

Reviewer 1:

This editorial provides a clear, logically structured, and well-written commentary that offers a comprehensive and insightful interpretation of the study by He et al. The author adeptly captures the dual role of Prdx1 in cancer including intracellular antioxidant protection versus extracellular DAMP inducing pyroptosis, and effectively contextualizes it within the complexity of the tumor immune microenvironment, highlighting the study's translational potential and challenges. The manuscript possesses significant academic value and is thought-provoking. This manuscript possesses several notable strengths: it addresses a timely and significant topic at the forefront of pyroptosis and cancer immunotherapy, grounded in timely, clinically relevant research. The author delivers a critical and in-depth analysis that moves beyond summary to rigorously evaluate mechanistic insights, experimental models, and clinical correlations. Its structure is clear and logical, seamlessly guiding the reader from background to future directions. The writing is precise, especially in explaining complex pathways like NLRP3/Caspase-1/GSDMD with admirable clarity. Most importantly, the editorial demonstrates sharp critical thinking by pinpointing key limitations, such as the unidentified receptor and model heterogeneity, and proposing concrete, actionable steps for future investigation.

Response: The author would like to thank the reviewer for appreciating this editorial.

It is recommended for publication after minor revisions, as detailed below:

Comment 1. Some sections could be more concise. For instance, the comparison of different cell death modalities in the "PYROPTOSIS" section could be slightly condensed to avoid repetition. Correspondingly, suggestions in the "FUTURE DIRECTIONS" could be more specific. For example, the idea of combining rPrdx1 with immune checkpoint blockade should mention

specific targets, such as PD-1/PD-L1 inhibitors, to provide a more concrete research direction.

Response: In the revised editorial we have removed few sentences to condense the "PYROPTOSIS" section to avoid repetition.

Comment 2: Consistency in reference formatting requires attention. For example, the year "202M4" in Reference 8 should be corrected to "2024". Journal name abbreviations should be unified according to PubMed standards.

Response: Thank you for pointing out the mistake. In the revised editorial, we have corrected it, and the journal name abbreviations have been unified according to PubMed standards.

Comment 3: The discussion could be enhanced by briefly mentioning other well-known DAMPs (e.g., HMGB1, ATP) and their roles in CRC when introducing Prdx1 as a DAMP, thus strengthening contextual links. The "CONCLUSION" could further emphasize the potential of "precision pyroptosis therapy" in personalized medicine, resonating with the "biomarker-driven" theme.

Response: In the revised discussion, we have included information about other well-known DAMPs (e.g., HMGB1, ATP) and their roles in CRC. The conclusion section has also been modified to incorporate the potential of "precision pyroptosis therapy" in personalized medicine and the "biomarker-driven" theme.

Comment 4: The manuscript alternates between "rPrdx1" and "recombinant Prdx1". It is recommended to consistently use the abbreviated form "rPrdx1" throughout the text for uniformity.

Response: The main reason is that, in the initial sections, we consistently used "Prdx1" instead of "Peroxiredoxin 1." However, since the authors He et al. used recombinant Prdx1, we referred to it as "rPrdx1" whenever discussing their findings and replaced all instances of "recombinant Prdx1" in the article with "rPrdx1." We continued to use "Prdx1" to denote "Peroxiredoxin 1."

Reviewer 2:

This editorial summarised the study performed by He et al. (World J Gastroenterol 2025; 31(36):111557) which identifies a novel mechanism by which peroxiredoxin 1 (Prdx1) inhibits CRC progression through induction of pyroptosis, a pro-inflammatory form of programmed cell death. Traditionally viewed as an intracellular antioxidant that protects tumors from oxidative stress, Prdx1 assumes a paradoxical immunogenic role when released extracellularly as a damage-associated molecular pattern (DAMP). Using patient samples, recombinant protein assays, and murine xenograft models, the authors demonstrate that Prdx1 activates the NLRP3 inflammasome/Caspase-1/GSDMD pathway, triggering membrane pore formation, tumor cell lysis, and release of IL-1 β /IL-18. This cascade not only halts tumor proliferation, invasion, and migration but may also enhance anti-tumor immune surveillance. The study's strengths include rigorous mechanistic validation, clinical cohort data, inhibitor-based causal proof, and in vivo confirmation. However, questions remain regarding the upstream receptor for Prdx1, heterogeneity across CRC subtypes, and the balance between therapeutic benefit and inflammatory toxicity. By establishing Prdx1-

induced pyroptosis as a driver of tumor suppression, this work advances a promising paradigm in CRC therapy, linking cell death to immune activation and pointing toward future biomarker-driven, pyroptosis-based interventions. This editorial provides a concise summary of the article and effectively identifies specific shortcomings, such as: the absence of clarity regarding the cell-surface receptor mediating Prdx1 recognition in CRC. While activation of the NLRP3 inflammasome and downstream Caspase-1/GSDMD is firmly established, the initial trigger remains undefined. Past literature implicates TLR4 as a plausible mediator in macrophages, but it remains unproven in epithelial cancer cells. Identifying this receptor will be essential to design targeted strategies that selectively exploit Prdx1's pyroptotic function. Another limitation is the restricted spectrum of tested cell lines. Only three CRC models were studied, with robust effects observed in RKO and SW480 cells but not in HCT116. This editorial also looks forward to the prospects of this research field, and I believe it can effectively help readers understand the article and related issues.

Response: The author would like to thank the reviewer for the critical evaluation of the editorial article and for recommending it for acceptance.

Re-review report of revised manuscript

Specific comments to authors

This editorial provides a comprehensive, insightful, and critical commentary on the study by He et al. concerning Peroxiredoxin 1 (Prdx1) inhibiting colorectal cancer through the induction of pyroptosis. The author clearly elucidates the dual role of Prdx1 in cancer (intracellular antioxidant vs. extracellular DAMP) and offers a detailed analysis of the mechanistic findings, strengths, and limitations of the He et al. study, while also proposing forward-looking future research directions. The topic is cutting-edge, the logical structure is sound, the language is fluent, and the manuscript holds significant academic value and is thought-provoking. Following the previous

round of revisions, the author has adequately addressed and incorporated the reviewers' suggestions: the "PYROPTOSIS" section has been condensed to avoid repetition in comparing different cell death modalities; reference formatting errors (e.g., the year "202M4") have been corrected, with a commitment to standardizing journal abbreviations; a paragraph discussing other well-known DAMPs like HMGB1 and ATP and their roles in CRC has been added to the "STRENGTHS AND LIMITATIONS" section, strengthening contextual links; and "recombinant Prdx1" has been consistently replaced with "rPrdx1" to maintain terminology uniformity.

Specific details requiring the author's further attention before final submission primarily involve formatting norms are as follows:

1. Manuscript title: According to Item 3 of the Checklist for Authors, except for the first word, all other words should be in lowercase. In the current title "Peroxiredoxin 1, Pyroptosis, and the Emerging Frontier in Colorectal Cancer Therapy", the words "Pyroptosis", "Emerging", "Frontier", "Colorectal", "Cancer", and "Therapy" are capitalized. It is recommended to revise it to: "Peroxiredoxin 1, pyroptosis, and the emerging frontier in colorectal cancer therapy".

Response: While revising the editorial, I have taken care of the suggestions.

2. Author contributions: According to Item 8 of the Checklist for Authors and the Science Editor's comments, the format of the 'Author contributions' description needs adjustment. The format "full family (sur)name, followed by abbreviated first and middle names" should be used. For example, "Dharmendra Kumar Maurya" should be written as "Maurya DK". It is recommended to revise to: "Maurya DK performed the review of literature and wrote the editorial."

Response: While revising the editorial, I have taken care of the suggestions.

3. Key words: According to Item 13 of the Checklist for Authors, 5-10 keywords are recommended. Currently, there are only 4. Consider adding 1-2 more, such as "NLRP3 inflammasome" or "Immunogenic cell death", to better cover the core content of the article.

Response: In the revised version of the editorial, I have added the keyword “Immunogenic cell death” to make the total number of keywords five.

4. References: The core article discussed in this editorial (He et al. World J Gastroenterol 2025; 31(36): 111557) needs to be formally added to the reference list and cited with the corresponding reference number in the main text (e.g., in the Introduction, Discussion sections). Additionally, as per Item 23 of the Checklist for Authors, use the "Auto-Analyser" tool for final proofreading and formatting of all references to ensure accurate PMID and DOI information, complete author lists, and fully unified formatting.

Response: I agree with the reviewer. However, when I tried to add the same, the “Auto-Analyser” tool did not accept it because the reference (He et al., World J Gastroenterol 2025; 31(36): 111557) was not recognized by the tool. I believe this can be included from the journal’s side. In the revised editorial it is reference no. 8.

5. Other formatting items: According to the Checklist for Authors, ensure that the format of sections like "Received/Revised" dates, the Open-Access statement, and the Specialty type complies with the journal's requirements.

Response: I have taken care of the same in the revised editorial.