Molecular base of tumor neoantigens: intracellular expression of non-self MHC class I- and II-restricted chimeric epitopes reverses resistance to cancer immunotherapy

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Abstract

Cancer tissue is composed of heterogeneous cancer cells expressing different neoantigens. The type of neoantigens that regulate tumor cell immunogenicity and how they affect overall antitumor immunity remain unclear. In this study, we found a fundamental rule: intracellular expression of non-self MHC class I- and II-restricted peptides chimerically linked in a single chain induces broad neoantigen-specific immune responses. Regardless of antigen specificity, expressing such chimeric antigens via live cell adjuvants or muscle transfection in vivo promoted antitumor activity. In tumors, this type of chimeric peptide was frequently identified in a long neoantigen. Cancers carrying long products of frameshift mutations or aberrant RNA splicing were associated with a good prognosis or better responses to PD-1 blockade therapy in mouse models and cancer patients in our study. Mechanistically, the chimeric antigens altered the dendritic cell phenotype in a CD4+ T cell-dependent manner in draining lymph nodes, consequently suppressing exhausted CD8+ T cells and expanding self-replicable CD8+ T cells at the tumor site. Our results suggest that a part of cancer cells expressing such type of neoantigens in the cancer tissue induce overall antitumor immune responses. These findings would provide new strategies for cancer immunotherapy and responsive biomarkers.

Biography

2006	Ph.D. Medicine, Hokkaido University, Hokkaido, Japan
2006-2010	Staff Member, Dept. of Medicine, Hokkaido University, Japan
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Specialty and Research Field of Interest

Immune metabolism, Cancer immunology, Immunotherapy, Autoimmunity, Aging