In the Spotlight

Cancer Immunology Research

Seeking Synergy of Checkpoint Blockade through TGFβ Inhibition

Ellen Puré

Immunotherapy, including checkpoint blockade, is revolutionizing the treatment of cancers, but efficacy has, however, been limited to a subset of patients and can be of limited duration due to primary and acquired resistance to treatment. An article in this issue shows that inhibiting TGFβ can overcome resistance to blockade of one immune checkpoint, but not another, unless one follows where the mechanism leads. Cancer Immunol Res; 6(12); 1444. ©2018 AACR.

See article by Zhao et al., p. 1459

The capacity of the immune system to recognize and mount an initially effective response against immunogenic tumors is well established. Melanomas, although immunogenic with readily detectable tumor-associated antigen–reactive lymphocytes, often progress, due to tumor cell escape from immunity.

Self-limiting mechanisms have evolved to protect against overly robust and protracted immune responses. These include checkpoints such as CTLA-4 and PD-1 that, when engaged by their ligands (CD80/CD86 and PD-L1, respectively), act as brakes on T cell–mediated immunity. Although efficacious for some patients, most patients treated with anti–CTLA-4 and anti–PD1/PD-L1 exhibit resistance to checkpoint blockade. Anti–CTLA-4 and anti–PD-1/PD-L1 work through distinct mechanisms, however, and their combined use nearly doubles the response rate. To move into the clinic with any combination of immunotherapies with other modalities requires prioritization that is built upon scientific rationales and fundamental mechanistic insights.

TGFβ plays multiple protumoral roles such as suppressing $CD8^+$ T cell activity while driving regulatory T cell (Treg) differentiation. TGFβ also enhances the generation of tumor-associated fibroblasts (TAFs), which form a physical barrier that can exclude T cells from tumors. Subsets of TAFs also produce immunosuppressive factors. The abundance of TAFs in melanoma correlates with resistance to checkpoint inhibitors (1, 2), providing the rationale for the studies from Zhao and colleagues in this issue (3). Small molecule inhibitors of TGFβ type I receptors were utilized to investigate stromal fibroblast-dependent effects of inhibition of TGFβ signaling and their impact on the efficacy of checkpoint inhibition, in an autochthonous $PTEN^{-/-}$ oncogenic $BRAF^{V600E}$-driven murine model of melanoma.

As hypothesized, inhibition of TGFβ signaling enhanced efficacy of anti–CTLA-4, correlating with an increase in $CD8^+$ cells and an increased ratio of $CD8^+$ T cells to Tregs, suggesting reduced competition from Treg CTLA-4 for binding of effector T-cell CD28 to CD80 and CD86.

In contrast, inhibition of TGFβ signaling conferred resistance to anti–PD-1 by increasing fibroblast-derived MMP-9 cleavage of PD-L1 from melanoma cells, suppressing PD-1/PD-L1 signaling while conferring resistance to anti–PD-1. Cleavage of PD-L1 might be expected to enhance tumor growth if the tumors in the models used are immunogenic; however, the concomitant expansion of fibroblasts that exert multiple immunosuppressive functions might explain why this was not the case. Silencing fibroblast MMP-9 overcame resistance to anti–PD-1 and correlated with an enhanced ratio of $CD8^+$ cells to Tregs. Thus, fibroblast-derived MMP-9 may be important in regulation of PD-L1 expression in melanoma and thereby, in turn, play a role in determining sensitivity versus resistance to anti–PD-1/PD-L1 therapy.

At first glance, these results appear to negate the concept that inhibition of TGFβ signaling might enhance efficacy of PD-1/PD-L1 checkpoint blockade. However, additional studies revealed that although initially responsive, melanomas in $BRAF^{V600E}PTEN^{-/-}$ mice uniformly acquire resistance to anti–PD-1 alone. As resistance was associated with expansion of stromal fibroblasts and TGFβ signaling, they revisited the potential for synergy using a protocol in which TGFβ inhibition was delayed until emergence of anti–PD-1 resistance. This resulted in more effective antitumor immunity, resurrecting the therapeutic potential of this combination while highlighting the need for a mechanism-driven rational design of dosing regimens for combination therapies. These data also highlight the potential benefit of targeting TAFs to indirectly boost anti-tumor immunity and of taking indirect mechanisms into consideration when interpreting the impact of interventions designed to directly regulate anti-tumor immunity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Tirosh I, Izar B, Prakadan SM, Wadsworth MH 2nd, Treacy D, Trombetta JJ, et al. Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. Science 2016;352:189–96.
2. Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. Cell 2016;165:35–44.
3. Zhao F, Evans K, Xiao C, DeVito N, Theivanthiran B, Holtzhausen A, et al. Stromal fibroblasts mediate anti–PD-1 resistance via MMP-9 and dictate TGFβ inhibitor sequencing in melanoma. Cancer Immunol Res 2018;6:1459–71.

Department of Biomedical Sciences, University of Pennsylvania, Philadelphia, Pennsylvania.

Corresponding Author: Ellen Puré, University of Pennsylvania, 380 S. University Avenue, 410E Hill Pavilion, Philadelphia, PA 19104. Phone: 215-573-9406; E-mail: epure@upenn.edu

doi: 10.1158/2326-6066.CIR-18-0784

Cancer Immunology Research

Seeking Synergy of Checkpoint Blockade through TGFβ Inhibition

Ellen Puré

Cancer Immunol Res 2018;6:1444.