Citation (Summary) of the work:

In many forms of cancer, targeting immune-checkpoint-inhibitors including PD1 has achieved promising and durable response, but it is unclear why some patients show only transient or no response. Among the two targeted $PD1^{+}$T-cell subpopulations, terminally-exhausted, $CD8^{+}TCF1^{-}$TEX remain most resistant towards anti-PD1-therapy in comparison to progenitor, $CD8^{+}TCF1^{+}$PEX. However, in tumor settings functional status of TEX remains elusive. Given the prime importance of CSCs in metastatic cancer progression by evading therapies, she studied the influence of $CD8^{+}$TEX on CSCs. Her research suggested that TEX does actively participate in tumor progression by modulating a violent malignant subset-CSC. Screening of human primary tumors disclosed that both $CD8^{+}$TEX and CSCs remain strongly enriched across cold (low- <6%TIL frequency) advanced-carcinomas, compared to hot (high->6%TIL frequency) advanced-carcinomas; suggesting their interdependency on tumor advancement. TEX directly upregulates CSC frequency which was not brought down by anti-PD1 therapy. These T_{TEX}-influenced-CSCs remain in an EMT-MET-hybrid-state and are highly clonogenic, drug resistant, invasive and induce hepatic metastasis. T_{TEX} involves the LAMP3/NRP1-VEGFR2 axis in instigating this CSC-aggression. Thus, the results suggest that screening carcinoma patients for TEX frequency or LAMP3/NRP1 on $CD8^{+}PD1^{+}$ T-cells prior to administering anti-PD1-therapy would predict the therapeutic-outcome. Additionally, LAMP3, NRP1 in conjunction to VEGFR2 could be strategically targeted at advanced carcinoma patients with high TEX frequency.This study advances our understanding of anti-PD1 therapy resistance in some patients and also about exhausted-T cells and CSCs to provide fundamental insight into an unappreciated aspect of tumor-immunology by improvising more specific targeting options in cancer management.

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