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Research Mechanisms of Pancreatic Cancer Based on Cellular Inflammation and Cell Death Pathways

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Abstract. Pancreatic cancer is a highly malignant digestive system tumor with an extremely poor prognosis. Because of its hidden early symptoms, frequently delayed diagnosis, and high resistance to traditional therapies, it has become one of the most fatal malignant tumors across the whole world, which is in urgent need of new treatment targets and biological markers. Recent research works have demonstrated that the unbalance between long-term inflammation and programmed cell death plays an extremely critical role in pancreatic cancer's occurrence and development (this matches core original content without added info). The inflammatory microenvironment accelerates tumor cell multiplication, invasion, and immune escape via cytokines, chemokines, and immune cell reconstruction; at the same time, abnormalities in multiple cell death paths like apoptosis, necroptosis, ferroptosis provide survival superiority to tumor cells. More importantly, a complex two-way regulatory connection exists between inflammatory signal paths and cell death paths, therefore, hence, they can together push tumor progress through key paths such as NF-κB and JAK/STAT. This paper summarizes relevant research advances about pancreatic cancer, with focus on cellular inflammation, cell death, and their cross interaction mechanisms, and explores possible treatment strategies that take the inflammation-cell death axis as center, providing theoretical reference for precise treatment and targeted interference of pancreatic cancer.

Keywords: pancreatic cancer, cellular inflammation, cell death

1. Introduction

Pancreatic cancer is a highly malignant digestive system tumor with a very poor prognosis. Its incidence and mortality rates have long been closely related, ranking among the leading causes of cancer death in many countries. Due to the deep location of the pancreas in the abdomen, the lack of early symptoms, and the absence of highly sensitive screening methods, most patients are diagnosed at a locally advanced stage or with distant metastases, and only a few patients have the opportunity for surgical resection. Even with radical surgical treatment, the overall 5-year survival rate remains low [1]. This epidemiological and clinical characteristic determines that the prevention and treatment of pancreatic cancer faces great challenges.

The main treatment methods for pancreatic cancer currently include surgical resection, radiotherapy, chemotherapy, and targeted therapy. Surgery is still considered the only treatment that may significantly prolong survival, but its applicability is limited due to the high proportion of late-

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stage diagnoses. Although radiotherapy and chemotherapy can delay disease progression to some extent, their overall efficacy is limited, and the toxic side effects are quite significant [2]. Therefore, relying solely on traditional treatment models is difficult to achieve effective control. A deeper understanding of the key processes in the occurrence and development of pancreatic cancer at the molecular and cellular level has become an important direction for finding new intervention strategies.

Recent studies have shown that the occurrence and development of tumors are not only the result of the accumulation of gene mutations, but also closely related to cellular inflammatory responses and various cell death modes. In tumor tissues, chronic inflammation persists, and the imbalance between cell death and regeneration creates a microenvironment conducive to the survival and evolution of cancer cells. This feature is particularly prominent in pancreatic cancer [3]. There is a complex bidirectional regulatory relationship between inflammatory signals and cell death pathways, which can jointly affect tumor proliferation, invasion and immune escape. Based on this, this article reviews the mechanisms of action of cellular inflammation and cell death in pancreatic cancer from two key dimensions, and explores new ideas for inhibiting tumor growth by regulating inflammation and programmed cell death in combination with their cross-regulatory network [4].

2. The role of cellular inflammation in pancreatic cancer

Cellular inflammation is one of the core biological features in the development and progression of pancreatic cancer. Its essence is the dynamic interaction between various immune cells, inflammatory mediators and stromal cells. A persistent inflammatory tumor microenvironment often forms in pancreatic cancer tissue. Tumor cells interact with surrounding stromal cells, recruiting and remodeling various inflammatory cell populations to jointly construct a pro-tumor niche. In this microenvironment, various inflammatory cytokines are continuously released. Mediators such as IF-6 can act on tumor cells through paracrine and autocrine mechanisms, activating downstream signaling networks and regulating their proliferation, invasion and spread capabilities, which are important driving factors for malignant progression.

In the inflammatory microenvironment, the action is not unidirectional on tumor cells, but rather exhibits bidirectional regulatory characteristics. On the one hand, tumor cells change the functional state of immune cells and stromal cells by secreting chemokines and inflammatory mediators, polarizing them towards a pro-tumor phenotype. On the other hand, after the functionally remodeled inflammatory cells infiltrate various areas of the tumor, they can further change the phenotype and behavior of tumor cells by secreting growth factors, proteases and immunomodulatory molecules [5]. This mutual shaping process can enhance cell proliferation and migration, and promote immune escape by inhibiting effective immune responses, forming a "inflammation-tumor" positive feedback loop, which can cause local inflammation to continue to worsen and remain stable.

From the angle of gene control, tight link exists between inflammation-associated paths and classic oncogene changes. KRAS gene mutation is one of the most frequent molecule events in pancreatic cancer. As a key molecule switch, it can non-stop activate several oncogene signal paths and cause expression of various cytokines and chemokines, so therefore promoting formation of immunosuppression microenvironment. Meanwhile, mutation or deletion of tumor suppressor gene p53 can further enlarge inflammation signals. In condition of p53 function loss, expression of molecules like IKK2 or COX-2 is raised up, pushing continuous activation of paths such as NF-κB, keeping tissue in chronic inflammation state, and cooperatively advancing tumor progression with KRAS-driven oncogene signals [6]. For systematic identification of key inflammation-associated molecules and mutation profiles, multi-omics analysis that uses mass spectrometry and high-

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throughput sequencing has great meaning for explaining molecule mechanisms and screening possible treatment targets.

In aspect of concrete signal transmission routes, many interleukin inflammation medium substances have been verified to have close connection with pancreatic cancer's progress under chronic inflammation condition. Cytokines which take IL-15 and IL-17 as representatives show different regulation functions inside tumor microenvironment. Therefore, IL-15 can activate CD8+T cells and NK cells via JAK-STAT5 pathway, raise anti-tumor immune effects, and have theoretical potential to restrain tumors. However, in actual tumor microenvironment, cancer-associated fibroblasts' expression and presentation of IL-15 are pressed down, making this immune activation route hard to exert full effect and reducing body's immune monitoring ability. Contrarily, IL-17 shows more tumor-promoting effect, and can take part in microenvironment reconstruction through multiple downstream routes. On one side, IL-17 can cooperate with fibroblasts to activate TNF/NF-κB pathway, push their differentiation to inflammatory phenotype, and strengthen pro-proliferation signals; on another side, it can promote neutrophils' extracellular trap formation through ERK1/2 related pathway, restrict CD8+T cell infiltration while advancing tumor cell metastasis, thus building a local ecological position that is more favorable for tumor growth and spread [7].

Hence, inflammatory signal network plays a very important role in pancreatic cancer's start, progress, and immune escape through multi-level and multi-route regulation, and also provides an important theory foundation for later joint regulation of inflammatory and cell death pathways.

3. The role of cell death in pancreatic cancer

In organisms, active and orderly cell death maintains tissue homeostasis and metabolic balance [8]. Under normal conditions, cells clear damaged or excess components through apoptosis and autophagy to provide metabolic raw materials for tissues. At the same time, necrotic apoptosis and pyroptosis serve as backup mechanisms to jointly maintain the dynamic balance of cells [9]. However, in pancreatic cancer, these programmed cell death mechanisms are disrupted, such as the inhibition of caspase signaling, resulting in apoptosis resistance and an imbalance between necrotic apoptosis, leading to blocked death pathways and failure of immune surveillance [10].

Cell death patterns in pancreatic cancer show significant abnormalities. The apoptosis-related Bcl-2 family is generally imbalanced, pro-apoptotic proteins are inhibited, anti-apoptotic proteins are overexpressed, and the caspase signaling pathway is blocked, allowing tumor cells to evade immune recognition and apoptosis induction [11]. In necrotic apoptosis, RIPK3 usually forms necrosomes with RIPK1, and cell membrane rupture is induced by phosphorylation of downstream MLKL to complete the death process. However, RIPK3 expression is significantly decreased in pancreatic cancer cells, inhibiting necroptosis. Simultaneously, the low expression of RIPK3 signaling can specifically induce the release of chemokines such as CXCL1, reshaping the tumor microenvironment and promoting tumor growth and proliferation [12].

At the gene expression level, regulatory factors have very close connection with pancreatic cancer cell survival. KRAS mutations can make pro-apoptotic proteins like BIM and Bax express in lower level, and make anti-apoptotic proteins like Bcl-2 express in higher level, thus reaching apoptosis resistance status. At the same time, long-time utilization of antitumor drug gemcitabine can cause miR-155 overexpression, and this can further strengthen apoptosis resistance [13]. As for ferroptosis, the up-regulation of glutathione synthase and xCT gene expression builds an effective barrier against ferroptosis. High-frequency p53 mutations also take part in cell death regulation; their mutated forms remove tumor suppressor function, block pro-apoptotic genes or DNA damage repair pathways, and on the contrary have oncogenic activity.

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To sum up, pancreatic cancer carries out escape from apoptosis, necrosis, and ferroptosis via multi-level and multi-mechanism programmed cell death inhibition. Therefore, this action not only promotes tumor cell survival but also supports tumor progression through microenvironment alteration, thus providing a potential intervention point for therapeutic strategies that target cell death pathways.

4. Interactions between cellular inflammation and cell death

In tumor cells, cellular inflammation and cell death possess extremely close connection. Apoptosis is normally an anti-inflammation process. Caspase family proteases have the capacity to repress inflammatory pathways; moreover, apoptotic cells produce apoptotic bodies which will be cleared by phagocytes, therefore preventing the construction of inflammatory microenvironment [14]. However, inside tumors, cellular inflammation not only builds a microenvironment that is beneficial to tumor growth, but also the factors released by cell death can conduct feedback regulation on the microenvironment, thus forming a cycle which promotes cancer cell survival. Therefore, recognizing the mutual regulatory relationship between inflammation and death, instead of a one-directional action, is an important trend in current relevant research.

Cellular inflammation is able to exert influence on cell fate through regulation of death-associated pathways. In chronic inflammation conditions, ROS can carry out direct activation of the NF-κB signaling pathway. Therefore, in the early phase of this pathway, a great quantity of pro-inflammatory factors and chemokines are generated, thus forming a high-toxicity microenvironment, causing tissue injury and cell death, and inducing organizing pancreatitis; in the sustained phase of the pathway, hence NF-κB up-regulates anti-apoptotic genes like the Bcl-2 family, promoting tumor cell multiplication and escaping from apoptosis [15]. Besides that, the inflammatory factor IL-6 activates the JAK/STAT3 pathway. After it enters into the cell nucleus, STAT3 carries out regulation on genes that advance cell cycle and anti-apoptosis, therefore inhibiting apoptosis. In pancreatitis environment, STAT3 can produce synergistic effect with K-ras mutations to induce acinar cell dedifferentiation, resulting in loss of normal function but enhancement of proliferative ability [16]. In summary, the release of inflammatory factors tends to enhance the anti-apoptotic ability of tumor cells while selectively eliminating normal cells.

Conversely, inflammation can also be influenced by cell death. When cells experience unplanned or unregulated death, for instance necrosis, cellular contents are discharged to the outside of cells, forming death-related molecular patterns(DAMPs). Through pattern recognition receptors, innate immune cells such as macrophages can identify DAMPs, thus starting or enlarging inflammatory responses [17], and forming a positive feedback loop of damage-death-inflammation. Therefore, free fatty acids attack acinar cells, cause ischemia and necrosis, and worsen local inflammation [18].

In pancreatic cancer, inflammation and cell death construct a mutually promoting vicious cycle which drives each other. At first, inflammation arouses cell death, and DAMPs enlarge inflammatory reaction to cause damage to pancreatic tissue. Therefore, microenvironment alterations lead to cellular inflammation that makes proliferation and dedifferentiation become dominant, cell death that restrains apoptosis, and screening of mutant cells with proliferation potential; hence, this finally promotes cancer development and maintains its growth and metastasis [19]. Understanding this interaction mechanism provides new strategies for combined therapy. Therefore, curcumin can be applied to inhibit NF-κB signaling, so as to block the inflammation-driven oncogenic network from upstream; alternatively, we can develop STAT3 inhibitors, IL-6 antagonists and so on to cut off cancer initiation at inflammatory level and restrain pancreatic cancer progression [20].

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5. Summary and future perspectives

The occurrence and progression of pancreatic cancer are not only caused by gene mutations, but also closely related to the imbalance of cellular inflammatory response and programmed cell death. Inflammation shapes the immunosuppressive tumor microenvironment by releasing cytokines and chemokines, promoting the survival and proliferation of tumor cells; abnormal cell death releases DAMPs to amplify inflammation and continuously change the microenvironment. The two form a mutually reinforcing regulatory network, playing an important role in the occurrence, development and metastasis of tumors, and may therefore become an important breakthrough point for the treatment of pancreatic cancer [21]. However, current related studies are still mainly based on basic experiments and lack large-scale clinical sample verification; at the same time, the cell death pathway is complex and has extensive crosstalk, and the results of different research models vary greatly, which limits the stability and reproducibility of the mechanism conclusions. Future research needs to further analyze the key regulatory nodes of the inflammation-cell death axis, combine multi-omics technology and real-world clinical data, and clarify the functional characteristics and prognostic value of different inflammatory subtypes and cell death patterns in pancreatic cancer. At the same time, we should explore joint intervention strategies targeting inflammatory signals and cell death pathways, promote the establishment of a precision diagnosis and treatment system, and provide a new theoretical basis and translational direction for the early diagnosis and individualized treatment of pancreatic cancer.

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