Background Harnessing the immune system through the attenuation of immune checkpoints has led to durable tumor rejection in a subset of tumors. However, the majority of epithelial cancers remain resistant to existing immunotherapies. It is imperative to understand how these resistant tumors escape the immune system in order to design more efficacious therapies. Often, nonresponsive tumor types, such as pancreatic cancer and head and neck cancers (HNCC), possess a complex tumor microenvironment (TME) infiltrated by immune and stromal cells, as well as nerve fibers arising from the peripheral nervous system. In comparison with other members of the TME, the role of tumor-infiltrating nerve fibers in oncogenesis and treatment resistance is understudied. Studies across murine models of prostate and pancreatic cancer have shown that ablation of portions of the peripheral nervous system prevents cancer progression.1 2 We recently showed that existing nerves sprout and undergo reprogramming to an adrenergic-like phenotype as a result of orchestrated microRNA shuttling from cancer cells to neurons, resulting in activation of transcriptional programs that establish new neuronal identity.3 Given that activated T-cell subsets express high levels of adrenergic receptors, we hypothesized that adrenergic signaling may also influence tumor-infiltrating T-cell function.

Methods We used murine models of HNCC to discern the effect of adrenergic signals on overall immune infiltration, tumor growth, and efficacy in combination with immune checkpoint inhibitors. We correlated our findings with patient cohorts using immunohistochemistry. We studied intratumoral and intra-T-cell pathway changes by RNA sequencing.

Results In T-cell cytotoxicity studies, a variety of adrenergic agonists, particularly $b_2$ agonists, enhanced T-cell activity against tumor cells. Adrenergic agonists exerted this effect on T-cells not directly on adrenergic receptors on the T-cells themselves, but indirectly on adrenergic receptors on the cancer cells, forcing an increased release of cytokines and chemokines, most notably CXCL10. This dysregulation in immune signaling promoted not only recruitment but also activation/exhaustion pathways within CD8+ T-cells. Intriguingly, this signaling axis was dependent on p53 loss within the cancer cell.

Conclusions These results describe a new mechanism for p53’s regulation of cancer, and contrast with the known role of adrenergic signaling in cancer. Although nerve-cancer crosstalk drives cancer progression, tumor innervation may also play a positive role in regulating the host’s adaptive immune response. Therapeutic approaches targeting this critical component of tumor biology may lead to new efficacious, personalized treatments, expanding the use of immunotherapy and/or combination therapies in new cancer types and ultimately improving patient survival.

REFERENCES