The receptor is activated

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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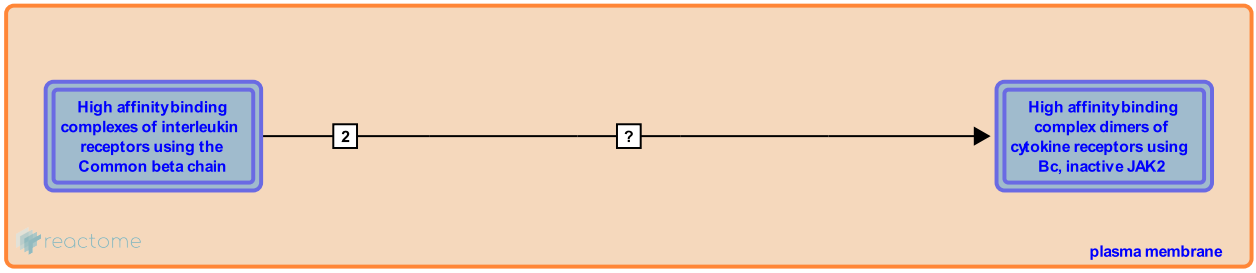
Stable identifier: R-HSA-879942

Type: uncertain

Compartments: plasma membrane



Upon ligand binding to the alpha subunit, the alpha and Bc subunits asociate, forming a high affinity receptor. Subsequent signaling may require a disulfide-linked association between the alpha and beta chains (Stomski et al. 1996). While the formation of a 1:1:1 complex of interleukin:alpha subunit:common beta subunit represents a high-affinity binding complex, receptor activation involves the formation of higher order multimeric structures. The stoichiometry of endogenous active receptor complexes is not clear, but studies using dominant-negative, chimeric, and mutant receptors and modeling studies all suggest that a minimum of two Bc subunits are required for receptor activation and signaling (Guthridge et al. 1998, Hansen et al. 2008).

The cytoplasmic region of Bc contains several tyrosines that become phosphorylated on cytokine binding (Sorensen et al. 1989, Duronio et al. 1992, Sakamaki et al. 1992, Pratt et al. 1996). One such site is Y766, numbered according to the Uniprot canonical sequence. Note that in many publications this position is numbered as 750, referring to the mature sequence with signal peptide removed. These phosphorylations are mediated by receptor-associated kinases with JAK2 as the most likely candidate (Quelle et al. 1994, Guthridge et al. 1998). Specific phosphorylations appear to mediate association with different signaling components (Sato et al. 1993), e.g. substitution of F for Y766 prevents Shc phosphorylation (Inhorn et al. 1995) but not JAK2 phosphorylation. Modeling and structural data suggest that the active receptor is at least a dimer of ligand:alpha subunit:common beta subunit complexes (Bagley et al. 1997, Guthridge et al. 1998, Hansen et al. 2008). This fits a model of receptor activation whereby dimerization leads to Jak2 activation by transphosphorylation of the activation sites (Ihle et al. 1995, Guthridge et al. 1998, Hansen et al. 2008), leading to Bc activation by phosphorylation. The active receptors are represented here as dimers of ligand:alpha subunit:common beta subunit complexes.

Literature references

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Editions

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