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Meeting abstract

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CD95 as a negative or positive costimulatory receptor for primary T cell activation

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The CD95/CD95L- (Fas/FasL-) system is best known for its capacity to induce cell death. However, recent data indicate an additional role for Fas (CD95) in obviously conflicting functions namely activation and proliferation. We therefore investigated the effect of Fas co-ligation during TCR/CD3/CD28-triggered activation of freshly isolated human T-lymphocytes. We noted that plate-bound but not soluble agonistic anti-Fas antibodies led to an accelerated proliferation, suggesting a strong positive costimulatory effect of Fas. Consistent with this observation, more IL-2 and IFNg was produced and we observed enhanced phosphorylation of STAT5, increased MAPK and caspase activation and strong upregulation of activation markers and cell cycle proteins including CDKs and cyclins. Also, as a consequence of ERK1/2 activation, the phosphorylation of the Retino Blastoma Protein (Rb) at serine 780 and 795 was more pronounced. Moreover, activation-induced TCR internalization was enhanced upon Fas-costimulation, allowing improved TCR translocation and generation of signal platforms for optimal T cell activation. Much to our surprise, ligation of Fas by plate-bound but not soluble FasLFc fusion protein had an opposite effect and blocked TCR-induced proliferation almost completely. In this context, crucial events associated with T cell activation, i.e. tyrosine and ERK1/2 phosphorylation, expression of activation markers, IL-2 production and caspase activation were abrogated. Although we do not have a clear explanation for the opposite effects of the two types of ligation of the very same receptor, we hope to find the answer in ongoing experiments using a number of contructs that allow for differential oligomerziation or using FasL-transfectants to replace the fusion proteins and monoclonal antibodies to establish a more physiological situation for primary T cell activation.

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