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Gene Section
Review

XIAP (X-linked inhibitor of apoptosis)

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Abstract

X-linked inhibitor of apoptosis (XIAP), also referred to as BIRC4 or IAP3, is one of the most studied members among the proteins known as Inhibitors of Apoptosis Proteins (IAPs). This protein family portrays its main role by preventing apoptotic cell death through direct or indirect inhibition of caspase activity. All members of the IAPs carry at least one BIR domain in their structure, which are generally responsible for caspase interaction. XIAP has three BIR domains, enabling interaction with both initiation and effector caspases. Moreover, it is also structured with a RING finger domain, which functions as a ubiquitin ligase (E3), and one UBA domain, for binding to ubiquitin, further rendering XIAP a central role in the ubiquitination process and, thus, implicating such IAP in multiple signaling pathways, including cell death, autophagy, immunity, inflammation, cell cycle, and cell migration. XIAP overexpression is found in a variety of cancer types and is frequently associated with chemoresistance and increased risk of relapse. Furthermore, there are many evidences that XIAP inhibition may sensitize tumor cells to chemotherapy agents, which make this protein a potential target in cancer.

Keywords

XIAP; Interact with caspases; Apoptosis; Bladder cancer; Brain cancer; Breast cancer; Cervical carcinoma; Colorectal cancer; Esophageal cancer; Gastric cancer; Head and neck squamous cell carcinoma; Kidney cancer; Leukemia; Liver cancer; Lung cancer; Lymphoma; Medulloblastoma; Melanoma; Multiple myeloma; Neuroblastoma; Oral cancer; Osteosarcoma; Ovarian cancer; Pancreatic Cancer; Prostate cancer; Thyroid cancer;

Identity

Other names

X-Linked Inhibitor of Apoptosis, E3 Ubiquitin Protein Ligase, Baculoviral IAP Repeat-Containing Protein 4, RING-Type E3 Ubiquitin Transferase XIAP, E3 Ubiquitin-Protein Ligase XIAP, Inhibitor of Apoptosis Protein 3, IAP-Like Protein 1, IAP-Like Protein, X-Linked IAP, hIAP-3, hIAP3, BIRC4, IAP-3, API3, ILP1, MIHA, XLP2

HGNC (Hugo): XIAP

Location: Xq25

DNA/RNA

Description

The entire XIAP gene is approximately 54.2 Kb (start: 123859724 bp; end: 123913979 bp; orientation: plus strand).
There are two transcript variants deposited in the NCBI database (https://www.ncbi.nlm.nih.gov/gene).

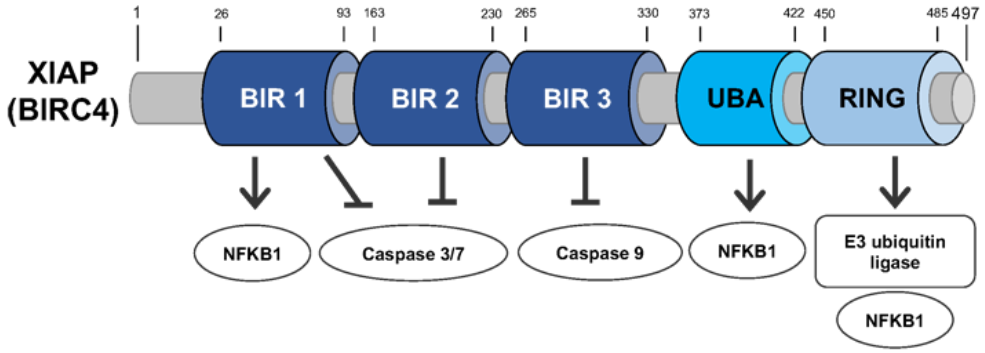

Figure 1. XIAP protein structure. XIAP (also known as BIRC4 or IAP3) presents two transcripts variants deposited in NCBI database. The protein structure presents 497 amino acids (aa) and is composed of three BIR domain being one of them that responsible for its anti-apoptotic activity, one RING zinc finger domain and an UBA domain. The XIAP structure containing their domains and the specific interactions of each domain, signaling the importance of XIAP in apoptotic pathways through interaction with caspases. The aa positions are indicated.

The transcript variant 1 is the longest transcript (cDNA: 8460 bp), while transcript variant 2 differs in the 5' UTR, compared to transcript variant 1 (cDNA: 8427 bp); however, both transcripts encode the same protein (497 aa). There are nine additional transcript variants reported in Ensembl (http://www.ensembl.org/): a transcript variant containing 8415 bp, which generates a protein of 497 aa; a transcript variant containing 528 bp, which generates a protein of 156 aa; a transcript variant containing 390 bp, which generates a protein of 16 aa; and six long non-coding RNA-related transcripts that do not generate proteins (764, 628, 598, 533, 495 and 157 bp).

Protein

Description

X-linked inhibitor of apoptosis (XIAP), also referred to as BIRC4, belongs to a family of proteins known as Inhibitors of Apoptosis Proteins (IAPs). This protein family is recognized, mainly, for inhibiting caspase activity, either directly or indirectly, thus preventing apoptotic cell death. Such propriety is generally associated to their distinctive BIR (baculovirus IAP repeat) domain, a conserved sequence of nearly 80 amino acids with a centered Zn+2, which may occur in numbers of one or three among members of this family. In fact, eight human IAPs have been described so far: BIRC1 (NAIP), BIRC2 (cIAP1), BIRC3 (cIAP2), BIRC4 (XIAP), BIRC5 (Survivin), BIRC6 (Bruce), BIRC7 (Livin) and BIRC8 (ILP-2) (Silke and Vucic, 2014).

XIAP presents three BIR domains located at the N-terminus region as demonstrated in Figure 1. Despite similarities shared among BIR domains, their functions may vary according to the IAP member. BIR1 interacts with proteins that modulate NFKB1 (NFκB) signaling (Lu et al., 2007). BIR2 and the linker region between BIR1 and BIR2 domain are necessary for inhibition of effector CASP3 and CASP7 (caspases-3 and -7) (Suzuki et al., 2001). BIR3 domain is responsible for inhibiting CASP9 (caspase-9), thus, preventing the intrinsic apoptosis pathway (Lukacs et al., 2013). By contrast, diablo IAP-binding mitochondrial protein binds to both BIR2 and BIR3 domains, thus inhibiting their function, increasing the activation of CASP3, CASP7 and CASP9 (caspases-3, -7 and -9), and promoting apoptosis (Suzuki et al., 2001, Obexer and Ausserlechner, 2014).

At its C-terminus region, XIAP carries a RING zinc finger domain. Although a BIR domain occurs among all IAPs, the RING domain, in turn, is found only in XIAP, BIRC2 and BIRC3. For XIAP, the RING domain involves an E3 ligase effect, indicating an important activity on protein ubiquitin process (Nakatani et al., 2013). Additionally, the RING domain was shown to be involved in NFKB1 signaling and MYC proto-oncogene stability, contributing to cancer progression (Jiang et al., 2019), and also on the migratory and invasive potential of cancer cells (Liu et al., 2012).

Expression

Vischioni and colleagues (2006) assessed XIAP expression in a variety of normal adult human tissues in an extensive study using immunohistochemistry, where it displayed an heterogenous pattern. Higher intensity immunoreactivity was mainly observed in the small intestine (specifically in Paneth cells and absorptive epithelium) and in epidermal keratinocytes within all the layers of the skin (except in stratum corneum). XIAP also displayed considerable immunoreactivity in specific areas of the stomach, large intestine, thymus, testicles, ovary and mammary gland. It has been found in a gradient within tissues such as squamous epithelia and in more differentiated cells in other tissues like esophageal epithelium (Vischioni et al., 2006).

Indeed, the expression of XIAP is not limited to cell types that are constantly undergoing apoptosis or tissues with faster cell turnover.

Given that the main function of XIAP is to impair both intrinsic and extrinsic apoptosis pathways, this finding is of particular interest in oncology research, as mechanisms to avoid cell death are one of the main factors that contribute to the formation of solid tumor masses. Not coincidentally, upregulating XIAP expression is one of the means by which tumor cells may accomplish such resistance. Therefore, XIAP expression levels may directly determine the sensitivity of tumor cells to apoptosis (Eckelman et al., 2006; Yang et al., 2018).

XIAP was found to be overexpressed in a variety of cancer types and is frequently associated with chemoresistance and increased risk of recurrence, being, generally, a predictive marker of poor prognosis of the disease (Srinivasula & Ashwell., 2008; Obexer Ausserlechner, 2014). In this matter, Gao and colleagues (2019) conducted a systematic review and metanalysis to determine the prognostic value of XIAP in patients with different tumor types. The analysis included 40 articles and more than 6,500 patients and concluded that the majority of the studies correlated high XIAP expression levels to an unfavorable prognostic factor for clinical outcomes in cancer patients (Gao et al., 2019). However, some discrepancies have been noted, as higher XIAP levels was also correlated to longer overall survival in non-small cell lung cancer patients (Ferreira et al., 2001b). Additionally, XIAP expression did not show any prognostic significance in cervical carcinoma (Liu et al., 2001) nor was that able to predict the response to chemotherapy in patients with advanced NSCLC (Ferreira et al., 2001a) .

An extensive study was conducted by Hussain and colleagues (2017) to assess the expression of XIAP in over 1000 Middle Eastern breast cancer cases by immunohistochemistry, and found this IAP to be overexpressed in 29.5% of the cases with an association to tumor size, extra nodal extension, triple negative breast cancer and poorly differentiated breast cancer subtype (Hussain et al., 2017). Expression and clinical significance of XIAP in a wide variety of cancer was further assessed and demonstrated in ovarian, lung, colorectal, thyroid, prostate, cervical, melanoma, salivary gland, pancreatic, cervical cancers, kidney, liver, neuroblastoma, oral, among others. Some of these will be further discussed herein.

XIAP expression was shown to be regulated at multiple levels, including transcriptional, post-transcriptional and translationally regulation. Transcriptional activation of XIAP may be controlled via NFkB pathway and ATP7A (ATPase copper transporting alpha) (Karin & Lin, 2002; Dai et al., 2005; Evans et al., 2018). XIAP protein but not its mRNA was found to be highly increased in childhood acute lymphoblastic leukemia compared to control bone marrow mononuclear cells, and no correlation between protein levels and mRNA was seen either, indicating post-transcriptional regulation (Hundsdoerfer et al., 2010). XIAP expression may also be regulated by an alternative translation initiation by a 162-nucleotide internal ribosome entry site (IRES) located in the 5' untranslated region of XIAP mRNA (Holcik et al., 1999; Holcik Korneluk, 2000).

In addition, different expression levels in normal cells of the same lineage in different organs indicates that IAP expression is also influenced by cell type and organ-dependent regulatory mechanisms (Vischioni et al., 2006). Moreover, Yan and colleagues (2004) demonstrated a tumor stage-dependent increase of both XIAP mRNA and protein expression in renal cell carcinoma (Yan et al., 2004).

At a protein level, XIAP activity may also be negatively regulated by the interaction with specific endogenous inhibitors, i.e. DIABLO (diablo IAP-binding mitochondrial protein), HTRA2 and XAF1 (XIAP-associated factor-1) (Srinivasula & Ashwell., 2008; Desplanques et al., 2009; Ye et al., 2019; Abbas & Larisch, 2020), or stabilized by other IAPs and proteins to enhance its activity (Dohi et al., 2004; Rajalingam et al., 2006). XIAP also forms a complex with SIVA1 and NR2C2 (TAK1), which inhibits XIAP/TAK1/ TAB1 -mediated NFκB activation, activates JNK activity and modulates apoptosis responses (Resch et al., 2009).

Localisation

Subcellular localization of XIAP is heterogenous, but it is predominantly cytoplasmic, being found in the nucleus also in the membrane. Immunofluorescence of transfected HeLa cells indicated that XIAP localized to the cytoplasm, being more prominent in the peri-nuclear region. The study also aimed to evaluate if co-expression of XIAP and XAF1 could alter its localization and concluded that the expression of XAF1 induced redistribution of XIAP from cytoplasm to nucleus (Liston et al., 2001).

Germ and Sertoli cells displayed XIAP in both cytoplasm and nucleoli (Vischioni et al., 2006). Fluorescence staining of hNOKs (human normal oral keratinocytes) revealed XIAP to be localized mainly in the cytoplasm and perinuclear areas, whereas in Tca8113 cell line (squamous cell carcinoma of the human tongue) high levels of this IAP were found both in the cytoplasm and the nucleus (Gao et al., 2006). In gastric cancer tissue samples, XIAP expression was detected exclusively in the cytoplasm (Dizdar et al., 2017).

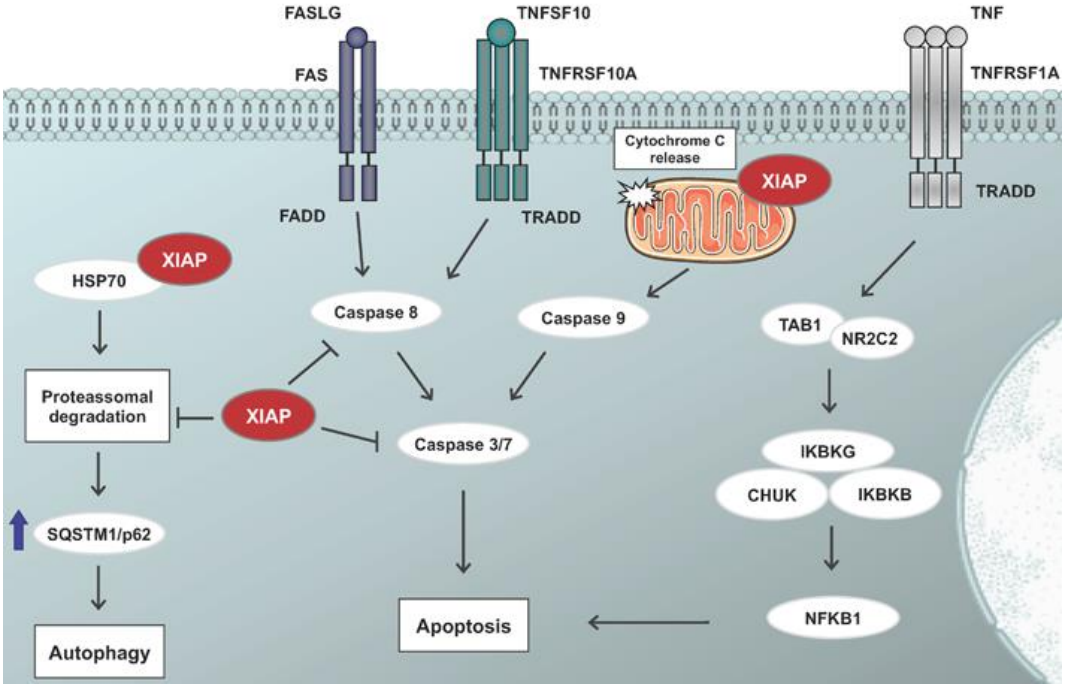

Figure 2. XIAP (BIRC4) is a multi functional protein. XIAP is involved in multiple cellular signaling pathways and cellular processes, including cell death, inflammation, cell cycle, and cell migration. The multifunctionality of XIAP is possible due to the different domains presented. The main function attributed to XIAP is its antiapoptotic activity, acting on intrinsic and extrinsic apoptotic pathways. XIAP binds and inhibits CASP9 (caspase 9) and its effectors CASP3 and CASP7 (caspase 3 and caspase 7). XIAP also acts on caspase inhibition by ubiquitination. XIAP has also a role in the suppression of autophagy, once its depletion resulted in increased expression of SQSTM1 (p62), a feature induced, in fact, by prevention of the ubiquitin-proteasomal degradation of SQSTM1 mediated by E3 ligase activity of XIAP. XIAP has been linked to cytochrome C release, suggesting that XIAP may enhance mitochondrial membrane permeabilization. It was demonstrated that XIAP physically interacts with HSP70 and, interestingly, that the use of HSP70 inhibitors promotes down-regulation of XIAP. In addition, XIAP regulates TAB1/NR2C2/NFKB1 axis modulating apoptosis.

XIAP displayed different patterns of localization in pancreas: acinar exocrine cells showed stronger staining in a granular supranuclear position (alike in glands of the small intestine and in the bronchial epithelium); while ductal cells presented XIAP diffused in the cytoplasm (Vischioni et al., 2006). A granular pattern in the cytoplasm had already been described in NSCLC cells, mainly in adenocarcinoma sections (Ferreira et al., 2001a; Ferreira et al., 2001b).

XIAP membrane localization was described in endometrial glands, more prominently in brush border or basolateral type. The interaction of XIAP with bone morphogenetic protein (BMP) type I receptors via its RING-finger domain also suggests a possible localization in the plasma membrane (Yamaguchi et al., 1999; Vischioni et al., 2006).

Function

XIAP function has been widely described, presenting involvement in multiple cellular signaling pathways, including cell death, immunity, inflammation, cell cycle, and cell migration (Vucic, 2018). This multiplicity of activities is partially due to the distinct domains present in XIAP. Still, the main function of this protein is the inhibition of the apoptosis cascade due to its binding to the initiator CASP9 (caspase-9), and the effector CASP3 and CASP7 (caspases 3 and 7), via its BIR3 and BIR2 domains, respectively, as demonstrated in figure 2 (Obexer and Ausserlechner, 2014)

Another important mechanism for caspase inhibition by XIAP involves the E3 ligase activity of the RING domain, which is correlated with ubiquitination of XIAP-bound caspases. Thus, it can be concluded that XIAP interferes with extrinsic as well as intrinsic death pathways (Pistritto et al., 2016). Such ubiquitination activity may be associated with XIAP itself, XIAP-interacting proteins involved in apoptosis, and other different targets involved in apoptosis (Galban and Duckett, 2010). XIAP has also been correlated to suppression of autophagy, once depletion of this IAP resulted in increased expression of SQSTM1 (p62), a feature induced, in fact, by prevention of the ubiquitin-proteasomal degradation of SQSTM1 mediated by E3 ligase activity of XIAP (Huang et al., 2019).

Another study evidenced that XIAP also localizes to the mitochondria, deregulating its functions, especially concerning cytochrome c release, suggesting that XIAP may enhance mitochondrial membrane permeabilization and control cytochrome c release (Chaudhary et al., 2016). Furthermore, the tumor suppressor protein SEPTIN4, expressed in the

outer mitochondrial membrane, promotes cell death through the antagonism of XIAP, leading XIAP to execute ubiquitination and degradation of BCL2 and, consequently, apoptosis (Edison et al., 2017), reinforcing the role the mitochondria plays in XIAP homeostasis.
Recently, it was demonstrated that XIAP physically interacts with HSP70 and, interestingly, that the use of HSP70 inhibitors promotes down-regulation of XIAP in both cancer cell lines and xenograft tumors (Cesa et al., 2017) .
In normal development, XIAP levels and function were studied using XIAP-deficient mice. Histopathological analysis revealed no differences compared to wild-type mice and, moreover, no defects in induction of caspase-dependent or -independent apoptosis were observed. However, other IAPs proteins were found to be upregulated, including BIRC2 and BIRC3, which suggests the existence of a compensatory mechanism (Harlin et al., 2001). Still, in cancer, high XIAP levels have been correlated with a poor prognosis (Cossu et al., 2019).

Homology

XIAP has high homology among different species (Table 1).

% Identity for: *Homo sapiens* BIRC7	Symbol	Protein	DNA
vs. *P. troglodytes*	XIAP	98.4	98.9
vs. *C. lupus*	XIAP	87.4	91.1
vs. *B. taurus*	XIAP	87.7	91.8
vs. *M. musculus*	Xiap	89.5	90.1
vs. *R. norvegicus*	Xiap	89.9	89.8
vs. *G. gallus*	XIAP	59.2	66.7
vs. *X. tropicalis*	xiap	53.0	61.7
vs. *D. rerio*	xiap	51.1	55.6
vs. *A. gambiae*	AgaP_AGAP012677	43.0	52.1

Table 1. Comparative identity of human XIAP with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

Mutations

Somatic

Recurrent mutations in the XIAP gene are rare. Among the 47,186 samples reported in COSMIC (Catalogue of Somatic Mutations in Cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic), 182 mutations were reported in XIAP (138 missense substitutions, 23 synonymous substitutions, 14 nonsense substitutions, 3 frameshift deletions and 2 frameshift insertions). In cBioPortal (http://www.cbioportal.org), among the 42,119 (159 studies) cancer samples accessed, only 0.5% presented XIAP mutations (corresponding to 195 mutations, of which 171 are missense substitutions, 22 truncated genes and 2 other mutation). When mutations, amplifications, deep deletions and multiple alterations were considered, the total of cancer samples bearing any type of genetic alteration in XIAP was 351 (0.8%).

Implicated in

Bladder cancer

XIAP, BIRC7, and BIRC5 were found to be simultaneously expressed in bladder cancer cells, with synergistic effects on cell growth and apoptosis. Knockdown assays targeting these three genes synergistically inhibited the proliferation and in vitro transformation ability, while also promoting apoptosis (Yang et al., 2010).
XIAP levels can be considered a biomarker of malignancy for bladder carcinoma, once it was found up-regulated in urine samples from bladder carcinoma patients compared to samples of patients with non-malignant bladder diseases (Srivastava et al., 2015). In urinary cancer, XIAP expression was shown to play a key role in the maintenance of tumor phenotype mediating multiple pathways: XIAP overexpression promoted bladder cancer invasion in vitro and lung metastasis in vivo through activation of the MAPK1 / NCL/ ARHGDIB axis (Yu et al., 2018). Also, its BIR domain regulated the EGFR translation by suppressing MIR200A expression and promoting cancer development and progression (Huang et al., 2017). The RING domain of XIAP also contributed to malignant transformation in bladder cancer, once it inhibited the expression of TP63, a known tumor suppressor, critical for the transformation of normal urothelial cells (Jin et al., 2016).
In T24 and 5637 cell lines, XIAP overexpression was reverted by embelin treatment that promoted a dose-dependent cell death mediated by the PI3K/AKT pathway (Fu et al., 2016). The use of DIABLO IAP-binding mitochondrial protein mimetics (UMUC-6, UMUC-12, and UMUC-18) in combination with typical chemotherapy drugs like cisplatin and gemcitabine promoted increased apoptosis, decreased microvessel density and decreased cellular proliferation that was shown to be related to the inhibition of IAPs, including XIAP (Lee et al., 2013).

Brain cancer

New potential therapeutic targets in glioblastomas were investigated by analyzing the expression and function of eight proteins that are known to play a role in cell survival and therapy resistance. The analysis of 50 samples from glioblastoma patients by immunohistochemistry revealed high expression of XIAP and ABCG2 (also known as BCRP, a member of the ABC transporters that use ATP to efflux endogenous small molecules and exogenous cytotoxic drugs) at the protein level were related to

poor survival (Emery et al., 2017). Another study evaluated the expression of anti and pro-apoptotic genes in 30 samples of glioblastoma patients by real-time PCR, which found higher levels of XIAP and BCL2 in glioblastoma samples compared to 10 samples from white matter control (Tirapelli et al., 2017).

Additionally, higher XIAP mRNA levels were found on CD133+ compared to CD133- adult glioblastoma primary cultured cells (LIU et al., 2006). Higher levels of XIAP were also seen in DAOY and D283MED cells compared to normal human astrocytes and immortalized fibroblasts. Moreover, expression of XIAP inversely correlated with that of CDKN1A (p21), suggesting IAPs may be involved in cell cycle control by CDKN1A suppression (CHEN et al., 2018).

Treatment with IAP inhibitors LCL161 or LBW242 alone or in combination with conventional chemotherapeutic agents, i.e. vincristine or cisplatin, as well as RNAi-mediated knockdown of XIAP, arrested the cell cycle at the G2/M phase through downregulation of CCNB1 - CDK1 and CCNA2 - CDK1/ CDK2 complexes in DAOY and D283MED cells (Chen et al., 2018). These IAP inhibitors combined with chemotherapy also enhanced the antiproliferative effect on MB cell line through autophagy induction and CASP3/CASP7-activated apoptosis (Chen et al., 2016).

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In U87MG glioblastoma cells, treatment with isolinderalactone, a sesquiterpene found in the roots of L. aggregata, resulted in a significant dose-dependent reduction of XIAP, BIRC5 and BCL2 levels, and apoptosis induction (Hwang et al., 2019).

Crude extracts of medicinal herbs (crude alkaloid extract of R. stricta and crude flavonoid extract of Z. officinale) decreased mRNA expression levels of XIAP, BIRC5 and CCND1, while expression of CDNK1A and PMAIP1 were upregulated in U251MG cell line (Elkady et al., 2014).

XIAP and MYC expression were significantly decreased in 51A and SU-2 cell lines after treatment with HDAC6 inhibitor, resulting in decreased CHEK1 activity through proteasomal degradation, leading to radio-sensitivity and reduced DNA damage repair capacity of glioma stem cells, a group of 'stem-like' cells hardly to be completely removed, thus conferring resistance to radio and chemotherapy in glioblastoma (Yang et al, 2017).

Breast cancer

IAPs were shown to be overexpressed in various numbers of cancers, including breast cancer and were associated with a poor prognosis and drug resistance (Moraes et al., 2015, Huang et al., 2018), making them an interesting target for therapy. In immunohistochemical experiments, it was shown that XIAP positively stained the majority of breast cancer cells with moderate or strong intensity (Zohny; Zamzami; El-Shinawi, 2018).

In another study, it was found that in one third of breast cancer patients presented XIAP overexpression, which was associated with a reduced overall survival (Hussain et al., 2017).

In a study with inflammatory breast cancer (IBC) was noticed that XIAP was also overexpressed in IBC patient tumors and high-grade breast cancers, corroborating XIAP overexpression in breast cancer (Evans et al., 2018).

Additionally, high XIAP expression was associated with reduced CASP3 activation and apoptosis rates in breast cancer tumors compared to benign breast lesions.

In immunoreactivity studies using breast cancer samples, high XIAP expression was found, but it did not correlate with age, tumor size, grade, status of lymph node, expression of ESR1 (estrogen receptor) and PGR (progesterone receptor). In addition, XIAP expression was found in 80% of patients with triple-negative invasive ductal breast cancer and it was related with primary tumor size and reduced disease-free survival and overall survival (Zohny; Zamzami; El-Shinawi, 2018).

Cervical carcinoma

Immunohistochemistry analysis of 15 cases of normal cervical tissues, 69 cases of cervical intraepithelial neoplasia (CIN) and 76 cases of cervical carcinoma revealed increased expression of XIAP in tumor than normal tissues, inversely associated with diablo (Smac) expression. In the same study, XIAP expression was associated with pelvic lymph node metastasis (Jin et al., 2017). A semi quantitative RT-PCR analysis of 6 normal and 41 cancer tissues, including 8 stage I cases, 16 stage II and 17 stage III revealed no differences in the expression of XIAP between normal and tumor samples. However, an unexpected positive association between low levels of XIAP and disease relapse was observed, and an inverse relation between XIAP expression and tumor aggressiveness (Espinosa et al., 2006).

The crude extract of the Chinese herb Antrodia camphorata induced apoptosis in HeLa and C-33A cells, showing a decrease in the expression of XIAP among other anti-apoptotic proteins (Yang et al.,

2013). Xanthohumol, a prenylated chalcone isolated from Humulus lupus, also downregulated expression of anti-apoptotic proteins such as XIAP in Ca Ski cervical cancer cell line, inhibiting proliferation (Yong et al., 2015).

Colorectal cancer

XIAP mRNA expression was shown to be upregulated in a study comparing 100 cancer to 100 normal tissues from patients with sporadic colorectal cancer by real time PCR, of which half were KRAS wild-type and the other half KRAS mutant (Devetzi et al., 2016). XIAP was also shown to be upregulated while pro-apoptotic BAX and BID were downregulated in HT-29 cells resistant to 5-FU compared to wild type (Manoochehri et al., 2014). In contrast, the expression of XIAP and other IAPs, except BIRC3, did not show significant differences in the normal mucosa of patients with advanced colorectal adenoma (Choi et al., 2017).

The diablo IAP-binding mitochondrial protein mimetic BV6, reduced cellular levels of XIAP, re-sensitizing BAX-deficient HCT-116, wildtype HCT-116, HCT-8 and DLD1 cells grown under hypoxic conditions to TNFSF10 and/or FASLG (CD95L) - induced cell death (Knoll et al., 2016). In addition, XIAP-deficient HCT-116 cells showed significant less TRAIL resistance under hypoxia compared to HCT-116 wild type cells (Knoll et a., 2016). BV6 also substantially increased 3D radiation response of HCT-15, HT-29 and SW480 cells upon BIRC2 and XIAP degradation, resulting in enhanced irradiation-induced apoptosis and DNA double-strand break repair hampering (Hehlgans et al., 2015). Agreeing with this, combinatorial treatments with TNFSF10 and Smac mimetics or XIAP-targeting drugs were reported to overcome hypoxia-induced TNFSF10 resistance, demonstrating that a reasonable alternative was to target XIAP as well as TNFSF10 in order to obtain stronger responses (Knoll et al., 2016).

Upregulation of XIAP might also be responsible for the acquired resistance to oxaliplatin, as established oxaliplatin-resistant SW480 and HT29 cells were shown to express significantly higher levels of XIAP and lower levels of MIR122 compared to wild types. A recovery of miR-122 expression was able to sensitize these colorectal cancer cells to oxaliplatin-mediated apoptosis through inhibition of XIAP expression. Thus, XIAP may offer a good strategy for reducing oxaliplatin resistance in colorectal cancer (Hua et al., 2018).

Transcriptomic analysis revealed that propionibacterial supernatant or its metabolites (propionate and acetate) increased pro-apoptotic gene expression (TNFSF10) and reduced anti-apoptotic gene expression of CFLAR and XIAP when administered in combination with TNFSF10 in HT-29 cells (Cousin et al., 2016).

In HT29 cells, mithramycin A selectively downregulated XIAP through inhibition of SP1 binding to its promoter.

Suppression of XIAP transcription, by siRNA, enhanced TNFSF10-induced apoptosis even though its overexpression significantly attenuated apoptosis induced by MithA plus TNFSF10, indicating a critical role for XIAP in the recovery of TRAIL sensitivity in various cancer cells (Lee et al., 2006).

Impaired CASP3 maturation by XIAP was also identified as one of the underlying mechanisms relating XIAP to TNFSF10 resistance in HCT-116 PIK3CA -mutant cells, as TNFSF10 sensitivity was efficiently restored after XIAP or proteasome inhibition, indicating that targeting XIAP or the proteasome in cells with PIK3CA mutations, which are found in 10-20% of colorectal tumors, may represent a good therapeutic strategy concerning TNFSF10 (Ehrenschwender et al., 2014).

COLO 205 and HCT-116 cells transfected with shRNA targeting AKAP4 (A-kinase anchor protein 4) resulted in XIAP downregulation among other anti-apoptotic molecules, while pro-apoptotic molecules were upregulated (Jagadish et al., 2015).

TGFB1 / PRKACB (PKA) / PP2A signaling deactivated AKT phosphorylation leading to downregulation of XIAP and BIRC5 in FET cell line (Chowdhury et al., 2011 A; Chowdhury et al., 2011 B).

Bufalin, a steroid-related molecule, in association with 5-fluorouracil reduced the expression of XIAP and other IAPs, while elevated the expression of pro-apoptotic proteins (Dai et al., 2018).

Moreover, MK-2206, an allosteric kinase inhibitor of AKT, dephosphorylated EZR (ezrin) at the T567 site and led to disruption of AKT-EZR-XIAP cell survival signaling (Agarwal et al., 2014). Phosphorylation of EZR at the T567 site was regulated by the IGF1R signaling pathway, and such activation enhanced cell survival in colorectal cancer cells by modulating XIAP and BIRC5 in both orthotopically implanted GEO tumors, as well as, human patient specimens (Leiphrakpam et al., 2014).

SATB2 (special AT-rich binding protein-2) overexpression resulted in upregulation of XIAP and CCND1 in CRL-1831 cells (Yu et al., 2017).

Silencing PIK3CA (PI3K p110α), by siRNA, also resulted in alterations in the expression of XIAP in KRAS/PIK3CA-mutant HCT-116 (Fernandes et al., 2016).

Placet et al. (2018) suggested that P2RY6 receptor could be targeted to block XIAP activity in colorectal cancer. P2RY6 stimulation with its selective agonist MRS2693 induced XIAP phosphorylation on Ser87 residue, concomitant to phosphorylation of AKT Thr3008 residue, and it was correlated to XIAP increase and maintenance over time. These findings suggested that P2Y6R

antagonists could be used to block XIAP activity and enhance the therapeutic effect of drugs such as 5-fluorouracil (Placet et al., 2018).

Esophageal cancer

Immunohistochemistry analysis of 120 esophageal squamous cell carcinoma (ESCC) and 90 esophageal adenocarcinoma (EAC) tissues with their corresponding normal mucosa samples revealed high expression levels of XIAP in tumor tissues. The same study identified XIAP as an independent negative prognostic marker in ESCC (Dizdar et al., 2018). Another study using immunohistochemistry of 78 ESCC patients treated with radiotherapy after surgery revealed increased XIAP expression and it was correlated with tumor differentiation and TNM stage (Zhou et al., 2013). Schiffmann and colleagues also reported XIAP expression might serve as a tool to improve outcome prediction and identify high-risk patients, whom may be a candidate for a more aggressive therapy strategy (Schiffmann et al., 2019). Additionally, 170 ESCC patients and 191 healthy people were genotyped and related polymorphisms rs8371 and rs9856 with susceptibility to ESCC, and rs8371 polymorphism might serve as an indicator improved clinical efficacy and prognosis (Peng et al., 2017) .

Treatment of five ESCC cell lines with TNF combined to cycloheximide (CHX) induced significant apoptosis and decreased expression of XIAP and BIRC2. This effect was not seen when cells were treated with either TNF or CHX alone, but XIAP or BIRC2 siRNA transfected cells underwent apoptosis when TNF was administered alone, a result that was further increased by double knockdown, suggesting XIAP along with BIRC2 might play an essential role in apoptosis-resistance of ESCC cells (Hikami et al., 2017).

Esophageal cancer cells treated with siRNA targeting XIAP in combination to radiotherapy presented decreased cell survival rate and colony forming efficiency. Besides, nude mice treated with siRNA had a decrease in tumor weight and volume compared to control group, indicating that XIAP gene silencing could be an allied in radiotherapy strategies for esophageal cancer (Wen et al., 2017).

Treatment with siRNA targeting XAIP also enhanced chemosensitivity of ESCC cells, as seen in a study that combined this strategy with paclitaxel, cisplatin, 5-fluorouracil and etoposide (Zhang et al., 2007).

Gastric cancer

An analysis for expression of IAPs in over 1,100 surgically resected gastric cancer (GC) tissue specimens revealed XIAP was present in 20% of the cases, whereas XIAP inhibitors, such as XAF1 and diablo IAP-binding mitochondrial protein, were seen in 76.6% and 13.9% of cases respectively. XIAP expression was strongly related to advanced stage. In the same study, high expression of XIAP was also related to decreased patient survival rates, indicating this as an independent prognostic factor for poor survival outcomes (Kim et al., 2011). Another study considering 144 patients also found that XIAP expression levels were significantly related to tumor size, serosal invasion and lymph node metastasis. The authors further demonstrated that XIAP expression was significantly elevated in HGC-27 and MGC803 gastric cancer cell lines compared to GES-1 normal gastric epithelial cells (Li et al., 2018). In addition, among other eight proteins, XIAP was seen to be upregulated in AFP (alpha-fetoprotein) producing gastric adenocarcinoma, and its overexpression was correlated to poor relapse-free survival and overall survival, but not in the AFP non-producing patients (He et al., 2016).

XIAP and BIRC5 levels were evaluated in 201 patients who underwent total or subtotal gastrectomy and extended (D2) lymphadenectomy. High levels of both IAPs were seen in gastric cancer tissue specimens when compared with normal mucosa and were correlated with an intestinal-type and well-differentiated gastric cancer, as also to low UICC stages. High levels of XIAP was detected in lymph node metastasis compared to corresponding primary tumors, which supports the hypothesis that it also plays an important role in metastatic tumors. XIAP overexpression was identified as an independent negative prognostic marker in diffuse and mixed type of gastric cancer. Tissue microarray revealed XIAP was present only in the cytoplasm, whereas BIRC5 was found in both the nucleus and the cytoplasm. The authors also identified a positive correlation between cytoplasmic BIRC5 and XIAP expression (Dizdar et al., 2017).

XIAP was downregulated after treatment with cycloheximide (CHX) and the effect was enhanced when combined CHX to TNF, resulting in induced apoptosis that may occur by accelerated proteasome-mediated degradation of XIAP and other IAP family members in addition to inhibition of NFKB1-dependent synthesis of anti-apoptotic molecules (Kitagawa et al., 2015).

Treatment with L-asparaginase in human gastric adenocarcinoma cells (AGS) significantly down-regulated anti-apoptotic genes i.e. XIAP, BID, MCL1, and death receptors TNF and TRADD, while pro-apoptosis genes i.e. BAK1, BAX, BIK, APAF1, CASP3, CASP7, and CASP9 were upregulated. Further analysis confirmed intrinsic apoptosis pathway activation (Sindhu et al., 2018). Treatment with H72, a synthetic brominated chalcone derivative, reduced protein levels of XIAP, BCL2L1, and BIRC5, while increased levels of BCL2L11 BIM, TNFRSF10A (DR4), and TNFRSF10B (DR5), with no changes in BAX levels in MGC803 cells (Zhang et al., 2016).

Furthermore, scutellarein, a flavone glycoside obtained by hydrolysis of scutellarin found in herbs from Scutellaria genus, induced apoptosis and inhibited cell proliferation via down regulation of MDM2, which activates the tumor suppressor protein TP53, leading to down regulation of XIAP, BIRC2 and BIRC3 in a dose-dependent manner in AGS and SNU-484 gastric cancer cells (Gowda Saralamma et al., 2017). CDK7 selective inhibition by BS-181, a pyrimidine-derived compound, induced apoptosis due to a significant decrease in XIAP and CCND1 expression in BGC823 cells (Wang et al., 2016).

A double knockdown of both XIAP and BIRC5 expression by siRNA resulted in a notable increase in apoptosis rates and suppression of cell proliferation compared to cells submitted to a single knockdown of either BIRC5 or XIAP (Li et al., 2018).

XIAP levels were inversely correlated to expression of MIR509-3p in tissue specimens collected from patients with gastric cancer, which was a clinically significant miRNA detected in higher abundancy in patients with favorable survival states, both in The Cancer Genome Atlas and in an independent cohort (Pan et al., 2016). Paired tissues revealed significant downregulation of miR-509-3p in tumor tissues, and such downregulation was strongly correlated to poor outcomes (Sun et al., 2017).

Head and neck squamous cell carcinoma

Immunohistochemistry assays revealed XIAP expression in 40 of out 59 sections from routinely processed specimens of head and neck squamous cell carcinoma (HNSCC), in which staining varied from weak or focal to strong or diffuse (Nagi et al., 2007).

XIAP expression was found in 17 out of 60 samples accessed, which was associated with cisplatin resistance and poor clinical outcome in advanced HNSCC patients. Chemotherapy with cisplatin induced XIAP expression. In HNSCC cells, cisplatin sensibility was significantly increased after inhibition of XIAP by siRNA. Along with alcohol consumption and lymph node metastasis, XIAP was found to be an independent prognostic marker of advanced HNSCC patients (Yang et al., 2012). Moreover, Yang and other colleagues (2018) reported that patients with HNSCC co-expressing high levels of XIAP and BIRC2 had shorter overall and disease-free survival compared to patients expressing low levels of both IAPs, indicating a synergistic effect of these proteins on prognosis (Yang et al., 2018).

Depletion of XIAP, by shRNA, significantly enhanced cell death after treatment with TNFSF10 combined to bortezomib in UPCI:SCC089 and UPCI:SCC090 cell lines (Bullenkamp et al., 2014).

Kidney cancer

XIAP expression was upregulated and associated with poor prognosis in kidney cancer patients (Mizutani et al., 2007; Bilimet al., 2008). It was also shown that the decrease in the expression of XIAP by antisense oligonucleotide enhanced sensibility of renal cell carcinoma cells to FAS/ TNFSF10-mediated cytotoxicity (MizutaniI et al., 2007). In renal cell carcinoma, XIAP expression increased from early (pT1) to advanced tumor stages (pT3), similarly to dedifferentiation stages and tumor aggressiveness (Yan et al., 2004; Ramp et al., 2004). Among the different histological renal cell carcinomas, it was observed that the clear cell type, that has a poor diagnosis, had a higher XIAP expression than the papillary (Yan et al., 2004). In addition, XIAP expression was found in 137 of 145 (95%) of the investigated clear cell renal cell carcinoma, a tumor of the kidney that accounts 70% of all renal cell carcinoma.

Leukemia

Leukemia cells appear to have anti-apoptotic proteins in order to survive under hostile conditions (Walsby et al., 2013), and studies have shown that these molecules may be useful as prognostic markers (Tamm, 2004). XIAP was frequently overexpressed in leukemia cells, serving as regulators in the cell survival (Hu et al., 2014).

In a panel made purposely for the study of the relation of IAPs and leukemia containing 60 human tumor cell lines showed, among acute myeloid leukemia (AML) blasts derived from newly diagnosed patients, that patients with low levels of XIAP had a longer survival rate and were inclined to a longer median remission duration. This finding implied that XIAP has a potential prognostic value in AML (Tamm et al., 2000). In adult acute myeloid leukemia (AML), XIAP expression was lower in AML cells with granulocytic differentiation when compared to myelomonocytic-differentiated cells, which suggests that XIAP plays a role in normal monocytic and malignant differentiation. Supporting this finding, downregulation of XIAP blocks monocytic differentiation induced by bryostatin 1 in leukemia cells (Tamm, 2004).

One of the most well-known XIAP inhibitor is embelin, a cell-permeable and small molecule that inhibits XIAP through DIABLO IAP-binding mitochondrial protein. Embelin was shown to promote downregulation of XIAP and release of CASP9, which normally initiates caspase cascades and leads to apoptosis. Furthermore, embelin induces apoptosis in leukemia cell line HL60 by XIAP downregulation (Hu et al., 2014). Additionally, it was demonstrated that low-toxicity embelin sensitization of HL60 cells to TNFSF10 - induced apoptosis was not intimately related to

XIAP inhibition, showing that low-toxicity embelin alone or jointly with TNFSF10 did not change the expression of XIAP (Hu et al., 2014). There are other molecules proposed as XIAP inhibitors, including CDKI-73, which also inhibited MCL1, BCL2, CCND1 and CCND2 (Walsby et al., 2013), and nilotinib, which was shown to inhibit the expression of XIAP in two MDM2-overexpressing cell lines, suggesting that nilotinib-mediated XIAP inhibition was dependent of MDM2, since this was not observed for MDM2-negative cell line (Zhang et al., 2014). In leukemia cells, the co-treatment with SAHA and S116836 repressed anti-apoptotic proteins, including XIAP (Bu et al., 2014).

Natural products were also studied regarding its effects on XIAP inhibition, for instance, AVO (an essential oil from Artemisia vulgaris L) decreased the expression of XIAP leading to inhibition of the activation of caspases 9 and 3 in HL60 leukemia cells (Saleh et al., 2014).

Liver cancer

In hepatocellular carcinoma patients, XIAP expression was associated with poor overall survival and, in cell lines, was shown to play an important role in modulating cell apoptosis and cell cycle progression through regulation of CDK4, CDK6 and CCND1 via NFKB1 and PTEN pathways (Che et al., 2012). Treatment of hepatocellular carcinoma cells with embelin resulted in increased apoptosis and decreased cell proliferation via an arrest at the G1 phase (Che et al., 2012). In contrast, it was observed that apoptosis resistance may be related to a significantly lower expression of XAF1, but not XIAP in poorly differentiated hepatocellular carcinoma tissues (Sakemi et al., 2007). Zhu and colleagues reported lower levels of XAF1 expression in SMMC-7721, HepG2 and BEL-7404 cell lines, as well as in liver cancer tissues compared to their paired non-cancer hepatic tissues. Adenovirus-mediated XAF1 expression (Ad5/F35-XAF1) significantly inhibited cell proliferation and induced apoptosis, while significantly suppressed xenograft tumor growth of hepatocarcinoma cells (Zhu et al., 2014).

XIAP was also associated with therapeutic resistance to the histone deacetylase (HDAC) inhibitor JNJ-2648158, which induced the transcription of XIAP through AP1 expression activation, conferring resistance to apoptosis (Wang et al., 2018). Moreover, Winkler and colleagues (2014) reported XIAP to play an important role in the pro-survival function of the exportin cellular apoptosis susceptibility (CAS) in hepatocellular carcinoma models (Winkler et al., 2014).

Cisplatin treatment downregulated XIAP expression, while XIAP knockdown by siRNA enhanced the pro-apoptotic effects of cisplatin in LM3 cell line (Shang et al., 2018). A fraction of the natural extract derived from Artemisia capillaris obtained in ethyl acetate displayed growth and proliferation inhibition, induced apoptosis, increased levels of cleaved caspase-3 and decreased XIAP, BIRC5, and MCL1 expression in HepG2 and Huh7 cell lines (Yan et al., 2018).

Lung cancer

In a study of the protein signature for non-small cell lung cancer (NSCLC) prognosis, XIAP was differentially expressed between NSCLC and benign lung tumor, indicating that XIAP is a potential biomarker for malignancy in lung tumors. Along with other proteins, XIAP was also correlated to invasion and lymph node metastasis, as well as squamous differentiation (Liu et al., 2014). In agreement, Huang and coworkers (2015), reported high levels of XIAP in lung cancer tissues compared to adjacent tissues samples (Huang et al., 2015).

In contrast, Moravcikova et al. (2014) indicated that XIAP was not an effective suppressor of the apoptosome apparatus activity in NSCLC cells, suggesting that apoptosome-generated caspase-3 activity can overcome the potential caspase inhibitory effect of XIAP.

Baykara and colleagues (2013) also investigated the relation of XIAP with clinical parameters in NSCLC. XIAP levels were determined by ELISA in samples from 34 NSCLC patients and 44 healthy individuals, but no correlation between serum XIAP levels and response to chemotherapy, progression free-survival or overall survival were found (Baykara et al., 2013).

Kang and colleagues (2008) performed an evaluation of the association between XIAP polymorphisms and the risk for lung cancer. The authors identified 12 SNPs and selected 4 of them for large-scale genotyping based on their frequencies and haplotype tagging status, but no evidence of relation of XIAP polymorphisms with the risk of lung cancer was observed (Kang et al., 2008).

XIAP-mediated ERK activation upregulated NCL (nucleolin) expression, which was able to stabilize ARHGDIB mRNA and mediate lung metastatic (Yu et al., 2018). In lung cancer cells, XIAP inhibited mature SMAC-induced apoptosis by degrading it through ubiquitination (Qin et al., 2016).

Combined treatment of lambetianic acid (LA) and TRAIL displayed significantly decreased antiapoptotic proteins such as XIAP, while also disrupting its binding with CASP3 or NFKB1, enhancing TNFSF10-induced apoptosis (Ahn et al., 2018).

Lymphoma

Mantle cell lymphoma, a poor prognosis and metastatic-related non-Hodgkin B-cell malignancy, presented overexpression of IAPs, including XIAP. In mantle lymphoma cells, B-PAC-1, a procaspase activating compound, induced apoptosis by the

sequester of Zn bound to procaspase- 3, (Sarkar et al., 2015) or when analyzing the anti-tumor properties of puerarin (Gan Yin, 2014).
Similar to findings in mantle cell lymphoma, XIAP protein was upregulated in other lymphomas, such as Burkitt's lymphoma, a highly aggressive type of non-Hodgkin B-cell lymphoma (Aaqarni et al., 2018). In lymphoma cells, antitumor properties of indole-3-carbinol was related to XIAP downregulation (Perez-Chacon; Rios; Zapata, 2014). In B-cell lymphomas, XIAP was overexpressed and associated with chemoresistance and shorter survival outcomes. Double knockdown of XIAP and USP9X delayed lymphoma development, corroborating XIAP as a target in lymphoma (Engel et al., 2016).

Medulloblastoma

XIAP was shown to be upregulated in medulloblastoma cells, while XIAP inhibitors reduced cell proliferation and induced cell death. In fact, this effect was also seen in the subpopulation CD133+ stem-like medulloblastoma cells, for which XIAP expression displayed even higher levels. In agreement, XIAP expression in cytoplasm was found in 75% of the medulloblastoma tissues compared with no expression in normal brain tissues (Chen et al., 2016). Inhibition of XIAP, BIRC2 or BIRC3 combined with conventional chemotherapy resulted in cell cycle arrest at G2/M phase in medulloblastoma cells (Chen et al., 2018). These findings indicated that XIAP was a potential diagnostic marker and therapeutic target in medulloblastoma.

Melanoma

In melanoma, the machinery behind the high resistance may be related to overexpression of proteins of the IAP family, including XIAP (Hiscutt et al., 2010; Mohana-Kumaran et al., 2014). XIAP was associated with cell growth, tumorigenesis, metastasis as well as progression in melanoma cells (Li; Ke; Wang, 2012), and it was shown to be overexpressed in primary cutaneous and metastatic melanoma tissues (Hiscutt et al., 2010). In a study where XIAP expression was investigated in 55 samples of clinical patients and where samples consisted mainly of superficial spreading melanoma, XIAP expression was found to be higher in late stage primary cutaneous melanoma. There was also a significant difference on the percentage of cells positive for XIAP in sample obtained from patients that were stage II melanoma and benign nevi. When analyzing the range of thickness of primary tumors, the increase on XIAP expression was associated with a greater Breslow thickness (Tian; Lee, 2010). In another study, XIAP expression was also higher on thick cutaneous melanoma than when compared to thin ones (Emanuel et al., 2008).

Multiple myeloma

Multiple myeloma cells exhibited high levels of XIAP protein, which was associated with myeloma-related growth factors. In the same study, XIAP silencing by RNAi increased drug sensitivity in in vitro assays and reduced in vivo tumor formation. Multiple myeloma cells also expressed XAF1, which antagonizes the caspase inhibitor function of XIAP (Desplanques et al., 2009).

Neuroblastoma

In neuroblastoma patients, XIAP was found in 18 among the 19 cases analyzed, and the level of XIAP was higher within patients that had no bone marrow metastasis. XIAP expression was also higher in patients with favorable histology regardless of bone marrow status. XIAP expression had no significant difference on tumors with undifferentiated/poorly differentiated histology compared to differentiating subtypes (Osman et al., 2013). Post transcriptional and transcriptional mechanisms were related with high XIAP expression, which had been targeted by diablo IAP-binding mitochondrial protein mimetic LBW242 in neuroblastoma. Using microarray analysis, XIAP mRNA was associated with risk of relapse in a cohort of 101 neuroblastoma patients (Eschenburg et al., 2012). In paired neuroblastoma cell lines obtained from a primary tumor of a female patient pre- and post-chemotherapy (CHLA-15 and CHLA-20), XIAP was highly expressed in CHLA-20 cells, which had undergone an intensive treatment with cyclophosphamide, doxorubicin, cisplatin and teniposide (Frommann et al., 2018).

Oral cancer

Using tissue microarray, high XIAP expression was associated with a significant reduction in overall survival in a cohort of 193 squamous cell carcinomas (Frohwitter et al., 2017). HSC-3 cells treated with ursodeoxycholic acid (UDCA) and Ca9-22 cells treated with furano-1,2-naphthoquino (FNQ) and PP2 (a Src-specific inhibitor) presented XIAP downregulation (Lin et al., 2014; Pang et al., 2015).

Osteosarcoma

Qu and colleagues reported that XIAP mRNA and protein levels were increased in osteosarcoma compared to adjacent non-tumoral tissues in a cohort of 60 tissues from osteosarcoma patients using quantitative PCR and immunohistochemistry analysis. The authors also correlated higher expression of XIAP to advanced clinical stage, larger tumor size and metastasis compared to patients expressing lower levels of XIAP. Using MG63 cellular model, a shRNA targeting XIAP efficiently decreased cell proliferation and colony formation, induced apoptosis and cell cycle arrest at G0/G1 phase, displayed enhanced chemosensitivity in combination with doxorubicin or cisplatin, and

inhibited tumor growth in nude mice (Qu et al., 2015).
Treatment with an aqueous plus a triterpene extract of Viscum album L. led to strong inhibition of proliferation and apoptosis, and enhanced sensitivity to doxorubicin, etoposide and ifosfamide in 143B and Saos-2 cell lines, which were associated with downregulation of XIAP, BIRC5 and CLSPN (Kleinsimon et al., 2017). In addition, the carotenoids fucoxanthin and its metabolite fucoxanthinol induced apoptosis and cell cycle arrest at G1 phase in osteosarcoma human and mouse cell lines by reducing expression of XIAP, BIRC5, BCL2, BCL2L1, CDK4, CDK6, and CCNE1 (Rokkaku et al., 2013).

Ovarian cancer

In ovarian cancer models, proteomic analysis demonstrated that XIAP had a positive coefficient correlation with IC50 values, indicating a role for XIAP in drug resistance (Zervantonakis et al., 2017). In agreement, high XIAP levels were inversely correlated with carboplatin response and progression-free survival in patients with ovarian cancer (Zhang et al., 2018). It was also reported that ADPRH, a tumor suppressor gene, was downregulated in 60% of ovarian cancers and promoted upregulation of antiapoptotic proteins, including XIAP (Washington et al., 2015).
In ovarian carcinoma cell lines, treatment with phenoxodiol promoted downregulation of XIAP, inhibited autophagy, as evidenced by decreased levels of ATG7, ATG12 and BECN1, and increased cisplatin sensitivity (Miyamoto et al., 2018). Treatment with 10-chlorocanthin-6-one, a cytotoxic agent against HO8910PM cell line, induces apoptosis through activation of PARP1 and caspase-3 cleavage, upregulation of BCL2, and downregulation of XIAP, BIM and BIRC5 (Li et al., 2018). MK-0752, a γ-secretase inhibitor, induced cell growth inhibition through downregulation of XIAP in a dose- and time-dependent manner (Chen et al., 2016).
Natural product butein, a polyphenol widely biosynthesized in plants, promoted downregulation of XIAP, BIRC5, BIRC2, and BIRC3 in ovarian cancer cell lines (Yang et al., 2015). Another natural product, an extract of Smilax china L. rhizome, reduced cell proliferation in a dose-dependent manner and induced apoptosis by activation of caspase-3, PARP1 and BAX and by inhibition of NFκB, BCL2, BCL2L1, BIRC2, XIAP and AKT in A2780 cells (Hu et al., 2015). Combined treatment with cisplatin and biothionol enhanced apoptosis through the downregulation of pro-survival factors (XIAP, BCL2 and BCL2L1) in ovarian cancer cell lines (Ayyagari et al., 2017). Similarly, 1-phenylpropadienyl phosphine oxide (PHPO) alone or combined with cisplatin inhibited the PI3K/AKT, MAPK and ATM / CHEK2 (CHK2) pathways, followed by suppression of the antiapoptotic factors BCL2L1, BCL2, and XIAP (Li et al., 2016).
Inhibition of NFKB1 and BIRC6-XIAP complex induced by 10H-3,6-diazaphenothiazine treatment reduced metastasis capacity of A2780 cancer cell line (Zhang et al., 2017). In SKOV3/DDP cells, inhibition of NFKB1 and reduced levels of XIAP was also observed after treatment with noscapine, a non-toxic benzylisoquinoline alkaloid extracted from opium (Shen et al., 2015).
The regulation of XIAP mediated by miRNAs has been addressed and multiple miRNAs can regulate XIAP via its 3'UTR. For instance, MIR137 sensitized ovarian cancer cells to cisplatin-induced apoptosis via XIAP downregulation in SKOV3 cells (Li et al., 2017). Similar results were observed for MIR155 that mediated cisplatin-induced apoptosis by targeting XIAP (Chen et al., 2016), and for MIR509-3p that can directly target XIAP via its 3'UTR in ovarian cancer cells leading to the inhibition of cell proliferation and increased sensitivity to cisplatin-induced apoptosis (Chen et al., 2016). In addition, it was demonstrated that MIR146A?5p regulated three important antiapoptotic genes, including XIAP, BCL2L2 and BIRC5 via their 3'UTRs. Decreased levels of MIR146A?5p led to increased IC50 values for cisplatin in OVCAR3 and SKOV3 cells (Li et al., 2017). The MIR149 (which also targets XIAP) was significantly downregulated in ovarian cancer tissues and cell lines, for which expression was correlated with patient prognosis and cisplatin chemoresistance (Sun et al., 2018). The downregulation of MIR215 increased cell proliferation, inhibited apoptosis and decreased sensitivity to chemotherapy drugs in ovarian cancer cells through the elevated expression of XIAP (Ge et al., 2016).
Extracellular matrix components have been addressed as one factor involved in chemoresistance in ovarian cells. The collagen COL11A1 was demonstrated to activate the signaling pathway SRC/PI3K/AKT/NFκB to induce the expression of three IAPs, including XIAP, which was correlated to the inhibition of cisplatin-induced apoptosis in ovarian cancer cells (Rada et al., 2018).

Pancreatic Cancer

XIAP was considered one of the most important factors in chemoresistance of pancreatic carcinoma, and its inhibition increased sensitivity to 5-fluorouracil (5-FU). In pancreatic carcinoma cell line SW1990, XIAP upregulation was observed in cells exposed to 5-FU for up to 30 days. Combined treatment of 5-FU and gemcitabine greatly increased apoptosis index when XIAP was inhibited (LI et al, 2006). High XIAP expression was also associated with poor outcomes in pancreatic carcinoma

patients, being an independent predictor and associated with tumor invasion status and histological grading (LI et al., 2013).
The treatment with 7-benzylidenenaltrexone maleate (BNTX) combined to TRAIL downregulated XIAP expression, promoting the release of cytochrome c from mitochondria with caspase activation (KIM et al., 2017). The authors suggested that the IAP-mediated resistance of pancreatic cancer cells could be overcome by PKCα/AKT pathway inhibition.
A small-molecule IAP antagonist, AT406, significantly inhibited cell survival and proliferation in Panc-1 and Mia-PaCa-2 cell lines, and in primary human pancreatic cancer cells, while displayed no cytotoxicity to pancreatic epithelial cells. Authors noted a degradation of IAP family members (such as XIAP and BIRC2), a release of cytochrome c and higher activity of CASP3 and CASP9 (JIANG et al., 2016).

Prostate cancer

The expression of XIAPs in normal human prostate (NP), benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia (PIN) and prostatic carcinoma (PC) was evaluated and showed a 20% expression among NPs, 27.27% in BPHs, 33.33% in high-grade PIN and varying from 17.39 to 39.21% in PC. The latter two did not present Gleason variation (Rodriguez-Barriguete et al., 2015).
Through immunohistochemical techniques, XIAP expression was seen on human prostate tissue samples, being observed in normal and malignant epithelium, basal cells, but not commonly on stromal fibromuscular cells. XIAP expression was typically diffused in the cytoplasm; however, a discrete supranuclear staining in coarse clusters was observed. On regions of benign prostatic hyperplasia (BPH), XIAP showed the lowest expression. XIAP expression in PC was shown to be significantly higher when compared to PIN, NP and BPH (Seligson et al., 2007). In a small cohort, it was found that higher levels of XIAP was associated with longer relapse-free survival (Krajewska et al., 2003); additionally, in another study, patients with positive immunostaining for XIAP had a better prognosis, which led to questions concerning the pro-tumor role of this IAP in prostate cancer (Rodrèguez-Berriguette et al., 2015).
The higher expression of XIAP also predicted the reduced risk of tumor recurrence in dichotomized and continuous variable in univariate analysis. When analyzing patients with primary low-grade cancer, none which had a high expression of XIAP displayed tumor recurrence (n=23). In contrast, patients with low levels of XIAP experienced tumor recurrence (n=89). The same study showed that patients with higher grade or non-confined tumors with an elevated XIAP expression have a better prognosis, when analyzing the group, when compared to those patients that express low levels of XIAP. An example of this finding is that 50% of patients whose tumors were not confined to the organ (n =92) had tumor recurrence, whereas the 12 patients with higher levels of XIAP did not experience recurrence. Patients with low grade tumors and low XIAP levels experienced recurrence (more than 25%), whereas none of the patients with higher levels of XIAP had recurrence of the tumors. In the PSA follow-up, 94% of patients that presented higher levels of XIAP were recurrence-free, against 58% of patients with lower XIAP levels (SELIGSON et al., 2007).
XIAP was found to constitutively express on DU145 cells, playing an important role on modulating chemosensitivity (Amantana et al., 2004), the presence of XIAP was also found on PC3 cells on immunohistochemistry assays showing that XIAP was localized mainly on the perinuclear region of this cells (Mceleney et al., 2002).

Thyroid cancer

XIAP elevated expression had been associated with a high degree of invasiveness, being related to lymph node metastasis in papillary thyroid cancer (Gu et al., 2010), and also was associated with old age, extrathyroidal extension, tumor size, nodal involvement, tall-cell variant, advanced stage disease, and significantly poor disease-free survival (Hussain et al., 2015).
XAF1 (XIAP-associated factor-1) antagonizes XIAP-mediated caspase inhibition. Loss of XAF1 expression correlates with tumor progression. It has been suggested that the G allele of rs34195599 of XAF1 may be a risk factor for the clinicopathological features of papillary thyroid carcinoma (Kim et al., 2013).
XIAP expression varied from 48.8% (Hussain et al., 2015) to 83% in papillary thyroid cancer (Xiao et al., 2007) and it was of 25% of insular carcinoma only moderate positive and non-staining in follicular, medullary, anaplastic carcinomas, oncocytic neoplasms (Xiao et al., 2007). In another study XIAP expression was positive in 75% of patients, whose expression was significantly associated with the presence of lateral cervical lymph node metastases. Additionally, XIAP expression was more frequent in BRAFV600E mutated PTCs than in BRAF wild type PTCs (Yim et al., 2014), however no correlation between these two markers were observed (Gu et al., 2009).
In papillary thyroid cancer, XIAP expression was associated with phosphorylated AKT, BCL2L1, and Ki67 proteins leading to increase cell proliferation and reduced apoptosis rate that was reverted with treatment with embelin (Hussain et al., 2015).
TPC-1 and BCPAP cell lines silenced for NFKB1 and treated with radiation (131I treatment) demonstrated a decrease in cell viability mediated by XIAP and BIRC2 reduction levels and increased is

CASP3 levels, demonstrating an induction of apoptosis cascade (Chen et al.,2018). The cell line TPC-1 treated with HSP90 inhibitor promoted cell apoptosis and tumor decreased size caused by inhibition of IAP members, such as XIAP, BIRC5, and BIRC2 (Kim et al., 2016).

In follicular thyroid carcinoma, XIAP expression was observed in comparison to non-tumoral thyroid tissue. Additionally, XIAP silencing reverted malignant phenotype, causing a decrease in cell proliferation and an increase in cell apoptosis rate (Werner et al., 2017).

In anaplastic thyroid carcinoma, similar results were observed in patients' tissues where XIAP expression was significantly elevated in the invasive area of anaplastic thyroid carcinoma samples, while XIAP expression was negative in either normal thyroid follicular epithelial cells or differentiated papillary thyroid carcinoma. Moreover, silencing XIAP in vitro decreased cancer cell proliferation, migration and invasion (Liu et al., 2017).

For anaplastic thyroid carcinoma, it was demonstrated that XIAP repression may be caused by overexpression of miR-618 (Cheng et al., 2014).

In medullary thyroid carcinoma elevated BIRC5 or XIAP expression was associated with metastatic condition. XIAP, as well as BIRC5 levels, were negatively associated with patient survival (Werner et al., 2016).

To be noted

Pharmacological advances targeting XIAP in cancer

Development of XIAP inhibitors has been explored in the last few years with significant advances. The use of mimetics has gained considerable attention, especially concerning their pharmacological and physiochemical properties. One strategy refers to employing modifications in amino acids, such as using non-natural amino acids, replacing some residues - e.g. P2 and P3 -, and modifying the C-terminal region. These approaches have been carefully reviewed in Jaquith (2014). Another strategy refers to the development of antagonists of XIAP based on the N-terminus of mature Smac, where a synthetic compound (GDC-0152) revealed interesting results. This compound binds to the XIAP BIR3 domain with K(i) values of 28 nM, activating apoptosis cell death and, consequently, decreasing viability and inhibiting tumor growth of breast cancer cell lines and xenografted tumors, respectively (Flygare at al., 2012).

The use of antisense oligonucleotide to target XIAP has also been proposed. One example is the AEG35156, a second-generation 19-mer antisense oligonucleotide, which, in combination with docetaxel, has been undergoing clinical trials for treatment of locally advanced, metastatic, or recurrent solid tumors, such as pancreatic cancer, advanced breast cancer, advanced NSCLC and acute myeloid leukemia. Side effects were limiting factors in the majority of these studies (Tamm, 2006). However, a posterior study demonstrated that it is generally well tolerated in combination with standard chemotherapy in acute myeloid leukemia (Katragadda et al., 2013). In fact, a phase II clinical trial conducted with patients with advanced hepatocellular carcinoma revealed that treatment with AEG35156 in combination with sorafenib yielded positive results, mainly regarding objective responses rates (Lee et al., 2016).

Using structure-based drug design, a nonpeptidomimetic small-molecule functioning as a duas antagonist of XIAP and BIRC2, designated AT-IAP, demonstrated IC50 values in the nM range for breast cancer cell lines. Moreover, this compound binds to the BIR 3 domain causing disruption of XIAP and CASP9 and increased levels of cleaved PARP1, indicating activation of apoptosis pathway. Additionally, tumor size reduction was demonstrated in xenograft models (Tamanini et al., 2017).

Others XIAP inhibitors have been previously reported, however such inhibition was not always in a direct-manner. This is the case for embelin, a natural product that promotes down-regulation of XIAP and was reported to have promising effects in leukemia (Hu et al., 2014), pancreatic cancer (Mori et al., 2007) and gastric cancer (Wang et al., 2013).

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