SYSTEMS BIOLOGY ANALYSIS OF ANTI-TUMOR IMMUNITY

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Background Initiation of an immune response requires activation of one or more naïve T cells. Each naïve T cell has a unique T cell receptor, and these cells traffic through the blood and lymphatic vasculatures, visiting each of the ~500 lymph nodes in search of matching antigen. If a match is made, then the naïve T cell activates and proliferates. This process is potentially rate-limiting, given the few naïve T cells capable of recognizing tumor antigen and the random nature of their entry into each lymph node. We propose that stochastic nature of this process affects the probability of T cell activation and may contribute to the poor response to ICB therapy seen in most patients.

Methods Here, we use multiscale computational modeling to identify potential reasons for clinical failure of immune checkpoint therapies and develop strategies for improving naïve T cell activation and tumor killing. The model provides a mechanistic framework for optimizing cancer immunotherapy and developing testable solutions to unleash anti-tumor immune responses for more patients with cancer.

Results The results show that tumor antigen production rate is a critical parameter, and that patients with low tumor antigen production rate need additional treatment to enhance antigen level and improve immune checkpoint inhibition therapy.

Conclusions The co-localization of antigen with appropriate naïve T cells is a critical step in immune activation, and affects the anti-tumor response in the context of immune checkpoint therapy.