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Inhibiting the inhibitors: Targeting anti-apoptotic proteins in cancer and therapy resistance

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ABSTRACT

The cytotoxic effect of anti-cancer drugs relies on their ability to induce programmed cell death known as apoptosis. Evading apoptosis is a common characteristic of cancer cells and it is linked to both carcinogenesis and anticancer drug resistance. To escape apoptosis, cancer cells often express high levels of anti-apoptotic proteins and become "addicted "to them for their survival. Consequently, anti-apoptotic proteins have emerged as attractive druggable targets for the development of cancer therapeutics. In this review we focus on two major anti-apoptotic protein families: IAPs (Inhibitor of Apoptosis) proteins and Bcl-2 (B-cell lymphoma-2) family members. We also discuss insights into the regulation of these proteins by natural antagonists, which has provided the conceptual basis for developing novel anti-cancer drugs. Significantly, the pro-apoptotic protein ARTS (apoptosis-related protein in the TGF-β signaling pathway; Sept4_i2) acts as a dual antagonist of both X-linked inhibitor of apoptosis protein (XIAP) and Bcl-2. Because upregulation of anti-apoptotic proteins in response to cancer therapy contributes to drug resistance, targeted inhibition of these proteins is expected to enhance the efficacy of chemotherapy. Finally, we discuss the role of proteasome-mediated degradation in the regulation of apoptosis, and how this mechanism can be harnessed to develop small molecules that stimulate degradation of anti-apoptotic proteins for cancer therapy. This strategy has the potential to overcome drug resistance more effectively than mere inhibition. Therefore, this approach may allow use of lower drug concentrations and thereby reduce cytotoxicity and untoward side effects.

1. Introduction

Apoptosis is a form of programmed cell death that plays a major role in development, tissue homeostasis, and as a defense mechanism against unwanted and potentially dangerous cells (Fuchs and Steller, 2015; Kerr et al., 1972; Malin and Shaham, 2015). Evasion of apoptosis is a fundamental trait of many cancers (Hanahan and Weinberg, 2000, 2011; Sharma et al., 2019; Van Opdenbosch and Lamkanfi, 2019). Resistance towards apoptosis also contributes to drug resistance and is associated with poor clinical prognosis (Assaraf et al., 2019; Gonen and Assaraf, 2012; Niewerth et al., 2015; Stiewe and Haran, 2018; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). Apoptosis can be initiated by both extrinsic (i.e. via death receptors pathway) and intrinsic signals (mitochondrial signaling pathway) which induce a coordinated activation of a family of cysteine proteases termed "caspases" (Shalini et al., 2015; Van Opdenbosch and Lamkanfi, 2019). The extrinsic apoptotic pathway is activated by ligands, such as Fas ligand (FasL) and Tumor Necrosis Factor (TNF), which engage with their apoptotic

Abbreviations: ABC, ATP-binding cassette; AM, ARTS-mimetic; AML, acute myeloid leukemia; ARTS, apoptosis-related protein in the TGF-β signaling pathway; AS, ODN - antisense oligonucleotide; B-Cell, NHL – B-cell non-hodgkin lymphoma; Bcl-2, -B-cell lymphoma-2; BET-PROTACS, bromodomain extra-terminal PROTACS; BH, Bcl-2 homology; BIR, baculoviral IAP repeats; cAMP, cyclic adenosine monophosphate; CDK9, cyclin-dependent kinase 9; CLL, chronic lymphocytic leukemia; DKO, double knock out; FL, follicular lymphoma; HFSC, hair follicle stem cells; HGSC, high-grade Serous ovarian cancer; HSC, hematopoietic stem cell; HSPC, hematopoietic stem and progenitor cell; IAP, Inhibitors of apoptosis proteins; MAC, mitochondrial apoptosis-inducing channel; MAPK, mitogen-activated protein kinase; MCL, mantle cell lymphoma; MDR, multidrug resistance; MM, multiple myeloma; MOM, mitochondrial outer membrane; MOMP, mitochondrial outer membrane permeabilization; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; NHL, non-hodgkin lymphoma; NSCLC, non-small cell lung cancer; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PKC, δprotein kinase C-delta; POI, Protein of interest; PROTAC, proteolysis targeting chimera; RCC, renal cell carcinoma; RTK, receptor tyrosine kinase; SM, Smac-mimetic; Smac, second mitochondria-derived activator of caspase; SSOs, splice-switching oligonucleotides; TM, Transmembrane; TNF, tumor necrosis factor; TNFR, TNF receptor; TRAF, TNF-associated factors; UPS, ubiquitin proteasome system; VDAC, voltage-dependent anion channel; XIAP, X-linked inhibitor of apoptosis

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receptor: FAS receptor (CD95) and TNF receptor (TNFR), respectively (Lavrik et al., 2005; Pfeffer and Singh, 2018; Shalini et al., 2015). The mitochondrial (also termed “intrinsic”) pathway is induced by a wide range of apoptotic signals, including DNA damage and oxidative damage, growth factor withdrawal, loss of cell adhesion, steroid hormones, and it is the prominent mechanism by which cells are removed during normal organismal development (Li et al., 1998; Luo et al., 1998; Sharma et al., 2019). In response to upstream apoptotic stimuli, the mitochondrial outer membrane's integrity is compromised, resulting in Mitochondrial Outer Membrane Permeabilization (MOMP) and release of Cytochrome c (Cyto c) to the cytosol (Kerr et al., 1972; Santucci et al., 2019). Cyto c forms a complex with APAF-1 and procaspase 9 called “apoptosome” which cleaves and activates caspase 9 (Rodriguez and Lazebnik, 1999). In turn, caspase 9 can further activate and cleave "effector" caspases (caspase 3, 7, and 6), promoting the cleavage of multiple cellular proteins, resulting in disassembly of the cell (Donepudi and Grutter, 2002; McComb et al., 2019; Thornberry and Lazebnik, 1998). In living cells, caspases are kept under scrutiny by anti-apoptotic - Inhibitors of Apoptosis Proteins (IAP) (Deveraux and Reed, 1999; Jost and Vucic, 2019). IAPs contain between one to three Baculoviral IAP Repeats (BIR), which serve as protein–protein interaction domains (Takahashi et al., 1998). IAPs are negatively regulated by IAP-antagonist proteins, such as Smac/Diablo and ARTS. Another staple of apoptotic propagation are the Bcl-2 family proteins, which regulate the stability and integrity of the mitochondrial outer membrane (MOM). This is especially critical for the release of Cyto c and activation of caspases downstream to the mitochondria (Dispersyn et al., 1999; Santucci et al., 2019; Strasser et al., 2011; Youle and Strasser, 2008). Bcl-2 family members are defined by their pro- or anti-apoptotic role and by their Bcl-2 homology (BH) domains (Adams and Cory, 1998; Kale et al., 2018; Lomonosova and Chinnadurai, 2008; Strasser et al., 2000). Out of four different BH domains, BH3 has been shown to facilitate the interaction between family members by serving both as a ligand and binding domain (Delbridge et al., 2016; Glab et al., 2017; Huang and Strasser, 2000; Schendel et al., 1997; Suvarna et al., 2019). The balance between expression levels of pro- and anti-apoptotic protein regulators is a critical point to determine if a cell will undergo apoptosis (Pistritto et al., 2016).

Cancer cells can escape apoptosis by either inactivating pro-apoptotic genes, or by counteracting their function (Jarpe et al., 1998; Opferman and Kothari, 2018). The best-studied example for the loss of a pro-apoptotic protein is the p53 tumor suppressor gene, which is mutated in approximately half of solid tumors derived from a wide range of tissues (Aylon and Oren, 2007; Evan and Vousden, 2001; Hollstein et al., 1991; Stiewe and Haran, 2018). Because p53 mediates the response to DNA damage that is induced by a wide range of cytotoxic agents, mutations in p53 blunt the response to both radiation therapy and many conventional chemotherapeutic agents, and this topic has been extensively covered by previous reviews (Cao et al., 2020; Cree and Charlton, 2017; Stiewe and Haran, 2018). Another way by which cancer cells can avoid apoptosis is by expressing high levels of anti-apoptotic proteins (Amarante-Mendes et al., 1998; Maji et al., 2018). For this reason, anti-apoptotic proteins have been identified as key targets for therapeutic intervention (Oltersdorf et al., 2005; Opferman, 2016). In the current review, we describe the regulatory mechanisms of anti-apoptotic proteins, their role in inducing drug resistance, and the latest therapeutic approaches to overcome resistance due to upregulation of anti-apoptotic proteins. We focus on two major protein families: the anti-apoptotic members of the B-cell lymphoma-2 (Bcl-2) family of proteins, and the Inhibitor of Apoptosis (IAP) proteins.

Cancer cells can become “addicted “to high levels of anti-apoptotic proteins, on which they depend for their survival (Inoue-Yamauchi et al., 2017). Several mechanisms are responsible for upregulation of anti-apoptotic proteins: A) genetic alterations at the DNA level (chromosomal translocation, mutations), B) RNA modulations (miRNAs, differential alternative splicing), and C) regulation at the protein level, mainly through modulation of the stability of anti-apoptotic proteins. Insights into these mechanisms can guide therapeutic approaches to overcome drug resistance by targeting anti-apoptotic proteins.

1.1. Acquired versus intrinsic drug resistance

Cancers have the ability to develop multidrug resistance (MDR) to various treatments which target different molecular pathways (Gacche and Assaraf, 2018; Gottesman et al., 2006; Leonetti et al., 2019; Li et al., 2016a; Robey et al., 2018; Taylor et al., 2015). Many tumors exhibit an intrinsic resistance to chemotherapy, without prior exposure to anti-cancer agents, hence the initial response to treatment is poor; whereas, malignancies may also acquire drug resistance due to the chemotherapeutic treatment (Gacche and Assaraf, 2018; Gottesman, 2002; Leonetti et al., 2019; Li et al., 2016a; Robey et al., 2018; Taylor et al., 2015). Among the plethora of molecular mechanisms underlying intrinsic and acquired drug resistance are: (a) Enhanced drug efflux predominantly via ATP-binding cassette (ABC) transporters residing in the plasma membrane, (b) Impaired influx due to inactivation or down-regulation of dedicated influx transporters, (c) Altered expression or function of the drug target, (d) Metabolic drug inactivation, (e) Drug compartmentalization within intracellular organelles or intercellular compartments, and (f) Enhanced DNA repair (Assaraf et al., 2019; Goler-Baron and Assaraf, 2011; Gottesman, 2002; Ifergan et al., 2005; Mansoori et al., 2017; Nikolaou et al., 2018; Sherlach and Roepe, 2014; Stark et al., 2020; Zhitomirsky and Assaraf, 2015, 2016). Specific examples for the involvement of apoptosis modulating proteins in intrinsic as well as acquired resistance are described below.

2. Role of Bcl-2 family proteins in apoptosis, cancer and drug resistance

The Bcl-2 family includes both anti-apoptotic members such as (Bcl-2, Bcl-xl, and Mcl-1), and pro-apoptotic proteins such as (Bax, Bak, and Bid) (Cory et al., 2003; Maji et al., 2018; Opferman and Kothari, 2018; Suvarna et al., 2019). All Bcl-2 members contain at least one or more Bcl-2 homology (BH) domains (Adams and Cory, 1998; Kale et al., 2018; Lomonosova and Chinnadurai, 2008; Strasser et al., 2000). Out of four different BH-domains, BH3 is particularly important for mediating the formation of various Bcl-2 protein complexes that dictate the outcome between cell death and survival (Delbridge et al., 2016; Glab et al., 2017; Huang and Strasser, 2000; Schendel et al., 1997; Suvarna et al., 2019). BH3-BH3 interactions are responsible for both the formation of pro-survival complexes, but are also responsible to antagonize them.

Many Bcl-2 family proteins contain a hydrophobic transmembrane (TM) anchoring domain at their C-terminus allowing them to localize to the outer membrane of the mitochondria (Goping et al., 1998; Stehle et al., 2018; Tanaka et al., 1993). Upon apoptotic stimuli, pro-apoptotic Bcl-2 proteins, such as Bax and Bak, can oligomerize at the mitochondrial outer membrane and promote apoptosis by inducing Mitochondrial Outer Membrane Permeabilization (MOMP) (Borner, 2003; Campbell and Tait, 2018; Chipuk and Green, 2008; Kale et al., 2018; Volkmann et al., 2014; Youle and Strasser, 2008). Bax, is found predominantly in the cytosol of living cells, although it translocates between the surface of mitochondria and the cytosol, while Bak resides mostly on the outer membrane of the mitochondria (Edlich, 2015; Edlich et al., 2011; Schellenberg et al., 2013; Todt et al., 2015). Notably, Bcl-2, Bcl-xl and Mcl-1 inhibit apoptosis by blocking the Bax channel-forming activity that promotes MOMP (Antonsson et al., 1997; Edlich et al., 2011; Oltersdorf et al., 2005). In addition, caspase-induced cleavage of Bid generates truncated Bid (tBid) which translocates to the MOM where tBid induces MOMP by directly binding Bax/Bak (Adams, 2019; Gross et al., 1999; Jeng et al., 2018; Stehle et al., 2018). Alternatively, tBid and the mitochondrial-specific phospholipid cardiolipin can also promote Bax/Bak oligomerization (Raemy and Martinou,

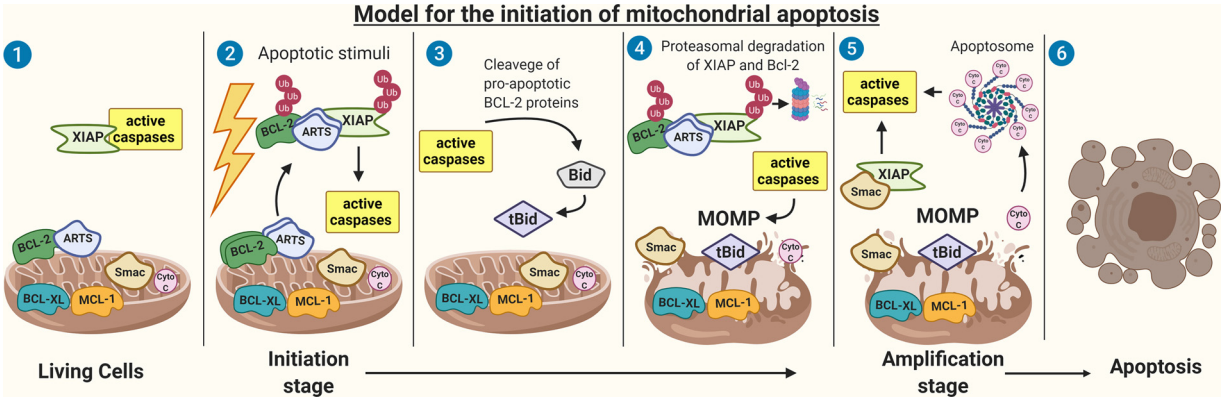

Fig. 1. Model for the initiation of mitochondrial apoptosis. (1) In living cells, XIAP is localized in the cytosol where it binds to and represses caspases to prevent unwanted apoptosis. ARTS and Bcl-2 reside at the Mitochondrial Outer Membrane (MOM), along with Bcl-xl and Mcl-1. Smac and Cyto c are localized in the mitochondrial inter membrane space. (2) Upon induction of apoptosis, ARTS acts as a scaffold to promote the formation of a ternary complex with XIAP and Bcl-2, leading to the ubiquitylation and degradation of both Bcl-2 and XIAP. This allows the activation of non-lethal caspase activity through de-repression of XIAP. We term this phase the "initiation stage" of caspase activation. (3) This early, non-lethal caspase activity can cause cleavage of pro-apoptotic Bcl-2 proteins, such as Bid, which are known to promote MOMP (Mitochondrial Outer Membrane Permeabilization). (4) Degradation of XIAP and Bcl-2 reduces the threshold towards apoptosis and permits amplification of caspase activity. The process of MOMP causes opening of pores at the MOM, enabling the release of Smac/Diablo (Smac) and cytochrome c (Cyto c) from the mitochondrial inter-membrane space into the cytosol (5) Upon MOMP, Cyto c forms a complex with pro-caspase 9 and APAF-1, termed "apoptosome", which leads to activation of caspase 9. This is the caspase "amplification stage. (6) High levels of lethal active caspases cleave multiple cellular proteins, resulting in apoptotic cell death.

2014). Therefore, these proteins regulate MOMP and the release of pro-apoptotic proteins such as Cytochrome c (Cyto c) from the mitochondrial inter-membrane space (Dispersyn et al., 1999; Santucci et al., 2019; Strasser et al., 2011; Youle and Strasser, 2008). Anti-apoptotic Bcl-2 family proteins can block MOMP by sequestering pro-apoptotic Bcl-2 proteins (Inoue-Yamauchi et al., 2017; Maji et al., 2018; Voss and Strasser, 2020). Voltage-dependent anion channel (VDAC) can act as an anchoring platform for pro- and anti-apoptotic proteins (such as Bcl-2 and Bcl-xl) determining the creation of pores directly or indirectly in the mitochondrial outer membrane (Mazure, 2017). For example, it has been shown that VDAC is essential for Bax-induced, but not Bid-induced, Cyto c release (Madesh and Hajnoczky, 2001; Shimizu et al., 2001; Shoshan-Barmatz et al., 2015; Zheng et al., 2004). Mitochondrial apoptosis-inducing channel (MAC) was also proposed as providing the pathway for Cyto c release (Fishelson and Kirschfink, 2019; Kinnally and Antonsson, 2007). Depletion of Bax significantly diminished MAC activity, suggesting that Bax is an essential constituent of MAC. MAC activation is tightly regulated by the Bcl-2 family (Dejean et al., 2010; Kinnally et al., 2006; Martinez-Caballero et al., 2009).

Upregulation of anti-apoptotic Bcl-2 family proteins is a common phenomenon associated with carcinogenesis. For example, transgenic mice overexpressing Bcl-2 develop spontaneous tumors, albeit at a relatively low occurrence rate (Maji et al., 2018; McDonnell and Korsmeyer, 1991). High levels of Bcl-2 also shift the balance of cancer cells towards survival and can contribute to chemoresistance (Quinn et al., 2011).

2.1. Bcl-2

Upregulation of Bcl-2 has been observed in breast carcinomas, prostate carcinomas, glioblastomas, leukemias and lymphomas (Delbridge et al., 2016; Kelly and Strasser, 2011; Placzek et al., 2010; Youle and Strasser, 2008). Moreover, Bcl-2 overexpression in cancer cells is a poor prognostic marker for chemotherapy and radiotherapy in patients with bladder cancer, and patients with diffuse large B cell lymphoma. (Assaraf et al., 2019; Hussain et al., 2003; Kiss et al., 2015; Urun et al., 2019). Increased levels of Bcl-2 can be due to either elevated levels of transcription, or increased protein stability. The underlying mechanisms include genetic alterations, expression of miRs (miRNAs), or decreased activity of E3-ligases that promote proteasome-mediated degradation of Bcl-2. Bcl-2 overexpression was originally discovered in follicular lymphoma (FL) as a result of (14;18) chromosome translocation (Tsujimoto et al., 1984; Vaux et al., 1988). The Bcl-2 gene cooperates with another oncogene, c-myc, to immortalize pre-B cells (Strasser et al., 1990). It has been shown that mice co-expressing Bcl-2 and c-myc transgenes exhibit accelerated lymphogenesis (Vaux et al., 1988). C-myc has dual roles contributing on the one hand to cell proliferation and growth and on the other hand to cell death through apoptosis. The involvement of Bcl-2 blocks c-myc-dependent apoptosis without inhibiting cell cycle progression which results in increased tumorigenesis (Bissonnette et al., 1992; Fanidi et al., 1992; Riedell and Smith, 2018).

This indicates that high levels of anti-apoptotic proteins can promote tumorigenesis. Another mechanism for Bcl-2 upregulation is via a genomic deletion in chromosome locus 13q14 (Grygalewicz et al., 2016). This genomic deletion results in the loss of miR15 and miR16 which function to reduce the levels of Bcl-2. Therefore, the loss of miR15 and miR16 leads to upregulation of Bcl-2 protein expression in 50 % of Mantle cell lymphoma (MCL) patients (Stilgenbauer et al., 1998). In addition, miR-15/16 are either deleted or downregulated in more than 70 % of chronic lymphocytic leukemia (CLL) patients resulting in markedly increased levels of Bcl-2 (Pekarsky et al., 2018).

Another modality by which Bcl-2 protein levels can be upregulated is as a result of loss of the relevant E3-ligases. Keap1 is an E3 ligase that targets Bcl-2 and Bcl-xl for degradation, and inactivating Keap1 mutations have been described in several cancers (Niture and Jaiswal, 2011a) (Kansanen et al., 2013; Shibata et al., 2008; Taguchi and Yamamoto, 2017). Overexpression of Keap1 results in decreased levels of Bcl-xl, which increases pro-apoptotic factors and apoptosis (Tian et al., 2012). In addition, Keap1 functions as an adaptor protein for Cul3-Rbx1-dependent degradation of Bcl-2 (Niture and Jaiswal, 2011b). Keap1-mediated degradation of Bcl-2 results in decreased Bcl-2/Bax heterodimers and increased levels of Bax, thereby stimulating apoptosis in response to treatment with etoposide and radiation.

Another way by which the stability of Bcl-2 can be increased is through the loss of the pro-apoptotic ARTS protein. ARTS is encoded by the *Sept4* gene and can act as a scaffold to bring Bcl-2 into close proximity with XIAP. XIAP, with its E3-ligase activity, ubiquitylates and promotes the proteasome-mediated degradation of Bcl-2 (Fig. 1) (Edison et al., 2017).

2.2. Bcl-xl

Upregulation of Bcl-xl is associated with tumor progression, lower survival rates, and resistance to radiotherapy and chemotherapy (de Jong et al., 2018; Scherr et al., 2016; Watanabe et al., 2002). Bcl-xl is highly expressed in chondrosarcoma, colon cancer, colorectal cancer, liver cancer and Non-Hodgkin lymphoma (NHL) (de Jong et al., 2018; Hernandez-Luna et al., 2013; Liu et al., 2014; Scherr et al., 2016; Shimizu et al., 2010). Bcl-xl can stimulate the retro-translocation of Bax from the MOM to the cytosol (Edlich et al., 2011; Todt et al., 2013). Therefore, the survival of cells overexpressing Bcl-xl may also be attributed to their compromised ability to assemble mitochondria-localized activated Bax which promotes MOMP (Renault et al., 2017;Renault et al., 2015).

The Bcl-x gene encodes two distinct proteins with antagonistic functions that are generated by alternative splicing: Bcl-xl (long isoform), is anti-apoptotic, and Bcl-xs (short isoform), is pro-apoptotic (Stevens and Oltean, 2019). A higher proportion of Bcl-xl is frequently found in both non-small cell lung cancer (NSCLC) and small cell lung cancer, which alters the balance between pro- and anti-apoptotic signals and thereby may contribute to tumor progression (Karczmarek-Borowska et al., 2006; Pio and Montuenga, 2009). NEK2 is a regulator of alternative splicing, which favors the splicing of the anti-apoptotic Bcl-xl (Naro et al., 2014). NEK2 is overexpressed in a number of human cancers (Barbagallo et al., 2009; Hayward et al., 2004; Landi et al., 2008). It is likely that enhanced splicing of the anti-apoptotic variant Bcl-xl contributes to this pro-survival effect (Naro et al., 2014). Accordingly, knockdown of NEK2 induces the expression of pro-apoptotic Bcl-xs (Naro et al., 2014). Thus, differential splicing favoring the expression of Bcl-xl in cancers, can play a role in drug resistance developed in these cancers due to evasion of apoptosis.

2.3. Mcl-1

Mcl-1 is another anti-apoptotic Bcl-2 family protein that is upregulated in a range of malignancies, including prostate carcinomas, leukemias, pancreatic cancers, oral cancers and hepatocellular carcinomas (Derenne et al., 2002; Placzek et al., 2010; Selzer et al., 1998; Sieghart et al., 2006; Wei et al., 2008; Zhuang et al., 2007). For example, in mantle cell lymphoma, Mcl-1 overexpression correlated with high-grade morphology, high levels of cancer cell proliferation, and p53 overexpression (Khoury et al., 2003). Conversely, knockdown of Mcl-1 results in decreased tumor size and weight in mouse xenograft models with pancreatic adenocarcinoma (Wei et al., 2008).

Mcl-1 is a very short-lived protein, undergoing UPS-mediated degradation concerted by the E3 ubiquitin ligases Mule (HUWE1) and SCF (Ding et al., 2007; Inuzuka et al., 2011). Mule is a key regulator of the UPS in cancer development. An increasing body of evidence has linked alterations in Mule to malignancies, including esophageal cancer, gastric cancer, multiple myeloma, colorectal cancer, uterine cancer, cervical cancer, prostate tumors, melanoma and lung cancer (Cancer Genome Atlas, 2012; Cancer Genome Atlas Research, 2014; Gong et al., 2020; Inoue et al., 2013; Walker et al., 2018). Mule is considered an important tumor suppressor, which has been confirmed in some *in vivo* studies. *huwe1* knockout has been shown to promote cancer development and increase in the penetrance, number and severity of tumors (Gong et al., 2020; Myant et al., 2017; Peter et al., 2014).

Evasion of apoptosis can promote oncogenic transformation at multiple stages through facilitating sustained tumor growth and survival during metastatic processes as well as resistance to therapy (Campbell and Tait, 2018). Therefore, Bcl-2 anti-apoptotic proteins are potential therapeutic targets to restore cell death in chemoresistant cancers (Maji et al., 2018). Bcl-2 inhibitors either alone or in combination with existing chemotherapeutics can overcome therapy-resistant/recurrent tumors to increase the disease-free survival of cancer patients (Maji et al., 2018).

3. Therapeutic strategies to target anti-apoptotic Bcl-2 proteins

Upregulation of anti-apoptotic Bcl-2 family members both as a result of intrinsic, as well as acquired drug resistance, has prompted the development of various therapeutics aimed at reducing the levels of these anti-apoptotic proteins in order to sensitize cancer cells towards apoptosis (Kale et al., 2018; Maji et al., 2018; Suvarna et al., 2019).

3.1. BH3-mimetics

Proteins of the Bcl-2 family regulate mitochondrial apoptosis through protein-protein interactions, all involving the same BH3 helix-in-groove structure (Czabotar et al., 2014; Jeng et al., 2018). In recent years, most efforts to target anti-apoptotic Bcl-2 proteins have focused on mimicking the inherent regulation of these proteins by pro-apoptotic BH3-only proteins. Small-molecule compounds mimicking the BH3 domain (i.e. BH3-mimetics) can bind the hydrophobic groove of the anti-apoptotic Bcl-2 proteins, inhibiting their functional activity, and thus inducing apoptosis (Chen et al., 2005; Khaw et al., 2011; Suvarna et al., 2019). Notably, BH3-mimetics can initiate apoptosis by activating Bax/Bak or by inactivating anti-death Bcl-2 members (Jeng et al., 2018).

Among the various BH3-mimetic compounds generated, ABT-737 and ABT-263 (Navitoclax) engage multiple anti-apoptotic Bcl-2 family members: Bcl-2, Bcl-xl and Bcl-W. Unfortunately however, monotherapy with Navitoclax resulted in thrombocytopenia due to Bcl-xl inhibition, a key survival protein in platelets (Roberts et al., 2012). This precluded the use of Navitoclax as effective chemotherapeutics, but prompted the pursuit to find more selective Bcl-2 inhibitors which can induce cell death without inflicting serious side effects (Mason et al., 2007). Indeed, in 2016, ABT-199 (Venetoclax) became the first FDA approved BH3 mimetic used as monotherapy, for the treatment of relapsed or refractory CLL with 17p deletion. ABT-199 was also found to be active in multiple myeloma (MM), acute myeloid leukemia (AML) and MCL patients (Mihalyova et al., 2018). In addition, ongoing clinical trials are examining various combination treatments for CLL. These include combination regimens of ABT-199 with monoclonal anti-CD20 antibody (rituximab or obinutuzumab), and combination of ABT-199 with the chemoimmunotherapy agents fludarabine, cyclophosphamide, and rituximab (Cramer et al., 2018; Fischer et al., 2017; Hillmen et al., 2019; Jain et al., 2017; Mihalyova et al., 2018; Rogers et al., 2018; Stilgenbauer et al., 2016).

S55746 is a BH3-mimetic which selectively inhibits Bcl-2 and impairs tumor growth (Casara et al., 2018). S55746 occupies the P1, P2 and P3 regions in the BH3 domain of Bcl-2 (Souers et al., 2013). This compound induces mitochondrial apoptosis by initiating MOMP in tumor cells expressing high levels of Bcl-2 (Casara et al., 2018). *In vivo*, S55746 is highly effective against tumors overexpressing Bcl-2, without causing thrombocytopenia. Phase 1 clinical trials using this compound in patients with CLL, B-Cell Non-Hodgkin Lymphoma (B-Cell NHL) and MM are currently ongoing (NCT02920697 and NCT02603445).

3.2. Targeting Bcl-xl

Downregulation of Bcl-xl can restore the sensitivity of recurrent and acquired chemoresistant cancer cells to cisplatin (Brotin et al., 2010; Lee et al., 2019; Varin et al., 2010). Selective Bcl-xl inhibitors have been developed, but no reports are available to attest for their efficacy (Lessene et al., 2013; Leverson, 2016; Opferman, 2016; Tao et al., 2014). Co-treatment of melanoma, ovarian cancer and mesothelioma cells with a combination of Bcl-xl and Mcl-1 inhibitors was shown to effectively induce cell death in melanoma, ovarian cancer, and mesothelioma cells (Brotin et al., 2010; Lee et al., 2019; Varin et al., 2010).

Splice-switching oligonucleotides (SSOs) are anti-sense oligonucleotides that hybridize to pre-mRNA sequences and blocking the binding of splice factors. Thus, they can redirect the splicing machinery

to an alternative pathway, modifying the splicing pattern of the gene (Li et al., 2016b; Stevens and Oltean, 2019). A common therapeutic effect of SSOs is targeting the *Bcl-x* pre-mRNA to redirect splicing from Bcl-xl to Bcl-xs resulting in pro-apoptotic and chemosensitizing effects (Bauman et al., 2009; Li et al., 2016b; Mercatante et al., 2002). However, the effects of the Bcl-x SSOs vary, depending on the expression profile of Bcl-xl in the target cells. Tumor cells with higher endogenous levels of Bcl-xl were reported to be more susceptible to the effects of Bcl-x SSOs (Mercatante et al., 2001; 2002).

3.3. Targeting Mcl-1

Many types of cancers, become addicted to high levels of Mcl-1 for survival as well as resistance to chemotherapy (Quinn et al., 2011). Furthermore, loss of Mcl-1 sensitized pancreatic adenocarcinoma resistant cells to the current first line treatment for pancreatic cancer, gemcitabine (Quinn et al., 2011; Wei et al., 2008). Additionally, Mcl-1 knockdown has also been demonstrated to sensitize cells to Rituximab (anti-CD20 antibody) treatment, while patients with resistance to Rituximab exhibited increased levels of Mcl-1 (Hussain et al., 2007).

A variety of selective Mcl-1 inhibitors were developed, such as S64315, A1210477, AMG17620, VU661013 and AZD5591 (Fletcher, 2019). Most Mcl-1 inhibitors share two common features – an acidic functionality to engage Arg263, and atypically large, hydrophobic groups that anchor the inhibitor deep in the P2 pocket of the BH3 domain (Fletcher, 2019). Mcl-1 retains a general α helical structure, similar to the other Bcl-2 proteins, but differs in the surface of its binding groove and position of some surface helices (Day et al., 2005). Interestingly, Obatoclax (GX15), a broad-range BH3 mimetic targeting Bcl-2, Bcl-xl, Bcl-w, Mcl-1 and Bfl-1, displayed cytotoxic effects which are partially mediated through its effect on Mcl-1 (Quinn et al., 2011). Obatoclax can disrupt the constitutive Bak-Mcl-1 interaction on the MOM (Nguyen et al., 2007; Or et al., 2020).

Mcl-1 can also be targeted indirectly through cyclin-dependent kinase 9 (CDK9) which acts as a transcriptional regulator for Mcl-1. Inhibition of CDK9 causes downregulation of Mcl-1 transcription and a reduction in the protein level (Tibes and Bogenberger, 2019). To counteract the upregulation of Mcl-1, several approaches have been used. For example, CDK9-inhibitors have been shown to synergize with BH3 mimetics (Bogenberger et al., 2017; Luedtke et al., 2018; Zhang et al., 2017). Receptor tyrosine kinase (RTK) inhibitors were shown to promote Mcl-1 degradation thereby stimulating apoptosis in combination with ABT-737/263 (Arai et al., 2018). Selective Mcl-1 inhibitors, A1210477, S64315 and S63845 sensitized resistant AML cell lines to treatment in combination with ABT-199 (Kotschy et al., 2016; Li et al., 2019). Clinical studies of combination treatments with both selective Mcl-1 and Bcl-2 inhibitors, S64315 and ABT-199, respectively, are ongoing in patients with relapsed/refractory AML (NCT03672695) (Knight et al., 2019).

3.4. Inducing upregulation of pro-apoptotic Bcl-2 proteins to overcome drug resistance

It may be possible to counteract high levels of anti-apoptotic Bcl-2 proteins with elevated protein expression of specific pro-apoptotic Bcl-2 proteins. Puma is a BH3-only protein which acts as a key mediator of cytosolic pro-apoptotic p53 function by freeing cytosolic p53 from inactive complexes with Bcl-xl. Cytosolic p53 can directly activate Bax or Bak, thereby triggering the apoptotic signaling cascade via mitochondrial outer membrane permeabilization (MOMP) (Chipuk et al., 2008; 2004; Follis et al., 2013). p53 upregulates ARTS, which in turn neutralizes Bcl-xl to promote apoptosis (Hao et al., 2020). In that respect, inhibiting p53 antagonists (such as Nutlin-3 and Mdm2) could upregulate p53 levels, promoting the expression of pro-apoptotic proteins. Certain ARTS mimetic (AMs) small molecules can upregulate the levels of p53 in cancer cells, providing a therapeutic avenue worth further exploration (Shahar and Larisch, unpublished results). In addition, downregulation of pro-apoptotic BH3-only proteins, such as Noxa, can contribute to drug resistance due to its interaction with anti-apoptotic Bcl-2 family proteins in lymphoid cells (Smith et al., 2011). BH3-only proteins have different binding affinities towards specific anti-apoptotic relatives (Opferman et al., 2003): while Bim, Puma and truncated Bid (tBid) bind to all anti-apoptotic relatives, Bad binds only Bcl-2, Bcl-xl and Bcl-W, and Noxa mostly engages with Mcl-1, A1/Bfl-1 and Bcl-2 (Adams and Cory, 2018; Smith et al., 2011). Therefore, inducing upregulation of Noxa may inhibit Mcl-1 and sensitize BH3-mimetic-resistant cells to apoptosis.

3.5. Promoting degradation of anti-apoptotic Bcl-2 family members

An emerging trend in targeting anti-apoptotic proteins has been to develop therapeutic approaches that promote protein degradation rather than binding and inhibition of activity. Proteolysis Targeting Chimeras (PROTACs) are designed to ubiquitylate target proteins by hijacking the activity of ubiquitin ligases (Crew et al., 2018; Sakamoto et al., 2001; Sun et al., 2019). Typical small molecule drugs bind and inhibit the occupied binding site of the target protein. Yet, targeted protein degradation is much less limited in its mechanism of action (Paiva and Crews, 2019). The degradation of target proteins rather than inhibition, opens up opportunities to target undruggable proteins, and new possibilities for synergistic combination of treatments (Crews, 2010; Lai and Crews, 2017; Overington et al., 2006). Degradation is initiated when PROTACs engage the protein of interest (POI) and E3 ligases to form ternary complexes which are polyubiquitylated and cleared by UPS-mediated degradation. PROTACs can later dissociate from the complex and continue to target other POIs (Sun et al., 2019). PROTACs have shown the potential to overcome instances of mutation-induced drug resistance via binding site alterations. Moreover, induced protein degradation not only reduces the number of active proteins needed to be inhibited but also counteracts compensatory protein overexpression which can lead to drug resistance (Lai and Crews, 2017).

ARV-825 and ARV-771 are Bromodomain Extra-Terminal (BET-PROTACS) chimeric molecules which promote ubiquitylation and proteasomal degradation of specific target proteins. BET-PROTAC treatment induces perturbations in the RNA and protein expression of various transcription factors including Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFkB). This in turn leads to the down regulation of mRNA of Bcl-xl and XIAP (Sun et al., 2018). The use of ARV-771 has been tested in MCL cells resistant to ibrutinib. The resistance in these cells is attributed to mutations resulting in sustained NFk-B signaling. ARV-771 has been shown to synergize with the Bcl-2 inhibitor, ABT-199, in killing ibrutinib-resistant MCL cells lines (Sun et al., 2018). Although, further studies are necessary to confirm these results *in vivo*, BET-PROTACS are promising agents for the treatment of MCL. An example for the utility of PROTACs to counteract drug resistance resulting from elevated Bcl-2 is XZ424. Development of anticancer drugs targeting Bcl-xl has been hampered by severe on-target platelet toxicity. XZ424 is a new selective PROTAC which showed increased selectivity for targeting Bcl-xl in cultured cells, without compromising platelet count, thereby providing a potential therapeutic path to overcome drug resistance due to high levels of Bcl-xl (Zhang et al., 2019).

4. Mechanisms for acquired drug resistance to BH3-mimetics

Many types of cancers acquire resistance towards chemotherapeutic drugs by overexpressing anti-apoptotic proteins (Andersen et al., 2005; Apakama et al., 1996; Del Bufalo et al., 1997; Kitagawa et al., 1996; Nakano et al., 2020; Sieghart et al., 2006; Watanabe et al., 2002). Anti-apoptotic Bcl-2 members can sequester BH3-mimetics and activated Bax/Bak containing an exposed BH3 domain to inhibit apoptosis (Jeng

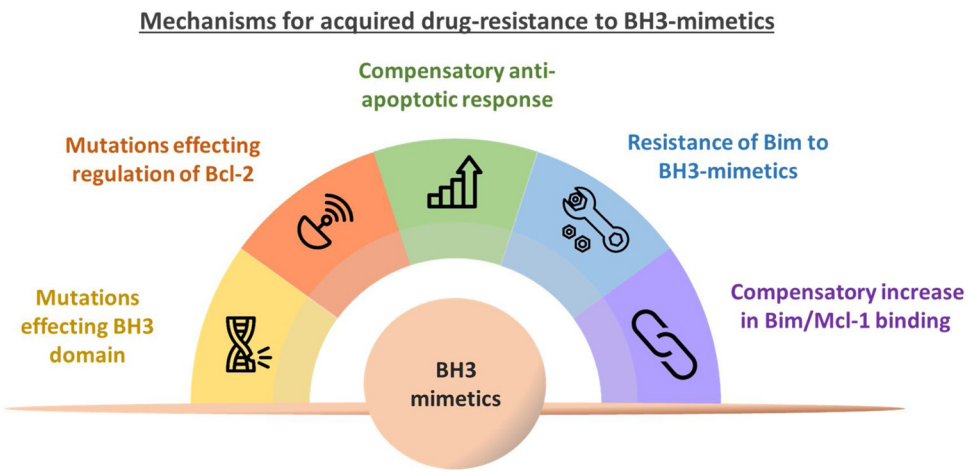

Fig. 2. Mechanisms for acquired drug-resistance to BH3-mimetics. Various mechanisms contribute to drug resistance towards BH3-mimitics including; missense mutations (such as G101 V) in the BH3-domain of Bcl-2 that reduce the compound's affinity. Mutations in signal transduction pathways (FLT3-ITD). Increased expression of anti-apoptotic Bcl-2 family members (Bcl-xl and Mcl-1). Pro-apoptotic proteins containing binding sites to anti-death proteins in addition to a BH3 domain. Finally, discharge of Bim from a complex with Bcl-2, leading to a compensatory increase in free Bim and Bim/Mcl-1 complexes.

et al., 2018). In this section we will review the mechanisms of acquired drug resistance to BH3-mimetics (Fig. 2).

4.1. Mutations resulting in resistance to ABT-199 treatment

A common mechanism by which malignant cells evade therapy is through acquisition of mutations in drug binding sites. For example, CML patients treated with the BCR-ABL inhibitor imatinib (Gleevec) can acquire resistance to the ABL tyrosine kinase inhibitors due to a mutation in the kinase binding site (Shah et al., 2002; von Bubnoff et al., 2002). Recently, a missense mutation, G101 V, within the BH3-binding groove of Bcl-2, has been shown to render cells resistant to ABT-199 (Birkinshaw et al., 2019; Blombery et al., 2019). This mutation was found in CLL patients from clinical trials who had initially responded to treatment but developed CLL-type clinical progression after 19–42 months (Blombery et al., 2019). Notably, this G101 V Bcl-2 mutant maintained high affinity for pro-apoptotic proteins, such as Bax and Bim, and thus can still function to suppress apoptosis (Birkinshaw et al., 2019; Fletcher et al., 2020). Developing future analogues of ABT-199 which can bind to the G101 V mutated Bcl-2 may overcome the resistance to the drug in patients bearing this mutation (Birkinshaw et al., 2019).

Another drug resistance mechanism towards ABT-199 is through mutations in the *FLT3* gene. The receptor tyrosine kinase FLT3 is expressed in $CD34^+$ hematopoietic stem/progenitor cells and plays an important role in hematopoiesis (Levis et al., 2005). 20–30 % of AML patients display internal tandem duplication (ITD) mutation in the *FLT3* gene which results in increased relapse rate and resistance to ABT-199 (Rosnet et al., 1996; Turner et al., 1996). These phenomena are attributed to upregulation of Bcl-xl and Mcl-1 (Knight et al., 2019; Mali et al., 2018; Yoshimoto et al., 2009). Combination treatment of FLT3 inhibitors with ABT-199 is sufficient to overcome FLT3-induced resistance. A clinical trial evaluating a combination therapy with the FLT3 inhibitor gilteritinib in ABT-199 treated patients with relapsed/refractory AML is under way (NCT03625505). In summary, mutations can cause resistance towards BH3-mimetics by altering the binding site to the drug, or indirectly by inducing compensatory upregulation of other anti-apoptotic Bcl-2 proteins.

4.2. Compensatory up-regulation of anti-apoptotic Bcl-2 proteins

Selectively inhibiting one member of the anti-apoptotic Bcl-2 proteins can promote the upregulation of other anti-apoptotic relatives (Ewald et al., 2019; Kale et al., 2018; Lee et al., 2019; Maji et al., 2018). A common response to prolonged treatment with ABT-199 is the overexpression of Mcl-1 (Ewald et al., 2019; Hird and Tron, 2019; Luedtke et al., 2018). Thus, targeting Mcl-1 either directly with selective Mcl-1 inhibitors, or indirectly through inhibition of transcription factors (CDK9) may overcome drug resistance due to elevated Mcl-1.

Altering the Bcl-xs/Bcl-xl ratio by targeting their splicing pattern may have therapeutic potential to overcome drug resistance (Stevens and Oltean, 2019). The Bcl-xl/Bcl-xs ratio can be quite high *in vivo*. However, several physiological conditions and external stimuli can alter this ratio by modulating the splicing machinery (Akgul et al., 2004). Therefore, increasing the ratio of Bcl-xs/Bcl-xl would not only lower cell resistance to chemotherapy, it would also sensitize the cells to undergo apoptosis (Akgul et al., 2004; Mercatante et al., 2001; 2002; Stevens and Oltean, 2019; Taylor et al., 1999).

4.3. Resistance of Bim to BH3-mimetics

BH3-mimetics act as decoy drugs that mimic the BH3-sequences of pro-apoptotic family members and, by disrupting heteromeric complexes (such as Bcl2-Bax), they free pro-apoptotic proteins to induce apoptosis (Chen et al., 2005; Liu et al., 2019). However, the pro-apoptotic Bcl-2 relative Bim is quite refractory to the release from Bcl-xl and Bcl-2 by BH-3 mimetics, which contributes to apoptotic resistance (Pecot et al., 2016). A recent study provided insights into the underling mechanism by showing that Bim contains two distinct binding sites for the anti-apoptotic proteins Bcl-xl and Bcl-2 (Liu et al., 2019). These include the BH3-motif shared with other pro-apoptotic proteins and sequences near the Bim carboxyl-terminus. These two binding interfaces enable Bim to "double-bolt lock" Bcl-xl and Bcl-2 in complexes resistant to displacement by BH3-mimetics. This work indicates that BH3-mimetics may have unexpected effects, it suggests that effective killing of some cancer cells may require targeting multiple sites in Bcl-xl and/or Bcl-2 (Liu et al., 2019).

4.4. Compensatory increase in Bim/Mcl-1 binding

One consequence of Bcl-2 inhibition via ABT-199 is the discharge of Bim from a complex with Bcl-2, leading to a compensatory increase in free Bim and Bim/Mcl-1 complexes. As a result there is decreased binding of Bim to Bax/Bak, which in turn attenuates MOMP (Knight et al., 2019; Niu et al., 2016). Concurrent inhibition of Mcl-1, however, diminishes Bim/Mcl-1 association and thereby overcomes ABT-199 resistance (Luedtke et al., 2018). In B-ALL cell lines, ABT-737 resistance can occur due to Mcl-1 phosphorylation, which increases Mcl-1 protein stability and sequestration of Bim (Mazumder et al., 2012).

5. Role of IAP proteins in apoptosis, cancer and drug resistance

The Inhibitors of Apoptosis (IAP) protein family controls ubiquitin

(Ub)-dependent signaling events that regulate expression of genes which are important for inflammation, immunity, cell migration, and cell death (Silke and Meier, 2013).

IAPs can promote cell survival by a number of means: preventing the activation of caspases, disrupting signaling pathways, and regulating each other (Cheung et al., 2008; Devi, 2004; Eckelman and Salvesen, 2006; Fulda and Vucic, 2012; Mahoney et al., 2008; Silke and Meier, 2013; Vince et al., 2007). The human IAP family includes eight members that contain at least one baculovirus IAP repeat (BIR) domain: XIAP (X-linked IAP), cIAP1, cIAP2, ILP2, Bruce, Survivin, Livin and NAIP (Hauser et al., 1998; Kasof and Gomes, 2001; Liston et al., 1996; Mahotka et al., 1999; Shin et al., 2005; Vitte-Mony et al., 1997). XIAP contains three BIR domains that mediate direct binding to caspase 3, 7 and 9 (Manns et al., 2011; McComb et al., 2019; Takahashi et al., 1998). cIAP1 and cIAP2 are considered poor caspase inhibitors even though they can bind caspases directly *in vitro* (Eckelman et al., 2006). Their main pro-survival function is attributed to the E3 ubiquitin ligase zinc-finger (RING) domain, which they and XIAP have in common (Gyrd-Hansen and Meier, 2010; Schile et al., 2008; Sun et al., 1999; Vince et al., 2007).

cIAPs can interact with TNF-associated factors (TRAFs) to prevent the formation of pro-apoptotic signaling complexes in the extrinsic apoptotic pathways initiated by TNFR (Gyrd-Hansen and Meier, 2010; Rathore et al., 2017; Shu et al., 1996; Varfolomeev et al., 2007). cIAPs affect cell survival through both canonical and non-canonical NF-κB signaling (Bertrand et al., 2008; Bonizzi and Karin, 2004; Gaither et al., 2007; Vallabhapurapu et al., 2008; Varfolomeev et al., 2007, 2008; Vince et al., 2007). The canonical NF-κB pathway involves the assembly of a signaling complex comprised of TRADD, TRAF2, RIPK1, and cIAPs. cIAPs can also induce non-degradative ubiquitylation of RIPK1, as well as auto-ubiquitylation (Gyrd-Hansen and Meier, 2010; Rathore et al., 2017; Shu et al., 1996; Varfolomeev et al., 2007). The latter leads to activation of downstream pro-survival NF-κB signaling. In addition, cIAPs can also stimulate proteasomal degradation of NF-κB-inducing kinase (NIK) and thereby promote survival through the non-canonical NF-κB signaling pathway (Fig. 3).

XIAP is the only IAP family member that directly binds to, and inhibits effector caspases (Eckelman et al., 2006). In addition, XIAP promotes the ubiquitin-proteasome mediated-degradation of caspases (Bornstein et al., 2011; Deveraux et al., 1998; Schile et al., 2008). XIAP contains three BIR domains that bind caspase 3, 7 and 9 and a RING domain for binding E2-enzymes (Manns et al., 2011; McComb et al., 2019; Takahashi et al., 1998). Remarkably, deletion of the XIAP-RING virtually abolished the anti-apoptotic function of XIAP in mutant mice, similarly to XIAP-Null mice (Garcia-Fernandez et al., 2010; Schile et al., 2008). The function of ubiquitylation for XIAP-mediated caspase inhibition can be demonstrated by the fact that XIAP-ΔRING mice express elevated levels of mutant protein that can effectively bind to caspases.

5.1. Role of IAPs in cancer

Elevated IAP protein levels have been reported in various types of cancer (Mohamed et al., 2017). In particular, XIAP is overexpressed in leukemia as well as the following carcinoma: lung, colon, melanoma, ovarian, bladder, renal, breast, prostate, and thyroid (Dubrez et al., 2013; Krajewska et al., 2003; Tamm et al., 2000). Increased levels of cIAP1 have been found in colon and bladder cancer and cervical B-cell chronic lymphocytic leukemia (Dubrez et al., 2013; Tamm et al., 2000). cIAP2 overexpression was observed in mucosa-associated lymphoid tissue (MALT) lymphoma and can be attributed to the t(11;18)(q21;q21) chromosomal translocation (Gyrd-Hansen et al., 2008). High cIAP1/2 expression has also been shown in CLL, acute B lymphoblastic leukemia (B-ALL) and FL samples (Akyurek et al., 2006; Munzert et al., 2002). In addition to the previously discussed signaling pathways, cIAP2 and XIAP can be upregulated through mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), protein kinase C-delta (PKCδ), and cyclic adenosine monophosphate (cAMP) pathways (Dumetier et al., 2020; Nishihara et al., 2003; Seol, 2008; Terragni

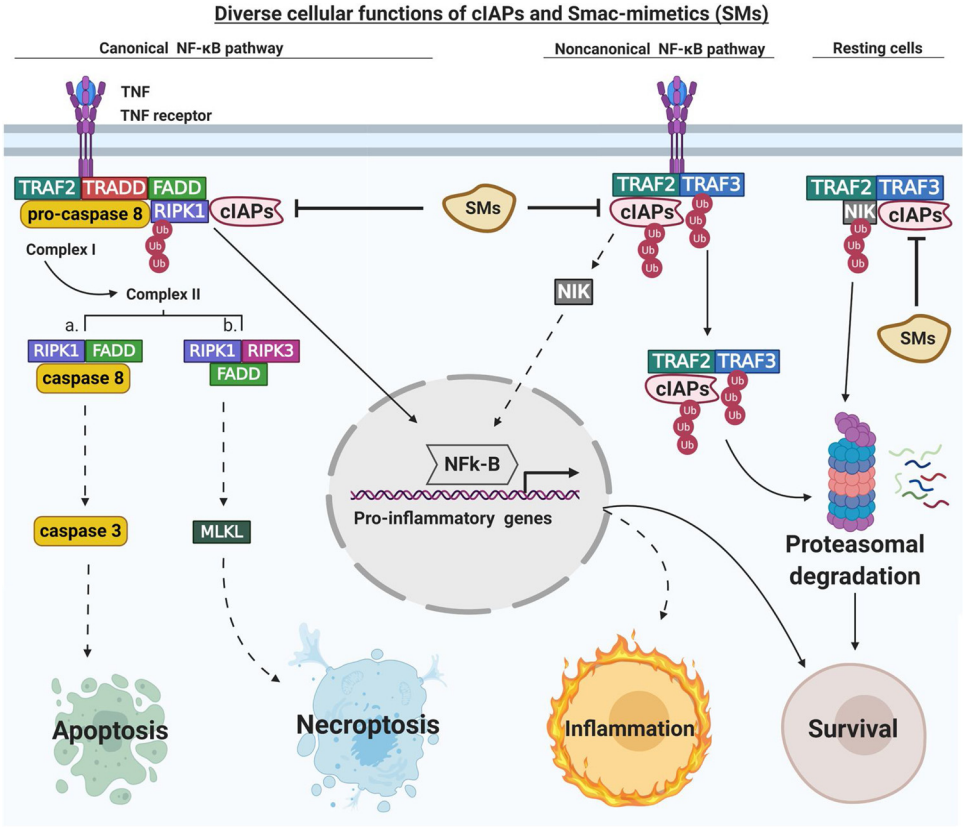

Fig. 3. Diverse cellular functions of cIAPs and Smac-mimetics (SMs). The canonical and non-canonical NF-κB pathway control the expression of genes that mediate inflammation and cell survival. Treatment with Smac-mimetics (SMs) inhibits the NF-κB canonical pathway by binding to and degrading cIAPs. This prevents the ubiquitylation of RIPK1 and leads to the formation of complex 2a containing RIPK1, caspase 8, and FADD, which can activate caspase 3 and promote apoptosis. Alternatively, if caspases are inhibited, a complex with RIPK3 can form (complex 2b). RIPK3 auto-phosphorylates and also phosphorylates the pseudo kinase MLKL, which leads to necroptotic cell death - "Necroptosis". In resting cells, the cIAPs-TRAF2-TRAF3 complex constitutively ubiquitylates NIK, resulting in proteasomal degradation of NIK and cell survival. Treatment with SMs causes degradation of cIAPs and prevents degradation of NIK. Elevated NIK levels activate non-canonical NF-κB signaling and the expression of NF-kB pro-inflammatory target genes.

et al., 2008; Wang et al., 2003). Significantly, loss of the XIAP-antagonist ARTS results in high levels of XIAP, increased resistance to apoptosis and tumorigenesis (Abbas and Larisch, 2020; Fuchs et al., 2013; Garcia-Fernandez et al., 2010).

5.2. IAP-antagonists

IAPs are negatively regulated by IAP-antagonist proteins, such as Smac/Diablo and ARTS (Sept4_i2) (Abbas and Larisch, 2020; Bornstein et al., 2011; Gottfried et al., 2004). Both Smac/Diablo and ARTS promote apoptosis by inhibiting and degrading IAPs (Abbas and Larisch, 2020). While Smac/Diablo binds to both XIAP and cIAPs, it induces degradation of only cIAPs through the Ubiquitin-Proteasome-System (UPS) (Creagh et al., 2004; Yang and Du, 2004). In contrast, ARTS binds to, and selectively promotes the degradation of XIAP through the UPS (Abbas and Larisch, 2020; Edison et al., 2012b; Garrison et al., 2011; Gottfried et al., 2004). In living cells, ARTS resides at the mitochondrial outer membrane (MOM). In response to apoptotic stimuli, ARTS translocates to the cytosol in a caspase-independent manner and binds to XIAP (Edison et al., 2012a). Binding of ARTS to XIAP causes derepression of caspases bound to XIAP, which facilitates the cleavage of substrates (such as Bid) that promote MOMP (Edison et al., 2012a). Furthermore, ARTS acts as a scaffold bringing XIAP with its E3-ligase activity into close proximity with Bcl-2 to promote the ubiquitylation and degradation of Bcl-2 (Edison et al., 2017).

Although Smac/Diablo binds to XIAP and cIAPs, it can only degrade cIAPs (Cossu et al., 2019; Yang and Du, 2004). Consistent with this, inactivation of Smac in mice led to elevated levels of cIAP1 and cIAP2 but did not affect the expression of XIAP (Kohli et al., 2004; Okada et al., 2002; Qiu et al., 2013). Interestingly, while Sept4/ARTS-Null mice show increased tumorigenesis, Smac-deficient mice do not display spontaneous tumorigenesis (Kohli et al., 2004; Okada et al., 2002; Qiu et al., 2013). In addition, Smac knockout mice have no detectable apoptotic defects (Kohli et al., 2004; Okada et al., 2002).

The pro-apoptotic ARTS protein is a splice variant of the Septin 4 (*Sept4*) gene (Larisch et al., 2000; Mandel-Gutfreund et al., 2011). ARTS expression is lost in more than 70 % of ALL patients, in 50 % of lymphoma patients, and in a significant fraction of hepatocellular carcinoma (HCC) patients (Elhasid et al., 2004; Garcia-Fernandez et al., 2010); Larisch & Steller, unpublished data). Furthermore, Sept4/ARTS-deficient mice express increased XIAP protein, demonstrating that ARTS limits XIAP levels *in vivo*. These mice are also prone to developing spontaneous tumors, and they have highly accelerated lymphomagenesis in the Eu-Myc model (Garcia-Fernandez et al., 2010). Significantly, Sept4/ARTS-deficient mice have increased numbers of hematopoietic stem and progenitor cells (HSPCs) which are resistant to apoptosis (Garcia-Fernandez et al., 2010). Inactivation of both ARTS and XIAP in DKO (Double Knock out) mice suppresses both the stem cell and tumor phenotypes of Sept4/ARTS-null mice (Garcia-Fernandez et al., 2010). This demonstrates that the tumor suppressor function of ARTS is largely mediated through XIAP-antagonism in the context of stem cell apoptosis (Abbas and Larisch, 2020; Garcia-Fernandez et al., 2010). Interestingly, ARTS and XIAP play a similar function in restricting the number of stem cells through apoptosis in the skin and intestine (Fuchs et al., 2013; Garcia-Fernandez et al., 2010; Koren and Fuchs, 2019; Koren et al., 2018). Stem cells, in contrast to differentiated cells, rely more heavily on anti-apoptotic proteins for their survival (Goff et al., 2013; Soteriou and Fuchs, 2018; Van Houdt et al., 2011). Unsurprisingly, overexpression of Bcl-2 in hematopoietic stem cells (HSCs) and other cancer stem cells (CSCs) was associated with chemoresistance (Domen and Weissman, 2003; Goff et al., 2013; Lagadinou et al., 2013). Similarly, conditional deletion of Mcl-1 in human HSCs reduced their regenerative capacity, while overexpression of Mcl-1 and Myc promoted HSC malignancy, development of lymphoma and increased chemoresistance of various tumors (Campbell et al., 2010a, b). Additionally, dysregulation of Wnt signaling robustly fuels intestinal tumorigenesis (Drost et al., 2015). Collectively, these results demonstrate the ARTS exerts its tumor suppressor function by controlling stem cell apoptosis through regulation of XIAP levels.

5.3. Therapeutic strategies to target IAPs

The critical role of anti-apoptotic proteins in tumorigenesis suggests that they are promising targets for inhibition for drug development (Dimitrov, 2012). The development of small-molecule agents which mimic the activity of natural IAP-antagonists was first explored by generating Smac-mimetics (SMs). SMs were based on the conserved IBM (AVPI/F) of IAP-antagonists found originally in Reaper, Hid and Grim, and later in the mammalian IAP-antagonists Smac and Omi (Bergmann et al., 2003; Goyal et al., 2000; Grether et al., 1995; Li et al., 2004; Oost et al., 2004; Shi, 2002; White et al., 1994). SMs were initially designed to bind and inhibit XIAP (Liu et al., 2000; Sharma et al., 2006; Shi, 2002; Sun et al., 2004; Zobel et al., 2006). However, these compounds are primarily active against cIAPs (Corti et al., 2018; Darding et al., 2011; Varfolomeev et al., 2007; Welsh et al., 2016). SMs bind to BIR3 and BIR2 domains of IAPs and inhibit their interaction with partner proteins (Liu et al., 2000; Wu et al., 2000). Additionally, the binding of SMs to cIAP1 and cIAP2 stimulates their E3-ligase activity and causes their proteasomal degradation through the apoptotic or necroptotic pathways (Cho et al., 2009; Darding et al., 2011; Dueber et al., 2011; Feltham et al., 2011; He et al., 2009; McComb et al., 2012). Necroptosis is a form of regulated necrotic cell death that can be activated under apoptosis-deficient conditions (Degterev et al., 2005; Gong et al., 2019; Qin et al., 2019; Shan et al., 2018; Wang et al., 2017; Yuan et al., 2019). Necroptosis can elicit strong adaptive immune responses that may protect against tumor progression; however, the recruited inflammatory response may also promote tumorigenesis and cancer metastasis, and necroptosis may generate an immunosuppressive tumor microenvironment (Gong et al., 2019; Qin et al., 2019; Wang et al., 2017).Treatment with SMs inhibits the canonical NF-κB pathway by binding to and degrading cIAPs. This prevents the ubiquitylation of receptor-interacting protein kinase 1 (RIPK1) and leads to the formation of a complex-2a containing RIPK1, caspase 8, and FADD, which can activate caspase 3 and promote apoptosis (Fig. 3) (Oberst et al., 2011; Vandenabeele et al., 2010). Alternatively, if caspases are inhibited, a complex with receptor-interacting protein kinase 3 (RIPK3) can form a different complex-2b. RIPK3 auto-phosphorylates and also phosphorylates the pseudo kinase mixed lineage kinase domain-like protein (MLKL), which leads to necroptotic cell death (Fig. 3). This necroptotic mechanism provides a way to bypass tumor cell resistance to apoptosis (Abbas and Larisch, 2020; Silke and Meier, 2013; Zhu et al., 2019).

Various SMs have been developed and are currently at different stages of pre-clinical and clinical evaluation. Birinapant/TL32711 is a bivalent Smac mimetic compound tested in several past clinical trials (Amaravadi et al., 2015; Benetatos et al., 2014; Condon et al., 2014). In addition, it is currently evaluated in a trial for AML (NCT01486784). Birinapant is more potent towards cIAP1 and cIAP2 than XIAP as it induces a conformational change in cIAPs that causes their ubiquitination and degradation (Dueber et al., 2011; Varfolomeev et al., 2007). Prolonged Birinapant-treatment promotes cIAP1/2 degradation, reduces NIK levels and decreases NF-κB activity, suggesting the induction of a negative feedback loop (Yang et al., 2016). Birinapant has also shown clinical benefits when combined with the chemotherapeutic drug irinotecan in patients with irinotecan-refractory colorectal cancer (Senzer et al., 2013).

Another SM, LCL-161, is an orally available agent with preclinical activity mostly in combination with different agents (West et al., 2016). The compound initially demonstrated promising results by degrading cIAP1 in multiple myeloma, glioblastoma and sarcoma (Houghton et al., 2012; Ramakrishnan et al., 2014). However, in the clinical setting, no objective responses were observed in solid tumors despite cIAP1 degradation and cytokine release at well-tolerated level (West

et al., 2016). SMs have also been shown to induce TRAIL target genes as a result of NF-κB signaling (Kulms and Schwarz, 2006; Wang et al., 2008). As it stands, Birinapant or LCL161 can be combined safely with a range of chemotherapeutic agents, and both have entered phase 2 trials (Fulda, 2015).

DEBIO 1143 is an orally active SM targeting cIAP1, cIAP2 and XIAP (Cai et al., 2011). The compound displayed anti-tumor effects as a single agent, and in combination with chemotherapeutics in breast and ovarian xenograft mouse models (Brunckhorst et al., 2012; Zhang et al., 2013). *In vitro*, DEBIO 1143 was able to sensitize carboplatin-resistant tumor cell lines to carboplatin (Thibault et al., 2018). In this respect, phase I/II clinical trials for squamous cell carcinoma of the head and neck have been initiated (NCT02022098) (Hurwitz et al., 2015).

SMs are unlikely to be effective as monotherapy agents (Lalaoui and Vaux, 2018). SMs can stimulate the non-canonical NF-κB pathway and cause increased production of inflammatory cytokines (Fulda, 2017). Thus, it is challenging to maximize the anti-tumor activity of SMs while minimizing potential undesired side effects (Fulda, 2017). Although several SMs have entered clinical trials to treat cancers, the identification of molecular and immune biomarkers of response to SMs is still lacking (Lalaoui and Vaux, 2018).

5.4. Selective targeting of XIAP

Elevated levels of XIAP are a marker for poor prognosis in AML, renal cell carcinoma (RCC), gastric cancer, and head and neck cancer (Assaraf et al., 2019; Gao et al., 2019; Mizutani et al., 2007; Tamm et al., 2004). Importantly, although Smac-mimetics were initially developed to target XIAP to promote apoptosis, they preferentially target cIAPs and elicit their effects mostly through non-apoptotic pathways (Lalaoui and Vaux, 2018). Therefore, targeting XIAP using selective and specific compounds remains a major goal and challenge. Selective XIAP-targeted therapies have the potential to overcome cancer cell resistance by directly stimulating caspase activity and apoptosis.

The use of antisense oligonucleotides (AS ODNs) has been investigated as a strategy to neutralize IAPs for the past decade. AS ODNs are short stretches of synthetic DNA designed to complement a specific mRNA (Stein et al., 1988). For years, AS ODNs have been investigated as selective inhibitors for gene expression and protein translation for a variety of genetic diseases (Galderisi et al., 1999; Gleave et al., 2002; Jansen and Zangemeister-Wittke, 2002). XIAP-specific AS ODNs were designed to downregulate both XIAP mRNA and protein levels (Hu et al., 2003). AEG35156 is a XIAP AS ODN with high stability and potency. Initial AEG35156 trials yielded promising results as it has an acceptable safety profile with some signs of anti-cancer activity (Cheung et al., 2006; Danson et al., 2007; Dean et al., 2007; Schimmer et al., 2009). However, clinical trials were halted after only two cycles due to liver toxicity (LaCasse, 2013). Furthermore, in a subsequent clinical trial, AEG35156 showed no significant benefits in patients at acceptable levels of toxicity (Lee et al., 2016). These efforts provide yet another example that translating results from cell-based and mouse models to the clinic is challenging and often not successful (Johnson et al., 2001).

5.5. Role of IAPs in acquired drug resistance

Several mechanisms for acquired drug resistance to SMs were described (Fig. 4). A number of cancer cell lines tested for their response to SMs were non-responsive (Maas et al., 2013; Petersen et al., 2010, 2007). Preclinical studies showed that xenograft tumors that initially responded to SM-treatment would regrow after treatment, indicating the emergence of SM-resistant cells (Petersen et al., 2007). In lung cancer cells, cIAP2 protein levels rebounded following SM-treatment, and inhibition of cIAP2 expression sensitized resistant cells to SM-treatment *in vitro* (Petersen et al., 2010). This suggests that one mechanism by which tumor cells evade SM-induced apoptosis is through compensatory up-regulation of cIAP2 which prevents the release of RIPK1 from the receptor (Petersen et al., 2010). Thus, these CLL cultured cells display resistance to SMs due to their inability to form the RIPK1-dependent death-inducing complex (Maas et al., 2013). It has been suggested that resistant CLL may also acquire mutations in other signaling pathways, such as PI3K, which can lead to elevated levels of cIAP2 (Petersen et al., 2010).

Tumors which lack the ability to produce or respond to TNF are more likely to be resistant to SM-treatment (Morrish et al., 2020; Petersen et al., 2007; Varfolomeev et al., 2007; Vince et al., 2007). Therefore, increasing TNF expression *in vivo* may sensitize cancer cells to SMs. However, systemic administration of exogenous TNF to patients is highly toxic and therefore not practical in the clinic (Roberts et al., 2011). Combination therapy of AAVP-TNF and LCL161 in mice bearing human xenografts showed increased expression of TNF in tumor tissues and prolonged survival of mice (Yuan et al., 2013). However, this approach is challenging vis a vis implementation to the clinic since raising TNF-levels in human cancer patients has proven to be toxic in the past (Roberts et al., 2011). Another potential approach might be to enhance the levels of TNF by targeting parallel signaling pathways. MAPK inhibitors were effective in combination with a precursor of Birinapant to increase TNF-production and macrophage killing (Lalaoui et al., 2016). TNF can also be produced by neighboring cells in the TME. The release of TNF by cells in close proximity to resistant cells may possibly enhance SM-mediated killing (Beug et al., 2014).

P-glycoprotein (P-gp/ABCB1) is a key player in the formation of the multidrug-resistance phenotype in cancer. The protein confers resistance by mediating the ATP-dependent efflux of an astonishing array of anticancer drugs. Its broad specificity has been the subject of numerous attempts to inhibit the protein and restore the efficacy of anticancer drugs (Callaghan et al., 2014). Chemoresistant tumors that display increased P-gp overexpression acquire cross-resistance to multiple structurally unrelated drugs, which leads to MDR (Hugle et al., 2019). cIAP1 levels in chemoresistance cells which have increased P-gp expression were less affected by SMs-treatment. However, combined treatment with P-gp transport inhibitors sensitized the cells to SMs and apoptosis (Gacche and Assaraf, 2018; Hugle et al., 2019; Leonetti et al., 2019; Li et al., 2016a; Robey et al., 2018; Taylor et al., 2015).

A general strategy to overcome the resistance of cancer cells to chemotherapy is to apply combination chemotherapeutic regimens (Chen et al., 2018; Fulda, 2017; Scheurer et al., 2019; Shekhar et al., 2019). In glioblastoma, SMs have been found to increase the sensitivity toward the anchor chemotherapeutic drug temozolomide (Fulda, 2017; Wagner et al., 2013). In childhood ALL, SMs synergized with chemotherapeutic drugs, such as Ara C, gemcitabine, cyclophosphamide, doxorubicin, etoposide, vincristine, and paclitaxel to promote apoptotic cell death (Loeder et al., 2009; Schirmer et al., 2016). In AML, SMs treated cells induced cytarabine-mediated cell death (Chromik et al., 2014). In High-grade Serous Ovarian Cancer (HGSC) primary samples, a small proportion of cells were platinum resistant and had high expression of IAP proteins. These cells possessed stem cell characteristics with respect to tumor initiation, multi lineage differentiation, and self-renewal (Janzen et al., 2015). Co-treatment of birinapant with the chemotherapeutic agent carboplatin sensitized these cells and increased killing in a caspase-8 dependent mechanism *in vitro* and in xenograft HGSC models (Janzen et al., 2015; Morrish et al., 2020).

5.6. Mitogenic signaling by apoptotic cells

Another mechanism that can contribute to cancer relapse and the emergence of tumors that are resistant towards chemotherapy and radiation therapy is mitogenic signaling by apoptotic cells (Bergmann and Steller, 2010). Work in *Drosophila* originally revealed an unexpected role of caspases in the production of mitogenic signals that stimulate the proliferation of stem and progenitor cells to aid in tissue regeneration (Perez-Garijo et al., 2004; Ryoo et al., 2004). Since then,

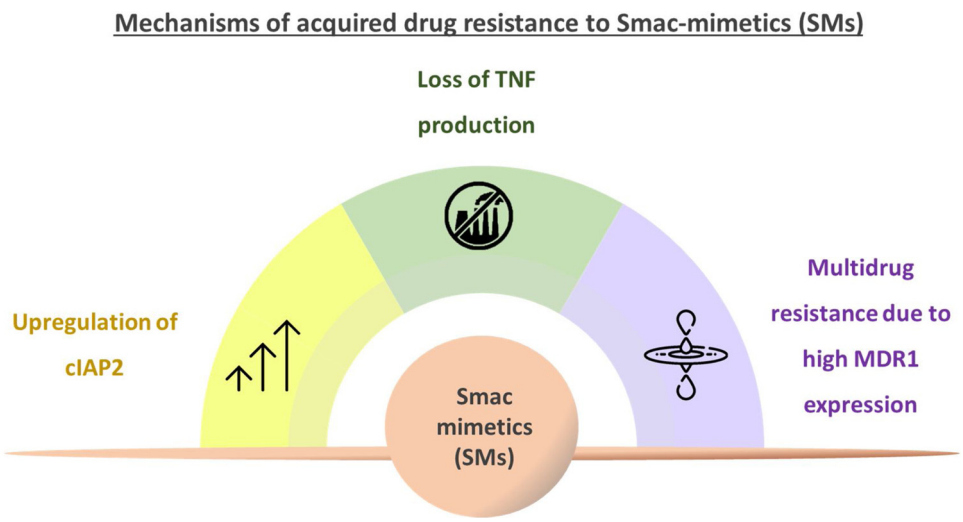

Fig. 4. Mechanisms of acquired drug resistance to Smac-mimetics (SMs). Resistance to SMs can result from the upregulation of cIAP2, reduced TNF-production or reactivity, and multi-drug resistance due to high MDR1 expression.

similar phenomena have been described in a wide range of organisms, including *Hydra*, planaria, amphibians and mice (Fuchs and Steller, 2015). Importantly, tumor cells undergoing apoptosis in response to radiation therapy also generate potent growth-stimulating signals that facilitate repopulation of tumors (Huang et al., 2011). These observations are in line with many other studies showing that tumors coopt wound healing pathways for maintenance and growth (Dvorak, 2015; Laughney et al., 2020). Because virtually all current forms of cancer therapy induce apoptosis, it is to be expected that mitogenic signaling by apoptotic cells is a widespread phenomenon that contributes to metastasis and relapse. Conversely, apoptotic cells can also induce more cell death by releasing death-inducing factors, such as TNF, a phenomenon termed apoptosis-induced apoptosis (AiA) (Perez-Garijo et al., 2013). In particular, following large-scale radiation-induced apoptosis in the developing wing in *Drosophila*, apoptotic cells release Eiger, the *Drosophila* ortholog of TNF, which activates the JNK pathway and causes apoptosis in a non-autonomous manner (Perez-Garijo et al., 2013). Likewise, apoptosis of hair follicle cells in mice induces additional non-autonomous apoptosis through secretion of TNF (Perez-Garijo et al., 2013). These findings help explain the “waves” of apoptosis seen in tissues experiencing large-scale cell death, such as the “bystander effect” in radiobiology (Azzam and Little, 2004; Morata and Herrera, 2013). One promising future research direction will be to investigate ways to stimulate AiA for efficient tumor elimination.

In recent years, emerging new evidence suggests that many apoptotic proteins have also non-apoptotic functions (Aram et al., 2017; Fujita et al., 2008; Ichim and Tait, 2016; Ishizaki et al., 1998; Perez-Garijo et al., 2013). Caspase-3, for example, (Aram et al., 2017) plays a critical role in cell differentiation, proliferation and organ size (Fernando et al., 2002; Fujita et al., 2008; Ishizaki et al., 1998; Yosefzon et al., 2018). These functions involve sub-lethal levels of effector caspase activity, as opposed to the fully-blown activity that triggers apoptosis (Aram et al., 2017). Mechanistically, in organ growth signaling, caspase-3 activates a cascade of proteins responsible for organ size (Yosefzon et al., 2018). Interestingly, this results in upregulation of XIAP, which in turn inhibits caspase-3 activity (Yosefzon et al., 2018). Therefore, XIAP functions as a feedback antagonist for proteins which influence organ size (Yosefzon et al., 2018). Recently it has been shown that a minority of mitochondria can undergo MOMP in a stress-regulated manner (Ichim et al., 2015). This leads to limited caspase activation, which is insufficient to trigger cell death (Ichim et al., 2015). However, the activation of caspases can result in DNA damage and subsequently cellular transformation and tumorigenesis (Ichim et al., 2015). Thus, the utilization of caspase modulators for therapeutic purposes may have significantly broader consequences than affecting apoptosis (Yosefzon et al., 2018). These findings have important implications for the clinic since they suggest that combining conventional anti-cancer therapies with drugs that target mitogenic signaling pathways will blunt tumor relapse and improve the long-term success of treatment. Therefore, combination treatments that include antagonists of the relevant mitogenic signaling pathways may improve the long-term success of radiation and conventional chemotherapy.

5.7. *Targeting XIAP to induce apoptosis in cancer cells*

It has become increasingly clear that targeting cIAP1/2 results in a myriad of responses, many of which are not directly related to the regulation of apoptosis. It remains unclear whether SMs exert their effects through apoptosis, inflammation or necroptosis (Fulda, 2017; Fulda and Vucic, 2012; Li et al., 2018; Yabal et al., 2014). On the other hand, the available evidence indicates that XIAP is a promising target for directly overcoming the innate resistance of cancer cells towards apoptosis.

The pro-apoptotic ARTS protein has a distinct function of antagonizing both XIAP and Bcl-2 by promoting their ubiquitin-mediated degradation (Edison et al., 2017, 2012b). Furthermore, studies in mice and human patients have shown that ARTS acts as a potent tumor suppressor protein, and that this function is largely mediated through its role as a physiological XIAP antagonist (Elhasid et al., 2004; Garcia-Fernandez et al., 2010). We therefore propose that ARTS-mimetic small molecules may be promising anti-tumor therapeutics, especially for cancers with high levels of XIAP and Bcl-2. In order to develop small-molecule ARTS-mimetics, a structure-based computational screen was conducted that identified candidate compounds predicted to bind the unique binding site for ARTS in XIAP/BIR3 (Mamriev et al., 2020). The highest scoring compounds were synthesized and tested for their ability to induce apoptosis in several types of cancer cells (Mamriev et al., 2020). Some ARTS-mimetic compounds were indeed able to degrade XIAP and Bcl-2 and induce apoptosis. These ARTS-mimetics can directly bind to BIR3/XIAP and promote the degradation of XIAP, but not cIAP1 (Mamriev et al., 2020). Moreover, overexpression of XIAP reduced the activity of ARTS-mimetics, suggesting that XIAP is the main target for these compounds. Therefore, ARTS-mimetics may provide the basis for developing a new class of specific XIAP-antagonists which are expected to inhibit XIAP by degrading it. Degrading XIAP, as opposed to allosteric inhibition, may facilitate the development of compounds with reduced systemic load and less unspecific cytotoxic effects (Lai and Crews, 2017). Although efforts to develop ARTS-mimetics for the clinic

require further efforts, these compounds are unique in their ability to antagonize the two major anti-apoptotic proteins with well-established roles in cancer, Bcl-2 and XIAP.

6. Concluding remarks

In conclusion, direct inhibition of anti-apoptotic Bcl-2 proteins have proven effective for the treatment of lymphatic cancers. However, the goal of targeting a single member of the anti-apoptotic Bcl-2 family is shifting due to the compensatory influence of other family members. As for IAPs, at this moment in time, no therapeutic advancement has shown clinical benefits upon monotherapy. However, the clinical utility of potent and specific XIAP-inhibitors deserves more rigorous exploration. These efforts have been hampered in the past due to the lack of suitable compounds. A plethora of clinical data on elevated XIAP levels in certain tumors, combined with the direct role of XIAP as a direct inhibitor of apoptotic caspases provides a strong mechanistic rationale for targeting this protein. In addition, XIAP and its natural antagonist ARTS play critical physiological roles for the regulation of stem cell apoptosis, and data from mouse indicate that the tumor suppressor function of ARTS is mediated through killing of inappropriate stem cells. Therefore, XIAP-targeted therapies have the potential to eradicate cancer stem cells or related tumor-initiating cell populations and thereby prevent or reduce tumor relapse. Finally, attention should be given to blocking mitogenic signaling from cancer cells that undergo apoptosis in response to radiation or chemotherapy in order to counteract a “wound healing” response that can aid tumor regeneration and seeding of metastases. Continued advances in understanding the mechanism and role of apoptosis in tumor-initiating cells, and how these pathways adapt in response to therapeutics, is likely to suggest powerful new approaches to overcome drug resistance of cancers in the clinic.

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