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Signaling Pathways of 4-1BB for T Cell Survival and Expansion

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4-1BB, a T cell costimulatory receptor, prolongs $CD8^+$ T cell survival, and enhances cell cycle progression and proliferation of $CD8^+$ T cells in both an IL-2-dependent and -independent manner. In the case of survival, 4-1BB stimulation increased expression of the anti-apoptotic genes *bcl-X_L* and *bfl-1* via 4-1BB-mediated NF-κB activation. This signaling pathway was specifically inhibited by PDTC and was different from the pathways that enhanced $CD8^+$ T cell proliferation.

For cell cycle progression, 4-1BB costimulation induced cyclin D2 and cyclin E expression, and concomitantly down-regulate the expression of the cyclin-dependent kinase (cdk) inhibitor $p27^{kip1}$. 4-1BB increases cyclin D2 transcription via MEK1/2 and LY294002-sensitive PI3K signaling pathways. In addition it up-regulates cyclin D2 translation via PI3K/Akt/mTOR pathways, presumably triggered by IL-2/IL-2R ligation. The enhanced cyclin D2 expression initiates up-regulation of cyclin E expression and down-regulation of $p27^{kip1}$. The results suggest a role for the anti-apoptotic activities of Bcl-X_L and Bfl-1 proteins, and proliferative activities of cyclin D2, cyclin E and $p27^{kip1}$ proteins in 4-1BB-mediated $CD8^+$ T cell survival and cell cycle progression *in vivo*, respectively.