483 EXTRA-NODAL MEMORY T CELL POPULATIONS CONFER DURABLE ANTICANCER IMMUNITY FOLLOWING SUCCESSFUL PRIMARY TUMOR RESPONSES TO ICI

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Background While immune checkpoint inhibitor (ICI) therapy has demonstrated remarkable efficacy for treating cancers, achieving complete and durable immunity memory to prevent tumor recurrence remains elusive. Understanding the mechanisms of immunologic memory after complete responses to ICI therapy is essential for optimizing treatment to achieve sustained anticancer responses.[1] This study aimed to investigate the long-lasting immune memory induced by ICI therapy in an orthotopic murine model of tobacco-signature head and neck cancer (HNC) – the 4MOSC1 model. Specifically, this work addresses the hypothesis that durable antitumor immunity is conferred peripherally in the host and can effect responses independent from locoregional lymphatics,[2] which are routinely ablated with curative-intent oncologic therapies in HNC patients.

Methods 4MOSC1 tumor-bearing animals treated with aCTLA-4 monotherapy achieve complete primary tumor responses and, subsequently, feature durable immunity when re-challenged with parental 4MOSC1 following primary tumor clearance to a similar extent as animals subjected to classical tumor vaccination. By leveraging this in vivo model of tumor vaccination with ICI monotherapy along with a tamoxifen-inducible reporter animal model in which we can precisely and spatiotemporally label immune effectors, we elucidate the mechanistic underpinnings of durable anticancer responses and address the necessity of preserving regional tumor-draining lymphatics after successful primary tumor responses.

Results An analysis of key immunologic effectors in ICI-responder animals reveals a diffuse and peripheral distribution of T cell populations known to confer durable immunity – namely, the CD8 T central memory (Tcm) and progenitor exhausted (Tex-stem) populations. Adoptive transfer of these key effectors into naïve tumor bearing animals is sufficient to mediate tumor rejection. Interestingly, both Tcm and Tpex populations were found both within and beyond draining, regional lymphatics. Moroever, by employing the OVA-expressing 4MOSC1 model, we find antigen-specific Tcm/Tpex in a similarly broad, spatial distribution. We next evaluated the role of regional lymphatics in conferring durable immunity by performing neck dissections in animals following successful primary tumor response. Surprisingly, the ablation of regional tumor lymphatics in vaccinated animals did not impair host immunity, suggesting that the T cell reservoir in extra nodal and peripheral sites confers durable immunity following primary response to ICI therapy.

Conclusions This study demonstrates that successful primary immune responses require intact regional lymphatics, but that systemic immune memory persists independently from regional lymphatics. These insights have critical and immediate implications for translating meaningful treatment sequencing strategies into the clinic.

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