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Therapeutic Exploitation of Targeting Programmed Cell Death for Cervical Cancer

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1. Introduction

Programmed cell death (PCD) is a basic biological phenomenon that plays an important role during development, preservation of tissue homeostasis, and elimination of damaged cells. Several nomenclature systems have been proposed to classify PCD. One widely accepted system describes three major morphologies of programmed cell death, and classifies PCD as type I, apoptosis; type II, autophagy; and type III, programmed necrosis.

Type I, apoptotic cell death, acts as part of a quality-control and repair mechanism by elimination of unwanted, genetically damaged, or senescent cells, and as such is critically important for the development of organisms. Highly conserved in both plants and animals, it is also the cell-death mechanism best characterized at both genetic and biochemical levels. Type II, autophagic cell death, is a catabolic process conserved among all eukaryotes from yeast to mammals; it is a mechanism by which organelles are removed. Autophagic cell death is the primary degradation mechanism for long-lived proteins, and thus maintains quality control for proteins and organelles to enhance survival under conditions of scarcity or starvation. Type III, programmed necrosis, is a passive process that usually affects large fields of cells; in contrast, apoptosis and autophagy are controlled and energy-dependent and can affect individual cells or clusters of cells. Perhaps the most remarkable characteristic of programmed necrosis is that this death outcome appears as a distinct entity, not by exclusive engagement of selected effectors, but rather, by combinatorial use of the effectors shared with other cell-death outcomes.

Although all three types of PCD can occur normally as a homeostatic mechanism to maintain the cell population in tissues, dysregulation of the delicate balance between cell life and PCD has tremendous pathological implications. The type of cell death that occurs depends on the stimulus and the cellular context, because every cell-death program is a net result of self-propagating signals and other signals that suppress the other cell-death programs. Deficient cell death is frequently involved in early cancer development and tumour resistance to chemotherapy or radiotherapy. Increasingly, evidence suggests that PCD is closely related to anti-cancer therapy. The cancer therapy is improved by targeting the PCD pathway.
Cervical cancer is the most prevalent malignancy of the female reproductive system. Several randomized controlled studies have shown survival benefits of platinum-based neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer. Survival benefit of neoadjuvant chemotherapy depends on high chemoresponsiveness. Considerable evidence indicates that platinum can kill cells through the induction of apoptosis; however, cancer cells, in their relentless drive to survive, hijack cell processes, resulting in resistance to apoptosis. This resistance underlies not only tumorigenesis, but also the inherent resistance of certain cancers to chemotherapy and radiotherapy. Fortunately, in addition to inducing apoptosis, a number of chemotherapeutic agents have been shown to induce nonapoptotic forms of cell death. The significance of nonapoptotic cell death in chemotherapy, and the mechanisms by which it is induced remain less well understood. Given the fact that most cancer cells have defects in the response to induction of apoptosis, it would be desirable if therapeutic agents could kill cancer cells resistant to apoptosis through alternative mechanisms.

In this chapter, we firstly review the main features and functions of all three types of programmed cell death, and further elucidate the intricate relationship between apoptosis, autophagy and necrosis. We discuss the dual roles of autophagy in cancer and highlighted their relationship to tumor suppression and tumor progression. We also review several key autphagic mediators that play pivotal roles in autophagic signaling networks in cancer. Understanding the signaling pathways involved in the regulation of autophagy as well as the autophagy process itself represents new directions in the development of cervical cancer therapies.

2. Basic features of PCD

Programmed cell death displays several cellular phenotypes affecting various intracellular organelles and membranes, and the cell nucleus. For example, the well-characterized processes of cytoplasmic and chromatin condensation, nuclear fragmentation, membrane blebbing, and formation of membrane-bound apoptotic bodies are part of apoptosis. Autophagy involves the formation of a double-membrane vesicle which encapsulates cytoplasm and organelles, and fuses with lysosomes, thus resulting in the degradation of the vesicle contents. Programmed necrosis is characterized by the presence of swelling organelles followed by the appearance of “empty” spaces in the cytoplasm that merge and make connections with the extracellular space. The plasma membrane is fragmented, but the nucleus is relatively preserved.

2.1 Apoptosis

The major biochemical features of apoptosis are activation of intracellular proteases especially caspases, and internucleosomal DNA fragmentation. Changes in several cell surface molecules also ensure that apoptotic cells are immediately recognized and phagocytized by neighboring cells in tissues, with the result that many cells can be deleted from tissues in relatively short time. Therefore, apoptosis results in the orderly elimination of cells without generating an inflammatory response.

The apoptosis cascade can be initiated via two major pathways, involving either activation of death receptors in response to ligand binding (extrinsic or death-receptor pathway), or
the release of proapoptotic proteins, such as cytochrome c, from mitochondria to cytosol (intrinsic or mitochondrial pathway)\(^8\). Some evidence has indicated that the two pathways are linked and that molecules involved in one pathway can influence the other\(^9\). The death receptor pathway is activated through the tumour necrosis factor (TNF) family of cytokine receptors, and has a fundamental role in maintaining tissue homeostasis, particularly in immune recognition. The Bcl-2 family of proteins plays a central role in controlling the mitochondrial pathway. Different members of the Bcl-2 family localize to the cytoplasm or to different subcellular compartments in healthy cells. However, upon receiving a death stimulus, most of these proteins carry out their functions at various intracellular membranes, particularly the endoplasmic reticulum (ER) and mitochondrial membranes. More than 20 members of this family have been identified to date in humans, including suppressors (Bcl-2, Bcl-XL, Mcl-1, Bfl-1/A1, Bcl-W, Bcl-G) and promoters (Bax, Bak, Bok, Bad, Bid, Bik, Bim, Bcl-Xs, Krk, Mtd, Nip3, Nix, Nora, Bcl-B) of apoptosis\(^10\).

The central players in both pathways are the caspases (the cysteine-dependent, aspartate-specific family of proteases), which also function as the executioner in apoptotic cell death\(^11\). Regulated at the post-translational level, caspases are synthesized as pro-caspases. Under stimulation of pro-apoptotic signals from different sources, pro-caspases are digested by protease to become active caspases. Mitochondrial dynamics contribute substantially to apoptotic pathways by stimulation of caspases, and by chromosomal fragmentation\(^12,13\).

The extrinsic pathway is triggered at the cell surface through cytokine-induced death by receptor-mediated activation of caspase-8 or caspase-10, followed by activation of caspase-3 and -7\(^3\). The intrinsic pathway is characterized by mitochondrial dysfunction, resulting in cytochrome c release followed by formation of apoptosomes and subsequent activation of caspase-9 followed by caspases-3 and -7. Bid connects the extrinsic and intrinsic pathways. Cleavage of Bid by caspase-8 produces a truncated Bid fragment\(^14\) that initiates mitochondrial outer membrane permeabilization (MOMP) through the multidomain pro-death molecules Bax or Bak\(^15\). In turn, Bax/Bak translocation to mitochondria induces the release of cytochrome c into the cytosol and subsequent activation of the executioner caspases.

An additional pathway involves T-cell-mediated cytotoxicity and perforin-granzyme-dependent cell death. The perforin/granzyme pathway can induce apoptosis via either granzyme A or granzyme B. The granzyme A pathway activates a parallel, caspase-independent cell-death pathway via single-stranded-DNA damage\(^16\). The extrinsic, intrinsic, and granzyme B pathways converge on the same terminal pathway.

### 2.2 Autophagy

Autophagy is a physiological process that plays an important role in the turnover of cellular proteins and other macromolecules. Moreover, it is the major catabolic route for eukaryotic cells to salvage essential molecules, and to maintain an adequate amino acid level to sustain protein synthesis during nutritional deprivation\(^17\). It is characterized by mitochondrial dilation, extensive intracellular membrane remodeling, and the generation of autophagosomes, large organelles that engulf various cellular constituents in double or multiple membranes. Autophagosomes subsequently fuse with lysosomes to become autolysosomes, where sequestered cellular components are digested\(^18\). Amino acids and fatty acids generated by this process can be used for protein synthesis, or can be oxidized by...
the mitochondrial electron transport chain to produce ATP for cell survival under starvation conditions\textsuperscript{19}. In addition to promoting cell survival, autophagy can lead to cell death.

Based on the mechanisms used for the delivery of cargo to lysosomes, autophagy has been classified into three different types: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA)\textsuperscript{20}. Unlike apoptosis, which relies on the activation of caspases that cleave hundreds of target proteins\textsuperscript{21}, autophagic cell death is caspase-independent\textsuperscript{22}. Indeed, autophagic cell death has been demonstrated in cells with profound defects in the apoptosis machinery\textsuperscript{23} and in cells grown in the presence of caspase inhibitors\textsuperscript{24}. Cells undergoing autophagic cell death look different from cells undergoing apoptosis. The characteristic cellular morphology of apoptosis results from caspase cleavage of cytoskeletal and other structural proteins\textsuperscript{21}; apoptotic cells show early degradation of the cytoskeleton, but preserve organelles until fairly late in the process. In contrast, autophagic cell death is associated with accumulation of large numbers of autophagic vesicles, which degrade organelles early in the process, while the cytoskeleton remains intact and functional until late in the process\textsuperscript{25}.

Morphologic changes, such as chromatin condensation or membrane blebbing, may also occur in autophagic cell death, but there is no DNA fragmentation or formation of apoptotic bodies\textsuperscript{26}. Over 30 ATG genes have been identified in yeast and at least 11 (ATG1, 3, 4, 5, 6, 7, 8, 9, 10, 12 and 16) have orthologs in mammals, ATG6 is also known as BECN1 (Beclin 1) and ATG8 is commonly called LC3 in mammals.

### 2.3 Programmed necrosis

Accumulating evidence supports a ‘sequence’ of events that characterize necrotic cell death at both the phenomenological and the biochemical level, thereby reflecting a programmed course of events in the dying necrotic cell, and contributing to a definition of necrotic cell death. In addition, in some circumstances the ‘occurrence’ of necrotic cell death is also programmed. Type III PCD, programmed necrosis, is not due to one well-described signalling cascade, but is the result of interplay between several signalling pathways.

The lack of caspase and lysosomal involvement distinguishes programmed necrosis from other types PCD. Programmed necrosis is characterized by early swelling of intracellular organelles such as mitochondria, ER, and Golgi apparatus, followed by loss of plasma membrane integrity. After signalling- or damage-induced lesions, necrosis can include signs of controlled processes such as mitochondrial dysfunction, enhanced generation of reactive oxygen species, ATP depletion, or proteolysis by calpains and cathepsins\textsuperscript{27}. In addition, programmed necrosis is also typically associated with nuclear degradation that is accompanied by the release of nuclear factors such as high mobility group box 1 (HMGB1) that triggers a potent inflammatory response\textsuperscript{28,29}. Recent reports describe that this programmed necrosis is firmly regulated and, depending on the cell-death system and/or PCD insult, implicates different proteins, such as TRAIL, TRADD, TRAF2, JNK1, RIP1, XRCC1, AIF, calpains, Bax, or Drp1\textsuperscript{6,30-32}.

### 3. PCD-based therapeutic strategies against cancer

Deregulation of the cellular pathways leading to PCD in mammals can cause a number of disease states, including neurodegenerative diseases, autoimmunity, and most prominently, various cancers\textsuperscript{33}. 

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3.1 Apoptosis based therapeutic strategies

Apoptosis is a major defense mechanism against malignant transformation. In fact, failures in normal apoptotic pathways contribute to carcinogenesis by creating a permissive environment for genetic instability and the accumulation of gene mutations. Tumour cells use a variety of molecular mechanisms to suppress apoptosis.

Cancer cells can acquire resistance to apoptosis by the expression of anti-apoptotic proteins such as Bcl-2 or by the down-regulation or mutation of pro-apoptotic proteins such as Bax. The expression of both Bcl-2 and Bax are regulated by the product of the \( P53 \) tumour suppressor gene, a transcription factor that regulates the cell cycle, and which mutation occurs in over half of all human tumors. Among the remaining tumors, although they may process a wild-type \( P53 \), the pathways of \( P53 \)-induced cell-cycle arrest and apoptosis are deficient. Therefore, \( P53 \) serves as a unique molecular target for cancer therapy. PRIMA-1 (\( P53 \) reactivation and induction of massive apoptosis) is the second class of compounds reported to have the capability of restoring tumor-suppressor function to mutant \( P53 \), and it does not appear to have an effect on wild-type \( P53 \). This makes PRIMA-1 unique among all the chemotherapeutics currently used in the clinic\(^34\). In addition, p73 belongs to a small but important family of p53-related proteins (p53, p63, p73). The \( \text{Trp73} \) gene contains two promoters that drive the expression of two major groups of p73 isoforms with opposing cellular actions: The TAp73 isoforms contain the p73 transactivation domain (TA) and exhibit proapoptotic activities, whereas the \( \Delta \text{Np73} \) isoforms lacking the N-terminal TA domain are anti-apoptotic. It has been proposed that a loss of p73 function might lead to tumorigenesis\(^35\), and that TAp73 down-regulation may be coupled with \( \Delta \text{Np73} \) up-regulation in some tumors\(^36\). Therefore, \( \Delta \text{Np73} \) is a marker of poor prognosis in many cancers, and pharmacological attempts are being made to inhibit \( \Delta \text{Np73} \) expression. Another mechanism of apoptosis-suppression in cancer involves evasion of immune surveillance\(^37\).

An agent that can selectively induce cell death in transformed cells without affecting normal cells would be an ideal anti-cancer chemotherapeutic agent. In fact, the molecular mechanisms that control and execute apoptotic cell death in cancer growth and resistance have been coming into focus and are enabling a new era of drug development for cancer treatment\(^38\).

A variety of experimental approaches have been explored in the development of anti-cancer compounds that block Bcl-2 function. These include the use of antisense oligonucleotides to Bcl-2 that target gene expression at the mRNA level, peptides that mimic BH3 domains and bind to the pocket of Bcl-2 where pro-apoptotic BH3-only proteins would normally bind, and small molecule inhibitors of Bcl-2 function. The first attempt to introduce an agent that specifically targets Bcl-2 was made by Genta with their antisense DNA agent, oblimersen. On the basis of preclinical studies that found that antisense inhibition of Bcl2 levels could induce death in cancer cell lines, they designed a phosphorothioate DNA molecule complementary to Bcl2. More recently, in a study of chronic lymphocytic leukaemia (CLL), an improvement in response rate was observed in relapsed CLL patients when oblimersen was added to fludarabine and cyclophosphamide\(^39\). Albeit limited and not as diverse, some studies have also designed gene therapy approaches to enhance the activities of pro-death Bcl-2 proteins. Adenoviral vectors expressing these genes have recently been constructed with the goal of delivering them into cancer cells. Adenovirus-mediated overexpression of Bax, Bcl-Xs, Bik and others has been a successful strategy for killing various cancer cell lines\(^40,41\). In addition, Cancer cells produce higher levels of ROS (reactive oxygen species) than normal cells due to increased
metabolic stress and proliferative rate.\textsuperscript{42-44} Excessive ROS production may increase the permeability of lysosomal membranes, leading to release of lysosomal proteases, which further contribute to mitochondrial membrane impairment\textsuperscript{13} and cancer progression\textsuperscript{43-45}. It has been reported\textsuperscript{42} that increasing ROS generation selectively sensitizes oncogenically transformed cells to β-phenylethyl-isothiocyanate-induced cell death, suggesting that increasing ROS generation in cancer cells could be a strategy for cancer therapy.

The selective activation of caspases might be a valuable strategy for combating cancer where pathogenesis is related to insufficient cell death. Several strategies that trigger caspase activation have been developed, and several drugs that act in this way are currently being tested in preclinical trials. Therapeutic strategies have included adenovirus-mediated expression of caspases-3, -6, -8 and -9, which has resulted in both \textit{in vivo} and \textit{in vitro} antitumourogenic activities\textsuperscript{46}. In addition, adenoviral gene therapy approaches have also been used in the delivery of caspase constructs that can be activated on demand by the addition of a compound readily able to penetrate the cell membrane. The strategy relies on the fusion of caspases to one or chimeric “death switches”, which can be activated by chemical inducers of dimerization specific for a given construct\textsuperscript{47}. There is considerable evidence that cysteine cathepsins play an important role in executing the apoptotic program in several tumour cell lines induced by death ligands such as TNF-α\textsuperscript{48,49} or TNF-related apoptosis inducing ligand (TRAIL)\textsuperscript{50}. In the last few years, an apoptosis inducing agent, TRAIL, that was shown to target cancer cells specifically without damaging normal cells and tissues has received special interest in cancer therapy. Several groups recently discovered a cathepsin-mediated proteolytic event in the apoptotic pathway triggered by TRAIL. First, the inhibition of TRAIL-induced apoptosis was observed upon treatment of oral squamous carcinoma cells with cathepsin inhibitors\textsuperscript{51}. Subsequently, the pathway for apoptosis induction through Bid activation was confirmed in several other tumour cell lines\textsuperscript{50,52,53}.

3.2 Autophagy based therapeutic strategies

In tumour cells in which the quality control mechanisms of both apoptosis and autophagy are disabled, failure to maintain energy homeostasis accelerates the generation of damaged cells\textsuperscript{54}. This failure of protein/organelle quality control to curtail the accumulation of damaged proteins and organelles through autophagy may have a broad impact on cellular functions, leading either directly or indirectly to genome damage that promotes tumourigenesis. This may mean that autophagy is one of the mechanisms that contribute to the breakdown of cell growth control in cancer\textsuperscript{55}.

In contrast to the potential cancer-promoting effect of autophagy, numerous observations have demonstrated that loss-of-function mutations in the autophagy pathway are associated with tumour progression\textsuperscript{56,57}. Furthermore, constitutive activation of the PI3K pathway is one of the most common events in human cancer\textsuperscript{58}, and the downstream kinase mTOR restricts autophagy induction in response to starvation\textsuperscript{59}. Although many human cancers exhibit mutations in pro-autophagy genes, and several tumour suppressor genes (e.g., \textit{DAPK}, \textit{PTEN}, and \textit{TP53}) can stimulate autophagy\textsuperscript{60}, the molecular mechanism through which autophagy inhibits oncogenesis is currently unclear.

Therapeutically induced autophagic cell death is another method for tumour-cell killing. Especially in apoptosis-defective cells, autophagy is often induced by cytotoxic drugs; the excessive cellular damage and attempt to remediate that damage through progressive
autophagy can promote autophagic cell death\textsuperscript{23}. Inhibition of autophagy is important in cancer therapy. The process of cancer metastasis necessarily requires that tumour cells survive in isolation from the primary tumour, without its nutrient support system. Thus, early metastases may be particularly susceptible to inhibition of autophagy.

Potential synergy with proteasome inhibitors is another reason for the use of autophagy inhibitors. The ubiquitin-mediated proteasome protein degradation pathway is functionally compensatory with protein turnover by lysosomal degradation through the autophagy pathway\textsuperscript{61,62}. Therefore, protein degradation that is mediated by autophagy and proteasomes may be lethally exclusive to tumour cells with a high metabolic rate, or with increased susceptibility to the production of unfolded proteins. The ubiquitin-proteasome pathway is an intracellular proteolytic system which regulates the degradation of a broad spectrum of intracellular proteins, including diverse regulators of cell proliferation or apoptosis. Both bortezomib- and lenalidomide-based therapies are especially active, with bortezomib in particular being shown to provide a platform for combination, which is able to overcome resistance in this setting. Bortezomib, a first-in-class proteasome inhibitor, represents the prototypic member of a class of peptide boronate proteasome inhibitors of 26S proteasome activity, and has been approved by the US Food and Drug Administration, shows efficacy in treating multiple myeloma\textsuperscript{63}.

3.3 Programmed necrosis based therapeutic strategies

Type III PCD, programmed necrosis, is usually defined in a negative fashion, as a type of cell demise that involves rupture of the plasma membrane without the hallmarks of apoptosis and without massive autophagic vacuolization. Necrosis lacks specific biochemical markers apart from the presence of plasma membrane permeabilization, and can be detected only by electron microscopy. Necrosis is considered to be harmful because it is often associated with pathological cell loss and because of the ability of necrotic cells to promote local inflammation that may support tumour growth\textsuperscript{64}. However, necrotic cell death is induced in cancer cells by the therapeutic administration of alkylating DNA damaging agents\textsuperscript{65} and photosensitizing molecules that preferentially accumulate in tumour cells and generate ROS following excitation with light from various spectra\textsuperscript{66,67}.

4. The relationship of PCD to cervical cancer therapy

The ultimate goal of anticancer therapy is to kill cancer cells quickly and effectively. Over the past two decades, it has become clear that cell death, in both malignant and non-malignant cells, can be an active, regulated program. Thus, elucidation of the programmed cell-death pathways will provide new insight into tumour biology, revealing novel strategies for combating cancer. Tumour cells can only persist if they ignore the requirement for senescence that is imposed on all cells of organisms. Failure to execute PCD is usually a reflection of defective or absent molecular components of the cell-death machinery. Cervical cancer is second only to breast cancer in women as the most common of gynecologic malignancies, and it remains one of the most important causes of mortality in women worldwide. In recent years, cervical cancer has been affecting younger women. Because radiation therapy will negatively affect ovarian function in women of reproductive age, chemotherapy for cervical cancer has been receiving increased attention from clinicians. Although platinum-based neoadjuvant chemotherapy is an attractive option for
chemotherapy given prior to surgery, and can reduce tumor size and lead to improvement in overall survival, cancer cells often harbor mutations that confer resistance to apoptosis, suggesting the need for other therapeutic approaches that would exploit non-apoptotic cell modes of death or enhance cell apoptosis for cervical cancer therapy.

4.1 Apoptosis autophagy and cervical cancer therapy

The mechanism of tumour cell killing by an anti-cancer agent determines the way that the agent selects for resistance to the therapy. A drug that induces apoptosis might provide quite different selective pressures on the tumour cell compared with a drug that induces autophagic cell death. Thus, drugs with different mechanisms of action would be expected to have different levels of efficacy against a particular tumour. On the other hand, the close connections between the apoptosis machinery and other PCD machinery under investigation would be expected to result in simultaneous activation of these PCD processes.

When treating cancer, we often use drugs that cause severe damage to the cell. Regulation of PCD using caspase activators/inhibitors can constitute a treatment for cancer or for other PCD defective/excessive diseases. Blockage of caspase activation causes degradation of catalase; the resultant increase in ROS generation leads to cell death. Degradation of catalase is also mediated by autophagy, thus suggesting a role for autophagy in caspase-independent cell death. So, when cancer cells are treated, the induction of autophagy, and the interactions between autophagy and apoptosis could have profound effects on the outcome for the tumour cell.

Some connections occur upstream of the apoptotic and autophagic machinery where signalling pathways regulate both processes. For example, the autophagy gene beclin1 is part of a Type III PI3 kinase complex that is required for the formation of the autophagic vesicle, and that interacts with Bcl-2. A study found that the protein level of Beclin1 is lower in cervical cancer tissues than in normal tissues, and is closely related to pelvic lymph node metastases and histologic tumor grade. Overexpression of Beclin1 in human cervical cancer SiHa and HeLa cell lines may induce the massive cells from to autophagy and inhibit tumor cell growth. Another experiment indicates that beclin1 may be the critical molecular switch that plays an important role in fine tuning the autophagy and apoptosis through caspase-9 in cervical cancer cells. Beclin1 also interacts with the other major anti-apoptotic Bcl family protein (Bcl-xL). It has been shown that autophagy can be regulated by this interaction. In addition to inhibiting apoptosis by binding to and interfering with the action of the pro-apoptotic proteins Bax and Bak, Bcl-2/Bcl-xL also inhibits autophagy by binding with beclin1. This latter interaction is particularly important in the regulation of starvation-induced autophagy. Bcl-2 can inhibit autophagy not only by interacting with beclin1, but also by blocking calcium release from the ER. Conversely, DRAM (damage-regulated autophagy modulator), a well known component of the autophagic machinery, is essential also for p53-mediated apoptosis. Similarly, activation of the PI3 kinase/Akt pathway, a well-known way to inhibit apoptosis, also inhibits autophagy. Thus important signalling pathways apparently simultaneously increase and decrease both autophagy and apoptosis. In our laboratory, we achieved stable transfectants expressing Beclin1 in cervical cancer CaSki cells, and observed that Beclin1 induced cell arrest in the G0/G1 phase. We then selected several drugs that can induce apoptosis to cancer cells by various mechanisms, including a anti-microtubule agent (paclitaxel), a platinum agent (cisplatin), an anti-metabolite (5-fluorouracil), and an
anthracycline (epirubicin), to detect the role of Beclin1 in chemosensitivity. We found that Beclin1 overexpression in CaSki cells reduced cell survival following exposure to all four anti-cancer drugs. However, down-regulation of endogenous Beclin1 by siRNA in the CaSki cells did not lead to obvious resistance to the anti-cancer drugs. Taken together, these data provide evidence that Beclin1 is associated with chemosensitivity and the level of expression causes changes in response to chemotherapeutic drugs in cervical cancer, at least in vitro, despite the distinct damage mechanisms to cancer cells of these drugs\textsuperscript{28,79}.

It has been suggested the mitochondrion may be the central organelle that integrates apoptosis and autophagy\textsuperscript{80}. A positive feedback mechanism can be elicited by the activation and maturation of pre-apoptotic factors from autophagic processes in mitochondria, and lead to cell destruction through apoptotic and autophagic mechanisms. Autophagy can stop cells from undergoing apoptosis by sequestration of damaged mitochondria\textsuperscript{81}. Moreover, some of the signals that are involved in apoptosis may also be involved in autophagy. For example, in both apoptosis and autophagy, there is the coordinated regulation of Akt and p70S6 kinase. Other proteins that may be part of the network connecting the two types of cell death include DAPK, Beclin1, BNIP3, HSpin1, or protymosin-\alpha\textsuperscript{82}. In our previous study\textsuperscript{73}, we found that both autophagy and apoptosis were activated during carboplatin-induced death of cervical cancer cells. Beclin1 may act as an orchestrator, integrating apoptotic and autophagic activities. Another study demonstrated that autophagy and apoptosis contribute to etoposide-induced CaSki cervical cancer cell death, and autophagy may be the predominant mechanism of etoposide-induced cell death\textsuperscript{83}. In addition, multiple death stimuli converge on mitochondria to provoke MOMP and release of apoptogenic factors such as cytochrome c, Smac/Diablo, Omi/HtrA2, Endonuclease G (Endo G), or AIF. Once released into the cytosol, these proteins initiate apoptosis, autophagy, or programmed necrosis\textsuperscript{30,31,84}.

4.2 Programmed necrosis and cervical cancer therapy

Increasing evidence indicates that programmed necrosis can occur as a result of the activation of specific signal transduction cascades, and subsequently can be actualized only on inhibition of apoptosis and/or autophagy. Thus, it might be therapeutically desirable to trigger necrotic cell death in tumour cells that might have been selected to resist apoptotic or autophagic cell death.

Studies suggest that cell death that usually manifests with an apoptotic morphology can be shifted to a more necrotic morphology when caspase activation is prevented by pharmacological inhibitors, or by the elimination of essential caspase activators such as Apaf-1\textsuperscript{85}. In some situations, caspase inhibition can even sensitize cells to the induction of necrosis, thereby reducing the dose of TNFa required to kill some cell lines\textsuperscript{86}. A study found that heat treatment can induce cervical cancer CaSki cell apoptosis and necrosis\textsuperscript{87}. Of the thermal conditions, 45°C exhibited the best induction of apoptosis, while 47°C induced direct fierce necrosis. This was further demonstrated by examining the expression level of several key apoptosis-related genes: caspase-3, Smac and Survivin. During apoptosis, caspase-3 and Smac levels were up-regulated, whereas anti-apoptotic Survivin was down-regulated, enhancing programmed cell death. Similarly, inhibition of autophagy by transfection with constitutively active Akt protein kinase, or knockout of one of the alleles encoding the Beclin1 protein also determines a shift from type II (autophagy) to type III (programmed necrosis) cell death\textsuperscript{86}. Another study\textsuperscript{88} also suggests that necrotic cell death...
induces an immune response against the dying cell through the release of pro-inflammatory cytokines, which help to initiate the repair of damaged tissue. In this way, programmed necrosis differs fundamentally from apoptosis. Death by programmed necrosis is passive, causes cellular contents to be released into the extracellular space, and often causes inflammation. In addition, oxidative-stress-induced cell death is not completely blocked by inhibiting either apoptosis or autophagy. Indeed, in the hypoxic region of a tumor, where both apoptosis and autophagy are inhibited, increased necrosis with infiltration of macrophages and production of cytokines and chemokines has been observed in mouse models. What specifically triggers necrosis is unknown, but ATP production insufficient to maintain plasma-membrane integrity results in metabolic catastrophe, making cell lysis highly probable. Thus, it is also reasonable to assume that cells under oxidative stress could undergo cell death through multiple pathways including necrosis.

5. Summary

PCD is a genetically regulated process that allows for the maintenance of tissue homeostasis and cell numbers, and provides protection against damaged or infected cells that threaten this balance. It is becoming increasingly clear that PCD is involved in cancer formation and survival; the process of PCD responds to several forms of cancer treatments. Elimination of cancer cells might occur not only via apoptosis, but could also be mediated by other forms of cell death such as autophagy and programmed necrosis. In recent years, the PCD-based pharmacological therapies were mainly focused on apoptosis and the main regulators of this PCD pathway, the caspase family of cysteine proteases. Drug resistance limits the effectiveness of existing medical treatments, and is still a major challenge in the current research on PCD. To better understand the pathology and the potential therapeutic strategies for human cancer that are characterized by enhanced cell death, it is crucial to elucidate the death mechanism(s) directly involved in each cancer. Treatment should depend on the actual mechanism of cell death that plays a role in disease onset. Modulation of the autophagic pathway may be a novel way of sensitizing cervical cancer cells to anticancer drug therapy, and further studies of autophagy, apoptosis and necrosis may provide new insights into the mechanisms accommodating or contributing to PCD, thereby unveiling new strategies for cervical cancer therapy.

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7. References


Cervical Cancer is one of the leading cancers among women, especially in developing countries. Prevention and control are the most important public health strategies. Empowerment of women, education, "earlier" screening by affordable technologies like visual inspection, and treatment of precancers by cryotherapy/LEEP are the most promising interventions to reduce the burden of cervical cancer. Dr. Rajamanickam Rajkumar had the privilege of establishing a rural population based cancer registry in South India in 1996, as well as planning and implementing a large scale screening program for cervical cancer in 2000. The program was able to show a reduction in the incidence rate of cervical cancer by 25%, and reduction in mortality rate by 35%. This was the greatest inspiration for him to work on cervical cancer prevention, and he edited this book to inspire others to initiate such programs in developing countries. InTech - Open Access Publisher plays a major role in this crusade against cancer, and the authors have contributed to it very well.

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