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Hu D, Yu J, Wang MX, Zhang HL. Redefining therapeutic thresholds and global guidelines: Toward precision management of intermediate-sized rectal neuroendocrine tumors. *World J Gastroenterol* 2025; 31(44): 114263 [DOI: 10.3748/wjg.v31.i44.114263]

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ORIGINAL ARTICLE**Case Control Study**

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Randomized Controlled Trial

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Smirnova A, Eygel D, Kondrasheva I, Baranovskii DS, Klabukov ID. Peroxiredoxin 1 inhibits tumorigenesis by activating the NLR family pyrin domain containing 3/gasdermin D pathway: Advanced therapies targeting heterogeneous cell death mechanisms. *World J Gastroenterol* 2025; 31(44): 114404 [DOI: 10.3748/wjg.v31.i44.114404]

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Peroxiredoxin 1 inhibits tumorigenesis by activating the NLR family pyrin domain containing 3/gasdermin D pathway: Advanced therapies targeting heterogeneous cell death mechanisms

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Abstract

We read with great interest the advanced research article by He *et al*, which reported a marked upregulation of peroxiredoxin 1 mRNA and protein levels in colorectal cancer tissues. A central finding of this study was the demonstration of distinct heterogeneity in cell death mechanisms between normal and malignant cells. Current evidence indicates the existence of at least 12 subtypes of programmed cell death, each characterized by unique molecular signatures. The findings of this study have the potential to advance the development of personalized therapies that target cancer cells, representing a promising step forward in cancer treatment. Further advances in targeted mRNA therapy could be achieved by selectively shifting the regulation of cancer cells toward specific pathways of cellular death.

Key Words: Cancer; Cell death; Colorectal cancer; Extracellular matrix; Mechanotransduction; mRNA therapy; Programmed cell death; Pyroptosis; Tumor microenvironment

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Core Tip: The molecular patterns of the special types of programmed cell death, such as apoptosis, pyroptosis, ferroptosis, and necroptosis, in cancer cells caused by altered regulation, could improve the effectiveness of mRNA vaccines and targeted therapies by overcoming the barrier function of the tumor microenvironment. Activation of specific pathways to overcome the barrier function in cancer treatment represents a promising strategy for targeted cellular and gene therapies, and also enhances radiosensitivity in radiation therapy.

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TO THE EDITOR

We read with great interest the advanced research article by He *et al*[1], which reported a marked upregulation of peroxiredoxin 1 levels in colorectal cancer (CRC) tissues, and related this pattern effects on pyroptosis. A key finding of this study was the demonstration of distinct heterogeneity in cell death mechanisms between normal and malignant cells in CRC biopsy material. This cancer-related heterogeneity is not surprising overall, but the identification of special genes and regulation signatures offers significant value for developing targeted cancer treatments.

Specific pathways in cancer cell pyroptosis

The NLR family pyrin domain containing 3 (NLRP3)/gasdermin (GSDMD) pathway influences the tumor microenvironment by modulating cancer-associated fibroblasts and endothelial cells. This affects tumor progression and metastasis [1,2]. NLRP3-dependent signaling can initiate pyroptosis, which is a form of programmed cell death that leads to tumor suppression[3,4]. Current evidence indicates the existence of at least twelve distinct subtypes of programmed cellular death (*e.g.*, apoptosis, pyroptosis, ferroptosis, necroptosis), each characterized by unique molecular signatures[5]. The heterogeneity of cancer cell death can arise not only from intrinsic alterations in cancer cell regulation but also from secondary regulatory effects mediated by the tumor extracellular matrix (ECM)[6,7]. The NLRP3 inflammasome can be activated by both receptor signaling and mechanical stimuli resulting from ECM remodeling within the tumor microenvironment[8,9]. Therefore, altered cellular microenvironments and heterogeneous forms of cell death may serve as potential targets for precision cancer therapy.

The regulation of NLRP3 and subsequent pyroptosis are influenced by intracellular signaling, including several caspase/GSDM pathways that are directly involved in puncturing the cellular membrane. Cytokines and growth factors, such as interleukin 1 beta, as well as mitochondrial reactive oxygen species, are known to fuel NLRP3 activation[10]. Another approach is targeting to increase intracellular calcium levels, which trigger calcium flux, can also activate NLRP3, and this process is often dysregulated in cancer cells. Alterations in metabolism (*e.g.*, reactive oxygen species production from glycolysis) can also modulate the activation states of the NLRP3 inflammasome[11].

The NLRP3 inflammasome-based mechanisms in advanced cancer therapeutics could be realized by shifting cancer cell caspase/GSDM regulation or the activation of mediator release[12-14]. Shifting cancer cells toward pyroptotic cell death through NLRP3 activation may enhance the effectiveness of treatments like chimeric antigen receptor T-cell therapy, oncolytic viruses and neopeptidic mRNA vaccines[13,15]. In addition, pro-inflammatory cytokines released during pyroptosis can stimulate the immune response further, which may improve the efficacy of advanced therapies.

Therefore, the combination of specific cancer cell regulation and altered properties of the microenvironment in tumor tissues manifests as cancer-associated patterns. These patterns may be significant targets for NLRP3 inflammasome activation in cancer cells without affecting normal cells[16,17]. Activation of specific pathways to overcome the barrier function of the tumor microenvironment in cancer treatment represents a promising strategy for targeted cellular and molecular therapies, as well as for enhancing radiosensitivity in radiation therapy. Drug carriers like nanoparticles or antibody-conjugates that deliver NLRP3 activators or caspase/GSDM mediators specifically to tumor sites can enhance tissue-specific activation, and could also be considered as CAR T-cell therapy adjuvants for solid tumors. The selective uptake of these therapies by tumor cells is crucial for preserving the integrity of surrounding healthy cells.

CONCLUSION

The subtle differences in NLRP3 inflammasome-dependent regulation between cancer cells and normal cells may be key to developing therapeutics that can alter the fate of cancer cells by inducing specific forms of cell death or metabolic reprogramming. He *et al*'s findings have the potential to advance personalized therapies that selectively target cancer cells [1], representing a promising step forward in cancer treatment. Improving these strategies by targeting particular pathways of cellular death could be beneficial.

FOOTNOTES

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