

Generation of Protective HP CD8⁺ T-cells Requires CD4⁺ T-cell Help

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Upon antigenic stimulation, specific T-cells proliferate rapidly and produce short-lived effector cells and this is followed by the appearance of long-lived memory T-cells. Due to their increased frequency and enhanced responsiveness following restimulation, memory T-cells are a critical component of lasting immunity and therefore a desired outcome of vaccination. However, memory-like T-cells are also produced without foreign antigen stimulation, through lymphopenia-induced homeostatic proliferation (HP). Such cells are generated during development of the immune system and following immunodepletion (as a result of infectious diseases or therapeutic treatments), yet the capacity of such memory-like cells to control pathogens is unclear. Here we show that HP memory CD8⁺ T-cells control a bacterial infection similar to true memory cells, but that the protective capacity of HP memory cells varied dramatically depending on the nature of the lymphopenic environment: HP memory CD8⁺ T-cells produced in the sustained absence of CD4⁺ T-cells failed to mediate protection. Furthermore, our data indicate that the defective response of “helpless” HP memory cells involves their production of tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL, Apo-2L). Intriguingly, however, TRAIL appears not to operate by inducing loss of HP memory CD8⁺ T-cells in this system. Thus, while HP and true memory CD8⁺ T-cells are generated by very different pathways, both exhibit dependence on CD4⁺ T-cells for their protective function.