

2003

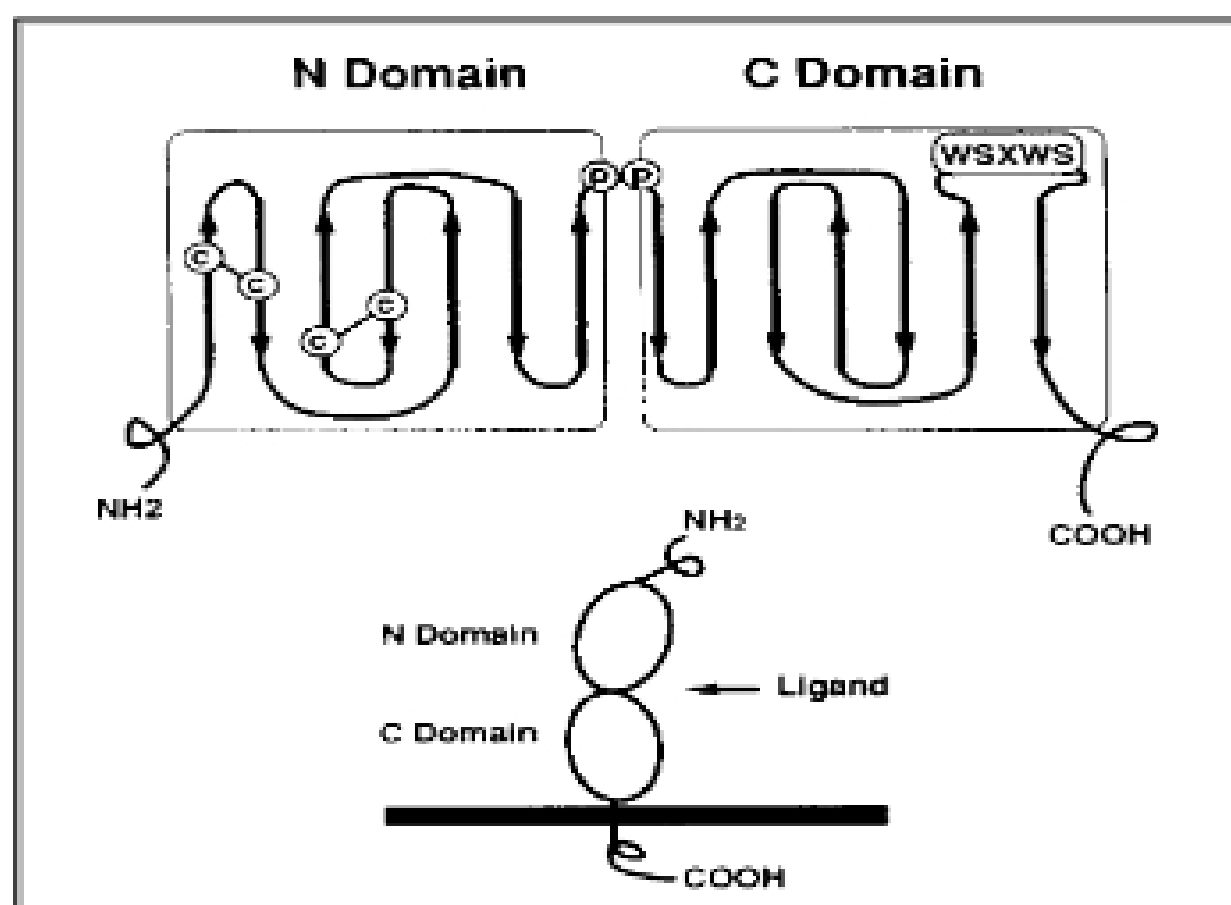
Readings:
 Abbas, Ch 12
 Janeway 6:15– 6:19
 Website pdf files

CYTOKINE RECEPTORS

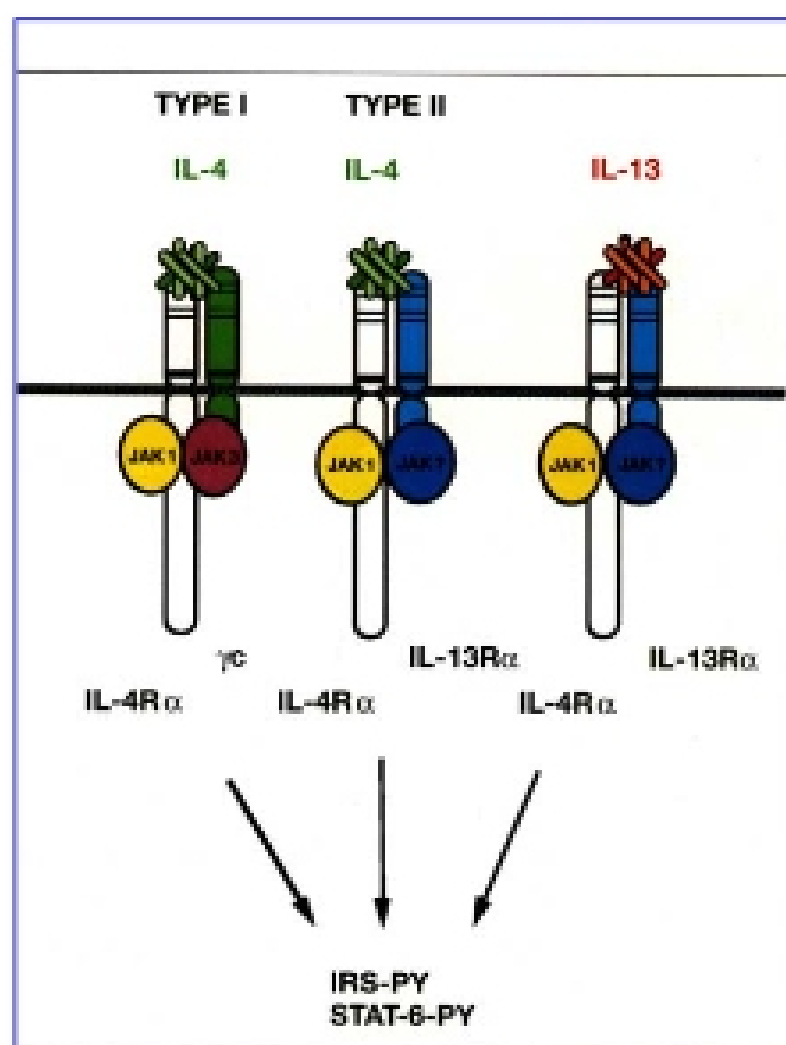
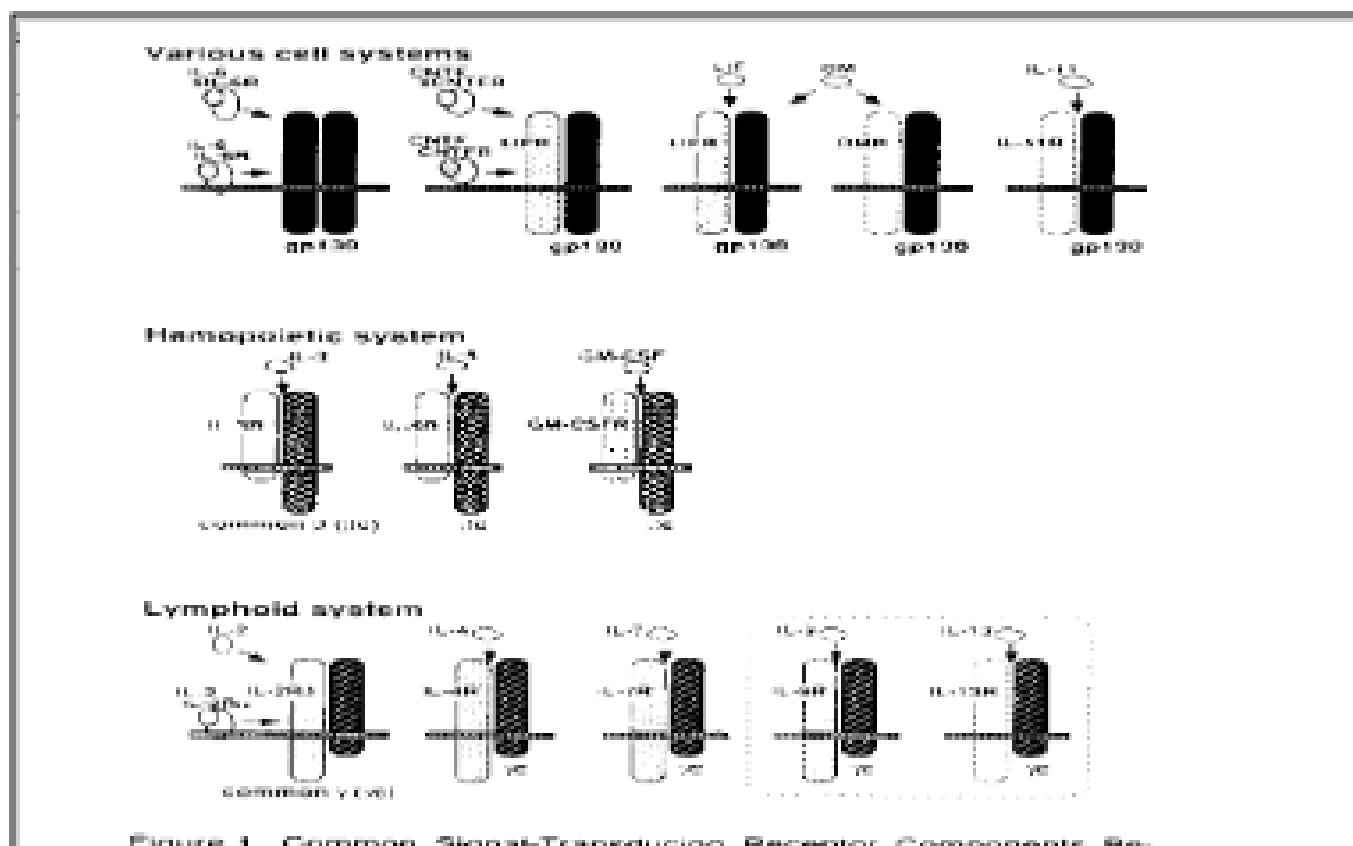
- I. A great deal of progress has been made in the past few years on cloning cytokines and cytokine receptors. In most cases this has been accomplished by expression cloning technology.
 - A. Expression cloning means isolation of protein is not needed

- II. Cytokines act by interaction with highly specific cell surface receptors on the respective target cells.
 - A. Affinities are usually in the $10^{10} M^{-1}$ range.
 - B. Receptor numbers vary from a high of 10^5 /cell to quite low - 10^2 /cell range - so it is obvious that only a small amount of ligand/receptor interaction is necessary for biological activity.
 - C. Complete receptors -- defined as what is necessary to deliver a biological signal -- usually consist of more than one polypeptide chain
 1. Considerable "sharing" of chains is seen --esp. with the hem. family receptors

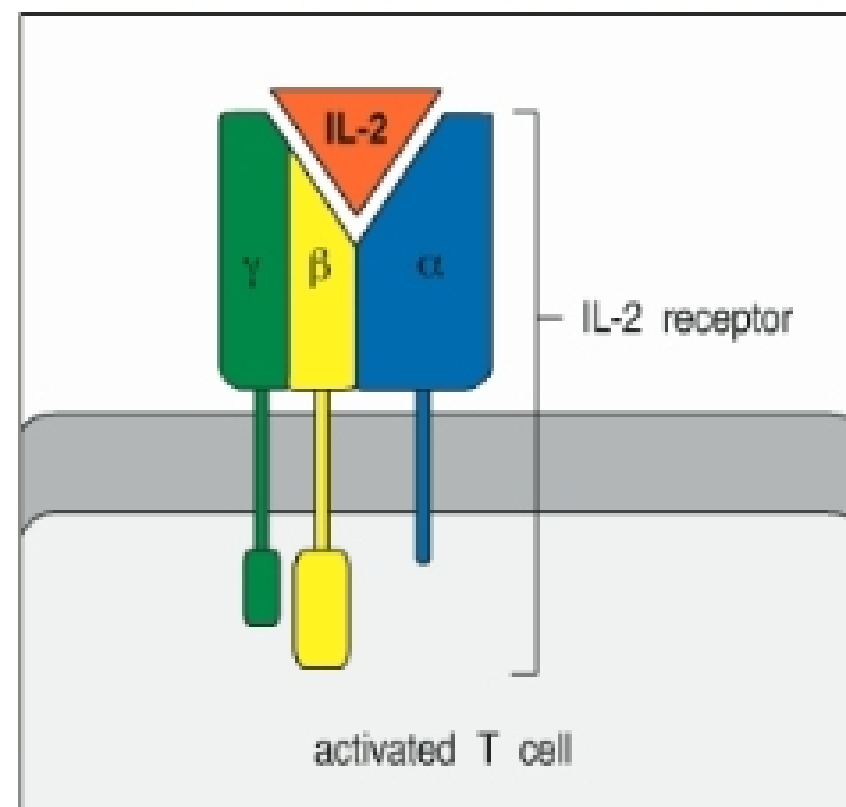
- III. Cloning has revealed several cytokine receptor families.
 - A. Hematopoiesis receptor family - =200 a.a. homologous region characterized by having four conserved cysteins in the amino-terminal half and WSXWS "motif" at its carboxy terminal end -- also is viewed as being composed of two fibronectin type III modules which results in a predicted "barrel-like" shape. The trough formed between two barrel-like modules may act as the cytokine binding pocket.



1. Both hematopoietins and hem. receptors have similar architecture.
2. Common characteristics of many of these receptors is presence of at least two chains.
3. Cytokines which are known to have two chain receptors (usually are dual affinity):
 - a. IL-2 - α (TAC), β , γ -- γ subunit is shared with IL-4 and IL-7
 - b. IL-3/GM-CSF/IL-5 - In man these three have a unique α but common β chain



- c. IL-6 - α is binding entity, GP-130 (2nd chain) is required for biological activity -- recent evidence indicates that gp130 may be the "trigger" for a number of other cytokines (LIF, OSM, CNTF, IL-11?, IL-12?)
- d. IL-4 / IL-13 – common alpha chain
- e. Multiple chains means a dual affinity if the cytokine binds to each chain vs single affinity. IL-4 - high affinity; IL-2, 3, 5, 7, GM-CSF - dual affinity. IL-6 has 2 chains -- but α has full affinity



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- f. Shared chains can represent a "weak link" in the redundancy of the system -- X-linked SCID with γ -chain of IL-2/4/7; hyperIgM with CD40L.

IV. Interferon receptor family

- A. Either one (γ -IFN) or two 200 a.a. domains containing conserved cys in both the amino and carboxy-terminal domains -- as with the hematopoietin receptor family, the domain is predicted to also be related to the fibronectin type III module
- B. Both Type I IFN α/β and IFN γ have two chain receptors.

V. TNF Receptor Gene Family

- A. Only example you were given was TNF α and TNF β which bind to two related receptors; these receptors have four extracellular repeats of a cysteine rich domain, usually with six conserved cys.
- B. CD40 -- natural ligand is a protein structurally related to TNF that is present on activated T cells and is crucial in T cell dependent B cell activation