Activation of the NGF receptor TrkA is regulated through homo- and hetero-dimer transmembrane domain interactions with p75 neurotrophin receptor

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An unsolved question in neurotrophin signaling is the molecular mechanism of how p75 modulates TrkA activation and the structural basis of their interaction. p75 sensitizes TrkA to lower concentrations of NGF but the mechanism is unknown. Here we found that TrkA activation is modulated by homo and hetero transmembrane domain (TMD) interactions with itself and with p75. NMR spectroscopy, cysteine-scanning mutagenesis and functional studies revealed the structural basis of TrkA-TMD dimerization and the active dimer interface. NGF induce a rotation of the transmembrane domain of TrkA. NMR titration experiments reveal the formation of a heterocomplex between the transmembrane domains of TrkA and p75 through an interaction the N-terminus of the TMD a-helix. In the absence of NGF p75 keeps TrkA activity in check by reducing TrkA autoactivation. These findings support a conformational mechanism of TrkA activation by p75 and provide a new structural framework for understanding the nature of the NGF high-affinity complex.