

# Targeting Inhibitor of Apoptosis Proteins (IAPs) for Diagnosis and Treatment of Human Diseases

Simone Fulda\* and Klaus-Michael Debatin

University Children's Hospital, Eythstr.24, 89075 Ulm, Germany

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**Abstract:** Since cell death by apoptosis plays a key role in the regulation of tissue homeostasis, any defect in this intrinsic death program may result in tumor formation. "Inhibitor of apoptosis proteins" (IAPs) block apoptosis at the core of the apoptotic machinery by inhibiting effector caspases. Aberrant expression and/or function of IAPs have been implied to be involved in the pathogenesis and progression of various human diseases including cancer, autoimmune disorders or neurodegeneration. Recent insights into the regulation of IAPs have provided the basis for various exciting discoveries aimed at modulating expression or dysfunction of IAPs. Thus, targeting IAPs, e.g. by antisense approaches, RNA interference or small molecules, may prove to be a novel strategy for the diagnosis and treatment of human diseases.

**Keywords:** Apoptosis, cancer, IAP, Smac, survivin, caspases.

## 1. INTRODUCTION

Tissue homeostasis critically depends on the balance between proliferation and cell death [1]. Programmed cell death or apoptosis is a distinct, intrinsic cell death program that occurs in various physiological and pathological situations and which is highly conserved throughout evolution [2]. Too much apoptosis may lead to tissue destruction, e.g. in autoimmune disorders, neurodegenerative diseases or AIDS. Vice versa, too little apoptosis is involved in tumor formation [3]. In addition, cancer treatment response is coupled to apoptosis induction, since killing of cancer cells by most cytotoxic strategies currently used in clinical oncology, for example chemotherapy, has been shown to depend on induction of apoptosis in target cells [4,5]. Accordingly, defects in apoptosis programs may confer resistance to cytotoxic therapies [5]. "Inhibitor of apoptosis proteins" (IAPs) are expressed at high levels in many human cancers, which has been associated with treatment resistance and dismal prognosis [6]. Since IAPs block apoptosis at the core of the apoptotic machinery by inhibiting activation of caspases, therapeutic targeting of IAPs has attracted considerable attention in recent years. Accordingly, a variety of inventions to detect and modulate IAP expression and function for diagnostic and/or therapeutic purposes have been claimed. Since unbalanced activation or inactivation of apoptosis has been linked to various human disorders, these novel diagnostic devices and experimental therapeutics may prove to be valuable tools for the treatment of human diseases.

## 2. APOPTOSIS SIGNALING PATHWAYS

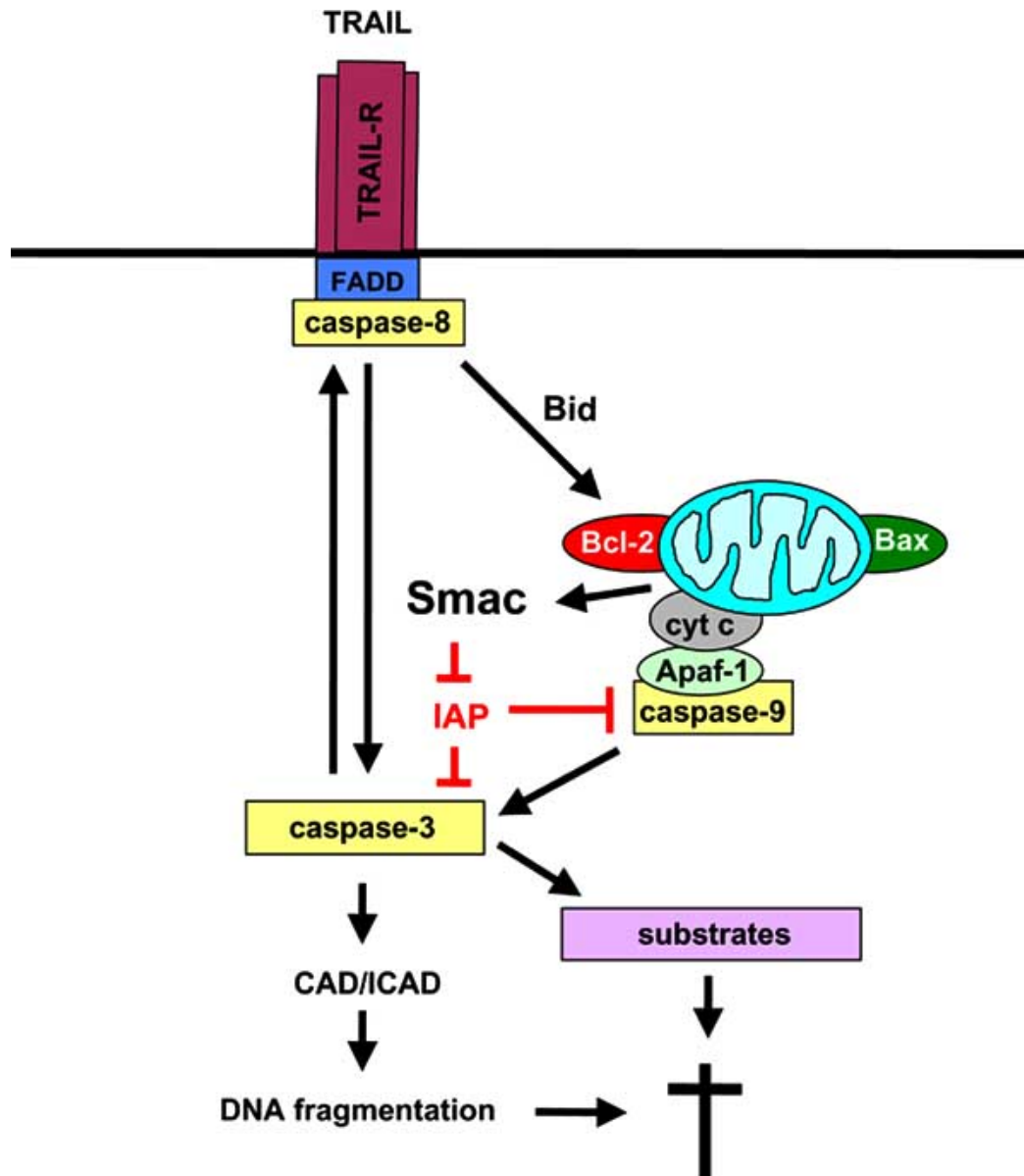
Under many circumstances, activation of apoptosis pathways eventually leads to activation of caspases. Caspases are cysteine proteases that act as common death

effector molecules in various forms of cell death throughout evolution [7]. Caspases are synthesized as inactive proenzymes, which upon activation cleave various substrates in the cytoplasm or nucleus leading to many of the morphologic features of apoptotic cell death [7]. For example, polynucleosomal DNA fragmentation, one of the morphological hallmarks of apoptosis, involves caspase-mediated activation of an endonuclease that cleaves DNA into the characteristic oligomeric fragments [8]. Loss of cell shape is the result of proteolytic degradation of cytoskeletal proteins, while cleavage of nuclear lamin results in shrinkage of the nucleus [7].

Activation of caspases can be initiated at different sites, e.g. at the plasma membrane upon ligation of death receptors (receptor pathway) or at the mitochondria (mitochondrial pathway) (Fig. 1) [2]. Ligation of death receptors of the tumor necrosis factor (TNF) receptor superfamily such as CD95 (APO-1/Fas) or TRAIL receptors by their cognate ligands or agonistic antibodies results in activation of the initiator caspase-8 which can propagate the apoptosis signal by direct cleavage of downstream effector caspases such as caspase-3 [9]. The mitochondrial pathway is initiated by the release of apoptogenic factors such as cytochrome c, apoptosis inducing factor (AIF), Smac/DIABLO or Omi/HtrA2 from the mitochondrial intermembrane space [10]. The release of cytochrome c into the cytosol results in caspase-3 activation through formation of the cytochrome c/Apaf-1/caspase-9-containing apoptosome complex. Smac or Omi promote caspase activation through neutralizing the inhibitory effects of IAPs on activation of effector caspases [10]. In addition, apoptosis inducing factor (AIF) has been described to mediate caspase-independent death and large scale DNA fragmentation after release from mitochondria [11].

Links between the receptor and the mitochondrial pathway exist at different levels. Upon death receptor triggering activation of caspase-8 may result in cleavage of Bid, a Bcl-2 family protein with a BH3 domain only [12]. Upon cleavage, Bid translocates to mitochondria to release

\*Address correspondence to this author at the University Children's Hospital, Eythstr.24, D-89075 Ulm, Germany; Tel: +49-731 5002 5980; Fax: +49-731 5002 6765; E-mail: simone.fulda@medizin.uni-ulm.de



**Fig. (1). Apoptosis pathways.**

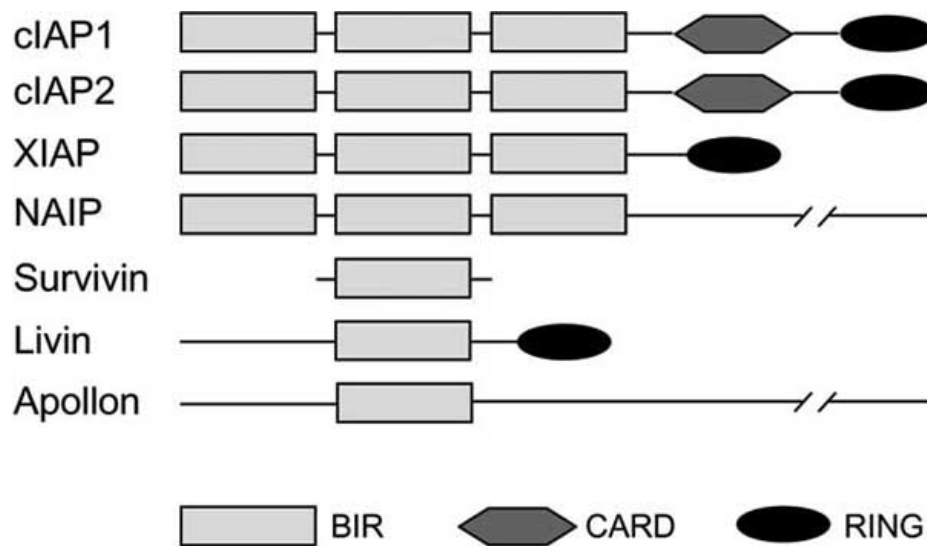
Apoptosis pathways can be initiated by ligation of death receptors such as TRAIL receptors or CD95 followed by receptor trimerization, recruitment of adaptor molecules (FADD) and activation of caspase-8 (receptor pathway). The mitochondrial pathway is initiated by the release of apoptogenic factors such as cytochrome c or Smac from mitochondria in the cytosol. Apoptosis can be negatively regulated by Bcl-2 or by inhibitor of apoptosis proteins (IAPs). Smac promotes apoptosis by antagonizing IAP-mediated inhibition of caspase-3 and -9. See text for more details.

cytochrome c thereby initiating a mitochondrial amplification loop [12]. In addition, cleavage of caspase-6 downstream of mitochondria may feed back to the receptor pathway by cleaving caspase-8 [13]. Because of the potential detrimental effects on cell survival in case of inappropriate caspase activation, activation of caspases has to be tightly controlled. These anti-apoptotic mechanisms controlling cell death are also involved in conferring drug resistance of cancers [5]. Although caspases are crucial for cell death execution in many systems, caspase-independent apoptosis as well as nonapoptotic modes of cell death have also been described, for example necrosis, autophagy or paraptosis [14,15].

### 3. INHIBITOR OF APOPTOSIS PROTEINS (IAPs)

#### 3.1. IAPs: Structure and Function

“Inhibitor of apoptosis proteins” (IAPs), a family of endogenous caspase inhibitors, are highly conserved throughout evolution and comprise the human analogues XIAP, cIAP1, cIAP2, survivin, apollon and livin (ML-IAP) [6,16]. The IAP family of proteins contains three conserved structural motifs, the baculoviral IAP repeat (BIR), RING (RING zinc-finger) and the Caspase Activating and Recruitment Domain (CARD) domain (Fig. 2) [16]. Classification as IAP protein requires the 70-80 amino acid long BIR domain, referring to the original discovery of these



**Fig. (2). Schematic diagram of domain structure of human IAP proteins.**

BIR, Baculovirus IAP Repeats; CARD, Caspase Activating and Recruitment Domain; RING, Ring zinc-finger.

proteins in baculoviral genomes [16]. Human IAPs contain from one to three copies of the BIR domain and usually, except survivin, also harbor one or more of the other functional domains [16]. Of the mammalian IAP proteins known to be involved in apoptosis, XIAP has been characterized most extensively [16]. XIAP contains three BIR domains and a C-terminal RING motif [16]. The second and third BIR domains of XIAP are potent inhibitors of caspase-3/-7 and caspase-9, respectively, *via* distinct mechanisms [17]. The linker segment preceding the BIR2 domain binds to the active site of effector caspase-3 or -7, thereby preventing substrate binding and subsequent catalysis [18,19]. XIAP-BIR3 sequesters active caspase-9 in a monomeric state through two separate interaction sites [20,21]. The surface groove on XIAP-BIR3 binds to the IBM on the N-terminus of the small subunit of caspase-9, while a distinct part of XIAP-BIR3 heterodimerizes with an interface of caspase-9, which is required for homodimerization of caspase-9 [20,21].

The second structural motif found within many IAPs, the RING zinc-finger, functions as E3 ubiquitin ligase [16]. For example, the RING domain can mediate ubiquitination and degradation of IAPs, Smac and selected caspases [22]. Moreover, the CARD is found within c-IAP1 and c-IAP2, located between the three N-terminal BIR domains and the C-terminal RING-finger domain [16]. CARD domains are structurally related to death and death effector domains and typically mediate oligomerization with other CARD-containing proteins.

IAPs are negatively regulated by caspase-mediated cleavage, processing by the serine protease Omi/HtrA2 or by proteasomal degradation, for example through RING domain-mediated auto- or heteroubiquitination [16]. In addition, mitochondrial proteins, e.g. Smac/DIABLO or Omi/HtrA2, translocate into the cytosol upon induction of apoptosis and promote apoptosis through binding and antagonizing [10]. Besides mitochondrial proteins, a nuclear

protein, XIAP-associated factor 1 (XAF-1), has been identified to negatively control IAP activity [23].

### 3.2. IAPs in Cancer

IAPs were found to be aberrantly expressed in the majority of human cancers, which has been correlated with tumor progression and resistance to standard cancer regimens [24]. In gene profiling studies, survivin was found to represent the fourth most common transcriptome of the human genome, while survivin was not expressed in normal adult tissues indicating that survivin may contribute to the malignant phenotype of cancer cells [25]. The cIAP2 gene is affected by the t(11;18)(q21;q21) translocation, which occurs in 50% of mucosa-associated lymphoid tissue (MALT) lymphoma [26].

In a number of retrospective trials, expression of IAPs in tumor samples has been correlated to clinical parameters. For example, high survivin expression predicted poor prognosis in a variety of human cancers [27-33]. Furthermore, AML patients with lower levels of XIAP protein were found to have significantly longer survival [34]. Unexpectedly however, nuclear survivin expression was recently reported to be a significant independent prognostic indicator of favourable outcome in invasive primary breast carcinoma [35], indicating that the subcellular localization of apoptosis regulators has also to be taken into account. Thus, the prognostic significance of IAPs appears to be much more complex than a simple correlation between high IAP expression and poor prognosis. Inhibition of apoptosis by IAPs in response to cytotoxic therapy, e.g. chemotherapy, treatment with TRAIL or after -irradiation has been suggested by several experimental studies [36-42].

## 4. TARGETING IAPs

### 4.1. IAP Antisense and RNA Interference

Since IAPs are expressed at high levels in many human cancers and have been associated with tumor progression

and treatment resistance, strategies antagonizing IAPs have attracted considerable interest for both diagnostic and therapeutic purposes. For example, antisense oligonucleotides against XIAP were designed, which were claimed as single agents or in combination with chemotherapeutic or chemosensitizing agents (Tab. 1; 74-79). In addition, diagnostic tools for detection of IAPs were disclosed (Tab. 1; 75). Antisense targeting of XIAP has been reported to sensitize various tumor cell types (melanoma, breast, bladder, ovarian or lung carcinoma) to radiation- or chemotherapy-induced cell death [36,38,39,40,43]. Also, XIAP antisense oligonucleotides combined with anticancer drugs showed antitumor activity in a mouse model of lung cancer [37]. Currently, XIAP antisense strategies are being tested in clinical trials. In addition to antisense approaches, short interfering RNA (siRNA) molecules have been invented for inhibiting XIAP gene expression (Tab. 1; 80), which enhanced TRAIL- or anticancer drug-induced apoptosis in breast carcinoma cells [38,42].

#### 4.2. IAP Antagonists

Moreover, peptidic or non-peptidic small molecule IAP antagonists were developed to target aberrant IAP expression (Tab. 1; 81-83). Compounds antagonizing IAP-mediated inhibition of caspases as well as methods for identifying agents that derepress an IAP-inhibited caspase were claimed (Tab. 1; 82). Also disclosed were assays for identifying peptides and peptidomimetics for promoting apoptosis in cells, through a pathway involving the IAPs, as well as IAP-binding peptides and peptidomimetics identified through the use of those assays (Tab. 1; 81). Moreover, the use of IAPs for diagnosis and of IAPs inhibitors for treatment of Hodgkin's lymphomas was claimed (Tab. 1; 83).

#### 4.3. Smac/DIABLO Agonists

Smac (Second mitochondria-derived activator of caspase) and its murine homologue DIABLO (Direct IAP Binding protein with Low PI) are nuclear encoded mitochondrial proteins, which contain a mitochondrial localisation signal, that is proteolytically removed upon mitochondrial import to yield the mature 23 kDa protein [44-46]. This maturation step exposes the IAP binding motif at the N-terminus of Smac [44]. Smac acts as homodimer with the IAP binding motif present in a bivalent configuration [47]. Smac was shown to bind to XIAP, cIAP1, cIAP2, survivin and Apollon in a BIR-dependent way [46]. One Smac dimer binds one XIAP molecule by both IAP-binding motifs, one interacting with BIR2 and the other one with BIR3 [48]. Intriguingly, the same BIR3 groove binds the IAP-binding motif exposed at the N-terminus (Ala-Thr-Pro-Phe) of the small subunit of caspase-9 following its autocatalytic processing after Asp315 allowing Smac to displace caspase-9 from XIAP [20].

For the design of potentially therapeutic molecules to target XIAP, the tetrapeptide binding groove of the BIR3 domain of XIAP, to which either Smac or caspase-9 can bind to, has attracted most attention. Structural analysis has revealed that the four N-terminal amino acids of Smac (AVPI) tether to a hydrophobic surface groove on the BIR3 domain of XIAP with the first Ala residue binding a hydrophobic pocket and making hydrogen bonds with

neighbouring residues on BIR3 [47,49]. Experiments with oligopeptides demonstrated that a free N-terminal alanine residue of Smac was required for binding to the BIR3 groove and that only the first 4-5 amino acids mediated the binding [47]. The IAP-binding motif is highly conserved between the N-terminus of processed Smac and the small subunit of caspase-9 and is also found in Smac homologues in *Drosophila* [20,50]. These studies have provided a clear rationale for the synthesis of small molecules that can mimic the caspase-9 displacing activity of Smac from XIAP BIR3.

Consequently, cell-permeable Smac peptides of variable length containing the IAP-binding motif were designed (Tab. 1; 84-93). To enhance intracellular delivery Smac peptides were linked to a carrier, for example the protein transduction motif of the HIV Tat protein (Tab. 1; 90). Also disclosed were methods of using Smac peptides for diagnostic or therapeutic purposes and for rational drug design (Tab. 1; 87, 92, 93). As native Smac proteins translocate from mitochondria to cytosol during apoptosis, Smac proteins can be used as diagnostic markers for apoptosis during normal or disease stages, e. g. using labeled Smac proteins such as fusion proteins or using detectable Smac-specific binding agents. In addition, since undesirable activation or inactivation of apoptosis has been associated with many human diseases such as cancer, autoimmune disorders or neurodegeneration, the disclosed Smac mimetics provide regulators to promote or inhibit apoptosis in disease states. Smac mimetics proved to be efficacious in potentiating the killing of various cancer cell lines after cytotoxic drug treatment or upon death receptor ligation, while sparing normal cells [51-54]. Also, Smac peptides enhanced the antitumor activity of TRAIL in a mouse model of human malignant glioma *in vivo* [51].

#### 4.4. Omi/HtrA2

The mitochondrial serine protease Omi/HtrA2 belongs to the HtrA (high temperature requirement) protein family, which is characterized by a central trypsin-like catalytic domain and one or more C-terminal PDZ (postsynaptic density protein, disc large tumor suppressor and Zo-1 tight junction protein) domains [55-57]. Omi is a nuclear-encoded, 49 kDa protein with an N-terminal mitochondrial localization signal that mediates its translocation into the mitochondrial intermembrane space [55-57]. Omi is processed in the intermembrane space into the 37 kDa mature form, liberating an IAP-binding motif (AVPS in human; AVPA in mouse Omi/HtrA2) at its N-terminus [46]. Although recombinant Omi can catalyze its own maturation *in vitro*, the protease responsible for its maturation in cells remains unknown [46].

Omi plays an essential role in regulating mitochondrial homeostasis requiring its proteolytic activity, although the molecular targets and interaction partners of Omi in the mitochondrion have not yet been defined [10]. Once Omi is released from mitochondria into the cytosol it promotes cell death in a caspase-dependent way by antagonizing IAPs, and in a caspase-independent way as a protease [10]. Similar to Smac, Omi blocks IAPs through its N-terminal IAP-binding motif, presented in a trimeric configuration [58]. Accordingly, Omi polypeptides or derivatives that disrupt

Table 1

	Inventor	Patent number	Year	Title	Reference
<b>IAP antisense</b>	Bennett	WO0118024	2001	Antisense modulation of X-linked inhibitor of apoptosis expression	[74]
	Korneluk	US2002120121	2002	Detection and modulation of IAPs and NAIP for the diagnosis and treatment of proliferative disease	[75]
	Korneluk	US2004127694	2004	Antisense IAP oligonucleotides and uses thereof	[76]
	Dobie	WO2004047741	2004	Modulation of IAP-like expression	[77]
	LaCasse	WO2005042558	2005	IAP nucleobase oligomers and oligomeric complexes and uses thereof	[78]
	LaCasse	WO2005042030	2005	Treatment of proliferative diseases using an antisense IAP oligomer and chemotherapeutic agent	[79]
<b>XIAP siRNA</b>	McSwiggen	WO2005014811	2005	RNA interference mediated inhibition of XIAP gene expression using short interfering nucleic acid (siNA)	[80]
<b>IAP antagonists</b>	McLendon	WO02096930	2002	IAP binding peptides and assays for identifying compounds that bind IAP	[81]
	Reed	WO03045974	2003	Methods and compositions for derepression of IAP-inhibited caspase	[82]
	Krönke	WO2004017991	2004	Use of IAP for the diagnosis and of IAP-inhibitors for the treatment of Hodgkin's Lymphomas	[83]
<b>Smac agonists</b>	Wang	WO0149719	2000	Activators of caspases	[84]
	Wang	WO0216402	2002	Apoptotic compounds	[85]
	Fesik	WO0230959	2002	Peptides derived from Smac (DIABLO) and methods of use therefor	[86]
	Shi	WO0226775	2002	Compositions and methods for regulating apoptosis	[87]
	Alnemri	WO0216418	2002	An IAP binding peptide or polypeptide and methods of using the same	[88]
	Srinivasula	WO03010184	2003	A conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO for mediating apoptosis	[89]
	Debatin	EPI354952	2003	Smac-peptides as therapeutics against cancer and autoimmune diseases	[90]
	Sharma	WO2004005248	2004	Peptide inhibitors of Smac protein binding to inhibitor of apoptosis proteins (IAP)	[91]
	McLendon	WO2004072105	2004	IAP-binding cargo molecules and peptidomimetics for use in diagnostics and therapeutic methods	[92]
	McLendon	WO2004007529	2004	IAP binding compounds	[93]
<b>Omi agonists</b>	Alnemri	WO03006680	2003	Omi and domains thereof that disrupt IAP-caspase interaction	[94]
	Stowers Inst.	WO2004072241	2004	Compositions and methods for cleaving IAP	[95]
<b>XAF-1</b>	Korneluk	US2003215824	2003	XAF genes and polypeptides: methods and reagents for modulating	[96]
<b>Livin antagonists</b>	Butz	WO2004091388	2004	Livin-specific siRNAs for the treatment of therapy-resistant tumors	[97]
	Bennett	US2004005565	2004	Antisense modulation of livin expression	[98]
	Ben Yehuda	WO2004106371	2004	Livin-derived peptides, compositions and uses thereof	[99]
<b>Survivin</b>	Altieri	WO9950440	1999	A method for selectively modulating the interactions between survivin and tubulin	[100]
	Leason	WO0003693	2000	Survivin, and peptides thereof, as an anti-cancer vaccine	[101]
	Bennett	WO0157059	2001	Antisense modulation of survivin expression	[102]

(Table 1) Contd....

	Inventor	Patent number	Year	Title	Reference
	Tanaka	WO0233071	2002	Survivin-like polypeptides and DNAs thereof	[103]
	Altieri	US2003143232	2003	Methods for selectively modulating survivin apoptosis pathways	[104]
	Altieri	WO2004112570	2004	Detection of survivin in the biological fluids of cancer patients	[105]
	Altieri	MXPA02006167	2004	Survivin promotion of angiogenesis	[106]
	Hansen	WO2004069991	2004	Oligomeric compounds for the modulation of survivin expression	[107]
	Meye	WO2004070034	2004	Oligonucleotides directed against a survivin gene and use thereof	[108]
	Straten	WO2004067023	2004	Survivin-derived peptides and use thereof	[109]
	Bhat	WO2005002507	2005	Modulation of survivin expression	[110]

IAP-caspase interaction were claimed to modulate apoptosis, to identify modulators of apoptosis and also for therapeutic uses (Table 1; 94). Furthermore, serine protease activity at position 306 of Omi has been reported to trigger degradation of several IAPs including XIAP, cIAP1, cIAP2 and Apollon [59-61]. Consequently, Omi family polypeptides or polynucleotide sequences comprising Omi wild type or mutant versions were disclosed to promote cleavage of IAPs (Table 1; 95).

#### 4.5. XAF1

In addition to the control of IAP activity by the mitochondrial proteins Smac and Omi, a nuclear proteins, XAF1, has also been identified, which antagonizes XIAP [23]. In contrast to Smac or Omi, XAF1 does not need to be processed and appears to be constitutively able to interact with and inhibit XIAP, although the interacting domains of XIAP and XAF1 have not yet been identified [23]. Significantly, XAF1 expression is low or missing in a variety of human cancers [62,63]. The *XAF1* gene resides on chromosome 17p13.2, a region frequently targeted by mutation or loss of heterozygosity in human cancers [64], suggesting that *XAF1* acts as tumour suppressor gene. In addition to mutational inactivation, epigenetic silencing by CpG-island promoter hypermethylation of the *XAF1* gene was recently detected in advanced human gastric adenocarcinomas [63]. XAF1 nucleic acid sequences, XAF1 polypeptides and anti-XAF1 antibodies for detection and modulation of apoptosis have been patented (Table 1; 96).

#### 4.6. Livin

Livin/ML-IAP/KIAP is a IAP family member, which is expressed at high levels preferentially in melanoma [65,66]. Livin contains a single BIR domain at the N-terminus as well as a C-terminal RING domain [65,66]. Livin-specific siRNAs were developed for downregulation of livin and for sensitization of resistant tumors to apoptosis (Table 1; 97). Also, antisense compounds, particularly antisense oligonucleotides, were developed for modulation of livin expression and for treatment of diseases associated with aberrant expression of livin (Table 1; 98). Another invention

relates to livin-derived peptides with proapoptotic activity (Table 1; 99).

#### 4.7. Survivin

Survivin is the smallest mammalian member of the IAP gene family, containing a single BIR domain [67]. The *survivin* gene located on chromosome 17q25 in humans gives rise to four alternatively spliced survivin transcripts, survivin-2B, survivin-2 or survivin- Ex-3 in addition to wild-type survivin [67]. A unique property of survivin is a cell-cycle-dependent expression at mitosis, which is largely controlled at the level of gene transcription [67]. In addition, survivin protein stability is controlled by phosphorylation of survivin on Thr34 by p34cdc2-cyclin B1 during mitosis [68,69]. The role of survivin in regulation of apoptosis and proliferation is more complex compared to other IAP family proteins, since in addition to regulation of apoptosis, survivin is involved in control of mitosis [70]. Survivin functions at the interface between cell proliferation and cell death, intercalated in protection against mitochondrial cell death and regulating various aspects of cell division [67]. Recent evidence suggest that direct interaction between survivin and Smac/DIABLO is essential for the anti-apoptotic activity of survivin rather than binding to and inhibition of effector caspases [71]. Also, the antiapoptotic function of survivin has been related to inhibition of mitochondrial and AIF-dependent apoptotic pathways, protecting against both caspase-dependent and caspase-independent apoptosis [72]. Importantly, survivin appears essential for tumor cell maintenance and molecular or pharmacologic interference with the survivin pathway have been associated with tumor cell death and anticancer activity, alone or in combination with standard cytotoxic agents in several preclinical models [67,72,73].

Various tools for modulation of survivin expression were developed, e.g. antisense oligonucleotides or RNA interference tools, as well as methods of using these compounds for modulation of survivin expression and for the treatment of diseases associated with overexpression of survivin (Table 1; 100-110). Another invention provides methods and compositions for identifying agents that modulate the phosphorylation of survivin, the interaction between survivin

and the p34cdc2 cyclin B1 kinase complex, and the interaction between survivin and caspase-9 in order to modulate survivin-regulated apoptosis (Table 1; 104). Also for modulation of survivin-controlled apoptosis, methods and compositions for identifying compounds which target the interaction between survivin and polymerized tubulin or the mitotic spindles were claimed (Table 1; 100). Also disclosed were survivin-derived peptides or expression systems capable of expressing survivin antigen for vaccines capable of eliciting an antitumor response for a wide spectrum of cancers (Table 1; 101, 103, 109). In addition, a method for diagnosing cancer or predicting cancer recurrence by detecting the presence of survivin in biological fluids of a patient was claimed (Table 1; 105). Moreover, methods for promoting or inhibiting angiogenesis using agents that increase or decrease the activity and/or expression of survivin were disclosed (Table 1; 106).

## 5. CURRENT & FUTURE DEVELOPMENTS

In recent years a variety of approaches have been developed to exploit aberrant expression of IAPs for detection and/or treatment of human diseases. Numerous preclinical studies have provided convincing evidence that antagonizing IAPs, e.g. by antisense oligonucleotides, RNA interference or small molecule compounds, is a promising experimental approach for the treatment of cancer. The challenge now resides in addressing the question how these strategies can be used as diagnostic or therapeutic tools in clinical management of cancer, autoimmune disorders or neurodegenerative diseases.

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## ABBREVIATIONS

AIF	=	Apoptosis inducing factor
Apaf-1	=	Apoptotic protease activating factor-1
Bak	=	Bcl-2-Antagonist/Killer
Bax	=	Bcl-2-Associated X protein
Bcl	=	B-Cell lymphoma
BH	=	Bcl-2 homology domain
Bid	=	BH3 interacting domain death agonist
BIR	=	Baculovirus IAP repeats
CARD	=	Caspase activating and recruitment domain
caspase	=	CysteinyI aspartate specific protease
CIAP	=	Cellular inhibitor of apoptosis
DIABLO	=	Direct IAP binding protein with Low PI
HtrA	=	High temperature requirement protein A

IAP	=	Inhibitor of apoptosis protein
ML-IAP	=	melanoma-IAP
PARP	=	Poly (ADP-ribose) polymerase
PDZ	=	postsynaptic density protein, disc large tumor suppressor and Zo-1 tight junction protein
RING	=	Ring zinc-finger
Smac	=	Second mitochondria-derived activator of caspase
TNF	=	Tumor necrosis factor
TRAIL	=	TNF-related apoptosis-inducing ligand
XIAP	=	X-linked inhibitor of apoptosis protein

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