ISOFORM SPECIFIC ANTI-TGF β THERAPY ENHANCES ANTITUMOR EFFICACY IN MOUSE MODELS OF STROMA POOR CANCERS

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Background TGF β is a potential target in cancer treatment due to its dual role in tumorigenesis and homeostasis. There are three isoforms of TGF β (TGF β 1, TGF β 2 and TGF β 3), which are secreted by immune and non-immune cells as an inactive latent complex. Depending on the local context and players, TGF β can adopt opposing roles in carcinogenesis and in modulating the immune system. However, the expression of TGF β and its inhibition within the tumor microenvironment has mainly been investigated in stroma-rich tumors.

Methods We examined expression of TGF β 1 and TGF β 3 isoforms on immune cells in two stroma-poor mouse tumor models (B16 melanoma and CT26 colon carcinoma) and investigated the anti-tumor efficacy of antibodies that block TGF β 1 and TGF β 3 in these two models.

Results Depending on local expression of TGF β isoforms, specific inhibition of either TGF β 1 or TGF β 3 may be effective. The "TGF β signature" of CT26 colon carcinoma is defined by TGF β 1 expression on immune cells and TGF β 1 inhibition results in tumor delay; B16 melanoma has equal expression of both TGF β 1 or TGF β 3 isoforms and inhibition of either TGF β 1 or TGF β 3 controls tumor growth. We show that the mechanism of tumor growth delay is enhanced CD8+ T cell activation and effector function. In addition, we found that combining TGF β inhibition with immune checkpoint blockade results in improved tumor control and survival.

Conclusions Our findings suggests that expression of TGF β isoforms in the TME is variable in different tumor types and their expression may be used to predict anti-tumor responses to TGF β inhibition. Isoform specific TGF β inhibition in stroma poor tumors shifts the local immune environment to favor tumor regression alone or in combination with immune checkpoint blockade.

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