

T CELL-INSTRUCTED INFLAMMATION DRIVES IMMUNE CHECKPOINT INHIBITOR THERAPY RESISTANCE

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Background Resistance to immune checkpoint inhibitors (ICIs) is a significant barrier to improving cancer immunotherapy.¹ To this end, we interrogated ICI-induced inflammation. One type of inflammation, driven by nuclear factor- κ B (NF- κ B) activation in the tumor microenvironment (TME), can power tumor-promoting mechanisms including immunosuppression to limit ICI efficacy.² Conversely, the current paradigm predicts that another type of inflammation, characterized by T cell infiltration, improves ICI responsiveness.^{3,4} How these two units of inflammation can co-exist in the TME yet direct divergent responses to ICIs requires reconciliation. In particular, it is unknown whether conventional CD4 or CD8 T cells can themselves instruct NF- κ B inflammation in the TME, shaping the immunologic setpoint and, unexpectedly, limiting ICI efficacy.

Methods We generated new mouse syngeneic microsatellite instability-high (MSI-H) tumor models to study ICI response and resistance in the context of ample T cell inflammation. High-neoantigen-burden cell lines were implanted into syngeneic mice to assess responses to combination anti-PD-1 and -CTLA4 treatment.

Results Consistent with response in human tumors⁵, 50% of mouse MSI-H tumors were resistant to combination ICIs. Analysis of the TME in the resistant AT3 breast cancer model and responsive B16F10 melanoma model by mass cytometry revealed that ICIs increased tumor T cell infiltration in each model, but CD8 T cells in AT3 tumors assumed a non-cytotoxic but early-activated phenotype characterized by CD69 expression. T cell expansion in AT3 MSI-H tumors was accompanied by recruitment of T cell-suppressive polymorphonuclear myeloid-derived suppressor cells requiring cytokines G-CSF and CXCL1, absent in B16F10 tumors. Inhibition of the inflammatory NF- κ B circuit, which drives expression of these cytokines, via IL-1 receptor neutralization increased ICI efficacy against AT3 MSI-H tumors. Unexpectedly, in vivo depletion of T cells also abolished the NF- κ B circuit in AT3 MSI-H tumors, and activated CD8 T cells were sufficient to instruct tumor cells to increase G-CSF and CXCL1 expression. We found that TNF α , increased in T cells and neutrophils upon ICIs, perpetuated the NF- κ B circuit and contributed to ICI resistance in AT3 MSI-H tumors. Finally, analysis of single-cell RNA sequencing data from ICI-treated breast cancer patients revealed candidate human T cell correlates.

Conclusions We report a surprising, novel mechanism of ICI resistance whereby treatment-induced T cell infiltration and activation can paradoxically exacerbate a TNF α - and IL-1-dependent resistance circuit in tumors with active NF- κ B inflammation. Our findings refine the current models of ICI response and resistance with important therapeutic implications.

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