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Targeting Apoptosis to Overcome Chemotherapy Resistance

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Cite this chapter as: Dogan E, Kara HG, Kosova B, Cetintas VB. Targeting Apoptosis to Overcome Chemotherapy Resistance. In: Sergi CM, editor. *Metastasis*. Brisbane (AU): Exon Publications. Online first 2021 Nov 19.

Doi: https://doi.org/10.36255/exon-publications.metastasis.chemotherapy-resistance

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

In: Consolato M. Sergi, editor. *Metastasis*. Exon Publications, Brisbane, Australia. ISBN: 978-0-6453320-2-5. Doi: https://doi.org/10.36255/exon-publications.metastasis

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 diphosphoglucuronosyltransferase (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 caspase-9 activates the intrinsic pathway. 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 activate 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 intramembrane 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. Overexpression of anti-apoptotic BCL-2 proteins provide survival advantage to the malignant cells and promote the expansion of 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 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 drug dose (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 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 and ABT-199, repressed tumor growth in BRAF-V600E mutant advanced melanoma (85). Similar combination with AZD5991 and venetoclax provided a sharp decrease in the MCL-1 expression 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 lead 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 mimetic 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 responded well to TRAIL after SMAC mimetic 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 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-Hydroxylcinnamaldehyde 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 downregulation. 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 bind 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 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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