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Mini Review

Pyroptosis in Cancer Cells and its Perspectives in Nanomedicine

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Abstract

Pyroptosis is a cell death mechanism that appears as an inflammatory form of cell death triggered by inflammasomes and disrupts a human protein encoded by the GSDMD gene in chromosome 8 (Gasdermin D) and by cytokine activation. Scientific facts have already indicated that the association between pyroptosis and cancer is extremely complicated, since pyroptosis´ effects on cancer cells can change depending on the affected tissues and genetic differences. For example, pyroptosis can inhibit tumor progress; however, as a pro-inflammatory process, it can create an appropriate microenvironment for tumor growth. Nevertheless, literature in this field has recently addressed important cancer treatment perspectives enabled by this process. The aim of the current study was to address a new nanomedicine aspect associated with pyroptosis.

Keywords: Pyroptosis, Cancer, *in vivo, in vitro,* Nanomedicine

Introduction

Pyroptosis is defined as an inflammatory form of programmed cell death that often happens upon cell infections caused by pathogens.[1] Pyroptosis is different from apoptosis and other programmed cell deaths due to Caspase-1 activation. This process starts when cells receive specific "death" messages and produce cytokines; then, these cells undergo a swelling process, burst and, finally, die. Deficient Caspase-1 expression may lead to inflammation-mediated tumor growth. Therefore, molecular Caspase-1 activation mechanisms in tumor tissues are yet to be substantially prospected.[2]

Caspase-1 is activated by a supramolecular complex called inflammasome (pyroptosome) during pyroptosis and mediates the maturation and release of interleukin-1 beta and interleukin-18.[3]

The most common studies on pyroptosis focus on investigating infections caused by intracellular pathogens associated with different diseases affecting the central nervous system[4]; and on analyzing a wide variety of nanoparticles capable of activating pyroptosome and of causing pyroptosis during elicited nanotoxicity.[5]

Cancer perspective

General aspects

As previously described, pyroptosis leads to gasdermin D (GSDMD) cleavage and induces IL-18 and IL-1β cytokine activation. Moreover, it has been associated with diseases such as diabetic nephropathy[6] and atherosclerosis.[7] Pyroptosis is regulated by non-coding RNAs and other molecules, and can influence tumor growth through cell proliferation, invasion and metastatic processes.[8]

Pyroptosis is associated with cancer in a complex manner, since it depends on specific tissues and genetic behavior. If, on one hand, pyroptosis can inhibit tumor progress[9], as proinflammatory death type, it can generate adequate microenvironment for tumor cell growth and development.[10] However, tumor pyroptosis enhancement can also be adoptedas cancer treatment strategy in some cases. Ibrahim et al.[11] observed reduced DFNA5/GSDME (non-syndromic hearing impairment protein 5)/Gasdermin-E) mRNA methylation expression levels in tumor cells in comparison to healthy cells, a fact that hindered pyroptosis activation in nearly all tumor cells.[11] A strategy adopted to treat malignant tumor lies on selecting adequate chemotherapeutic medicines based on DFNA5/GSDME expression levels, which can be upregulated in malignant cells in order to increase tumor sensitivity, and diminish its resistance, to chemotherapeutic medicines. Therefore, induced pyroptosis may play a major role in cancer treatment. According to Wei et al.[12], pyroptosis may play a dual role in enabling and inhibiting tumor cell growth in different malignant cell types. However, it is necessary to conduct further investigations about the specific mechanism of pyroptosis and its association with tumorigenesis. Many studies focused on investigating the effect of pyroptosis on cancer cases (i.e. hepatocellular carcinoma, pancreatic ductal adenocarcinoma, as well as breast, colon, skin, gastric, lung, cervical, Barrett's esophageal cancer).[13]

A recent study has pointed out the morphological and molecular aspects of pyroptosis, as well as its adjustment mechanism and potential role played in tumor cells.[14]

It is known that the complex molecular regulation of intrinsic signal-mediated death phenomena plays a key role in cancer cell transformation, invasion and growth, followed by metastasis, as well as in tumor response to cancer therapies[15-17] Pyroptosis, apoptosis and necroptosis are involved in cell-intrinsic death mechanisms.[18] Apoptosis has been investigated for a long time as the predominant form of regulated cell death; however apoptosis induction and enforcement are significant causes of treatment failure in cancer-related issues.[19-21] Then, based on a therapeutic perspective, it is essential using non-apoptotic mechanisms to overcome apoptosis disadvantages in cancer treatment. With respect to intrinsic cell death forms, important advancements achieved in recent years have changed the role played by pyroptosis in the treatment of different cancer types. The implication of pyroptotic pathways in tumorigenesis has been associated with gasdermin family members, mainly with gasdermin D (GSDMD) and gasdermin E (GSDME).[22,23]

Reduced GSDMD expression can significantly promote gastric cancer proliferation *in vivo* and *in vitro* [24]. However, increased GSDMD expression indicates poor prognosis in lung adenocarcinoma, but not in squamous cell carcinoma. This outcome shows that GSDMD (biomarker) could be used for independent prognostic of lung adenocarcinoma.[25]

In addition, pyroptosis-associated procedures were capable of improving cancer patients' results, whereas GSDME overexpression was associated with better prognosis in esophageal squamous cell carcinoma patients (ESCC) a fact that has significant impact on clinical practice.[26] According to Zhou et al.[27], GSDME mediates pyroptosis downstream the mitochondrial apoptotic pathway (ROS/JNK/Bax-or ROS/Tom/Bax), as well as caspase-3 and 9 activation in colon and melanoma cancer cells, respectively.[27]

As previously mentioned, GSDMD and GSDME were pointed out as two key pyroptosis substrates in programmed cell death.[23] However, the validity of this statement remains unclear.[22]

Significant CD147 upregulation was found in bladder cancer samples and cell strains; such expression was correlated to patients' survival. A study has found increased CD147 and GSDMD expression in bladder cancer patients presenting pyroptosis in comparison to healthy controls. This report has evidenced that CD147 may act on tumor proliferation by regulating GSDMD, which may likely act as biomarker and therapeutic target for bladder cancer treatment.[28]

The NLRP3 gene polymorphisms were associated with myeloma, melanoma and colorectal cancer for a long time. According to Poli et al.[29], inflammasomes play a key role in bladder cancer. The aforementioned authors have analyzed mRNA in the urine of human patients with, and without, bladder cancer in order to investigate the expression of inflammasome components, as well as of cytokeratin 20 mRNA (CK20 - urothelial differentiation marker), which is greatly expressed in bladder cancer patients.[30] Bladder cancer patients presented high NLRP3 and NLR family expression [comprising the caspase recruitment domain 4 (NLRC4)], as well as apoptosis inhibiting protein inflammasome. Increased NLRP3 gene expression was also observed in patients whose biopsy evidenced non-malignant inflammatory lesions in comparison to control patients. In spite of the NLRP3 and NLRC4 inflammasome mechanisms in early, or progressed, bladder cancer cases remain unknown, their expression appears to prevail and they likely fit as feasible diagnostic biomarkers.[31,32]

Nanomedicine

There are many reports in the nanomedicine field which have focused on explaining nanostructures' action in cancer cells based on pyroptotic processes. Some examples presented below address contexts where this possibility is applicable.

Recently, carbon nanotubes have been used for biomedical applications associated with cancer imaging and therapy. The DOX which is a well-known anticancer medicine, was added with glycoblock copolymers in multiwall carbon nanotubes (MWCNTs). Coated MWCNTs have shown that hybrid-CNTs in MCF-7 and MDA-MB-231 human breast cancer cell strains enabled efficient cellular internalization. Ozgen et al.[33] have evidenced hybrid-CNTs effectiveness as a biocompatible medicine delivery system for breast cancer therapy.[33]

Interestingly, although it was not addressed by Ozgen et al.[33], it is known that CNTs acting in cell cultures can induce NLR pyrin domain-containing protein 3 (NLRP3) inflammasome, which depends on pyroptosis in the primary culture of HBE cells (human bronchial epithelial cells).[34] Weaker nano glycoprotein non-metastatic melanoma protein B (GPNNB)interaction in the single-walled carbon nanohorn (SNH) group has induced lower nano-membrane interplay level, pyroptosis/apoptosis ratio, lysosome stress and hypotoxicity in macrophages than that observed for CNT groups (MWCTs, single-walled carbon nanohorn-SNH). These results make it clear that the morphology of nanocarbons played an important role in their activities.[35]

. Graphene Oxide (GO) hybrids were administered *in vivo* (rats) against Non-Muscle Invasive Bladder Cancer (NMIBC). Histopathology results have shown that hybrids have successfully reduced bladder cancer aggressiveness. The

GO hybrids have potentiated tumor aggressiveness (60%) reduction in animals who did not show signs of lesions. Immunohistochemistry results have shown that GO hybrids were capable of reducing VEGF expression; besides, increased endostatin levels and low p53 level were observed. These data have evidenced that GO hybrids reduced VEGF expression and have great potential to be used in NMIBC treatment. Studies about pyroptosis mechanisms are currently in progress.[36]

Indeed, long and rigid CNTs, as well as ultrathin GO sheets, can trigger NRLP3-dependent IL-1β release in human macrophages.[37] NLRP3 was also a biomarker of several nanostructures.[5]

Metallic nanoparticles are also likely involved in pyroptosis mechanisms. The anticancer action and mechanisms used by ZnO nanoparticles (nZnO) to change proteins in bladder cancer T24 cells (histone) based on low-dose exposure of nZnO have led to small nZnO concentrations in S-phase cell cycle arrest, favored late cell apoptosis, as well as suppressed cell invasion and transposition after 48 exposure hours. This anticancer activity could be likely attributed to increased RUNX3 levels deriving from reduced H3K27me3 use in the RUNX3 protein, as well as to decreased amounts of histone methyltransferase EZH2 and to histone H3K27 trimethylation.[38]

Interestingly, Song et al.[39] reported that A549 cells exposed to zinc oxide nanoparticles for 8 hours have recorded increased caspase-1 and interleukin-1 beta levels, whereas cells exposed to these nanoparticles for 24 hours effectively presented high interleukin 1 beta levels.

Similarly, female C57BL/6Junib mice with NMIBC, who were treated with biogenic silver nanoparticles (AgNPs), recorded 57.1% tumor regression, 14.3% normal urothelium and 42.9% flat hyperplasia, which is acknowledged as a benign lesion. These outcomes have indicated dose-time dependent cytotoxicity. Cell death induction via feasible apoptosis has been suggested in this case.[40] However, it was previously demonstrated that AgNPs induced pyroptosome formation in THP-1 (human monocyte cells) and up-regulated caspase-1 expression, which indicated the emergence of pyroptosis in THP-1 cells rather than apoptosis.[41]

Chitosan has flexible biomedical applications in bladder cells because it is capable of momentarily inhibiting the barrier function of the urothelium and, therefore, of enabling the efficient penetration of anticancer drugs in deep cell layers. Biomaterials such as chitosan have a wide potential to be used in association with cytostatic and immunotherapy in clinical studies about bladder tumor treatments. Besides, it can be used as an adjuvant antimicrobial drug to treat urinary tract infections.[42]

Although it was not addressed in the study by Erman and Veranic[42], lower chitosan concentrations have increased NLRP3 inflammasome activation and mediated interleukin-1 beta release.[43]

The DOX was incorporated into GO. With respect to siRNA release, GO was associated with cationic Polyethyleneimine (PEI) by covalent bond and, then, RNA was added to it by complexation. Systems were administered (intraperitoneal route) *in vivo* in order to investigate their antitumor action in bladder cancer cases (NMIBC). This association was a highly promising procedure to be adopted in NMIBC treatment and inhibited the emergence of lesions in the assessed animals (60 %). This outcome is of paramount importance for the Onco-urology field. Some evidence of pyroptosis in the above study was observed.[44]

Interesting results reported in the literature have pointed out that intraperitoneal PEI administration was capable of activating NLRP3 inflammasome, which was followed by caspase-1 split through pyroptosis *in vivo*.[45] Again, the nanostructured systems described above appear as good candidates for pyroptotic mechanisms.

It was found that decoration of polystyrene nanoparticles with amino groups (PolyS-NH2)(amino-functionalized polystyrene) lead to G2 cell cycle arrest and restrict its proliferation in human monocytic leukemia cell lines THP-1 and U-937, as well as in promyelocytic cell line HL-60. Furthermore, PolyS-NH2 reduces angiogenesis and the proliferation of leukemia cell xenografts towards the chick chorioallantoic membrane. At the molecular mechanistic view, PolyS-NH2 suppresses mTOR signaling in THP-1 and U-937 leukemia cells.[46] It is known that amino-functionalized polystyrene nanoparticles in human macrophages can activate NLRP3 inflammasome and trigger interleukin-1 beta release in a more efficient way than carboxyl- and non-functionalized nanoparticles.[47]

The effect of Nanostructured Lipid Carrier (NLC) loaded with DOX on NMIBC was investigated. Based on histopathology analyses applied to rats subjected to NLC/siRNA applications (siRNA targeting vascular endothelial growth factor (VEGF)), 40% of animals presented benign lesions (papillary hyperplasia), whereas 60% of them had malignant lesions. However, 20% of malignant lesions were papillary carcinoma *in situ* (pTis), whereas 40% of them were low-grade papillary carcinoma (pTa). Thus, NLC/siRNA/DOX appears to be an excellent anticancer nanocarrier with very low toxicity *in vivo*.[48] A probable mechanism adopted by these lipid-structure nanoparticles lies on the fact that they can trigger neutrophil extracellular traps (NETs)[49]. However, suitable evidence has not yet been presented due to difficulty in differentiating neutrophil cell death with (passive) intracellular content release from NTEs generation.[37] NETs are a mix of meshwork chromatin fibers and granule-derived extracellular

antimicrobial enzymes and peptides that in general act through trapping and killing bacteria. It is believed that NETs induce macrophage (Mϕ) pyroptosis.

Accordingly, NET-derived high-mobility group box 1 (HMGB1), which is a highly conserved nuclear protein operating over advanced glycation end-product (RAGE) and dynamin-dependent signaling receptors, gives rise to an intra-Mϕ cascade of molecular occurrence including cathepsin B (CatB) release from broken lysosomes, followed by pyroptosome generation and caspase-1 activation and, subsequently, by Mϕ pyroptosis.[50]

Conclusion

Based on the current mini review, it has been observed that many studies involved with a pyroptotic process have been ignored compared to apoptosis and necrosis mechanism of cell death. It is also clear that we should pay more attention to this type of mechanism, since it could significantly help in preventing and monitoring new cancer treatment systems.

Ethical Approval

It is not applied.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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