Blocking Histamine Receptor H1 on Macrophages with Anti-Allergy Drugs Restores T-cell Anti-Tumor Immunity

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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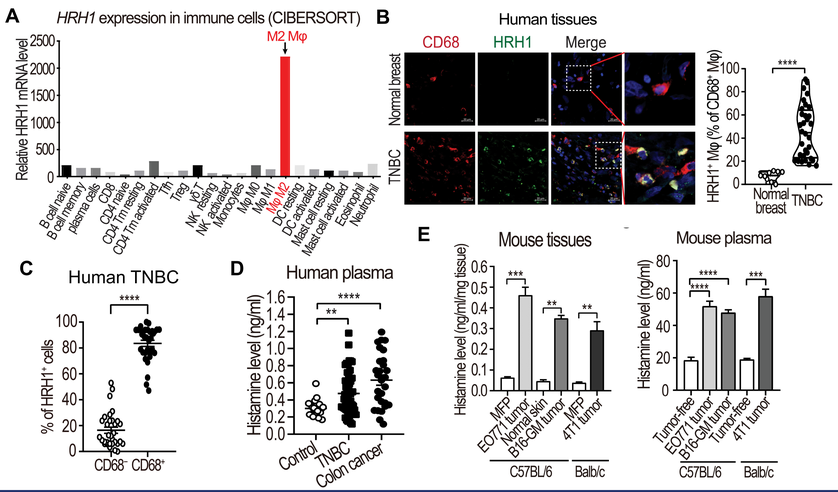
ABSTRACT

CD8⁺ T lymphocytes in tumors often become dysfunctional, prompting cancer immune escape and immunotherapy resistance. Restoring T-cell anti-tumor immunity remains an unmet challenge. Here, we show that histamine receptor H1 (HRH1) is highly expressed and tightly associated with T-cell dysfunction in human cancers. Histamine, the HRH1 ligand, is also increased in human and mouse tumors. HRH1 is predominantly expressed on tumor-associated macrophages (TAMs) and is activated by cancer cell-secreted histamine. The histamine/HRH1 axis in TAMs confers CD8⁺ T-cell dysfunction via increasing membrane localization of V-domain Ig suppressor of T cell activation (VISTA), an inhibitory immune checkpoint that promotes immunotherapy resistance. Blocking HRH1, genetically, or by anti-allergy drugs, reversed immunosuppressive TAMs, activated T-cells, and inhibited tumor growth in vivo. HRH1-targeting anti-allergy drugs more efficaciously enhanced immunotherapy response than anti-VISTA antibodies. Markedly, allergy-induced histamine also activates HRH1 on macrophages to induce T-cell dysfunction and immunotherapy resistance, which were reversed by the over-the-counter anti-allergy drug. Taken together, tumor cell-derived and allergy-released histamines activate HRH1 on TAMs to concede immunosuppression, pro-tumor function, and immunotherapy resistance, which can be negated by inexpensive and safer anti-allergy drugs.

RESULTS

Figure 1. Increased histamine levels and up-regulated HRH1 expression in tumor associated macrophages (TAMs) were detected in human and mouse tumors.



RESULTS

Figure 2. Knockout HRH1 or blockade of HRH1 by anti-allergy drug fexofenadine (FEXO) led to M1-polarized macrophages, activated T-cells, and inhibited tumor growth in immunocompetent mice.

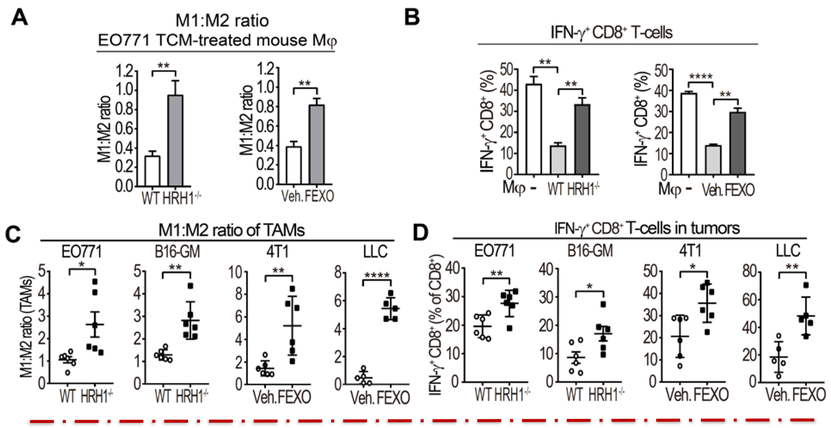


Figure 3. Knockout HRH1 changed tumor microenvironment landscape.

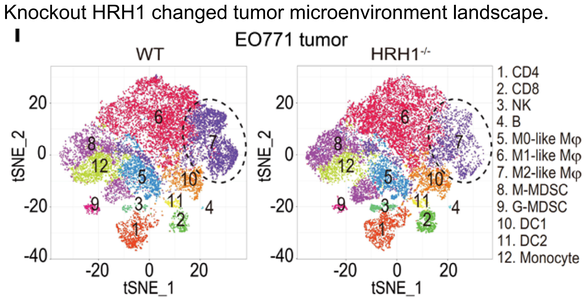


Figure 4. HRH1 knockout reshapes the transcriptomic landscape of macrophages.

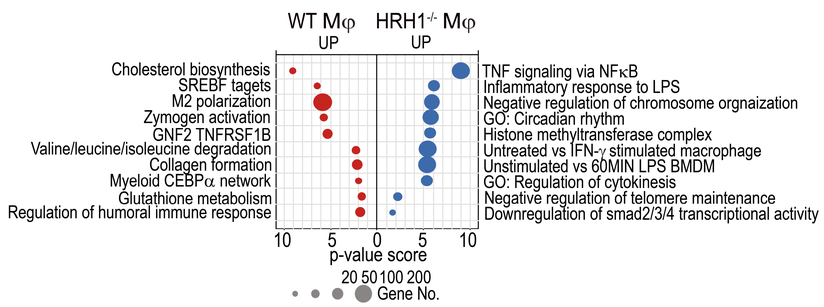
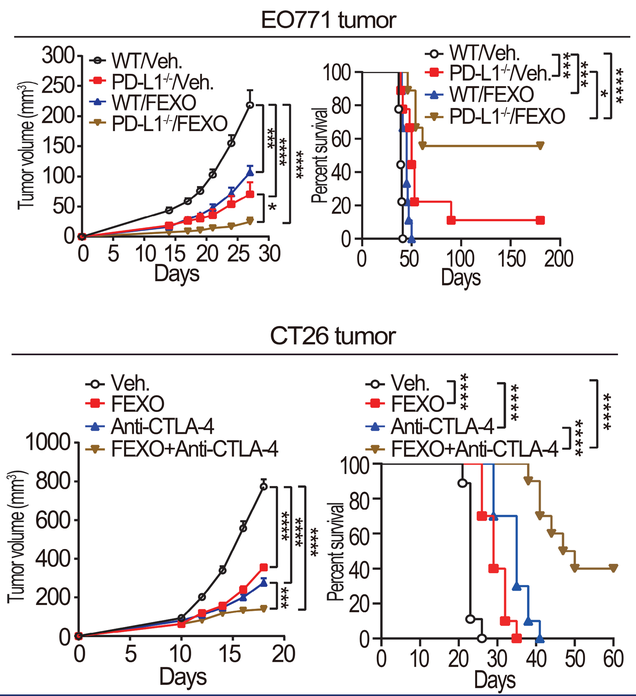


Figure 5. Blockade of HRH1 by FEXO enhanced immunotherapeutic efficacy and significantly prolonged survival in mouse tumor models.



CONCLUSIONS

- In this study, we identified that HRH1, as the major target of histamine, was predominantly expressed on macrophages, but not cancer cells, in both mouse and human. Functionally, we uncovered that activation of the histamine/HRH1 axis induces an immunosuppressive phenotype in TAMs and drives immune evasion, which can be effectively alleviated by H1-antihistamines. Our studies indicate that histamine/HRH1 axis could serve as potential biomarkers of TAM-mediated T-cell dysfunction and promising therapeutic targets for enhancing immunotherapy response.
- Our findings necessitate further clinical studies to prospectively test the effect of H1-antihistamines as adjuvant therapies for enhancing immunotherapy responses in cancer patients. Additionally, pre-existing allergy in cancer patients may impair anti-tumor immune response and lead to poor responses to immunotherapy. It is necessary to treat allergy symptoms in cancer patients before initiating immunotherapy treatment.