Cooperative Therapeutic Effect of Immune Checkpoint Blockade & Anti-sMIC

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Technology description

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The invention is a new immune-based therapy modality to treat MIC+ malignancies by the combination of a sMIC neutralizing antibody and an immune checkpoint agonist. This invention presents that a combination of sMIC antibody and anti-CTLA4 or anti-PD1/PD-L1 has superior therapeutic effect over monotherapy of individual reagents. This is a new therapeutic modality to improve the clinic response to anti-CTLA4 or anti-PD1/PD-L1 therapy.

Inventors have demonstrated that therapy with sMIC-neutralizing antibody B10G5 enhances responses to therapy with T cell checkpoint (CTLA4, PD-1) blockade antibodies. With TRAMP/MIC spontaneous tumor model, inventors further demonstrated that B10G5 therapy enhanced the therapeutic efficacy of immune checkpoint blockade of anti-PD-L1 antibody and anti-CTLA4 therapy in late stage of advanced prostate carcinoma. Late stage TRAMP/MIC mice that have developed advanced carcinoma showed no or nominal responses to anti-PD-L1 or anti-CTLA4 therapy. Using genetically engineered transplantable syngeneic sMIC+ tumor models, inventors demonstrated that combined therapy with B10G5 evoked strong responsiveness of TRAMP/MIC mice to anti-PD-L1 or anti-CTLA4 therapy. (Figure depicts one example withPD-L1). Mechanistically, B10G5 therapy induced active immune responses which enable effect of unleashing checkpoint blockade.

Overview

Immune checkpoint blockade therapy of cancer has achieved unprecedented clinical outcome, but the response rate is still very limited. Treatment options to advanced cancer are limited. According to American Cancer Society (ACS) cancer registry, it is estimated that 589,430 Americans would have died of cancer in 2015, or about 1,620 people per day. According to WHO, worldwide cancer-related death is still in multi-millions (>8 million) every year with a sharp increase in new cases being diagnosed. Cancer Immunotherapy, a treatment that harnesses the powers of the immune system to fight cancer, represents the most promising cancer treatment approach since the development of the first chemotherapy in late 1940s. Therapy with T cell checkpoint (CTLA4, PD-1) blockade antibodies has achieved unprecedented outcome in cancer patients and thus won FDA approval for advanced melanoma, kidney cancer, lung cancer, lymphoma etc. However, the response rate is still very limited in most cancer types. Even with melanoma, the most immunogenic cancer type, at best the combined therapy of anti-CTLA4 and anti-PD-1 can only reach 58% Objective Response and 11.5% complete

response, with considerable autoimmune-related toxicity. In other cancer types, the Objective Response rate can only reach 25% at best. Therefore, there is still urgent and significantly unmet need for more effective cancer therapeutic modalities.

PD-1/PD-L1 checkpoint blockade to unleash T cell therapy in cancer patients is the most profound breakthrough of current cancer immunotherapy. However, check point blockade therapy (releasing the "break") can only be effective when there are ongoing immune responses (a working "engine"). Providing that human tumor-derived sMIC has been well-described to be globally immune suppressive and that antibody neutralizing sMIC elicited remarkable anti-tumor responses through revamping host endogenous innate and adaptive immune responses with no autoimmune toxicity in clinically relevant animal models (CCR, 2015; 21(21):4819-30.).

To the current understanding, CTLA4 or PD-1 blockade therapy is aimed to release the "brake" of the T cell regulatory machinery to re-activate T cells non-discriminatively. The therapy is under the pre-assumption that the "machinery" or "the engine" of the immune system is functional. Under circumstances where the immune activation machinery is disabled, releasing the "brake" would present limited to no benefit. This simplified scenario would explain the limited clinical response with CTLA4 and/or PD-1 blockade therapy. Thus, ensuring that the "engine" or the machinery" of immune activation is functional is critical for generating optimal clinical outcomes.

Key Words:Cancer, immunotherapy, immune, antibody, tumor, NKG2D, ligand, sMIC, CTLA4Inventors:Jennifer Wu

Application area

Combination therapy for cancer

Improved outcomes for cancer therapies and tumor volume

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