“Dissecting resistance to PD-1 blockade, one cell at a time”

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PD-1 pathway blockade has been approved for 16 different cancer types and is being tested in an additional 15. Despite its dramatic activity, the majority of patients do not respond to anti-PD-1 antibodies. We have shown that neoadjuvant anti-PD-1 given to lung cancer patients prior to resection of their primary tumor results in a nearly 50% major pathologic response rate (<10% of tumor bed consisting of viable tumor cells). This clinical format allowed us to obtain large numbers of TIL after anti-PD-1 therapy so that we could perform single cell transcriptomics and TCR repertoire analysis. As part of this analysis we could determine which genes and genetic programs were associated with successful anti-tumor response vs non-response. We found that T cells from non-responding tumors exhibited a broad stress response signature, while T cells from MPR tumors did not. While T cells from both responding and non-responding tumors expressed high levels of PD-1, PD-1+ T cells from non-responding tumors had higher levels of the canonical exhaustion factor TOX and other exhaustion-associated genes, including CD39, Tim3 and other checkpoints. T cells from non-responders demonstrated Treg from non-responding tumors were more numerous and expressed specific Treg inhibitory molecules. Taken together, T cells ronr-responding tumor encounter a high stress microenvironment and express high levels of transcriptional and membrane inhibitory molecules, some of which are therapeutically targetable.