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Meeting abstract

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T Cell transformation by herpesvirus saimiri requires STAT5 pathways

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Aberrant growth stimulation by Signal Transducers and Activators of Transcription (STAT) is implicated in human carcinogenesis. The viral effector oncoprotein Tip, which binds to and is phosphorylated by the T-cell lymphocyte kinase Lck, is crucial in the activation of the cellular STAT5 signalling pathway in Herpesvirus-transformed T-cell lines, a model for malignant T-cell proliferation. While Tip-Lck interaction is required for transformation by HVS, mutation of Tip tyrosine residues had distinct effects. Two defined mutations of Tip can direct the phosphorylation and activation of either STAT3 *or* STAT5 by Lck. Tip Y114 mutation to phenylalanine (TipY114F) abolished the constitutive STAT3 activation observed in HVS-wildtype transformed T cells. Conversely, TipY114F enhanced the efficiency of human T cell transformation in absence of exogenous interleukin-2 (IL-2). In contrast, mutation of the major phosphorylation site, Y127, in Tip is compatible with viral transformation only when IL-2 is supplemented. This growth factor requirement correlated with STAT5 activation by Lck and Tip. Our current work focuses on the synergy among Tip, Lck, STAT5 and JAK family kinases. Interaction analysis will address whether Tip or the Y127F mutant mediate interactions between STAT5 and Lck or other Src family members. The role of the JAK-STAT pathway was elucidated using specific JAK inhibitors. We assume that, for viral transformation, Tip preferentially targets and reprograms the STAT5 pathway, which is central for T-cell growth and homeostasis. Comparable modulation of the STAT5 signalling may be involved in other forms of malignancy and cell differentiation; their analysis may therefore be a useful model for the development of new therapeutics.