

Role of T Cell Receptor Signaling in CD8 T Cell Memory

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Abstract

The development of memory CD8 T cells is required for long-term protection against intracellular pathogens, such as viruses, and tumors. While the importance of memory generation has been recognized for over 30 years, the mechanism by which memory CD8 T cells arise during immune responses is still not fully understood. T cell receptor (TCR) interaction with antigen-bound MHC (pMHC) is necessary for activation and differentiation of CD8 T cells. Yet, how the resulting TCR signal regulates T cell memory is unknown. In this dissertation, we investigated the role that the TCR signal plays in memory differentiation. First, we explain how the strength of pMHC-TCR interaction affects memory generation. We show that low affinity pMHC-TCR interactions preferentially promote memory CD8 T cell development by distinctly inducing the expression of memory-associated transcription factors. We also demonstrate that the signals for the development of CD8 T cell memory are different depending on TCR ligand strength. Finally, we define a mechanism by which TCR signaling programs memory differentiation. We show that TCR-dependent activation of NF- κ B signaling is required for the expression of memory associated transcription factors. In addition, we found that NF- κ B signaling is required late in the immune response to allow for proper memory differentiation and survival, thus implicating NF- κ B signaling as an important regulator of memory CD8 T cell generation. All

vaccines utilize pathogen-specific antigens to induce immunological memory. By understanding how antigenic signals program memory differentiation, it will be possible to specifically manipulate this process. We can then produce more effective and longer lasting memory cells.