Editorial

Pyroptosis-related signatures in bladder cancer prognosis and treatment—are we there yet?

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Cell death is a crucial biological event that functions as defense machinery that is required for homeostasis. Pyroptosis is a type of inflammatory programmed cell death mechanism, discovered about 30 years ago (1). The main executors of pyroptosis belong to gasdermin family (2). One of the representatives that forms pores, gasdermin D, must be cleaved and activated by inflammatory caspases so that the cell can undergo pyroptosis. The physical rupture results in the production of pro-inflammatory cytokines such as interleukins, alarmins, and endogenous danger-associated molecular patterns (3,4). It is therefore not surprising that pyroptosis has been widely studied in cancer immunotherapy (5). Literature data suggest that pyroptosis influences various tumors in different ways; either it can stall the cancer cells growth (exhibiting anti-tumor activity) (6) or produce inflammatory component during scorch death, activating pro-inflammatory cytokines that provide a tumor microenvironment (TME) for proper growth (7). Evidence indicates that cytokines that are released during pyroptosis, e.g., HMGB1, IL-1β, and IL-18, could influence the TME (8). Dynamic and reciprocal link exists between cancer (or cancer-associated) cells and components of the TME, influencing cancer cell survival, local invasion, and metastasis. For example, representatives of immune cells (being a critical cellular component of TME) are neutrophils which can either suppress tumor formation via production of reactive oxygen species (in anti-cancer microenvironment) or promote tumorigenesis via release of matrix metalloproteinase-9 and vascular endothelial growth factor (in immune suppressive microenvironment) (9).

The advancement in genomics and transcriptomics allowed to investigate the molecular properties of tumors and identify their clinical significance. This has resulted in a plethora of prognostic and predictive gene expression profiles that have the potential to be used in developing a classification of tumor subgroups based on biological factors. However, only a few gene signatures have progressed to the point where they may be used in clinical setting (10). In terms of e.g., bladder cancer (BLCA), existing treatments are scarce because relapse and metastasis hinder clinical management and shorten patients' survival (11). The approval of immune checkpoint inhibitors has improved these aspects but their beneficial effect is limited to certain muscle invasive BLCA subtypes (12). Thus, it is important to seek gene signatures that could guide clinical treatment, especially regarding targeted therapy and immunotherapy. In light of the present circumstances, we read with enthusiasm the manuscript "*Identification of a pyroptosis related gene signature for predicting prognosis and estimating tumor immune microenvironment in bladder cancer*" by Zhao *et al.* (13).

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The authors underlined that the exact function of pyroptosis in BLCA remains unclear and thus they aimed to investigate the impact of pyroptosis-related genes (PRGs) on BLCA prognosis and TME. Using RNA-Seq data of 411 bladder tumor samples and 19 corresponding normal tissues, the impact of 39 PRGs (identified through literature data) was determined. The clinical features included the age at diagnosis, patients' gender, tumor grade and clinical stage. The paper focused on exploring the cellular pathways, tumor mutation burden (TMB) and infiltration level of immune cells. Fifteen genes (*HMGB1*, *GPX4*, *PLCG1*, *GSDMD*, *CASP8*, *CASP3*, *BAK1*, *PYCARD*, *BAX*, *GSDMB*, *CASP6*, *NLRP2*, *AIM2*, *CASP5* and *NLRP7*) were up-regulated while four genes (*ELANE*, *IL6*, *NLRP3* and *NLRP1*) were down-regulated in tumor samples compared to normal tissues. From another point of view, *AIM2*, *CASP6*, *CASP8*, *CASP9*, *GSDMB*, *GZMA*, *GZMB* and *IRF1* were found to have significant impact on improving overall survival (OS) of BLCA patients. The last two genes were further excluded from risk signature based on Cox regression analysis. According to the median value of risk score, the BLCA samples were classified into low- and high-risk groups. Significant correlations were noted between increasing age or higher clinical stage and high-risk score i.e., group of patients having lower expression of *AIM2*, *CASP6*, *CASP8*, *CASP9*, *GSDMB*, *GZMA*. Based on functional annotation, the processes or pathways which distinguished two risk groups included the regulation of e.g., extracellular matrix organization, focal adhesion, glycosaminoglycan biosynthesis or retinoic acid-inducible gene I (RIG-I)-like receptor signaling pathway. TMB was found elevated in low-risk group with the top 5 highest mutation frequencies being *TP53*, *TTN*, *KMT2D*, *MUC16* and *ARID1A*. Regarding the immune cell infiltration, the high-risk group had less $CD8^+$ and $CD4^+$ T cells infiltration and more anti-inflammatory M2 macrophages compared to low-risk group, which could explain the worse clinical prognosis. Ultimately, analysis of TME and immune activity certified that the immune functions related to pyroptosis might be more active in low-risk score group.

Discussing the findings of this study, Zhao *et al.* suggested that the PRGs could be considered as protective factors in BLCA patients, referencing to the similar observations in ovarian cancer or melanoma (14,15). However, literature on pyroptosis in BLCA is not without contrasting results. He *et al.* (16) reported that the gasdermin B expression was lower in normal urothelium compared to BLCA, while its overexpression facilitated tumor progression via interaction with STAT3 and glycolysis enhancement in BLCA. Nevertheless, the fact that both the reduced amount of M2 macrophages and increased infiltration level of $CD4^+$ and $CD8^+$ T cells are related to poor prognosis (6), have been successfully certified by Zhao *et al.* findings.

Regarding future perspectives, the authors admitted that the data were obtained from public repository (The Cancer Genome Atlas; TCGA) while conducting further research on larger scale will undoubtedly strengthen the conclusions. Not only verification of findings using independent public cohort, but also recruitment of patients should be pursued in the future. Another point raised by Zhao *et al.* was that definitive functions of PRGs in BLCA still require further experiments. Indeed, mechanistic explanation will be of scientific interest, especially for therapy. What can also be suggested is that the authors could delve into more than the 39 genes that were identified through literature data; these genes were described in glioblastoma and ovarian or gastric cancers (15,17,18). As mentioned above, pyroptosis influences various tumors in different ways and thus some genes important for BLCA might have been inadvertently omitted. This of course does not detract the relevance of *AIM2*, *CASP6*, *CASP8*, *CASP9*, *GSDMB*, *GZMA* signature which will be of immense use in further research. Additionally, more clinical parameters and tumor heterogeneity could be considered when investigating this field. One could also analyze the relation to prognosis using disease-free survival (DFS) data, not just OS. Events caused by disease recurrence occur earlier than death from the disease and moreover DFS also include tumors that do not necessarily lead to death, which are not included in OS (19). Nonetheless, the study by Zhao *et al.* provided us the novel insights into pyroptosis in BLCA using solid methodology which include e.g., ESTIMATE (abbreviation of "Estimation of Stromal and Immune cells in Malignant Tumors using Expression data") score. Recently, we employed this scoring to identify new glioblastoma biomarkers (20). Although there is still much more to be explored in this field, such research is always a step forward. The inclusion of pyroptosis-related signatures in the forthcoming strategies of BLCA treatment is highly preferred and could also help in patients' stratification.

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Footnote

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