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MOLECULAR DETERMINANTS OF CD8+ T CELL MEMORY

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A number of studies have contributed to our understanding of how CD4+ T lymphocytes provide the ‘help’ necessary for optimal priming and memory establishment in CD8+ T lymphocytes. A central event in this process is believed to occur through the sequential interaction of CD4+ T cells with antigen-presenting cells (APC) leading to activation of the latter to a state in which they can autonomously provide the necessary signals for directly priming the CD8+ T cells in a subsequent interaction. Once “helped”, the progeny of these CD8+ T cells are endowed with the capacity for homeostatic survival and secondary expansion, while those primed in the absence of CD4+ T cells give rise to daughter cells which undergo TRAIL-mediated apoptosis upon restimulation. Although we, and others, have identified the CD40-L/CD40 pathway as being crucial for initiation of the “help” message from CD4+ T lymphocytes to APC, it has remained elusive how this message is delivered from the activated APC to the naïve CD8+ T cells, or what pathways govern the capacity for secondary responsiveness. Using *in vivo* models of immunization by infectious pathogens and cross-priming, we now show using blocking antibodies and knockout mice that the “help” message can be transmitted from activated APC to CD8+ T cells via the CD70/CD27 costimulatory pathway. Additionally, we find that the ability of “helped” CD8+ T cells to avoid TRAIL-mediated apoptosis involves their ability to produce autocrine IL-2 and to induce expression of the transcriptional repressor Nab-2, an inhibitor of the early growth response genes EGR-1, -2, and -3. Collectively, these findings shed new light on the molecular regulation of CD8+ memory by CD4+ T cell help.

References:

Schoenberger et al, Nature 393:480
Janssen et al, Nature 434:88
Janssen et al, Nature 421: 852