Some reflections on Engineering T cell response to cancer antigens by choice of focal therapeutic conditions

To the Editor,

We have recently read the article by Shao et al. [1] titled ‘Engineering T cell response to cancer antigens by choice of focal therapeutic conditions’ and are interested in it.

In recent years, we have witnessed great advances in immunotherapy. A few clinical trials exploring the effects of the combination of immune checkpoint blockades (e.g., anti-PD-1, anti-CTLA-4) and the local therapy have been conducted and have had some success. To acquire an ideal therapeutic effect, a deeper understanding of the immune mechanism of the local therapy and strategy choices across various focal therapeutic conditions and immune blockades is necessary.

In this research, Shao et al. compared the effects of three different focal therapies, namely cryosurgery (Cryo), thermal therapy (Heat), and irreversible electroporation (IRE), on triggering antigen release and T-cell response. They found that Cryo led to a more prominent antigen release and a greater T-cell response than those by Heat and IRE. Also, the author suggested an intriguing point that both “quality” (i.e., physiochemical conditions) and “quantity” (i.e., amount) of protein released from the tumor matters in inducing the T-cell response. The results of this study may guide future research and the conclusions thereby need to be validated empirically.

A few other studies [2,3] have reported that Cryo induced a remarkably higher post-ablative immune response than those by radiofrequency and microwave ablation, which was indicated by a higher expression of pro-inflammatory cytokines including IL-1, TNF-a, and IL-6. In case of melanoma, accumulation of DCs (Dendritic cells, DCs) increased more after Cryo than after Heat [4]. In addition, Cryo can lead to a more robust MHC class I CD8+ cytotoxic anti-cancer response, demonstrating that Cryo can change antigen presentation and the cytokine profile [5]. Thus, compared to radiation, Cryo tends to provide a higher level of self-antigens into circulation, which was consistent with the results of the in vitro experiment in this study. Despite the higher immune reaction elicited by Cryo, Liu et al. also pointed out that the combination of DC vaccine and Heat can cause greater antitumor immunogenicity and significantly reduce the recurrence of melanoma [6]. Heat can lead to local inflammation featuring a dense T-cell infiltrate, indicating that a heat shock and necrotic cell death results in immune activation and presentation of antigens [7]. Studies have shown that either Cryo or Heat provided DCs with antigens during tumor destruction in vivo, and both were able to facilitate DC maturation in vivo [4]. When combined with DC vaccine, although it seemed that radiofrequency ablation showed a lower efficiency in loading DC compared to Cryo, it efficiently enhanced immune modulation. We believe that manipulation of the immune response caused by thermal ablation cannot be ignored.

Additionally, one question regarding the conclusion of this study should be noted. Haggerty et al. [8] pointed out that heat shock protein (HSP) inhibitors could increase the expression of TRP-2 (Tyrosinase Related Protein 2, TRP-2), a specific antigen expressed by melanoma, which was considered as an indicator of antigen release. Hence, it was undetermined whether the decreased antigen release was due to Heat itself or HSP indirectly. Given that the heat shock response inside the tumor can influence some antigen expression, we suggest that others might measure certain antigens expressing independently of the HSP response, which would make the results more convincing.

Finally, we believe that the immune mechanism of different local therapies is highly complicated and more measurements and a strict study design should be considered during research. In addition, the mechanism of heat triggering immunogenicity should also be elucidated.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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