# Abstract

Two major phenotypes of human melanoma metastases have been observed based on gene expression profiling and confirmatory assays. One subgroup of patients has a T cell-inflamed phenotype that includes expression of chemokines, T cell markers, and a type I IFN signature. In contrast, the other major subset lacks this phenotype and appears to display immune “exclusion”. The mechanisms of immune escape are likely distinct in these two subsets, and therefore the optimal immunotherapeutic interventions necessary to promote clinical responses may be different.

The T cell-inflamed tumor microenvironment subset shows the highest expression of negative regulatory factors, including PD-L1, IDO, and FoxP3+ Tregs. Deep analysis of tumor antigen-specific T cells in the tumor microenvironment has identified additional mechanisms of immune dysfunction and new potential therapeutic targets.

Treatment strategies targeting several pathways have been translated back into the clinic, including anti-PD-1/PD-L1 mAbs and IDO inhibitors, and combinations of these agents also look promising. In contrast to the T cell-inflamed melanomas, non-T cell-inflamed tumors are largely immunotherapy resistant with current approaches. Natural innate immune sensing of tumors appears to occur via the host STING pathway, type I IFN production, and cross-priming of T cells via CD8α+ DCs, and these factors are absent in non-T cell-inflamed tumors.

New strategies are being developed to engage or mimic this pathway as a therapeutic endeavor, including STING agonists. The molecular mechanisms that mediate the absence of the T cell-inflamed tumor microenvironment in patients are being elucidated using parallel genomics platforms. The first oncogene pathway identified that mediates immune exclusion is the Wnt/β-catenin pathway, which argues that new pharmacologic strategies to target this pathway should be developed to restore immune access to the tumor microenvironment. Recent evidence has indicated that host factors, including the intestinal microbiota, are also critical.

We recently have identified commensal bacteria in mouse models that augment spontaneous anti-tumor immunity and increase efficacy of anti-PD-L1 therapy. Similar analyses in human melanoma patients have been performed, and commensal bacteria have similarly been identified that correlate with anti-PD-1 efficacy. These results have prompted the pursuit of new probiotics that may improve spontaneous immune infiltration and expand immunotherapy efficacy in the clinic.