Systemic Administration of Toll-like Receptor 7 (TLR7) Agonist Enhances the Efficacy of Immune Checkpoint Inhibitors

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RESEARCHERS LED BY TMDU proposed a new combination immunotherapy using a TLR7 agonist to improve treatment efficacy of immune checkpoint inhibitors (ICIs).

The release of negative regulators in immune activation (immune checkpoints) that interferes with beneficial antitumor immune responses brings a benefit to cancer patients. CTLA-4 and PD-1 are such immune checkpoint molecules that negatively regulate T-cell activation. Treatment with humanized antibodies against CTLA-4 and PD-1 (ICIs) have shown to a great achievement in patients with a variety of cancers. Now, immunotherapy has been accepted as the fourth pillar of cancer therapy, following surgery, radiotherapy and chemotherapy. However, patients who receive such benefits of ICIs are limited and differ by their clinical grade and tumor tissue type.

To improve the efficacy of ICI treatment and to reduce economic toxicity by the use of ICIs, the research group has invented a new way to use the synthetic compound of toll-like receptor 7 (TLR7) agonist (resiquimod) as a companion drug of ICIs. TLR7 is a member of the TLR family that recognizes the molecular patterns of various microbes. TLR7-mediated signals lead to the activation of dendritic cells that trigger innate immune responses and subsequently enhances the ability of killer T cells, resulting in the elimination of virally infected cells and tumor cells. Despite such promising effects of resiquimod, its clinical application has been limited in the usage of topical/local application to avoid cytokine storms.

The research group examined the antitumor effects of the systemic application of low-dose resiquimod in two PD-L1 blockade-resistant tumors that exhibited different profiles of tumor-infiltrating lymphocytes (TILs). Resiquimod monotherapy markedly inhibited tumor growth in a squamous cell carcinoma model with abundant infiltration of regulatory T cells (Treg) in the tumor microenvironment. The combinational treatment with PD-L1 blockade further reduced the tumor's growth. Resiquimod monotherapy and combined treatment markedly increased the ratio of CD8 T cell/Treg in the tumor. They found that systemic low-dose resiquimod administration induced earlier activation of two types of dendritic cells (plasmacytoid and conventional), resulting in the reduced recruitment of regulatory T cells and increased recruitment of effector killer T cells in the tumor microenvironment. They further demonstrated that limited doses of resiquimod or decreased frequency of the PD-L1 inhibitor could efficiently regress tumor growth. Their results suggest that limited doses of systemic resiquimod administration enable resistance to PD-1/PD-L1 blockades to be overcome, allowing for the decreased usage of PD-1/PD-L1 inhibitors.

The article, "Systemic administration of a TLR7 agonist attenuates regulatory T cells by dendritic cell modification and overcomes resistance to PD-L1 blockade therapy" was published in Oncotarget (2018, 9:13301, Nishi N et al. at DOI: org/10.18632/oncotarget.24327)

Summary: TMDU researchers developed a new use for TLR7 agonists in cancer immunotherapy. Systemic administration of low-dose resiquimod is useful as a companion drug with PD-1/PD-L1 blockade therapy. This may have great potential to eradicate tumors, especially in immunosuppressive tumors with abundant regulatory T cell infiltration.

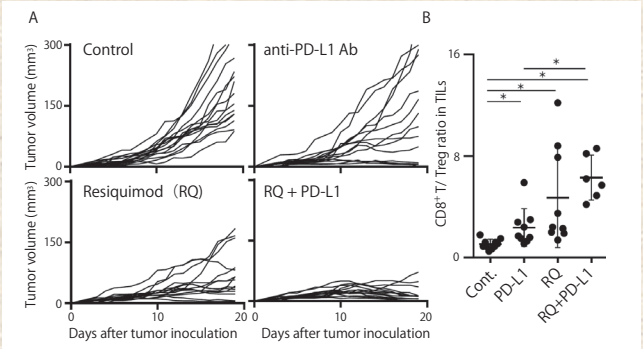

Fig.1: **The effects of treatments with resiquimod and/or PD-L1 blockade in a SCCVII tumor model**
A. Change of tumor volume. Treatments were started on day seven.
B. The ratio of CD8+ T cells/regulatory T cells (Treg) in tumor-infiltrating lymphocytes (TILs) on day 19.

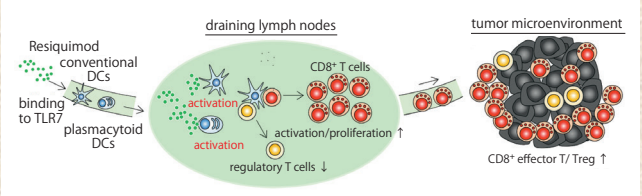

Fig.2: **PPossible mechanism of resiquimod action for enhancing anti-tumor effect**
Systemic administration of low-dose resiquimod induces a transient and rapid activation of plasmacytoid and conventional dendritic cells, resulting in enhanced priming of T cells in draining lymph nodes. Tumor-recruiting CD8⁺ effector T cells increased while regulatory T cells decreased in the tumor microenvironment.