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Activation of the p75 Neurotrophin Receptor through Conformational Rearrangement of Disulphide-linked Receptor Dimers

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Ligand-mediated receptor dimerization has emerged as a universal mechanism of growth factor receptor activation. Neurotrophins interact with dimers of the p75 neurotrophin receptor ($p75^{NTR}$), but the mechanism of receptor activation has remained elusive. Here, we show that $p75^{NTR}$ forms disulphide-linked dimers independently of neurotrophin binding through the highly conserved Cys^{257} in its transmembrane domain. Mutation of Cys^{257} abolished neurotrophin-dependent receptor activity but did not affect downstream signaling by the $p75^{NTR}$/NgR/Lingo-1 complex in response to MAG, indicating the existence of distinct, ligand-specific activation mechanisms for $p75^{NTR}$. FRET experiments revealed a close association of $p75^{NTR}$ intracellular domains that was transiently disrupted by conformational changes induced upon NGF binding. Although mutation of Cys^{257} did not alter the oligomeric state of $p75^{NTR}$, the mutant receptor was no longer able to propagate conformational changes to the cytoplasmic domain upon ligand binding.

In addition, we also show that cross-linking of $p75^{NTR}$ dimers by cysteine-scanning mutagenesis results in constitutive, ligand-independent activity in several pathways that are normally engaged upon neurotrophin stimulation of native receptors. The activity profiles of different disulfide-crosslinked $p75^{NTR}$ mutants were similar but not identical, suggesting that different configurations of $p75^{NTR}$ dimers might be endowed with different functions.

Together, these results indicate that dimeric mutants of $p75^{NTR}$ functionally resemble neurotrophin bound, not neurotrophin-free, receptors, support formation or stabilization of receptor dimers and oligomers as the mechanism by which neurotrophins activate $p75^{NTR}$, and reveal a genetic approach to generate gain-of-function receptor variants with distinct functional profiles.