Review

Clinical Cancer Research

Therapeutic Small Molecules Target Inhibitor of Apoptosis Proteins in Cancers with Deregulation of Extrinsic and Intrinsic Cell Death Pathways

Adeeb Derakhshan, Zhong Chen, and Carter Van Waes

Abstract

The Cancer Genome Atlas (TCGA) has unveiled genomic deregulation of various components of the extrinsic and intrinsic apoptotic pathways in different types of cancers. Such alterations are particularly common in head and neck squamous cell carcinomas (HNSCC), which frequently display amplification and overexpression of the Fas-associated via death domain (FADD) and inhibitor of apoptosis proteins (IAP) that complex with members of the TNF receptor family. Second mitochondria-derived activator of caspases (SMAC) mimetics, modeled after the endogenous IAP antagonist SMAC, and IAP inhibitors represent important classes of novel small molecules currently in phase I/II clinical trials. Here we review the physiologic roles of IAPs, FADD, and other components involved in cell death, cell survival, and NF-κB signaling pathways in cancers, including HNSCC. We summarize the results of targeting IAPs in preclinical models of HNSCC using SMAC mimetics. Synergistic activity of SMAC mimetics together with death agonists TNFα or TRAIL occurred *in vitro*, whereas their antitumor effects were augmented when combined with radiation and chemotherapeutic agents that induce TNFα *in vivo*. In addition, clinical trials testing SMAC mimetics as single agents or together with chemo- or radiation therapies in patients with HNSCC and solid tumors are summarized. As we achieve a deeper understanding of the genomic alterations and molecular mechanisms underlying deregulated death and survival pathways in different cancers, the role of SMAC mimetics and IAP inhibitors in cancer treatment will be elucidated. Such developments could enhance precision therapeutics and improve outcomes for cancer patients. *Clin Cancer Res; 23(6); 1379–87. ©2016 AACR.*

Introduction

Over the past decade, The Cancer Genome Atlas (TCGA) Network groups have described the genomic landscape for over 30 different cancer types (1). A number of these malignancies have a subset of cases harboring genomic alterations in components of intrinsic or extrinsic cell death pathways, including amplification and overexpression of the Fas-associated via death domain (FADD) and inhibitor of apoptosis proteins (IAP), as well as mutations in caspase-encoding genes (2–4). These molecules complex with members of the TNF and TNF-related apoptosis-inducing ligand (TRAIL) receptor families, critical in cell death and survival pathway signaling. Head and neck squamous cell carcinomas (HNSCC) are among the cancers with the highest frequency of deregulation in genes encoding for cell death pathway constituents, with nearly half of all cases exhibiting such genomic alterations (3). Many of these alterations occur in genes encoding mediators of apoptosis or necroptosis, potentially enabling the development of resistance to cell death, an important hallmark of cancer (5).

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doi: 10.1158/1078-0432.CCR-16-2172

Two primary death signaling cascades, the extrinsic and intrinsic pathways, have been extensively characterized (Fig. 1; ref. 6). The downstream effector molecules for both pathways that mediate apoptosis include caspases, a group of cysteine proteases that cleave a variety of cytoplasmic and nuclear substrates (7). The extrinsic, or death-receptor mediated, pathway is triggered by binding of death ligands such as Fas ligand (FasL), TNFα, or TRAIL to their corresponding receptors (e.g., Fas, TNFR1, TRAILR1/DR4, and TRAIL2/DR5; ref. 8). This leads to the recruitment of the cytoplasmic adaptor protein FADD to the cell surface. FADD contains death domains that can bridge the death receptor to procaspase-8, forming the death-inducing signaling complex (DISC; ref. 9). This results in activation of caspase-8 and -3, leading to apoptosis (10). Alternatively, the extrinsic pathway may also induce FADD, RIP kinases, and MLKL to mediate necroptotic cell death (Fig. 1 for details; ref. 11).

Activation of the intrinsic, or mitochondrial, pathway is induced by cytogenetic insults such as radiation or chemotherapy (12). Such cellular stress causes mitochondrial permeabilization and release of apoptogenic proteins, including cytochrome *c* and second mitochondria-derived activator of caspases (SMAC), from the mitochondria into the cytosol. Cytosolic cytochrome *c* interacts with apoptotic protease activating factor 1 (APAF1), creating a multimeric complex termed the apoptosome. The apoptosome recruits, cleaves, and activates caspase-9 and -3. SMAC promotes apoptosis by binding to and degrading multiple IAPs, including cellular-IAP1 (c-IAP1), cellular-IAP2 (c-IAP2), and X-linked IAP (XIAP; ref. 13). SMAC mimetics are recently engineered analogues of SMAC that work in a similar manner to induce cell death (Fig. 1).

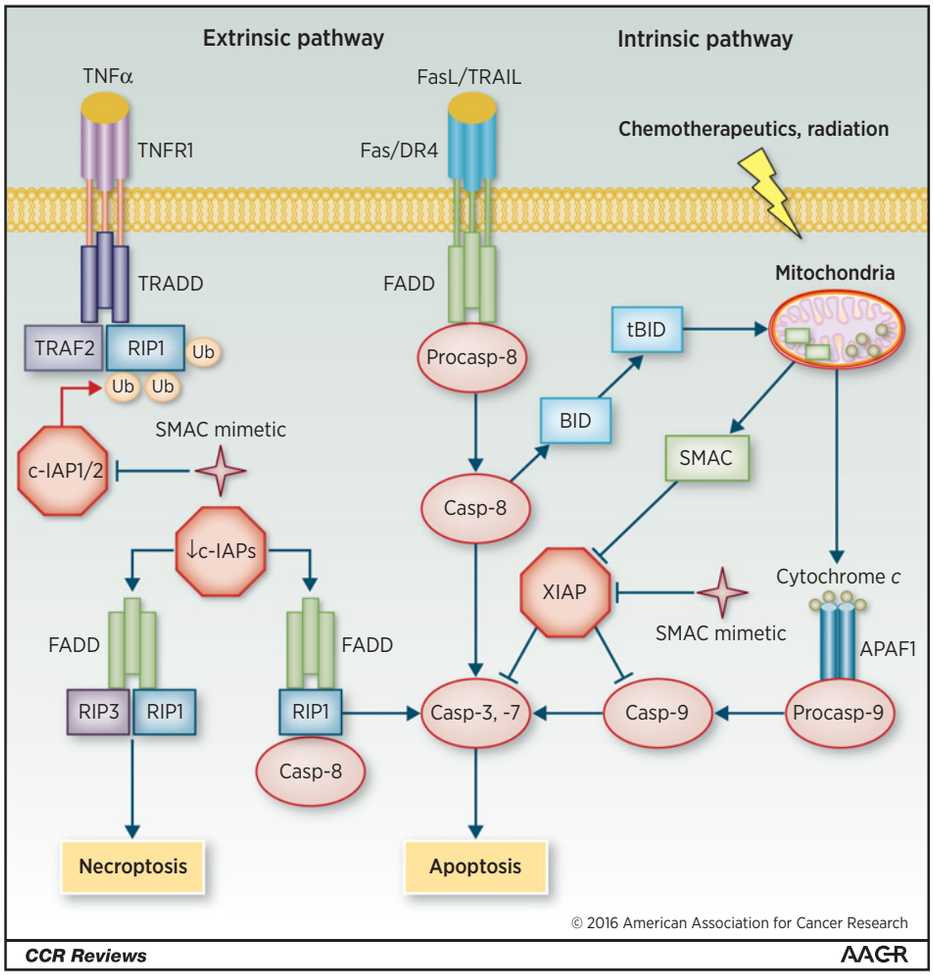

Figure 1.
Overview of cell death pathways. The extrinsic pathway of apoptosis is activated upon ligation of a death receptor (DR) such as TNFR1, Fas, or DR4 by their respective cognate ligands TNFα, FasL, or TRAIL. This interaction causes the trimerization of adaptor proteins such as TNF receptor 1–associated via death domain (TRADD) and FADD and their subsequent recruitment to the cell surface from the cytoplasm, which in turn results in activation of caspase-8 from the zymogen procaspase-8. Caspase-8 catalyzes the activation of downstream executioner caspases such as caspase-3 and -7, leading to apoptosis. Stimulation of the TNFR1 receptor in the absence of cellular IAPs (c-IAP) prevents the ubiquitination of receptor-interacting protein 1 (RIP1), thereby allowing RIP1 to associate with FADD and caspase-8 to form a proapoptotic cytoplasmic complex. Alternatively, non-ubiquitinated RIP1 can interact with FADD and RIP3 to induce necroptosis via caspase-independent mechanisms. As c-IAPs ubiquitination of RIP1 prevents the formation of these death-inducing complexes, SMAC mimetics can be used to drive cell death by causing degradation of c-IAPs and, therefore, preventing the ubiquitination of RIP1. The intrinsic pathway of apoptosis can be triggered by cytotoxic insults and involves release of mitochondrial contents such as cytochrome *c* and SMAC into the cytosol. Crosstalk from the extrinsic pathway via the caspase-8 induced conversion of BH3-interacting death domain agonist (BID) to truncated BID (tBID) can also cause mitochondrial permeabilization. Although cytochrome *c* acts to activate caspase-9, SMAC binds to and degrades multiple IAPs. This includes X-linked IAP (XIAP), a direct antagonist of caspase-3, -7, and -9.

The Roles of IAPs in Cell Death, Cell Survival, and Interaction with the NF-κB Pathway

The IAPs were initially discovered in baculoviruses in 1993 (14). IAPs are defined by the presence of one to three signature Baculoviral IAP Repeat (BIR) domains, a 70- to 80-amino acid zinc-binding region that mediates protein–protein interactions (15). In addition, members of the IAP family with clearly delineated roles in apoptosis possess a Really Interesting New Gene (RING) domain at their C terminus, which provides them with E3 ubiquitin ligase activity (16). The human IAP family is comprised of eight members, of which c-IAP1, c-IAP2, and XIAP have been found to inhibit caspase-mediated apoptosis and RIP-mediated necroptosis (17).

c-IAP1 and c-IAP2 exert their inhibitory effects on cell death indirectly via ubiquitination through their RING domains (18). By functioning as an E3 ubiquitin ligase, c-IAP1 promotes the ubiquitination of caspase-3 and -7 (19). XIAP is the only member of the IAP family capable of directly binding caspases and inhibiting their function (20). By blocking the functions of the initiator caspase-9 and executioner caspases-3 and -7, XIAP

can halt both the intrinsic and extrinsic pathways of apoptosis. Structural studies have revealed that the BIR3 domain of XIAP binds to procaspase-9, preventing the homodimerization necessary for its activation (21). Inhibition of caspase-3 is achieved via interaction between the BIR2 domain of XIAP and the active site of the caspase (22), whereas caspase-7 blockade occurs through its binding to the linker region between XIAP's BIR1 and BIR2 domains (23).

The critical role that c-IAPs play in regulating apoptosis is highlighted by the dual signaling roles of the TNFR1 receptor (24). When c-IAPs are present, ubiquitination of RIP1 takes place, along with subsequent recruitment of the IKK complex to the activated TNFR1 receptor (25, 26). This results in activation of the canonical NF-κB pathway, promoting cell survival. In contrast, the absence of c-IAPs results in TNFR1 acting as an apoptosis-inducing death receptor; when c-IAPs are depleted, non-ubiquitinated RIP1 interacts with FADD and caspase-8 to create a cytosolic, apoptosis-mediating complex upon its dissociation from the activated TNFR1 receptor (27, 28). Alternately, when caspase-8 activity is reduced or absent, this complex can interact with RIP3 to activate the caspase-independent cell death pathway of necroptosis via the mixed lineage kinase domain-like (MLKL) protein intermediary (Fig. 2; refs. 29, 30).

In addition to attenuating cell death pathway activation, c-IAP family members can promote ubiquitination of proteins that regulate signal activation of members of the NF-κB family of transcription factors and prosurvival target genes. The NF-κB family is comprised of five proteins which form homodimers and heterodimers that promote the expression of several target genes that are inhibitors of cell death pathways (31). Activation of NF-κB target genes can be achieved via the canonical (classical) and noncanonical (alternative) signaling pathways (see Fig. 2 for details).

Although c-IAPs upregulate canonical NF-κB signaling through their targets of ubiquitination, they dampen noncanonical NF-κB pathway signaling through their effects promoting the ubiquitination and degradation of NF-κB–inducing kinase (NIK; ref. 32). At baseline, NIK levels are constitutively low due to ubiquitination and proteasomal degradation of the kinase by a cytoplasmic complex consisting of c-IAP1, c-IAP2, TRAF2, and TRAF3 (33). Competitive binding of NIK by certain ligand-bound TNF receptor superfamily members, including TNF-related weak inducer of apoptosis (TWEAK), CD40, and lymphotoxin-β receptor (34), prevents TRAF–cIAP degradation, thereby allowing for NIK accumulation (35). NIK induces IKKα phosphorylation of the inactive NF-κB subunit p100, which is processed into the p52 subunit and translocates with transcriptionally active RELB to the nucleus (36). This results in upregulation of NF-κB target genes, which can include TNFα, an activator of the canonical NF-κB pathway (Fig. 2; ref. 37).

Mechanism of Action of SMAC Mimetics

Several endogenous antagonists of IAP proteins have been characterized (38–40), of which SMAC has been the most thoroughly investigated (41). Upon its release from the mitochondria, SMAC is cleaved and dimerized (42). The N-terminal of the protein contains a four-amino acid sequence (Ala-Val-Pro-Ile) that allows SMAC to bind to the BIR3 and BIR2 domains of IAPs (43). This four-residue peptide formed the basis for the design of small peptidomimetics (i.e., SMAC mimetics) that duplicate the binding activity of SMAC protein to c-IAP1, c-IAP2, and XIAP. SMAC mimetics' interaction with c-IAP1 and c-IAP2 causes these IAP proteins to undergo conformational changes. These alterations stimulate the endogenous E3 ubiquitin ligase activity of c-IAP1 and c-IAP2, resulting in autoubiquitination and proteasomal degradation (44). In addition, SMAC mimetic targeting of XIAP prevents it from binding to caspase-3, -7, or -9, thereby allowing caspase activation and apoptotic cell death to occur (45). Although endogenous SMAC effectively targets c-IAP1, c-IAP2, and XIAP for degradation (46), SMAC mimetics or non-SMAC IAP antagonists can be engineered to have more specificity toward certain IAPs over others (47).

Single-agent SMAC mimetic therapy induces cell death predominantly through mechanisms regulated by the TNF family of death receptors (48, 49). This is notable because TNFα is also a target gene of NF-κB (50), whose signaling pathways are affected by the use of SMAC mimetics. c-IAP depletion can result in activation of the noncanonical NF-κB pathway secondary to NIK accumulation (32, 34). This induction of NF-κB by SMAC mimetics leads to an autocrine production of TNFα, which subsequently engages TNF receptors such as TNFR1 (32, 44). In the absence of c-IAPs, activated TNFR1 acts as a death receptor and results in apoptotic activation secondary to an association formed between RIP1, FADD, and caspase-8 (27, 28). The presence of a death agonist, such as TNFα or TRAIL, is critical in ensuring optimal efficacy of SMAC mimetics. SMAC mimetics have also been shown to sensitize tumor cells to apoptotic death in the presence of FasL (51). Indeed, the combination of SMAC mimetics with these death ligands has evinced synergistic activity in numerous investigations (52, 53).

Expression of Intrinsic and Extrinsic Apoptosis Pathway Components in HNSCC

The TCGA Network recently published its analysis characterizing the genomic profile of 279 HNSCC tumor samples (3). Its findings unveiled that HNSCC tumors frequently harbor genomic alterations (i.e., mutation or copy number variation) in cell death pathways, with 44% of human papillomavirus (HPV)–negative cases and 31% of HPV-positive cases exhibiting deregulation of *FADD*, *BIRC2*, *CASP8*, and/or *TRAF3* (3). HPV-negative tumor samples commonly contained co-amplifications of chromosome 11q13, harboring the *FADD* gene, and 11q22, where genes *BIRC2* and *BIRC3*, encoding c-IAP1 and c-IAP2, respectively, reside. In addition to the genes evaluated in the HNSCC TCGA publication, we identified several more components of cell death and NF-κB pathways that displayed significant changes in genetic makeup or mRNA expression (Fig. 3A). Among 279 HNSCC cases analyzed, there were 205 cases (73%) with genetic and/or mRNA expression alterations.

Aberrant genomic copy number variation or mRNA expression of c-IAP1, c-IAP2, or XIAP was seen in 18%, 14%, and 12% of samples, respectively. Significantly, 37% of tumors analyzed demonstrated *FADD* amplification and/or overexpression. Deregulation of TNFR1, RIP1, and mutations of caspase-8 were also seen in a subset of samples. In addition, a minority of cases displayed genetic or expression alterations opposite that which

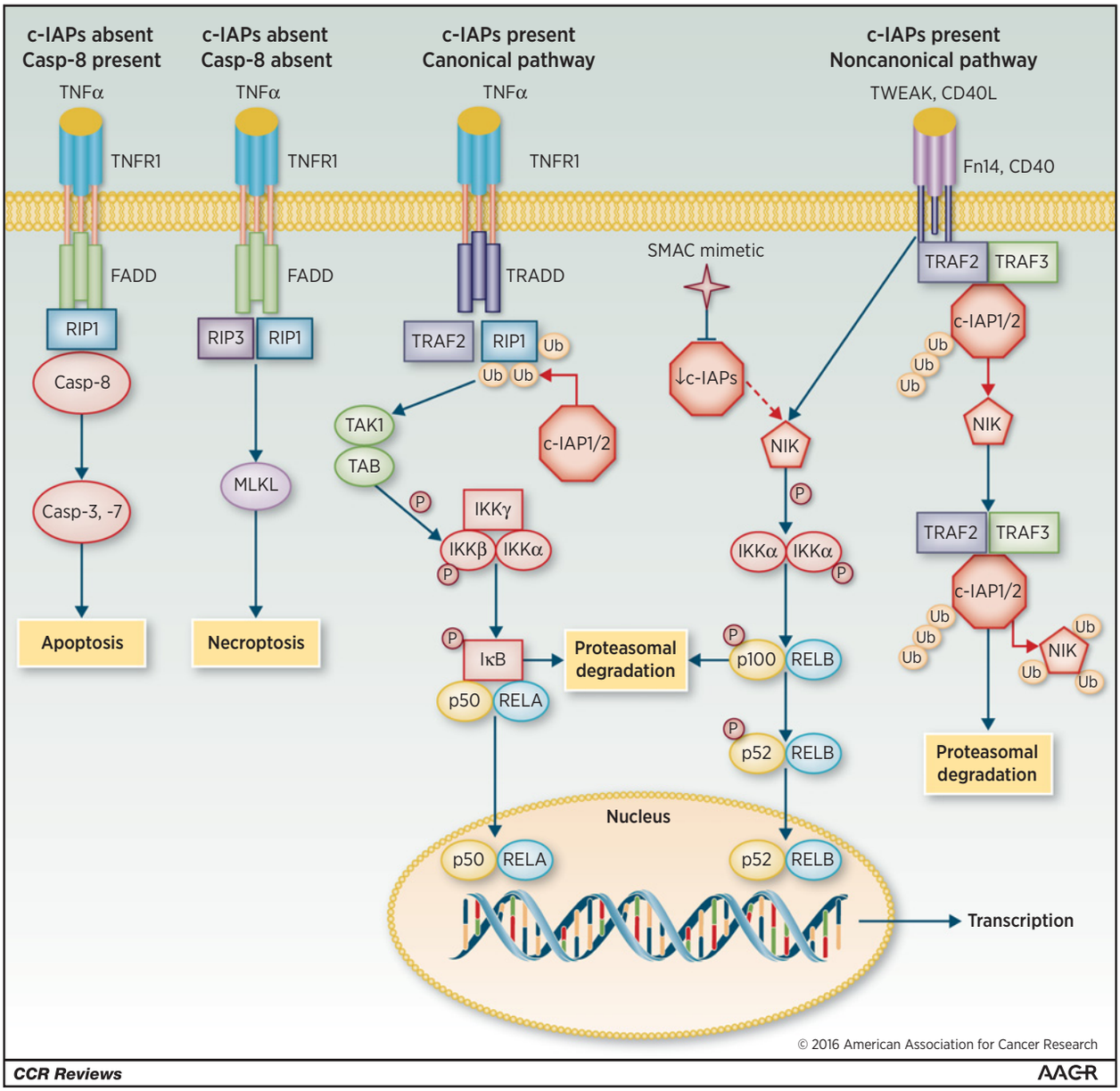

Figure 2.

Role of IAPs in cell death and NF-κB signaling pathways. The absence of c-IAPs results in the activation of cell death pathways. Activation of TNFR1 by its ligand TNFα results in formation of a complex consisting of FADD, RIP1, and caspase-8, which leads to downstream apoptosis. Should caspase-8 be absent, necroptosis is triggered through an FADD, RIP1, and RIP3 intermediary that results in activation of the MLKL protein. c-IAPs also upregulate canonical NF-κB signaling while concurrently downregulating noncanonical NF-κB pathway activation. In canonical NF-κB signaling, binding of TNFR1 by TNFα results in the recruitment of adaptor proteins TNF receptor 1–associated via death domain (TRADD) and TNF receptor-associated factor 2 (TRAF2) to TNFR1. In turn, RIP1 and c-IAP1/2 are recruited to the activated complex. c-IAP ubiquitination of RIP1 leads to the creation of a binding platform for TGFβ-activated kinase 1 (TAK1), TAK1 binding protein (TAB), and the inhibitor of NF-κB (IκB) kinase (IKK) complex. IKKβ is subsequently activated via phosphorylation and itself phosphorylates the inhibitory NF-κB subunit (IκB), leading to its degradation. This frees the NF-κB subunits p50 and RELA and allows their translocation to the nucleus. In the noncanonical NF-κB pathway, c-IAPs work to keep levels of NF-κB–inducing kinase (NIK) constitutively low. Acting as part of a cytoplasmic complex in concordance with TRAF2 and TRAF3, c-IAPs continuously ubiquitinate NIK, marking it for proteasomal degradation. Depletion of c-IAPs through the use of SMAC mimetics allows for a buildup of NIK to occur. This results in NIK-mediated phosphorylation of IKKα, which then phosphorylates the inactive NF-κB subunit p100 and leads to its partial proteasomal degradation. As a result, the active NF-κB subunit p52 is generated and translocates to the nucleus along with RELB to activation gene transcription.

would be expected to promote cell survival (e.g., deep deletion of *BIRC2/3*). The functional mechanisms of such alterations are unknown and require further investigation.

Although FADD serves a critical function in cell death pathways by serving as an adaptor protein (11, 54), it has also been shown to promote cell survival through activation of NF-κB signaling

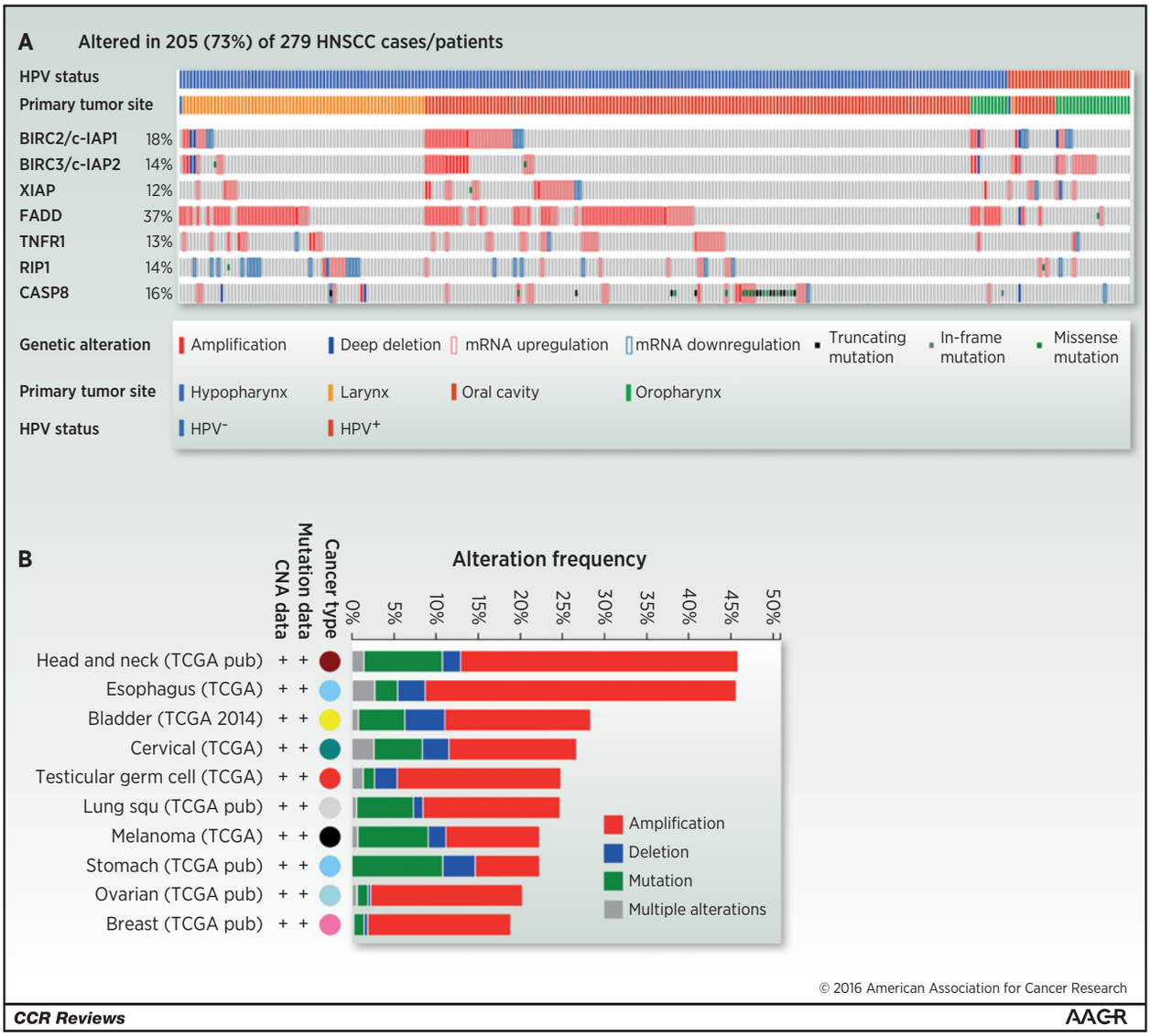

Figure 3.

Gene and mRNA expression alterations of cell death pathway components in HNSCC and other cancers. **A,** The frequency of genomic and mRNA deregulation for the listed genes was obtained from cBioPortal for Cancer Genomics (http://www.cbioportal.org), where the data generated from the TCGA project were collected. In total, 279 tumor samples from patients with HNSCC were analyzed via high-throughput sequencing technology, among other methods. Data was stratified by patients' HPV status (blue = HPV negative, red = HPV positive) as well as primary tumor site (red, oral cavity; blue, hypopharynx; orange, larynx; green, oropharynx). Genomic amplification (solid red bar), homozygous deletion (solid blue bar), mRNA upregulation (red rectangular outline), mRNA downregulation (blue rectangular outline), and/or mutation (square dots) of at least one of the listed genes occurred in 205 of 279 cases (73%). Gray bars indicate cases without genetic or expression alterations in the corresponding gene/mRNA. Percentages reflect the frequency with which samples express any of the listed alterations. **B,** The frequency of genomic alterations encompassing mutations, deletions, and amplifications is depicted for HNSCC and 9 other solid tumor types. mRNA expression is not included in this comparison. Data shown was obtained using each respective cancer's TCGA dataset as found on cBioPortal for Cancer Genomics (http://www.cbioportal.org). BIRC2/3, baculoviral IAP repeat containing 2/3; CASP8, caspase-8; c-IAP1/2, cIAPs 1/2; FADD, Fas-associated via death domain; Lung squ, lung squamous; RIP1, receptor-interacting protein 1; XIAP, X-linked IAP.

pathways (55). The role of FADD in NF-κB activation may help explain why amplification at the 11q13 locus is advantageous for cancer cells and why HNSCC patients with FADD amplification have a significantly shorter survival (4, 56). In such cases, co-amplifications of the nearby *BIRC2/3* locus and c-IAP1/2 expression could also enhance NF-κB activation while attenuating the proapoptotic function of FADD. In addition, the 11q13 region harbors another oncogene (*CCND1*), which promotes cell-cycle progression and tumor proliferation (57, 58). Thus, the high rate of *FADD* amplification and expression in HNSCC could serve as an Achilles' heel to potentiate the effect of SMAC mimetics and death ligands in inducing cancer cell death in this subset of patients with mutant TP53 and poor prognostic outcomes. In addition to HNSCC, TCGA analysis of several

Table 1. Characteristics of SMAC mimetics and IAP antagonists

Compound	Manufacturer	Structure[a]	Selectivity[b]
AT-406/Debio-1143	Debiopharm	Monovalent	$K_i = 1.9$ nmol/L for c-IAP1, 5.1 nmol/L for c-IAP2, 66.4 nmol/L for XIAP (70)
GDC-0917/CUDC-427	Curis	Monovalent	$K_i < 60$ nmol/L for c-IAP1, c-IAP2, and XIAP (71)
LCL-161	Novartis	Monovalent	No published data available
GDC-0152	Genentech	Monovalent	$K_i = 17$ nmol/L for c-IAP1, 43 nmol/L for c-IAP2, 28 nmol/L for XIAP (72)
Birinapant	TetraLogic	Bivalent	$K_d = <1$ nmol/L for c-IAP1, 36 nmol/L for c-IAP2, 45 nmol/L for XIAP (73)
HGS-1029/AEG-40826	Aegera	Bivalent	No published data available
ASTX-660[c]	Astex	N/A	$EC_{50} = 0.32$ nmol/L for c-IAP1, 5.1 nmol/L for XIAP, N/A for c-IAP2 (74)

Abbreviation: N/A, not applicable.

[a]Monovalent SMAC mimetics contain one tetrapeptide moiety (Ala-Val-Pro-Ile) mimicking endogenous SMAC, whereas bivalent compounds contain two mimicking sequences connected with a chemical linker.

[b]K_i is the inhibitory constant and K_d is the dissociation constant, which represent concentrations at which 50% of protein activity was inhibited or 50% of binding sites were occupied, respectively. These were determined by fluorescence-polarization competition assay to determine binding affinity of SMAC mimetic to BIR domains of IAP proteins. EC_{50} is the half maximal effective concentration, which was determined using Meso Scale Discovery platform.

[c]ASTX-660 is a non-peptidomimetic IAP antagonist. See text for details.

other solid tumor subtypes has demonstrated a high frequency of genomic alteration in cell death and NF-κB pathway components (Fig. 3B). Given these characteristics, investigation of SMAC mimetics in patients with HNSCC or other SCCs, such as esophageal carcinoma, may be warranted.

Use of SMAC Mimetics in Preclinical Models of HNSCC

Supporting the above hypothesis, our group recently investigated the SMAC mimetic birinapant in combination with death agonists TNFα or TRAIL in HNSCC (4). We showed that TNFα or TRAIL significantly enhanced birinapant-induced cell death across 11 HNSCC cell lines as compared to either single agent. Cell lines containing *FADD* amplifications displayed increased sensitivity to IAP antagonism, and forced FADD overexpression sensitized a previously resistant, low-FADD expressing HNSCC cell line to birinapant and TNFα. Further, FADD-overexpressing tumors were more sensitive to the combination of SMAC mimetic with radiation, which enhances expression of TNFα. Interestingly, we showed that this combination therapy resulted in a synergistic increase of TNFα expression, potentially explaining the synergistic activity seen with the concurrent use of SMAC mimetics and radiation *in vivo*.

Other SMAC mimetics have been shown to sensitize HNSCC cells to radiation, a mainstay in the treatment of head and neck cancer. Matzinger and colleagues described a synergistic effect in 5/6 HNSCC cell lines using the SMAC mimetic Debio-1143 in combination with radiotherapy, as assessed by clonogenic assay (59). Treatment with both Debio-1143 and radiation significantly increased TNFα expression *in vitro* in two cell lines tested. In addition, a complete cure of 8/10 mouse xenografts bearing FaDu tumor cells was observed after treating with Debio-1143 and radiation. The radiosensitizing potential of SMAC mimetics was also described by Yang and colleagues, who used Smac-164 *in vivo* in combination with radiation and showed a significant response in an HNSCC xenograft model (60). They further demonstrated that *in vitro* SMAC mimetic radiosensitization in sensitive cells was associated with TNFα secretion.

The use of SMAC mimetics in combination with chemotherapy in HNSCC models has also been explored. We explored the effect of birinapant together with docetaxel and demonstrated a synergistic relationship when tested in two cell lines *in vitro* and *in vivo* (61). Of note, previous reports have indicated that docetaxel stimulates TNFα production (62), potentially explaining the synergistic effect seen when it is combined with birinapant. Sun and colleagues showed that a SMAC mimetic combined with gemcitabine sensitized cells to apoptosis (63). This effect remained intact following the addition of a TNFα-neutralizing antibody, leading the authors to postulate that SMAC mimetic chemosensitization may have occurred secondary to mitochondrial permeabilization and intrinsic pathway activation.

Other studies suggest that potential exists in combining IAP inhibitors with agonistic TRAIL antibodies or FasL. Rault and colleagues investigated the sensitivity of nine HNSCC cell lines to the SMAC mimetic Smac-164 and/or recombinant human TRAIL (64). They found three cell lines to be sensitive to Smac-164 but resistant to TRAIL and, conversely, six cell lines to be sensitive to TRAIL but resistant to Smac-164. Interestingly, the cell lines sensitive to SMAC mimetic had high TNFα expression, whereas the Smac-164–resistant cells were sensitized upon co-treatment with TNFα. This is in line with previous reports indicating the importance of TNFα in SMAC mimetic therapy. Finally, Brands and colleagues combined LCL-161 with FasL in five HNSCC cell lines and found significant enhancement in cytotoxicity when co-therapy was employed (65). One of two FasL-resistant cell lines was sensitized upon addition of LCL-161 to the treatment regimen.

Clinical Trials Incorporating SMAC Mimetic Therapy in HNSCC and Other Solid Cancers

SMAC mimetics were engineered either as monovalent compounds, which contain one tetrapeptide moiety mimicking endogenous SMAC, or as bivalent compounds, which contain two mimicking sequences connected with a chemical linker. Thus far, four monovalent (AT-406/Debio-1143, GDC-0917/CUDC-427, LCL-161, and GDC-0152) and two bivalent (TL-32711/birinapant and HGS-1029/AEG-40826) SMAC mimetic compounds have entered clinical testing to determine pharmacologic, dosing, and safety characteristics (Table 1; refs. 46, 66). The routes of administration of the two classes of SMAC mimetics are different, with monovalent compounds being orally available, but bivalent compounds requiring intravenous injection. In addition, a non-peptidomimetic IAP antagonist that is orally administered (ASTX-660) has recently been developed. Studies recruiting patients with HNSCC exclusively or patients with solid tumors (including HNSCC) are listed in Table 1.

To date, there is one clinical trial initiated to investigate SMAC mimetic therapy in patients with head and neck cancer (Table 2).

Table 2. Ongoing and completed clinical trials involving SMAC mimetics and IAP antagonists in HNSCC and other solid tumors

Compound	Adjuvant therapy	Cancer type	Phase	Enrollment	Reference[a]	Status (June 2016)
AT-406/Debio-1143	Cisplatin, radiation	HNSCC	I/II	118	NCT02022098	Ongoing
AT-406/Debio-1143	None	Solid tumors	I	31	NCT01078649	Completed
GDC-0917/CUDC-427	None	Solid tumors	I	36	NCT01908413	Ongoing
GDC-0917/CUDC-427	None	Solid tumors	I	42	NCT01226277	Completed
LCL-161	Paclitaxel	Solid tumors	I	9	NCT01968915	Completed
LCL-161	Paclitaxel	Solid tumors	I	76	NCT01240655	Completed
LCL-161	None	Solid tumors	I	53	NCT01098838	Completed
GDC-0152	None	Solid tumors	I/II	72	NCT00977067	Completed
Birinapant	Chemotherapy[b]	Solid tumors	I/II	176	NCT01188499	Completed
Birinapant	None	Solid tumors	I	50	NCT00993239	Completed
HGS-1029/AEG-40826	None	Solid tumors	I	66	NCT00708006	Completed
ASTX-660	None	Solid tumors	I/II	86	NCT02503423	Ongoing

[a]Clinical trials incorporating SMAC mimetics or IAP antagonists in the treatment of HNSCC and other solid tumors were identified by searching the NIH's ClinicalTrials.gov database at https://clinicaltrials.gov/. This table includes information on clinical trials dating from June 2008 until June 2016. Trials that did not recruit patients with HNSCC were excluded.

[b]Either carboplatin, irinotecan, docetaxel, gemcitabine, or liposomal doxorubicin.

This is a dose-finding and efficacy phase I/II study (NCT02022098; ClinicalTrials.gov) involving Debio-1143, a monovalent SMAC mimetic, in combination with concurrent cisplatin and radiation in patients with previously untreated stage III/IV head and neck cancer. The current trial aims to first determine the maximum tolerated dose of Debio-1143 by employing a period of dose escalation (phase I), followed by a randomized phase II trial in which 94 participants receive Debio-1143 in addition to chemoradiation. Debio-1143 will be administered daily for 14 days out of every 3 weeks; the estimated completion of the trial is January 2019.

Limited published data exist regarding the clinical efficacy of SMAC mimetics in head and neck cancer specifically. Results from phase I dose-escalation studies of SMAC mimetic monotherapy in the treatment of solid tumors included some patients with HNSCC. A first-in-human dose-escalation study using Debio-1143 was recently published in which the drug was investigated as a single-agent therapy in patients with advanced solid tumors (67). The cohort consisted of 31 patients who received oral doses ranging from 5 to 900 mg once daily on days 1 to 5 every 2 to 3 weeks. The best treatment response achieved was stable disease in five patients (17%). No breakdown of patients' tumor type was provided. Based on these preliminary results, the authors suggested future studies incorporate Debio-1143 together with other treatment modalities, in addition to screening eligible participants to identify more sensitive subpopulations.

The dose-escalation study for the bivalent SMAC mimetic birinapant was carried out in a cohort of 50 patients with treatment-refractory solid malignancies (68). Seven patients (14%) had a primary diagnosis of head and neck cancer. Birinapant was given at a range of 0.18 to 63 mg/m^2 in a 3 + 3 dose-escalation design once weekly every 3 of 4 weeks. Three patients (6%), none of whom had HNSCC, experienced prolonged stable disease. These findings led the authors to conclude that further investigation into birinapant's efficacy as an antitumor agent is merited.

A phase I study investigating the use of LCL-161 in solid malignancies recruited 53 total patients, an undisclosed number of whom had HNSCC (69). The study administered the SMAC mimetic to patients orally once a week on a 21-day cycle with a total dose range of 10 to 3,000 mg. There were no patients that achieved an objective response to LCL-161. In addition, circulating levels of several different cytokines, including TNFα, increased in LCL-161–treated individuals. Given the favorable tolerability and significant pharmacodynamic activity at the doses investigated, the authors determined further development of LCL-161 was warranted.

Conclusions and Future Directions

The use of SMAC mimetics in the treatment of HNSCC as well as other cancers is at a nascent stage in development. Further investigations will solidify numerous unanswered questions that remain surrounding the use of this relatively new class of antineoplastic agents. The efficacy of bivalent versus monovalent SMAC mimetics needs to be better established, as does the determination of optimal combination treatments to achieve maximal response. More work is required to determine the mechanistic effects of various SMAC mimetics on different IAP family members in a biological setting and, more importantly, whether any potential differences would have an associated clinical relevance.

Recent data suggest the important role of death ligands and genomic alterations affecting components of cell death pathways in defining sensitivity to single-agent or combined therapies involving SMAC mimetics. The limited activities observed in earlier phase SMAC mimetic monotherapy trials may be because these agents were utilized in cancers with infrequent alterations in these pathways.

With the burgeoning shift toward precision medicine and the use of targeted therapies, the optimal genetic profile of HNSCC and other cancers sensitive to SMAC mimetic or IAP antagonist therapy will hopefully soon be identified. Gaining a deeper understanding of the players involved in the intrinsic and extrinsic death apoptotic cascades, their crosstalk with NF-κB signaling pathways, and the relationship between IAPs and various cell death modalities will be critical in deciphering which pieces of genetic and environmental information are most vital in predicting a response to treatment with SMAC mimetics. Such advances will ultimately lead to a higher degree of individualized treatment and an improvement in outcomes for patients with HNSCC.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

A. Derakhshan, Z. Chen, and C. Van Waes were supported by the National Institute on Deafness and Other Communication Disorders intramural projects ZIA-DC-000016, ZIA-DC-000073, and ZIA-DC-000074. A. Derakhshan was supported through the NIH-Medical Research Scholars Program, a public–private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, The American Association for Dental Research, The Howard Hughes Medical Institute, and the Colgate-Palmolive Company, as well as other private donors.

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Received August 29, 2016; revised November 30, 2016; accepted December 1, 2016; published OnlineFirst December 30, 2016.

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