



INTEGRATING SIGNALS FROM THE T-CELL RECEPTOR AND THE INTERLEUKIN-2 RECEPTOR

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The ability of T cells to orchestrate the adaptive immune response makes them an attractive target for modulating the immune response during allergy, transplantation, or autoimmune disease. Traditional immune suppressive therapies prevent disease progression but also leave the patient susceptible infections, as they block all T-cell responses and not just those involved in the disease. To develop more specific therapies and to identify novel targets for modulating T-cell responses we have established a model describing T-cell receptor (TCR) signaling that includes the TCR, the co-receptor CD4/8 and the co-stimulatory molecule CD28. However, to be of value for predicting new intervention strategies, the current receptor signaling pathways that are already utilized as targets must also be included to compare the effectiveness of each approach. Therefore we generated the interleukin-2 receptor (IL-2R) signaling network to supplement our existing TCR model. We developed a tool that allows one to merge logical models of signaling networks, predict potential cross-talk and aid the design of corresponding experiments. The merged model allows us to investigate the interplay of signals given by the two receptors and their relative contribution to downstream signaling events.

We show that STAT after IL-2 stimulation is independent of both Src family kinases and PI3K while, in contrast, ERK activation is dependent on these kinases and in addition requires novel PKCs similar to TCR signaling. Our model predicted that TCR triggering should activate STATs. Interestingly, we could indeed demonstrate different effects of TCR stimulation on the activation of STAT3 and STAT5 in human T cells. The combined network allows us to predict potential pathways for JNK and p38 activation in IL-2 signaling that were previously unreported. In summary, the merged model of two receptor systems enables us to unravel potential cross-talk and suggests new experimental designs.

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