

MUTUAL INTERACTIONS BETWEEN NEOANTIGEN-SPECIFIC CD8+ T CELL RESPONSES FACILITATE IMMUNE EVASION IN SUB-CLONAL TUMORS<http://dx.doi.org/10.1136/jitc-2023-SITC2023.0929>

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Background Intra-tumoral heterogeneity (ITH) and sub-clonal neoantigen presentation can impair anti-tumor T cell responses and are closely linked to poor efficacy of checkpoint blockade immunotherapy. Yet, an understanding of the mechanisms by which ITH facilitates immune evasion remains elusive, impeding the rational design of neoantigen-based immunotherapies, including cancer vaccines, for sub-clonal tumors.

Methods We used lentiviral transduction to express single or multiple neoantigens in a transplantable, syngeneic mouse model of lung adenocarcinoma (driven by an oncogenic Kras^{G12D} mutation and a deletion of p53). Clonal and sub-clonal neoantigen presentation were modeled to systematically analyze their impact on neoantigen-specific T cell responses, elucidating involved mechanisms. Recapitulating clinically relevant neoantigen architectures, we investigated the ability of immunotherapy approaches to overcome the impaired immunogenicity of tumors with ITH.

Results Clonal co-presentation of neoantigens led to mutual interactions between corresponding T cell responses. Based on neoantigen characteristics, these interactions induced synergistic or competitive effects. Synergistic effects were observed between T cell responses when poorly (weak) and highly immunogenic (strong) neoantigens were co-expressed, inducing greater T cell expansion, tumor infiltration as well as more effective target-specific killing in vivo. Analysis of cross-presenting dendritic cells (cDC1) in the tumor-draining lymph node implicated differential T cell priming as a pivotal mechanism for neoantigen synergy, as cDC1 mirrored the tumor's neoantigen presentation pattern and synergistic effects were associated with a more stimulatory cDC1 phenotype. In contrast, clonal co-expression of multiple strong neoantigens restricted to the same MHC allele led to immunogenic competition with immunodominant responses. The sub-dominant T cell response was characterized by an impaired expansion and tumor infiltration, as well as impaired target-specific killing. In sub-clonal tumors, synergistic effects were reduced and enabled sub-clonal immune evasion, leading to a loss of immune-mediated tumor control. Immunodominance was maintained in sub-clonal tumors and drove immune evasion of sub-clones lacking presentation of the dominant neoantigen. Mirroring observations in human patients, immune checkpoint blockade therapy failed to overcome the lower immunogenicity of sub-clonal tumors.

Conclusions Clonal co-presentation of neoantigens induces mutual interactions between corresponding T cell responses, which can be synergistic or competitive depending on neoantigen characteristics. In sub-clonal tumors, diminished synergistic effects and impaired sub-dominant T cell responses can facilitate immune evasion, and warrant tailored treatment strategies. Our study provides novel mechanistic insights to explain the diminished immunogenicity of sub-clonal tumors and has strong implications for the design of immunotherapy approaches.

Ethics Approval The study was approved by MIT's Committee on Animal Care, Protocol Number 0220-006-23.