Class I cytokine receptors:
A model for cytokine receptor interactions.
Composed of 2 or 3 polypeptide chains (subunits)

- @ least 1 cytokine binding subunit
- @least 1 signal transducing subunit

Conserved AA seq motifs:

- 4 cysteine residues
- WSXWS
Fig. 12-7:

(a) GM-CSF receptor subfamily (common β subunit)

Unique subunit

responsible for cell signaling
(b) IL-6 Receptor subfamily (common gp130 subunit)

responsible for
cell signaling
(c) IL-2 receptor subfamily (common γ subunit)

responsible for cell signaling
What is the impact of sharing receptor subunits.
Sharing the signal-transduction subunit may lead to competition & antagonism:

Fig. 12-8, p. 310
Sharing of multiple subunits can explain redundancy:

All share the same beta ST subunit!

Same signal from all three
Cells expressing different receptor subunits may lead to low or high affinity receptors that modulate responses.
IL2 Receptor:
- $\beta$ chain
- $\gamma$ chain
- $\alpha$ chain - only expressed on activated T cells.

Required for signal transduction
Multisubunit receptors allows for possible differences in how different cell types respond to a cytokine.
Cytokine Binding mediates Cell Signaling Transduction
Overview of Cell Signal Transduction

- Neurotransmitters
- Chemokine receptors
  - Class I receptors
  - Class II receptors

Has enzymatic activity or interacts with a protein that has the enzymatic activity
Signal Transductions often involves phosphorylation:

- **Kinase** - enzyme that places phosphate groups on proteins.
  - Tyrosine kinase-
  - Serine-threonine kinase-
  - Histidine kinase

- Either receptor is a kinase OR associates with one.

- **Phosphatase** - enzyme that removes phosphates
  - Regulatory- OFF
In one class of receptors, the kinase domain is an intrinsic part of the receptor.

Ligand binding dimerizes the receptor, activating the kinases, which phosphorylate each other.

The activated kinases phosphorylate downstream substrates.

Figure 6-1 part 1 of 2 Immunobiology, 7ed. (© Garland Science 2008)
In another class of receptors, a kinase is noncovalently associated with the receptor.

Ligand binding dimerizes the receptor, activating the associated kinases, which phosphorylate each other.

The activated kinases phosphorylate downstream substrates.

Figure 6-1 part 2 of 2 Immunobiology, 7ed. © Garland Science 2008
Cytokine signal transduction depends upon a cytoplasmic protein tyrosine kinase:

Janus Kinase Family (JAKs):
- “2 heads”- 2 symmetrical kinase domains.
- Cytoplasmic tyrosine kinases
  - Associate with cytoplasmic tails of the receptors.
- Function-
Who are the activated Transcription Factors?

- STATs - Signal Transducer & Activator of Txn:
  - Contain SH2 domains:
    - Binds phosphorylated tyr.
    - Permits dimer formation.
    - Activated dimers function astxn activators (DNA binding domain).

![Diagram of STAT protein domains]
Figure 15–53 part 1 of 2. Molecular Biology of the Cell, 4th Edition.
SH2 domains creates a hole so that the tyr-P from other proteins can plug in!

Cytokine receptors consist of at least two chains, the cytoplasmic domains of which bind JAKs.

Cytokine binding dimerizes the receptor, bringing together the cytoplasmic JAKs, which activate each other and phosphorylate the receptor.

Transcription factors (STATs) bind to the phosphorylated receptors, and are, in turn, phosphorylated by the activated JAKs.

Phosphorylated STATs form dimers that move into the nucleus to initiate gene transcription.

Figure 6-25 The Immune System, 2/e (© Garland Science 2005)

Fig 6-25, p. 165, Parham.
Cytokine receptors consist of at least two chains, the cytoplasmic domains of which bind Janus kinases (JAKs).

Cytokine binding dimerizes the receptor, bringing together the cytoplasmic JAKs, which activate each other and phosphorylate the receptor.

Transcription factors (STATs) bind to the phosphorylated receptors, and are in turn phosphorylated by the activated JAKs.

Phosphorylated STATs form dimers that translocate into the nucleus to initiate new gene transcription.

Figure 6-30 Immunobiology, 7ed. (© Garland Science 2008)
Cytokine binding to the receptor leads to dimerization and activation of JAK family tyrosine kinases, which phosphorylate the receptor and STAT proteins. Tyrosine phosphorylation of STAT by JAK kinase results in dimerization of STAT, DNA binding, and specific gene transcription.
AFTER STATs DOCK ON SPECIFIC PHOSPHOTYROSINES ON THE RECEPTOR, THE Jaks PHOSPHORYLATE THEM

STATs MIGRATE TO NUCLEUS, BIND TO DNA AND OTHER GENE REGULATORY PROTEINS

STATs DISSOCIATE FROM RECEPTOR AND DIMERIZE VIA THEIR SH2 DOMAIN

DNA

α-interferon response element in target gene

TARGET GENE TRANSCRIPTION

Model applies to other cytokine receptors: (IL2)

http://binfo.ym.edu.tw/mb/images/stat_dimer.gif
How do cytokines mediate specific results in different cell types?

1. Use of individual receptors or different subfamily of receptors.

2. There are different STAT proteins & different JAKs.
   - Recognize different genes!

3. Same STATs may recognize different genes in different cell types.
Cytokines are grouped into those sharing receptor chains with IL-2, those using βe and others. IL-13Rα and γc appear to be alternative partners with IL-4Rα in the formation of functional IL-4 receptors. The murine IL-3R also has an alternative β-chain (not shown) which is not shared with the IL-5 and granulocyte/macrophage colony stimulating factor (GM-CSF) receptors. A second obligatory chain of the IL-10R (IL-10R2) has recently been identified. Reported Janus-activated kinase (Jak) and signal transducers and activators of transcription (STAT) usage is shown for each receptor, with the major STATs underlined in some cases, different usage has been reported in different cell types. Not distinguished here are the two isoforms identified for each of STAT1 and STAT5, whose different functions are poorly understood.

KELSO, ANNE
Cytokines: Principles and prospects.
Immunology and Cell Biology 76 (4), 300-317.