

POSTER PRESENTATION

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Fas expression in memory CD8⁺ T cell subsets augments cellular differentiation and effector function

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Memory CD8⁺ T cells (T_{Mem}) have the capacity to provide lifelong host protection against intracellular pathogens and cancer. Despite phenotypic and functional heterogeneity among T_{Mem}, the expression of Fas — a tumor necrosis family receptor (TNFR) superfamily member conventionally known as a death receptor — is held in common among all T_{Mem} subsets across multiple species. As Fas has been shown to mediate non-death signaling in other cell types, we set out to elucidate the role of Fas signaling in defined T_{Mem} subsets, including T stem cell memory (T_{SCM}), T central memory (T_{CM}), and T effector memory (T_{EM}). We found that augmenting Fas signaling in stimulated T_{SCM} using an oligomerized form of its ligand FasL resulted in augmented cellular differentiation and a loss in IL-2 secretion capacity. Conversely, antibody blockade (anti-FasL) of Fas signaling in T_{CM} retarded cellular differentiation both phenotypically and functionally. To genetically disentangle the pro-apoptotic and differentiation signals from Fas, we made use of a mutant Fas lacking a transmembrane cysteine residue (FasC194V) that is unable to undergo S-palmitoylation and aggregate efficiently in lipid rafts. Using transgenic mice expressing this C194V Fas construct on a Fas-deficient *lpr* background, we found that FasC194V T_{Mem} can still undergo cellular differentiation in the absence of death signaling. *In vivo*, T_{Mem} expanded with anti-FasL showed greater expansion, on-target immunity and withheld differentiation. Additionally, in a relevant syngeneic model of current human T cell immunotherapy, T_{Mem} cells expanded with anti-FasL and genetically engineered with an anti-CD19 chimeric antigen receptor (CAR) exhibited enhanced CAR expression,

reduced differentiation, and augmented anti-lymphoma activity compared to controls. These studies demonstrate that Fas signaling promotes not only cell death but also T_{Mem} effector differentiation, a finding that has implications for the design and execution of T cell-based immunotherapies in patients with cancer or infectious disease.

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