Chapter 7

Role of Apoptosis in Cancer Resistance to Chemotherapy

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Additional information is available at the end of the chapter

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Abstract

Cancer is a leading cause of death in human beings. Surgery, chemotherapy, radiotherapy, immunotherapy, and biologically targeted therapy are common modalities for cancer treatment. However, cancer resistance is common in chemotherapy and often leads to therapeutic failure. This chapter addresses the role of apoptosis in tumor's resistance to chemotherapy and the underlying mechanisms. Cancer cells are always resistant to apoptotic signals via a series of biochemical changes. Cancer cells are resistant to chemotherapeutic agents that are potent apoptosis inducers via multiple mechanisms, such as upregulated anti-apoptotic signals and downregulated pro-apoptotic signals, faulty apoptotic signaling, faulty apoptosis initiation and implementation, etc. We also discuss the possible approaches to overcoming cancer resistance to chemotherapy due to altered apoptosis.

Keywords: apoptosis, cancer resistance, chemotherapy

1. Chemotherapy and cancer resistance: fact, evidence, and outcome

Cancer is a major public health problem. According to the International Agency for Research on Cancer (IARC), about 14.1 million new cancer cases were reported in 2012 worldwide, and 8 million occurred in developing countries [1]. Cancer ranks second among the leading causes of death in the United States. US Final Mortality Data (2015) showed that lung cancer is the first leading cause of death in all ages with 5-year survival rate around 18% [2]. The main reason for high mortality is that most cancers are difficult to be diagnosed by routine examinations in the early stage, due to the slight change in the tumor biomarker level and the

unapparent symptoms. Fortunately, benefiting from the advances in cancer treatment and the alteration in personal habits (e.g. reduction of smoking), cancer mortality has been declining over the past two decades [2].

Among cancer treatments, chemotherapy is one of the most effective modalities. The patients are given first-line treatments after the clinical diagnosis. With the promising and wide spectrum of anticancer effects, the first-line drugs are very likely to kill the cancer cells and increase survival rate among patients. However, some patients may suffer relapse or cancer metastasis, and second-line treatments come to stage. Chemotherapy usually uses alkylate and anthracyclines as antimetabolic agents in clinical treatments. These chemotherapeutic drugs mainly take effect through activation of caspases and calcium-dependent nucleases to induce cancer cell apoptosis. For example, taxol, a microtubule inhibitor, promotes cancer cell apoptosis by inhibiting phosphorylation of apoptotic protein Bcl-2 [3], while glucocorticoid, the chemotherapeutic drug for acute lymphoblastic leukemia, induces apoptosis by regulating a sequence of apoptosis-related genes in malignant cells [4]. The chemotherapeutic drugs can also transfer the pro-apoptotic signals to cancer cells, ending the cell cycle and programing cell death.

However, cancer resistance is common in chemotherapy and leads to therapeutic failure. Cancer resistance can be sorted into primary resistance and acquired resistance. The primary resistance originates from the natural immunity, while the acquired resistance is gained and developed during treatment. Drug resistance can be caused by changing drug targets. For example, DNA-targeting drugs take effect in the nucleus; however, the drugs would disperse into the cytoplasm in the presence of a non-ABC transporter [5]. As a result, the chemotherapeutic drugs fail to target DNA in the nucleus, but accumulate in the extracellular environment. In addition, patients would develop drug resistance after long exposure to the same agent, and may even develop cross-resistance to non-related drugs and multidrug resistance (MDR). The mechanism of drug resistance is intricate, involving the alteration of transporter pump, the aversion of apoptosis and autophagy, the mutation and amplification of oncogenes and tumor suppressor genes, the variation of drug metabolism, etc. To remedy cancer resistance, researchers have tried many solutions. For instance, Wang et al. have used gambogic acid (GA) as an auxiliary to remedy doxorubicin (DOX) resistance in breast cancer [6, 7]. GA could reduce the expression of P-glycoprotein (P-gp), a key protein in DOX resistance, and promote the accumulation of DOX in cancer cells [6]. Furthermore, GA has been reported to induce apoptosis via p38 MAPK pathway. GA increases the apoptotic rate by downregulating the expression of survivin mRNA [6]. Even though the mechanism of the combined treatment is still unclear, it seems to be a promising approach for DOX resistance in breast cancer. To further improve the efficacy of chemotherapy, the mechanism of cancer resistance should be fathomed.

2. Mechanisms of cancer cells evading apoptosis

Apoptosis is an autonomous process that involves the activation, expression, and regulation of a wide range of genes, leading to programed cell death to remove unwanted or abnormal cells in organisms and maintaining a stable internal environment. Apoptosis mediates the

programed cell death either in a caspase-dependent or in a caspase-independent pathway. The caspase-dependent pathway can be classified into the extrinsic pathway and the intrinsic pathway, as illustrated in **Figure 1**. Caspases, a cysteine protease family, can be divided into the apoptotic subfamily and the inflammatory subfamily according to the pathway they involve. Among the known 18 mammalian caspases, caspases 2, 3, 6, 7, 8, 9, and 10 can be categorized as apoptotic caspases: caspase 2 is involved in various cell death pathways; caspases 3, 6, and 7 work as apoptotic executors, while caspases 8 and 10 are essential in the extrinsic pathway and caspase 9 is essential in intrinsic pathway. As shown in **Figure 1**, the extrinsic pathway facilitates apoptosis by activating caspases through the death receptor ligands on the cell surface. The death receptor ligands are closely related to the tumor necrosis factor (TNF) receptor superfamily, including the TNF-related apoptosis-inducing ligand (TRAIL), TNFR1 (CD120a), Fas (APO-1/CD95), Weasl (APO-2/DR3), TRAIL-R1 (DR4), TRAIL-R2 (DR5), and DR6. Take Fas as an example. Fas/FasL is one of the well-known death receptors associated with signaling pathways in immune and pro-apoptotic effect [8]. The Fas exists in two forms: membrane Fas (mFas) and soluble Fas (sFas). mFas and sFas bind to FasL in a competitive way. The binding of mFas and FasL induces pro-apoptosis, while the binding of sFas and FasL has no similar effect. With the binding of mFas and FasL, mFas-associated death domain

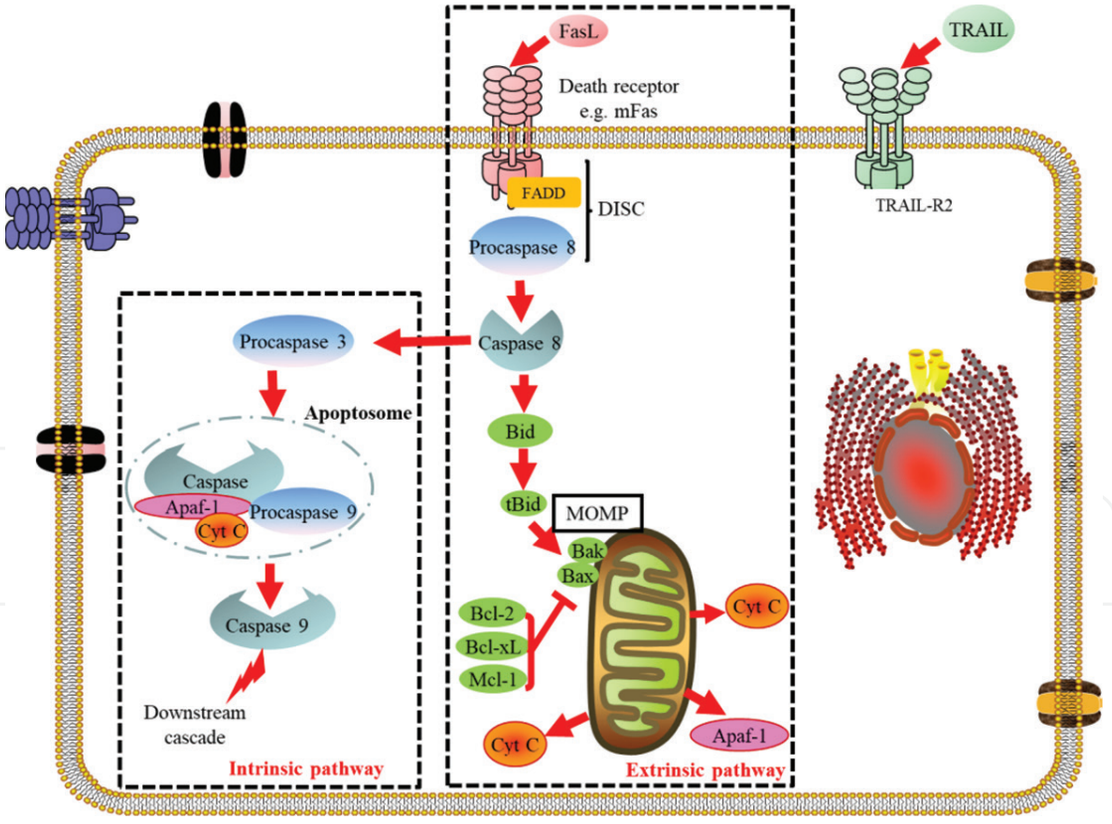

Figure 1. The intrinsic and extrinsic apoptotic pathways. The extrinsic pathway facilitates apoptosis by activating caspases through the death receptor ligands (e.g. mFas) on the cell surface. With the binding of mFas and FasL, mFas-associated death domain (FADD) combines with procaspases 8 and 10, leading to the formation of death-inducing signaling complex (DISC) which activates the downstream signal cascade. MAC forms on the mitochondrial outer membrane and releases cytochrome C into the cytosol. The intrinsic pathway of apoptosis is initiated by cytochrome C released from mitochondria to the cytosol. In the presence of ATP/dATP, cytochrome C interacts with the apoptotic protease-activating factor (Apaf-1) to promote the formation of apoptosome with procaspase 9.

(FADD) combines with procaspases 8 and 10, leading to the formation of death-inducing signaling complex (DISC), which activates the downstream signal cascade [9]. The activated caspase 8 modifies Bid into tBid. tBid binds with Bak and Bax, which are pro-apoptosis proteins that control the permeability of mitochondrial outer membrane, to form mitochondrial apoptosis-induced channel (MAC). The intrinsic pathway of apoptosis, also known as the mitochondrial pathway, is initiated by cytochrome C. Cytochrome C is a key protein for electron transfer in mitochondria. Mitochondria releases cytochrome C into the cytosol through MAC in response to stresses of apoptosis-inducing factors [9]. In the presence of ATP/dATP, cytochrome C interacts with the apoptotic protease-activating factor (Apaf-1) in the cytosol to form a complex and promotes the formation of apoptosome that activates procaspase 9 [9]. The activated caspase 9 further activates the downstream caspases.

Notably, a class of proteins exerts anti-apoptosis and pro-apoptosis effects in the apoptosis pathway. These proteins include the Bcl-2 family and inhibitors of apoptosis proteins (IAPs). The Bcl-2 protein family can be classified into two functional groups—one of which has an inhibitory effect on apoptosis through inhibition of MAC formation, such as Bcl-2, Bcl-XL, Bcl-w, Mcl-1, Ced-9, while the other has a promoting effect on apoptosis by promotion of MAC formation, such as Bax, Bak, Bik, Bid, and Harakiri [10]. IAPs are the family of caspase inhibitors, including survivin, livin, Bruce (Apollon), cIAP1, cIAP2, IAP-like protein 2 (ILP-2), the X-linked inhibitor of apoptosis protein (XIAP), and neuronal apoptosis inhibitory protein (NAIP) [11]. Obviously, the homeostasis between anti-apoptosis proteins and pro-apoptosis proteins is essential for cell survival.

In addition to the extrinsic pathway and the intrinsic pathway, there also exists caspase-independent pathway. This pathway relies on apoptosis-inducing factors (AIFs). AIFs are flavoproteins present in the inner mitochondrial membrane [12], and exhibit the pro-apoptosis effect. AIFs are released into cytoplasm along with the increased permeability or the cleavage of mitochondria. Then, AIFs enter the nucleus and lead to chromatin condensation and break into fragments. Polster has studied the relationship of AIFs and mitochondrial ROS production [13]. Insufficient AIF would reduce the electron transport chain complex I, which relates to chronic neurodegeneration [14].

The cancer cells evade apoptosis via various mechanisms. Theoretically, in order to resist apoptosis, cancer cells would upregulate anti-apoptotic signals (e.g. Bcl-2, Akt, Mcl-1, etc.) and downregulate pro-apoptotic signals (e.g. Bax, Bak, Bad, etc.), initiate and implicate faulty apoptosis, etc. The detail is discussed below.

2.1. Cancer cells resisting pro-apoptotic signals

In human cancer cells, the downregulation of pro-apoptotic proteins (e.g. Bax, Bak, Bad, Bim, etc.) and the upregulation of anti-apoptotic proteins (e.g. Bcl-2, Akt, Mcl-1, etc.) hinder the formation of MAC, inhibiting the release of cytochrome C from mitochondria and leading to the immortal character of the cancer cells. For example, the increased ubiquitination level of Bax has been found to be positively correlated to tumor malignant degree [15]. The decreased expression of Bad has been observed in small-cell lung cancers (SCLC), breast carcinoma, and gastric cancer. Furthermore, cancer cells regulate Bim in the pro-transcriptional,

transcriptional, and post-translational levels to disturb the interaction between Bim and Bak/Bax, and thus change the mitochondria's outer membrane permeabilization (MOMP). Overexpression of Bcl-2 inhibits cell death induced by a variety of cytotoxins, and enhances cell resistance to DNA damage factors and most chemotherapeutic drugs [16]. Bcl-2 has been shown to inhibit p53-mediated apoptosis but cannot inhibit p53 translocation toward nucleolus or p53-mediated growth arrest. The possible role of Bcl-2 is to block the activation of the apoptotic signals to their target molecules.

In addition, the abnormal expression of IAPs in cancer cells also increases cancer malignancies. The overexpression of IAPs abolishes the downstream caspase cascade. IAPs form a complex with the baculovirus-IAP repeat (BIR) domain of caspases, inhibiting the catalytic activity of caspases 3, 7, and 9 and blocking the process of apoptosis. cIAP1 inhibits apoptosis by binding to the BIR2 domain, which is used for activating caspases 3 and 7, resulting in ubiquitin-mediated proteasomal degradation. Werner et al. [17] have reported that upregulation of cIAP1/2 inhibits TRAIL-mediated apoptosis in follicular thyroid cancer. The IAPs have also been reported in interaction with NF-κB [18]. They are key molecules that regulate tumor cell apoptosis and chemo-sensitivity, developing new targets for reversing tumor cell resistance and improving treatment efficacy.

2.2. Cancer cells reducing anti-apoptosis signals

A variety of signal pathways are involved in the anti-apoptosis process. The TNF family is associated with apoptosis and malignant tumorigenesis. It has been reported that the translational level of Fas is downregulated in prostate cancer and liver cancer. TRAIL, another membrane of TNF family, intrigues wide anticancer effect by exerting pattern-like function of mFas. It has been found that some cancers show primary resistance and even develop multiple-mechanism resistance to TRAIL-induced apoptosis [19]. For example, overexpression of TRAIL receptor 3 (TRAIL-R3/DcR1) and TRAIL receptor 4 (TRAIL-R4/DcR2) is considered to contribute to the TRAIL-mediated apoptosis evasion of cancer cells. TRAIL-R3 and TRAIL-R4 are decoy receptors without intercellular death domain. The incapability of TRAIL-3 and TRAIL-4 to associate with procaspases 8 and 10 to form DISC attenuates the activation of downstream signaling pathway [20]. Furthermore, gene mutation of diverse proteins generates the anti-apoptotic effect. Shlyakhtina Y. and his colleagues [21] have studied TRAIL-R2 (DR5) within isogenic cancer cell populations. The models were pretreated with distinctive inhibitors, and the results showed that apoptosis evasion involves kinase cascades of functional Erk1/2, p38, and Akt.

Alteration of the p53 pathway also contributes to apoptosis evasion. The p53 gene is a human tumor suppressor gene. The p53 protein endows anticancer effect by activating defected gene repair and causing apoptosis of cancer cells if the damage is irreparable. p53 regulates apoptosis through Bax/Bcl-2, Fas/Apol, IGF-BP3, and other proteins. Inactivation, elimination, and abnormal expression of the p53 gene play important roles in tumorigenesis. About 80% of human tumors are caused by dysfunctional p53 signaling and 50% by p53 gene mutation [22]. Abnormal expression of p53 downregulates Bax/Noxa/Puma expression and upregulates Bcl-2. The upregulation of Bcl-2 prevents cytochrome C release from the mitochondria, inhibiting p53-mediated apoptosis. The downregulation of Bax prevents the formation of MAC on the

outer membrane of mitochondria, reducing the pro-apoptotic effect [23]. Furthermore, mouse double minute 2 homolog (MDM2) has also been found to play a pivotal role in the inhibition of p53-mediated apoptosis by negative regulation. In cancer cells, the increase of MDM2 transcription and p53 ubiquitination attenuates p53-mediated apoptosis [24].

NF-κB pathway, one of the highly conserved signal pathways of activating gene transcription, takes complicated apoptotic effects in different cells. Activated NF-κB improves the transcription level of survivin, Bcl-2, Bcl-$X_{L,}$ and XIAP, resulting in resistance to the chemotherapeutic pro-apoptotic signals [5]. However, NF-κB renders pro-apoptotic effect through upregulating caspase 4 in Fas-induced neuroblastoma cell apoptosis [25]. In addition, NF-κB upregulates pro-survival genes via Akt activation.

PI3/AKT pathway mediates the survival signals in cancer cells. Akt is correlated to phosphorylation of diverse signal molecules and has a profound effect on cell survival, cell cycle progression, cell growth, and metabolism. The overexpression and overactivation of Akt have been observed in malignant tumors. For example, Zheng [5] has revealed that the paclitaxel-resistance developed in NSCLC can be ascribed to Akt-1 overexpression and Akt-2 gene amplification. In addition, Akt promotes the phosphorylation of Bad on Ser136/Ser112, leading to the suppression of apoptosis [26]. Akt phosphorylates Forkhead-box Class O (FoxO), a protein family governing a line of apoptotic gene transcription in PI3K/Akt pathway. The phosphorylated FoxO binds with 14-3-3, stays in the cytoplasm, and fails to execute transcription in nucleus [27].

2.3. Abnormal cross talk of autophagy and apoptosis

Autophagy is the process of self-digestion and degradation of proteins, organelles, and cell to obtain essential elements and energy for cell survival. Under normal physiological conditions, autophagy allows the cells to maintain homeostasis by transporting damaged or senescent substances into the lysosome, preventing the intercellular accumulation of toxic or carcinogenic substances and inhibiting cell carcinogenesis. However, in the tumor microenvironment, autophagy supplies nutrients to cancer cells and promotes tumor growth. The cross talk between autophagy and apoptosis contributes to cell viability (**Figure 2**). Apoptosis regulates autophagy either through specific apoptotic protein regulation or by caspase activation, while autophagy regulates apoptosis through: (1) specific autophagy protein regulation; (2) caspase activation (autophagosome required); (3) autophagic degradation (both autophagosome and lysosome required) and mutual signal pathways [28].

The abnormal apoptosis-autophagy cross talk helps cell death evasion. First, the unusual autophagy proteins would result in apoptosis evasion. In normal apoptotic cells, autophagosome with the regulation of autophagy protein 9 (ATG9), ATG16L1, ATG5, and ATG12 shows a pro-apoptotic effect. However, in abnormal apoptotic cells, less ATG5 translocation and interaction with Bcl-X_L in mitochondria reduces cytochrome C release; meanwhile, the dwindling binding of ATG12 to Bcl-2 and Mcl-1 decreases caspase activation [28]. In addition, the Beclin-1 interacting UV radiation resistance-associated gene (UVRAG) shows an inhibitory effect on apoptosis by binding to Bax [29]. Second, aberrant activations of caspases lead to the longevity of cancer cells. For example, caspase 8 is recruited by autophagosome, and caspase 8/RIPK1 is important for apoptosis-autophagy cross talk [28]. The inefficient activated

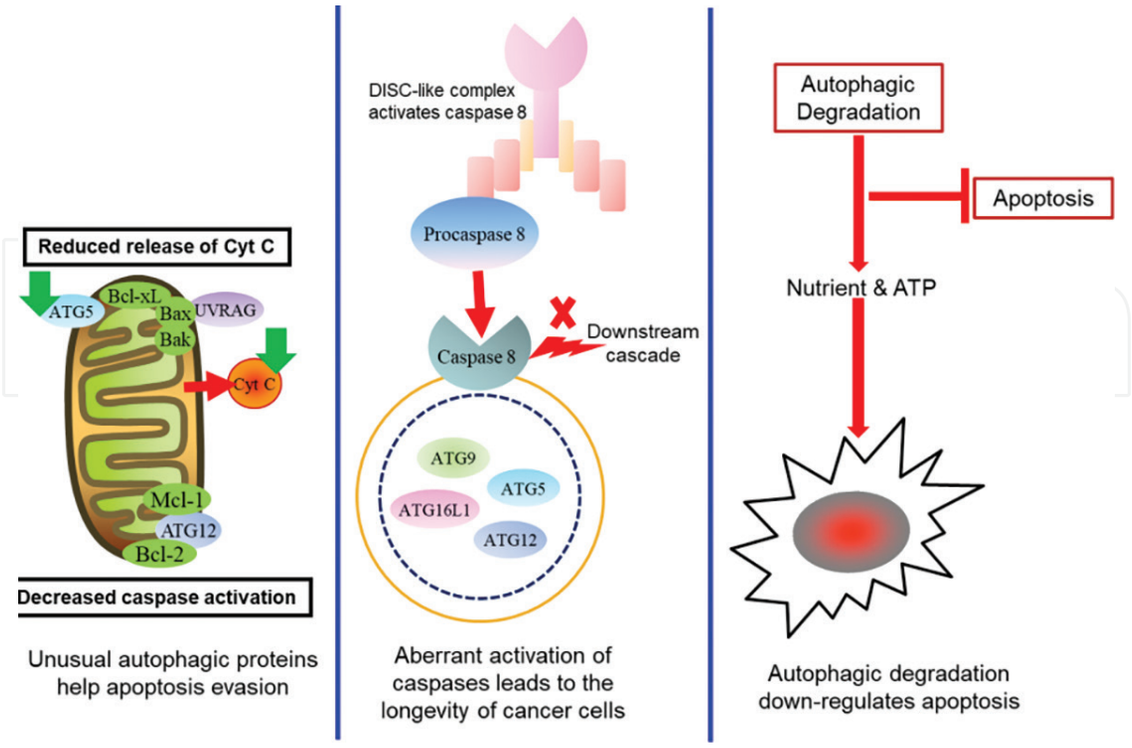

Figure 2. Abnormal apoptosis-autophagy cross talk. (1) The unusual autophagy proteins would result in apoptosis evasion. In abnormal apoptotic cells, fewer ATG5 translocate and interact with Bcl-X_L in mitochondria, reducing the release of cytochrome C; meanwhile, the dwindling ATG12 binds to Bcl-2 and Mcl-1 results in the decrease of caspase activation. (2) Aberrant activation of caspases leads to cell immortality. For example, caspase 8 activated by DISC-like complex is recruited by autophagosome. (3) Autophagic degradation downregulates apoptosis.

caspase 8 may fail to trigger the downstream cascade of apoptosis. Furthermore, Beclin-1 is mediated by caspases; mutant D133A+D146A Beclin-1 has been reported to be resistant to chemotherapy [29]. Third, autophagic degradation downregulates apoptosis. In normal condition, starving cells accelerate apoptosis. However, the apoptosis is attenuated in tumors because the neighboring cancer cells degraded by autophagy provide nutrient and ATP for tumorigenesis. Fourth, malfunctioned signal pathways hinder the cell death process. The p53 protein can be regulated by AMPK pathway and degraded by chaperone-mediated autophagy. In p53-induced apoptosis, the downregulation of damage-regulated autophagy modulator (DRAM) mRNA has been observed in tumor with wild-type; the deficiency of DRAM promotes cell survival [30]. Han et al. [31] have reported that suberoylanilide hydroxamic acid (SAHA) may promote autophagy by stimulating TRAIL-R2-CTSB via AKT pathway.

3. Possible approaches to overcoming cancer resistance

In clinical treatments, the principle to treat drug-resistant cancer is targeting the specific target with the coordinated agent. However, the strategy is idealized since drug-resistant cancer usually involves multiple signaling pathways as well as multiple targets, and the contributions of each target is hard to be calculated. Therefore, treating drug-resistant cancer with the drugs against

the wide-array targets would be more realistic. Similarly, drugs that would induce multiple cell death pathways are likely to circumvent cancer resistance to chemotherapy. Targeting drug transporter protein would be an effective approach to overcome cancer resistance to chemotherapy.

Combined therapies are also considered to be a possible way to overcome cancer resistance to chemotherapy. An ongoing clinical study, led by Okonogi and his colleagues [32], applied maximum dose of carbon ion radiotherapy (C-ion RT) with concurrent chemotherapeutic drugs in uterine cervical carcinoma. The overall survival rate of 31 patients with recommended dose (RD) treatment is 88%; only 2 patients suffered from gastrointestinal toxicities. The studies still require developing a better drug delivery method for longer treatment duration and larger crowd of patients.

Taking advantages of the advance in material science and nanotechnology, nanomedicine delivery systems show a promising potential to guarantee the efficacy of chemotherapy. For example, cerium oxide nanoparticles (CNPs) have been used as carriers to deliver curcumins [33]. The nanoscale delivery systems maintain the stability of curcumins in alkalescency environment and exert anticancer effects. The treatment with nanomedicines increases ROS accumulation and decreases the ratio of Bcl-2/Bax in human neuroblastoma cells, improving the therapeutic efficacy. Zhang et al. [34] used Dox-loaded DNA tetrahedron to target folate receptors in HT-29 colon cancer cells. The treatment efficacy was also enhanced.

4. Conclusions

Apoptosis is an essential process for the growth and development of organisms, while cancer cells obtain immortality by escaping programed cell death. Understanding the underlying mechanism of cancer resistance to chemotherapy is fundamental for efficient cancer treatment agents. In this chapter, we have discussed the mechanisms of cancer cells evading apoptosis, including downregulation of pro-apoptotic signals, upregulation of anti-apoptotic signals and abnormal cross talk of autophagy and apoptosis. Chemotherapeutic drugs induce pro-apoptosis in cancer cells; however, the upregulation of anti-apoptotic proteins, e.g. Bcl-2 and IAPs, would cause cancer resistance. Death receptors including NF-κB-, PI3/AKT-, and p53-related signaling pathways are also involved in the chemoresistance. Additionally, the aberrant autophagy may cause apoptosis evasion as well through autophagic protein regulation, caspase activation, and autophagic degradation. A further, in-depth understanding of apoptosis evasion would be helpful for developing strategies to circumvent cancer resistant to chemotherapy. Combined chemotherapeutic treatment, drugs targeting multiple targets, and using nanoscale drug delivery (nanomedicine) show promising potentials to overcome chemoresistance and achieve precision therapy.

Acronyms and abbreviations

AIF	Apoptosis-inducing factor
Apaf-1	Apoptotic protease-activating factor

ATG9	Autophagy protein 9
DISC	Death-inducing signaling complex
DOX	Doxorubicin
FoxO	Forkhead-box class O
GA	Gambogic acid
IAP	Inhibitors of apoptosis protein
MDM2	Mouse double minute 2 homolog
MDR	Multidrug resistance
NSCLC	Non-small cell lung cancer
P-gp	P-glycoprotein
TOP-1	Topoisomerase-1
TNF	Tumor necrosis factor
BH3-only protein	Bcl-2 homology domain only protein
DRAM	Downregulated damage-regulated autophagy modulator
MAC	Mitochondrial apoptosis-induced channel
UVRAG	UV radiation resistance-associated gene
MOMP	Mitochondria outer membrane permeabilization

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