

Cell Death Mechanisms in Human Cancers: Molecular Pathways, Therapy Resistance and Therapeutic Perspective

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Abstract

Cancer is considered as one of the leading causes of death after cardiovascular diseases. Until now, various kinds of therapeutic modalities have been introduced for the treatment of cancer including chemotherapy, surgical resection, radiotherapy and immunotherapy. However, efficacy of these therapeutics have been reduced due to the resistance development. As a result, the attention has been paid towards the development of novel therapeutics for cancer. Regarding the genomic and epigenetic changes in the tumor cells as well as dysregulation of biological processes, it is suggested to develop therapeutics based on targeting. In the recent years, the dysregulation of cell death mechanisms has been highlighted in human cancers, capable of regulating proliferation, metastasis and therapy resistance. In the present review, a special focus will be on the abnormal changes in the cell death pathways in solid and haematological tumors, related molecular pathways, association with tumorigenesis and therapy resistance. The induction of apoptosis can reverse tumorigenesis and promote drug sensitivity. Apoptosis and necroptosis share some features such as caspases and they may be stimulated simultaneously. Moreover, regulation of autophagy can affect carcinogenesis and other cell death pathways such as ferroptosis, apoptosis and immunogenic cell death. Ferroptosis induction is based on iron changes and increase in lipid peroxidation that decreases cancer progression. Immunogenic cell death is of importance in cancer therapy, as it can activate dendritic cell maturation and improving the activity of T cells in cancer immunotherapy. Furthermore, pyroptosis has also a similar function in cancer therapy and in addition of being a cell death pathway, it is able to stimulate immune reactions. Various kinds of cell death regulators have been developed including small molecules, natural products and nanoparticles that can be further utilized in the clinical studies for the treatment of cancer patients.

1. Introduction

A multifaceted chronic disease is cancer with abnormal proliferation and it is a challenging disease in the recent years. In spite of the advances in the understanding the underlying mechanisms involved in the progression of cancer [1,2], it continues to be a major threat to the human health and both diagnosis and treatment of cancer are in priority. The genomic mutations and cellular abnormalities can cause the tumorigenesis. The number and type of mutations are different based on the cancer kind and even in the patients with a specific type of cancer, challenging the development of universal treatments for cancer and the need for the precision medicine that has been a hot topic in the recent years [3-5]. One of the main challenges in cancer is the diagnosis that they are asymptomatic in early stages or have general symptoms. Therefore, most of the tumors are diagnosed in the advanced stages with poor response to therapy. As a focus, the attention has been directed towards the development of novel therapeutics in cancer such as application of nanoparticles in cancer

phototherapy and immunotherapy [6,7] as well as regulation of cell death mechanisms [8,9].

The cell death mechanisms contribute to the elimination of damaged cells to provide homeostasis and they show dysregulation in pathological events [10]. Based on the morphology, biochemistry and function, the cell death mechanisms can be divided into accidental cell death and regulated cell death (RCD) [11]. In response to the damaged stimuli, the accidental cell death can occur [12]. On the other hand, the RCD is modulated by the molecular pathways and it contributes to the developmental stages and tissue renewal [13]. Although apoptosis was the first recognized cell death, the advances in science led to the identification of other cell death pathways including necroptosis, pyroptosis, ferroptosis, and cuproptosis that can occur in response to exogenous environmental or intracellular disruptions [14-16]. On the other hand, the tumor cells have shown potential in the evasion of cell death pathways [17]. Moreover, RCD participates in the evaluation of prognosis in cancer patients and the regulation of tumorigenesis, metastasis and immune surveillance [18-

23]. The various kinds of RCD have been recognized to mediate changes in the tumor microenvironment (TME) through the release of PAMPs or DAMPs for cancer therapy [24-26]. Therefore, the present review is dedicated to understand the role of cell death mechanisms in cancers.

2. Apoptosis in Cancer

2.1 An overview of Apoptosis Mechanism

The apoptosis word was first coined in 1972 by Kerr, Wyllie, and Currie that they tried to report a unique kind of cell death pathway in spite of the fact that apoptosis regulators have been understood already in the previous year's [27-30]. The knowledge towards the apoptosis mechanisms emanates from the evaluation of cell death in the development of *Caenorhabditis elegans* [31]. Since then, apoptosis was widely approved as a distinct kind of cell death and it is also worth mentioning that other kinds of cell death mechanism have been understood and there are also others that have not been described [32-34]. The apoptosis mechanism commonly occurs during the developmental processes and aging. Moreover, apoptosis is recognized as a mechanism participates in the tissue homeostasis. There are several conditions in which apoptosis can occur including during immune reactions or the presence of damage to the cells as a result of disease or toxic compounds [35]. Apoptosis has a number of characteristics including membrane blebbing, cell shrinkage, nuclear fragmentation and DNA fragmentation [36]. Apoptosis can be categorized into intrinsic and extrinsic pathways

(Figure 1) [37]. In the intrinsic pathway of apoptosis, there are a number of stimuli including DNA damage, oxidative damage and lack of growth factors to mediate apoptosis. The balance of pro- and anti-apoptotic proteins such as BCL-2 family can determine the intrinsic pathway of apoptosis. The pro-apoptotic proteins mainly include BAX and BAK, while anti-apoptotic proteins include BCL-2, BCL-XL and MCL-1. The presence of the signals including DNA damage and oxidative damage can induce pro-apoptotic proteins and their translocation into mitochondria to cause loss of mitochondrial membrane potential. Upon this, cytochrome C is released from mitochondrial membrane into cytosol and then, cytochrome C is attached to Apaf-1 in the cytoplasm. This causes the generation of apoptosome to recruit and induce pro-caspase-9 and transform it into active caspase-9. The active caspase-9 stimulates the caspase cascade by inducing caspase-3 and caspase-7. More information regarding apoptosis in cancer can be found in these reviews [38-40]. The attachment of death ligands including FasL, TRAIL and TNF- α to the death receptors (DR4 and DR5) on the surface of cells can mediate the extrinsic pathway of apoptosis through the formation of DISC complex comprised of FADD and procaspase-8/10. At the next step, DISC participates in the induction of caspase-3, -6 and -7 to mediate cell death or induces BCL-2 cleavage to accelerate mitochondria-induced apoptosis [37]. In spite of versatile function of apoptosis in the physiological processes and preserving homeostasis, the increasing evidences have shown that dysregulation of apoptosis can lead to the development of diseases and cancer [41-45].

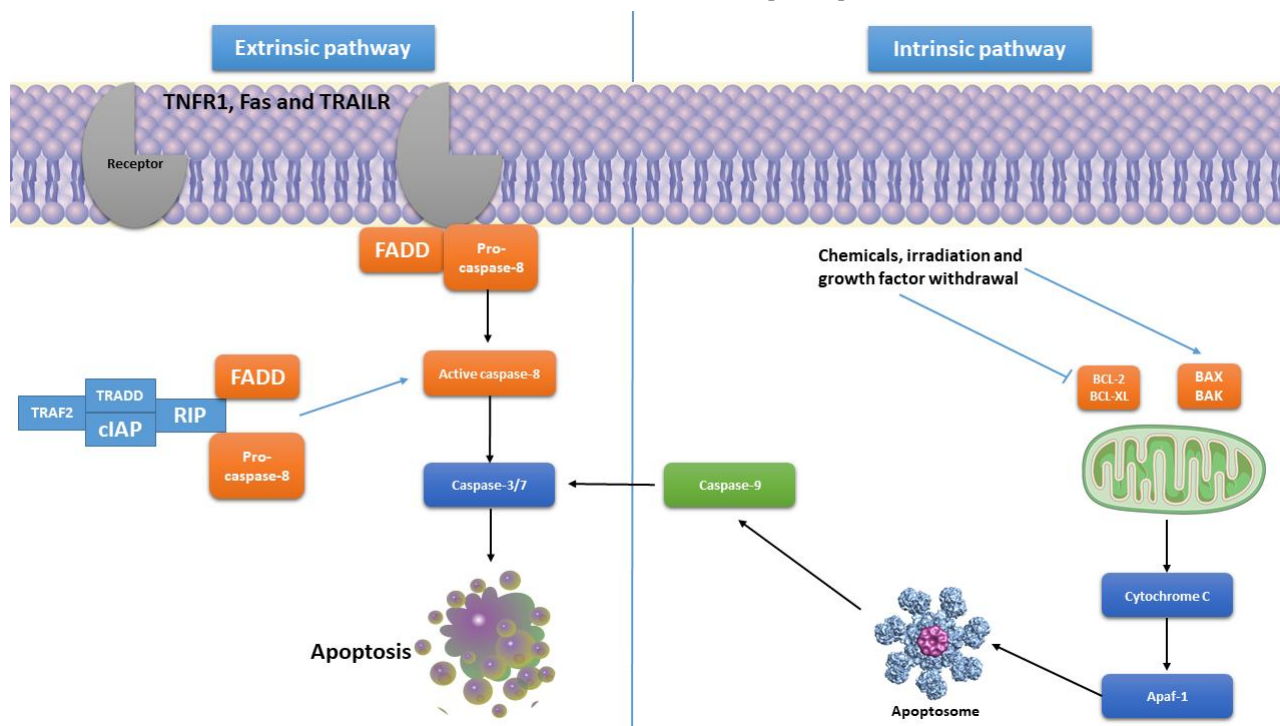


Figure 1. The intrinsic and extrinsic pathways of apoptosis. In the intrinsic pathway of apoptosis, the increase in the levels of apoptotic proteins such as BAX and BAK, and the downregulation of BCL-2 can cause mitochondrial membrane potential loss to release cytochrome C. Then, cytochrome C interacts with Apaf-1 protein to generate apoptosomes. At the next step, the caspase-9 is recruited to induce caspase-3/7 to mediate apoptosis. In the extrinsic pathway of apoptosis, the attachment of ligands to death receptors can cause the formation of FADD and pro-caspase-8 complex. Then, active form of caspase-8 is formed to induce caspase-3/7 cascade for the induction of apoptosis.

2.2 Apoptosis Dysregulation in Cancer

Regarding the importance of apoptosis induction in the treatment of cancer, a number of studies have focused on the factors modulating apoptosis. Notably, various kinds of apoptosis regulators demonstrate dysregulation in cancer that their targeting can provide valuable insights in tumor suppression. TRIM17 has been shown to enhance the viability of gastric cancer cells and it is able to reduce stability of BAX through increasing its ubiquitination to reduce apoptosis [46]. One of the regulators of apoptosis in cancer is autophagy that is discussed in further details in next section. Notably, the induction of protective autophagy can increase the tumorigenesis through apoptosis inhibition. At the final stage of autophagy, there is a need for the fusion of autophagosomes and lysosomes. Therefore, the suppression of autophagosome-lysosome fusion via SNAP29 O-GlcNAcylation can enhance apoptosis through enhancing ROS generation [47]. The reduction in apoptosis can disrupt the response of tumor cells to chemotherapy. Therefore, the function of galectin-7 in enhancing cisplatin sensitivity in cervical tumors is related to the induction of apoptosis and enhancement in the degradation of G3BP1 [48]. The upregulation of Akt has been suggested as a mechanism to reduce apoptosis in the tumor cells. Therefore, suppression of PI3K/Akt/mTOR axis and increase in Akt ubiquitination can elevate apoptosis in gastric tumor [49]. Two other important regulators of apoptosis in cancer include MAPK and XIAP. Notably, the inhibition of XIAP and the downregulation of MAPK can enhance apoptosis in the treatment of oral tumor [50]. The epigenetic changes are the most common reasons of tumorigenesis. Among them, the alterations in the levels of long non-coding RNAs (lncRNAs) can affect the important biological mechanisms in the human cancers, especially apoptosis. Notably, lncRNA TM4SF1-AS1 has been shown to sequester RACK1 and enhance stress granule formation in preventing apoptosis in tumor [51]. Furthermore, the downregulation of lncRNA SBF2-AS1 can increase PTEN levels to mediate apoptosis in colorectal tumor [52]. The main pathway for the induction of apoptosis in the tumor cells is to increase oxidative stress. However, there are a number of antioxidant factors in the cells preventing oxidative damage in increasing tumorigenesis. The increase in the degradation of GPX4 through ubiquitination can enhance apoptosis in hepatocellular carcinoma [53]. The direct upregulation and induction of BAK can also mediate apoptosis [54]. Therefore, both direct and indirect mechanisms can be applied for the induction of apoptosis in human cancers.

The irradiation has been shown to cause apoptosis in tumor cells. For instance, carbon ion irradiation can mediate DNA damage to cause apoptosis [55]. LED irradiation can also impair tumorigenesis and cause damage in the tumor cells through DNA damage-related apoptosis [56]. Notably, the application of hypofractionated irradiation can cause apoptosis in head and neck cancer cells and improves their accumulation by M1-like macrophages [57]. Another mechanism is that irradiation mediates endoplasmic reticulum stress to

promote apoptosis and induces JNK phosphorylation in the treatment of cervical cancer [58]. Furthermore, diode irradiation has been shown to suppress Akt/mTOR axis in promoting apoptosis in pancreatic cancer [59]. The irradiation can cause synergistic impact with chemotherapy such as low-frequency ultrasound irradiation that facilitates paclitaxel-mediated apoptosis [60]. However, the tumor cells can obtain resistance into radiation effects and in this case, the combination therapy is suggested to promote radiosensitivity and apoptosis [61].

Although apoptosis is a kind of cell death mechanism, there are evidences shown that apoptosis can demonstrate interaction with invasion and metastasis of cancer. The downregulation of UBR5 can increase the levels of CDC73 and p53 to facilitate apoptosis in the breast tumor cells and prevent their lung metastasis [62]. In addition to the molecular pathways capable of apoptosis regulation in cancer, targeting the organelles related to apoptosis can affect this cell death. Notably, the induction of mitochondrial dysfunction can enhance apoptosis in gastric tumor [63]. This is maybe related to the impact of mitochondrial dysfunction on the ROS production that can finally enhance oxidative damage and predispose the tumor cells to apoptotic cell death. The upregulation of AZGP1 in cholangiocarcinoma can downregulate TRIM25 to enhance apoptosis [64]. The regulation of apoptosis in cancer chemotherapy. In reversing cancer drug resistance, DYRK2 is able to accelerate p53-induced apoptosis to enhance chemosensitivity [65]. This has been also confirmed in other studies showing that suppression of BET and NAE can enhance BIM-mediated apoptosis [66]. In order to overcome the progression of ovarian tumor, the upregulation of FNDC4 has been followed to facilitate apoptosis and suppress proliferation [67].

2.3 Therapeutic Modulation of Apoptosis in Cancer

Since the induction of apoptosis can impair the tumorigenesis, several strategies have been developed for the induction of apoptosis. One of the most important ones is the application of natural products and drugs for the induction of apoptosis. Phytochemicals demonstrate multi-targeting and desirable biocompatibility. Therefore, the induction of apoptosis by these natural products can pave the way for the treatment of cancer. Acevaltrate is able to reduce the expression levels of HIF-1 α in enhancing apoptosis and reducing growth of tumor [68]. Morusin is also able to increase the levels of p53 and p21 along with upregulation of PARP and caspase-3 to enhance apoptosis in melanoma therapy [69]. The direct regulators of apoptosis can be also regulated by anti-cancer compounds. Notably, cowanin is able to accelerate apoptosis and necrosis through the downregulation of BCL-2 to disrupt progression of breast tumor [70]. Lung cancer is one of the leading causes of death and in spite of the introduction of several strategies for its treatment, the tumor cells have been able to mediate drug resistance. Therefore, the natural products have been significantly applied in the treatment of lung cancer [71]. Another valuable

compound in the treatment of cancer is baicalein capable of decreasing glutamine synthesis and suppressing mTOR axis to enhance apoptosis in the treatment of lung cancer [72]. Therefore, natural products are promising compounds for the treatment of lung cancer [73,74].

One of the most common compounds in the treatment of cancer is curcumin. Curcumin is derived from the *Curcuma longa* and it has been used for the treatment of different tumors including breast [75], lung [76], prostate [77], bladder [78], brain [79], gastric [80] and colorectal [81,82] tumors, among others. In order to improve the potential of curcumin in cancer therapy, the analogs of this compound have been developed. L48H37 is a curcumin analog capable of inducing caspase cascade and upregulation of MAPK to facilitate apoptosis in oral tumor [83]. The stimulation of both apoptosis and ferroptosis by platinum(IV) complexes has been shown to be beneficial in overcoming oxaliplatin resistance in colon tumor [84]. The BCL-2 downregulation and BAX upregulation are the most common pathways for the induction of apoptosis in cancer therapy [85].

Atractylodes macrocephala is a popular plant that has been utilized with other Chinese medicines for the cancer therapy [86]. Atractylenolide II (AT-II) is a bioactive compound derived from the Rhizome of *Atractylodes macrocephala*, that has a number of biological activities in the treatment of cancer [87]. AT-II impairs the proliferation and invasion, it mediates apoptosis and it overcome drug resistance in human cancers [88-93]. AT-II downregulates PADI3/ERK axis to mediate apoptosis and disrupt glycolysis in the treatment of endometrial cancer [94]. However, a

number of compounds can regulate both apoptosis and autophagy in cancer such as cannabidiol [95]. The high expression of ASCT2 is a hurdle towards the apoptosis induction. Lobetyolin can decrease ASCT2 levels to mediate apoptosis and impair growth of gastric tumor cells [96]. According to the studies, the introduction of natural products and compounds in the treatment of cancer can be based on apoptosis induction [97-100]. The changes induced in the metabolism of cancer cells can also mediate apoptosis. Notably, erianin has been shown to suppress function of Akt in glycolysis to facilitate apoptosis in tumors [101]. In spite of the promises provided by the natural compounds, they suffer from poor pharmacokinetic profile and therefore, the application of nanoparticles can improve their therapeutic index and enhance apoptosis. Moreover, sometimes, phytochemicals mediate protective autophagy along with apoptosis [102] that in this case, the suppression of autophagy promotes apoptosis in cancer therapy. In the recent years, nanostructures have been also utilized for the induction of apoptosis in cancer [103]. Notably, the nanostructures can be assembled by the function of copper and from the photosensitizer Zinc Phthalocyanine (ZnPc)-chemotherapeutic (DOX) prodrug with a thioketal (TK) spacer and an IDO inhibitor (1-methyl tryptophan, 1-MT) as building blocks for Cu^{2+} -coordination self-assembly. These nanostructures were able to induce apoptosis, cuproptosis and accelerate immunotherapy. The laser irradiation enhances the ROS production to promote function of DOX in apoptosis induction. Moreover, Cu^{2+} can mediate the accumulation of toxic agents in the mitochondrial to promote cuproptosis [104]. The importance of apoptosis in cancer has been shown in Figure 2.

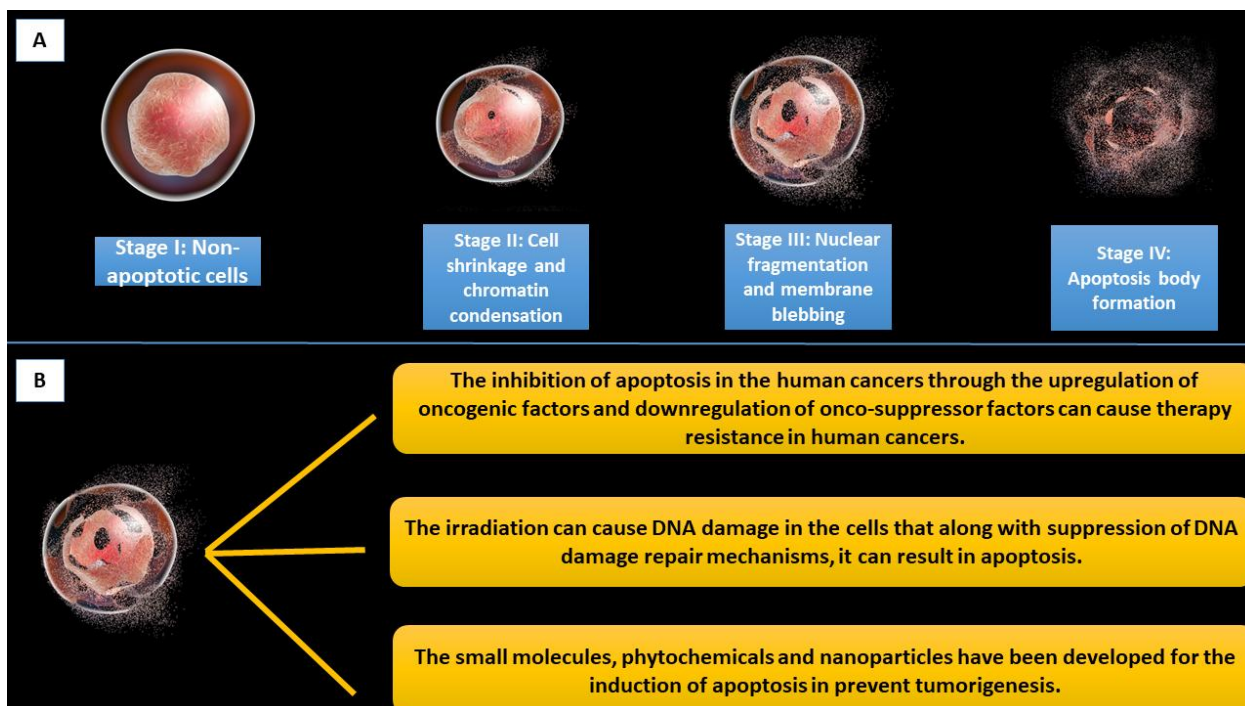


Figure 2. The different stages of apoptosis and importance of apoptosis in cancer. Apoptosis is morphologically identified by the cell shrinkage and chromatin condensation. Then, nuclear fragmentation and membrane blebbing occur to finally generate apoptotic body. The induction of apoptosis has been beneficial in overcoming therapy resistance and causing synergistic effect with other therapeutics such as chemotherapy, radiotherapy and immunotherapy.

According to these discussions, the therapeutic regulation of apoptosis is of importance for combination cancer therapy such as along with immunotherapy to improve treatment efficacy. The apoptosis-inducing agents can be loaded on nanostructures to selectively target tumor cells for reducing damage to healthy tissues. In order to improve the efficacy in targeting apoptosis, the agents can be developed for modulating the specific apoptosis pathways such as intrinsic and extrinsic pathways through modulation of BAX and BCL-2 proteins. However, there are still a number of limitations regarding targeting apoptosis including the resistance mechanisms. The side effect is still a challenge in which selective targeting of cancer cells and lacking impact on normal cells should be improved. Moreover, since different pathways can regulate apoptosis, it is completely challenging to develop universally effective therapeutics.

3. Autophagy in Cancer

3.1 An Overview of Autophagy Mechanism

The eukaryotic cells rely on autophagy for preserving the physiological homeostasis [105]. The first recognition of autophagy in mammalian cells is in 1960s and then, it was discovered in *Saccharomyces cerevisiae* in the early 1990s [106]. In this time, the role of autophagy-related genes (ATG) and the functional protein complexes were recognized [107]. Then, more progress was made in understanding the role of microautophagy in *S. cerevisiae* and other yeast species [108]. Autophagy is a highly evolutionary conserved mechanism capable of sequestering the superfluous, aging or damaged the cytoplasmic materials and deliver it to the lysosomes for the degradation [109]. These cytoplasmic components are degraded into the structures known as autophagosomes as double-membrane compartments and their cargo can be endogenous including redox-active protein aggregates or exogenous including cytoplasmic bacteria [109,110]. The mechanism of autophagy depends on the lysosomal degradation [111]. The basal levels of autophagy are maintained at the physiological conditions, while it can respond to stimuli such as nutritional, metabolic, hormonal, physical, chemical and biological cues [112,113]. The induction of autophagy in these conditions is essential for adapting to stress and supporting the cellular viability. In line with this, the genetic tools and pharmacological compounds have been developed to suppress autophagy for enhancing death in the conditions of lethal perturbations of homeostasis [114-116]. The biological function of autophagy has been understood in the recent years and its dysregulation can be observed in aging-related disorders [117], kidney homeostasis [118], neurological diseases [119], cardiovascular diseases [120], diabetes [121] and cancer [122,123].

Autophagy or macroautophagy is suggested to be a homeostatic process to trigger the degradation of cellular components [122]. The autophagy-related genes (ATGs) contribute to the generation of autophagosomes

as double-membrane compartments for engulfing the cargo and subsequent delivery to lysosomes [124]. UNC-51-like kinase 1 (ULK1) and ULK2, FIP200, ATG13 and ATG101 comprise the ULK complex to induce autophagosome generation and it also interacts with mTORC1. VPS34, Beclin-1, ATG14 and VPS15 comprise the VPS34 complex to facilitate the generation of PI3P on the membrane of autophagosomes. The stimulation of ATG16L1-ATG5-ATG12 complex, ATG3 and ATG7 occurs by PI3P to further proceed the autophagosome maturation [107,125].

3.2 Autophagy in Cancer

In cancer, the function of autophagy is not certain and the studies have shown that autophagy can be considered as a multifunctional mechanism that not only regulates cancer hallmarks (proliferation, metastasis and chemoresistance), but also has dual function in tumors [126-128]. This double-edged sword function of autophagy has been of importance and the tumor-suppressor function of autophagy can emanate from its role in removal of oncogenic factors, elimination of unfolded protein and damaged organelles [129]. The tumor-promoting function of autophagy is related to increasing survival, accelerating cancer metabolism and acting as a supportive factor. The therapeutic regulation of autophagy can impair tumorigenesis. Notably, tanshinone I has been shown to stimulate both apoptosis and autophagy that can result from downregulation of PI3K/Akt/mTOR [130]. A number of changes in the tumors can also facilitate the induction of autophagy. The increase in mitochondrial fusion by Mfn2 can upregulate AMPK to induce autophagy and reduce ROS levels in impairing tumorigenesis [131]. On the other hand, the supportive autophagy can enhance cancer progression. CircRAB11FIP1 has been shown to sequester miR-129 in overexpressing ATG7 and ATG4 to induce oncogenic autophagy [132]. The PSMD14 enhances LRPPRC stability to impair autophagy in enhancing progression of ovarian tumor [133]. The therapeutic compounds have been utilized to regulate autophagy. Nitidine chloride has been shown to stimulate apoptosis and autophagy through downregulation of Akt/mTOR [134]. However, the function of autophagy is not always tumor-suppressor and there should be caution regarding its induction or inhibition. An example is the function of matrine that suppresses Akt/mTOR axis, but it mediates supportive autophagy [135]. Another confirmation is that Cx32 upregulates AMPK to induce supportive autophagy for decreasing apoptosis [136]. This highlights the fact that autophagy and apoptosis demonstrate interaction in the regulation of carcinogenesis.

One of the most common gynaecological tumors is cervical cancer [137]. In spite of the application of radiotherapy and immunotherapy, there is still risk of metastasis and relapse in cervical tumor [138,139]. MAP7 is able to increase tumorigenesis in cervical cancer and in this case, MAP7 regulates autophagy to induce EMT and increase metastasis [140]. In addition, the 5-year survival rate of cervical cancer is unfavourable [141]. The human papillomavirus (HPV)

is also a risk factors for the development of cervical cancer [142]. However, the changes in the genomic and epigenetic levels can cause the progression of cervical cancer. DARS-AS1 promotes the recruitment of METTL3/METTL14 to trigger mRNA m6A modification in DARS for mediating supportive autophagy in cervical cancer progression [143]. Silencing LINC00511 has been shown to enhance autophagy and apoptosis in cervical tumor [144].

The circular RNAs (circRNAs) are a class of non-coding RNAs with covalently closed loop structure lacking 5' caps and 3' tails [145]. The circRNAs demonstrate resistant to exonucleases and they possess high stability compared to linear RNAs [146]. Therefore, the circRNAs can be used as reliable biomarkers in cancer diagnosis and therapy [147,148]. The circCDYL demonstrates 3.2-fold upregulation in breast tumor compared to healthy tissues and through regulating miR-1275, it upregulates ATG7 and ULK1 to mediate autophagy in carcinogenesis [149]. Therefore, autophagy demonstrates a versatile function in the regulation of tumorigenesis [150-154]. Regarding the advances in the field of biology, different regulators of autophagy have been identified including MCOLN1/TROML1 [155], NEO212 [156], miR-106a [157], miR-152-3p/NCAM1/ERK [158] and ALK [159], among others. Furthermore, the different kinds of autophagy regulators have been introduced in cancer therapy including Anlotinib [160], Qiyusanlong Formula [161], carnosic acid [162], TCM Prescription Yi-Fei-Jie-Du-Tang [163] and Bai-He-Gu-Jin-Tang formula [164], among others. In the recent years, nanoparticles have been significantly applied in the treatment of cancer [6]. This approach has been also encouraged for the autophagy modulation and therefore, Pt(IV)/CQ/PFH nanostructures can release chloroquine to impair supportive autophagy in promoting tumor suppression [165].

3.3 Autophagy in Cancer Drug Resistance

Regarding the function of autophagy in tumorigenesis, a number of studies have focused on understanding the role of autophagy in cancer drug resistance. As a well-known autophagy suppressor, chloroquine has been shown to suppress autophagy and enhance p21 levels in ovarian cancer suppression [166]. Autophagy is not only related to the cancer cells and it can also affect the cancer stem cells. The suppression of pro-survival autophagy can impair drug resistance and promote the potential in the inhibition of cancer stem cells [167]. However, the function of protective autophagy is different and it can enhance drug sensitivity. The presence of endoplasmic reticulum stress can stimulate both apoptosis and autophagy to overcome chemoresistance [168]. The smoking has been shown to be associated with tumorigenesis. Notably, the presence of (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a risk factor for cancer progression. NNK is able to develop a feedback loop of β 2AR-Akt to mediate autophagy in enhancing drug resistance in pancreatic cancer [169].

The SH3 domain binding glutamate-rich protein-like, also known as SH3BGRL that can mediate protein-protein interaction in the regulation of molecular and cellular events [170]. SH3BGRL is able to mediate central nervous system formation and intestine of zebrafish as well as pathogenesis of Parkinson's disease [171,172]. The increasing evidences have shown the upregulation of SH3BGRL in the different human tumors including breast tumor [173-175]. In breast tumor, SH3BGRL has been shown to mediate drug resistance. SH3BGRL upregulates PI3KC3 and enhances ATG12 stability to mediate drug resistance through autophagy induction [176]. The interactions occurring among the epigenetic factors can also mediate the drug resistance and modulate autophagy. The circ-0023404 is able to sequester miR-5047 in upregulating VEGFA and mediating pro-survival autophagy to facilitate chemoresistance in cervical tumor [177]. The function of autophagy in the induction of drug resistance in human cancers is related to the coordination of metabolism, cell cycle and survival [178]. As anti-cancer agent, cirsiolol is able to impair the AKT phosphorylation to enhance FOXO1 levels. This compound also induces autophagy and disrupt carcinogenesis of osteosarcoma [179]. Notably, the copper nanoparticles have been shown to be potent inducers of apoptosis. The copper nanostructures can cause oxidative damage through ROS generation and they promote BAX and p53 levels in apoptosis induction [180]. The copper nanoparticles can deliver chrysin to induce cell death through downregulation of MAPK/NF- κ B axis [181].

One of the factors involved in the induction of pro-survival autophagy in cancer is ATG2B. The miR-375 has been shown to suppress progression of osteosarcoma. MiR-375 is able to downregulate ATG2B in suppression of autophagy and impairing the progression of osteosarcoma cells resistant to cisplatin [182]. Increasing evidences demonstrate that autophagy participates in the development of cisplatin resistance in human cancers. Therefore, the various experiments have evaluated the role of autophagy in cisplatin resistance. The inhibition OGT in ovarian cancer can cause cisplatin resistance and this emanates from the increase in SNARE complex formation and induction of autophagic flux [183]. The function of autophagy in the induction of cancer drug resistance has been shown in the different tumors including pancreatic tumor [184], hepatocellular carcinoma [185], glioblastoma [186], ovarian cancer [187] and breast tumor [188], among others (Figure 3).

Exploiting the dual function of autophagy as tumor-promoting and tumor-suppressing factor through stimulation and suppression of this pathway can provide significant therapeutic results. As an example, the suppression of pro-survival autophagy at the early stage of tumorigenesis can promote apoptosis and at the other stages, the induction of autophagy can participate in the elimination of damaged cells and decreasing inflammation. The combination of autophagy modulators along with chemotherapy, immunotherapy and radiotherapy can exert synergistic impacts and

decrease the resistance risk. On the other hand, there are also a number of limitations for targeting autophagy in cancer therapy such as the dual function of autophagy, making it troublesome to regulate autophagy in cancer therapy. Moreover, the cancer cells have shown ability

to develop resistance into autophagy, reducing the efficacy of autophagy modulators in cancer therapy. Notably, the prolonged inhibition or induction of autophagy may negatively affect the healthy tissues. Therefore, the side effects should be considered.

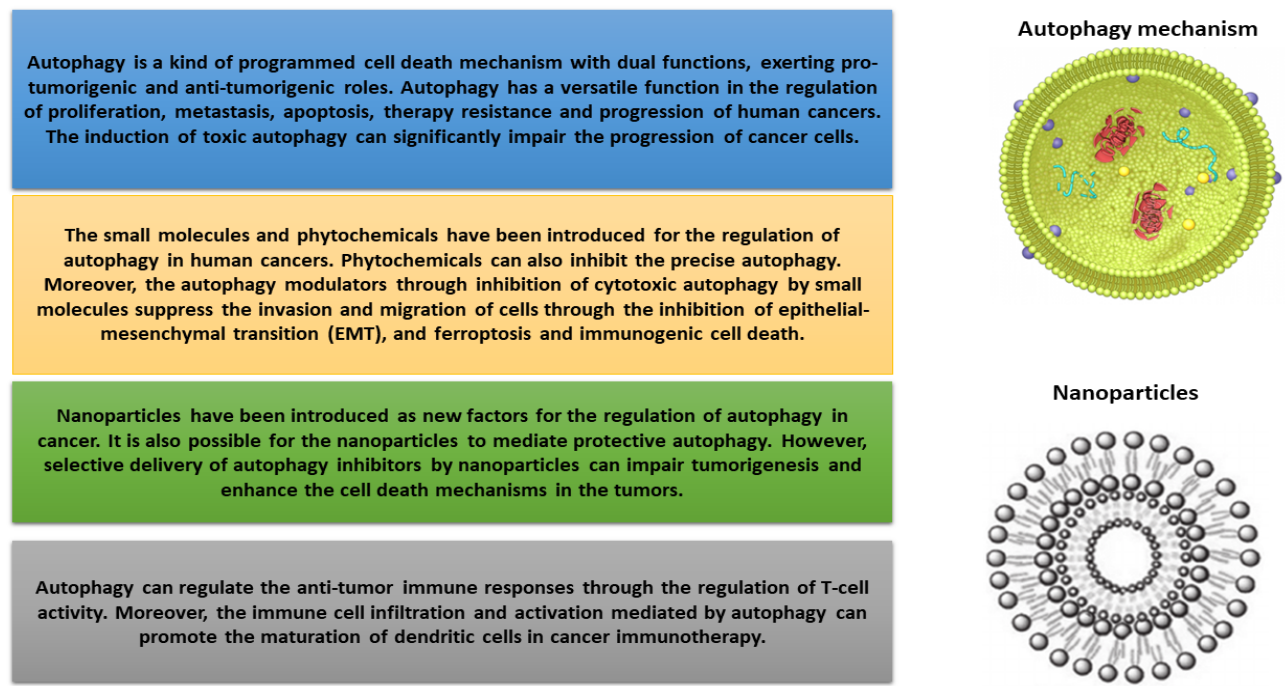


Figure 3. The double-edged sword function of autophagy in cancer. One of the most intriguing cell death mechanisms is autophagy with different function ranging with anti-cancer activity in the pre-cancerous lesions to tumor-promoting function in the advanced stages of carcinogenesis. The various kinds of therapeutics including small molecules, natural products and nanoparticles have been exploited for the regulation of autophagy in cancer therapy. Moreover, autophagy can regulate immune system through affecting T cells, dendritic cells and other immune cells for cancer immunotherapy.

4. Necroptosis in Cancer

4.1 Necroptosis Machinery

Necroptosis is considered as a caspase-independent cell death and it was discovered at the end of 20th century [189]. The cells undergoing necroptosis demonstrate a number of characteristics including organelle swelling, plasma membrane rupture and element leakage within the cells as damage-associated molecular pattern (DAMP) to cause inflammation [190]. Along with pro-inflammatory function, necroptosis has been shown to interact with innate immune mechanisms that along with apoptosis, participates in the elimination of pathogens. Necroptosis can be affected by receptor interacting protein kinase 3 (RIPK3) and mixed lineage kinase domain-like protein (MLKL) [191]. The ligands are able to bind to TNFR1 to mediate necroptosis through enhancing the activity of their cytoplasmic adaptor proteins. These receptors can increase the autophosphorylation of receptor-interacting protein kinase 1 (RIPK1) and assembly into RIPK3 [192]. The dysregulation of necroptosis has been observed in the different conditions and it is a therapeutic target for the treatment of different pathologies including cancer [193,194], cardiovascular diseases [195,196], inflammatory diseases [197] and diabetes [198].

Moreover, the selective regulation of necroptosis has been provided by nanoparticles in the disease therapy [199,200].

As an inflammatory cell death, necroptosis has been identified as another kind of apoptosis through engaging death domain receptors [201]. The necroptosis is a kind of nonapoptotic form of death and the canonical pathway for its induction involved RIPK1-RIPK3-MLKL that can mediate the downstream of death domain receptors including TNFR and Fas, as well as TLR3/4 [202-205]. The active form of RIPK1 is recruited in an oligomeric complex including FADD, caspase-8 and caspase-10. When caspase-8 is absent, RIPK1 can stimulate RIPK3 phosphorylation to generate ripoptosome that further induces MLKL phosphorylation in the formation of necrosome. Then, MLKL oligomers demonstrate potential in the induction of pores in the cell membrane for increasing ion influx, cell swelling and triggering membrane lysis [204-207]. ZBP1 and TRIF as RHIM-domain containing proteins have shown attachment to RIPK3 to enhance necroptosis independent of RIPK1 [208,209].

4.2 Necroptosis in Carcinogenesis

RIPK3 shows absence of reduction in the cancer cells [18,210,211]. Particularly, the poor expression of RIPK3 is observed in the two-third of cancer cells [210].

The downregulation of RIPK3 can be found in the breast cancer [210,212], colorectal tumor [213,214], leukemia [215,216] and melanoma [211]. Furthermore, Hockendorf and colleagues [215] demonstrated silencing RIPK3 increases leukemogenesis in mice. Moreover, low expression of RIPK3 has been shown to diminish DFS (disease-free survival) and OS (overall survival) in cancer patients [213]. Silencing RIPK3 has been shown to enhance the risk of colitis-associated colorectal cancer and mediate the generation of pro-inflammatory factors or oncogenic mechanisms [217]. In breast cancer patients, poor expression of RIPK3 can mediate poor prognosis [210]. Therefore, necroptosis is able to mediate anti-inflammation and anti-cancer function. The genomic methylation or hypoxia may participate in the RIPK3 downregulation in tumors [210,214,218].

Notably, there is an interaction between necroptosis and anti-cancer immunity [219-221]. The cells undergoing necroptosis demonstrate the induction of immune system and they can promote antigen presentation and activation of CD⁸⁺ T cells [222,223]. Moreover, Aaes and colleagues in 2016 demonstrated that necroptosis in cancer is similar to immunogenic cell death (ICD) [224]. The phagocytosis of necroptotic cancer cells can result in the induction of dendritic cell maturation [224]. The role of necroptosis in the anti-cancer immunity has been shown in vitro and in vivo through their potential in enhancing CD⁸⁺ T proliferation [224]. The investigation of underlying mechanisms has shown that necroptotic cells are able to mediate progression of tumor and this requires the BATF3+ cDC1 cells and CD⁸⁺ leukocytes [225]. In order to mediate necroptosis in cancer, a number of therapeutic compounds have been utilized [226]. Notably, the factors capable of induction of apoptosis in cancer cells have shown also potential in the regulation of necroptosis including staurosporine [227] or cisplatin [228,229].

Necroptosis has shown a dual function in the regulation of cancer metastasis [230]. The RIPK3 deficiency has been shown to decrease the number of nodules by 38% in lung tumor [231]. On the other hand, the upregulation of MLKL has been shown to mediate low histological grade and increase in lymphatic metastasis in cervical cancer, providing the unfavourable prognosis [232]. It is worth mentioning that tumor cells are able to mediate necroptosis in the endothelial cells for enhancing metastasis [233]. The pancreatic cancer cells undergoing necroptosis have been shown to upregulate CXCL5 and CXCR2 in enhancing metastasis and migration [234].

Since necroptosis has the ability to mediate inflammatory storm, it suggested to use this inflammatory reaction to improve anti-cancer immunity and combine it with immune checkpoint inhibitors in accelerating immunotherapy. Moreover, the application of combination therapy to stimulate both apoptosis and necroptosis can decrease risk of resistance. However, there are still a number of limitations including abnormal and uncontrolled limitation that may be induced necroptosis causing damage in the healthy tissues. Furthermore, the underlying mechanisms

regulating necroptosis in cancer should be understood more in the development of more novel therapeutics. Furthermore, understanding the balance between necroptosis stimulation for therapeutic aims and reducing excessive inflammation is still challenging.

5. Ferroptosis in Cancer

5.1 Ferroptosis Machinery

The increase in iron levels and lipids peroxides on the cellular membrane can lead to a type of cell death, known as ferroptosis [235]. The ferroptosis mechanism is different from other cell death mechanisms in terms of morphological view and mechanisms regulation. Morphologically, the ferroptosis mechanism do not have the features of apoptosis including chromatin condensation and apoptotic body formation, but they demonstrate other features including shrunken mitochondria and decreased number of mitochondrial cristae [236,237]. The characteristic step for the ferroptosis in the presence of lipid peroxides [238] and it participates in the antagonism between ferroptosis execution and ferroptosis defense system. The induction of ferroptosis is observed when the ferroptosis-inducing activities exceed than antioxidant defense system [239-245]. Ferroptosis is a kind of cell death can be regulated by iron-related phospholipid peroxidation. The byproducts of cellular metabolism including oxygen and iron can mediate ferroptosis through increasing the production of ROS. If the levels of ROS increase and the cells are not able to neutralize the ROS levels, it can cause disruption of cell membrane integrity to mediate ferroptosis [246]. This can create the notion that antioxidant-related factors may be able to reduce ferroptosis that one of them is glutathione peroxidase 4 (GPX4) [238]. In this way, Stockwell found that a number of compounds are able to mediate a kind of cell death distinct from apoptosis in 2003 [247]. Further evaluation demonstrated that iron chelators and lipophilic radical-trapping antioxidants (RTAs) can prevent this kind of cell death [248]. Since this kind of cell death depends on iron, the name of ferroptosis was chosen [236]. It was mentioned that the suppression of GPX4 and system xc⁻ cystine/glutamate antiporter by erastin and RSL3, respectively can be mediate ferroptosis [236,239,249]. The GPX4 is a catalysing enzyme capable of decreasing PLOOHs levels in the mammalian cells [250,251]. In addition to GPX4, the induction of phospholipid peroxidation can also mediate ferroptosis. The lipid peroxidation is a hallmark of ferroptosis and in 1950s, it was found that the inhibition of lipid peroxidation can occur by selenium, vitamin E and cysteine [252,253].

5.2 Ferroptosis Regulation in Cancer

The increasing evidences in the recent years have shown that stimulation of ferroptosis is of importance for the treatment of cancer [254-260]. The induction of ferroptosis in human cancers can significantly impair tumorigenesis and various kinds of underlying pathways are involved. Notably, the inhibition of UTP11 has been

shown to enhance nucleolar stress and ferroptosis through reducing 18S rRNA biosynthesis and decreasing MDM2-related p53 ubiquitination and degradation by RPL5 and RPL11. The loss of UTP11 can also downregulate SLC7A11 through increasing NRF2 levels in downregulation of GSH and promoting ferroptosis [261]. The upregulation of BAP31 is observed in gastric tumor and it mediates undesirable prognosis. Silencing BAP31 can impair cancer growth and mediate G1/S arrest. The downregulation of BAP31 can enhance lipid peroxidation and mediate ferroptosis [262]. The co-suppression of CDK4/6 and BRD4 has been shown to enhance senescence and it can accelerate ferroptosis sensitivity [263].

The regulation of mitochondria has been shown to control ferroptosis in cancers. METTL17 has shown upregulation in colorectal cancer and it causes ferroptosis resistance. METTL17 suppression can enhance ferroptosis and disrupt proliferation and metastasis. METTL17 suppression diminish the methylation of DNA in mitochondria to block the translation of mitochondrial protein-coding genes [264]. Therefore, one of the way for the regulation of ferroptosis is affecting mitochondria and these organelles participate in ferroptosis induction [265]. The ferroptosis can be regulated by autophagy in human cancers. One example is the function of erianin that can enhance autophagy-induced ferroptosis in colorectal cancer through enhancing Fe^{2+} levels, ROS generation and enhancement in lipid peroxidation [266]. The inhibition of ferroptosis can also increase the invasion and metastasis of cancer cells. The loss of AMER1 has been shown to suppress SLC7A11- and FTL-induced ferroptosis to enhance the metastasis of colorectal tumor [267]. One of the important aspects is the involvement of ferroptosis in cancer immunotherapy. The methionine deprivation in the intermittent periods can cause ferroptosis and show synergistic impact with checkpoint blockade [268]. STAT3 is a potent regulator of ferroptosis in human cancers that upon nuclear translocation, it increases levels of GPX4 and SLC7A11 to prevent lipid ROS in the inhibition of ferroptosis [269]. Ferroptosis can exert the synergistic impact with cancer immunotherapy. Notably, the downregulation of PGAM1 can enhance the ferroptosis in hepatocellular carcinoma and this causes synergistic impact with anti-PD-1 immunotherapy [270]. Moreover, the combination of ferroptosis induction along with suppressing myeloid-derived suppressor cells can enhance the sensitivity of metastatic tumor cells to immune checkpoint blockade [271]. According to this, the regulation of ferroptosis and other factors can significantly improve the cancer immunotherapy [272-274].

Although GPX4 targeting has been considered as a main target in the regulation of ferroptosis, there are also other factors that can be regulated. SMURF2 has been shown to enhance ferroptosis in cancer and it can function in an independent manner of GPX4 through enhancing GSTP1 degradation [275]. Sometimes, GPX4 and other factors are simultaneously affected in the induction of ferroptosis in cancer. One example is the

function of isoliquiritigenin that downregulates GPX4, while increases HMOX1 levels to accelerate ferroptosis in gallbladder cancer [276]. Furthermore, in some cancers including colorectal tumor, the gut microbiome can also suppress ferroptosis in acceleration of tumorigenesis [277] that in this case, the composition of gut microbiome can be regulated in cancer therapy. Therefore, understanding the factors involved in the ferroptosis in human cancers can provide novel and valuable insights in cancer therapy [278,279]. Notably, ferroptosis induction has been shown to enhance immunotherapy of cancer [280]. An injectable gel has been developed to deliver RSL-3 and PD-1 antibody providing the prolonged release of cargo in cancer the immunotherapy of pancreatic cancer and hepatocellular carcinoma. The induction of ferroptosis promotes anti-cancer immunity through enhancing the levels of helper T lymphocytes and cytotoxic T cells [281].

5.3 Ferroptosis in Cancer Drug Resistance

The resistance of cancer cells to chemotherapy can be also regulated by ferroptosis mechanism. The stimulation of ferroptosis has been shown to significantly increase the chemosensitivity. In this way, the metal-organic frameworks have been developed to suppress glutathione synthesis and deliver SLC7A11-siRNA in enhancing ferroptosis and reducing drug resistance in breast tumor [282]. The ferroptosis mechanism can be inhibited in neuroblastoma. Notably, the upregulation of TRIM59 can decrease the lipid ROS production and reduce ferroptosis through enhancing ubiquitination and degradation of p53 in developing drug resistance [283]. Overall, the increase in lipid peroxidation, decrease in glutathione levels through SLC3A2 and GPX4 downregulation can mediate ferroptosis to impair chemoresistance [284]. The oxaliplatin resistance in colorectal tumor can be mediated by the upregulation of RBMS1. Notably, RBMS1 is able to accelerate prion protein translation to prevent ferroptosis in oxaliplatin resistance [285]. The interaction of autophagy and ferroptosis can also determine the chemoresistance in human cancers. Noteworthy, circHIPK3 has been shown to suppress autophagy-mediated ferroptosis, accelerating cisplatin resistance in gastric tumor [286].

The TME remodelling can cause the drug resistance in human cancers. The cancer-associated fibroblasts (CAFs) demonstrate high abundance in the TME and they can secrete exosomes enriched with miR-522 to downregulate ALOX15 for reducing ferroptosis and causing paclitaxel and cisplatin resistance [287]. In this case, it is suggested to increase ATF3 levels in the induction of ferroptosis through suppressing Nrf2/Keap1/xCT axis, enhancing cisplatin sensitivity in gastric tumor [288]. The upregulation of Nrf2 or increase in Nrf2 stability can decrease the oxidative damage and reduce ROS levels that are a hurdle towards the induction of ferroptosis, since this kind of cell death can be mediated by the ROS accumulation and subsequent lipid peroxidation. LINC00239 can increase Nrf2 stability through Keap1 downregulation to reduce ferroptosis in colorectal cancer [289] and regarding the

risk of chemoresistance, this axis can be further targeted for suppressing drug resistance in colorectal tumor. Therefore, the studies highlight the function of ferroptosis in the regulation of cancer drug resistance [290-294].

The development and introduction of therapeutic regulating iron metabolism and enhancing lipid peroxidation can promote ferroptosis in tumor cells. Moreover, the application of nanoparticles delivering iron-chelating agents can enhance ferroptosis in tumor cells. The application of ferroptosis inducers along with antioxidant pathways such as GPX4 inhibitors can accelerate ferroptosis in cancer cells. The excessive induction of ferroptosis can promote iron overload and it negatively affects the normal tissues, causing some biosafety issues. Moreover, due to the heterogenous nature of tumors, they have different responses to ferroptosis inducers, challenging the efficacy of therapeutics. Cancer cells have shown resistance to ferroptosis inducers overtime, highlighting the urgency of combination therapy.

6. Immunogenic Cell Death

Laureate Ilya Metchnikoff described that cell-induced immunity awarded by the Nobel Prize [295]. Then, he pursued the experiment on starfish larvae and demonstrated the phagocytosis of foreign materials responsible for innate immunity. From this point of view, it can be considered as a response to injury by host. Then, Polly Matzinger described a theory known as “danger theory” in 1994 highlighting the capacity of the immune system for the distinction between dangerous and innocuous endogenous signals [296]. It was further highlighted that the cells undergoing death can release a number of factors capable of inducing innate immune system [296-298], known as DAMPs [298,299]. A number of DAMPs including ATP and HMGB1 demonstrate secretion from the cells, while other kinds of DAMPs demonstrate enrichment on the surface of plasma membrane such as CRT and HSP90. Moreover, a number of DAMPs can be generated as end-stage degradation products including uric acid upon cell death. These DAMPs demonstrate non-immunological function when they are within the cells and their function may be changed upon exposure to cell surface or secretion [296,298]. The DAMPs do not always trigger immune system and sometimes, a number of DAMPs including HMGB1 may be inhibited by oxidation [300] or proteolysis by IL-33 [301]. The immunogenic cell death (ICD) is considered as a hallmark of dying cells [302] and overall, the factors including CRT, HMGB1, IFNs, ATP and heat shock proteins are ICD-related molecules [303-305]. The studies have shown that DAMPs have ability of attracting immune cells including neutrophils, macrophages, DCs and NKs via pattern recognition receptors (PRRs) and capable of improving their maturation/activation [306]. The mature DCs and $\gamma\delta$ T cells have shown potential in the cross-priming of CD⁸⁺ T cells via IL-17 and IL-1 β and the T cells produce IFN- γ , perforin-1, and granzyme B to eliminate tumor

cells. The T cells mediate the antigen-specific adaptive immune responses and these events are tightly regulated to prevent autoimmunity [306].

ICD provides the new insights for the treatment of human cancers. The induction of ICD can be mediated by inducers as well as dying cancer cells functioning as tumor vaccine [307]. This can provide a long-term clinical benefits for the cancer patients in the clinical level [308]. The immunogenic dead cells have shown a number of hallmarks and they release a number of molecules for interaction with APCs or other related immune cells. These factors are known as DAMPs that can mediate the vaccine impact of ICD [309]. Before apoptosis, the immunogenic cells transfer CRT from the perinuclear ER to the peripheral of cell and provide the relocalization of ERp57 [310]. The exposure of CRT/ERp57 complex to the surface of cells can provide an “eat me” signal to mediate DC-induced phagocytosis [305,311]. Furthermore, the CRT exposure on the surface of tumor cells can mediate antigen presentation and tumor-specific CTL responses [305]. During ICD, the release of ATP can function as an attraction for the DC precursors [312]. This induces the P2X7 receptors on DCs to activate NALP3-ASC-inflammasome and mediate IL-1 β secretion [313]. In breast tumor, oleandrin has been shown to mediate ICD. Oleandrin is able to increase surface exposure of CRT and mediates the release of HMGB1, HSP70/90 and ATP to induce ICD for enhancing maturation of DC cells to promote the cytotoxicity of CD⁸⁺ T cells [314]. The inhibition of ERO1A has been also shown to enhance RE stress and mediate ICD in cancer immunotherapy [315]. The manganese zinc sulfide nanostructures have been demonstrated to mediate DAMP exposure for the induction of ICD to enhance function of CD⁸⁺ and CD⁴⁺ T cells [316]. Another function for the induction of ICD by the nanoparticles is to enhance irradiation-induced oxidative damage [317].

The stimulation of ICD is of importance for the development of personalized cancer vaccines for improving immune reactions in the identification and attacking tumor cells. The co-application of ICD inducers along with immune checkpoint inhibitors can improve anti-cancer immune response and enhance therapeutic efficacy. However, there are a number of limitations such as the interactions in the TME that can impair the immune responses, reducing the efficacy of ICD-based therapeutics. Moreover, ICD cannot be observed in the all tumor cells, providing the heterogeneous therapeutic responses. The interaction of ICD and immune reactions is complex and required more investigation to be fully understood.

7. Pyroptosis

Another kind of cell death is pyroptosis that is mediated by the caspase family through induction of inflammasomes and the cleavage of GSDM proteins. Then, the induced GSDM proteins expose their N-terminal domain and they transfer into the cell membrane for pore induction [318-320]. These pores can mediate the release of cellular components and

cytokines including IL-18 and IL-1 β to accelerate an inflammatory response [319,321]. The GSDMD protein can be cut in the junction region by upregulated caspase-1/4 or caspase-11. Then, GSDMD-NT is released upon cleavage to mediate pyroptosis [322-324]. The GSDME-induced pyroptosis has been shown in the different kinds of tumors by multiple compounds [325-327]. The cleavage site of GSDME is DMPD and it can be cleavage by caspase-3 [328,329]. Cisplatin and the small molecule inhibitors have been shown to facilitate GSDME-induced pyroptosis in lung cancer [330,331]. 5-fluorouracil has been also shown to upregulate caspase-3 and mediate GSDME cleavage in changing caspase-3-induced apoptosis into pyroptosis [332]. Lobaplatin has been shown to enhance ROS generation and upregulate JNK in colorectal tumor. Then, recruitment of BAX into mitochondria occurs to release cytochrome C and induce caspase-3/9 for the induction of GSDME-accelerated pyroptosis [333]. In liver cancer, neobavaisoflavone has been shown to enhance ROS generation and mediate caspase-3/GSDME axis in promoting pyroptosis [334]. Notably, the micelles designed for the co-delivery of nitric oxide and paclitaxel are able to enhance ferroptosis, ER stress and pyroptosis together to promote response of liver cancer cells to paclitaxel chemotherapy [335]. Moreover, pyroptosis may possess an immunogenic function and its induction enhances cancer immunotherapy [336].

The different kinds of stimuli have been understood to mediate GSDM protein fragmentation to induce pyroptosis and trigger the release of LDH, IL-1 β , and HMGB1. GSDMD and GSDME can be cleaved by caspases to mediate pyroptosis [329,337]. The transcriptional suppression of DRP1-induced mitochondrial fission by ruxolitinib can enhance apoptosis and pyroptosis in thyroid cancer [338]. The loss of ZNF-148 can increase the generation of ROS and mediate apoptosis and pyroptosis [339]. In addition, the elevation in the levels of TNF- α , IL-1 β , IL-18, and LDH, and upregulation of NLRP3, ASC and caspase-1 can mediate pyroptosis in gastric cancer [340]. Notably, the suppression of pro-survival mitophagy and enhancement in pyroptosis by the biomimetic nanostructures delivering Ca@GOx to mitochondria can impair tumorigenesis [341]. Moreover, the induction of GSDME-induced pyroptosis can increase the sensitivity of colorectal cancer into anti-PD-1 therapy [342]. Moreover, it has been shown the inhibition of pyroptosis by lncRNA Malat1 can impair the function of T cells in the removal of metastatic cells [343].

Similar to necroptosis and ICD, pyroptosis can also be related to the immunotherapy through enhancing release of inflammatory cytokines and recruitment of immune cells to the TME. Moreover, the selectivity should be increased through special induction in the tumor cells and reducing pyroptosis in the normal cells. There are still a number of limitations including potential of pyroptosis for mediating systemic inflammation and causing damage to the normal tissues. Moreover, due to the heterogeneous nature of tumors, all the tumor cells do not respond to pyroptosis inducers. The cancer cells

have also shown resistance to pyroptosis inducers, providing the fact for the combination therapy.

8. Conclusion, Summary, Limitations and Clinical Importance

The present study provided a comprehensive discussion regarding the function of cell death mechanisms in the regulation of tumorigenesis in human cancers. There are various major mechanisms in cancer that can be targeted for the regulation of tumorigenesis. One of the main mechanisms is the modulation of cell death mechanisms in cancer. Since different kinds of factors participate in the cancer development and demonstrate dysregulation in the different stages of tumorigenesis, it is essential to develop therapeutics based on targeting the major mechanisms. One of the major mechanisms with abnormal alterations in solid and haematological tumors is cell death. The induction of cell death mechanisms can impair cancer progression and provide a favourable prognosis. However, all the cell death mechanisms do not have a similar function including autophagy that its stimulation may facilitate the cancer progression. In this case, the exact function of autophagy should be highlighted and based on that, the induction or inhibition of autophagy can be followed. This is also applicable for pyroptosis that in spite of regulating immune reactions, it can negatively affect immune system. The present review discussed the multiple kinds of cell death mechanisms including apoptosis, necroptosis, ferroptosis, pyroptosis, autophagy and immunogenic cell death. The stimulation of apoptosis, ferroptosis and immunogenic cell death can significantly impair the progression of human cancers. However, necroptosis, pyroptosis and autophagy exert dual roles in the regulation of cancer and more attention should be on their induction or inhibition. The development of cell death regulators can provide a milestone in the treatment of human cancers and their future application in the clinical trials depends on their biocompatibility and long-term safety. In this case, the phytochemicals and natural-based nanoparticles are of importance. The investigation of cell death mechanisms in cancer and the current limitations can be summarized as follows:

A) The stimulation of apoptosis can impair the progression of human cancers. The inhibition of DNA damage repair mechanisms in acceleration of apoptosis in cancer requires more investigation. Furthermore, apoptosis can be regulated by autophagy in which pro-death autophagy enhances apoptosis in tumor cells. In order to accelerate the apoptosis induction in tumor cells, it is suggested to use apoptosis inducers along with survival inhibitors to significantly improve cancer suppression. Moreover, apoptosis can be used in combination therapy along with immunotherapy. Therefore, the novel phytochemicals and drugs with high efficacy should be introduced to accelerate pro-death autophagy in promoting apoptosis in tumor cells. One of the advances in the field of cancer therapy is the application of nanoparticles for the acceleration of apoptosis. However, phytochemicals have desirable

biosafety and their clinical application can be followed. For the future application of nanoparticles in clinical trials in the induction of apoptosis, a focus should be made on their biocompatibility and long-term safety that lipid-based nanostructures are good option. Moreover, the physico-chemical features and the aggregation of nanoparticles may be changed upon large-scale production that the development of effective and simple methods are required. Finally, for the development of biocompatible nanoparticles, it is suggested to develop them from green sources such as chitosan,

B) Autophagy is a programmed cell death pathway that in contrast to apoptosis, the investigations on various species and different cancers have not provided a certain function for autophagy. Therefore, the studies have shown that autophagy may exert both tumor-promoting and tumor-suppressing functions in cancer. As a result, the regulation of autophagy in the treatment of cancer should be followed upon determining its function. The direct autophagy regulators including AMPK, Beclin-1 and mTOR can be utilized as biomarkers for cancer prognosis and diagnosis. The regulation of autophagy by non-coding RNAs has been investigated, but more focus should be on the role of chromosome instability and DNA methylation on autophagy function. In addition to the regulation of proliferation and cell death, the increasing evidences have shown that autophagy has a tight association with the metastasis of human cancers, providing its impact more than regulation of cell death. Autophagy can affect the metastasis of tumor cells [344-347] and it also shows interaction with EMT in human cancers [348-350]. Hence, therapeutic regulation of autophagy can affect both proliferation and metastasis of cancer cells. In addition, the growing evidences have highlighted the function of autophagy in the regulation of cancer drug resistance [351-353]. Therefore, the inhibition of pro-survival autophagy can enhance chemosensitivity. In addition to drugs, the nanocarriers have been shown to regulate autophagy in a targeted way that can significantly affect the tumorigenesis [354-356]. Immunotherapy has been also emerged as a potential therapeutic modality for the tumors and autophagy interaction with the different components of immune system especially T cells, B cells and dendritic cells for clinical treatment of patients should be evaluated.

C) Necroptosis is another kind of cell death that can be also regulated in the treatment of cancer. The tumor cells that are resistant to apoptosis may still demonstrate sensitivity to necroptosis. Apoptosis is caspase-dependent and non-inflammatory mechanism, while necroptosis is an inflammatory cell death and caspase-independent that through inducing pore in the cell membrane and release of cellular components may cause inflammation. However, it should be noted that inflammation caused by necroptosis may affect cancer progression, providing some concepts for the combination with cancer immunotherapy. The key factors regulating necroptosis including RIPK1, RIPK3 and MLKL can be targeted for the cancer therapy. The combination of necroptosis induction with conventional treatments including chemotherapy and radiotherapy can enhance the potential in the tumor suppression.

Because of the release of DAMPs during necroptosis induction, the acceleration of immune system may be observed, since DAMPs are able to induce dendritic cells and other kinds of immune cells. Therefore, the combination of necroptosis induction along with immune checkpoint inhibitors including anti-PD-1 or anti-CTLA-4 can enhance the efficacy of cancer immunotherapy. However, the underlying mechanisms contributing to the necroptosis resistance in cancers has been ignored in the recent years and more studies are required to highlight the function of genomic and epigenetic factors.

D) Ferroptosis is an iron-dependent cell death that can be caused through increase in lipid peroxidation, ROS levels and decrease in GPX4 activity. The iron chelators have been shown to reduce ferroptosis. The stimulation of ferroptosis has a significant potential not only in reducing proliferation and survival, but also can impair metastasis in tumor cells. In order to induce ferroptosis in tumor cells, nanoparticles have been of importance, since they can selectively mediate ferroptosis. Furthermore, nanoparticles can be developed in a redox-sensitive way to mediate GPX4 depletion in enhancing ferroptosis. A number of pathways including Nrf2 can increase the antioxidant activity and decrease ROS generation to reduce ferroptosis. The inhibition of ferroptosis can mediate drug resistance in human cancers. Since ROS is vital for lipid peroxidation, a strategy can be increase in MDA levels and ROS levels to facilitate ferroptosis.

E) The ICD is of importance for the induction of anti-cancer immunity. The release of DAMPs including CRT, HMGB1 and ATP can participate in ICD-mediated immunity. This activates the DCs to induce T cell responses for the elimination of tumor cells. The ICD can be combined with other kinds of therapies including chemotherapy, radiotherapy and immune checkpoint inhibitors to exert synergistic impact. The drug discovery and high-throughput screening of chemical libraries can participate in the development of new ICD inducers in cancer therapy. Moreover, the nanoparticles have been emerged as potential inducers of ICD in cancer therapy. The ICD can be utilized for the development of vaccines in cancer therapy. Among the various cell death mechanisms, the role of epigenetic factors, especially non-coding RNAs in the regulation of ICD has been ignored. Moreover, nanoparticle-induced autophagy can enhance ICD-related cancer immunotherapy.

F) Overall, three factors are responsible for the induction of pyroptosis including inflammatory caspases (caspase-1, caspase-4, caspase-5, and caspase-11), GSDMD protein and inflammasome. The direct and indirect strategies can be utilized to mediate pyroptosis in cancer therapy including direct induction of caspases or inflammasomes, and the indirect way is the development of an inflammatory TME. The induction of pyroptosis can be combined with chemotherapy, radiotherapy and immunotherapy to enhance tumor suppression. The microbiome can be also regulated to induce inflammasomes and mediate pyroptosis in cancer therapy. However, there should be more effort regarding the selective induction of pyroptosis in the tumor cells

and minimizing the impact on normal cells. Moreover, the systemic inflammatory responses should be managed to prevent excessive inflammation and damage to the normal tissues.

G) In the recent years, the application of nanoparticles for the treatment of cancer has significantly increased. The nanostructures have been widely applied for the drug delivery [357], gene delivery [358], cancer phototherapy [359], immunotherapy [360], vaccine development [361], radiosensitivity [362] and chemosensitivity [363] to further improve the efficacy of conventional therapeutics in tumor suppression. In terms of cell death mechanism, although different kinds of modulators, small molecules and drugs have been developed, there is still a challenging issue that is the poor targeting feature of these therapeutics. Therefore, nanostructures have been introduced for the selective regulation of cell death mechanisms in cancer therapy. Nanoparticles can regulate apoptosis [364], autophagy [354], necroptosis [365] and immunogenic cell death [316], among others in improving tumor fight. Moreover, the biomimetic nanostructures have been widely applied in the treatment of cancer [366]. Therefore, their potential in the regulation of cell death mechanisms requires more attention, as these structures demonstrate high biocompatibility. Moreover, hydrogels have been recently introduced for the treatment of cancer [367] and their potential in the sustained delivery of bioactive molecules in controlling cell death mechanisms requires investigation.

Abbreviations

RCD: Regulated Cell Death

TME: Tumor Microenvironment

PAMPs: Pathogen-Associated Molecular Patterns

DAMPs: Damage-Associated Molecular Patterns

ICD: Immunogenic Cell Death

ROS: Reactive Oxygen Species

MDA: Malondialdehyde

CRT: Calreticulin

HMGB1: High Mobility Group Box 1

ATP: Adenosine Triphosphate

DCs: Dendritic Cells

GSDMD: Gasdermin D

GSDME: Gasdermin E

TNF- α : Tumor Necrosis Factor-alpha

IL-1 β : Interleukin-1 beta

IL-18: Interleukin-18

LDH: Lactate Dehydrogenase

NLRP3: NLR Family Pyrin Domain Containing 3

ASC: Apoptosis-Associated Speck-like Protein Containing a CARD

RIPK1: Receptor-Interacting Protein Kinase 1

RIPK3: Receptor-Interacting Protein Kinase 3

MLKL: Mixed Lineage Kinase Domain-Like Protein

GPX4: Glutathione Peroxidase 4

SLC7A11: Solute Carrier Family 7 Member 11

NRF2: Nuclear Factor Erythroid 2-Related Factor 2

UTP11: U3 Small Nucleolar Ribonucleoprotein Protein

DARS-AS1: Aspartyl-tRNA Synthetase Antisense RNA 1

METTL3: Methyltransferase Like 3

METTL14: Methyltransferase Like 14

PLD1: Phospholipase D1

RXRA: Retinoid X Receptor Alpha

ULK1: Unc-51 Like Autophagy Activating Kinase 1

ULK2: Unc-51 Like Autophagy Activating Kinase 2

VPS34: Phosphatidylinositol 3-Kinase Catalytic Subunit Type 3

PI3P: Phosphatidylinositol 3-Phosphate

AMPK: AMP-Activated Protein Kinase

PI3K: Phosphatidylinositol 3-Kinase

Akt: Protein Kinase B

mTOR: Mechanistic Target of Rapamycin

ATG: Autophagy-Related Gene

FIP200: FAK Family Kinase-Interacting Protein of 200 kDa

SNAP29: Synaptosomal-Associated Protein 29

O-GlcNAc: O-linked N-acetylglucosamine

DISC: Death-Inducing Signaling Complex

FADD: Fas-Associated Death Domain

Ca@GOx: Calcium-Glucose Oxidase

BCL-2: B-Cell Lymphoma 2

BAX: BCL-2-Associated X Protein

TRAIL: TNF-Related Apoptosis-Inducing Ligand

FasL: Fas Ligand

DAMPs: Damage-Associated Molecular Patterns

PAMPs: Pathogen-Associated Molecular Patterns

cDC1: Conventional Dendritic Cells Type 1

CD⁸⁺: Cluster of Differentiation 8 Positive

Conflict of interest

The author declares no conflict of interest.

Author contribution

Milad Ashrafizadeh developed the concept and wrote the paper.

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