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EGF Regulates the Interaction of Tks4 with Src through Its SH2 and SH3 Domains

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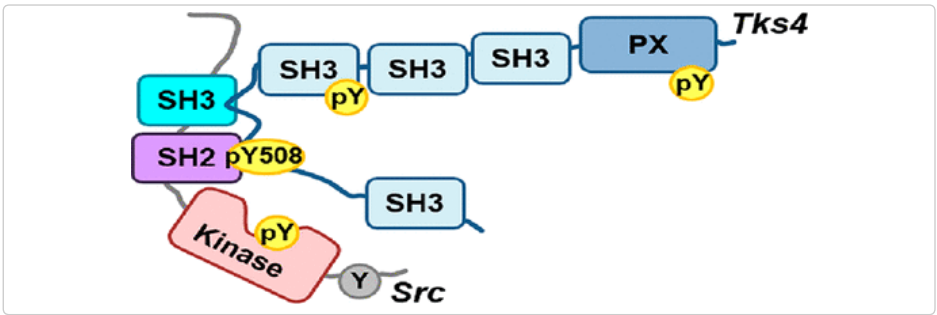
Abstract



The nonreceptor tyrosine kinase Src is a central component of the epidermal growth factor (EGF) signaling pathway. Our group recently showed that the Frank-ter Haar syndrome protein Tks4 (tyrosine kinase substrate with four Src homology 3 domains) is also involved in EGF signaling. Here we demonstrate that Tks4 and Src bind directly to each other and elucidate the details of the molecular mechanism of this complex formation. Results of GST pull-down and fluorescence polarization assays show that both a proline-rich SH3 binding motif (PSRPLPDAP, residues 466–474) and an adjacent phosphotyrosine-containing SH2 binding motif (pYEEI, residues 508–511) in Tks4 are responsible for Src binding. These motifs interact with the SH3 and SH2 domains of Src, respectively, leading to a synergistic enhancement of binding strength and a highly stable, “bidentate”-type of interaction. In agreement with these results, we found that the association of Src with Tks4 is permanent and the complex lasts at least 3 h in living cells. We conclude that the interaction of Tks4 with Src may result in the long term stabilization of the kinase in its active conformation, leading to prolonged Src activity following EGF stimulation.

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