Targeting Apoptosis to Overcome Chemotherapy Resistance

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Abstract
Chemotherapy resistance is a major limiting factor for the extensive use of chemotherapeutic drugs in cancer treatment. Despite the large number of newly discovered medications, treatment success rates are still unsatisfactory. Programmed cell death, called apoptosis, is one of the main tissue homeostasis mechanisms that balances cell survival and death. Apoptosis can be induced through extrinsic and intrinsic pathways or repressed by inhibitor proteins. During tumor progression, homeostasis between the anti-apoptotic and pro-apoptotic regulators is disturbed and shifted towards survival through various escape mechanisms. Dysregulation of apoptosis-regulatory mediators, particularly high levels of anti-apoptotic proteins, is one of the main mechanisms by which tumor cells acquire resistance to chemo- and radiotherapy. Therefore, it is important to restore apoptosis in the chemo- and radiotherapy-resistant tumor cells. In this chapter, we summarize general chemotherapy resistance mechanisms, discuss the role of extrinsic and intrinsic pathways in chemoresistance, and review the current experimental strategies to overcome chemotherapy resistance targeting the apoptotic pathways.
Keywords: apoptosis in chemotherapy resistance; death receptors; extrinsic pathway of apoptosis; intrinsic pathway of apoptosis; targeting apoptosis

Running Title: Overcoming chemotherapy resistance

INTRODUCTION
Cancer is an important global health problem causing death of ~10 million people in 2020 (1). The preeminent hallmarks of tumor cells are uncontrolled proliferation and the acquisition of invasive and/or metastatic properties (2). The therapeutic options for cancer largely depend on the stage of the disease; these include surgery, chemotherapy, immunotherapy, radiotherapy, hormone, and anti-angiogenic therapy (3). Cytotoxic chemotherapy is one of the treatment modalities for the control of invasive malignancies (4,5). Commonly used chemotherapeutic drugs are alkylating agents, anthracyclines, topoisomerase inhibitors, antimetabolites, microtubule inhibitors, molecular targeted drugs and immune antibodies (6). Limiting factor for the extensive use of chemotherapeutic drugs in cancer treatment is the development of chemotherapy resistance by which tumor cells often regain their invasive and metastatic properties (7,8).

MECHANISMS OF CHEMOTHERAPY RESISTANCE
Chemotherapeutic drug resistance can either occur through intrinsic or acquired mechanisms. Intrinsic mechanisms include natural resistance of tumor cells against chemotherapeutic drugs at the onset of treatment, while acquired mechanisms occur later during cancer treatment, where tumor cells that were initially sensitive to the administered chemotherapeutic drug develop resistance against it (8,9). Acquired mechanisms that result in drug resistance can vary from alterations in drug activation/inactivation to decreased drug uptake, increased drug release, changes in drug targets, inhibition of cell death, increased DNA repair, and changes in epigenetic regulation (7,10).

Uptake and efflux mechanisms
Limited or prevented access of targeted tumor cells to chemotherapeutics drugs often result in the development of drug resistance (11). ATP-binding cassette (ABC) transporter protein family members are located at the plasma membrane and use ATP as an energy source to effectively pump drugs out of the cell (2). ABC transporter proteins are usually substrate-
specific and mediate efflux of major cancer chemotherapeutics such as taxanes, topoisomerase inhibitors, and antimetabolites. Increased expression of ABC transporter proteins such as MDR1, MRP1 and BCRP can reduce intracellular drug concentrations, thus leading to chemotherapy resistance (12). MDR1 and BCRP are highly expressed in the blood-brain barrier which complicates treatment of metastatic tumor cells in the central nervous system and brain (11). Reduced uptake of chemotherapeutic drugs into tumor cells has also an unfavorable effect on cancer treatment (13). For instance, the solute carrier (SLC) transporter protein family members are involved in processes like drug uptake or absorption, distribution, metabolism, and elimination. Therefore, changes in SLC transporter protein expression levels are often associated with chemotherapy resistance (14).

**Drug metabolism**

Some chemotherapeutic drugs must be activated by metabolic enzymes before reaching their clinical efficacy. Irregularities or defects of these processes can lead to reduced drug activation, and chemotherapy resistance (15). Cytochrome P450 (CYP) superfamily members, glutathione-S-transferase (GST), uridine diphospho-glucuronosyltransferase (UGT), thiopurine methyltransferase (TPMT), and dihydropyridine dehydrogenase (DPD) are the most prominent enzymes responsible for chemotherapeutic drug activation and detoxification. Genetic variations in specific CYP genes with effects on the protein structure or expression levels can cause functional differences in drug absorption or clearance leading to chemotherapy resistance; for instance, CYP3A5 polymorphisms that are associated with premature lapatinib inactivation are responsible for drug resistance occurring during breast cancer treatment (16,17). On the other hand, GSTs are phase-II detoxification enzymes that are protecting cellular macromolecules from reactive electrophile attacks, catalyzing conjugation reactions with xenobiotics, inactivating conjugated drugs, and presenting them to ABC transporters (11,18). Elevated GST expression levels have been found to be associated with chemotherapy resistance in various cancer types (19). In addition, GSTs can also indirectly cause drug resistance by inhibiting the RAS-MAPK signaling pathway (7).

**DNA damage repair**

Many chemotherapeutic drugs cause DNA damage, either directly (for example, platinum-based drugs) or indirectly (for example, topoisomerase inhibitors). Tumor cells can counteract these damages by using several DNA repair mechanisms such as homologous recombination,
base excision repair, mismatch repair, nucleotide excision repair or translesion synthesis (20–22). Elevated expressions of repair systems genes are often associated with chemotherapy resistance and therefore excellent molecular drug targets to overcome chemotherapy resistance in many cancer types (20,23–25).

**Epigenetic regulation**
Heritable changes in gene expression that are not caused by variations and mutations of the genomic DNA sequence are usually epigenetically regulated (26). This can be achieved by different mechanisms, including the creation of specific DNA methylation and histone modification patterns that are crucial in regulating gene expression. Upregulation of genes encoding DNA repair, anti-apoptosis, and ABC transporter proteins by epigenetic mechanisms can contribute to the development of chemotherapy resistance during cancer treatment (7,27).

In the human genome, about 2% of all transcripts encode for proteins, while the majority of the remaining are non-protein coding RNA transcripts (28). MicroRNAs (miRNAs) are short RNA transcripts consisting of ~22-24 nucleotides that bind to the 3'-untranslated region (3'UTR) of their target mRNA and inhibit their translation (29). It has been shown that miRNAs that target genes involved in carcinogenesis, drug metabolism, drug efflux, and uptake are also responsible for the development of chemotherapy resistance (30,31). miRNAs can serve as biomarkers for the assessment of prognosis and survival of cancer patients undergoing chemotherapy (7). Long non-coding RNAs (lncRNAs) are another class of non-protein coding RNA transcripts, ~200 nucleotides long, with important functions in gene expression. Especially, those that regulate the expression of drug metabolism enzymes, ABC transporter proteins, DNA repair proteins, and proteins involved in the apoptotic pathway have been found to be responsible for the development of chemotherapy resistance (28,32). Recently a new class of non-protein coding RNA transcripts, named circular RNAs (circRNAs), have been found to be associated with chemotherapy resistance and are currently used as prognostic biomarkers (33).

**Inhibition of cell death**
The main goal of cancer chemotherapy is to inhibit cancer cell survival by inducing cell death. Apoptosis, or programmed cell death, is a genetically regulated and evolutionarily conserved process with important roles in all developmental stages and tissue homeostasis (34). Defects in the apoptotic pathway can cause abnormal cellular proliferation and accumulation of genetic
defects, mostly leading to cancer development and later also chemotherapy resistance (35). The apoptotic regulatory molecules constitute important molecular targets in cancer therapy; most anticancer treatments like chemotherapy, radiotherapy, and immunotherapy primarily aim to activate apoptosis, and they fail when cancer cells gain apoptotic resistance (36).

ROLE OF APOPTOSIS IN CHEMOTHERAPY RESISTANCE
Apoptosis is regulated by extracellular and intracellular signals from extrinsic and intrinsic pathways (37). The extrinsic pathway is mediated by cell surface death receptors while the intrinsic pathway is initiated from the mitochondria. Caspases (cysteine aspartic acid-specific proteases) are the regulatory proteins in both pathways and divided in two groups: initiators and effectors (38). Initiator caspases are activated by binding to an adaptor molecule and then activate effector caspases. Caspases-8 and caspase-10 are the initiators of the extrinsic pathway while intrinsic pathway is activated by caspase-9. Although they are triggered by different initiators, effectors (caspases-3, -6 and -7) are similar for both extrinsic and intrinsic apoptosis (39).

Extrinsic pathway
The extrinsic or death receptor-mediated pathway is activated by binding of death-inducing ligands to the death receptors on the cell surface. Membrane death receptors belong to the tumor necrosis factor (TNF) receptor superfamily and include tumor necrosis factor-receptor 1 (TNF-R1/DR1), Fas (Apo-1/CD95/DR2), death receptor-4 (DR4) and -5 (DR5) (40). These receptors are activated by specific ligands such as TNF-alpha, FasL and TNF-Related apoptosis inducing ligand (TRAIL). Ligand binding leads to the recruitment of adapter proteins, activation of initiator caspases, and formation of death-inducing signaling complex (DISC) (41). Cell death is accomplished through executioner caspases activation (35,37,42). Decreased expression of death receptors was associated with reduced sensitivity to apoptosis in several cancers. For instance, transcriptional downregulation of FAS/CD95 (43), constitutive endocytosis of DR4 and DR5 (44), and decoy receptors (45,46) are the potential sources of the resistance mechanism.

Intrinsic pathway
Cellular stress signals resulting from radiation, cytotoxic drugs, toxins, pollutants, hypoxia, or loss of cell survival factors activates intrinsic pathway (47-51). The main characteristics of the intrinsic pathway are mitochondrial outer membrane permeabilization, cytochrome-c release, formation of apoptosome complex and activation of caspase-9 (42).
B-cell lymphoma 2 (BCL-2) protein family, key regulator of cell survival and death, initiates the release of pro-apoptotic proteins from the mitochondrial intra-membrane space and regulates the intrinsic or mitochondria-mediated apoptotic pathway. BCL-2 members are well characterized by the presence of the BCL-2 homology (BH) domain and divided into three groups according to their structural and functional properties (52). The balance between pro- and anti-apoptotic subfamily members is regulated by cell signaling pathways and the fate of the cell is determined according to “survive or die” signals. Over expression of anti-apoptotic BCL-2 proteins provide survival advantage to the malignant cells and promotes the expansion of the radiotherapy or chemotherapy resistant colonies (53,54). Besides that, decreased expression of pro-apoptotic proteins such as BAX and BAK are associated with chemotherapy resistance (55).

BCL2 family members have remarkable potential as molecular prognostic markers to predict chemotherapy response in myeloma (56), leukemia (57,58), breast cancer (59), and solid tumors (60). Furthermore, dynamic BH3 profiling has recently been used to identify the best BH3 mimetic combinations in the resistant xenograft mouse models (61) and non-small cell lung cancer (NSCLC) cell lines (62).

TARGETING APOPTOSIS TO OVERCOME CHEMOTHERAPY RESISTANCE

With the increasing knowledge of cancer molecular biology, numerous candidate molecules have been identified and some of them approved as molecular targeted therapies (63). However, chemotherapy resistance is still the major obstacle to successful cancer treatment in the 21st century. Because apoptosis is the main cell death mechanism, targeting apoptotic pathways has a remarkable potential to overcome chemotherapy resistance.

Targeting extrinsic pathway

TRAIL and agonists for TRAIL specific receptors, DR4 (TRAIL-R1) and DR5 (TRAIL-R2), are extrinsic pathway inducers that selectively kill tumor cells while harmless to the normal cells. Although they are very advantageous in this regard, inefficient receptor multimerization, poor pharmacokinetic properties, and tumor intrinsic resistance limit their usage in the clinical practice (40).

Death receptor agonists (DRAs) have been developed in different forms such as monoclonal antibodies (64,65), genetically modified specific death receptor agonists (66), drug conjugates (64), or nanobody constructs (67), to enhance selectivity, increase antitumor activity, and
overcome chemotherapy resistance. TRAIL resistance, exhibited by ~70% of cancers, was re-sensitized by targeting apoptosis pathways even at a low dose of the drug (68). A ferritin-based nanocage loaded with native-like trimeric TRAIL and doxorubicin showed antitumor efficacy both in vitro and in vivo experiments (68). CRISPR-Cas9 knockout screen in the TRAIL and DRA-resistant colorectal cancer cells (CRCs) revealed that XIAP, BCL-XL and CDK6 genes are associated with resistance (69). Combination of death receptor agonists with BCL-XL and/or XIAP inhibitors overcame chemoresistance in patient-derived xenografts (69).

It has been shown that RALB GTPase which has functions downstream of RAS, also controls apoptotic priming of the cells (70). Interestingly, RALB regulates DR5 expression in the KRAS mutant CRCs which are resistant to MEK1/2 inhibition. Furthermore, RALB depletion increased cell surface DR5 levels, induced caspase-8 mediated activation of the extrinsic pathway, and sensitized KRAS mutant CRCs to recombinant human TRAIL (70).

Combination therapy regimens are commonly used to overcome chemotherapy resistance in clinical trials. A recent report showed that sequential treatment might be more effective than combined treatment to block drug resistance (71). To be specific, chemotherapeutic agents simultaneously stimulate the expression of TRAIL death and decoy receptors. Sequential treatment of cells with chemotherapeutic agents, followed by DR5-B remarkably sensitized resistant cancer cell to the DR5-B (71). Likewise, androgen-independent and TRAIL-resistant prostate cancer cells were sensitized to TRAIL-mediated apoptosis via pre-treatment with taxane (72). Additionally, DRAs can increase the efficacy of other drugs and convert the response from anti-proliferative to apoptotic state (73).

**Targeting intrinsic pathway**

Human tumors generally express high levels of anti-apoptotic proteins and shut down themselves to the death signals. Thus, numerous molecules have been developed to inhibit anti-apoptotic signals, and some of them have been approved by the FDA (74). We would like to focus on chemotherapy-resistant tumors and discuss potential treatments that can restore drug sensitivity.

BH3 mimetics are small molecules that can mimic the binding of the BH3-only proteins to the hydrophobic groove of anti-apoptotic proteins of the BCL-2 family (75). Among them ABT-199 (Venetoclax) is approved for use in the chronic lymphocytic leukemia (CLL); ABT-263
(Navitoclax), S55746, and S63845 are under Phase I/II trials (52). Although venetoclax provides high remission rates, recurrence develops. A novel mutation, Gly101Val, in the BCL-2 gene has been reported in CLL patients as a source of the venetoclax resistance (76). This mutation reduces the affinity of venetoclax to BCL-2 and leads to acquired resistance (76). Combination of venetoclax with the PI3K/AKT/mTOR inhibitors (NVP-BEZ235 and GS-1101) restored venetoclax sensitivity in the resistant cells (77). Cisplatin and ABT737 combination increased the sensitivity of ovarian cancer cells to cisplatin via regulation of mitochondrial fission (78). It is also possible to prevent drug resistance by using the synergistic effects of BCL-2 inhibitors. For instance, resistance to osimertinib (AZD9291) could be overcome with ABT263 and ABT199 combination (79).

MCL-1 is an important anti-apoptotic member of the BCL-2 family, and its stabilization has a critical function in the intrinsic resistance. Patients with increased MCL-1 expression have shown drug resistance, relapse, and poor prognosis (80). Following venetoclax treatment, binding of released BIM by MCL-1 caused intrinsic resistance in acute myeloid leukemia (AML) cells and combination of venetoclax with conventional chemotherapeutic agents daunorubicin or cytarabine restored drug sensitivity (81). pan-BCL-2 inhibitor (-)BI97D6 suppressed MCL-1 and abolished ABT-737 resistance in AML (82). MCL-1 inhibitor, VU661013, induced apoptosis in venetoclax-resistant AML cells and patient-derived xenografts (83). Another MCL-1 inhibitor, S63845, killed MCL-1 dependent cancer cells by activating the BAX/BAK dependent mitochondrial apoptotic pathway (84). MCL1 and BCL2 inhibitor combination, S63845 + ABT-199, repressed tumor growth in BRAF-V600E mutant advanced melanoma (85). Similar combination with AZD5991 + venetoclax provided a sharp decrease in the MCL-1 and tumor regression in the mouse AML model (86).

**Targeting the inhibitors of apoptosis**

Inhibitors of apoptosis proteins (IAPs) family includes X-linked IAP (XIAP), cIAP1, cIAP2, ILP2, Bruce, Survivin, Livin and NAIP (87,88). Overexpression of these proteins leads to chemoresistance and poor prognosis (89). Targeting IAPs is a safe therapeutic option that has limited effect on non-cancer cells and more attractive upstream signaling on initiator and effector caspases (90). XIAP is the most potent IAP with three binding domains to the effector caspases and directly blocks apoptosis. IAPs can be targeted by antagonist proteins, such as Smac/Diablo, Omi/HtrA2, XIAP-associated factor 1 (XAF1), and apoptosis related protein in the TGF-β signaling pathway (ARTS) (88).
Transmission of exosomal circular RNA of XIAP (Circ-XIAP) to the docetaxel-resistant prostate cancer cells acted as a miRNA sponge for miR-1182 and promoted resistance (91). A recent report showed that anti-apoptotic proteins FLICE-like inhibitory protein (FLIP) and XIAP are downregulated after hydrogen peroxide in the imatinib-resistant CML cells (92). Mechanism of XIAP and FLIP degradation is explained as: ROS-activated ERK decreases AKT phosphorylation which inhibits AKT-XIAP binding and increases ubiquitin-mediated XIAP degradation (92).

Survivin is the smallest member of the IAPs family and associated with chemoresistance and poor prognosis (93). Survivin inhibitors MX106/MX107 suppressed chemotherapeutic resistance of triple-negative breast cancer (TNBC) cells by inhibiting nuclear factor-κB (NF-κB) activation in vitro and in vivo orthotopic xenograft model (94).

Hagenbuchner et al. reported the effects of SMAC-mimetics, and combination of them with the glycolysis inhibitors, on mitochondrial dynamics (95). SMAC mimetic treatment induced mitochondrial fragmentation, inhibited ROS accumulation, and caused Warburg effect, thus cells drifted into a highly glycolytic state and become highly sensitive to non-genotoxic treatments in vitro and in vivo (95). This metabolic shift was used to sensitize cancer cells to the non-toxic glycolysis inhibition which can overcome chemoresistance.

DEBIO-1143, a SMAC mimic that targets cIAP1, cIAP2, and XIAP, is currently in phase III clinical trial for the treatment of locally advanced squamous cell carcinoma of the head and neck (NCT04459715). DEBIO-1143 treatment reversed carboplatin-resistance of ovarian cancer cells by inducing apoptotic or necroptotic cell deaths (96). Similarly, first line chemotherapy-resistant urothelial cancer cells well responded to TRAIL after SMAC mimic treatment (97).

Down-regulation of the tumor suppressor protein prostate apoptosis response-4 (PAR-4) is frequent in human cancers and associated with tumor cell survival and recurrence (98). Stability of cIAP1 is regulated by PAR-4 and targeting cIAP1 restores caspase-8 activation and overcomes chemoresistance induced by the loss of PAR-4 (98). Castration-resistant prostate cancer cells were sensitized to enzalutamide using AEG40995 which is an IAP antagonist (99). AEG40995 degrades cIAP1 protein and combination with enzalutamide increases apoptosis via activation of caspase-8 (99).
**Targeting non-protein coding RNAs**

Targeting resistance-related miRNAs or lncRNAs has been studied in several cancers. Ectopic overexpression of let-7i inhibited resistance in breast cancer cells via targeting KRAS and BCL2 (100). Upregulation of BCL2 targeting miR-153-3p increased imatinib sensitivity in tyrosine kinase inhibitor (TKI)-resistant CML cells (101). Overexpression of BCL-xL led to acquired resistance to the BCL-2 inhibitor ABT-199 (venetoclax). Ectopic expression of BCL-xL targeting miR-377 increased apoptosis in chronic lymphocytic leukemia (CLL) cells (102). miR-214-3p is another tumor suppressor that regulates ABCB1 and XIAP, and inhibits chemoresistance; it is a potential therapeutic target in retinoblastoma (103).

A recent report indicated that signal transducer and activator of transcription 3 (STAT3) transcription factor translocates to the nucleus and mitochondria, and dysregulates apoptotic pathways and ROS production in gemcitabine-resistant lung adenocarcinoma cells (104). Silencing of STAT3 inhibited the proliferation of resistant cells through two main mechanisms: blocking the ROS production, and anti-apoptotic proteins (104).

LncRNA NONHSAT141924 was associated with paclitaxel resistance in breast cancer cells, and its inhibition reversed resistance (105). LINC00473 promotes taxol resistance in CRCs, and its inhibition using tumor suppressor miR-15a reversed resistance via inducing apoptosis (106). In gastric cancer cells, urothelial carcinoma associated 1 (UCA1) reversed adriamycin resistance through the upregulation of cleaved PARP and downregulation of BCL-2 (107). In doxorubicin-resistant bladder transitional cell carcinoma (BTCC) cells, GAS5 restored sensitivity to doxorubicin, and inhibited malignant proliferation (108). Resistance-associated circRNAs were investigated in doxorubicin-resistant AML cell lines, and patients-derived bone marrow specimens (109). Among the 49 differentially expressed circRNAs, circPAN3 was found as a potential target for reversing drug resistance via miR-153-5p/miR-183-5p-XIAP axis (109).

**Targeting endoplasmic reticulum - mitochondria interactions**

The unfolded protein response (UPR) is an acute stress response of mammalian cells and regulated by the endoplasmic reticulum (ER) localized proteins such as HSPA5, PERK, IRE1, and ATF6. Furthermore, ER can produce pro-apoptotic signals that amplify the apoptotic signaling cascade via ER-localized BCL-2 family proteins and this crosstalk might be involved in the chemotherapy resistance (110).
Anti-apoptotic HSPA5 protein (also known as BIP or GRP78) is generally overexpressed in solid tumors and associated with increased malignancy and chemotherapy resistance. Doxorubicin-conjugated cell penetrating cyclic anti-HSPA5 peptide induced apoptosis in chemotherapy-resistant B-lineage acute lymphoblastic leukemia (ALL) cells (111).

BAG3 is an anti-apoptotic, co-chaperone protein that is highly expressed in chemoresistant breast cancer cells (112). Inhibition of BAG3 down-regulated anti-apoptotic proteins (MCL-1, BCL-2 and BCL-X) and restored chemosensitivity (112). 4-HPR is a synthetic retinoid that induces apoptosis and cell death in cancer cells. It was reported that 4-HPR stimulated the expression of ER stress-related and pro-apoptotic genes, and sensitized breast cancer cells resistant to TRAIL (113).

**Natural compounds targeting apoptosis**

Numerous studies have shown that natural compounds can be used to induce TRAIL-mediated apoptosis or overcome TRAIL resistance. For example, Galbanic acid, a natural bioactive compound from *Ferula* species, induced TRAIL mediated apoptosis in the resistant NSCLC cells (114). p-Hydroxycinnamaldehyde from *Cochinchina momordica* seeds reversed TRAIL resistance in esophageal squamous cell carcinoma xenograft model (115). Imatinib-resistant CML cells sensitized to TRAIL via hydroxychavicol, a polyphenol from piper betel leaf (116). Thymoquinone downregulated the expression of anti-apoptotic proteins and sensitized hepatocarcinoma cells to TRAIL-induced apoptosis (117). Marine actinomycetes-derived secondary metabolites reduced survivin and XIAP proteins and overcame TRAIL resistance in the TNBC cells (118). Skyrin, the active metabolite of *Hypericum spp* induced DR5 expression and reversed TRAIL resistance in hypoxia and normoxia in the CRC cell lines (119). Periplocin upregulated DR4 and DR5 receptors and induced apoptosis in the TRAIL resistant gastric cancer cells (120).

A xanthonoid compound α-mangostin showed apoptotic functions inducing mitochondrial depolarization, upregulating BAX, and downregulating MCL-1 and BCL-2; it enhanced the cytotoxicity of cisplatin in cancer stem cells-like cervical cancer cells with chemotherapy-resistant and metastatic phenotype (121). Essential oil fraction from *Vitex agnus-castus* induced caspase-3/-7 activation and extrinsic and intrinsic pathways in the multidrug resistant lung carcinoma cells (122).
Echinatin, derived from *G. inflata*, suppressed EGFR and MET, blocked kinase activity, and induced cell cycle arrest and apoptosis via the intrinsic pathway in lung cancer cells that were resistant to gefitinib (123). A combination of hypericin (plant product) and manumycin A (yeast product) showed anti-cancer effects on the oxaliplatin-resistant CRCs (124). This synergistic combination decreased IAPs proteins (cIAP1, cIAP2, XIAP and survivin), induced PARP cleavage, and restored chemosensitivity to oxaliplatin (124). The curcumin analog EF24 decreased the expression of the anti-apoptotic protein BCL-2 and apoptosis inhibitor proteins (XIAP, cIAP1, Birc7) through the inhibition of the NF-κB in the chemotherapy-resistant melanoma cells (125).

**Others**

Induction of apoptosis can be achieved indirectly in therapy-resistant cells. For example, celecoxib, a cyclooxygenase-2 inhibitor, stimulated apoptosis through AKT suppression in 5-fluorouracil (5-FU)-resistant gastric cancer cells (126). Sulforaphane treatment downregulated anti-apoptotic proteins (BCL-2 and XIAP) and sensitized cholangiocarcinoma cells to cisplatin (127). PPARγ ligands, CB13 and PPZ023, sensitized radioresistant NSCLC cells via induction of apoptosis and ER stress (128,129).

Enalapril is an antihypertensive drug that inhibits angiotensin-converting enzyme (ACE) and so angiotensin I to angiotensin II conversion. In this way, angiogenesis is suppressed through VEGF and NF-κB down regulation. In a mouse model of colorectal cancer, enalapril overcame 5-FU resistance (130); also, a combination of 5-FU and enalapril synergistically inhibited NF-κB/STAT3 signaling and increased the expression levels of NF-κB/STAT3-regulated genes including BCL-2, and XIAP both in vitro and in vivo (130).

Salinomycin-mediated DNA damage induced mitochondrial membrane potential loss in cisplatin-resistant breast cancer cells through the downregulation of NF-κB regulated expression of pro-survival proteins, e.g., survivin, XIAP and BCL-2 (131). PR-619, a deubiquitinating enzyme (DUB) inhibitor, enhanced the antitumor effects of cisplatin in cisplatin-naïve and -resistant metastatic urothelial carcinoma both in vitro and in vivo through suppressing anti-apoptotic BCL-2 protein (132). The pterocarpanquinone LQB-118 compound induced apoptosis and reversed cytarabine-resistance in AML cells (133). Calmodulin can directly biund to DR5 in a Ca^{2+} dependent manner. Calmodulin antagonist, trifluoperazine, enhanced TRA-8-activated DR5 oligomerization, DISC formation, caspase cleavage, and
decreased anti-apoptotic pERK, pAKT, XIAP, and cIAP-1 expressions in TRA-8 resistant TNBC cells (134).

CONCLUSION
Inhibition of apoptosis has shown promising results in overcoming chemotherapy resistance. However, the effects of these inhibitors or agonists depend on the cells’ physiological state and gene expression status. Therefore, profiling of apoptosis regulators might be useful to identify the best drug combinations (61,62,135). In addition, instead of combination, sequential administration of chemotherapeutics might prevent resistance and increase treatment success rates (71).

Specific delivery of chemotherapeutic agents to the tumor cells can be improved with exosome or nanoparticle conjugations. For instance, exosome-mediated transfer of apoptosis inducers such as circRNA and miRNA may help overcome chemotherapy resistance (91,136). Cancer-specific, pro-apoptotic drug-drug conjugate for SMAC and doxorubicin suppressed tumor growth in drug-resistant lung cancer model (137). Development of such nanoparticle designs might provide tumor-specific therapeutic options without drug resistance.

With the development of CRISPR-Cas technology, genomic screening studies have revealed novel candidate targets to overcome chemotherapy resistance. In a chemotherapy-resistant ovarian cancer model, knock-out screening showed that loss of BCL2L1 decreases cell survival whereas loss of pro-apoptotic genes promotes resistance (138). Inhibitors of BCL-XL or MCL1 promote cell death in combination with chemotherapy (138). In the near future, it would be possible to overcome chemotherapy resistance with the development of new drug targets revealed by large scale screening studies.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest with respect to research, authorship, and/or publication of this chapter.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
https://doi.org/10.3322/caac.21660

2. Al-Dimassi S, Abou-Antoun T, El-Sibai M. Cancer cell resistance mechanisms: A mini review. Clin Transl Oncol. 2014;16(6):511-6.
https://doi.org/10.1007/s12094-014-1162-1

3. Abbas Z, Rehman S. An Overview of Cancer Treatment Modalities. Neoplasm. 2018;
https://doi.org/10.5772/intechopen.76558

4. Thirumaran R, Prendergast GC, Gilman PB. Cytotoxic Chemotherapy in Clinical Treatment of Cancer. Cancer Immunotherapy. Elsevier Inc.; 2007. 101-116 p.
https://doi.org/10.1016/B978-012372551-6/50071-7

5. Kibria G, Hatakeyama H, Harashima H. Cancer multidrug resistance: Mechanisms involved and strategies for circumvention using a drug delivery system. Arch Pharm Res. 2014;37(1):4-15.
https://doi.org/10.1007/s12272-013-0276-2

6. Asano T. Drug resistance in cancer therapy and the role of epigenetics. J Nippon Med Sch. 2020;87(5):244-51.
https://doi.org/10.1272/jnms.JNMS.2020_87-508

7. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: A brief review. Adv Pharm Bull. 2017;7(3):339-48.
https://doi.org/10.15171/apb.2017.041

8. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol. 2005;205(2):275-92.
https://doi.org/10.1002/path.1706

9. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: An evolving paradigm. Nat Rev Cancer. 2013;13(10):714-26.
https://doi.org/10.1038/nrc3599

10. Nikolaou M, Pavlopoulou A, Georgakilas AG, Kyrodimos E. The challenge of drug resistance in cancer treatment: a current overview. Clin Exp Metastasis. 2018;35(4):309-18.
https://doi.org/10.1007/s10585-018-9903-0

11. Ward RA, Fawell S, Floc'H N, Flemington V, McKerrecher D, Smith PD. Challenges and Opportunities in Cancer Drug Resistance. Chem Rev. 2021;121(6):3297-351.
https://doi.org/10.1021/acs.chemrev.0c00383

12. Zahreddine H, Borden KLB. Mechanisms and insights into drug resistance in cancer. Front Pharmacol. 2013;4 MAR(March):1-8.
https://doi.org/10.3389/fphar.2013.00028

13. Joyce H, McCann A, Clynes M, Larkin A. Influence of multidrug resistance and drug transport proteins on chemotherapy drug metabolism. Expert Opin Drug Metab Toxicol.
14. Li Q, Shu Y. Role of solute carriers in response to anticancer drugs Qing. Mol Cell Ther. 2014;2(5).
https://doi.org/10.1186/2052-8426-2-15

15. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: An overview. Cancers (Basel). 2014;6(3):1769-92.
https://doi.org/10.3390/cancers6031769

16. Luqmani YA. Mechanisms of drug resistance in cancer chemotherapy. Med Princ Pract. 2005;14(SUPPL. 1):35-48.
https://doi.org/10.1159/000086183

17. Ho HK, Chan JCY, Hardy KD, Chan ECY. Mechanism-based inactivation of CYP450 enzymes: A case study of lapatinib. Drug Metab Rev. 2015;47(1):21-8.
https://doi.org/10.3109/03602532.2014.1003648

18. Kaur G, Gupta SK, Singh P, Ali V, Kumar V, Verma M. Drug-metabolizing enzymes: role in drug resistance in cancer. Clin Transl Oncol. 2020;22(10):1667-80.
https://doi.org/10.1007/s12094-020-02325-7

19. Singh RR, Reindl KM. Glutathione S-Transferases in Cancer. Antioxidants (Basel). 2021;10(5).
https://doi.org/10.3390/antiox10050701

20. Redmond KM, Wilson TR, Johnston PG, Longley DB. Resistance mechanisms to cancer chemotherapy. 2008;5138-54.
https://doi.org/10.2741/3070

21. Martin LP, Hamilton TC, Schilder RJ. Platinum resistance: The role of DNA repair pathways. Clin Cancer Res. 2008;14(5):1291-5.
https://doi.org/10.1158/1078-0432.CCR-07-2238

22. Aldossary SA. Review on pharmacology of cisplatin: Clinical use, toxicity and mechanism of resistance of cisplatin. Biomed Pharmacol J. 2019;12(1):7-15.
https://doi.org/10.13005/bpj/1608

23. Bukowski K, Kciuk M, Kontek R. Mechanisms of multidrug resistance in cancer chemotherapy. Int J Mol Sci. 2020;21(3233).
https://doi.org/10.3390/ijms21093233

24. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, Kepp O, et al. Molecular mechanisms of cisplatin resistance. Oncogene. 2012;31(15):1869-83.
https://doi.org/10.1038/onc.2011.384

25. Rocha CRR, Silva MM, Quinet A, Cabral-Neto JB, Menck CFM. DNA repair pathways and cisplatin resistance: An intimate relationship. Clinics. 2018;73(8):1-10.
https://doi.org/10.6061/clinics/2018/e478s
26. Kelly TK, Carvalho DD De, Jones PA. Epigenetic Modifications as Therapeutic Targets. Theresa. Nat Biotechnol. 2010;28(10):1069-1078. https://doi.org/10.1038/nbt.1678

27. Wilting RH, Dannenberg JH. Epigenetic mechanisms in tumorigenesis, tumor cell heterogeneity and drug resistance. Drug Resist Updat. 2012;15(1-2):21-38. https://doi.org/10.1016/j.drup.2012.01.008

28. Liu K, Gao L, Ma X, Huang JJ, Chen J, Zeng L, et al. Long non-coding RNAs regulate drug resistance in cancer. Mol Cancer. 2020;19(1):1-13. https://doi.org/10.1186/s12943-020-01162-0

29. Zhang Y, Wang J. MicroRNAs are important regulators of drug resistance in colorectal cancer. Biol Chem. 2018;398(8):929-938. https://doi.org/10.1515/hsz-2016-0308

30. Si W, Shen J, Zheng H, Fan W. The role and mechanisms of action of microRNAs in cancer drug resistance. Clin Epigenetics. 2019;11(1):1-24. https://doi.org/10.1186/s13148-018-0587-8

31. Çalışkan M, Güler H, Bozok Çetintaş V. Current updates on microRNAs as regulators of chemoresistance. Biomed Pharmacother. 2017;95(August):1000-12. https://doi.org/10.1016/j.biopha.2017.08.084

32. Loewen G, Jayawickramarajah J, Zhuo Y, Shan B. Functions of IncRNA HOTAIR in lung cancer. J Hematol Oncol. 2014;7(1):1-10. https://doi.org/10.1186/s13045-014-0090-4

33. Xu T, Wang M, Jiang L, Ma L, Wan L, Chen Q, et al. CircRNAs in anticancer drug resistance: Recent advances and future potential. Mol Cancer. 2020;19(1):1-20. https://doi.org/10.1186/s12943-020-01240-3

34. Fulda S. Tumor resistance to apoptosis. Int J Cancer. 2009;124(3):511-5. https://doi.org/10.1002/ijc.24064

35. Jessica Plati, Octavian Bucur RK-F. Apoptotic cell signaling in cancer progression and therapy. Bone. 2011;3(4):1-7. https://doi.org/10.1039/c0ib00144a

36. Fulda S. Evasion of apoptosis as a cellular stress response in cancer. Int J Cell Biol. 2010;2010:1-6. https://doi.org/10.1155/2010/370835

37. Rehmat Jan G-SC. Understanding Apoptosis and Apoptotic Pathways Targeted Cancer Therapeutics. Adv Pharm Bull. 2019;9(2):205-18. https://doi.org/10.15171/apb.2019.024

38. Khan KH, Blanco-Codesido M, Molife LR. Cancer therapeutics: Targeting the apoptotic pathway. Crit Rev Oncol Hematol. 2014;90(3):200-19. https://doi.org/10.1016/j.critrevonc.2013.12.012

39. Pommier Y, Sordet O, Antony S, Hayward RL, Kohn KW. Apoptosis defects and chemotherapy resistance: Molecular interaction maps and networks. Oncogene. 2004;23(16
40. Kretz AL, Trauzold A, Hillenbrand A, Knippschild U, Henne-Bruns D, von Karstedt S, et al. Trailblazing strategies for cancer treatment. Cancers (Basel). 2019;11(4):1-30. https://doi.org/10.3390/cancers11040456

41. Humphreys LM, Fox JP, Higgins CA, Majkut J, Sessler T, McLaughlin K, et al. A revised model of TRAIL-R2 DISC assembly explains how FLIP (L) can inhibit or promote apoptosis. EMBO Rep. 2020;21(3):1-16. https://doi.org/10.15252/embr.201949254

42. Zaman S, Wang R, Gandhi V. Targeting the apoptosis pathway in hematologic malignancies. Leuk Lymphoma. 2014;55(9):1980-92. https://doi.org/10.3109/10428194.2013.855307

43. Wu J, Nihal M, Siddiqui J, Vonderheid EC, Wood GS. Low FAS/CD95 expression by CTCL correlates with reduced sensitivity to apoptosis that can be restored by FAS upregulation. J Invest Dermatol. 2009;129(5):1165-73. https://doi.org/10.1038/jid.2008.309

44. Zhang Y, Zhang B. TRAIL resistance of breast cancer cells is associated with constitutive endocytosis of death receptors 4 and 5. Mol Cancer Res. 2008;6(12):1861-71. https://doi.org/10.1158/1541-7786.MCR-08-0313

45. Mansour NM, Bernal GM, Wu L, Crawley CD, Cahill KE, Voce DJ, et al. Decoy receptor DcR1 Is Induced in a p50/Bcl3-Dependent manner and attenuates the efficacy of temozolomide. Cancer Res. 2015;75(10):2039-48. https://doi.org/10.1158/0008-5472.CAN-14-2144

46. Duru AD, Sutlu T, Wallblom A, Uttervall K, Lund J, Stellan B, et al. Deletion of chromosomal region 8p21 confers resistance to bortezomib and is associated with upregulated decoy TRAIL receptor expression in patients with multiple myeloma. PLoS One. 2015;10(9):1-16. https://doi.org/10.1371/journal.pone.0138248

47. Cao X, Wen P, Fu Y, Gao Y, Qi X, Chen B, et al. Radiation induces apoptosis primarily through the intrinsic pathway in mammalian cells. Cell Signal. 2019;62(March). https://doi.org/10.1016/j.cellsig.2019.06.002

48. Cao X, Fu M, Bi R, Zheng X, Fu B, Tian S, et al. Cadmium induced BEAS-2B cells apoptosis and mitochondria damage via MAPK signaling pathway. Chemosphere. 2021;263:128346. https://doi.org/10.1016/j.chemosphere.2020.128346

49. Li S, Yang L, Zhang Y, Zhang C, Shao J, Liu X, et al. Taurine ameliorates arsenic-induced apoptosis in the hippocampus of mice through intrinsic pathway. Adv Exp Med Biol. 2017;975:183-92. https://doi.org/10.1007/978-94-024-1079-2_16

50. Wang XD, Li CY, Jiang MM, Li D, Wen P, Song X, et al. Induction of apoptosis in human leukemia cells through an intrinsic pathway by cathachunine, a unique alkaloid isolated from Catharanthus roseus. Phytomedicine. 2016;23(6):641-53. https://doi.org/10.1016/j.phymed.2016.03.003
51. Ko CL, Lin JA, Chen KY, Hsu AC, Wu SY, Tai YT, et al. Netrin-1 Dampens Hypobaric Hypoxia-Induced Lung Injury in Mice. High Alt Med Biol. 2019;20(3):293-302. https://doi.org/10.1089/ham.2018.0116

52. Warren CFA, Wong-Brown MW, Bowden NA. BCL-2 family isoforms in apoptosis and cancer. Cell Death Dis. 2019;10(3). https://doi.org/10.1038/s41419-019-1407-6

53. Lucantoni F, Salvucci M, Düssmann H, Lindner AU, Lambrechts D, Prehn JHM. BCL(X)L and BCL2 increase the metabolic fitness of breast cancer cells: a single-cell imaging study. Cell Death Differ. 2021;28(5):1512-31. https://doi.org/10.1038/s41418-020-00683-x

54. Abou El Hassan MAI, Mastenbroek DCJ, Gerritsen WR, Giaccone G, Kruyt FAE. Overexpression of Bcl2 abrogates chemo- and radiotherapy-induced sensitisation of NCI-H460 non-small-cell lung cancer cells to adenovirus-mediated expression of full-length TRAIL. Br J Cancer. 2004;91(1):171-7. https://doi.org/10.1038/sj.bjc.6601910

55. Olejniczak SH, Hernandez-Ilizaliturri FJ, Clements JL, Czuczman MS. Acquired resistance to rituximab is associated with chemotherapy resistance resulting from decreased Bax and Bak expression. Clin Cancer Res. 2008;14(5):1550-60. https://doi.org/10.1158/1078-0432.CCR-07-1255

56. Punnoose EA, Leversen JD, Peale F, Boghaert ER, Belmont LD, Tan N, et al. Expression profile of BCL-2, BCL-XL, and MCL-1 predicts pharmacological response to the BCL-2 selective antagonist venetoclax in multiple myeloma models. Mol Cancer Ther. 2016;15(5):1132-44. https://doi.org/10.1158/1535-7163.MCT-15-0730

57. Stamati L, Avgeris M, Kosmidis H, Baka M, Anastasiou T, Piatopoulou D, et al. Overexpression of BCL2 and BAX following BFM induction therapy predicts ch-ALL patients’ poor response to treatment and short-term relapse. J Cancer Res Clin Oncol. 2015;141(11):2023-36. https://doi.org/10.1007/s00432-015-1982-6

58. Haselager M V., Kielbassa K, ter Burg J, Bax DJC, Fernandes SM, Borst J, et al. Changes in Bcl-2 members after ibrutinib or venetoclax uncover functional hierarchy in determining resistance to venetoclax in CLL. Blood. 2020;136(25):2918-26. https://doi.org/10.1182/blood.2019004326

59. Abdel-Fatah TMA, Perry C, Dickinson P, Ball G, Moseley P, Madhusudan S, et al. Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings. Ann Oncol. 2013;24(11):2801-7. https://doi.org/10.1093/annonc/mdt277

60. Bhola P, Ahmed E, Guerriero JL, Sicinska E, Su E, Lavrova E, et al. High-throughput dynamic BH3 profiling (HT-DBP) may quickly and accurately predict effective therapies in solid tumors. Sci Signal. 2021;13(636):1-24. https://doi.org/10.1126/scisignal.aay1451

61. Olesinski EA, Bhatt S. Dynamic BH3 profiling method for rapid identification of active therapy in BH3 mimetics resistant xenograft mouse models. STAR Protoc. 2021;2(2):100461. https://doi.org/10.1016/j.xpro.2021.100461
62. Potter DS, Du R, Bhola P, Bueno R, Letai A. Dynamic BH3 profiling identifies active BH3 mimetic combinations in non-small cell lung cancer. Cell Death Dis. 2021;12(8). https://doi.org/10.1038/s41419-021-04029-4

63. Lim B, Greer Y, Lipkowitz S, Takebe N. Novel apoptosis-inducing agents for the treatment of cancer, a new arsenal in the toolbox. Cancers (Basel). 2019;11(8):1-39. https://doi.org/10.3390/cancers11081087

64. Zhang S, Zheng C, Zhu W, Xiong P, Zhou D, Huang C, et al. A novel anti-DR5 antibody-drug conjugate possesses a high-potential therapeutic efficacy for leukemia and solid tumors. Theranostics. 2019;9(18):5412-23. https://doi.org/10.7150/thno.33598

65. Lee YR, Hwang E, Jang YJ. Involvement of p38 activation and mitochondria in death of human leukemia cells induced by an agonistic human monoclonal antibody FaB specific to TRAIL receptor 1. Int J Mol Sci. 2019;20(8). https://doi.org/10.3390/ijms20081967

66. Yagolovich A V., Artykov AA, Karmakova TA, Vorontsova MS, Pankratov AA, Andreev-Andrievsky AA, et al. Genetically Modified DR5-Specific TRAIL Variant DR5-B Revealed Dual Antitumor and Protumoral Effect in Colon Cancer Xenografts and an Improved Pharmacokinetic Profile. Transl Oncol. 2020;13(4):100762. https://doi.org/10.1016/j.tranon.2020.100762

67. Sadeghnezhad G, Romão E, Bernedo-Navarro R, Massa S, Khajeh K, Muyldermans S, et al. Identification of new DR5 agonistic nanobodies and generation of multivalent nanobody constructs for cancer treatment. Int J Mol Sci. 2019;20(19). https://doi.org/10.3390/ijms20194818

68. Je H, Nam GH, Kim GB, Kim W, Kim SR, Kim IS, et al. Overcoming therapeutic efficiency limitations against TRAIL-resistant tumors using re-sensitizing agent-loaded trimeric TRAIL-presenting nanocages. J Control Release. 2021;331:7-18. https://doi.org/10.1016/j.jconrel.2021.01.016

69. Manzari MT, Anderson GR, Lin KH, Soderquist RS, Çakir M, Zhang M, et al. Genomically informed small-molecule drugs overcome resistance to a sustained-release formulation of an engineered death receptor agonist in patient-derived tumor models. Sci Adv. 2019;5(9). https://doi.org/10.1126/sciadv.aaw9162

70. Khawaja H, Campbell A, Roberts JZ, Javadi A, O'Reilly P, McArt D, et al. RALB GTPase: a critical regulator of DR5 expression and TRAIL sensitivity in KRAS mutant colorectal cancer. Cell Death Dis. 2020;11(10). https://doi.org/10.1038/s41419-020-03131-3

71. Artykov A, Belov DA, Shipunova VO, Trushina DB, Deyev SM, Dolgikh DA, et al. Chemotherapeutic agents sensitize resistant cancer cells to the DR5-specific variant DR5-B more efficiently than to TRAIL by modulating the surface expression of death and decoy receptors. Cancers (Basel). 2020;12(5):1-17. https://doi.org/10.3390/cancers12051129

72. Grayson KA, Hope JM, Wang W, Reinhart-King CA, King MR. Taxanes sensitize prostate cancer cells to TRAIL-induced apoptotic synergy via endoplasmic reticulum stress. Mol Cancer
73. Ralff MD, Jhaveri A, Ray JE, Zhou L, Lev A, Campbell KS, et al. TRAIL receptor agonists convert the response of breast cancer cells to ONC201 from anti-proliferative to apoptotic. Oncotarget. 2020;11(42):3753-69. https://doi.org/10.18632/oncotarget.27773

74. Carneiro BA, El-Deiry WS. Targeting apoptosis in cancer therapy. Nat Rev Clin Oncol. 2020;17(7):395-417. https://doi.org/10.1038/s41571-020-0341-y

75. Wang JL, Liu D, Zhang ZJ, Shan S, Han X, Srinivasula SM, et al. Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells. Proc Natl Acad Sci U S A. 2000;97(13):7124-9. https://doi.org/10.1073/pnas.97.13.7124

76. Blombery P, Anderson MA, Gong JN, Thijssen R, Birkinshaw RW, Thompson ER, et al. Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. Cancer Discov. 2019;342-53. https://doi.org/10.1158/2159-8290.CD-18-1119

77. Choudhary GS, Al-Harbi S, Mazumder S, Hill BT, Smith MR, Bodo J, et al. MCL-1 and BCL-xL-dependent resistance to the BCL-2 inhibitor ABT-199 can be overcome by preventing PI3K/AKT/mTOR activation in lymphoid malignancies. Cell Death Dis. 2015;6:1-12. https://doi.org/10.1038/cddis.2014.525

78. Hou L, Wang R, Wei H, Li S, Liu L, Lu X, et al. ABT737 enhances ovarian cancer cells sensitivity to cisplatin through regulation of mitochondrial fission via Sirt3 activation. Life Sci. 2019;232(126):116561. https://doi.org/10.1016/j.lfs.2019.116561

79. Liu Z, Gao W. Synergistic effects of Bcl-2 inhibitors with AZD9291 on overcoming the acquired resistance of AZD9291 in H1975 cells. Arch Toxicol. 2020;94:3125-36. https://doi.org/10.1007/s00204-020-02816-0

80. Wu X, Luo Q, Liu Z. Ubiquitination and deubiquitination of MCL1 in cancer: deciphering chemoresistance mechanisms and providing potential therapeutic options. Cell Death Dis. 2020;11(556):1-11. https://doi.org/10.1038/s41419-020-02760-y

81. Niu X, Zhao J, Ma J, Xie C, Edwards H, Wang G, et al. Binding of released Bim to Mcl-1 is a mechanism of intrinsic resistance to ABT-199 which can be overcome by combination with daunorubicin or cytarabine in AML cells. Clin Cancer Res. 2017;22(17):4440-4451. https://doi.org/10.1158/1078-0432.CCR-15-3057

82. Pan R, Ruvolo VR, Wei J, Konopleva M, Reed JC, Pellechcia M, et al. Inhibition of Mcl-1 with the pan-Bcl-2 family inhibitor (-)Bi97D6 overcomes ABT-737 resistance in acute myeloid leukemia. Blood. 2015;126(3):363-72. https://doi.org/10.1182/blood-2014-10-604975

83. Ramsey HE, Fischer MA, Lee T, Gorska AE, Arrate MP, Fuller L, et al. A novel MCL1 inhibitor combined with venetoclax rescues venetoclax-resistant acute myelogenous Leukemia.
84. Kotschy A, Szlavik Z, Murray J, Davidson J, Maragno AL, Le Toumelin-Braizat G, et al. The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models. Nature. 2016;538:477-82.  
https://doi.org/10.1038/nature19830

85. Mukherjee N, Amato CM, Skees J, Todd KJ, Lambert KA, Robinson WA, et al. Simultaneously inhibiting bcl2 and mcl1 is a therapeutic option for patients with advanced melanoma. Cancers (Basel). 2020;12:1-16.  
https://doi.org/10.3390/cancers12082182

86. Tron AE, Belmonte MA, Adam A, Aquila BM, Boise LH, Chiarparin E, et al. Discovery of Mcl-1-specific inhibitor AZD5991 and preclinical activity in multiple myeloma and acute myeloid leukemia. Nat Commun. 2018;9(5341):1-14.  
https://doi.org/10.1038/s41467-018-07551-w

87. Shin H, Renatus M, Eckelman BP, Nunes VA, Sampaio CAM, Salvesen GS. The BIR domain of IAP-like protein 2 is conformationally unstable: Implications for caspase inhibition. Biochem J. 2005;385(1):1-10.  
https://doi.org/10.1042/BJ20041107

88. Abbas R, Larisch S. Targeting XIAP for Promoting Cancer Cell Death-The Story of ARTS and SMAC. Cells. 2020;9(3).  
https://doi.org/10.3390/cells9030663

89. Devi GR, Finetti P, Morse MA, Lee S, de Nonville A, Van Laere S, et al. Expression of x-linked inhibitor of apoptosis protein (Xiap) in breast cancer is associated with shorter survival and resistance to chemotherapy. Cancers (Basel). 2021;13(11).  
https://doi.org/10.3390/cancers13112807

90. Finlay D, Teriete P, Vamos M, Cosford NDP, Vuori K. Inducing death in tumor cells: Roles of the inhibitor of apoptosis proteins. F1000Research. 2017;6:1-18.  
https://doi.org/10.12688/f1000research.10625.1

91. Zhang H, Li M, Zhang J, Shen Y, Gui Q. Exosomal circ-xiap promotes docetaxel resistance in prostate cancer by regulating mir-1182/tpd52 axis. Drug Des Devel Ther. 2021;15:1835-49.  
https://doi.org/10.2147/DDDT.S300376

92. Paul T, Roy R, Sarkar RD, Sinha S, Biswas N. H2O2 mediated FLIP and XIAP downregulation involves increased ITCH expression and ERK-Akt crosstalk in imatinib resistant Chronic Myeloid Leukemia cell line K562. Free Radic Biol Med. 2021;166(January):265-76.  
https://doi.org/10.1016/j.freeradbiomed.2021.02.024

93. Peery RC, Liu JY, Zhang JT. Targeting survivin for therapeutic discovery: past, present, and future promises. Drug Discov Today. 2017;22(10):1466-77.  
https://doi.org/10.1016/j.drudis.2017.05.009

94. Wang W, Zhang B, Mani AM, Wu Z, Fan Y, Li W, et al. Survivin inhibitors mitigate chemotherapeutic resistance in breast cancer cells by suppressing genotoxic nuclear factor-kB activations. J Pharmacol Exp Ther. 2018;366(1):184-93.  
https://doi.org/10.1124/jpet.118.249151
95. Hagenbuchner J, Oberacher H, Amhard K, Kiechl-Kohler, U, Ausserlechner MJ. Modulation of respiration and mitochondrial dynamics by SMAC-mimetics for combination therapy in chemoresistant cancer. Theranostics. 2019;9(17):4909-22. https://doi.org/10.7150/thno.33758

96. Thibault B, Genre L, Le Naour A, Broca C, Mery E, Vuagniaux G, et al. DEBIO 1143, an IAP inhibitor, reverses carboplatin resistance in ovarian cancer cells and triggers apoptotic or necroptotic cell death. Sci Rep. 2018;8(1):1-12. https://doi.org/10.1038/s41598-018-35860-z

97. Vallo S, Stege H, Berg M, Michaelis M, Winkelmann R, Rothweiller F, et al. Tumor necrosis factor-related apoptosis-inducing ligand as a therapeutic option in urothelial cancer cells with acquired resistance against first-line chemotherapy. Oncol Rep. 2020;43(4):1331-7. https://doi.org/10.3892/or.2020.7487

98. Guo H, Treude F, Krämer OH, Lüscher B, Hartkamp J. PAR-4 overcomes chemoresistance in breast cancer cells by antagonizing cIAP1. Sci Rep. 2019;9(1):1-12. https://doi.org/10.1038/s41598-019-45209-9

99. Pilling AB, Hwang O, Boudreault A, Laurent A, Hwang C. IAP Antagonists Enhance Apoptotic Response to Enzalutamide in Castration-Resistant Prostate Cancer Cells via Autocrine TNF-α Signaling. Prostate. 2017;77(8):866-77. https://doi.org/10.1002/pros.23327

100. Qin M, Chun Pu, Gang Feng, Jian Zhang RZ, Liu X. [Let-7i reduces chemotherapy resistance in breast cancer cells through down-regulation of K-Ras and Bcl2 expression]. 2019;35(11):992-9.

101. Li YL, Tang JM, Chen XY, Luo B, Liang GH, Qu Q, et al. MicroRNA-153-3p enhances the sensitivity of chronic myeloid leukemia cells to imatinib by inhibiting B-cell lymphoma-2-mediated autophagy. Hum Cell. 2020;33(3):610-8. https://doi.org/10.1007/s13577-020-00367-1

102. Al-harb S, Choudhary GS, Ebron JS, Hill BT, Vivekanathan N, Ting AH, et al. miR-377-dependent BCL-xL regulation drives chemotherapeutic resistance in B-cell lymphoid malignancies. Mol Cancer. 2015;14(1):1-17. https://doi.org/10.1186/s12943-015-0460-8

103. Yang L, Zhang L, Lu L, Wang Y. MiR-214-3p regulates multi-drug resistance and apoptosis in retinoblastoma cells by targeting ABCB1 and XIAP. Onco Targets Ther. 2020;13:803-11. https://doi.org/10.2147/OTT.S235862

104. Liu JS, Yeh CA, Huang IC, Huang HY, Chiu CH, Mahalakshmi B, et al. Signal transducer and activator of transcription 3 mediates apoptosis inhibition through reducing mitochondrial ROS and activating Bcl-2 in gemcitabine-resistant lung cancer A549 cells. J Cell Physiol. 2021;236(5):3896-905. https://doi.org/10.1002/jcp.30133

105. Gu M, Zheng W, Zhang M, Dong X, Zhao Y, Wang S, et al. LncRNA NONHSAT141924 promotes paclitaxel chemotherapy resistance through p-CREB/Bcl-2 apoptosis signaling pathway in breast cancer. J Cancer. 2020;11(12):3645-54. https://doi.org/10.7150/jca.39463
106. Wang L, Zhang X, Sheng L, Qiu C, Luo R. LINC00473 promotes the Taxol resistance via miR-15a in colorectal cancer. Biosci Rep. 2018;38(5):1-10. https://doi.org/10.1042/BSR20180790

107. Shang C, Guo Y, Zhang J, Huang B. Silence of long noncoding RNA UCA1 inhibits malignant proliferation and chemotherapy resistance to adriamycin in gastric cancer. Cancer Chemother Pharmacol. 2016;77(5):1061-7. https://doi.org/10.1007/s00280-016-3029-3

108. Zhang H, Guo Y, Song Y, Shang C. Long noncoding RNA GAS5 inhibits malignant proliferation and chemotherapy resistance to doxorubicin in bladder transitional cell carcinoma. Cancer Chemother Pharmacol. 2017;79(1):49-55. https://doi.org/10.1007/s00280-016-3194-4

109. Shang J, Chen WM, Wang ZH, Wei TN, Chen ZZ, Wu WB. CircPAN3 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p-XIAP axis. Exp Hematol. 2019;70:42-54.e3. https://doi.org/10.1016/j.exphem.2018.10.011

110. Su J, Zhou L, Xia MH, Xu Y, Xiang XY, Sun LK. Bcl-2 family proteins are involved in the signal crosstalk between endoplasmic reticulum stress and mitochondrial dysfunction in tumor chemotherapy resistance. Biomed Res Int. 2014;2014:26. https://doi.org/10.1155/2014/234370

111. Uckun FM, Qazi S, Ozer Z, Garner AL, Pitt J, Ma H, et al. Inducing apoptosis in chemotherapy-resistant B-lineage acute lymphoblastic leukaemia cells by targeting HSPA5, a master regulator of the anti-apoptotic unfolded protein response signalling network. Br J Haematol. 2011;153(6):741-52. https://doi.org/10.1111/j.1365-2141.2011.08671.x

112. Das CK, Linder B, Bonn F, Rothweiler F, Dikic I, Michaelis M, et al. BAG3 Overexpression and Cytoprotective Autophagy Mediate Apoptosis Resistance in Chemoresistant Breast Cancer Cells. Neoplasia (United States). 2018;20(3):263-79. https://doi.org/10.1016/j.neo.2018.01.001

113. Anding AL, Jones JD, Newton MA, Curley RW, Clagett-Dame M. 4-HPR is an endoplasmic reticulum stress aggravator and sensitizes breast cancer cells resistant to TRAIL/Apo2L. Anticancer Res. 2018;38(8):4403-16. https://doi.org/10.21873/anticancerres.12742

114. Kim YH, Shin EA, Jung JH, Park JE, Ku JS, Koo J II, et al. Galbanic acid potentiates TRAIL induced apoptosis in resistant non-small cell lung cancer cells via inhibition of MDR1 and activation of caspases and DR5. Eur J Pharmacol. 2019;847(January):91-6. https://doi.org/10.1016/j.ejphar.2019.01.028

115. Ma M, Zhang C, Xiang X han, Deng X qing, Dai S ii, Wei S si, et al. p-Hydroxylcinnamaldehyde from cochinchinamomordica seed reverses resistance to TRAIL in human oesophageal squamous cell carcinoma via the activation of the p38 mitogen-activated protein kinase signalling pathway. Biomed Pharmacother. 2020;121(October 2019):109611. https://doi.org/10.1016/j.biopharm.2019.109611

116. Paul T, Banerjee A, Reddy SVB, Mahato SK, Biswas N. Hydroxychavicol sensitizes imatinib-resistant chronic myelogenous leukemia cells to TRAIL-induced apoptosis by ROS-
mediated IAP downregulation. Anticancer Drugs. 2019;30(2):167-78. https://doi.org/10.1097/CAD.0000000000000710

117. Zhang R, Wu T, Zheng P, Liu M, Xu G, Xi M, et al. Thymoquinone sensitizes human hepatocarcinoma cells to TRAIL-induced apoptosis via oxidative DNA damage. DNA Repair (Amst). 2021;103(January):103117. https://doi.org/10.1016/j.dnarep.2021.103117

118. Elmallah MIY, Cogo S, Constantinescu AA, Elifio-ESposito S, Abdelfattah MS, Micheau O. Marine Actinomycetes-Derived Secondary Metabolites Overcome TRAIL-Resistance via the Intrinsic Pathway through Downregulation of Survivin and XIAP. Cells. 2020;9(8). https://doi.org/10.3390/cells9081760

119. Babinčák M, Jendželovský R, Košuth J, Majerník M, Vargová J, Mikulášek K, et al. Death receptor 5 (Tnfrsf10b) is upregulated and trail resistance is reversed in hypoxia and normoxia in colorectal cancer cell lines after treatment with skyrin, the active metabolite of hypericum spp. Cancers (Basel). 2021;13(7):1-30. https://doi.org/10.3390/cancers13071646

120. Zhao LM, Li L, Huang Y, Han L juan, Li D, Huo BJ, et al. Antitumor Effect of Periplocin in TRAIL-Resistant gastric cancer cells via upregulation of death receptor through activating ERK1/2-EGR1 pathway. Mol Carcinog. 2019;58(6):1033-45. https://doi.org/10.1002/mc.22991

121. Chien HJ, Ying TH, Hsieh SC, Lin CL, Yu YL, Kao SH, et al. α-Mangostin attenuates stemness and enhances cisplatin-induced cell death in cervical cancer stem-like cells through induction of mitochondrial-mediated apoptosis. J Cell Physiol. 2020;235(7-8):5590-601. https://doi.org/10.1002/jcp.29489

122. Ilhan S. Essential Oils from Vitex agnus castus L. Leaves Induces Caspase-Dependent Apoptosis of Human Multidrug-Resistant Lung Carcinoma Cells through Intrinsic and Extrinsic Pathways. Nutr Cancer. 2020;73(4):694-702. https://doi.org/10.1080/01635581.2020.1823439

123. Oh HN, Lee MH, Kim E, Kwak AW, Seo JH, Yoon G, et al. Dual inhibition of EGFR and MET by Echinatin retards cell growth and induces apoptosis of lung cancer cells sensitive or resistant to gefitinib. Phyther Res. 2020;34(2):388-400. https://doi.org/10.1002/ptr.6530

124. Macejová M, Sačková V, Hradická P, Jendželovský R, Demečková V, Fedoročko P. Combination of photoactive hypericin and Manumycin A exerts multiple anticancer effects on oxaliplatin-resistant colorectal cells. Toxicol Vitr. 2020;66:104860. https://doi.org/10.1016/j.tiv.2020.104860

125. He Y, Li W, Zhang J, Yang Y, Qian Y-W. The curcumin analog EF24 is highly active against chemotherapy-resistant melanoma cells. Curr Cancer Drug Targets. 2021;

126. Choi SM, Cho YS, Park G, Lee SK, Chun KS. Celecoxib induces apoptosis through Akt inhibition in 5-fluorouracil-resistant gastric cancer cells. Toxicol Res. 2021;37(1):25-33. https://doi.org/10.1007/s43188-020-00044-3

127. Račkauskas R, Zhou D, Uselis S, Strupas K, Herr I, Schemmer P. Sulforaphane sensitizes human cholangiocarcinoma to cisplatin via the downregulation of anti-apoptotic proteins. Oncol
128. Kim TW, Hong DW, Hong SH. CB13, a novel PPARγ ligand, overcomes radio-resistance via ROS generation and ER stress in human non-small cell lung cancer. Cell Death Dis. 2020;11(10).
https://doi.org/10.1038/s41419-020-03065-w

129. Kim TW, Hong DW, Kang CM, Hong SH. A novel PPARγ ligand, PPZ023, overcomes radioresistance via ER stress and cell death in human non-small-cell lung cancer cells. Exp Mol Med. 2020;52(10):1730-43.
https://doi.org/10.1038/s12276-020-00511-9

130. Yang Y, Ma L, Xu Y, Liu Y, Li W, Cai J, et al. Enalapril overcomes chemoresistance and potentiates antitumor efficacy of 5-FU in colorectal cancer by suppressing proliferation, angiogenesis, and NF-kB/STAT3-regulated proteins. Cell Death Dis. 2020;11(6).
https://doi.org/10.1038/s41419-020-2675-x

131. Tyagi M, Patro BS. Salinomycin reduces growth, proliferation and metastasis of cisplatin resistant breast cancer cells via NF-kB deregulation. Toxicol Vitr. 2019;60:125-33.
https://doi.org/10.1016/j.tiv.2019.05.004

132. Kuo KL, Liu SH, Lin WC, Chow PM, Chang YW, Yang SP, et al. The Deubiquitinating Enzyme Inhibitor PR-619 Enhances the Cytotoxicity of Cisplatin via the Suppression of Anti-Apoptotic Bcl-2 Protein: In Vitro and In Vivo Study. Cells. 2019;8(10):1-13.
https://doi.org/10.3390/cells8101268

133. Hancio T, Robaina LMGGM, Mendonça BDS, Moraes GN De, Monte-Mor BDCR, Gutiyama LM, et al. The pterocarpanquinone LQB-118 compound induces apoptosis of cytarabine-resistant acute myeloid leukemia cells. Int J Oncol. 2021;58(6).
https://doi.org/10.3892/ijo.2021.5204

134. Fancy RM, Kim H, Napier T, Buchsbaum DJ, Zinn KR, Song Y. Calmodulin antagonist enhances DR5-mediated apoptotic signaling in TRA-8 resistant triple negative breast cancer cells. J Cell Biochem. 2018;119(7):6216-30.
https://doi.org/10.1002/jcb.26848

135. Ye T, Yao H, Xu Y, Zhao X, Lu H, Zhang R. Role of Smac, survivin, XIAP, and Omi/HtrA2 proteins in determining the chemotherapeutic response of patients with cervical cancer treated with neoadjuvant chemotherapy. Cancer Biomark. 2019;26(3):249-59.
https://doi.org/10.3233/CBM-182165

136. Chenyu Ding, Yi X, Wu X, Bu X, Wang D, Wu Z, et al. Exosome-mediated transfer of circRNA CircNFIX enhances temozolomide resistance in glioma. Cancer Lett. 2021;479:1-12.
https://doi.org/10.1016/j.canlet.2020.03.002

137. Shim MK, Moon Y, Yang S, Kim J, Cho H, Lim S, et al. Cancer-specific drug-drug nanoparticles of pro-apoptotic and cathepsin B-cleavable peptide-conjugated doxorubicin for drug-resistant cancer therapy. Biomaterials. 2020;261(April):120347.
https://doi.org/10.1016/j.biomaterials.2020.120347

138. Stover EH, Baco MB, Cohen O, Li YY, Elizabeth L, Wei G, et al. Pooled genomic screens identify anti-apoptotic genes as targetable mediators of chemotherapy resistance in ovarian
cancer. Mol Cancer Res. 2020;17(11):2281-93.
https://doi.org/10.1158/1541-7786.MCR-18-1243