MODULATING THE TUMOR MICROENVIRONMENT BY A TARGETING TGFβ1 WITH VACCINE-INDUCED IMMUNE RESPONSES

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Background Recent clinical results provide a rationale for cancer immunotherapy based on activation of “anti-regulatory” T cells. Anti-regulatory T cells recognize antigens expressed by immunosuppressive cells and thereby target pro-inflammatory signals to the tumor microenvironment. TGFβ1 promotes immune suppression in diverse cancers. We hypothesize that activating T cells against TGFβ1 may allow targeting of pro-inflammatory immune response to TGFβ1-expressing tumors while avoiding the toxicities associated with TGFβ1 pan-inhibition. TGFβ1-specific T cells are frequently detected in humans. Vaccination with a TGFβ1 peptide ameliorates fibrosis in a model of chronic colitis and enhances the anti-tumor activity of an HPV16 E7-specific vaccine, indicating a therapeutic potential of a TGFβ1 vaccine. Here we sought to enhance the specificity anti-TGFβ1 immune responses and identify peptides with high TGFβ1 selectivity (vs TGFβ2/3), thereby mitigating potential off-target toxicities. To understand the TGFβ1 landscape in human tumors we performed a multiplexed IHC analysis of TGFβ1 expression on tumor cells and the multiplicity of cells in the tumor microenvironment.

Methods PBMCs were assayed by ELISPOT to measure responses to peptides from TGFβ1, TGFβ2, and TGFβ3. TGFβ1 expression was examined by multiplex immunofluorescence in a tissue microarray panel of tumor indications with hyperplexed visualization of markers on a single section. Vaccination is evaluated in mouse models expressing TGFβ1. Tumor growth monitored, organs and tumor samples collected. Histopathological examination is performed on multiple tissues. Vaccine activity is determined and immune infiltrate analysis conducted by FACS and RNAseq.

Results Healthy human donors exhibited robust immune responses to TGFβ1 peptides selected for improved TGFβ1-specificity. Stimulation of PBMCs with TGFβ1 peptides did not result in cross-reactivity to homologous TGFβ2 or TGFβ3 peptides. Analysis of PBMCs with TGFβ1 peptides showed widespread TGFβ1 expression in cancers and provides a rationale for targeting TGFβ1 in selected indications. Anti-TGFβ1 T cell clones functional activity and TGFβ1-specificity were confirmed. Therapeutic activity of TGFβ1 vaccine in mouse models and in addition to the cellular and molecular analysis of the tumors in the various cohorts will be presented.

Conclusions A TGFβ1 vaccine is an attractive new approach for cancer immune therapy. Optimal synthetic long peptides able to elicit robust and highly selective TGFβ1-immune responses were developed. These peptides showed ability to change an immune suppressive TME to a pro-inflammatory state and drive efficacy in mouse models. These data support the preclinical development of an TGFβ1 vaccine for the treatment of multiple solid tumors.

REFERENCES


