

Identifying Novel Regulators of CD28 Signaling in T Cells

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Activation of naive CD4+ T lymphocytes requires the presence of two synergistically acting signals provided by the T cell receptor (TCR) and the CD28 costimulatory receptor. While TCR signal transduction is a well characterized pathway, CD28 downstream signaling remains nebulous. Our lab has previously generated a panel of Jurkat signaling mutant cell lines (the J.REMs) in which TCR/CD28 stimulation fails to upregulate the RE/AP composite element of the IL-2 promoter. However, TCR signaling is not globally altered, as TCR stimulation leading to NFAT activation is normal in this panel of Jurkat mutant cell lines. Examination of the J.REM's for defects in previously characterized signaling intermediates implicated in CD28 costimulation did not yield any clues as to the nature of the molecular defect in these Jurkat mutant cell lines.

Therefore, a retroviral based genetic screen was utilized to identify cDNAs which could rescue the defect and restore RE/AP activation in one of these mutant cell lines. From this screen, we would predict that we may re-express a wild-type copy of the mutated gene responsible for the signaling defect.

Alternatively, we may also identify regulators of T cell activation whose expression may compensate for the signaling defect. In our initial screen, we have identified one cell line in which RE/AP activation was restored by retroviral rescue. Preliminary data will be presented.