IL-1ß BLOCKADE MITIGATES IMMUNOTHERAPY-INDUCED GUT TOXICITY AND PROMOTES ANTITUMOR RESPONSE

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Background Understanding the exact immunobiology of immune checkpoint blockade (ICB)-related toxicity would be essential to augmenting ICB-induced antitumor immunity and overcoming resistance. In response to ICB or vaccination, proinflammatory cytokines, such as interleukin 1 beta (IL-1ß) and interleukin-6 (IL-6) levels increase in inflamed tissues and tumor microenvironment indicating these cytokines play essential role in the regulation of immune response to, and have prognostic significance in cancer and immune related adverse events. We previously showed that combination therapy with blockade of IL-6 and CTLA-4 or PD-1 could potentially ameliorate ICB-induced experimental autoimmune encephalomyelitis (EAE) disease symptoms while retaining therapeutic activity against established B16 melanoma and CT26 colon carcinoma. Since mechanisms related to encephalomyelitis could likely be different from mechanisms sustaining colitis in ICB treated patients, we choose Dextran Sodium Sulfate (DSS) colitis model in the present application to test a central hypothesis: treating with IL-1ß blockade could ameliorate CTLA-4/PD-1 blockade induced colitis disease severity and promotes antitumor response.

Methods To evaluate whether IL-1ß blockade would allow more effective dual ICB (anti-CTLA-4 and anti-PD-1) antitumor response without increasing colitis disease severity, we used a previously described protocol (2) for induction of colitis in C57BL/6 mice by combining 3% per weight Dextran sulfate sodium (DSS) with autoclaved water 6 days after mice were injected with B16 melanoma. Once mice had developed tumors of approximately 20mm², they were treated with either IgG control, anti-IL-1ß, dual ICB, or combination.

Results No control mice, nor any mice receiving IL-1ß blockade alone, were alive at day 52, whereas 33% of mice receiving dual ICB therapy and 70% of mice receiving combined IL-1ß blockade and dual ICB were alive at day 120. IL-1ß blockade was associated with improved tumor control and significantly increased density of B cells (p<0.002) and reduced density of type-2 dendritic cells (p<0.02) in tumor; B cells were more prevalent within tumor than inflamed intestine (p<0.04). Dual ICB resulted in weight loss, a thickening of the wall of the large intestine as detected by Magnetic resonance imaging (MRI) compared to combined dual ICB and IL-1ß blockade. We observed significant increase in CD8+ T cell level in spleen (p<0.03) and peripheral blood (p<0.04) in mice treated with IL-1ß blockade and dual ICB.

Conclusions Our preliminary results from treatment of mice with implanted tumor and receiving dual ICB suggest that IL-1ß blockade might ameliorate ICB induced colitis disease severity and promote antitumor immunity.

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