Interleukin-3, Interleukin-5 and GM-CSF signaling


European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

30/03/2020
**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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

**Literature references**


Reactome database release: 72

This document contains 3 pathways and 25 reactions (see Table of Contents)
Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-512988

**Compartments:** plasma membrane

The Interleukin-3 (IL-3), IL-5 and Granulocyte-macrophage colony stimulating factor (GM-CSF) receptors form a family of heterodimeric receptors that have specific alpha chains but share a common beta subunit, often referred to as the common beta (Bc). Both subunits contain extracellular conserved motifs typical of the cytokine receptor superfamily. The cytoplasmic domains have limited similarity with other cytokine receptors and lack detectable catalytic domains such as tyrosine kinase domains.

IL-3 is a 20-26 kDa product of CD4+ T cells that acts on the most immature marrow progenitors. IL-3 is capable of inducing the growth and differentiation of multi-potential hematopoietic stem cells, neutrophils, eosinophils, megakaryocytes, macrophages, lymphoid and erythroid cells. IL-3 has been used to support the proliferation of murine cell lines with properties of multi-potential progenitors, immature myeloid as well as T and pre-B lymphoid cells (Miyajima et al. 1992). IL-5 is a hematopoietic growth factor responsible for the maturation and differentiation of eosinophils. It was originally defined as a T-cell-derived cytokine that triggers activated B cells for terminal differentiation into antibody-secreting plasma cells. It also promotes the generation of cytotoxic T-cells from thymocytes. IL-5 induces the expression of IL-2 receptors (Kouro & Takatsu 2009). GM-CSF is produced by cells (T-lymphocytes, tissue macrophages, endothelial cells, mast cells) found at sites of inflammatory responses. It stimulates the growth and development of progenitors of granulocytes and macrophages, and the production and maturation of dendritic cells. It stimulates myeloblast and monoblast differentiation, synergises with Epo in the proliferation of erythroid and megakaryocytic progenitor cells, acts as an autocrine mediator of growth for some types of acute myeloid leukemia, is a strong chemoattractant for neutrophils and eosinophils. It enhances the activity of neutrophils and macrophages. Under steady-state conditions GM-CSF is not essential for the production of myeloid cells, but it is required for the proper development of alveolar macrophages, otherwise, pulmonary alveolar proteinosis (PAP) develops. A growing body of evid-
ence suggests that GM-CSF plays a key role in emergency hematopoiesis (predominantly myelopoiesis) in response to infection, including the production of granulocytes and macrophages in the bone marrow and their maintenance, survival, and functional activation at sites of injury or insult (Hercus et al. 2009).

All three receptors have alpha chains that bind their specific ligands with low affinity (de Groot et al. 1998). Bc then associates with the alpha chain forming a high affinity receptor (Geijsen et al. 2001), though the in vivo receptor is likely be a higher order multimer as recently demonstrated for the GM-CSF receptor (Hansen et al. 2008).

The receptor chains lack intrinsic kinase activity, instead they interact with and activate signaling kinases, notably Janus Kinase 2 (JAK2). These phosphorylate the common beta subunit, allowing recruitment of signaling molecules such as Shc, the phosphatidylinositol 3-kinases (PI3Ks), and the Signal Transducers and Activators of Transcription (STATs). The cytoplasmic domain of Bc has two distinct functional domains: the membrane proximal region mediates the induction of proliferation-associated genes such as c-myc, pim-1 and oncostatin M. This region binds multiple signal-transducing proteins including JAK2 (Quelle et al. 1994), STATs, c-Src and PI3 kinase (Rao and Mufson, 1995). The membrane distal domain is required for cytokine-induced growth inhibition and is necessary for the viability of hematopoietic cells (Inhorn et al. 1995). This region interacts with signal-transducing proteins such as Shc (Inhorn et al. 1995) and SHP and mediates the transcriptional activation of c-fos, c-jun, c-Raf and p70S6K (Reddy et al. 2000).

Figure reproduced by permission from Macmillan Publishers Ltd: Leukemia, WL Blalock et al. 13:1109-1166, copyright 1999. Note that residue numbering in this diagram refers to the mature Common beta chain with signal peptide removed.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
The common beta chain IL3RB binds JAK2

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879937

**Type:** binding

**Compartments:** cytosol, plasma membrane

**Inferred from:** Mouse JAK2 binds human common beta chain (Homo sapiens)

JAK2 associates with IL3 receptor beta chain (IL3RB) better known as the cytokine receptor common beta chain (Bc). This association was not found to be dependent upon, or influenced by, the presence of GM-CSF or the GM-CSF receptor alpha chain, suggesting that JAK2 and Bc may be constitutively associated (Quelle et al. 1994).

**Followed by:** Interleukin-3 receptor alpha: Interleukin-3 binds IL3RB:JAK2, Interleukin-5:Interleukin-5 receptor alpha binds IL3RB:JAK2, GM-CSF receptor alpha:GM-CSF binds Bc

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
The GM-CSF receptor alpha subunit has a single transmembrane domain, a glycosylated extracellular domain and a short (54 amino acids) cytoplasmic tail, containing no tyrosine kinase domain (Gearing et al. 1989). It binds GM-CSF with a relatively low affinity, and is not capable of signaling. The cytoplasmic domain of the alpha chain appears to be critical for GM-CSF signaling (Matsuguchi et al. 1997).

Followed by: GM-CSF receptor alpha:GM-CSF binds Bc

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
GM-CSF receptor alpha:GM-CSF binds Bc

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-913371

Type: binding

Compartments: plasma membrane

The alpha subunit of the GM-CSF receptor binds GM-CSF with relatively low affinity. Binding of this dimer to the common beta subunit (Bc) confers high affinity binding. Recent models of receptor activation suggest a sequential activation that is initiated by the low-affinity interaction of GM-CSF with the alpha chain to form a binary complex. This binary complex is then able to bind preformed Bc dimers generating a 2:2:2 hexameric complex (Hansen et al. 2008).

Preceded by: GM-CSF receptor alpha subunit binds GM-CSF, The common beta chain IL3RB binds JAK2

Followed by: Tyrosine kinases phosphorylate the receptor, The receptor is activated

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored</th>
<th>Edited</th>
<th>Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Ray, KP.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-08-06</td>
<td></td>
<td>Jupe, S.</td>
<td></td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Lopez, AF.</td>
<td>Hercus, TR.</td>
<td></td>
</tr>
</tbody>
</table>

https://reactome.org
Interleukin-5 is a homodimer

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-913446

Type: binding

Compartments: extracellular region

Human IL-5 is a disulphide-linked homodimer with 115 amino-acid residues in each chain.

Followed by: Interleukin-5 receptor alpha subunit binds Interleukin-5

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
**Interleukin-5 receptor alpha subunit binds Interleukin-5**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-913456

**Type:** binding

**Compartments:** extracellular region, plasma membrane

The Interleukin-5 receptor alpha subunit (IL5Ra) has a single transmembrane domain, a glycosylated extracellular domain and a short (58 amino acids) cytoplasmic tail, containing no tyrosine kinase domain. It binds IL-5 with a relatively low affinity and is not capable of signaling by itself.

The alpha subunit has alternatively spliced soluble forms that are capable of binding IL-5 and act as natural antagonists of IL-5 signaling. The cytoplasmic domain of the alpha chain appears to be critical for IL-5 signaling (Takaki et al. 1993). IL5R alpha chain was found to be constitutively associated with JAK2 (Ogata et al. 1998); the same study found that JAK1 was constitutively associated with Bc, though the consensus is that JAK2 is associated with Bc.

**Preceded by:** Interleukin-5 is a homodimer

**Followed by:** Interleukin-5:Interleukin-5 receptor alpha binds IL3RB:JAK2

**Literature references**

Tavernier, J., Devos, R., Cornelis, S., Tuypens, T., Van der Heyden, J., Fiers, W. et al. (1991). A human high affinity interleukin-5 receptor (IL5R) is composed of an IL5-specific alpha chain and a beta chain shared with the receptor for GM-CSF. *Cell*, 66, 1175-84.

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
Interleukin-5: Interleukin-5 receptor alpha binds IL3RB:JAK2

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-913370

**Type:** binding

**Compartments:** plasma membrane

The alpha subunit of the IL5 receptor binds IL-5 with relatively low affinity. Binding of this dimer to the common beta subunit (Bc) confers high affinity binding. Recent models of receptor activation suggest a sequential activation that is initiated by the low-affinity interaction of ligand with the alpha chain to form a binary complex. This binary complex may bind preformed Bc dimers generating a 2:2:2 hexameric complex (Hansen et al. 2008).

**Preceded by:** Interleukin-5 receptor alpha subunit binds Interleukin-5, The common beta chain IL3RB binds JAK2

**Followed by:** Tyrosine kinases phosphorylate the receptor, The receptor is activated

**Literature references**

Tavernier, J., Devos, R., Cornelis, S., Tuypens, T., Van der Heyden, J., Fiers, W. et al. (1991). A human high affinity interleukin-5 receptor (IL5R) is composed of an IL5-specific alpha chain and a beta chain shared with the receptor for GM-CSF. Cell, 66, 1175-84.


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
<td></td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
<td></td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF.,</td>
<td>Hercus, TR.</td>
</tr>
</tbody>
</table>
**Interleukin-3 receptor alpha subunit binds Interleukin-3**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-450074

**Type:** binding

**Compartments:** extracellular region, plasma membrane

The Interleukin-3 receptor alpha subunit (IL3Ra) has a single transmembrane domain, a glycosylated extracellular domain and a short (53 amino acids) cytoplasmic tail, containing no tyrosine kinase domain (Kitamura et al. 1991). It binds interleukin-3 with low affinity, and is not capable of signaling by itself.

**Followed by:** Interleukin-3 receptor alpha: Interleukin-3 binds IL3RB:JAK2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
**Interleukin-3 receptor alpha: Interleukin-3 binds IL3RB:JAK2**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-450031

**Type:** binding

**Compartments:** plasma membrane

The alpha subunit of the IL3 receptor binds IL 3 with low affinity. Binding of this dimer to the common beta subunit (Bc) confers high affinity binding. Recent models of receptor activation suggest a sequential activation that is initiated by the low-affinity interaction of ligand with the alpha chain to form a binary complex. This binary complex is then able to bind preformed Bc dimers generating a 2:2:2 hexameric complex (Hansen et al. 2008). Covalent linkage of the receptor subunits is required for receptor signalling (Stomski et al. 1996).

**Preceded by:** Interleukin-3 receptor alpha subunit binds Interleukin-3, The common beta chain IL3RB binds JAK2

**Followed by:** The receptor is activated, Tyrosine kinases phosphorylate the receptor

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
The receptor is activated

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-879942

Type: uncertain

Compartments: plasma membrane

Upon ligand binding to the alpha subunit, the alpha and Bc subunits associate, 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 (Innhorn 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.

Preceded by: Interleukin-3 receptor alpha: Interleukin-3 binds IL3RB:JAK2, Interleukin-5:Interleukin-5 receptor alpha binds IL3RB:JAK2, GM-CSF receptor alpha:GM-CSF binds Bc

Followed by: IL3RB is phosphorylated on Ser-585, JAK2 is phosphorylated, activated, Tyrosine kinases phosphorylate the receptor

Literature references


<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
**JAK2 is phosphorylated, activated**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879910

**Type:** transition

**Compartments:** cytosol, plasma membrane

JAK2 is tyrosine phosphorylated in response to IL-3 (Silvennoinen et al. 1993), GM-CSF (Quelle et al. 1994) and IL-5 (Cornelis et al. 1995) leading to kinase activity. Although structures of JAK kinase domains exist (e.g. Lucet et al. 2006) no complete structures of Janus kinases (JAKs) are available and the activation mechanism is poorly understood. Activation is believed to be a consequence of conformational changes, propagated from conformational changes in the common beta chain (Bc) following alpha-beta dimerization. This is believed to result in a trans-activation event whereby JAKs bound to activated, dimerized receptors phosphorylate and thereby activate each other (Quelle et al. 1994, Hou et al. 2002). This model is similar to IL2R activation of JAK1/3. In addition to the observed activation of JAK2 following stimulation with IL-3, IL-5 or GM-CSF, other supporting observations include: phosphorylation of JAK2 at Y1007 is critical for kinase activation (Feng et al. 1997, Lucet et al. 2006) and autophosphorylation at several other sites appears to regulate activity (e.g. Feener et al. 2004, Argetsinger et al. 2004, 2010). Only the critical Y1007 phosphorylation is represented for this reaction.

Constitutive activation of JAK2 resulting from the V617F mutation is present in over 95% of Polycythemia Vera patients (Dusa et al. 2010). F595 is indispensible for constitutive activation by V617F, but not for JAK2 activation, suggesting that this is not part of the cytokine-induced mechansim of JAK2 activation.

**Preceded by:** The receptor is activated

**Followed by:** STAT5 is recruited by JAK2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
STAT5 is recruited by JAK2

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879930

**Type:** transition

**Compartments:** cytosol, plasma membrane

Activated JAK2 binds to unphosphorylated STAT5; cytokine treatment of cells leads to JAK2 activation and promotes binding of JAK2 to unphosphorylated STAT5.

STAT5 proteins are considered the main targets of IL-3, IL-5 and GM-CSF signaling (Mui et al. 1995a, Mui et al. 1995b, Ihle, 2001), but other members of this family including STAT3 and STAT1 (Chin et al. 1996) can be involved, the STAT family member activated appears to depend on the cell line used in the study, rather than the cytokine (Reddy et al. 2000). IL-5 and GM-CSF increase STAT3 and 5 signaling (Caldehnoven et al. 1995, Stout et al. 2004).

Unphosphorylated STATs are cytoplasmic; tyrosine phosphorylation facilitates dimerization and translocation to the nucleus where they act as transcription factors. STATs were originally described as ligand-induced transcription factors in interferon-treated cells, subsequently they were shown to be critical in many signal transduction pathways associated with cytokines and neurokines including several interleukins, the interferons, erythropoietin, prolactin, growth hormone, oncostatin M (OSM), and ciliary neurotrophic factor (Darnell 1997, Reddy et al. 2000). JAK-STAT signaling is widely accepted as a primary signaling route for receptors that share the common beta subunit (Bc).

The role of the receptor itself in STAT5 binding is somewhat controversial because while STAT proteins can be recruited to tyrosine phosphorylated receptors via their SH2 domains (Greenlund et al. 1995, Li et al. 1997) binding of STAT5 to Bc has not been formally demonstrated (Guthridge et al. 1998), though tyrosine-phosphorylated peptides of Bc have been demonstrated to associate with STAT5, and anti-Bc or phosphotyrosine antibodies inhibited GM-CSF induced STAT5 DNA binding activity (Sakurai et al. 2000). Binding of JAK2 to STAT5 can occur in vitro when no receptor is present (Flores-Morales et al. 1998). STAT5 activation was seen when all six conserved cytoplasmic tyrosines in Bc were mutated to P (Okuda et al. 1997), but a C-terminal deletion mutant of Bc while able to activate JAK2 was unable to activate STAT5 (Smith et al. 1997). These observations suggest that JAK2 activation is a critical step in STAT signaling from Bc-containing receptors, but other factors may be required. It is not clear whether Bc is directly involved or not in STAT5 activation, but the specificity for particular STAT members is believed to be determined by STAT docking sites present on the receptor molecules, not JAK kinase preference (Reddy et al. 2000).
Preceded by: JAK2 is phosphorylated, activated

Followed by: Activation of STAT5a/b by JAK2

Literature references

**Activation of STAT5a/b by JAK2**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879909

**Type:** transition

**Compartments:** cytosol, plasma membrane

JAK2 phosphorylates STAT5; phosphorylated STAT5 dimerizes and translocates to the nucleus (Darnell et al., 1994), binds DNA and activates target genes including c-fos, pim-1, oncostatin M, and Id-1 (Mui et al. 1996). STAT5 activation is believed to be the primary signaling mechanism for Bc (Ihle, 2001).

**Preceded by:** STAT5 is recruited by JAK2

**Followed by:** p-STAT5 dissociates from the receptor complex

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
p-STAT5 dissociates from the receptor complex

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-921155

Type: transition

Compartments: cytosol, plasma membrane

Deletion mutants have demonstrated that STAT dimerization can occur independently of the binding of 2 STAT molecules by a dimeric receptor. Although this does not exclude the possibility that STATs may dimerize while still associated with the receptor complex, dimerization is believed to occur following the release of phosphorylated monomers (e.g. Turkson & Jove 2000).

**Preceded by:** Activation of STAT5a/b by JAK2

**Followed by:** p-STAT5 dimerizes

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
p-STAT5 dimerizes

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-452102

Type: binding

Compartments: cytosol

Inferred from: Phosphorylated Stat5 dimerizes (Mus musculus)

Phosphorylated STAT5A and STAT5B form homodimers and heterodimers in the cytosol (Gaffen et al. 1996, Rosenthal et al. 1997, also inferred from mouse homologs). Phosphorylation of a critical tyrosine residue in the SH domain (Y694 in STAT5A and Y699 in STAT5B) and intramolecular interactions between hydrophobic residues in the SH domain are required for dimerization (inferred from mouse homologs).

Preceded by: p-STAT5 dissociates from the receptor complex

Followed by: STAT5 dimers translocate to the nucleus

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored</th>
<th>Edited</th>
<th>Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Ray, KP.</td>
<td>Jupe, S.</td>
<td></td>
</tr>
<tr>
<td>2010-08-06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011-02-11</td>
<td></td>
<td></td>
<td>Villarino, A.</td>
</tr>
<tr>
<td>2011-03-17</td>
<td></td>
<td></td>
<td>Dooms, H.</td>
</tr>
</tbody>
</table>
**STAT5 dimers translocate to the nucleus**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-507937

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

Interleukin-7 (IL7)-activated Signal transducer and activator of transcription 5A or 5B (typically referred to as STAT5) is recruited rapidly to the promoters of IL7-regulated genes (Ye et al. 2001, Stanton & Brodeur 2005).

**Preceded by:** p-STAT5 dimerizes

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Type</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2011-02-11</td>
<td>Reviewed</td>
<td>Villarino, A.</td>
</tr>
<tr>
<td>2011-03-17</td>
<td>Reviewed</td>
<td>Dooms, H.</td>
</tr>
<tr>
<td>2011-06-23</td>
<td>Reviewed</td>
<td>Waters, MJ.</td>
</tr>
</tbody>
</table>
Tyrosine kinases phosphorylate the receptor

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879907

**Type:** transition

**Compartments:** cytosol, plasma membrane

Phosphorylation of the receptor common beta chain (Bc) creates binding sites for proteins that trigger subsequent signaling cascades (Pawson & Scott, 1997). 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 site is Y766 (numbered as Y750 by Sakamaki et al. 1992 and many other publications). Phosphorylation of Bc in response to GM-CSF/IL3 is observed at low temperatures (4 degrees C) that prevent the phosphorylation of other proteins, suggesting that the kinase responsible is likely to be physically associated with the receptor complex prior to stimulation (Miyajima et al. 1993). JAK2 is activated in response to IL-3, IL-5 and GM-CSF but signaling via JAK/STAT is not dependent on Bc tyrosine phosphorylation (Okuda et al. 1997). Based on these observations and the role of JAK1/3 in IL-2 signaling, JAK2 is believed to be the most likely candidate responsible for the phosphorylation of Bc (Guthridge et al. 1998). To represent the possible phosphorylation of Bc by kinases other than JAK2, this reaction includes receptor complexes with both active and inactive JAK2. Phosphorylation is represented only where this is necessary for subsequent signaling; phosphorylation at other positions is probable.

**Preceded by:** The receptor is activated, Interleukin-5:Interleukin-5 receptor alpha binds IL3RB:JAK2, GM-CSF receptor alpha:GM-CSF binds Bc, Interleukin-3 receptor alpha: Interleukin-3 binds IL3RB:JAK2

**Followed by:** SHP1 and SHP2 bind the common beta chain, Recruitment of SHC1 is mediated by Y593 of the common beta chain

**Literature references**


Recruitment of SHC1 is mediated by Y593 of the common beta chain

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879934

**Type:** transition

**Compartments:** cytosol, plasma membrane

Upon receptor activation, Shc is recruited to the receptor complex, where it becomes tyrosine phosphorylated. The recruitment of Shc is mediated by Y593 (Y577 in the mature peptide) of the common beta chain (Bc), which binds the PTB domain of Shc (Pratt et al. 1996).

Phosphorylated Shc interacts with Grb2 within a Grb2:Gab2 complex, promoting tyrosine phosphorylation of Gab2. The p85 subunit of PI3Kinases associates with phosphorylated Gab, and this induces activation of the catalytic p110 PI3K subunit leading to activation of Akt kinase, thereby regulating cell survival and/or proliferation.

**Preceded by:** Tyrosine kinases phosphorylate the receptor

**Followed by:** SHC1 bound to the common beta chain becomes tyrosine phosphorylated

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
SHC1 bound to the common beta chain becomes tyrosine phosphorylated

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-879925

**Type:** transition

**Compartments:** plasma membrane

IL-3, IL-5 and GM-CSF all induce tyrosine phosphorylation of Shc (Dorsch et al. 1994). Three sites are known to mediate specific downstream associations; tyrosine Y427 (Salcini et al. 1994) mediates the subsequent association of Shc with Grb2 (Salcini et al. 1994). The identity of the kinase is unknown. Y349 and Y350 phosphorylation is not required for Ras-MAPK signaling but are involved in IL-3-induced cell survival (Gotoh et al. 1996).

Residue numbering used here refers to Uniprot P29353 where the p66 isoform has been selected as the canonical form. Literature references given here refer to the p52 isoform which lacks the first 110 residues, so Y427 is referred to as Y317 in Salcini et al. 1994, Y349 and Y350 as Y239 and Y240 in Gotoh et al. 1996.

**Preceded by:** Recruitment of SHC1 is mediated by Y593 of the common beta chain

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
Phosphorylation of Shc at three tyrosine residues, 239, 240 (Gotoh et al. 1996) and 317 (Salcini et al. 1994) involves unidentified tyrosine kinases presumed to be part of the activated receptor complex. These phosphorylated tyrosines subsequently bind SH2 signaling proteins such as Grb2, Gab2 and SHIP that are involved in the regulation of different signaling pathways. Grb2 can associate with the guanosine diphosphate-guanosine triphosphate exchange factor Sos1, leading to Ras activation and regulation of cell proliferation. Downstream signals are mediated via the Raf-MEK-Erk pathway. Grb2 can also associate through Gab2 with PI3K and with SHIP.


Copyright American Society for Microbiology. All Rights Reserved.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2011-02-11</td>
<td>Reviewed</td>
<td>Villarino, A.</td>
</tr>
<tr>
<td>2011-03-17</td>
<td>Reviewed</td>
<td>Dooms, H.</td>
</tr>
</tbody>
</table>
Regulation of signaling by CBL

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-912631

Compartments: cytosol

Cbl is an E3 ubiquitin-protein ligase that negatively regulates signaling pathways by targeting proteins for ubiquitination and proteasomal degradation (Rao et al. 2002). Cbl negatively regulates PI3K via this mechanism (Dufour et al. 2008). The binding of Cbl to the p85 subunit of PI3K is mediated at least in part by tyrosine phosphorylation at Y731 (Dufour et al. 2008). Fyn and the related kinases Hck and Lyn are known to be associated with Cbl (Anderson et al. 1997, Hunter et al. 1999). Fyn is proven capable of Cbl Y731 phosphorylation (Hunter et al. 1999). The association of Fyn and Cbl has been described as constitutive (Hunter et al. 1999). CBL further associates with the p85 subunit of PI3K (Hartley et al. 1995, Anderson et al. 1997, Hunter et al. 1997), this also described as constitutive and mediated by the SH3 domain of p85. Binding of the SH2 domain of p85 to a specific phosphorylation site in Cbl is postulated to explain the increase in Cbl/p85 association seen in activated cells (Panchamoorthy et al 1996) which negatively regulates PI3K activity (Fang et al. 2001). The negative effect of increased Cbl-PI3K interaction is mediated by Y731 of Cbl. Cbl binding increases PI3K ubiquitination and proteasome degradation (Dufour et al. 2008).

Cbl is constitutively associated with Grb in resting hematopoietic cells (Anderson et al. 1997, Odai et al. 1995, Park et al. 1998, Panchamoorthy et al. 1996). Both the SH2 and SH3 domains of Grb2 are involved. Cbl has 2 distinct C-terminal domains, proximal and distal. The proximal domain binds Grb2 in resting and stimulated cells, and in stimulated cells also binds Shc. The distal domain binds the adaptor protein CRKL. Tyrosine phosphorylation of Cbl in response to IL-3 releases the SH3 domain of Grb2 which then is free to bind other molecules (Park et al. 1998). Cbl is tyrosine phosphorylated in response to many cytokines including IL-3, IL-2 (Gesbert et al. 1998) and IL-4 (Ueno et al. 1998).
Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
IL3 stimulation induces Vav binding to Tec kinase

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-879914

Type: binding

Compartments: cytosol

IL3 stimulation induces rapid and transient tyrosine-phosphorylation of Vav and the binding of Vav to Tec kinase through Tec homology domains. (Machide et al. 1995). Vav1 and Tec were seen to associate into a complex with the activated prolactin receptor (Kline et al. 2001). These reports were interpreted as Tec enhancing Vav GEF activity, but it has been suggested that Vav might contribute to Tec activation in T cell signaling (Reynolds et al. 2002). Tec kinases generally require PI3K-dependent membrane translocation and phosphorylation of the kinase domain, often by an Src family kinase, for activation (Takesono et al. 2002).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
**SHP1 and SHP2 bind the common beta chain**

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-909738

**Type:** binding

**Compartments:** cytosol, plasma membrane

The common beta chain (Bc) has at least at least one direct binding site for SHP-1/SHP-2 (P-TPN6/PTPN11). The SH2 domains of SHP1 and SHP2 associate with Y628 of Bc following IL-3 stimulation (Pei et al. 1994, Bone et al. 1997). SHPs act as regulators of signaling. SHP1 is thought to be a negative regulator of growth that terminates signals. Binding of SHP1 to EpoR leads to SHP1 activation and dephosphorylation of JAK2, terminating proliferative signals (Klingmuller et al. 1995). SHP1 has also been shown to interact directly and dephosphorylate JAK2 (Jiao et al. 1996). Although SHP-2 competes for the same binding site, it is thought to be a positive modulator. SHP2 associates with JAK1/2 and is phosphorylated at Y304 by these kinases, creating a GRB2 recognition motif (Yin et al. 1997). IL-3 induces the phosphorylation of SHP2 and its association with Grb2 (Welham et al. 1994). SHP2 could thereby act as an adaptor between Bc and Grb2 leading to activation of the ras/mitogen-activated protein kinase pathway. SHP2 can also associate with the p85 subunit of phosphatidylinositol 3-kinase (Welham et al. 1994) so SHP2 may also regulate this pathway.

**Preceded by:** Tyrosine kinases phosphorylate the receptor

**Followed by:** SHP2 can recruit GRB2, SHP1 and SHP2 dephosphorylate Y628 of IL3RB

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
SHP1 and SHP2 dephosphorylate Y628 of IL3RB

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-914036

**Type:** transition

**Compartments:** plasma membrane

Synthetic phosphopeptides based on Bc were dephosphorylated by SHP1 and SHP2, peptides phosphorylated at Y628 were the best substrate followed by those phosphorylated at Y766.

**Preceded by:** SHP1 and SHP2 bind the common beta chain

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
SHP2 can recruit GRB2

Location: Interleukin-3, Interleukin-5 and GM-CSF signaling

Stable identifier: R-HSA-914022

Type: binding

Compartments: cytosol

Inferred from: Shp2 can recruit Grb2 (Mus musculus)

SHP2 can associate with GRB2 (Stein-Gerlach et al. 1995). IL-3 induces the phosphorylation of SHP2 and its association with GRB2 (Welham et al. 1994).

SHP2 may act as a scaffold protein to recruit other signaling molecules, e.g. SHP2 was reported to link GRB2 to the receptor tyrosine kinase c-kit (Tauchi et al. 1994).

Preceded by: SHP1 and SHP2 bind the common beta chain

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
IL3RB is phosphorylated on Ser-585

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-913451

**Type:** transition

**Compartments:** cytosol, plasma membrane

GM-CSF and IL-3 application lead to Ser-585 phosphorylation of the Common beta chain (Bc) shared with the IL-3 and IL-5 receptors (Stomski et al. 1999, Guthridge et al. 2000). PKA was identified as capable of phosphorylating Bc at S585 (Guthridge et al. 2000).

**Preceded by:** The receptor is activated

**Followed by:** p-S585-IL3RB binds 14-3-3 proteins

**Literature references**

Stomski, FC., Dottore, M., Winnall, W., Guthridge, MA., Woodcock, J., Bagley, CJ. et al. (1999). Identification of a 14-3-3 binding sequence in the common beta chain of the granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and IL-5 receptors that is serine-phosphorylated by GM-CSF. *Blood*, 94, 1933-42.


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
p-S585-IL3RB binds 14-3-3 proteins ➔

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-912757

**Type:** binding

**Compartments:** cytosol, plasma membrane

The common beta chain (Bc), binds 14-3-3 zeta at a site that requires phosphorylation of Serine 585 (Stomski et al. 1999). Bc modifications that prevent Ser-585 phosphorylation do not recruit 14-3-3 zeta (Guthridge et al. 2000).

**Preceded by:** IL3RB is phosphorylated on Ser-585

**Followed by:** 14-3-3 zeta binding allows recruitment of PI3K

**Literature references**

Stomski, FC., Dottore, M., Winnall, W., Guthridge, MA., Woodcock, J., Bagley, CJ. et al. (1999). Identification of a 14-3-3 binding sequence in the common beta chain of the granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and IL-5 receptors that is serine-phosphorylated by GM-CSF. *Blood*, 94, 1933-42. ➔

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
14-3-3 zeta binding allows recruitment of PI3K

**Location:** Interleukin-3, Interleukin-5 and GM-CSF signaling

**Stable identifier:** R-HSA-914182

**Type:** binding

**Compartments:** cytosol, plasma membrane

Immunoprecipitation and kinase activity experiments demonstrated that Ser-585 phosphorylation of the common beta chain (Bc) was required for activation of PI3K activity in response to IL-3 and co-precipitation of Bc, 14-3-3 zeta and the p85 subunit of Class IA PI3 kinases (Guthridge et al. 2000). Subsequent experiments confirmed that Ser-585 phosphorylation and PI3K activation are required to promote cell survival in response to GM-CSF, but not for proliferation responses, and that this mechanism is independent of Bc tyrosine phosphorylation (Guthridge et al. 2004). This is one of two mechanisms described for the recruitment of PI3K to the IL-3/IL-5/GM-CSF receptors; the other involves Bc tyrosine-593 phosphorylation-mediated recruitment of SHC1, GRB2 and GAB2.

**Preceded by:** p-S585-IL3RB binds 14-3-3 proteins

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-05-17</td>
<td>Authored</td>
<td>Ray, KP.</td>
</tr>
<tr>
<td>2010-08-06</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-09-06</td>
<td>Reviewed</td>
<td>Lopez, AF., Hercus, TR.</td>
</tr>
</tbody>
</table>
# Table of Contents

- **Introduction**
- Interleukin-3, Interleukin-5 and GM-CSF signaling
  - The common beta chain IL3RB binds JAK2
  - GM-CSF receptor alpha subunit binds GM-CSF
  - GM-CSF receptor alpha:GM-CSF binds Bc
  - Interleukin-5 is a homodimer
  - Interleukin-5 receptor alpha subunit binds Interleukin-5
  - Interleukin-5:Interleukin-5 receptor alpha subunit binds IL3RB:JAK2
  - Interleukin-3 receptor alpha subunit binds Interleukin-3
  - Interleukin-3 receptor alpha: Interleukin-3 binds IL3RB:JAK2
- **The receptor is activated**
  - JAK2 is phosphorylated, activated
  - STAT5 is recruited by JAK2
  - Activation of STAT5a/b by JAK2
  - p-STAT5 dissociates from the receptor complex
  - p-STAT5 dimerizes
- **STAT5 dimers translocate to the nucleus**
  - Tyrosine kinases phosphorylate the receptor
  - Recruitment of SHC1 is mediated by Y593 of the common beta chain
  - SHC1 bound to the common beta chain becomes tyrosine phosphorylated
- Interleukin receptor SHC signaling
  - **Regulation of signaling by CBL**
    - IL3 stimulation induces Vav binding to Tec kinase
    - SHP1 and SHP2 bind the common beta chain
    - SHP1 and SHP2 dephosphorylate Y628 of IL3RB
    - SHP2 can recruit GRB2
    - IL3RB is phosphorylated on Ser-585
    - p-S585-IL3RB binds 14-3-3 proteins
    - 14-3-3 zeta binding allows recruitment of PI3K

Table of Contents

https://reactome.org