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MHC II NEOANTIGEN VACCINES IMPROVE ANTITUMOR IMMUNITY AND RESPONSE TO IMMUNE CHECKPOINT INHIBITOR IN COLD TUMOR

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Background Cold tumor is one of the most refractory solid tumors and experience dismal response to immune checkpoint blockade (ICBs). Most therapeutic vaccines provided prerequisite for ICBs by priming tumor specific CD8⁺ T cells but failed to meet satisfactory efficacy due to highly inhibitory tumor microenvironment (TME). Recently, activated CD4⁺ T cells were proved to assist the priming of CD8⁺ T cell and regulate TME. Therapeutic vaccines targeting MHC II neoantigens are expected to mobilize CD4⁺ T cell response. However, the role and mechanism of MHC II neoantigen vaccines in tumors are largely unknown. Here, we aimed to reveal the effect of MHC II neoantigen vaccines on cold TME and its synergistic antitumor efficacy with ICBs.

Methods Flow cytometry, immunohistochemistry and single cell RNA sequencing (scRNA-seq) was performed to analyze the phenotypic, functional, and intercellular interactions of immune cells. Cell communication analyses were performed to screen the most significantly changed immune checkpoint signaling axis after treating the vaccines. In vivo tumor inhibition experiment in mouse model was used to estimate the efficacy of the combination therapy.

Results The inoculation of vaccines improved the quantity and quality of T cell response in draining lymph nodes, which includes the polarization of CD4⁺ T cell to Th1 cell, the increase of CD8⁺ T cell proportion and cytokine secretion (IFN γ , etc.), the differentiation of CD8⁺ T cell to effect and memory subtypes. As for TME, the infiltration and effect of T cells were significantly improved as well. Furthermore, the vaccines promoted the transformation of DCs and macrophages to inflamed phenotype. However, scRNA-seq assay showed the inhibitory immune checkpoint signaling axis was significantly enriched after vaccine inoculation, which mainly hampered the proliferation and effector function of Th1 cells and effector memory CD8⁺ T cells. As a result, the combination therapy of MHC II neoantigen vaccines and ICB exhibited the best anti-tumor efficacy than monotherapy group. Mechanistically, we found that the combination therapy enhanced the tumor-killing function of neoantigen-specific CD4⁺ T cells, expanded the proportion of proliferative T cells, and promoted the differentiation of CD8⁺ T cells into effector and memory phenotypes while delaying the exhausted process.

Conclusions We first found that MHC II neoantigen vaccines could remodel the inhibitory tumor microenvironment with insufficient T cell infiltration. The combination therapy of MHC II neoantigen vaccine and ICB exhibits a synergistic anti-tumor efficacy by enhancing T cell response. Our combination strategy provides a new idea for the treatment of cold tumors.

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Ethics Approval All animal experiments were approved by the Animal Care and Use Committee of Drum Tower Hospital, Nanjing, Jiangsu, China (approval number: 2021AE01018).

Consent A copy of the written consent is available for review by the Editor of this journal.

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