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ENGINEERING ANTI-TUMOR IMMUNE RESPONSE WITH CUSTOMIZED FUNCTIONAL PROFILE

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Donor-specific anti-tumor T cells have been generated by engineering human primary T cells with tumor-associated antigen-specific T cell receptor (TCR) or chimeric antigen receptor (CAR). Both of these approaches have produced remarkable clinical outcomes, however, success rate of these approaches require significant improvement. In this context, availability of methods to generate T cells with customized effector function profiles would be useful. Although activation induced cell death (AICD) and program cell death (PCD) are essential immune homeostasis mechanisms, characterization of the mechanism of epitope-specific AICD in human primary T cells could help generate anti-tumor T cells that would sustain longer in the physiology and produce superior clinical outcomes. Utilizing human melanoma-associated antigen-specific anti-tumor T cell-derived MHC class I restricted transgenic TCRs, we have recently generated $CD4^+$ and $CD8^+$ multifunctional anti-tumor T cells. We have found that human melanoma-associated antigen-specific MHC class I restricted transgenic T cell receptor (TCR) engineered (TCR engg) $CD4^+$ and $CD8^+$ T cells exhibit differential susceptibility to epitope-specific AICD, such that while TCR engg $CD8^+$ T cells undergo AICD even upon encountering their target epitope for the very first time, TCR engg $CD4^+$ T cells become susceptible to AICD following one encounter with the target epitope. We have also characterized the mechanism of AICD in TCR engg human primary T cells and shown that JNK, BCL-family proteins, and p53-mediated non-transcription dependent pathway plays an essential roles in it. We will discuss different approaches being pursued towards generating long-lasting anti-tumor T cells with customized anti-tumor effector function profile that could help improve the efficacy of current immunotherapy approaches.

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