INTRODUCTION

The Ras-Raf-MEK-ERK pathway is a ubiquitously expressed signalling module and activated by receptor tyrosine kinases, G-protein coupled receptors and integrins. This pathway can regulate different biological programs. Deregluation of this pathway is involved in development of human tumors. The kinase activity of Raf-1 is tightly regulated. This includes phosphorylation and dephosphorylation by Src and PP2A, respectively. GTPases that recruit Raf to the plasma membrane e.g. Ras and scaffold proteins that are platforms for signalling complexes e.g. CNK1 as shown here.

I. CNK1 regulates Src-mediated Raf-1 activation

Fig. 1: (Top) Schematic representation of human CNK1. SAM: sterile alpha motif domain; CRIC: conserved region in CNK; PDZ: PSD-95/Dlg/ZO-1 domain; PRO: proline-rich domain; PH: pleckstrin homology region. (Bottom) Schematic representation of Raf-1 and B-Raf. RBD: Ras-binding domain; PK: protein kinase domain; YY: two neighboured tyrosine residues; DD: two neighboured proline-rich residues.

II. CNK1 interacts with the angiotensin II type 2 receptor

Fig. 2: HEK 293 cells were transfected with plasmids as indicated. Interaction between CNK1 and Raf proteins were analysed by immunoprecipitation with anti-Flag antibody followed by immunoblotting with anti-HA antibody. (Left) Interaction of Flag-Raf and the activated Raf-1 mutant Flag-RafK375E with HA-CNK1 in the absence or presence of activated RasV12. (Right) Interaction of Flag-B-Raf with HA-CNK1 proteins.

CNK1 binds to Src and forms a trimeric complex with Raf-1 and Src

Fig. 3: HEK 293T cells were cotransfected with HA-CNK1, Flag-Raf and the activated Raf-1 mutant Flag-RafK375E with HA-CNK1 in the absence or presence of activated RasV12. (Right) Interaction of Flag-B-Raf with HA-CNK1 proteins.

Putative role of CNK in AT2-dependent signalling pathways

Fig. 3: (Left) CNK may be involved in the AT2-dependent inhibition of proliferation via activation of protein tyrosine phosphatases. (Right) CNK proteins and the AT2 receptor act in differentiation of neuronal cells mediated by the Raf-MEK/ERK pathway.