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REVIEW

Inhibitors of apoptosis: clinical implications in cancer

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Abstract Inhibitor of apoptosis (IAP) family comprises a group of endogenous proteins that function as main regulators of caspase activity and cell death. They are considered the main culprits in evasion of apoptosis, which is a fundamental hallmark of carcinogenesis. Overexpression of IAP proteins has been documented in various solid and hematological malignancies, rendering them resistant to standard chemotherapeutics and radiation therapy and conferring poor prognosis. This observation has urged their exploitation as therapeutic targets in cancer with promising pre-clinical outcomes. This review describes the structural and functional features of IAP proteins to elucidate the mechanism of their anti-apoptotic activity. We also provide an update on patterns of IAP expression in different tumors, their impact on treatment response and prognosis, as well as the emerging investigational drugs targeting them. This aims at shedding the light on the advances in IAP targeting achieved to date, and encourage further development of clinically applicable therapeutic approaches.

Keywords Apoptosis · Inhibitor of apoptosis · Caspases · Smac mimetics · Cancer target therapy

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Introduction

Apoptosis, or programmed cell death, is an essential cell process in homeostasis of multicellular organisms. Strict regulation of apoptosis has been involved in many human diseases, including cancer [1]. The inhibitor of apoptosis (IAP) proteins are a class of apoptosis regulators, that perform a critical role in the control of survival and cell death by regulating crucial factors in signaling events such as caspase activation and NF-κB signaling [1]. Targeting critical apoptosis regulators, like IAPs, is an attractive therapeutic way undertaken for the development of new classes of therapies for cancer. Overexpression of IAPs has been repeatedly encountered in various cancer cells, and is hypothesized to be associated with tumorigenesis, treatment resistance, and poor prognosis. These features render IAPs promising therapeutic targets in a wide range of human tumors by either direct induction of cell death or reduction of the threshold for cell death caused by anticancer drugs [2].

IAP family members

The IAP gene was first recognized in insect SF-21 cells infected by baculovirus, and was identified as a potent inhibitor of apoptosis in insect cells [3]. IAP homologs, sharing similar structure, were subsequently discovered in various species including nematode, yeasts, and mammals [4]. The first cellular IAP to be identified was the mammalian gene neuronal apoptosis inhibitory protein (NAIP) [5]. Since the discovery of NAIP, the human IAP gene family has expanded to include seven more members: cellular IAP1; cellular IAP2; X-linked inhibitor of apoptosis (XIAP) [6–8]; IAP-like protein 2 [9, 10]; BIR-containing ubiquitin conjugating enzyme (BRUCE/Apollon) [11]; Survivin [12];

and Livin (ML-IAP) [13, 14]. Among IAP family members, XIAP is the only one that can inhibit caspases through direct physical interaction. Cellular IAPs (cIAP1 and cIAP2) have similar roles as XIAP in regulating caspases activity, but are also involved in regulating NF-κB pathways [15]. The mechanism by which other IAP family members inhibit apoptosis is less understood. Several IAPs are capable of binding to caspases, yet lack the ability to directly inhibit the proteolytic activity of those enzymes [16].

Structural features of IAPs

The IAP family is characterized by the presence of Baculovirus IAP Repeat (BIR) at the N-terminal end of the protein, which constitutes of one to three tandem specific motifs of approximately 70 amino acids. The BIRs have a core component of cysteine-histidine (Cys-His) motif that coordinates a zinc ion [17]. The structure is organized in a series of short alpha-helices with intervening β-sheets, yielding a specific fold stabilized by Zinc tetrahedrally coordinated by three cysteine and one histidine residues [17]. BIRs are protein interacting modules with distinct binding properties, necessary for the anti-apoptotic activity of most IAPs [18]. Three subtypes of BIR domain, BIR1, BIR2, and BIR3, have been identified so far [19]. Most BIRs form a hydrophobic groove which binds conserved IAP binding motifs (IBMs), located in the extreme N-terminus of some caspases and IAP antagonists. The N-terminal exposure of IBM is essential for the recognition and binding by IAPs. Thus, only processed, activated caspases can bind to the BIR hydrophobic groove [17]. There are numerous proteins that bind to BIR in an IBM-dependent fashion, including caspases [16], the second mitochondrial activator of caspase (SMAC—also known as DIABLO) [20], HtrA2 (also known as Omi) [21], and the *Drosophila* proteins Hid, Grim and Reaper [22]. Different IAP family members possess specific intrinsic binding selectivity, which explains why subtle changes in the peptide-binding groove of BIR domains can markedly alter the target protein selectivity [18]. As opposed to BIR2, type I BIRs do not possess the binding properties with IBM, but can interact with a different set of proteins primarily involved in cell signaling pathways [23, 24].

At the C-terminal, the second conserved motif of IAP subsists, namely the really interesting new gene (RING) which displays a characteristic E3-ubiquitin ligase activity. It also enables homo- or hetero-dimerization of IAP proteins, which is crucial for their stability and possibly their activity [25]. For example, the RING domain is required for cIAP1 and 2 homodimerization, autoubiquitylation and subsequent proteasomal degradation [25, 26]. It is also noteworthy that cIAP1 exists in an inactive state due to the interaction between its BIR3 and RING domains which precludes intermolecular RING–RING dimerization [26, 27]. Other conserved protein domains are also found in some IAPs including caspase activation recruitment domain (CARD) which regulates E3-ubiquitin ligase activity [28]. The ubiquitin-associated domain (UBA) recognizes mono- and poly-ubiquitin chains allowing the recruitment of IAP in protein complexes [29, 30]. All IAPs are homologs sharing remarkably conserved sequences. The distinct association between baculoviral IAPs and insect IAPs proposes that the former might have been acquired by gene transfer from infected host insect cells. Some baculoviral IAPs can even represses apoptosis in mammals [31].

Regulatory mechanisms of IAP in apoptosis

Apoptosis is considered one of the main mechanisms of programmed cell death, which can be triggered in response to variable endogenous and exogenous stimuli. Key morphological changes occurring during apoptosis include nuclear condensation and fragmentation, as well as blebbing of plasma membranes leading to apoptotic body formation [32]. This process is strictly regulated by a series of signal cascades, under the influence of three critical factors: IAP, IAP antagonists, and caspases [33]. The regulation of these factors is crucial for cellular homeostasis, and their disruption is noted in many diseases, including cancer [34].

Apoptotic pathways

In mammals, apoptosis is mediated by a sequential activation cascade of cysteine proteases (caspases) that are responsible for distinct biochemical and morphological changes [35]. Caspases are inactive-zymogens constituting of one pro-domain and two active subunits. According to the length of the pro-domain and the activation mechanism, they are further sub-divided into initiator and effector caspases. The initiator caspases are characterized by the presence of a long pro-domain that allows their recruitment into caspase-activating complexes. In mammals, there are four apoptotic initiator caspases (caspase-2, -8, -9 and -10) [36, 37]. The effector caspases-3 and -7 are activated by proteolytic cleavage leading to the assembly of two large and two small subunits into a single active tetramer. They can cleave a wide spectrum of cellular proteins leading to loss of cellular integrity [17]. Caspases can also mediate other non-apoptotic processes, such as cellular proliferation and inflammatory response [35].

It has been documented that caspases are activated through several overlapping pathways for apoptosis initiation: (1) the mitochondrial pathway (intrinsic pathway) in which cytochrome c is released from the mitochondria and apoptosomes are generated activating caspase-9 and in turn

caspase-3; (2) the death receptor pathway (extrinsic pathway), activated by the ligand binding of extracellular signals and death receptors on cell membrane [FasL (Fas ligand)/Fas, tumor necrosis factor (TNF)/TNF receptor] (Fig. 1); (3) the endoplasmic reticulum (ER) stress-induced apoptotic pathway that activates caspase-2 and caspase-9; and (4) the apoptosis-inducing protease, granzyme B, mediated activation of effector caspases, specifically in cytotoxic T lymphocytes and natural killer cells [19]. (5) A nuclear pathway that depends on specific nuclear organelles, named Pml oncogenic domains (PODs) or nuclear bodies (NBs) was proposed. The mechanism of caspase activation in this pathway is not clearly understood. Several apoptosis-promoting proteins have been localized to PODs, and their defects have been linked to tumorigenesis [38]. Given the dire consequences of caspase activation, strict regulation of these pathways at each step is of paramount importance.

The intrinsic pathway is largely regulated by BCL2 family, which comprises several anti- and pro-apoptotic proteins. Anti-apoptotic proteins (eg: BCL2 and BCLXL) share a structural homology in specific domains, namely BCL2 homology (BH) 1, 2, 3 and 4. On the other hand, some pro-apoptotic proteins share only BH3 domain homology and thus named BH3-only proteins, including PUMA, NOXA, BIM, BAD and BIK. The effector pro-apoptotic proteins, Bcl2- associated X protein (BAX) and Bcl2 homologous antagonist/killer (BAK) share multi-domain homology (BH1, 2 and 3). Apoptotic stimuli result in an imbalance between pro- and anti-apoptotic proteins, which consequently activates the effector BAX and BAK proteins [39].

Upon activation, BAX translocates from the cytosol to be integrated in the mitochondrial outer membrane. Together with BAK, a membrane-resident protein, they become fully inserted in the mitochondrial membrane leading to mitochondrial outer membrane permeabilization (MOMP) [40]. This eventually leads to supramolecular channels releasing several proteins from the mitochondrial inter-membrane space (IMS), the most important of which is cytochrome c [41, 42]. Other released proteins include the IAP antagonists Smac/Diablo (second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI) [43] and Omi/HtrA2 (Omi stress-regulated endoprotease/High temperature requirement protein A2) [44]. Cytochrome c initiates apoptosome formation through binding the apoptotic protease activating factor 1 (Apaf-1), triggering its oligomerization into a wheel-like heptamer and exposing its caspase activation and recruitment domains (CARDs) [45]. The latter bind to procaspase-9 CARDs inducing autocatalysis, and active

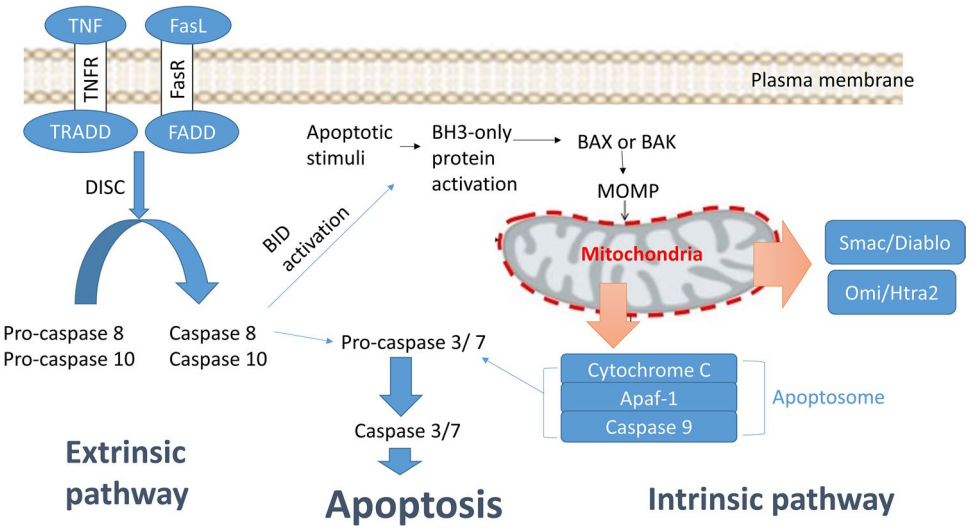

Fig. 1 Schematic diagram of the extrinsic (death receptor) and intrinsic (mitochondrial) apoptotic pathways. The first step in initiation of the extrinsic pathway is the binding of death ligands to their respective receptors on the plasma membrane: tumor necrosis factor (TNF) with TNF receptor (TNFR) and Fas ligand (FasL) with Fas receptor (FasR). This is followed by the binding of TNF receptor-associated death domain (TRADD) and/or Fas-associated death domain protein (FADD) to the intracellular domains of death receptors. These reactions result in the formation of death-inducing signaling complex (DISC) which promote the activation of pro-caspases 8 and 10. Once they become in the active state, they either activate the executioner caspases-3 and -7 resulting in apoptosis, or converge onto the intrinsic pathway via BID activation (mitochondrial amplification loop). On the other hand, the intrinsic pathway is initiated in response to apoptotic stimuli which activate the pro-apoptotic BCL2 family members: BH3-only proteins. Bax and/or BAK are consequently activated and induce mitochondrial outer membrane permeabilization (MOMP). Several proteins are released from the mitochondria, including second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI (Smac/Diablo), Omi stress-regulated endoprotease/High temperature requirement protein A2 (Omi/HtrA2) and cytochrome c. The latter, together with apoptotic protease activating factor 1 (Apaf-1) and pro-caspase 9, form the apoptosome. The latter induces the activation of caspase 9 and subsequent activation of caspase-3 and 7, which eventually lead to apoptosis

caspase 9 consequently activates caspases 3 and 7, executing cell death within minutes [46].

Notably, MOMP eventually results in energy depletion and cell death caused by progressive mitochondrial dysfunction, even in the presence of inactive caspases [40, 41]. Moreover, the mitochondrial pathway seems to be crucial for amplification of upstream signals of the extrinsic apoptotic pathway, highlighting the importance of MOMP in apoptosis execution [40]. Several other pro-apoptotic proteins, including p53-upregulated modulator of apoptosis (PUMA) and NOXA, can also be activated in response to DNA damage. The latter can alternatively lead to p53-dependent caspase 2 activation, which in turn induces MOMP. The mitochondrial proteins released, including endonuclease G (EndoG) and apoptosis-inducing factor (AIF), are capable of initiating caspase-independent apoptosis. This process can also be induced through lysosomal membrane permeabilization that releases MOMP-triggering cathepsins into the cytosol [32].

In the extrinsic pathway, caspases-8 and -10 are activated in response to death receptor signals from tumor necrosis factor (TNF) receptor superfamily. Death ligands are mainly produced by the immune system (eg: T-cells, macrophages, natural killer cells, and dendritic cells) and include TNF, Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL) [47]. The TNF receptor superfamily is characterized by distinct protein motifs, namely death domains (DD) and death effector domains (DED), which are capable of monovalent interactions and pivotal for apoptotic signal transduction [46]. Stimulation of Fas (DR2, CD95) or TRAIL Receptor I or II (DR4 and DR5) induces the recruitment of DD-containing molecules, FADD (Fas-associated death domain protein) and/or TNF receptor-associated death domain (TRADD). FADD triggers pro-apoptotic pathways by activating procaspases-8 and -10 in a receptor-associated platform called DISC (death-inducing signalling complex) [17, 37]. Once those caspases are activated, they amplify death signaling, by either direct activation of effector caspases-3, -6 and -7, or engaging the intrinsic apoptotic pathway [46]. This convergence is mediated by caspase-8 that triggers cleavage of the pro-apoptotic BH3 family member BID. This results in its activation and subsequent involvement of BAX and BAX which eventually induce MOMP, in a mitochondrial amplification loop [47]. In contrast, TRADD initiates anti-apoptotic signals via forming complex I with receptor interacting protein-1 (RIP1), TNF receptor-associated factors 2 and 5 (TRAF2 and TRAF5), and the inhibitor of apoptosis protein-1 and -2 (cIAP1/2). This complex promotes survival signaling, such as those regulated by NF-κB [46, 48, 49].

The endoplasmic reticulum (ER) majorly contributes to both mitochondrial and ER stress-induced apoptotic pathways [50–52]. It has been proven that ER stress induces down-regulation of the anti-apoptotic Bcl2, up-regulation of the pro-apoptotic BIM and PUMA, as well as BAX activation with subsequent apoptosis execution [53]. Some studies also showed a correlation between ER stress and regulation of the tumor suppressor p53. The latter is stabilized in response to ER stress, promoting transcriptional activation of pro-apoptotic PUMA and NOXA [54]. This pathway is mainly mediated by caspases-2 and -9 which in turn activate the executioner caspases-3 and -7 leading to cell death [19, 55].

Mechanism of action of IAP

IAPs are considered to be the only known endogenous proteins that are capable of suppressing both initiator and effector caspases, the key executioners of apoptosis [56]. They impose negative regulation on apoptotic pathways by direct inhibition of caspases through several mechanisms. First, their conserved BIR domains bind the active site of caspases inhibiting their proteolytic function, as do XIAP, cAP1/2 and Survivin to caspases-3 and -7 [57]. This results in stimulating the breakdown of active caspases, or their isolation away from their substrates [57]. Also, IAPs repress caspases-2 and -9 in the ER stress-induced apoptotic pathway through BIR domain binding [55]. Second, direct inhibition of pro-caspase 9 activation by XIAP. Third, some IAP family members are capable of targeting effector caspases for ubiquitination and proteasomal degradation. Additionally, cIAPs may play some role in the activation of anti-apoptotic signals, such as NF-κB, which explains their pivotal role in regulating NF-κB during TNF signaling [58].

While different IAPs can suppress caspases-2, -3, -7 and -9, other caspases, such as -1, -6, -8 and -10, are thought to be resistant to IAP inhibition. IAPs do not bind caspase-8 but rather inhibit its substrate, namely caspase-3 [19]. Caspase-8 can also be negatively regulated through the induction of survival signaling pathways that in turn inhibit its activation. The BIR domain, CARD and RING E3 ligases in cIAP1/2 act to recruit TRAF1 and 2 and inhibit TNFα-apoptotic signaling. Thus, cIAP1/2 have the potential of inhibiting caspase-8 by inducing pro-survival signals, mainly NF-κB pathway [46, 59, 60]. Moreover, cIAPs are capable of interacting with caspases-9 and -7 in an IBM-dependent fashion, and with the pro-domain of caspase-3 independently of IBM [61]. It has been observed that neither BIR2 nor BIR3 domains of cellular IAPs can directly inhibit caspases; so they execute their anti-apoptotic function through caspase binding, with a lower affinity than XIAP [19]. Of note, cellular IAP 2 is the only IAP family member that is capable of binding and inhibiting caspase-2, through its BIR2 domain [55]. cIAPs can also control the stability of activated caspases through a UPS (ubiquitin/proteasome system)-dependent mechanism [61]. Furthermore, cellular IAPs, as well as Melanoma IAP (ML-IAP/Livin) and Apollon, have the ability of binding to SMAC, to prevent

XIAP neutralization [62]. In addition to SMAC binding and degradation, Livin can also exert its anti-apoptotic activity by inhibiting caspases-3, -7 and -9 [63]. On the other hand, neuronal apoptosis inhibitory protein (NAIP) can distinctly interact with pro-caspase 9 inhibiting its cleavage when present in the apoptosome complex. This mechanism is ATP-dependent and IBM-independent, resulting in early inhibition of the intrinsic pathway [64]. The anti-apoptotic functions of NAIP have been demonstrated both in vivo and in vitro, and extend to include inhibitory action on caspases-3 and -7 as well [19].

XIAP, the best identified IAP so far, is regarded as the most powerful caspase inhibitor. It possesses three BIR domains (BIR1, BIR2, and BIR3) of high affinity and varying functions to caspases [16]. BIR2 domain binds the executioner caspases-3 and -7, while BIR3 binds initiator caspase 9 [16]. The interaction with effector caspases is believed to be via steric hindrance, where BIR2 domain blocks the substrate entry site [65]. On the other hand, the interaction between BIR3 and the Apaf-1/caspase 9 complex occurs via sequestration of the N-terminus of caspase-9 small subunit [19]. The latter distinctly resembles the N-terminus of mitochondrial SMAC/Diablo, raising the suspicion that both compete for XIAP-BIR3 binding [19]. XIAP BIR3 domain, together with caspase 9, form a heterodimer which results in stabilization of inactive caspase 9 by preventing its homodimerization and subsequent autocatalytic activity [66]. It has been shown that the capacity of XIAP to control capase-9 activity is directly correlated to the level of APAF-1 and apoptosome activity [67]. Thus, in cells harbouring low Apaf-1 levels, such as neuronal cells and cardiac myocytes, XIAP is an effective regulator of response to apoptotic stimuli [68]. Furthermore, the E3 ligase activity of the XIAP RING domain plays an important role in caspase inhibition. Surprisingly, neither BIR2, BIR3 nor RING domains alone is capable of caspase inhibition [19]. Of note, XIAP is cleaved in response to Fas-induced apoptosis into two separate fragments; one contains both BIR1 and 2 domains while the other consists of BIR3 and RING domains [69]. How these fragments contribute to the apoptotic process is still unclear [65].

Several studies have documented the ability of Survivin to inhibit both intrinsic and extrinsic apoptotic pathways [12, 70]. The exact mechanism of Survivin-mediated caspase inhibition is not yet fully understood, as its capability of binding caspases-3 and -9 is still controversial [70]. The inhibitory action of Survivin on apoptosis is mainly mediated by co-operative interactions with other apoptotic regulators in vivo. One example is the interaction between Survivin and XIAP BIR 1 and three domains, expanding its functional repertoire [71]. Survivin also exerts an indirect action through hepatitis B X-interacting protein (HBXIP) that binds pro-caspase 9 [70], and through triggering XIAP inhibitory effect on caspases-3 and -9 [72]. Another mechanism is Survivin binding with the pro-apoptotic Smac/Diablo, hindering caspase activation [70]. Notably, it also plays a pivotal role in regulating chromosomal segregation during cell division [73]. These two vital cellular functions are mediated by the characteristic structure of Survivin, where the C-terminal is involved in cell division and the N-terminal is responsible for regulating apoptosis [74].

Another mechanism of caspase inhibition by IAP proteins is through the ubiquitination process. This regulated process entails post-translational protein modification, where ubiquitin is covalently bonded to lysine on a substrate protein [75]. Through the interplay of ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2), and ubiquitin protein ligase (E3), ubiquitins attach to target proteins and undergo proteasome-mediated degradation [19, 76], as illustrated in Fig. 2. A fine balance between ubiquitination and auto-ubiquitination is one way of IAP regulation. The loss of one IAP protein has been noted to cause an increase in the levels of other IAP family members [77]. The RING domain of cIAP1 has been proven to play an important role in the degradation of RING-containing IAPs, as well as being involved in XIAP binding and degradation [78]. Moreover, the E3 ligase activity of cIAP2 mediates both auto-ubiquitination and mono-ubiquitination of caspases-3 and -7 [79]. These

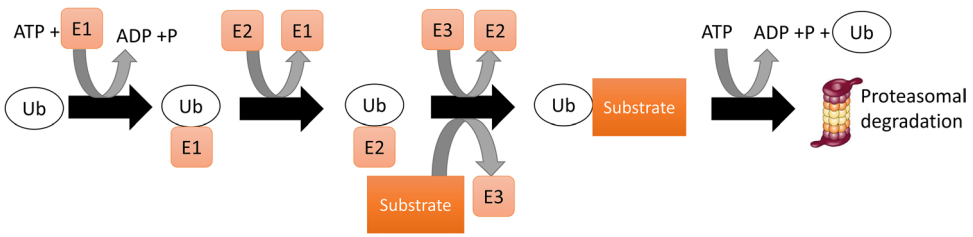

Fig. 2 Illustrative diagram of ubiquitination enzymatic reactions. The first step in this cascade of events is the ATP-dependent activation of ubiquitin by E1 via formation of a thioester bond. Ubiquitin then binds to E2 conjugating enzyme, followed by subsequent isopeptide bond formation between the carboxyl-terminal glycine in ubiquitin and lysine residue in a substrate protein, via the action of E3 ligase. This process eventually results in proteasomal-mediated substrate degradation

different regulatory mechanisms act to control the endogenous IAP levels and activities, promoting apoptosis.

All BIR-containing proteins, with the exception of NAIP, are associated with ubiquitin. In addition, the RING-containing IAPs, including XIAP, cellular IAPs 1/2, and ML-IAP act as ubiquitin E3 ligases [80]. Huang et al. demonstrated that both full-length cellular IAP 2, and its RING domain alone, possess the capacity of acting as an E3 ligase in vitro [79]. It has also been demonstrated that in-vivo removal of the RING domain results in XIAP protein stabilization, increase in caspase 3 activity and TNF sensitivity [81]. Similar to cIAP1/2, the XIAP-RING domain can conjugate various ubiquitin chain types to target proteins [82, 83]. XIAP also has the ability to induce caspase 3 ubiquitination by itself [80]. This demonstrates the role of ubiquitination of XIAP-bound caspases in the inhibition of apoptosis. BRUCE/Apollon is a distinct IAP with dual function owing to the possession of two specific domains [11]. At the N-terminal, the BIR domain mediates anti-apoptotic functions by antagonizing Smac/Diablo and multiple caspases. On the other hand, the C-terminal ubiquitin conjugating (UBC) domain mediates E2 ubiquitination activities. BRUCE has been discovered to be a hybrid E2/E3 enzyme owing to the dual function of its UBC domain as both conjugating enzyme (E2) and protein ligase (E3) [84].

IAP antagonists

IAP activities are strictly regulated through several feedback mechanisms that involve pro-apoptotic proteins. Numerous mammalian IAP antagonists have been identified, including second mitochondrial activator of caspases/direct IAP binding protein with low pI (Smac/Diablo) [85], high temperature-regulated A2/Omi (HtrA2/Omi) [86], X-linked IAP associated factor 1 (XAF1) [87], the endoplasmic reticulum protein, GSPT1/eRF3 (G1 to S phase transition protein/eukaryotic Release Factor 3) [88], the septin-like mitochondrial protein ARTS [89, 90], glutamate dehydrogenase, Nipsnap 3 and 4, and 3-hydroxyisobutyrate dehydrogenase [91]. The functional execution of IAP binding proteins entails their physical interaction with IAPs through a conserved IAP Binding Motif (IBM). The latter specifically binds IAP BIR domain promoting apoptosis partly by replacing the bound caspases [20]. The whole spectrum of actions of IAP antagonists and their role in IAP regulation are not yet fully understood. For example, various apoptotic triggers, such as DNA damaging agents, seem to induce IAP degradation and possibly RIPoptosome assembly without a clear role for IAP antagonists [17, 92].

Smac/Diablo and HtrA2 are perhaps the most studied mammalian IAP antagonists [21, 43, 44, 85, 86]. During apoptosis, they are released into the cytosol and activated into arc-shaped dimmers and pyramid-shaped homotrimers, respectively [19, 41]. Smac/Diablo has a characteristic ability of binding both BIR2 and BIR3 domains halting XIAP-mediated caspase inhibition, namely caspases-9 and -3 [85]. It can also inhibit cellular IAPs 1/2, and induce their degradation through auto-ubiquitination [30, 93]. Similar to Smac, its isoform Smac3 can also inhibit XIAP by binding with BIR2 and BIR3 domains. Smac3, produced as a result of exon 4 splicing, stimulates XIAP ubiquitination and destruction [94]. HtrA2/Omi exerts its pro-apoptotic function via binding XIAP, thus releasing its inhibitory effect on caspases, as well as irreversible proteolytic cleavage of XIAP and cellular IAPs [21]. However, it has a weaker affinity than Smac as regards XIAP BIR3 binding [19]. Notably, the tumor suppressor p53 upregulates and activates HtrA2, which is one of the mechanisms by which p53 promotes apoptosis and supresses carcinogenesis [95].

XIAP-associated factor (XAF1) is a tumor suppressor gene that acts as an IAP antagonist, sequestrating XIAP in the nucleus and counteracting its anti-caspase activity [87]. Arora et al. demonstrated the ability of XAF1 to directly bind all IAP members, with the exception of Survivin which is indirectly inhibited through XIAP-Survivin complex [96]. Also, the destruction of Survivin is regulated by XAF1 through activating the E3 activity of XIAP RING domain [96]. Another proposed mechanism of XAF1 action is through promoting IFN-mediated sensitization to TRAIL in tumors [97]. Several studies have shown that XAF1 is expressed in normal tissues, but is nearly undetectable in cancer cell lines and its suppression in several tumors has been confirmed [98–101]. Moreover, the ratio of expression levels of both XIAP and XAF1 seems to be crucial for determination of cell fate. Carcinogenesis is favoured when XIAP is overexpressed with respect to XAF1, evading apoptotic pathways [102]. Interestingly, a regulatory relationship has been established between the tumor suppressor genes XAF1 and p53 [103]. Wild type p53 exerts a negative feedback and transcriptional repression of XAF1, which is probably a mechanism to avoid duplication of function. On the other hand, XAF1 induces p53 phosphorylation in response to DNA damage, leading to its nuclear accumulation and enhanced transcriptional activity. These findings illustrate the function of XAF1 as a promoter of p53-mediated apoptosis in cancer [103]. Hence, induction of XAF1 expression could be exploited in cancer therapy, especially in cancers having low expression levels of wild type p53 [99, 103, 104].

Another identified IAP antagonist is the endoplasmic reticulum protein, GSPT1/eRF3 (G1 to S phase transition protein/eukaryotic Release Factor 3). During apoptosis, its IBM is exposed and selectively mediates cellular IAP1 auto-ubiquitination and degradation [88]. On the other hand, the septin-like mitochondrial protein, ARTS, is a peculiar IAP antagonist that lacks the characteristic IAP binding motif [89]. In spite of that, it can bind XIAP and induce its

ubiquitination [105, 106]. An increased incidence of lymphomas and leukemias has been observed with ARTS inactivation in mice, which can be reversed by XIAP inactivation. This phenomenon highlights the key role of ARTS-mediated XIAP inhibition in maintaining normal hematopoiesis and tumor suppression [17, 107]. Edison et al. have concluded that ARTS is capable of activating caspases upstream of MOMP. It is localized in the outer mitochondrial membrane and is rapidly translocated to the cytoplasm upon induction of apoptosis, in a caspase-independent manner. This leads to XIAP binding and inhibition prior to the release of cytochrome c and Smac [90]. Furthermore, it has been shown that ARTS knockdown precludes the release of cytochrome c from the mitochondria, suggesting that ARTS is pivotal for the regulation of mitochondrial proteins release in response to MOMP [90]. In addition to well characterized IAP binding proteins, various other proteins have the capacity of antagonizing IAP actions. For example, interleukins-3 and -5 as well as granulocyte-macrophage colony stimulating factor (GM-CSF) have been shown to regulate cIAP2 and Survivin [108]. Some mitochondrial proteins, including glutamate dehydrogenase, can also inhibit XIAP via BIR2 binding [91]. However, their detailed mechanism of action and regulatory process in cancer are yet to be fully understood.

Clinical applications of IAP

Evasion of apoptosis is one of the fundamental hallmarks of carcinogenesis. Cancer cells are known to enhance survival and proliferation by overexpressing anti-apoptotic and inactivating pro-apoptotic proteins [46]. Members of IAP and tumor necrosis factor families are known to promote cancer cell survival synergistically. For instance, TNFα can increase the expression levels of XIAP and cellular IAPs in cancer cell lines [109]. On the contrary, IAP antagonists induce degradation of various IAPs, and stimulate NF-κB that in turn activates TNFα-mediated apoptosis [93, 110]. Besides apoptosis, IAPs are capable of regulating various other processes that are known to be culprits in carcinogenesis. These include cell cycle regulation, cancer-mediated inflammation, tumor invasion and metastasis [59, 111].

IAP overexpression has been documented in various malignancies (Table 1), possibly rendering them resistant to standard chemotherapeutics and radiation therapy. In prostate cancer, adverse clinic-pathological features seem to be correlated with IAPs, including cellular IAPs 1/2 and tumor stage, cIAP2 and positive surgical margins, as well as survivin and perineural invasion [112].

Survivin, normally limited to embryonic tissues, is correlated with treatment resistance and increased incidence of relapse when overexpressed in tumor tissues [12, 202].

Table 1 Inhibitors of apoptosis overexpression in cancer

Malignancy	IAP	Reference
Solid malignancies		
Adrenocortical carcinoma	Livin	[113]
	Survivin	[114]
Bladder cancer	cIAP 1	[115]
	cIAP2	[115]
	XIAP	[116]
	Survivin	[116]
	Livin	[116]
	NAIP	[117]
Brain gliomas	XIAP	[118]
	cIAP 1/2	[118]
	Survivin	[119]
	Livin	[120]
	Apollon	[11]
Breast cancer	XIAP	[121, 122]
	Survivin	[121]
	NAIP	[123]
	Livin	[124]
Cancer cervix	Survivin	[125]
	cIAP 1	[126]
	XIAP	[127]
Colorectal cancer	Survivin	[128]
	Livin	[129]
	XIAP	[128]
	cIAP 2	[130]
	NAIP	[131]
Endometrial cancer	Survivin	[132]
	XIAP	[133]
	cIAP 1/2	[134]
Esophageal cancer	XIAP	[135]
	Survivin	[136]
	Apollon	[137]
Gastric cancer	Survivin	[138]
	XIAP	[139]
	Livin	[140]
Gastrointestinal stromal tumor (GIST)	XIAP	[141]
	Survivin	[141]
	cIAP1	[141]
HCC	XIAP	[142, 143]
	Survivin	[143]
	Livin	[144]
	cIAP 1/2	[143]
Head and neck cancers	cIAP 1	[145]
	Survivin	[146, 147]
	XIAP	[148]
Malignant peripheral nerve sheath tumor	Survivin	[149]
Medulloblastoma	XIAP	[150]
	cIAP 1/2	[150]
	Survivin	[151]

Table 1 (continued)

Malignancy	IAP	Reference
Melanoma	XIAP	[152]
	Survivin	[153, 154]
	Livin	[155]
	Apollon	[156]
Mesothelioma	cIAP 1/2	[157]
	XIAP	[157]
	Survivin	[157]
Neuroblastoma	Livin	[158]
	XIAP	[159, 160]
	cIAP 1	[160]
	Survivin	[161]
NSCLC	XIAP	[162]
	Survivin	[163]
	Livin	[164]
	Apollon	[165]
Osteosarcoma	Survivin	[166]
	Livin	[167]
	XIAP	[168]
Ovarian cancer	XIAP	[169]
	Survivin	[170]
	Livin	[171]
	cIAP 2	[172]
	Apollon	[173]
Pancreatic carcinoma	cIAP 2	[174, 175]
	Survivin	[175, 176]
	XIAP	[175]
	Livin	[175]
Prostate cancer	XIAP	[177, 178]
	cIAP 1/2	[178]
	Survivin	[178]
	NAIP	[178]
RCC	XIAP	[179]
	Survivin	[180]
	Livin	[181]
Rhabdomyosarcoma	Survivin	[182]
	XIAP	[182]
Thyroid cancer	cIAP 1	[183]
	Survivin	[183, 184]
	XIAP	[185]
Hematological malignancies		
ALL	Livin	[186]
	XIAP	[187]
	Survivin	[188]
	Apollon	[189]
AML	XIAP	[190]
	Survivin	[191]
	Livin	[186]
	Apollon	[189]
CLL	Survivin	[192]
	cIAP 2	[192]
	cIAP 1	[192]
	XIAP	[192]
CML	XIAP	[193]
	Survivin	[194]
	Apollon	[195]
Hodgkin lymphoma	XIAP	[196]
	cIAP 1/2	[196]
	Survivin	[197]
Multiple myeloma	XIAP	[198]
	cIAP 1/2	[198]
	Survivin	[199]
Non hodgkin lymphoma	XIAP	[196, 200]
	cIAP 1/2	[196]
	Survivin	[201]

IAP Inhibitor of apoptosis, *cIAP* cellular inhibitor of apoptosis, *XIAP* X-linked inhibitor of apoptosis, *HCC* hepatocellular carcinoma, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma, *ALL* acute lymphoblastic leukemia, *AML* acute myelogenous leukemia, *CLL* chronic lymphocytic leukemia, *CML* chronic myeloid leukemia

It is of particular importance in diagnosis and prognostication of gastric and colorectal cancers, a finding that has been consistent in several studies [203, 204]. In addition to evasion of apoptosis and induction of tumor proliferation [202], Survivin also promotes angiogenesis. It is known to upregulate vascular endothelial growth factor (VEGF) and enhance proliferation of vascular endothelial cells [205]. Under normal physiological condition, Survivin plays an important role in regulation of stem cell homeostasis, in intestinal, hematopoietic and nervous systems [206–208]. This drives the speculation that Survivin may be involved in cancer stem cell regulation as well [70].

XIAP overexpression has been identified as a well characterized prognostic factor in various malignancies. In pediatric acute myeloid leukemia (AML), XIAP confers poor response to induction therapy, short relapse-free survival as well as intermediate and poor cytogenetics [209, 210]. In adult AML, as well, XIAP is associated with poor cytogenetics, monocytic differentiation and short overall survival [211]. Moreover, XIAP expression in pediatric acute lymphoid leukemia (ALL) heralds resistance to glucocorticoid-mediated apoptosis, an established poor prognostic factor [187]. As for solid malignancies, XIAP is identified as a biomarker of poor survival, chemoresistance and metastatic potential in ovarian and hepatocellular carcinomas, respectively [142, 212]. In breast cancer, nuclear overexpression of XIAP was identified as

an independent prognostic factor, harbouring threefold increased risk of disease-specific death [122].

Cellular IAPs 1 and 2 have been characterized in pancreatic neoplasms conferring short overall survival [174]. Endo et al. revealed a preferential overexpression of cIAP2 and Survivin in elderly colon cancer patients, compared with younger ones [213]. This observation suggests dysregulation of apoptosis in the elderly population contributing to increased incidence of tumors. It is hypothesized that cellular IAPs adversely impact prognosis of head and neck cancer patients. Tanimoto et al. stated that nuclear overexpression of cIAP1 was associated with advanced disease stage, lymph node involvement and poor prognosis in head and neck cancers [145]. In a more recent study in oral squamous cell carcinomas, cIAP2 overexpression was linked to advanced disease stage, but had no impact on survival [214]. Bladder carcinogenesis is also affected by expression levels of cIAP1, where its nuclear overexpression correlates with muscle invasive disease, tumor grade, short recurrence-free and overall survival [115].

Promising therapeutic targets

In cancer, any defect along the apoptotic pathways may offer an interesting therapeutic target. The pivotal role of IAPs in development and progression of cancers compelled their targeting as a promising strategy of cancer treatment. Drugs that can restore the apoptotic signaling pathways towards normality have the potential to eliminate cancer cells which depend on these defects for survival. Many recent and important discoveries have opened new doors into potential new classes of anticancer drugs. To date, several studies investigated different IAP inhibiting agents, achieving a breakthrough in cancer treatment:

IAPs

Novel therapy targeting inhibitor of apoptosis proteins include antisense strategies that are capable of reducing IAP mRNA, short interfering RNA (siRNA) molecules, and Smac mimetics [65, 215]. The latter are synthetic small molecules that mimic the action of endogenous Smac, antagonize IAP actions and induce apoptosis [215]. Using the antisense approach, inhibition of XIAP has been reported to improve tumor control by radiotherapy and chemotherapy [216]. Moreover, when used together with anticancer drugs, XIAP antisense oligonucleotides have been recognized to exhibit enhanced chemotherapeutic activity [217]. On the other hand, some researchers reported that siRNA targeting of XIAP increased radiation sensitivity of human cancer cells, especially in the presence of p53 mutation [218]. Others reported that targeting XIAP or Survivin by siRNAs sensitize hepatoma cells to death receptor- and chemotherapeutic agent-induced cell death [219]. However, when AEG 35156 -a second generation antisense oligonucleotide- was tested in several clinical trials, it yielded contradictory results as shown in Table 2.

Another approach of targeting IAP is the concomitant use of Smac mimetics with chemotherapeutics, which has been proven to induce cancer cell apoptosis in various tumor types [118, 224–229]. In pancreatic tumors, apoptosis can be initiated by the combined effect of Smac mimetic with gemcitabine chemotherapy. This process is mediated by NF-κB resulting in caspase activation and subsequent cell death [226]. Reversal of TRAIL resistance is another mechanism by which Smac mimetics exert their pro-apoptotic function [225, 230]. This results in cleavage and activation of procaspases -3 and -7 which mediate apoptotic cell death [225]. Servida et al. have proven that Smac mimetics sensitize leukemic cells to cytotoxicity of chemotherapy and biological agents augmenting TRAIL [227]. In a preclinical animal model, concomitant administration of Smac mimetic with combination chemotherapy, resembling ALL induction, was tested. Significant reduction in tumor load and prolonged survival were observed with combination treatment [231]. The synergy between Smac mimetics and chemotherapy is regulated by RIP1, the inhibition of which by Necrostatin-1 results in inhibition of caspases [228]. In addition, Smac mimetics have been proven to sensitize tumor cells to radiotherapy as well [118]. This approach is of specific interest in malignant gliomas that are usually resistant to standard treatment. The addition of Smac mimetics to radiotherapy and temozolomide can offer a favourable therapeutic ratio in brain gliomas [118, 229]. Synergy between Smac mimetics and oncolytic viruses has also been described [232]. When the Smac mimetic LCL161 was combined with oncolytic rhabdovirus vesicular stomatitis virus, they exerted a synergistic bystander cell death in tumor cells. Moreover, when tested in vivo, they also induced significant tumor regression and durable response [232]. Notably, combination of Smac mimetics with standard cancer therapy seems crucial for tumor cytotoxicity, as the former is ineffective when used as single agent [230]. Several Smac mimetics have been tested in clinical trials, with promising outcomes (Table 3).

A natural small molecule XIAP inhibitor, namely Embelin, was discovered to block the binding of caspase 9, but not caspase 3, to XIAP BIR3 domain [246]. Its anti-cancerous activity is also partially mediated by PTEN-dependent suppression of the oncogenic STAT3 pathway [247]. Embelin has been proven to be of therapeutic value in non-small cell lung cancer (NSCLC), as it reverses XIAP-mediated cisplatin resistance [162]. It can also potentiate fluorouracil cytotoxicity in gastric carcinoma, leading to reduced tumor viability [139]. Moreover, Embelin has been shown to sensitize prostate cancer cells to radiation therapy both in vitro

Table 2 Clinical trials evaluating AEG 35156

Identifier/reference	Cancer type	Phase/status	Trial start date	Outcome measure/result
NCT00363974 [220]	- Refractory/ relapsed AML	Phase I/II: completed	October 2005	In combination with high-dose cytarabine and idarubicin, the drug was safe with a high rate of XIAP target knockdown and improved response rate
NCT00557596 [221]	- Advanced pancreatic cancer	Phase I: terminated	September 2007	In combination with gemcitabine, the drug was safe but failed to show additional clinical benefit
NCT00558922	- Stage IIIb/IV NSCLC	Phase I/II: terminated due to significant neurotoxicity	September 2007	- Safe tolerable dose in combination with carboplatin and paclitaxel - Progression free survival
NCT00558545	- Advanced breast cancer	Phase I/II: terminated	November 2007	- Safe tolerated dose in combination with paclitaxel - Progression-free survival
NCT00768339	- Relapsed/refractory CLL/ indolent B-cell lymphomas	Phase I/II: terminated due to slow recruitment	September 2008	- Safe tolerated dose - Objective tumor response
NCT00882869 [222]	- HCC	Phase I/II: completed	March 2009	In combination with sorafenib, the drug was well tolerated and enhanced anti-tumor activity
NCT01018069 [223]	- Primary refractory AML	Phase II: terminated	November 2009	In combination with high-dose cytarabine and idarubicin, the drug was well tolerated but failed to improve remission rate

AML Acute myeloid leukemia, *XIAP* X-linked inhibitor of apoptosis, *NSCLC* non-small cell lung cancer, *CLL* chronic lymphocytic leukemia, *HCC* hepatocellular carcinoma

and in vivo [248]. In vitro, it induced cell cycle arrest in the S-phase, inhibiting tumor proliferation and inducing apoptosis in a caspase-independent manner. In vivo, it suppressed angiogenesis, delayed tumor progression and improved survival in combination with radiotherapy [248].

To date, several other XIAP inhibitors have been identified to exert anti-tumor activity. For example, XIAP antagonist compound (XAC) 1396-11, has shown considerable activity in NSCLC in combination with vinerolbine chemotherapy [224]. An adamantane thiadiazole derivative, ATD-4, was recently characterized for its binding affinity to XIAP-BIR3 domain. It has been shown to stimulate mitochondrial apoptotic pathway in lung carcinoma cell lines, exerting anti-tumor activity [249]. Two cyclopeptidic Smac mimetics were found to bind to XIAP and cIAP-1/2, restoring the activities of caspases-9 and -3/-7 [250]. On the other hand, SM-164, a non-peptidic IAP inhibitor was reported to strongly enhance TRAIL activity by concurrently targeting XIAP and cIAP1 [251]. Interestingly, Mitsuuchi et al. have recently proven bivalent IAP antagonists to be superior to monovalent compounds in inhibiting TNF-mediated NF-κB [252]. They demonstrated high levels of residual TRAF2-associated cIAP1 following monovalent compound treatment. This reflects the lack of formation of cIAP1 E3-ubiquitin ligase complex which is responsible for TRAF2-associated cIAP1 degradation [252]. These findings warrant tailoring the choice of specific IAP antagonist classes according to their biochemical properties, and emphasize that bivalent compounds are the drug of choice for targeting TNF-dependent signaling in cancer.

Survivin is another IAP family member that has been extensively investigated as a therapeutic target in cancer. One example of its targeting is the use of antisense oligonucleotides that were described in human melanoma cells [253]. It was shown that transfection of antisense Survivin into YUSAC-2 and LOX malignant melanoma cells resulted in their spontaneous apoptosis. This approach has also been applied in head and neck squamous cell carcinoma and has been reported to induce apoptosis and sensitize these cells to chemotherapy [254]. In colorectal cancer cells, Survivin antisense oligonucleotides enhanced tumor response to radiotherapy as well [255]. Moreover, it has been found to inhibit growth and proliferation of medullary thyroid carcinoma cells [256]. However, these findings didn't translate into clinical benefit when antisense oligonucleotide, LY2181308, was investigated in combination with docetaxel in a phase II study involving NSCLC patients [257].

Another approach of Survivin therapeutic targeting entails its downregulation by the use of siRNAs. This mechanism can be exploited to overcome radio-resistance in pancreatic carcinoma and NSCLC [258, 259], as well as enhancing chemotherapy effects in AML [260], HCC [261, 262], bladder [263], ovarian [264], and breast cancers [265]. In addition, several small molecule antagonists of Survivin have shown promising anti-tumor activity [266]. For example, YM-155, which directly binds to Survivin promoter

Table 3 Smac mimetics/IAP inhibitors under clinical evaluation

Drug	Identifier/reference	Cancer type	Phase/status	Trial start date	Outcome measure/result
LCL 161	NCT01098838 [233]	- Advanced solid tumors	Phase I: completed	November 2008	The drug was well tolerated with induction of cIAP1 degradation, but no objective response
	NCT01240655 [234]	- Advanced solid tumors	Phase Ib: completed	April 2011	In combination with paclitaxel, the drug was safe to administer
	NCT01617668 [235]	- Triple negative breast cancer	Phase II: completed	August 2012	The combination of LCL 161 with paclitaxel in the neoadjuvant setting yielded favorable efficacy in gene expression signature positive patients, with significant toxicity
	NCT01968915	- Advanced solid tumors in Japanese population	Phase I: completed	November 2013	- Dose limiting toxicity - Tumor response
	NCT01955434	- Relapsed/refractory multiple myeloma	Phase II: recruiting	November 2013	- Confirmed overall response rate with single agent LCL 161 or in combination with cyclophosphamide - Event-free and overall survival
	NCT01934634	- Metastatic pancreatic cancer	Phase I: ongoing	March 2014	- Maximum tolerated dose in combination with gemcitabine and nab-paclitaxel - Dose-limiting toxicity - Objective response rate
	NCT02649673	- Relapsed/refractory SCLC - Relapsed/refractory ovarian cancer	Phase Ib: recruiting	March 2016	- Maximum tolerated dose in combination with Topotecan - Dose-limiting toxicity - Best overall response
	NCT02890069	Advanced/metastatic - NSCLC - Colorectal cancer - Triple negative breast cancer	Phase Ib: recruiting	October 2016	- Dose limiting toxicity in combination with PDR001 - Best overall response - Progression free survival
	NCT03111992	- Relapsed/refractory multiple myeloma	Phase I/Ib: recruiting	August 2017	- Maximum tolerated dose in combination with PDR001 - Overall response rate - Disease control rate - Progression-free survival

Table 3 (continued)

Drug	Identifier/reference	Cancer type	Phase/status	Trial start date	Outcome measure/result
Debio 1143 (AT-406)	NCT01078649 [236]	- Advanced solid tumors and lymphomas	Phase I: completed	February 2010	- The drug was well tolerated with limited antitumor activity
	NCT01930292	- Squamous NSCLC - Platinum-refractory ovarian cancer - Triple negative breast cancer	Phase I: terminated	April 2013	- Dose limiting toxicity in combination with carboplatin and paclitaxel - Overall response - Progression free survival
	NCT02022098	- Stage III/IV head and neck squamous cell carcinoma	Phase I/II: ongoing	October 2013	- Maximum tolerated dose in combination with cisplatin & radiotherapy - Loco-regional control - Complete/best overall response rate - Progression free survival - Distant relapse rate - Overall survival - Late toxicity rate
	NCT03270176	- Advanced solid tumors - Stage IIIb/ IV NSCLC after platinum-based treatment	Phase Ib: not yet open for recruitment	September 2017	- Maximum tolerated dose in combination with Avelumab - Objective response rate - Best overall response and its duration - Disease control rate - Progression free survival - Overall survival
GDC 0917 (CUDC-427)	NCT01226277 [237]	- Refractory solid tumors and lymphomas	Phase I: completed	October 2010	- The drug has a favorable safety profile
	NCT01908413 [238]	- Advanced/refractory solid tumors and lymphomas	Phase I: terminated	July 2013	- The drug was safe to administer with preliminary anti-tumor activity

Table 3 (continued)

Drug	Identifier/reference	Cancer type	Phase/status	Trial start date	Outcome measure/result
Birinapant (TL32711)	NCT00993239 [239]	- Refractory solid tumors/lymphomas	Phase I: completed	November 2009	- The drug was well tolerated with promising antitumor activity
	NCT01188499 [240, 241]	- Advanced/metastatic solid tumors	Phase Ib/IIA: completed	October 2010	- The drug was safe in combination with various chemotherapeutic drugs, with promising clinical activity
	NCT01486784	- AML - ALL - MDS	Phase I/II: ongoing	November 2011	- Adverse events - Overall survival
	NCT01681368 [242]	- Advanced/ metastatic ovarian cancer	Phase II: terminated due to lack of clinical benefit	August 2012	- Despite consistent suppression of cIAP1 in tumor samples, no clinical antitumor activity was demonstrated
	NCT01940172 [243]	- Relapsed ovarian cancer	Phase Ib: completed	November 13	- The drug is well tolerated in combination with conatumumab
	NCT02147873 [244]	- Myelomonocytic leukemia - MDS	Phase II: terminated due to lack of efficacy	June 2014	- The addition of birinapant to azacitidine resulted in significant toxicity, without clinical benefit
	NCT02756130	- High grade serous ovarian/endometrial cancer	Phase II: not yet open for recruitment	January 2017	- Progression free survival achieved by combination of birinapant with platinum-based therapy - Response at interval debulking surgery - Overall survival
	NCT02587962	- Advanced/metastatic solid tumors	Phase I/II: recruiting	August 2017	- Safety and tolerability in combination with pembrolizumab - Tumor response
HGS1029 (AEG40826)	NCT00708006 [245]	- Advanced solid tumors	Phase I: completed	May 2008	- The drug was well tolerated, with significant suppression of cIAP1
	NCT01013818	- Relapsed/ refractory lymphoid malignancies	Phase I: terminated due to slow accrual	October 2009	- Adverse events - Antitumor activity
ASTX660	NCT02503423	- Advanced solid tumors and lymphomas	Phase I/II: recruiting	July 2015	- Dose limiting toxicity - Change in tumor size - Progression free survival

cIAP1 Cellular inhibitor of apoptosis 1, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *AML* acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome

Table 4 Survivin targeted therapy under clinical evaluation

Drug	Identifier/reference	Cancer type	Phase/status	Trial start date	Outcome measure/result
EM-1421 (transcription inhibitor)	NCT00404248 [273]	- Recurrent high grade glioma	Phase I/II: completed	January 2007	The drug was proved to be safe, with modest anti-tumor activity (when used as single agent)
	NCT00664586	- Refractory solid tumors/lymphomas	Phase I: terminated due to financial constraints	May 2007	- Maximum tolerated dose - Dose limiting toxicity - Anti-tumor activity
	NCT00664677	- Leukemias	Phase I: terminated due to financial constraints	August 2007	- Maximum tolerated dose - Dose limiting toxicity - Anti-tumor activity
	NCT02575794	- Recurrent high grade glioma	Phase I: suspended recruiting due to drug production issues	November 2017 (anticipated)	- Maximum tolerated dose - Anti-tumor activity
YM155 (small molecule Survivin inhibitor)	NCT00328588 [274]	- Previously treated stage IIIb/ IV NSCLC	Phase II: completed	December 2006	The drug was safe & tolerable, with modest single-agent activity
	NCT00514267	- Advanced hormone refractory prostate cancer - Solid Tumors	Phase I/II: completed	May 2007	- Dose limiting toxicity - Safety & efficacy
	NCT00498914 [275]	- Refractory DLBCL	Phase II: terminated for futility	June 2007	- Response rate outcome was not met (when used as single agent)
	NCT01007292 [276]	- Relapsed aggressive B-cell NHL	Phase II: completed	November 2009	In combination with rituximab, the drug was tolerable with durable response
	NCT01009775 [277]	- Stage III/ IV melanoma	Phase II: completed	November 2009	In combination with docetaxel, the drug was well-tolerated but did not achieve 1ry endpoint of improving progression-free survival
	NCT01038804 [278]	- Her-2 negative metastatic breast cancer	Phase II: completed	December 2009	In combination with docetaxel, the drug was well tolerated but the study end-points were not met
	NCT01100931 [279]	-Solid tumors (phase I) - Advanced NSCLC (phase II)	Phase I/II: completed	February 2010	In combination with carboplatin and paclitaxel, the drug was safe but did not show improvement in response rate
EZN-3042 (Survivin mRNA antagonist)	NCT01186328 [280]	- Relapsed ALL in paediatric patients	Phase I: terminated	August 2010	In combination with re-induction chemotherapy, the drug resulted in significant toxicity

Table 4 (continued)

Drug	Identifier/reference	Cancer type	Phase/status	Trial start date	Outcome measure/result
LY2181308 (antisense oligonucleotide)	NCT00620321 [281]	- Relapsed/ refractory AML	Phase II: completed	March 2008	In combination with idarubicin and cytarabine, the drug exhibited favourable safety profile, with modest clinical benefit
	NCT00642018 [282]	- Castration resistant prostate cancer	Phase II: completed	March 2008	In combination with docetaxel/ prednisone, the drug was safe but did not achieve significant clinical benefit
	NCT01107444 [257]	- Stage IIIb/ IV NSCLC	Phase II: completed	May 2010	In combination with docetaxel, the drug was safe but anti-tumor activity was not improved

NSCLC Non-small cell lung cancer, *DLBCL* diffuse large B-cell lymphoma, *NHL* non-Hodgkin lymphoma, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia

inhibiting its activation, has shown activity in osteosarcoma [267], rhabdomyosarcoma [268], prostate [269], and pancreatic cancers [270]. Another small molecule inhibitor, namely FL 118, has the potential of inhibiting Survivin, XIAP and cIAP2. It has been proven to be more effective than standard chemotherapy in human tumor xenograft models [271]. Clinical trials evaluating these drugs are demonstrated in Table 4. More recently, Survivin gene therapy is being investigated as an alternative method of its targeting. A substitution mutation in Survivin, for example Thr34 to Ala, prevents its phosphorylation and the mutant form acts as a competitive antagonist of the wild form [272].

Caspases

Several drugs have been developed to synthetically activate caspases. For example, Apoptin is a caspase-inducing agent which was initially derived from chicken anaemia virus [283]. It is characterized by selective induction of apoptosis in malignant, but not normal cells, owing to its differential cellular localization. The nuclear aggregation of Apoptin, or its truncated variant, in tumor cells promotes its pro-apoptotic function and tumor cytotoxicity, whereas its cytoplasmic localization in normal cells leads to its degradation [284]. Small molecule caspase activators are peptides which contain the arginin-glycine-aspartate motif. They possess a pro-apoptotic activity by directly inducing auto-activation of procaspase 3. They have also been demonstrated to decrease the activation threshold of caspases, contributing to an increase in drug sensitivity of cancer cells [285]. In addition, caspase gene therapy has been investigated in several studies. For instance, human caspase-3 gene therapy was used with etoposide in an AH130 liver tumor model and was observed to induce extensive apoptosis and tumor regression [286]. Gene transfer of constitutively active caspse-3 into HuH7 human hepatoma cells selectively induced apoptosis in these cells [286]. Also, a recombinant adenovirus carrying immunocaspase-3 has been indicated to exert anticancer effects in hepatocellular carcinoma, both in vitro and in vivo [287].

Conclusion

Inhibitors of apoptosis and their antagonists, along with caspases, are complex key players in apoptosis regulation. Over expression of various IAP family members has been repeatedly documented in solid and hematological malignancies. They are culprits in mediating hallmarks of carcinogenesis, as evasion of apoptosis and sustained proliferation. This heralds their use as therapeutic targets in cancer treatment through different approaches. The promising preclinical data existing to date support the notion that IAPs can be

effectively used in combination with standard anti-cancer therapy yielding favourable outcome. However, this mandates further extensive research to validate these data on clinical grounds.

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Compliance with ethical standards

Conflict of interest Mervat S. Mohamed has received a research Grant S – 1438-0013 from University of Tabuk, Kingdom of Saudi Arabia. Other authors declare that they have no conflict of interest.

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