Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

19th March 2023

Dear Li Ma,

We would like to thank you as Editor and the reviewer's for their comments and time in reviewing our paper. We have addressed the comments below.

It is not clear to me how much of the HMGB1 would retain on the cell surface and if the cell surface-retained HMGB1 is also a good DAMP indicator? As the authors cannot go back to analyze the released HMGB1 for this study, the authors need to discuss the issue with some previous studies (papers) to support their assumptions. One minor point: The following existing references need correct or additional information: Ref #4. Article number (AN)? Ref #18. AN? Ref #27. AN?

This is an excellent and thought-provoking point. Unfortunately, there is a paucity of data to address this question and the relationship of HMGB1 to the immune system is a fluid one with the majority of studies to date demonstrating dual pro-and anti-tumourigenic properties.
It is involved in various intracellular (eg, chromatin remodeling, transcription, autophagy) and extracellular (inflammation, autoimmunity) processes with paradoxical and conflicting results in the literature and it is still unclear whether HMGB1 mainly acts as an oncogene or a tumour suppressor (1). Mechanistically, intracellular HMGB1 induces radiation tolerance in tumour cells by promoting DNA damage repair and autophagy. Extracellular HMGB1 plays a more intricate role in radiation-related immune responses, wherein it not only stimulates the anti-tumour immune response by facilitating the recognition of dying tumour cells but is also involved in maintaining immunosuppression. Factors that potentially affect the role of HMGB1 such as chemotherapy or chemoradiotherapy in the context of oesophageal adenocarcinoma (OAC) may also have a role in the context of possible therapeutic applications, to develop effective and targeted radio-sensitization therapies (2).
A sentinel study also demonstrated that suppression of dendritic cells by HMGB1 is associated with lymph node metastasis of human colon cancer. The 8 nodal metastasis-positive cases showed higher nodal HMGB1 concentrations in lymph node tissues and lower CD205-positive nodal dendritic cell numbers than those in the 8 metastasis-negative cases (3). Furthermore, soluble HMGB1 is a promising biomarker for prediction of therapy response and prognosis in advanced NSCLC patients with high concentrations of HMGB1 at cycles 2 and 3 associated with shorter overall survival in NSCLC patients (4).
As alluded to in the paper this is novel due to this being the first paper to specifically look at DAMP expression by T cells in OAC patients in the context of conventional therapeutic strategies. Based on these papers and our own data, we extrapolate that HMGB1 will function as a biomarker of disease biology and proxy of treatment response in the future.

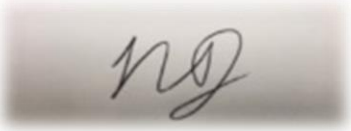
We have updated the references as requested.

References

1. Hubert P, Roncarati P, Demoulin S, Pilard C, Ancion M, Reynders C, et al. Extracellular HMGB1 blockade inhibits tumor growth through profoundly remodeling immune microenvironment and enhances checkpoint inhibitor-based immunotherapy. J Immunother Cancer. 2021;9(3).
2. Liao Y, Liu S, Fu S, Wu J. HMGB1 in Radiotherapy: A Two Headed Signal Regulating Tumor Radiosensitivity and Immunity. Onco Targets Ther. 2020;13:6859-71.
3. Kusume A, Sasahira T, Luo Y, Isobe M, Nakagawa N, Tatsumoto N, et al. Suppression of dendritic cells by HMGB1 is associated with lymph node metastasis of human colon cancer. Pathobiology. 2009;76(4):155-62.
4. Handke NA, Rupp ABA, Trimpop N, von Pawel J, Holdenrieder S. Soluble High Mobility Group Box 1 (HMGB1) Is a Promising Biomarker for Prediction of Therapy Response and Prognosis in Advanced Lung Cancer Patients. Diagnostics (Basel). 2021;11(2).

We hoped we have adequately addressed the reviewer's comments and we look forward to hearing from you.

Yours sincerely



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