Caspase-Linked Programmed Cell Death in Prostate Cancer

Subjects: Biodiversity Conservation

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Prostate cancer (PCa) is a complex disease and the cause of one of the highest cancer-related mortalities in men worldwide. Annually, more than 1.2 million new cases are diagnosed globally, accounting for 7% of newly diagnosed cancers in men. Programmed cell death (PCD) plays an essential role in removing infected, functionally dispensable, or potentially neoplastic cells. Apoptosis is the canonical form of PCD with no inflammatory responses elicited, and the close relationship between apoptosis and PCa has been well studied. Necroptosis and pyroptosis are two lytic forms of PCD that result in the release of intracellular contents, which induce inflammatory responses.

Keywords: prostate cancer ; apoptosis ; necroptosis ; pyroptosis

1. Introduction

Prostate cancer (PCa) is the most common type of nonskin malignancy and one of the leading causes of cancer-related death in men [1][2]. Owing to PCa heterogeneity, patients in different clinical states benefit from different treatments [3][4]. Surgery and radiation therapy are common forms of treatment for localized PCa [5]. Considering that 25~35% of PCa patients will relapse and develop advanced PCa, androgen deprivation therapy (ADT) is recognized as the cornerstone therapy for recurrent PCa. However, almost all patients will develop resistance to androgen deprivation therapy and inevitably relapse into the hormone-independent stage, that is, castration-resistant prostate cancer (CRPC), within a few years [2][6][7]. In this case, a considerable number of studies have focused on the mechanism and therapeutic potential of inhibiting the androgen receptor (AR) pathway. Nevertheless, therapies targeting the AR pathway have gradually been shown to be resistant [8]. PCD has been a hot spot in the spotlight in recent years. Mechanisms underlying apoptosis, necroptosis, pyroptosis, and PANoptosis in PCa are perfect subjects with which to study the role of PCD in PCa.

Cell death is as important as cell proliferation in the development and homeostasis of multicellular organisms [9][10]. As a crucial member of cell death, PCD plays an indispensable role in maintaining biological balance in cells and tissues and responding to infection, tumors, and some other pathologies [11][12]. Apoptosis, pyroptosis, and necroptosis are three extensively studied and understood forms of PCD. As the earliest form of PCD to be discovered, apoptosis is a nonlytic PCD with an integral cellular membrane and is considered immunologically silent [9]. Necrosis is a lytic and inflammatory form of unregulated and accidental cell death. However, studies have revealed that some subtypes of necrosis are driven by specific molecules, and these molecules determine the cell death modality named programmed necrosis or necroptosis [13]. Necroptotic cells undergo swelling and membrane rupture, which causes the release of intracellular damage-associated molecular patterns (DAMPs) into the extracellular microenvironment [14][15]. Pyroptosis is characterized by a series of events initiated by rapid caspase-dependent plasma membrane rupture and the release of inflammation-inducing intracellular contents [16][17][18]. Apoptosis, necroptosis, and pyroptosis are mediated by specific pathways and molecules that eliminate damage factors.

2. The Mechanisms of Apoptosis, Necroptosis, and Pyroptosis and Their Connection

2.1. Mechanisms of Apoptosis

First proposed by Kerr et al. [19] in 1972, apoptosis is characterized by the shrinkage and condensation of cells, the crumbling of the nuclear envelope, the condensation of chromatin with fragmentation of DNA, and the formation of small apoptotic vesicles known as ApoBDs [20]. Apoptotic cells do not release cellular contents into their surroundings and activate an inflammatory response, which makes apoptosis a mild type of PCD [21].

Two major pathways contribute to cell apoptosis: the intrinsic pathway involving B-cell lymphoma-2 (BCL-2) family proteins and the extrinsic pathway mediated by death receptor (DR) ligands [22]. The extrinsic pathway is initiated by the activation of apoptotic death receptors, including tumor necrosis factor (TNF) receptor 1 (TNFR1), Fas, and TNF-related apoptosis-inducing ligand (TRAIL) receptors (DR4 and DR5) when bound to their ligands (TNFα, FasL, and TRAIL) [23][24][25]. Then, adaptor proteins are recruited, namely TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein (FADD), which activate the downstream interactor procaspase-8/10 and form the death-inducing signaling complex (DISC) [26]. Activated caspase-8 initiates the execution phase of apoptosis by cleaving the downstream effector caspase-3 or caspase-7 [27]. Inhibitors of apoptosis (IAP) proteins such as XIAP and IAP1/2 can bind to and inhibit the activation of caspase-3/9 [28]. In the intrinsic pathway, stimuli such as toxicity-inducing substances or DNA damage dysregulate intracellular homeostasis and cause mitochondrial outer membrane permeabilization (MOMP), which leads to the release of cytochrome c into the cytosol. Cytochrome-c, regulated by the Bcl-2 family, recruits procaspase-9 by binding to apoptotic protease-activating factor-1 (APAF-1), which triggers the formation of apoptosomes [29][30]. Through the apoptosome, procaspase-9 is cleaved to generate activated caspase-9, which then activates the effector caspase-3 [31]. The Bcl-2 family plays an indispensable role in regulating mitochondrion-related apoptosis and can be divided into proapoptotic proteins (such as Bax and Bak) and antiapoptotic proteins (such as Bcl-2 and Bcl-XL) [32]. Another important proapoptotic protein, namely BH3-only proteins, shares a homologous BH3 region, through which they bind and directly activate Bax and/or Bak-1 or inhibit antiapoptotic proteins to mediate apoptosis [33][34]. The transcription factor p53, encoded by the TP53 gene, can be detected in normal conditions but is silenced or mutated in cancer. DNA damage and oncogene activation can increase cellular p53 levels via phosphorylation and acetylation. p53 induces the extrinsic pathway and the mitochondrial pathway by regulating DRs and Bcl-2 proteins such as Bax and PUMA [35]. Cyclin-dependent kinases (CDKs) are regulators of cell-cycle progression and transcription. CDK transcriptionally enhances the activity of antiapoptotic BH3-only proteins such as myeloid cell leukemia (Mcl-1) while repressing sensitizers [36].

2.2. Mechanism of Necroptosis

As a counterpart of apoptosis, necrosis was long thought to be an unregulated form of cell death. However, in 2005, as suggested by Degterev et al. [37], necroptosis was reconsidered to be a necrotic form of PCD. The morphology of necroptotic cells is the same as that of necrotic cells, including a disrupted plasma membrane, and both types of cells passively release intracellular contents [38].

In necroptotic cells, death receptors (such as TNFR1 and Fas) and pattern recognition receptors (PRRs) such as Toll-like receptor 3 (TLR3) are activated by binding to their cognate ligands [15]. Then, these activated receptors recruit interacting kinase 1 (RIPK1) and a series of proteins to form an oligomeric complex, in which RIPK1 is polyubiquitinated and cleaved [39][40]. The NF-κB-dependent proinflammatory pathway and prosurvival pathway are involved in most of the abovementioned activities to promote cell survival [41]. An oligomeric complex, which consists of RIPK1, FADD, and CASP8, then exerts proapoptotic effects after dimerization by activating CASP8. However, in the absence of CASP8, active RIPK1 recruits and phosphorylates receptor-interacting kinase 3 (RIPK3) to form a RIPK1/RIPK3 complex, which then recruits and phosphorylates mixed lineage kinase domain-like (MLKL) to form the necrosome [39][42][43][44]. Phosphorylated MLKL can increase plasma membrane permeability by opening calcium or sodium ion channels or by directly forming pores in the plasma membrane, which leads to membrane rupture and the release of DAMPs. The released DAMPs inevitably cause inflammation and trigger immune responses [45][46].

2.3. Mechanism of Pyroptosis

Pyroptosis is an inflammatory form of PCD that was first observed in 1986 in primary mouse macrophages undergoing anthrax-induced lethality, which causes the rapid release of cell contents and cell death [47][48]. A series of caspase families are involved in pyroptosis in an inflammasome-dependent manner and are considered to play an indispensable role in the occurrence and development of cancer [48].

Pyroptosis is mediated through two main mechanisms: canonical and noncanonical pathways that trigger the gasdermin family [48][49]. In the canonical pathway, pathogen-associated molecular patterns (PAMPs) or DAMPs are detected by PRRs, such as TLRs and Nod-like receptors (NLRs), which activate inflammasome sensors, such as Nod-like receptor protein 3 (NLRP3), AIM2, and pyrin [48][50][51]. Activated inflammasome sensors recruit the adapter protein apoptosis-related speck-like protein (ASC) and pro-caspase-1 to form inflammasomes [52]. Procaspase-1 is then cleaved, which yields activated caspase-1, which can process procytokines such as interleukin (IL)-1β/18 to generate mature IL-1β/18. Activated IL-18/1β is secreted outside a cell through membrane pores and amplify the inflammatory response [53]. Activated caspase-1 can also process gasdermin D (GSDMD), thereby releasing the N-terminal fragment of GSDMD (GSDMD-N), which contributes to the nonselective formation of pores on the cell membrane and eventually results in cell

swelling and lysis [54][55]. In the noncanonical pathway, gram-negative bacterial lipopolysaccharide (LPS) triggers pyroptosis by activating caspase-4/5 in humans or caspase-11 in mice to cleave GSDMD [55]. GSDMD-N positively regulates pyroptosis by activating the NLRP3 or NLRC4 inflammasome [56]. In addition to the abovementioned pyroptosis pathways, the caspase-3-mediated GSDME pathway has also been shown to play an essential role in inducing pyroptosis, especially during chemotherapeutic treatment [57].

2.4. The Connection between Apoptosis, Necroptosis, and Pyroptosis

The apoptosis, necroptosis, and pyroptosis pathways have long been considered to function in parallel but have recently been shown to be tightly connected and to interact with each other. Acting as a bridge between apoptotic and necroptotic pathways, caspase-8 is a well-known PCD mediator. It can not only activate the downstream executioner caspase-3/7 in the apoptosis pathway but also cleave RIPK1 and RIPK3 in the ripoptosome in the necroptosis pathway, thereby preventing necroptosis and facilitating apoptosis [58][59][60]. In addition, FADD and caspase-8 mediate caspase-1 processing, NLRP3 inflammasome assembly, and GSDMD activation, indicative of crosstalk between apoptosis and pyroptosis pathways [61][62][63]. In a recent discovery, pannexin-1, a channel-forming glycoprotein in macrophages, promoted NLRP3 inflammasome activation in the extrinsic and intrinsic apoptosis pathways [64]. Necroptosis can also play an important role in initiating pyroptosis. For example, RNA viruses upregulate the expression of NLRP3 inflammasome components in a RIPK1/RIPK3-dependent and MLKL-independent manner [65]. Furthermore, the PANoptosome, the set of activated apoptosis, necroptosis, and pyroptosis components that converge within the same period, was recently proposed and has received significant attention [66][67]. In PANoptosis, the connection between apoptosis, necroptosis, and pyroptosis is particularly tight, and the specific mechanisms will become clearer as relevant literature is published in the future.

3. Role of Apoptosis, Necroptosis, and Pyroptosis in PCa

3.1. Role of Apoptosis in Prostate Cancer

Previous studies have shown that the normal growth and function of the prostate gland as well as the growth and progression of PCa largely depend on signaling by androgen-induced AR pathway activation [68]. After treatment with androgen deprivation therapy or castration, prostate glands undergo marked involution characterized by apoptotic cell death, which significantly inhibits the progression of PCa. Furthermore, intrinsic pathways induced by mitochondrial or extrinsic death pathway receptors are both involved in the apoptosis of prostate epithelial cells after androgen deprivation therapy or castration [69].

The activation of death receptors initiates the extrinsic death pathway. Among the death receptors, TRAIL-R2 (DR5) is a member of the TNFR family, and drugs targeting DR5 are the most advanced [70]. TRAIL-R2 was downregulated in PCa cell lines and was markedly reduced in high-grade tumors [71]. The agonistic monoclonal antibody lexatumumab targeting DR5 has been the subject of early-phase investigations for use against several solid malignancies, including PCa [34]. The extrinsic death pathway can also be activated in immune responses. A recent study cocultured human NK cells (KHYG-1) with human prostate cancer stem-like cells. They discovered that NK cells exerted a killing effect by initiating the TRAIL/DR5 cell death pathway [72]. In another study, a selenium-bearing ruthenium complex (RuSe) was designed. RuSe potentiated NK cell-mediated killing of PC3 cells by activating TRAIL-R and FasL [73].

Bcl-2 family proteins and their regulators are also key molecules in PCa progression and therapy resistance. Initially, researchers discovered that the expression of the antiapoptotic protein Bcl-2 was decreased in PCa epithelial cells but increased after castration [74][75]. Moreover, increased levels of the antiapoptotic proteins Bcl-X and Mcl-1 were identified in prostate tumor cells, especially in high-grade and metastatic tumors [76][77]. Increased expression of antiapoptotic proteins contributes to PCa cell resistance to apoptosis mediated by androgen independence and metastasis [77][78]. The expression of the proapoptotic effector protein Bax was increased in castrated mice and was associated with poor outcomes, while the other Bcl-2 family member, Bak, was detected in PCa cell lines, and its level was increased in therapeutic assays [69]. In addition, BH3-only protein (such as BAD) levels were dysregulated in PCa cells, and this dysregulation was correlated with biochemical recurrence (BCR) and overall survival (OS) [79]. The aforementioned data indicate that the normal balance between antiapoptosis and proapoptosis pathway activation was disrupted in PCa, and as tumor progression increased, PCa cells gradually exhibited resistance to apoptosis. In addition, Bcl-2 family members can be regulated by transcription factors such as NF-κB and p53 and signaling pathways such as the PI3K/AKT and RAS/ERK signaling pathways. The direct or indirect regulation of the intrinsic pathway leads to significant benefits for the development of drugs that reduce PCa resistance to apoptosis [69][70].

3.2. Role of Necroptosis in Prostate Cancer

Necroptosis is considered a programmed form of necrosis characterized by mitochondrial alterations and plasma membrane permeabilization, which results in the release of cytoplasmic content into the extracellular space, leading to inflammatory reactions [49]. Accumulated evidence emphasizes the importance of necroptosis in PCa, and greater comprehension of the necroptotic mechanism might be helpful in creating novel strategies for controlling PCa [80].

A study performed bioinformatics analyses using a dataset from The Cancer Genome Atlas (TCGA) database and identified necroptosis-related genes that were closely associated with PCa prognosis. Using them as a gene signature to construct a prognostic model led to the accurate prediction of 1-, 3-, and 5-year OS in prostate adenocarcinoma (PRAD) patients [81]. For one study, researchers collected 67 prostate tissues that had been used to histologically diagnose PCa and categorized them into different tumor progression stages. RNA expression, tumor growth, etc., were measured. The results showed that the expression of RIPK3 was significantly elevated in the early stage but profoundly decreased in the final cancer stage [82]. This finding demonstrated that necroptosis was activated in the early stages of tumor progression but was resisted by tumor cells during disease progression into the late stage. Another study reported research on the biological role and clinical significance of RIP3 in the PCa context. They discovered that RIP3 was significantly downregulated in PCa cell lines and clinical prostate tumor samples. Upregulated RIP3 alleviates PCa progression by activating the RIP3/MLKL signaling pathway. Furthermore, RIP3 inhibits the proliferation and tumorigenicity of PCa cells in an MLKL-dependent manner both in vitro and in vivo [83]. These studies indicate that necroptosis is closely related to the progression of PCa and that inducing necroptosis in PCa cells is a feasible treatment strategy; however, a larger number of experimental and clinical studies are needed to confirm these conclusions and optimize the therapeutic approach.

3.3. Role of Pyroptosis in Prostate Cancer

Pyroptosis is an inflammatory form of PCD that can affect the tumor immune environment. The abnormal expression of pyroptosis-related genes (PRGs) may be closely related to the tumor immune microenvironment and thus promote the occurrence and development of PCa. By analyzing data collected in an online database, Hu and colleagues discovered that the expression levels of PRGs were significantly different between tumor and normal tissues. They constructed a prognostic signature based on these PRGs, their expression profile, a clinical database that can be used to precisely predict BCR after radical intervention, which is a determining risk factor for PCa specificity and distant metastasis, and the progression-free survival (PFS) rate [84]. Other researchers who repeated this verified that the identified PRGs were closely related to carcinogenesis, tumor cell invasion, and the immune microenvironment in PCa [85][86].

Inflammation is an important prerequisite for the development of PCa [87]. The NLRP3 inflammasome is a well-studied inflammasome that induces pyroptosis in PCa. A recent study demonstrated that the expression level of NLRP3 was upregulated in LNCaP and PC3 cell lines. Activation of the NLRP3 inflammasome by LPS + ATP promoted the proliferation and migration of prostate tumor cell lines in vivo. NLRP3 knockdown inhibited the malignant progression of PCa cell lines [88]. Another study revealed the relationship between NLRP3 inflammasome and AR levels in high-grade PCa tumors. Compared with AR-dependent low-grade PCa cells, high-grade PCa cells showed increased NLRP3 levels. Furthermore, they identified an AR-related circular RNA (circRNA) named circAR-3-a, which can acetylate NLRP3 and promote NLRP3 inflammasome complex assembly. Disrupting NLRP3 acetylation or blocking inflammasome assembly with an inhibitor suppressed the progression of PCa xenograft tumors [89]. The NLRP12 inflammasome level was also shown to be significantly higher in malignant prostate tissues than in adjacent benign tissues, as indicated by immunostaining intensity [90].

Another pore-forming effector protein from the gasdermin family, GSDME, which is expressed in most normal tissue cells, is activated by apoptotic caspase (caspase 3), and its activation can switch the PCD from apoptosis to pyroptosis [91]. In contrast to NLRP3/caspase-1-mediated DSDMD cleavage, caspase-3-mediated DSDME cleavage plays a crucial role in the chemotherapeutic treatment of PCa. Tian et al. discovered that the expression level of GSDME in PCa cells did not significantly change, but its activity was profoundly increased by the poly polymerase (PARP) inhibitor olaparib. Simply upregulating GSDME conferred cells with sensitivity to olaparib but did not inhibit tumor cell proliferation [92]. These findings indicate that the DSDME level is physiologically low in both normal and PCa cells and that upregulation of DSDME may increase the sensitivity of PCa cells to chemotherapeutic drugs.

3.4. Role of PANoptosis in Tumors and PCa

PANoptosis is a recently proposed PCD that highlights the crosstalk and coordination among apoptosis, necroptosis, and pyroptosis pathways, which are interconnected via shared regulatory proteins and signaling pathways [93]. In combination with inflammatory cytokine-induced signaling through death domain-containing receptors, activated PRRs initiate this

highly interconnected form of cell death, PANoptosis. PANoptosis has been linked to the development of multiple systemic diseases, including infectious diseases, cancers, neurodegenerative diseases, and inflammatory diseases [94]. An accumulation of recent studies performed bioinformatics analysis of expression data of PANoptosis-related genes (PRGs) based on online databases. They identified several PRGs correlated with patient survival, immune responses, and/or cancer-related biological processes. PRGs were used to construct PANoptosis signatures and significantly predicted the prognosis and immunotherapeutic response of several cancers, including pancreatic cancer, colon cancer, gastric cancer, and prostate adenocarcinoma (PRAD) [95][96][97][98]. However, in vivo and in vitro experiments on prostate cancer and PANoptosis have not been performed.

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