genetic differences could be conceivable in the two individuals, they represent a confrontation between two opposite clinical approaches. Despite the difference in the clinical management, II.1 being managed with a wait and see approach and the second one receiving a standard chemotherapy regimen (steroid and etoposide), similar findings were noticed in both patients.

Through its BIR2 and BIR3 domains, XIAP binds and inhibits caspases −3, −7, and −9, acting as a key regulator of apoptosis.[16] Loss of these domains in the Lys396Ter variant likely abrogates this fundamental anti-apoptotic function, predisposing cells to caspase activation and apoptosis in response to stress or infection. This may contribute to the excessive cell death, immune activation, and inflammation observed in XIAP deficiency. In addition, the understanding of the roles of the UBA and RING domains have expanded XIAP's functions, including ubiquitination and targeting proteins to proteasomal degradation. XIAP also translocates from the cytosol to mitochondria, where it regulates the release of cytochrome c, mitochondrial membrane permeabilization and caspase activation.[17] With this study, we underscore the importance of XIAP in maintaining mitochondrial integrity. In XIAP-deficient monocytes, reduced mitochondrial membrane potential could have a role in the regulation of apoptotic pathways and contributing to inflammation.

ER-Tracker Red is a dye that accumulates in the ER based on membrane potential and integrity. While increased ER-Tracker signal is often interpreted as a marker of ER expansion during acute ER stress,[18] decreased signal—as observed in XIAP-deficient monocytes—may instead reflect compromised ER homeostasis or impaired stress responses. Prior studies have shown that reduced ER mass and downregulation of protein synthesis machinery can occur in specific contexts, such as pre-symptomatic type 1 diabetes[19] or in cancer cells with TCF4 overexpression,[20] where ER volume is actively repressed. In our study, both patients showed reduced ER-Tracker signal, suggesting altered ER dynamics that may be secondary to defective unfolded protein response or autophagy. Given the known role of XIAP in regulating autophagy and stress signaling, our findings support a model in which XIAP deficiency disrupts ER maintenance and contributes to inflammatory cell dysfunction. Interestingly, despite these significant cellular alterations, basal actin distribution was not affected in XIAP-deficient monocytes. The cytoskeleton is essential for various immune cell functions, including migration, vesicle trafficking, and immune synapse formation, and XIAP has previously been implicated in regulating cell motility.[21–23] In prior work, we demonstrated that basal actin abnormalities were detectable in PI4KA-deficient EBV-transformed lymphocytes, and further accentuated by pharmacological inhibition of PI4KA.[23] In contrast, our findings in XIAP deficiency suggest that cytoskeletal defects may not be

constitutive, but instead context-dependent. Such abnormalities might only become apparent under stress conditions, such as during infection or inflammation. Future studies under stimulated conditions will be required to clarify this possibility. Our results suggest a potential alteration in autophagy in XIAP-deficient monocytes. However, given that our current analysis was based on total LC3 intensity rather than LC3-II quantification or puncta counting, these findings should be interpreted with caution.[24] Future studies using more precise autophagy flux assays are warranted to clarify the role of XIAP in regulating autophagosome formation and degradation.

The consistency in the findings observed in both patients suggests that the observed abnormalities are inherent to XIAP deficiency, and they may not be modified by the current treatment approach. Etoposide and steroids do not target these underlying cellular dysfunctions and may open the path to explore additional therapeutic strategies, maybe in addition to current research aimed at cytokine targeting. The complex interplay between mitochondrial function apoptosis and ER stress may provide insights that could be investigated in other immune dysregulation disorders.

Our findings, restricted to monocytes, may not be extended to other immune cells involved in XIAP deficiency pathophysiology. The evaluation of cytokine production was not conducted, limiting the understanding of the cellular consequences of the standard treatment management. Confirmation of ER stress by means of additional techniques, such as measuring specific ER protein levels (PERK, BiP, etc.), assessing XBP1 mRNA splicing or electron microscopy to visualize ER morphology, is needed. A limitation of our study is also the absence of apoptosis or viability assays, and thus we cannot exclude that some of the observed mitochondrial and ER alterations reflect early apoptotic changes in XIAP-deficient monocytes.

In this study, we identified and characterized the novel Lys396Ter mutation in the XIAP gene, revealing its profound impact on cellular processes, such as mitochondria membrane potential and ER distribution, in patients' monocytes. Our findings may suggest a limitation in current chemotherapy approaches, as these cellular processes appear to be not modified by steroids and etoposide. Recent research on novel treatments, such as anti-IL18 drugs, have opened the path for targeted treatment in XIAP deficiency. By expanding the understanding of XIAP beyond its traditional role on apoptosis, we identified potential targets for novel and less toxic therapeutic strategies that could offer effective management options.

Disclosure statement

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