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Review Article

Manipulating Cell Death in Cancer

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Abstract

Cancer cells often evade regulated cell death to maintain uncontrolled proliferation and withstand therapy. Targeting cell death pathways has emerged as a promising tactic for enhancing anticancer outcomes and overcoming treatment resistance. In addition to highlighting recent developments in therapeutic interventions, this review investigates the molecular mechanisms underlying the various forms of regulated cell deaths in cancer. We discuss small molecule inhibitors and immune-based approaches that take advantage of cell death pathways. Additionally, we address difficulties in clinical translation, such as tumor heterogeneity and off-target effects. This work offers insights into precision therapies that aim to manipulate cell death for better cancer treatment by clarifying the interplay between oncogenic signaling and cell death susceptibility.

Keywords: Apoptosis, Autophagy, Cell death pathways, Cancer therapy, Necroptosis.

التلاعب بموت الخلايا في السرطان

الخلاصة

غالباً ما تتجنب الخلايا السرطانية الموت المنظم للحفاظ على التكاثر غير المنتظم وعلى مقاومة العلاج. وقد برز استهداف مسارات موت الخلايا كطريقة واعدة لتحسين نتائج علاج السرطان والتغلب على مقاومة هذا العلاج. بالإضافة إلى تسليط الضوء على التطورات الحديثة في التداخلات العلاجية، تبحث هذه المراجعة في الآليات الجزيئية الكامنة وراء الأشكال المختلفة لموت الخلايا المنظم في السرطان. نناقش في هذه الدراسة مثبطات الجزيئات الصغيرة والنهج المناعية التي تستفيد من مسارات موت الخلايا. بالإضافة إلى ذلك، نتناول صعوبات الترجمة السريرية، مثل عدم تجانس الورم والآثار غير المستهدفة. يقدم هذا العمل رؤى ثاقبة حول العلاجات الدقيقة التي تهدف إلى التلاعب بموت الخلايا لتحسين علاج السرطان من خلال توضيح التفاعل بين الاشارات المسرطنة وقابلية موت الخلايا.

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INTRODUCTION

The death of cells in an organism is a crucial pathway for maintaining cellular balance and response to stress [1,2]. In an average human, around 10^{11} cells die each day, amounting to the total weight of the individual over a year [3]. For an organism, sending cells down this avenue represents a key physiological mechanism that limits the expansion of the cell population. Evading this homeostatic route is considered an important hallmark of cancer [4]. A low rate of cell death contributes to conditions of excess proliferation, such as cancer, and a high rate of cell death correlates with degenerative disorders as manifested in neurodegenerative diseases [5]. There are two major modes of cell death: 1) accidental cell death (ACD), which is biologically uncontrolled and happens as a result of accidental injury stimuli such as physical, chemical, or mechanical insults, and 2) regulated cell death (RCD), which relies on dedicated gene-controlled signaling that can be modulated through pharmacologic and genetic interventions [6-8]. This narrative review will be mainly concerned with regulated cell death (RCD), which was previously referred to as programmed cell death. Regulated cell death (RCD) is initiated to eliminate unnecessary, irreversibly damaged, or potentially harmful cells [3,9,10]. However, cancer cells can acquire mutations that subvert the RCD pathways, allowing evasion of death and the acquisition of resistance to anticancer therapies [8,11]. The RCD pathways are driven and maintained by several molecular signals that show a considerable degree of interconnection and operate as a natural barrier against cancer. This is particularly important, as the disruption of elements of RCD not only initiates and maintains the tumor but also influences treatment outcomes and resistance to therapies [8]. Most current treatment strategies for cancer aim to selectively induce death in cancerous cells without harming the healthy ones. In this narrative review, we will examine the essential pathways of RCD, outline their mechanisms, and point to their possible implications for cancer therapy.

Types of Regulated Cell Death

A survey of the literature about regulated cell death reveals the existence of around sixteen distinct mechanisms through which cells can be eliminated (Figure 1 for the different types of RCDs).

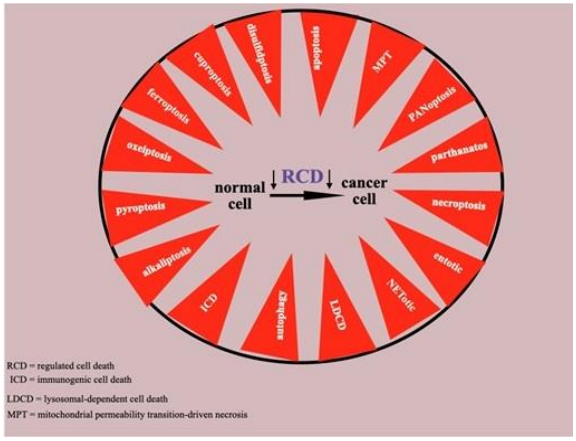

Figure 1: The different types of regulated cell death discovered so far. Suppressing these pathways plays an important role in the conversion of normal cells to cancer cells. Down-arrows represent suppression of regulated cell death.

These routes include 1) apoptosis (intrinsic and extrinsic), 2) mitochondrial permeability transition (MPT)-driven necrosis, 3) necroptosis, 4) autophagy, 5) ferroptosis, 6) pyroptosis, 7) parthanatos, 8) entotic cell death, 9) NETotic cell death, 10) lysosomal-dependent cell death, 11) immunogenic cell death, 12) PANoptosis, 13) alkaliptosis, 14) oxeiptosis, 15) cuproptosis, and 16) disulfidptosis. In this overview, we will be focusing on the main pathways of apoptosis, autophagy, necroptosis, ferroptosis, pyroptosis, immunogenic cell death, and parthanatos.

Apoptosis

Apoptosis was the first of the regulated cell deaths to be documented and deeply studied. It represents a tightly controlled program that is essential for maintaining cellular homeostasis and organismal development. Apoptosis is also believed to function as a natural barrier against malignancies [12,13]. This form of cell death is characterized by cell shrinkage, chromatin condensation, membrane blebbing, and the formation of apoptotic bodies, where the cell fragments into small vesicles containing cytoplasm and nuclear materials. Apoptosis occurs through two main routes, intrinsic and extrinsic, together with a third pathway that appears to be operative when dealing with cytotoxic lymphocytes (Figure 2 depicting the major mechanisms of apoptosis). Most of these pathways eventually converge on the activation of one or more members of a family of enzymes called caspases (cysteinyl aspartate-specific proteinases). Intrinsic apoptosis (mitochondrial apoptosis) is triggered by internal signals, including irreparable DNA damage, oxidative stress, growth factor withdrawal, microtubular alterations, mitotic defects, and oncogene activation [14-16]. The critical step for intrinsic apoptosis is the irreversible and widespread phenomenon of mitochondrial outer membrane permeabilization (MOMP) that leads to the release of mitochondrial proteins such as cytochrome c and the subsequent activation of the initiator caspase 9, casp9 [1,17,18]. The permeabilization of the mitochondria is controlled by pro- and anti-apoptotic members of the Bcl-2 family of proteins [19].

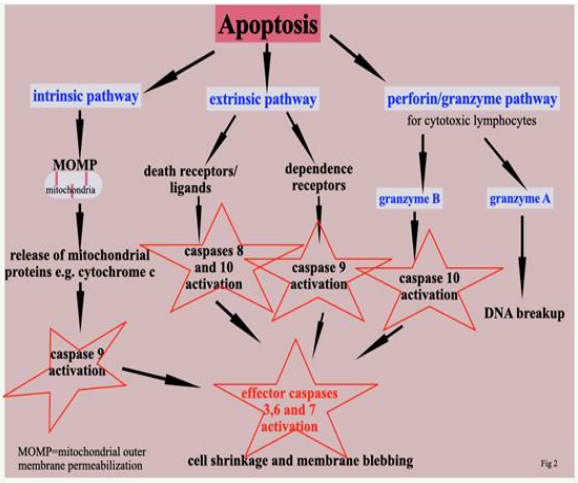

Figure 2: The three major mechanisms of apoptosis include the intrinsic pathway, the extrinsic pathway and the perforin/granzyme pathway. Apart from the perforin/granzyme A pathway, all other routes involve the contribution of caspase family proteins.

Cancer cells frequently overexpress the Bcl-2 proteins to enable them to continue proliferating after they sustain DNA damage. The anti-apoptotic members of the Bcl-2 family, such as Bcl-2, Bcl-XL, and Bcl-W, are antagonized in normal cells by the pro-apoptotic effector members, such as Bax and Bak proteins. However, when this delicate balance is shifted in favor of the effector proteins, pores are formed across the mitochondrial membrane, leading to the release of mitochondrial proteins. Eventually, effector caspases such as casp3, casp6, and casp7 are activated to execute cell death. There is a specific variant of intrinsic apoptosis that is initiated by the loss of integrin-dependent attachment to the extracellular matrix. This form of cell death is commonly known as anoikis and is generally considered a cancer-suppressive process, and accordingly, cancer cells need to acquire resistance to anoikis to initiate and progress through metastasis [20,21]. Extrinsic apoptosis is initiated through the engagement of two types of plasma membrane receptors: 1) death receptors and 2) dependence receptors [6]. The activation of the death receptors is dependent on their binding to cognate ligands. The death receptors include FAS, TNFR1, and DR4/5; their corresponding cognate ligands are FASL, TNF-α, and TRAIL, respectively. Following the recognition and binding of the death receptors to their ligands, caspases 8 and 10 are activated to induce the activation of the effector caspases. On the other hand, the activation of the independence receptors, e.g., UNC-5 netrin receptor B (UNC5B), occurs when the levels of their specific ligands drop below a certain threshold [22,23]. The dependence receptors may initiate extrinsic apoptosis through the activation of caspase 9 following the withdrawal of their cognate ligands, which in turn initiate the execution of the cell through the effector caspases. In the perforin/granzyme cell death pathway, cytotoxic lymphocytes are the main controller of this event once they acquire irreparable genomic irregularities. Functionally, this pathway is the main one used by cytotoxic lymphocytes to eliminate virus-induced or transformed cells [24]. The perforin, which

is the pore-forming protein, acts with either granzyme A or granzyme B to achieve apoptosis. Granzyme A activates apoptosis in a manner independent of caspases and characterized by single-stranded DNA damage, mitochondrial dysfunction, and loss of cell membrane integrity. Whereas granzyme B activates apoptosis through key caspase pathway substrates. Although apoptotic cells generally retain the integrity of the plasma membrane to allow for the rapid clearance by phagocytes, e.g., macrophages, apoptosis is not always immunologically silent, as cell envelopes sometimes break down, leading to the acquisition of a necrotic morphotype [25,26].

Autophagy-dependent cell death

Autophagy-dependent cell death (Figure 3) is a tightly regulated process that plays a dual role in cellular physiology, acting as a survival mechanism under certain conditions while contributing to cell death under others.

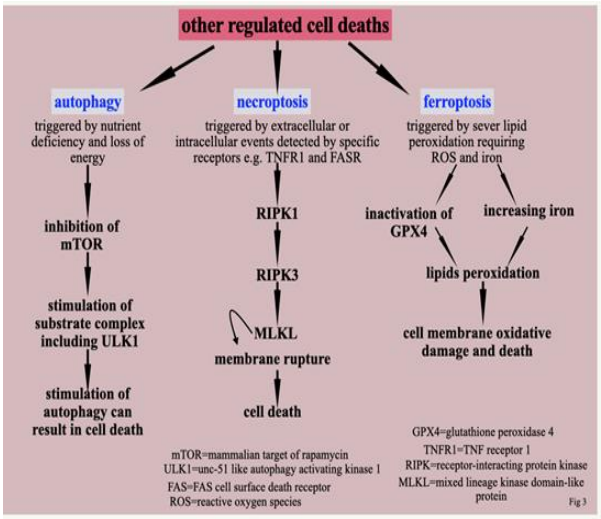

Figure 3: Regulated cell death mechanisms of autophagy, necroptosis and ferroptosis.

The definition of "autophagy-dependent cell death" does not refer to settings in which the autophagic machinery is activated alongside other RCD processes but rather when it is the driving force of cell death [27]. Autophagy involves the degradation and recycling of intracellular components through lysosomal activity. Deactivating autophagy through pharmacologic or genetic manipulations generally accelerates the death of cells responding to stress and has been associated with embryonic lethality and multiple disorders, including cardiovascular disease, neurodegeneration, and cancer [28,29]. Over 40 autophagy-related genes contribute to the execution of this process, with ULK1 (Unc-51-like autophagy activating kinase 1) acting to promote the initiation of the mechanism [30]. The ULK1 protein becomes activated when the mTOR, mammalian target of rapamycin (a master regulator of cellular homeostasis controlling metabolism, immune responses, autophagy, proliferation, and migration), is inhibited or when AMPK, 5`-adenosine monophosphate-activated protein kinase, is activated by stress signals. Previous studies have demonstrated a switch from autophagy initiation to senescence or apoptosis. In breast cancer models, autophagy leads to senescence [31], while in glioblastoma cells, a reduction in CDK4 protein, an important regulator of lysosomal function, induced an impaired autophagy leading to apoptosis [32].

Necroptosis

Necroptosis is a regulated caspase-independent form of cell death that combines features of the signaling pathways of apoptosis and the morphological outcomes of necrosis [33]. The process is driven by the activation of receptor-interacting protein kinases (RIPKs) and mixed lineage kinase domain-like (MLKL) proteins (Figure 3). Necroptosis is initiated by the activation of cell surface death receptors, like those that stimulate apoptosis, such as FASR, TNFR1, interferon receptors (INFRs), and toll-like receptors (TLRs), and by cytosolic nucleic acid sensing molecules [34,35]. For example, ligation of TNFR1 to its cognate molecule TNF-α can activate RIPK1 to bind to RIPK3, resulting in an activated complex in which RIPK3 can phosphorylate its target molecules. Moreover, the engagement of TLR3 and TLR4 to recruit adapter proteins and the sensing of cytosolic nucleic acids are both capable of activating RIPK3 without the requirement to involve RIPK1 [36,37]. The activated RIPK3 can then phosphorylate MLKL, which oligomerizes, mostly to trimers or tetramers, to form an activated necrosome complex. This necrosome is then translocated to the plasma membrane, leading to cell death characterized by permeabilization of the plasma membrane, cell swelling, and the loss of cellular integrity [38-41]. The breakup of the cell membrane results in the release of its contents, leading to inflammation and immune responses [42]. Inhibition of caspase 8, due to mutations or pharmacologic intervention, can divert the cell death pathway from apoptosis to necroptosis. Thus, in circumstances where the activity of caspases is blocked and apoptosis is inhibited, the process of necroptosis can serve as a backup pathway [7]. Necroptosis has the beneficial effect of defense against viral infections. However, excessive or dysregulated necroptosis can contribute to inflammatory diseases, neurodegenerative diseases, and cancer. In the latter, necroptosis can act to suppress tumor growth and promote metastasis depending on the context. The function of necroptosis is absent in normal development and homeostasis despite its implication in chemotherapy responses and tissue injury [43]. Necroptosis has been pharmacologically suppressed using compounds including necrostatin-1 [44]. Furthermore, knocking out the function of necroptosis proteins such as RIPK1, RIPK3, and MLKL can significantly inhibit the proliferation of cancer cells *in vitro* and their viability to form tumors *in vivo* [45]. Cancer cells downregulate RIPK3 to evade necroptosis, and that low expression of this protein is linked to reduced overall survival from cancer [46].

Ferroptosis

Ferroptosis is a distinct and regulated process of cell death characterized by iron-dependent lipid peroxidation that is under the constitutive control of GPX4, an enzyme that reduces lipid peroxides (Figure 3) and is independent of caspases. The enzyme GPX4 has emerged as the main inhibitor of ferroptosis due to its ability to limit lipid peroxidation. This form of RCD is implicated in various physiological and pathological contexts, including cancer, neurodegeneration, ischemic injury, and immune responses. One of its main hallmarks is the accumulation of lipid peroxides, particularly phospholipids, leading to cell membrane damage. The lipid peroxide formation is driven largely by reactive oxygen species, where iron plays a crucial catalytic role [47-49]. The canonical pathway of activating ferroptosis is by the inactivation of the major protective protein against peroxidation damage, and that is GPX4. This could happen directly using inactivating agents such as the FDA-approved anticancer agent altretamine [1,50,51]. Alternatively, the inactivation of GPX4 could be achieved indirectly through the deprivation of glutathione, a compound made by the liver from the amino acids glycine, cysteine, and glutamic acid to help tissue build up and repair. The noncanonical way of achieving ferroptosis is through increasing the labile iron pool using compounds like iron chloride, hemoglobin, or ferrous ammonium sulfate. The occurrence of ferroptosis is determined by the balance between iron-induced ROS and its counterbalance of antioxidant systems that avoid lipid peroxidation. An important antioxidant system located in cell membranes is the Xc^- system, which regulates the exchange of cysteine and glutamate [52]. Cystine is reduced in the cells to cysteine, and the latter compound is involved in the synthesis of glutathione (GSH). Glutathione reduces ROS and reactive nitrogen when GPX4 is present, leading to ferroptosis [53]. Polyunsaturated fatty acids (PUFAs) are the prime targets of lipid peroxidation of the cell membranes, particularly PUFAs containing phosphatidylethanolamine, such as arachidonic acid [54]. The deleterious effects of lipid peroxidation can be overcome using chemicals possessing lipophilic radicals such as vitamin E, ferrostatin-1, and liproxstatin-1 [1]. Membrane thinning may drive an increased access to ROS and ultimately lead to pores and micelle formation and the loss of membrane integrity [55]. Additionally, lipid hydroperoxides degrade to aldehydes that can inactivate proteins and cause further cell damage. The eventual cellular damage resulting from ferroptosis is characterized by dysmorphic small mitochondria as well as ruptured cell membranes with necrotic morphotypes [56,57]. An antioxidant pathway independent of GPX4 has been identified that relies on the presence of coenzyme Q (CoQ) [58]. Overactive ferroptosis can occur in certain conditions, such as neurodegenerative diseases and iron overload disorders, necessitating its suppression [59]. Protecting the cells against ferroptosis can be achieved by sequestering free iron, scavenging ROS, and limiting PUFA oxidation [7]. In contrast, the stimulation of ferroptosis can constitute a potential strategy in cancer therapy [59]. Ferroptosis represents a convergence of metabolic and oxidative pathways, and its regulation by iron, lipid peroxidation, and antioxidant systems can be targeted for therapeutic intervention for a wide array of diseases, including cancer. Cancer cells exhibit higher sensitivity to ferroptosis, and various primary cancers that are therapy-resistant can become dependent on it [60]. Several chemotherapy drugs can induce ferroptosis, and the dysregulation of this process often leads to chemotherapy resistance [61]. Ferroptosis is characterized by small mitochondria with broken outer membranes and the near absence of mitochondrial crests [59].

Pyroptosis

Pyroptosis is another regulated cell death that is characterized by its inflammatory nature (Figure 4).

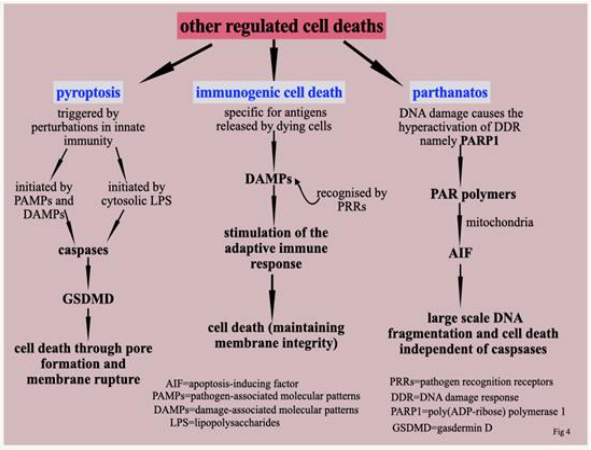

Figure 4: Regulated cell death mechanisms of pyroptosis, immunogenic cell death and parthanatos.

It plays a crucial role in the immune system's response to infections and pathological conditions as it leads to the release of pro-inflammatory cell contents. This process contributes to the resolution of infection and the exacerbation of inflammation-related diseases. Pyroptosis depends on caspases, particularly casp1, casp4, and casp5, and the gasdermin group of proteins, which form pores in the plasma membrane [62,63]. Pyroptosis is typically triggered by the recognition of pathogen-associated molecular patterns (PAMPs) and DAMPs (damage-associated molecular patterns) by cell receptors called pattern recognition receptors (PRRs) [64]. Following such encounters, the PRRs then oligomerize to form inflammasomes that recruit and activate caspases, particularly casp1 and casp3 [65]. Caspases cleave gasdermin D (GSDMD), a key regulator of pyroptosis, releasing its N-terminal domain to form pores in the cell membrane, leading to cell swelling and eventual rupture [1]. In some instances, the caspases can directly be activated by intracellular lipopolysaccharides (LPS—one of the many DAMPs) from Gram-negative bacteria, bypassing the need for traditional inflammasome formation [66]. Pyroptosis is a mechanism to eliminate infected cells and restrict pathogen

replication and is often associated with the secretion of IL-1B and IL-18, which possess pro-inflammatory effects [67]. It also alerts neighboring cells and recruits immune cells through the release of cytokines. Excessive dysregulated pyroptosis contributes to chronic inflammatory diseases such as sepsis and atherosclerosis, autoimmune diseases, and the progression of cancer under certain contexts. Pyroptosis is characterized by chromatin condensation, cellular swelling, and plasma membrane permeabilization [64]. The process is involved in pathological conditions such as lethal septic shock [68]. An association is emerging between pyroptosis and the development and progression of metastasis of various cancers [69]. A new pathway of pyroptosis was found that activates caspase-3 and induces the cleavage of gasdermin E under certain extracellular triggers [70,71]. It was also discovered that natural killer cells and cytotoxic T-lymphocytes can kill cells expressing gasdermin B (GSDMB) via cleavage of this latter protein with granzyme A [72].

Immunogenic cell death

Immunogenic cell death activates the immune system by training it to identify malignant cells and promoting their clearance in such a way as to recognize invading pathogens [8]. Unlike other RCDs, which might be immunologically silent, ICD actively alerts and recruits immune cells, leading to a robust antitumor or antiviral immune response. Under specific circumstances, such as in cancer, dying cells release their contents, including DAMPs, which act to stimulate the immune system, leading to an inflammatory response (see Figure 4 for an outline of the mechanism of ICD). These DAMPs attract a variety of innate immune cells, such as neutrophils, macrophages, dendritic cells, and natural killer cells, through specific recognition receptors, thus providing the foundation for triggering the adaptive immunity and eventually ICD [73-75]. The induction of ICD, through heightened innate and adaptive immunity, can counteract the immunosuppressive microenvironment in the tumor caused by the presence of malignant cells and ultimately contribute to the long-term control of cancer [52]. Several different DAMPs have been linked to ICD, including calreticulin, ATP, high-mobility group box 1 (HMGB1), annexin A1, IFN type I (interferon), and nucleic acids from cancer cells [6]. These DAMPs activate different pattern recognition receptors (PRRs), such as the toll-like receptors (TLRs). Many cytotoxic chemotherapeutic agents stimulate the immune system by stressing and killing the cancer cells in a way that results in the exposure of DAMPs and the consequent immune response [76]. In addition to cancer, ICD is also implicated in infectious diseases [73].

Parthanatos

The name of this distinct regulated cell death is derived from “par," referring to the involvement of poly(ADP-ribose) polymer and its polymerization by the enzyme poly(ADP-ribose) polymerase (PARP), particularly PARP1, and "thanatos,” from the ancient Greek mythology meaning “death." This form of RCD is driven by the hyperactivation of a specific component of the DNA-damage response (DDR) machinery, PARP1 (Figure 4) [6]. PARP1 is usually activated to repair the DNA damage, but its over-activation inadvertently triggers the parthanatos pathway to polymerize poly(ADP-ribose) (PAR) molecules. The PAR polymers then cause mitochondrial outer membrane permeabilization, leading to the release of apoptosis-inducing factor (AIF) into the cytoplasm [77,78]. The AIF protein is transferred to the nucleus, where it condenses and produces many DNA fragments ranging in size from 15 Kb to 50 Kb [78]. The initial DNA damage that causes the hyperactivation of PARP1 is usually induced by UV light, ROS, or alkylating agents. Parthanatos is involved in several pathological conditions, such as ischemia-reperfusion injury after cerebral ischemia or myocardial infarction [79]. This RCD is also involved in neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease [80]. Moreover, the pathway of parthanatos comprises some key molecules of significance in carcinogenesis, which could be of potential importance in developing cancer treatments [81]. Although caspases are possibly only activated at later stages of parthanatos, inhibitors of these enzymes cannot extinguish the regulatory necrosis, but PARP1 inhibitors or gene knockout can prevent its outcome [82]. Parthanatos cell death is associated with large DNA fragments and without the formation of apoptosis bodies [83]. It is also characterized by the absence of cell swelling accompanied by plasma membrane rupture [84].

Targeting Cell Death in Cancer Treatment

The development of therapies to treat cancer through the induction of various cell death mechanisms is an important goal from the clinical perspective. Complex, and often little-understood, connections between the different forms of cell death exist, and similar molecular players might be participating in more than one pathway. Signals from regulator cell death participants are also closely related to the induction of senescence and its phenotypes, and factors released by senescent cells are often the cause and consequence of cell death [85]. With that in mind, this section of the review will consider the targeting of individual, selected, and important components of RCDs as a means of disabling that pathway and arresting cancer growth. Developing resistance when targeting a particular regulated cell death protein is one of the major drawbacks in cancer therapy, as malignant cells often opt for an alternative RCD or upregulate other proteins with similar functions in the same pathway [86]. To overcome resistance problems, combination therapy is often employed whereby a drug targeting RCD protein is used together with other antitumor treatments such as chemotherapy or targeted therapy. Table 1 shows selected targets that can suppress regulated cell death in cancer.

Table 1: Selected targets to disable regulated cell death in the treatment of cancer

Drug/intervention	Action mechanism/target	Cancer type	Main RCD/comments	Reference or clinical trial identifier
Venetoclax (ABT-199)	Selective inhibition of Bcl-2	AML, CLL	Apoptosis, US FDA-licensed	117
Navitoclax (ABT-263)	Inhibition of Bcl-2 and Bcl-XL	Solid tumours and haematological cancers	Apoptosis, under phase I/II trials	118
Obtatoclax (GX15-070)	Inhibitor of multi members of Bcl-2 family proteins	Solid tumours and haematological cancers	Apoptosis, under phase II trials	91
Mapatumumab	Antibody acting as DR4 agonist	Solid tumours	Apoptosis, under phase II trials	119
Conatumumab	Antibody acting as DR5 agonist	Solid tumours	Apoptosis, under phase II trials	120
Drozitumab	Antibody acting as DR5 agonist	Solid tumours	Apoptosis, under phase I/II trials	121
CQ and its derivative HCQ	Inhibition of lysosomal acidification	Solid tumours	Autophagy, approved for malaria but under trials for cancer	99,122
Necrostatin-1	Inhibition of RIPK1	CRC	Necroptosis, under preclinical investigation	102
NSA	Inhibition of MLKL	Solid tumours	Necroptosis, under preclinical investigation	101,103
DHA	Inhibition of GPX4	PDA	Ferroptosis, under preclinical investigation	123
Sorafenib	Inhibition of system Xc-	HCC and RCC	Ferroptosis, already US FDA-approved for HCC and RCC but investigational for this RCD	124
Iron chelators e.g. deferoxamine	Reduction of intracellular free iron	Various cancers	Ferroptosis	125
Altretamine	Inhibition of GPX4 leading to lipid oxidation	Head and neck cancers and ovarian cancers	Ferroptosis, US FDA-approved	126,127
Erastin	Inhibition of system Xc-	Various cancers	Ferroptosis, under preclinical investigation	113
Metformin	GSDMD-mediated pyroptosis	Various cancers	Pyroptosis, approved for T2D but investigational for RCD	114
Chemotherapy e.g. paclitaxel and doxorubicin	Cancer cell death	Various cancers	ICD can be a pathway for cell death.	128
Radiotherapy	Cancer cell death	Various cancers	ICD can be a pathway for cell death.	129
Targeted anticancer therapy e.g. cetuximab	EGFR-specific antibody	Various cancers	ICD can be a pathway for cell death.	130
PDT e.g. hypericin-based	Cancer cell death	Skin cancers	ICD can be a pathway for cell death.	131
Oncolytic peptides and viruses e.g. LTX-315 and T-vec	Cancer cell death	Solid tumours	ICD can be a pathway for cell death.	132,133
Olaparib	Inhibition of PARP and DNA damage	Various cancers	Parthanatos, US FDA-approved	134
Niraparib	Inhibition of PARP and DNA damage	Ovarian cancer	Parthanatos, US FDA-approved	135
Rucaparib	Inhibition of PARP and DNA damage	Prostate cancer and BRCA-mutated BC	Parthanatos, US FDA-approved	136

AML: acute myeloid leukaemia, CLL: chronic lymphocytic l, CQ: chloroquine, HCQ: hydroxychloroquine, CRC: colorectal cancer, NSA: necrosulfonamide, DHA: dihydroartemisinin, PDA: pancreatic ductal adenocarcinoma, HCC: hepatocellular carcinoma, RCC: renal cell carcinoma, RCD: regulated cell death, T2D: type2 diabetes, ICD: immunogenic cell death, PDT: photodynamic therapy and BC: breast cancer.

Bcl-2 inhibitors

The interaction between members of the Bcl-2 proteins determines whether a cell will undergo apoptosis or survive. Under normal circumstances, the pro-survival anti-apoptotic Bcl-2 proteins restrain the effectors of apoptosis, BAX and BAK, to safeguard their survival. Venetoclax is a potent selective inhibitor of the Bcl-2 protein family that takes part in the intrinsic apoptosis pathway. The drug is licensed in the USA by the FDA for chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) in patients with genetic profiles showing Bcl-2 dependence [87,88]. Navitoclax is another Bcl-2/Bcl-XL (anti-apoptotic, pro-survival proteins) inhibitor developed for non-small cell lung cancer (NSCLC) [89]. It demonstrated good anticancer effects, particularly in combination with targeted therapies [90]. Navitoclax is a pan-Bcl2 inhibitor with activity against Bcl-XL and Bcl-W, acting by disrupting the interactions of the anti-apoptotic Bcl-2 proteins with the executioner members of the Bcl-2 protein family (pro-apoptotic, pro-death members), namely Bax and Bac, triggering cell death in the tumor. Obatoclax is another Bcl-2 inhibitor that demonstrates synergy with bortezomib in preclinical models of mantle cell

lymphoma (MCL), but that synergy was not confirmed in subsequent phase I/II clinical trials [91].

Mapatumumab, conatumumab, and drozitumab

These are monoclonal antibodies (mAbs) against DR4 (in the case of mapatumumab) or DR5 (in the case of conatumumab and drozitumab). DR4 and DR5 are death receptors for the TNF-related TRAIL ligands that, once activated, can trigger the extrinsic apoptosis pathway. Mapatumumab is a completely human DR4 agonistic antibody with selective and strong binding to DR4 that was tested against a variety of cancers, but none of the tests met their initial objectives [92]. The DR5 agonist antibodies, unlike those targeting DR4, have been developed and tested under clinical settings [93,94]. These compounds exhibited limited anticancer activity, possibly due to their short half-life in the blood of up to one hour. To address this issue, TLY012 was developed by attaching a polyethylene glycol molecule to its N-terminus end, increasing its size and, therefore, reducing its renal clearance. This resulted in the prolongation of its half-life to up to 18 hours and consequently a greater anticancer activity in colorectal cancer models [95]. One of the drawbacks of the first and second generations of TRAIL receptor mAbs and derivatives is the limited ability to promote efficient ligand-receptor complex clustering. To overcome this problem, a compound called eftozanermin alfa was developed and tested in patients with advanced solid tumors and hematological malignancies [96,97]. Furthermore, a third-generation tetravalent agonistic antibody targeting DR5 was developed called INBRX-109, which showed good results in phase I trials, which prompted the instigation of a phase II trial for the treatment of chondrosarcoma [98].

Chloroquine and hydroxychloroquine

These two drugs have been used for the treatment of malaria and autoimmune diseases for the better part of three-quarters of a century. They were also found to suppress autophagy by blocking lysosomal acidification and autophagosome degradation [99]. A meta-analysis showed that both chemotherapy and radiotherapy result in a better response to cancer when autophagy is inhibited using chloroquine or hydroxychloroquine [100].

Necrostatin-1

Necrostatin-1 was one of the first RIPK1 inhibitors targeting the necroptosis pathway. This compound was found to be effective in reducing colitis-associated tumorigenesis in mice [101]. Necrostatin-1 also inhibits apoptosis through targeting RIPK1 [102].

Necrosulfonamide

Necrosulfonamide provided good evidence of the role of necroptosis in tumor development through the targeting of MLKL protein [45,103]. Zhou *et al*. provided evidence that necrosulfonamide protects against focal ischemia/reperfusion injury through the inhibition of necroptosis via its effects on MLKL and RIPK3 proteins [104].

Dihydroartemisinin

Chen *et al*. have found that the malarial drug artemisinin and its derivative, dihydroartemisinin, can sensitize cancer cells to ferroptosis [105]. Artemisinin can induce ferritin degradation by lysosomes in an autophagy-dependent way, elevating the free iron levels in the cells and making them more prone to ferroptosis. This illustrates the crosstalk between autophagy and ferroptosis in working together to achieve cell death. The autophagy-dependent degradation of ferritin, ferritinophagy, is facilitated by the significant rise in ROS levels caused by artemisinin triggering ferroptosis in cancer cells [106].

Sorafenib

System Xc^- is an antiporter system that imports cystine, the oxidized form of cysteine, and exports glutamate from cells, influencing the survival of cancer cells, thus becoming a target for cancer treatment [107]. Inhibiting this system reduces glutathione (GSH) levels and induces ferroptosis. Sorafenib is a US FDA-approved drug that was shown to inhibit multiple surface kinases, leading to enhanced apoptosis and autophagy [108]. More recent studies suggest that the anticancer activity of sorafenib relies on the induction of ferroptosis by inhibiting system Xc^- and the production of GSH [109,110].

Iron chelators

Epidemiological evidence suggests that the risks of several cancer types, such as hepatocellular and breast cancers, can be increased through high dietary intake of iron [111]. Thus, activation of ferroptosis results in the non-apoptotic destruction of certain cancer cells [56]. Iron-chelating agents such as deferoxamine or compounds that increase iron-mediated toxicity, e.g., sulfasalazine and statins, could be a useful therapeutic strategy to reduce resistance to several cancer therapies [60,112].

Erastin

Erastin is well known for its activity in directly inhibiting system Xc^-, reducing GSH levels, and inducing ferroptosis [107]. Erastin, like glutamate, inhibits cystine uptake by the cystine/glutamate antiporter (system Xc^-), reducing the antioxidant defenses of the cell and ultimately leading to iron-dependent death. Our understanding of the involvement of erastin in the molecular mechanism behind ferroptosis in prostate cancer cells has recently been extended [113].

Metformin

Metformin inhibits cancer cell proliferation by inducing mitochondrial dysfunction and causing pyroptotic cell death [114]. It is a widely used anti-diabetes drug that can activate the GSDMD-mediated pyroptosis of esophageal squamous cell carcinoma by

targeting the miR-497/proline-, glutamic acid-, and leucine-rich protein-1 (PELP1) pathway [115].

Immunity modifiers

Under this general heading are the interventions that lead to immunogenic cell death, which include chemotherapy, radiotherapy, targeted anti-cancer therapies, and oncolytic and photodynamic therapy. The immunity modulators can either target cancer as standalone interventions or as a means of converting “cold tumors" (i.e., those that are insensitive to immunotherapies) into “hot tumors" (i.e., those that are immunologically sensitive). Their use to promote the death of cancer cells is the subject of separate topics and is only mentioned here for completeness.

Olaparib, niraparib, and rucaparib

This is a group of targeted drugs, called poly(ADP-ribose) polymerase (PARP) inhibitors, approved for the treatment of various malignancies [116]. The enzyme PARP helps DNA-damaged cancer cells to repair themselves, and the inhibition of its function allows them to undergo parthanatos and die.

Conclusions

Exploiting cell death pathways for cancer treatment is a potent and developing strategy. Researchers have created novel approaches to eradicate cancerous cells and overcome treatment resistance by investigating the details of regulated cell death mechanisms. Despite some promising developments in this field, there are still challenges, such as tumor heterogeneity, adaptive resistance, and the requirement for appropriate biomarkers to forecast therapy response. Combining cell death modulation with immunotherapies offers great promise for next-generation cancer therapeutics. Focusing on cell death pathways will probably become increasingly important in the battle against cancer as the science of targeted therapies continues to develop.

Conflict of interests

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