Activated WNT/β-catenin pathway induces resistance to immunotherapies in cancers harboring high tumor mutation burden

November 15, 2021

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[Highlights]

- A research team mainly based at National Cancer Center Japan identified a novel resistance mechanism to PD-1 blockade therapies in tumors with high tumor mutation burden (TMB).
- The team demonstrated the resistance mechanism mediated by activation of the WNT/β-catenin pathway in cancer cells, which can be targeted by WNT/β-catenin pathway inhibitors.
- The combination of WNT/β-catenin pathway inhibitors with PD-1 inhibitors will be a promising new therapeutic option for cancers with high TMB.

[Summary]

We found that the WNT/β-catenin pathway was activated in a subset of lung cancers with high tumor mutation burden (TMB), resulting in decreased infiltration of CD8+ cytotoxic T cells (CTLs) into the tumor microenvironment, which was associated with resistance to immunotherapy.

In mouse models, when cancer cells acquired high mutation burden, the activation of WNT/β-catenin pathway was required to grow in immune competent hosts. Activation of the WNT/β-catenin pathway in cancer cells reduced chemokine CCL4 production, leading to the decreased infiltration of dendritic cells, which prevented CD8+ CTLs infiltration in the tumor microenvironment.
Tumors with high TMB and activated WNT/β-catenin pathway were cured by the combination treatment of anti-PD-1 antibody with WNT/β-catenin pathway inhibitors, while anti-PD-1 antibody alone was not effective.

This is the first report that demonstrates the mechanism by which lung cancers with high TMB become resistant to immune checkpoint inhibitors through activating WNT/β-catenin. The combination of WNT/β-catenin pathway inhibitors with immune checkpoint inhibitors is possibly a new therapeutic strategy for lung cancer with high TMB.

The results of the research were published in the electronic version of the American scientific journal "*Science Immunology*" on 13 November 2021, Japan time.

This research was led by Dr. Hiroyoshi Nishikawa, Chief of Division of Cancer Immunology, Research Institute/Exploratory Oncology Research & Clinical Trial Center (EPOC), National Cancer Center (Professor of Department of Immunology, Nagoya University Graduate School of Medicine), Dr. Atsushi Kumanogoh, Osaka University Graduate School of Medicine (Professor of Department of Respiratory Medicine and Clinical Immunology) and Dr. Masatoshi Eto, Kyushu University Graduate School of Medical Sciences (Professor of Department of Urology)

[Publication]

Journal name: *Science Immunology*

Title: Highly Immunogenic Cancer Cells Require Activation of the WNT Pathway for Immunological Escape

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DOI: 10.1126/sciimmunol.abc6424

URL: https://www.science.org/doi/10.1126/sciimmunol.abc6424

Publication date: 13 November,2021

Japanese ver. https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_Imm_211112.pdf