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Reverse signaling by FasL inhibits primary human T cell activation

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The death-factor Fas Ligand (FasL) is best known for its capacity to induce cell death in Fas-expressing cells. Besides its death-promoting activity, FasL has been implicated in reverse signaling and might thus also play a role in T cell development and selection and the modulation of T cell activation by acting as a costimulatory receptor. Here we have analyzed the influence of FasL-costimulation on TCR/CD3/CD28-triggered activation of peripheral human T-lymphocytes. Interestingly, FasL engagement inhibited the proliferation of PBMC, $CD8^+$ as well as $CD4^+$ T cells. Plate-bound but not soluble FasFc fusion protein or anti-FasL pAb blocked CD3/CD28-induced proliferation almost completely. We observed not only less proliferation, but also decreased IL-2 production and reduced expression of the activation markers CD69 and CD25. Importantly, FasFc costimulation also resulted in a dramatic inhibition of TCR internalization, thereby preventing TCR translocation and the formation of signaling platforms essential for optimal T cell activation. Consistent with these findings, various crucial signaling components of the T cell receptor activation pathway were inhibited by FasL triggering and reverse signalling. In this context, the phosphorylation of ERK1/2, p38 MAPK as well as further upstream acting signaling proteins such as PLCγ was markedly reduced. Notably, the inhibition was also observed in the presence of exogenous rIL-2, indicating that a lack of IL-2 is not the cause of the proliferation block. Taken together, our data argue for a negative reverse signaling capacity of FasL on freshly isolated, TCR-triggered human T cells.