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Research progress of programmed cell death in colorectal cancer

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Abstract: Programmed cell death is an important biological process, including apoptosis, autophagy and other modalities, which is essential for maintaining tissue and organ homeostasis. In recent years, several studies have shown that aberrant regulation of programmed cell death plays an important role in the development of colorectal tumors. Therefore, it is important to reveal the fine regulatory network of programmed cell death in colorectal carcinogenesis and progression to develop new clinical treatment strategies for colorectal cancer. This paper aims to review the research progress of programmed cell death in colorectal cancer, and provide new approaches and ideas for the clinical diagnosis and treatment of colorectal cancer.

Keywords: Programmed cell death; Colorectal cancer; Clinical diagnosis and treatment; Apoptosis; Autophagy; Ferroptosis; Necrosis; Pyroptosis

According to the latest data from the International Agency for Research on Cancer of the World Health Organization, colorectal cancer (CRC) accounts for approximately 10% of all cancer diagnoses and cancer-related deaths globally each year. It is the third most common cancer worldwide and the fourth leading cause of cancer-related death, with around 1.2 million new cases and 600,000 deaths annually [1]. With ongoing socio-economic development, it is projected that by 2025, there will be an increase of 2.5 million new cases globally [2]. Despite significant progress in the prevention and treatment of CRC over the past decades, the disease still exhibits high incidence and mortality rates. Therefore, discovering new treatment strategies and targets to improve survival rates and quality of life for CRC patients is a major focus of current medical research.

Programmed cell death (PCD) is a crucial process in the normal cell lifecycle, essential for maintaining the function of tissues and organs [3]. However, this process is often disrupted in CRC, leading to enhanced anti-apoptotic capabilities of tumor cells and uncontrolled proliferation [4]. Thus, understanding the regulatory mechanisms and potential roles of PCD in CRC is important for developing new therapeutic strategies and improving patient prognosis.

Recent research on PCD in CRC has made significant progress, including the identification of many molecules and signaling pathways related to cell death regulation and the development of novel drugs targeting these pathways [5]. Additionally, the regulatory mechanisms of PCD show potential clinical value in prognosis assessment and prediction for CRC.

This review will summarize the progress in research on PCD in CRC, focusing on key molecules and signaling pathways involved in cell death regulation, as well as relevant therapeutic strategies and clinical prospects. We will explore the importance of these studies for understanding CRC development and treatment and examine how this knowledge can be used

to develop new treatments to improve survival and quality of life for CRC patients. By deepening our understanding of PCD in CRC, we hope to bring new breakthroughs in the treatment and management of the disease.

1.PCD and CRC

1.1 Apoptosis and CRC

Apoptosis is a conserved and regulated form of cell death that has historically been considered the only regulated type of cell death [6]. It generally occurs via two main pathways: the intrinsic pathway, triggered by intracellular imbalances due to toxic substances or DNA damage, and the extrinsic pathway, initiated by the activation of cell surface death receptors.

In 1984, scientists first identified and named the B-cell lymphoma-2 (*Bcl-2*) gene on chromosome 18 in patients with non-Hodgkin lymphoma. Many studies have shown that *Bcl-2* is one of the most important oncogenes involved in cancer by inhibiting apoptosis. The Bcl-2 protein family consists of pro-apoptotic and anti-apoptotic proteins that regulate apoptosis through the intrinsic pathway, primarily at the mitochondrial level. All Bcl-2 family members are located on the outer mitochondrial membrane and are involved in regulating membrane permeability either through dimerization or pore formation. The Bcl-2 family is divided into three main subfamilies: (1) Anti-apoptotic proteins that protect cells from apoptotic stimuli, including Bcl-2, Mcl-1, Bcl-xL, Bcl-w, A1/Bfl-1, and Bcl-B/Bcl2L10; (2) Pro-apoptotic effector proteins, such as BAK, BAX, and BOK; (3) Pro-apoptotic BH3 proteins [7]. The Bcl-2 family plays a crucial role in the development of CRC [8]. Imbalances between anti-apoptotic and pro-apoptotic Bcl-2 family members can lead to dysregulation of apoptosis. For example, Yes-associated protein (YAP) can promote CRC progression by upregulating Bcl-2 to inhibit autophagy in human CRC cells [9]. lncRNA LINC02418 can release Bcl-2 by competitively binding with microRNA miR-34b-5p, allowing cancer cells to evade cell death and re-enter the abnormal cell cycle. The anti-tumor drug lobaplatin can induce CRC cell death by phosphorylating JNK, recruiting BAX to the mitochondria, and stimulating cytochrome c release into the cytoplasm.

Programmed cell death protein 1 (PD-1) is a cell surface receptor that plays an important role in downregulating the immune system and promoting self-tolerance by inhibiting T cell inflammatory activity. PD-1 is a member of the immunoglobulin superfamily expressed on T cells and pre-B cells. As a receptor, PD-1 has two ligands, PD-L1 and PD-L2. When PD-1 binds to its ligands, it can induce PCD in antigen-specific T cells within lymph nodes while reducing the apoptosis of regulatory T cells. Studies have found that PD-L1 is responsible for tumor immune modulation. In the tumor microenvironment, PD-1 and its ligand PD-L1 evade immune surveillance and play a significant role in tumor progression and survival [12]. The classical Wnt signaling pathway, also known as the Wnt/β-catenin signaling pathway, is a recognized driver of colon cancer and one of the most representative signaling pathways, as activation of Wnt signaling can inhibit apoptosis [13]. The transforming growth factor-β (TGF-β) signaling pathway also plays a critical role. Disruption of TGF-β signaling in CRC cells often promotes early tumor formation, while its activation may enhance cancer invasion and metastasis. Moreover, its activation in the tumor microenvironment typically suppresses tumor immunity and supports cancer cell survival [14]. Nuclear factor (NF)-κB, a transcription factor of the Rel family proteins, is widely involved in various cellular activities such as the cell cycle, proliferation, apoptosis, migration, and invasion [15]. NF-κB signaling mediates cytoplasmic/nuclear signaling pathways by upregulating anti-apoptotic gene expression, including Bcl-xL, Bcl-2 related genes (A1/BFL1), cIAP, and c-FLIP [16]. Additionally, the PI3K/AKT/mTOR pathway, IL-6/STAT3 pathway, Ras signaling pathway, and p53 signaling pathway are also frequently dysregulated in CRC, affecting tumor development.

1.2 Autophagy and CRC

During fasting, one of the cellular responses is the activation of the lysosomal degradation pathway—autophagy, a process where cells digest their own components. This self-digestion not only provides nutrients to maintain essential cell functions during fasting but also clears excess or damaged organelles, misfolded proteins, and invading microbes, thus responding to differentiation and developmental updates and preventing genomic damage [17]. Macroautophagy is the most common form of autophagy and is a primary mechanism for degrading aged proteins and organelles in eukaryotic cells [18].

As mentioned, autophagy signaling pathways can also influence CRC development. Literature suggests that antigen-presenting cells (APC), as a regulator of the Wnt signaling pathway, can interfere with the occurrence of intestinal diseases by affecting autophagy, while CK1α inhibitors can reduce the AKT/β-catenin axis in CRC cell lines and inhibit CRC cell autophagy [19]. Other studies report that inhibition of PHLDA2 can partly suppress EMT and induce autophagy through the PI3K/AKT/mTOR and PI3K/AKT/GSK3β signaling pathways, thereby impacting CRC progression [20]. Hu *et al.* [21] found that IL-6 promoted the interaction between BECN1 and JAK2, enhancing BECN1 tyrosine phosphorylation and promoting autophagy in CRC cells. Cancer cells under hypoxic conditions use autophagy to maintain cell integrity, thus promoting survival; the hypoxia-

autophagy-PKC-EZR signaling axis can promote CRC tumor stem cell self-renewal and CRC progression [22]. At the same time, experiments by Tang *et al.* [23] showed that members of the G protein-coupled receptor superfamily and GPR176 could activate the cAMP/PKA signaling pathway and regulate mitochondrial autophagy, further promoting CRC tumor occurrence and development.

1.3 Necrosis and CRC

Cell necrosis primarily refers to the loss of cytoplasmic membrane integrity. For a long time, necrosis was considered a passive form of pathological cell death, but recent studies suggest that necrosis may be another form of "PCD" when apoptosis cannot occur properly, and necrosis serves as an "alternative" form of cell death. The classic death receptor-mediated necroptosis pathway consists of RIPK1-RIPK3-MLKL, triggered downstream of death domain receptors such as TNFR and Fas, and Toll-like receptors 3/4 (TLR3/4). Active RIPK1 recruits and phosphorylates RIPK3 in the absence of caspase-8, forming necrosome, which then phosphorylates MLKL to form necrotic bodies. MLKL oligomers translocate to phosphoinositide-rich patches on the plasma membrane, forming large pores, allowing ion influx, cell swelling, membrane rupture, and uncontrolled release of intracellular contents, leading to necrotic cell death [24]. Necrosis has been shown to have dual effects: promoting or reducing tumor growth in different cancer types. Inducing programmed necrosis can kill tumor cells and inhibit tumor development; however, cell death releases cellular contents into the extracellular environment, which can trigger inflammatory responses and potentially promote tumor development [25].

Han *et al.* [26] demonstrated that RIPK3 could mediate necrosis in CRC cells, inhibiting tumor development. The fragile X mental retardation protein (FMRP) binds to RIPK1, and *FMR1* anti-transcription therapy upregulates RIPK1, leading to the necrosis of CRC cells and inhibition of tumor growth. However, some studies suggest that SET and MYND domain-containing protein 2 (SMYD2) targets RIPK1 and limits TNF-induced apoptosis and necrosis, supporting colon tumor growth [27]. The A20-binding inhibitor of NF-κB1 (ABIN-1), also known as TNIP1, is a ubiquitin-binding protein that inhibits RIPK1-independent apoptosis, necrosis, and NF-κB activation, with ABIN-1 deficiency enhancing necrosis-based CRC therapy [28].

1.4 Ferroptosis and CRC

Ferroptosis is a ROS-dependent form of cell death associated with iron accumulation and lipid peroxidation, characterized by mitochondrial shrinkage and reduced mitochondrial cristae [29]. Ferroptosis affects various tumor suppressors, making it a natural barrier to cancer development. Downregulation of ferroptosis by oncogenes contributes to tumor onset, progression, metastasis, and treatment resistance. However, some studies have shown that iron-deficiency anemia can limit tumor cell migration, invasion, and proliferation. Unique cancer cell metabolism, high oxidative stress, and genetic mutations make some cells prone to ferroptosis, aiding the treatment of certain cancers. Current literature indicates that ferroptosis is closely related to various diseases, including cancer [30].

Wang *et al.* [31] found that knocking down annexin A10 (ANXA10) induces ferroptosis in CRC cells by inhibiting autophagy-mediated TFRC degradation, thus suppressing CRC progression. Overexpression of miR-15a-3p binds to GPX4, increasing ROS, Fe^{2+}, and malondialdehyde levels in CRC cells, inducing ferroptosis [32]. Besides directly inhibiting GPX4 expression, inhibiting the functional subunit SLC7A11 of system Xc- also induces ferroptosis in CRC cells. Zhang *et al.* [33] discovered that the IMCA, the derivatives of centchroman, downregulated SLC7A11 expression by modulating the AMPK/mTOR/p70S6k signaling pathway, thereby inhibiting CRC cell proliferation.

1.5 Pyroptosis and CRC

Pyroptosis was initially thought to be a form of apoptosis, sharing some features with apoptosis such as DNA damage and nuclear condensation. It is now recognized as a pro-inflammatory form of PCD. Pyroptosis can be triggered by extracellular or intracellular stimuli like bacteria, viruses, toxins, and chemotherapy drugs. In early stages, DNA damage in pyroptosis is minimal, and the nucleus remains intact. Initially, pyroptosis was associated with caspase-1, but recent studies show that other caspases, including caspase-3/4/5/6/8/9/11, can also induce pyroptosis in different cells. The effector proteins of pyroptosis are from the gasdermin family. Pyroptosis plays a significant role in various cancers, including CRC, gastric cancer, liver cancer, and breast cancer, making it a potential therapeutic target [34].

Chronic inflammation is a key pathogenic factor in CRC, with pyroptosis leading to the release of inflammatory factors that may contribute to CRC development. Downregulation of gasdermin C (GSDMC) weakens CRC cell proliferation, while overexpression of GSDMC supports proliferation and tumorigenesis, indicating that GSDMC has great potential as a therapeutic target for CRC [35]. Tan *et al.* [36] found that GSDME-mediated pyroptosis activated the ERK1/2 pathway via HMGB1 release, promoting tumor cell proliferation and proliferating cell nuclear antigen (PCNA) expression, which induced CRC development. lncRNA RP1-85F18.6 may inhibit pyroptosis by suppressing GSDMD activity, thus

promoting CRC cell proliferation, metastasis, and cell cycle disruption, ultimately leading to cancer progression [37].

2 PCD and Clinical Treatment of CRC

Current CRC treatments mainly include surgical resection, radiotherapy, and chemotherapy. Programmed cell death is crucial for controlling cancer cell growth and spread, and treatment methods may influence whether cancer cells undergo PCD, impacting treatment responses and patient prognosis. Dysregulation of PCD can lead to resistance to radiotherapy and chemotherapy, worsening CRC prognosis. For instance, curcumin can significantly inhibit CRC by inducing caspase-3/GSDME-dependent pyroptosis and modulating anti-tumor immune responses [38]. Short-chain fatty acids like propionate and butyrate can induce autophagy in colon cancer cells to reduce apoptosis, while autophagy inhibition enhances apoptosis, suggesting that autophagy inhibitors might improve the therapeutic effects of short-chain fatty acids in colon cancer treatment [39]. The SRPK1/AKT axis enhances IKK kinase and IκB phosphorylation, promoting NF-κB nuclear translocation and enhancing the anti-apoptotic ability of colon cancer cells, leading to oxaliplatin resistance and poor CRC prognosis [40]. Thus, combining interventions in PCD with radiotherapy and chemotherapy may improve clinical efficacy and prognosis. Bcl-2/Bcl-xL inhibitor ABT-263 enhances the cytotoxic effects of radiation under normoxic conditions and reduces radiation resistance in cells exposed to acute or cyclic hypoxia [41]. Acridine orange, by enhancing apoptosis via the p53-dependent mitochondrial pathway and endoplasmic reticulum stress signals, can act as a radiosensitizer [42]. NF-κB activation can inhibit tumor cell apoptosis and induce chemotherapy resistance. Aspirin completely eliminates 5-fluorouracil (5-Fu)-induced NF-κB activation and is a promising adjunctive therapy [43]. Alantolactone (ALT) has anti-tumor properties across various cancer cell lines. ALT induces CRC cell apoptosis through significant intracellular ROS accumulation and activation of JNK and p38 MAPK signaling pathways, showing stronger anti-tumor activity in combination with oxaliplatin, markedly reducing tumor cell proliferation, and can serve as an adjunctive treatment for oxaliplatin [44].

PCD is akin to a double-edged sword. Every defect or anomaly in the apoptotic pathway can potentially become an effective target in CRC treatment. There are many ways to alter the PCD pathways, leading to either reduced cell death or acquired resistance to cell death. Developing drugs targeting PCD and restoring the normal apoptosis signaling pathways to eliminate the defects that cancer cells rely on may represent a new treatment strategy for CRC. Anti-PD-1 or anti-PD-L1 therapies are currently among the most advanced drugs, with the main advantage being their potential to increase sensitivity to traditional cancer therapies while producing fewer harmful side effects. Nivolumab, a monoclonal antibody targeting the PD-1 receptor, has been used in clinical treatment for CRC patients and has shown good tolerability, with no patients developing antibodies even after multiple doses, potentially extending the survival of patients with advanced CRC [12]. Using PLGA nanoparticles loaded with PD-1 siRNA/PD-L1 siRNA to simultaneously inhibit the expression of PD-1 and PD-L1 on cytotoxic T lymphocytes (CTLs) and colon tumors has enhanced the effector functions of tumor-specific CTLs. Additionally, PD-L1 inhibition suppresses mTOR signaling, reducing tumor cell proliferation. Co-silencing PD-1 and PD-L1 has a more significant impact on inhibiting tumor growth and reducing recurrence and metastasis, providing an effective therapeutic strategy for immunotherapy in colorectal cancer [45]. BH3-only proteins from the Bcl-2 family can trigger apoptosis by binding to and neutralizing the anti-apoptotic members of this family. The concept of "BH3 mimetics" has led to the development of small molecules that mimic BH3 proteins to induce apoptosis. The prototype BH3 mimetic ABT-737 selectively targets three pro-survival proteins: Bcl-xL, Bcl-2, and Bcl-w. Its oral derivative ABT-263 has shown therapeutic potential in clinical trials [46].

3 Summary and Outlook

PCD occurs in various forms to address different environmental challenges, following specific mechanisms and appearing under certain conditions to determine cell fate. Dysregulation of PCD leading to abnormal cell growth can result in various diseases, particularly cancer. A large body of literature indicates that defects in the apoptotic pathways play a crucial role in cancer development, and many new therapeutic strategies targeting apoptosis are feasible for treating various types of cancer.

In CRC research and treatment, utilizing PCD to predict disease progression, assess patient prognosis, and develop more effective treatment strategies is a promising direction. In recent decades, extensive research into the molecular mechanisms of cancer cell apoptosis has identified various molecules involved in the apoptotic pathways. Alterations in key participants of the apoptosis mechanisms can lead to evasion of apoptosis, resulting in tumor development and drug resistance. Therefore, evasion of apoptosis is a hallmark of cancer, and apoptosis-related proteins may be effective therapeutic targets. Researchers are focusing on developing strategies to reactivate apoptosis. Some molecules or therapeutic strategies are undergoing preclinical trials, while others have entered clinical trials.

However, research on PCD related to colorectal cancer still faces several challenges. For instance, most research results are derived from two-dimensional cell culture systems, whereas tumors are three-dimensional entities, and the interactions between the microenvironment and cancer cells play a significant role. This makes manipulating PCD more complex and necessitates further exploration.

Overall, a deeper understanding of the regulatory mechanisms of programmed death in CRC cells can provide important guidance for prognosis assessment, treatment planning, and new drug development. This personalized approach is expected to improve treatment efficacy, reduce side effects, and enhance patient survival and quality of life.

Conflicts of Interest: None

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·学术前沿·

细胞程序性死亡在结直肠癌中的研究进展

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摘要：细胞程序性死亡是一种重要的生物学过程，包括凋亡、自噬等多种方式，对于维持组织和器官的平衡至关重要。近年来，多项研究表明细胞程序性死亡的异常调控在结直肠肿瘤的发生发展中发挥重要作用。因此，揭示细胞程序性死亡在结直肠癌发生和发展中的精细调控网络对开发新的结直肠癌临床诊疗策略具有重要意义。本文就细胞程序性死亡在结直肠癌中的研究进展作一综述，以期为结直肠癌的临床诊治提供新的思路和方法。

关键词：细胞程序性死亡；结直肠癌；凋亡；自噬；铁死亡；坏死；焦亡

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Research progress of programmed cell death in colorectal cancer

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Abstract: Programmed cell death is an important biological process, including apoptosis, autophagy and other modalities, which is essential for maintaining homeostasis of tissue and organ. In recent years, several studies have shown that aberrant regulation of programmed cell death plays an important role in the development of colorectal cancer. Therefore, it is important to reveal the fine-turned regulatory network of programmed cell death in colorectal carcinogenesis and progression to develop new clinical treatment strategies for colorectal cancer. This paper aims to review the research progress of programmed cell death in colorectal cancer, and provide new ideas and approaches for the clinical diagnosis and treatment of colorectal cancer.

Keywords: Programmed cell death; Colorectal cancer; Apoptosis; Autophagy; Ferroptosis; Necrosis; Pyroptosis

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根据世界卫生组织国际癌症研究机构最新的数据显示，结直肠癌（colorectal cancer，CRC）约占全球每年诊断的所有恶性肿瘤及其相关死亡的 10%，是全球第三大常见恶性肿瘤及第四大肿瘤常见死亡原因，每年约有 120 万新病例和 60 万人死亡[1]，随着社会经济的不断发展，2025 年全球预计将增加 250 万新病例[2]。虽然在过去几十年里，CRC 的预防和治疗取得了显著进展，但该疾病仍然具有高发病率和高死亡率。因此，寻找新的治疗策略和治疗靶点，以提高 CRC 患者的生存率和生活质量，是当今医学研究的重要方向之一。

细胞程序性死亡是正常细胞生命周期中的重要过程，对于维持组织和器官的正常功能至关重要[3]。然而，在 CRC 中，这个过程常常被破坏，导致肿瘤细胞抗凋亡能力增强进而无限增殖[4]。因此，研究细胞程序性死亡在 CRC 中的调控机制和潜在作用，对于开发新的治疗策略和改善患者预后具有重要意义。

近年来，针对细胞程序性死亡在 CRC 中的研究已经取得了显著的进展，这些研究包括发现了许多与细胞死亡调控相关的分子和信号通路，以及针对这些靶点的新型治疗药物的开发[5]。此外，细胞程序性死亡的调控机制在 CRC 预后评估和预测方面也显示出潜在的临床应用价值。

本文将综述细胞程序性死亡在 CRC 中的研究进展，重点关注细胞死亡调控的关键分子和信号通路，以及相关的治疗策略和临床前景。将进一步探讨这些研究对于理解 CRC 发展和治疗的重要性，并探索如何利用这些知识来开发新的治疗手段，以提高 CRC 患者的生存率和生活质量。通过加深对细胞程序性死亡在 CRC 中作用的理解，本文有望为该疾病的治疗和管理带来新的突破。

1　细胞程序性死亡与 CRC

1.1　凋亡（apoptosis）与 CRC　细胞凋亡是一种保守的、可调节的细胞死亡机制，在过去的研究中细胞凋亡甚至被认为是唯一受调节的细胞死亡类型[6]。细胞凋亡一般通过内在途径和外在途径两条主要途径，内在途径是由有毒物质或 DNA 损伤导致的细胞内稳态失调或失衡触发，外在途径是由细胞表面死亡受体的激活启动[6]。

1984 年，科学家在非霍奇金淋巴瘤患者的 18 号染色体上首次发现并命名了 B 淋巴细胞瘤-2（B-cell lymphoma-2，*Bcl-2*）基因，许多研究均表明 *Bcl-2* 是通过抑制细胞凋亡参与肿瘤的重要基因之一。Bcl-2 蛋白家族由促凋亡蛋白和抗凋亡蛋白组成，通过内在途径调节细胞凋亡，主要在线粒体中发挥作用。所有 Bcl-2 成员均位于线粒体外膜上，是二聚体，以离子通道形式或通过形成孔来负责膜的渗透性。Bcl-2 家族蛋白根据其功能和结构分为以下三个主要亚家族。（1）抗凋亡蛋白：保护细胞免收凋亡刺激，包括 Bcl-2、髓细胞白血病序列 1（Mcl-1）、Bcl-xL、Bcl-w、A1/Bfl-1 和 Bcl-B/Bcl2L10；（2）促凋亡效应蛋白：BAK、BAX 和 BOK；（3）促凋亡蛋白：BH3 蛋白[7]。Bcl-2 家族在 CRC 的发生发展中扮演了十分重要的角色[8]。当 Bcl-2 家族的抗凋亡和促凋亡成员平衡被破坏时，就会导致细胞凋亡失调。例如，Yes 相关蛋白（Yes-associated protein，YAP）可以通过转录上调 Bcl-2 来抑制人类 CRC 细胞的自噬，从而促进 CRC 进展[9]。lncRNA LINC02418 通过与 miR-34b-5p 竞争性结合释放 Bcl-2，使肿瘤细胞逃脱细胞死亡并重新进入异常细胞周期[10]。抗肿瘤药物洛铂可以使 C-Jun 氨基末端激酶（JNK）磷酸化，招募 BAX 到线粒体，刺激细胞色素 c 释放到胞质，从而诱导 CRC 细胞死亡[11]。

程序性细胞死亡蛋白 1（programmed cell death protein 1，PD-1），是一种细胞表面受体，通过抑制 T 细胞炎症活性，在下调免疫系统和促进自我耐受方面发挥重要作用。PD-1 是免疫球蛋白超家族的一员，在 T 细胞和前 B 细胞上表达。PD-1 作为受体，有两个配体，程序性细胞死亡蛋白配体 1（PD-L1）和 PD-L2。当 PD-1 与配体结合时，可诱导淋巴结内抗原特异性 T 细胞发生程序性细胞死亡，同时减少调节性 T 细胞的凋亡。研究发现 PD-L1 负责肿瘤免疫调节。在肿瘤微环境中，PD-1 及其配体 PD-L1 逃避肿瘤中和免疫监视，在肿瘤进展和存活中发挥着重要作用[12]。经典 Wnt 信号通路（也称为 Wnt/β-catenin 信号通路）是公认的结肠癌驱动因素，也是最具代表性的信号通路之一，Wnt 信号通路的激活可以抑制细胞凋亡[13]。转化生长因子-β（transforming growth factor-β，TGF-β）信号通路也发挥着关键作用。CRC 细胞中 TGF-β 信号传导的破坏会促进早期肿瘤的形成，而其激活可能会促进肿瘤的侵袭和转移。此外，它在肿瘤微环境中的激活通常会抑制肿瘤免疫并支持肿瘤细胞存活[14]。核因子（nuclear factor，NF）-κB 是 Rel 家族蛋白的转录因子，广泛参与细胞周期、细胞增殖、凋亡、迁移和侵袭等多种细胞活动[15]。NF-κB信号介导细胞质/核信号通路，通过上调抗凋亡基因表达来抑制细胞凋亡，包括 Bcl-xL、Bcl-2 相关

基因(*A1/BFL1*)、小牛肠碱性磷酸酶(cIAP)和细胞半胱天冬酶 8(FLICE)样抑制蛋白(c-FLIP)等[16]。另外,PI3K/AKT/mTOR 通路、白细胞介素(IL)-6/STAT3 通路、Ras 信号通路和 p53 信号通路等在 CRC 中也经常失调,影响肿瘤的发生发展。

1.2　自噬(autophagy)与 CRC　在有机体禁食时,细胞反应之一是溶酶体降解通路——自噬的激活,这是一种细胞自身消化其组分的过程。这种自我消化不仅在禁食期间提供营养以维持关键的细胞功能,还可以清除多余或受损的细胞器、错折蛋白和入侵的微生物,应对分化和发育过程中的更新以及预防基因组损伤[17]。巨自噬是最常见的自噬方式,是真核细胞降解老化蛋白质和细胞器的主要机制[18]。

如前所述,自噬信号通路也可以影响 CRC 的发生发展。抗原呈递细胞(APC)作为 Wnt 信号通路的 APC 调节剂,可以通过影响自噬来干扰肠道疾病的发生。而酪蛋白激酶 1α(CK1α)抑制剂可以降低 CRC 细胞系中的 AKT/β-catenin 轴,抑制 CRC 细胞自噬[19]。另有文献报道抑制 PHLDA2 可分别通过 PI3K/AKT/mTOR 和 PI3K/AKT/GSK3β 信号通路抑制上皮间充质转化(EMT)并诱导自噬,进而影响 CRC 进展[20]。Hu 等[21]发现 IL-6 促进 BECN1 和 JAK2 之间的相互作用,并增强 BECN1 酪氨酸磷酸化,进而促进 CRC 细胞发生自噬。肿瘤细胞在缺氧状态下会利用自噬维持细胞完整性,从而增强其生存能力,缺氧-自噬-PKC-EZR 信号轴可以促进 CRC 肿瘤干细胞自我更新和促进 CRC 进展[22]。同时,Tang 等[23]的实验表明 G 蛋白偶联受体超家族成员和 GPR176 可激活 cAMP/PKA 信号通路并调节线粒体自噬,进而促进 CRC 肿瘤发生和发展。

1.3　坏死(necrosis)与 CRC　细胞坏死主要是指细胞质膜完整性的丧失,长期以来细胞坏死被认为是因病理而产生的被动死亡,但是近期的研究表明细胞坏死可能是细胞“程序性死亡”的另一种形式,当细胞凋亡不能正常发生而细胞必须死亡时,坏死作为凋亡的“替补”方式被采用。经典死亡受体介导的坏死性凋亡途径由受体相互作用蛋白激酶(RIPK)1-RIPK3-MLKL 组成,在死亡域受体(例如 TNFR 和 Fas)和 Toll 样受体 3/4(TLR3/4)的下游被触发。活性 RIPK1 包含 FADD、caspase-8 和 caspase-10。在缺乏 caspase-8 的情况下,RIPK1 募集并磷酸化 RIPK3,形成核凋亡体,然后磷酸化 MLKL 形成坏死体。MLKL 寡聚物易位到质膜中富含磷脂酰肌醇磷酸(phosphoinositides, PIP)的斑块,并形成大孔,通过允许离子流入、细胞肿胀和膜裂解,然后不受控制地释放细胞内物质,从而导致坏死性细胞死亡[24]。细胞坏死已被证明具有双重作用:在不同类型的恶性肿瘤中促进或抑制肿瘤生长。程序性坏死的诱导杀死肿瘤细胞,从而抑制肿瘤的发展,另一方面,细胞死亡释放细胞内容物进入细胞外环境,进而引发炎症反应和可能导致肿瘤的发展[25]。

Han 等[26]表明 RIPK3 可介导 CRC 细胞坏死,从而抑制肿瘤发育脆性 X 染色体智力迟钝蛋白(fragile X mental retardation protein, FMRP)与 RIPK1 结合,脆性 X 染色体智力迟钝 1 基因(fragile X mental retardation 1 gene, *FMR1*)抗转录治疗上调 RIPK1,导致 CRC 细胞坏死和肿瘤生长抑制。但一些研究表明,MYND 结构域的蛋白 2(SET and MYND domain-containing protein 2, SMYD2)靶向 RIPK1 并限制肿瘤坏死因子(TNF)诱导的细胞凋亡和坏死以支持结肠肿瘤生长[27]。NF-κB1 和 A20 结合抑制剂(A20-binding inhibitor of NF-κB1, ABIN-1),也称为 TNIP1,是一种泛素结合蛋白,可抑制 RIPK1 非依赖性细胞凋亡、坏死、NF-κB 活化和 ABIN-1 缺乏,增强了基于坏死的 CRC 治疗[28]。

1.4　铁死亡(ferroptosis)与 CRC　铁死亡是一种活性氧(ROS)依赖性细胞死亡形式,与铁积累和脂质过氧化相关,铁死亡细胞的特点为线粒体萎缩和线粒体嵴数量减少[29]。铁死亡影响多种肿瘤抑制因子的活性,使之成为肿瘤发展的天然屏障,而原癌基因介导的铁死亡下调有助于肿瘤的发生、进展、转移和耐药治疗。但也有研究已经证明缺铁性贫血可以限制肿瘤细胞的迁移、侵袭及增殖,肿瘤细胞独特的代谢、活性氧的高负荷以及基因突变使一些细胞铁死亡易感,有利于某些肿瘤的治疗,根据现有的文献报道,铁死亡与包括肿瘤在内的多种疾病密切相关[30]。

Wang 等[31]研究发现,敲低膜联蛋白 A10(annexin A10, ANXA10)后可通过抑制自噬介导的铁轻蛋白受体(TFRC)降解来诱导细胞铁死亡,进而抑制 CRC 进展。miR-15a-3p 过表达后可与 GPX4 结合后,导致 CRC 细胞内 ROS、Fe^{2+}水平和丙二醛增加诱发 CRC 细胞铁死亡[32]。除了直接抑制 GPX4 表达外,抑制系统 Xc-的功能亚基 SLC7A11 也可诱导 CRC 细胞发生铁死亡,Zhang 等[33]研究发现,苯并吡喃衍生物 IMCA 通过调控 AMPK/mTOR/p70S6k 信号通路下调 SLC7A11 表达,从而抑制 CRC 细胞增殖。

1.5　焦亡(pyroptosis)与 CRC　细胞焦亡最初被认为

是细胞凋亡,它的一些特征与细胞凋亡相似,例如 DNA 损伤和核浓缩,后来科学家观察到这种形式的细胞死亡与细胞凋亡不同,是一种促炎性程序性细胞死亡方式。细胞焦亡可引起炎症,由细胞外或细胞内刺激激活,如细菌、病毒、毒素和化疗药物。细胞焦亡早期 DNA 损伤的强度较低,细胞核保持完整。最初,焦亡被认为是与 caspase-1 相关的细胞死亡。最近的研究表明其他 caspase,包括 caspase-3/4/5/6/8/9/11 也会引起其他不同细胞的焦亡。细胞焦亡的效应蛋白是焦孔素(gasdermin)家族。细胞焦亡在 CRC、胃癌、肝癌、乳腺癌等多种肿瘤中都发挥着重要的作用,是治疗的可能靶点之一[34]。

慢性炎症是 CRC 的关键致病因素之一,细胞焦亡导致炎症因子的释放,这可能有助于 CRC 的发展。焦孔素 C(gasdermin C, GSDMC)表达的下调减弱了 CRC 细胞的增殖,而GSDMC的过表达有助于其增殖和肿瘤发生,这意味着 GSDMC 作为 CRC 的治疗靶点具有很大的潜力[35]。Tan 等[36]发现焦孔素 E(GSDME)介导的细胞焦亡会通过释放高迁移率族蛋白 B1(HMGB1)激活 ERK1/2 通路,促进肿瘤细胞增殖和增殖细胞核抗原(PCNA)表达,进而诱导 CRC 发生发展。lncRNA RP1-85F18.6 可能通过抑制 GSDMD 的活性,从而抑制 CRC 细胞的焦亡,以促进 CRC 细胞的增殖、转移和细胞周期的破坏,最终导致肿瘤的进展[37]。

2　细胞程序性死亡与 CRC 的临床治疗

CRC 目前的治疗手段主要包括手术切除、放疗、化疗等,细胞程序性死亡对于控制肿瘤细胞的生长和扩散至关重要,治疗方法可能会影响肿瘤细胞是否发生细胞程序性死亡,从而影响治疗反应和患者的预后。

细胞程序性死亡的失调可能导致肿瘤细胞对放化疗产生耐药性,进而使 CRC 预后不良。例如藤黄酸可通过诱导 caspase-3/GSDME 依赖性细胞焦亡和抗肿瘤免疫反应的调节细胞焦亡,显著抑制 CRC[38]。短链脂肪酸丙酸和丁酸能够诱导结肠癌细胞发生自噬以减轻凋亡,而抑制自噬则增强了凋亡,应用自噬抑制剂可能会提高短链脂肪酸诱导结肠癌抑制的治疗效果[39]。SRPK1 /AKT 轴增强 IKK 激酶和 IκB 磷酸化,促进 NF-κB 核转位,增强了结肠癌细胞的抗凋亡能力,使 CRC 产生奥沙利铂耐药性,导致 CRC 患者预后不良[40]。因此人们将干预程序性细胞死亡和放化疗联合应用,以期可改善临床疗效,改善预后。Bcl-2/Bcl-xL 抑制剂 ABT-263 改善了常氧条件下放射治疗对肿瘤细胞的细胞毒作用,而且减弱了暴露于急性或循环缺氧的肿瘤细胞的放射抗性[41]。吖啶黄通过 p53 依赖性线粒体途径和内质网应激信号增强细胞凋亡,可作为放射治疗的增敏剂[42]。NF-κB 激活可以抑制肿瘤细胞凋亡并诱导化疗耐药,阿司匹林完全消除了 5-氟尿嘧啶(5-Fu)诱导的 NF-κB 激活,是一种有前景的辅助治疗药物[43]。土木香内酯(alantolactone)在多种肿瘤细胞系中具有抗肿瘤特性。ALT 通过细胞内 ROS 显著积累以及 JNK 和 p38 MAPK 信号通路激活,诱导 CRC 细胞凋亡,在联合奥沙利铂治疗显示出更强的抗肿瘤活性,肿瘤细胞增殖明显减少,可作为奥沙利铂的辅助治疗药物[44]。

细胞程序性死亡就像一把双刃剑,细胞凋亡途径中的每一个缺陷或者异常也可能成为 CRC 治疗中的一个有效的目标。有许多方法可以改变细胞程序性死亡途径,从而导致细胞死亡减少或获得细胞死亡抗性。开发针对细胞程序性死亡的药物。将细胞凋亡信号通路恢复正常,消除肿瘤细胞赖以生存的缺陷,可能成为 CRC 新的治疗策略。抗 PD-1 或抗 PD-L1 疗法是目前最成熟的药物之一,其主要优点是它们可能会增加对传统肿瘤疗法的敏感性,并且产生有害的副作用较少。纳武利尤单抗是一种针对 PD-1 受体的单克隆抗体,已经应用在 CRC 患者的临床治疗中,纳武利尤单抗耐受性良好,即使在接受多次剂量后,也没有患者产生抗体,可以延长晚期 CRC 的患者的生存期[12]。使用装载 PD-1 siRNA/PD-L1 siRNA 的 PLGA 纳米粒子同时抑制细胞毒性 T 淋巴细胞(CTL)和结肠肿瘤上的 PD-1 和 PD-L1 表达,促进了肿瘤特异性 CTL 的效应功能。此外,PD-L1 抑制的肿瘤抑制 mTOR 信号传导,可以减少肿瘤细胞的增殖。PD-1 和 PD-L1 共沉默为更显著的抑制结肠癌肿瘤生长,减少复发转移,为实现结肠癌的免疫治疗提供了有效的治疗策略[45]。Bcl-2 家族的 BH3-only 蛋白可以通过与该家族的抗凋亡成员结合并中和其功能活性来触发细胞凋亡。“BH3 模拟物”概念促使人们开发出能够模拟 BH3 蛋白的小分子,从而诱导细胞凋亡。原型 BH3 模拟物 ABT-737 选择性靶向三种促存活蛋白 Bcl-xL、Bcl-2 和 Bcl-w,其口服衍生物 ABT-263 在临床试验中已被证明具有治疗前景[46]。

3　总结及展望

细胞程序性死亡以多种形式发生以应对不同的环境挑战,它们遵循其特定的机制程序并在相应的条

件下出现,决定细胞的命运。细胞程序性死亡失调引发的异常细胞生长可导致多种类型的疾病,特别是肿瘤。大量文献表明,细胞凋亡途径的缺陷在肿瘤发生中起着至关重要的作用,许多针对细胞凋亡的新治疗策略是可行的,可用于治疗各种类型的肿瘤。

在 CRC 的研究和治疗中,利用细胞程序性死亡来预测疾病发展、评估患者预后,以及制定更有效的治疗策略,是非常有研究前景的方向之一。过去几十年来,对肿瘤细胞凋亡分子机制的深入研究已经鉴定出多种参与凋亡途径的分子。细胞凋亡机制的关键参与者的改变会导致细胞凋亡逃避,从而导致肿瘤的发展和对治疗的耐药性。因此,逃避细胞凋亡是肿瘤的一个标志,而细胞凋亡蛋白可能是有效的治疗靶点。因此,研究者将研究注意力集中在细胞凋亡重新激活策略的开发上。一些分子或治疗策略正在进行临床前试验,其他分子或治疗策略已经进入临床试验。

然而,细胞程序性死亡与 CRC 相关的研究仍然面临诸多挑战,例如,大多数研究结果都是在二维细胞培养系统中产生的,而肿瘤是一个三维实体,并且微环境与肿瘤细胞的相互作用发挥着重要作用,因此操纵细胞程序性死亡存在更多的影响因素,这需要进一步的探索研究。

总体而言,通过深入了解 CRC 细胞中的程序性死亡调控机制,可以为预后评估、治疗方案制定以及新药物研发提供重要的指导。这种个体化的方法有望提高 CRC 患者的治疗效果,降低治疗的副作用,并改善患者的生存率和生活质量。

利益冲突　无

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