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**STING SIGNALING COMPENSATES FOR MUTATION BURDEN-LOW TUMORS TO STIMULATE THE IMMUNE RESPONSE**Jiayi Tan\*, Colt Egelston, Weihua Guo, Peter Lee. *City of Hope, Duarte, CA, USA*

**Background** Tumor mutation burden (TMB) is known to predict the immune response, especially tumor-infiltrating lymphocytes (TILs) in various tumor types. Besides, it's also one of the most well-accepted biomarkers to select responsive patients for immunotherapy. However, increasing evidence indicates the complex association between TMB and immune infiltration, and the overall response rate to immunotherapy selected based on TMB in clinical trials was not satisfied.

**Methods** Bulk RNA-seq and somatic mutation datasets from The Cancer Genome Atlas (TCGA) of 10 major cancer types were downloaded to investigate the role of TMB and other determinants in immune response. Unsupervised patient clustering analysis with UMAP using major immune components and TMB was performed to further identify different types of tumor microenvironment (TME).

**Results** Mutation burden was found poorly correlated with active immune response in various cancer types. The unsupervised clustering analysis revealed the tumor group with low mutation burden but inflamed TME as well as the group with high mutation burden but poor immune response. Notably, the stimulator of interferon genes (STING) signaling was upregulated in that low TMB group to enhance the immune response. In contrast, the tumors harboring high mutation burden with robust proliferation and DNA damage repair machinery failed to stimulate STING signaling leading to poor immune activation, which may result from minimal cell death and apoptosis to release tumor DNA.

**Conclusions** This study demonstrates the non-linear relationship between TMB and inflamed TME. High mutation burden in tumors is not always necessary for the active immune response which instead may lead to non-inflamed TME. Moreover, this study emphasizes the initial step of tumor apoptosis to stimulate either antigen-presenting cells (APCs) to uptake tumor antigens or STING signaling for further immune activation. Together these data suggest the application of STING agonist in high mutation burden tumors with non-inflamed TME to interrupt the aggressive replication cycle and enhance the immune response.

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