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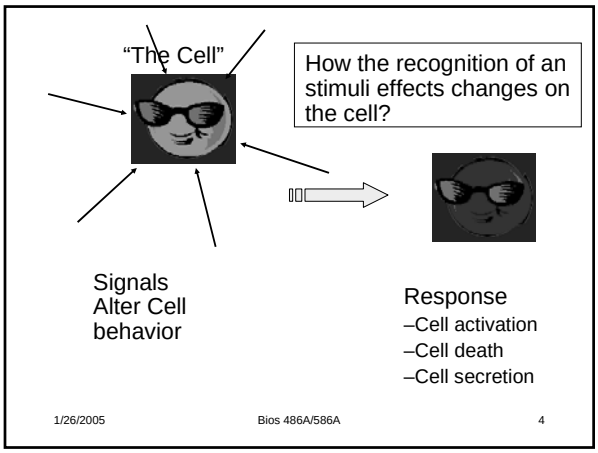
Signaling through lymphocyte receptors

- Overview
- Clustering
- Phosphorylation
- Signal trasduction
- Receptor signaling pathways
  - Antigen receptors
  - Other signaling pathways

Overview

- Cells communicate with their environment through surface receptors
- Receptors recognize and bind molecules
- Binding creates intracellular signals


"The Cell"
How the recognition of an stimuli effects changes on the cell?
Signals Alter Cell behavior
Response
–Cell activation
–Cell death
–Cell secretion
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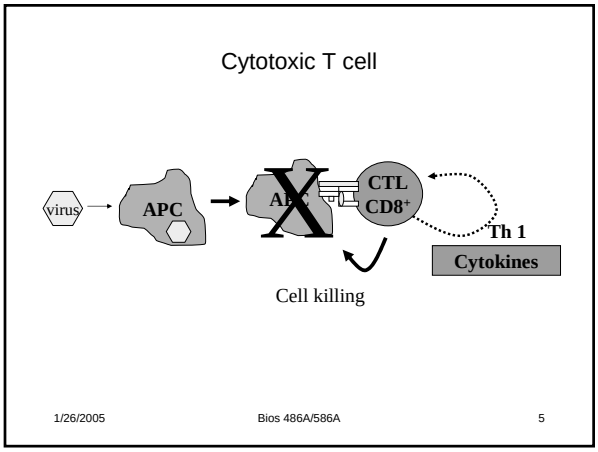
Cytotoxic T cell
virus
APC
CTL
CD8+
Th 1
Cytokines
Cell killing
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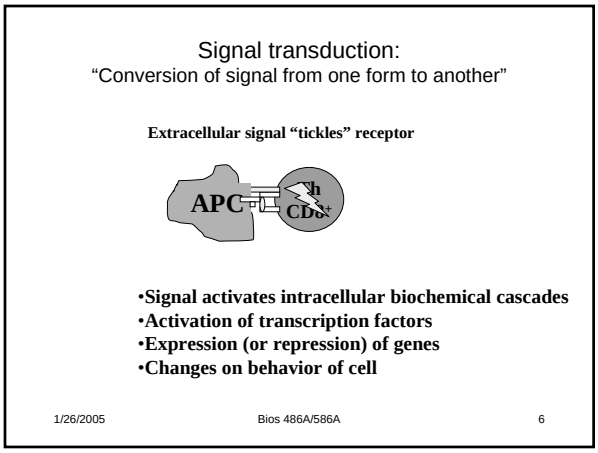
Signal transduction:
"Conversion of signal from one form to another"
Extracellular signal "tickles" receptor
APC
•Signal activates intracellular biochemical cascades
•Activation of transcription factors
•Expression (or repression) of genes
•Changes on behavior of cell
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Signal Transduction
Transmission of a physical signal into a biochemical signal

Extracellular receptor binding => activation of gene expression

Clustering

- Binding to 1 receptor => no signal
- Binding to 2 receptors
  Cross linking => weak signal
- Binding many receptors
  Large cross linking => strong signal

Clustering

1.- Cross-linking of receptors leads to Clustering/aggregation

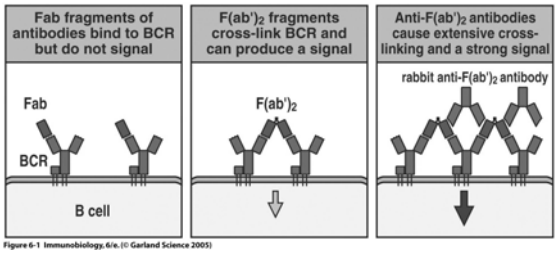
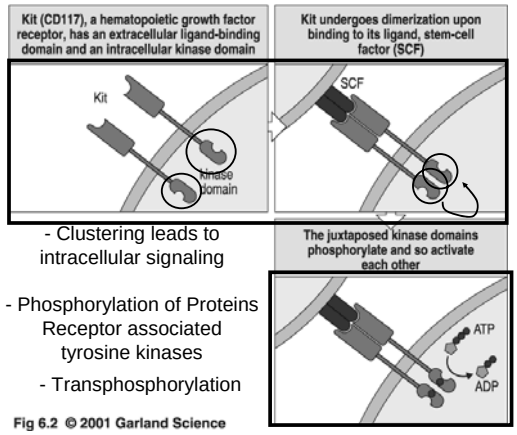


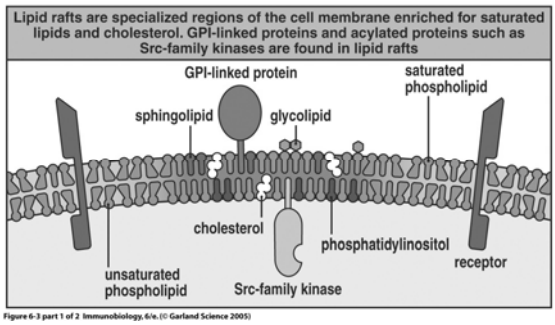
Figure 6-1 Immunobiology, 6/e. (© Garland Science 2005)

Why clustering?

- Receptors complexes have extracellular and intracellular components
- Clustering brings together the intracellular components of the receptor complex
- The physical proximity of the intracellular components triggers the initiation of the signaling cascade



- Clustering leads to intracellular signaling
- Phosphorylation of Proteins Receptor associated tyrosine kinases
- Transphosphorylation



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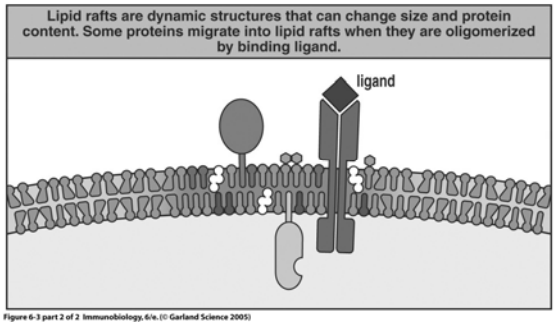

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Phosphorylation by protein kinases

- Protein kinases Phosphorylate proteins
  - Rapid
  - No new synthesis of proteins
  - Reversible by phosphatases
    - Enzyme Phosphorylated = Active
    - Enzyme de-phosphorylated = Inactive
  - Phosphorylation creates new binding sites for other proteins
    - Phosphorylation creates SH2 & SH3 binding domains
    - Inmobilize cytosolic proteins that are only active if bound to membrane
    - Increase the local concentration of proteins – amplification of the signal
- Only **tyrosine, serine**, threonine and histidine residues can be phosphorylated

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Adaptor molecules

- Phosphorylation creates binding sites for other molecules.

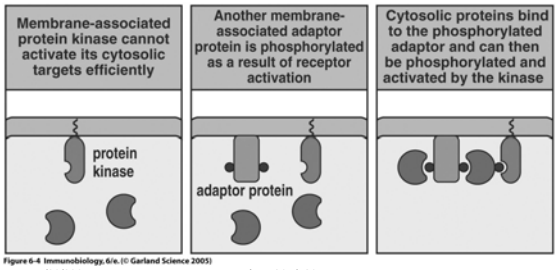

Figure 6-4 Immunobiology, 6/e. (© Garland Science 2005)

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Adaptor molecules = bridges

Phosphorylation creates a SH2 binding domain

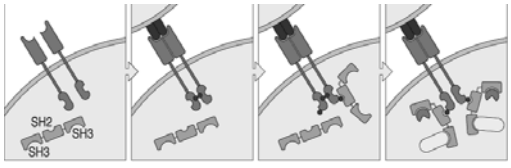

Fig 6.5 © 2001 Garland Science

- Adaptor molecules containing an SH2 domain
- These molecules also have SH3 domains
- Downstream proteins bind to the SH3 domain and get activated

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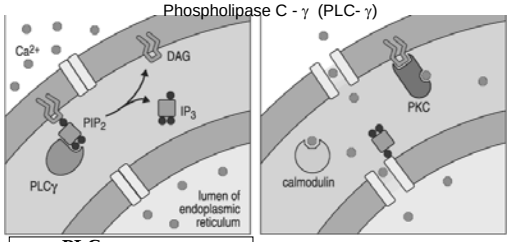
Phospholipase C - γ (PLC- γ)

- Contains 2 SH2 domains
- PLC- γ binds to the adaptor molecule bound to the receptor complex
- Phosphorylation of (PLC- γ) activates the enzyme
- Activated PLC- γ propagates and amplifies the signal

Membrane phospholipid Catabolism

Intracellular signaling molecules carry the signal onward and amplify it.

Figure 6.4 Phospholipase C - γ (PLC- γ)



PIP_2 **PLC-γ** DAG $+IP_3$

- Phosphatidylinositol-bisphosphate (PIP_2)
- diacylglycerol (DAG)
- Inositol triphosphate (IP_3)

IP_3 opens Ca^{2+} channels that allow entry from ER.
Ca^{2+} activates calmodulin
DAG activates PKC

G-Protein activation

- GEFs also bind to adaptor molecules
- GEFs activate G-Proteins
- G proteins activate the MAP Kinase cascade => activation of transcription factors

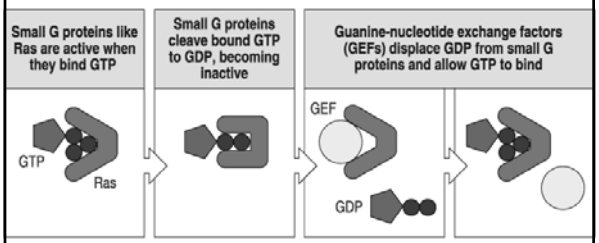


Fig 6.6 © 2001 Garland Science

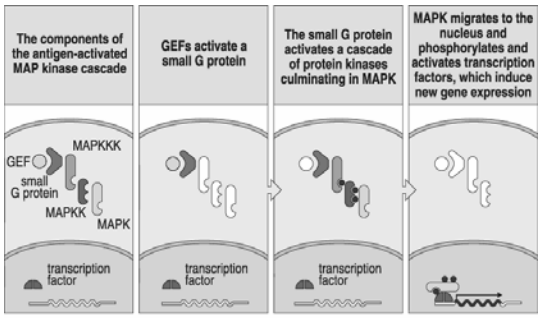
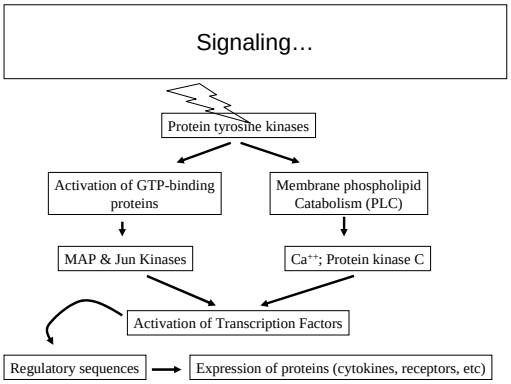


Fig 6.16 © 2001 Garland Science



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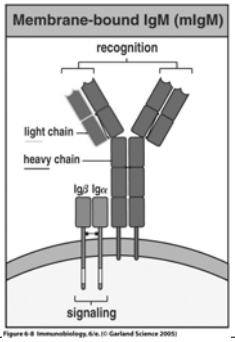
Receptor complex structure



- Ag receptors are associated with invariant accessory proteins
- Variable chains provide specificity (short cytoplasmic tail)
- Invariant accessory proteins participate in
  1. Transport of receptor to the membrane
  2. Signaling (long cytoplasmic tail)

- ITAMS = immunoreceptor tyrosine-based activation motifs
  1. Composed of 2 tyrosine residues

Immunoreceptor tyrosine-beased activation motifs (ITAMS)

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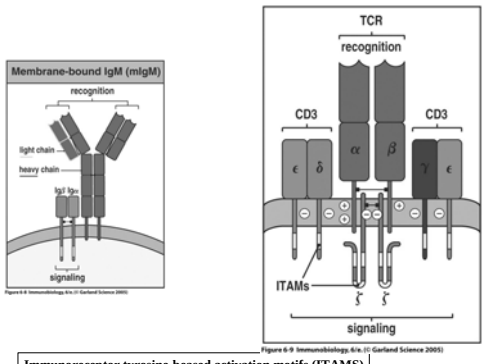
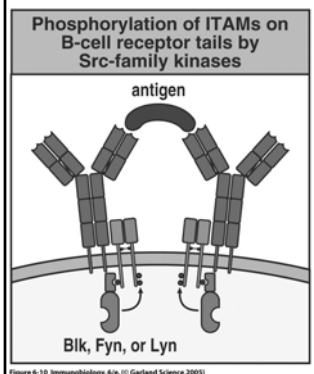
Receptor structure



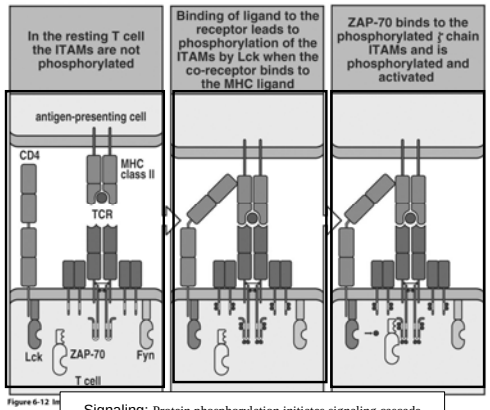
Immunoreceptor tyrosine-beased activation motifs (ITAMS)

Figs. 6.7; 6.8



First steps

- Clustering brings together ITAMS
- In B-cells ITAMS are phosphorylated by Src family kinases (Blk, Fyn, Lyn)
- In T cells Lck, associated with CD4 & CD8 co-receptor molecules also phosphorylates ITAMS



Signaling: Protein phosphorylation initiates signaling cascade

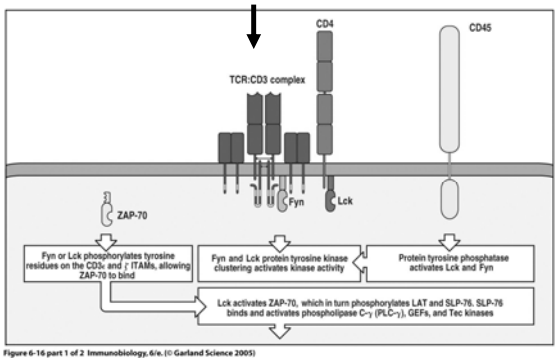


Figure 6-16 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

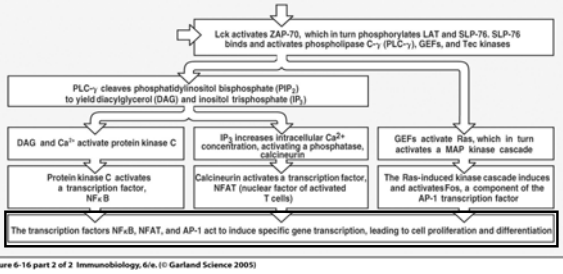


Figure 6-16 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Other signaling pathways

- Cytokines
- Toll Like Receptors
- Fas-Fas ligand
- Apaf1 activation

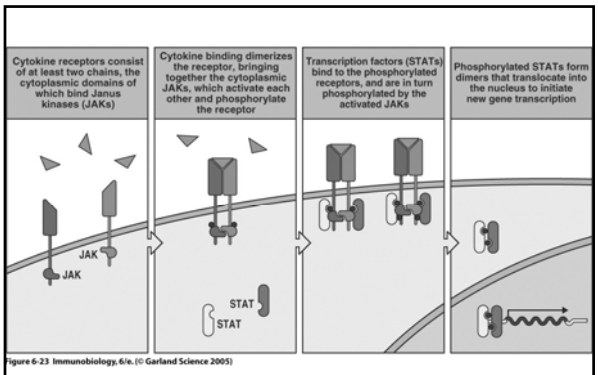


Figure 6-23 Immunobiology, 6/e. (© Garland Science 2005)

Cytokine signaling

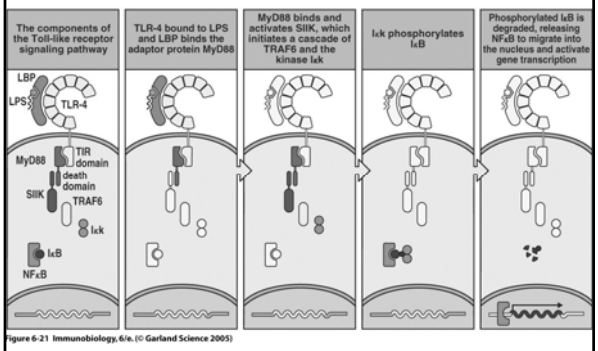


Figure 6-21 Immunobiology, 6/e. (© Garland Science 2005)

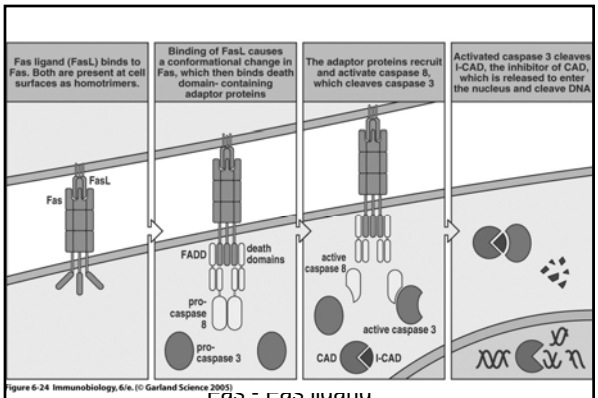
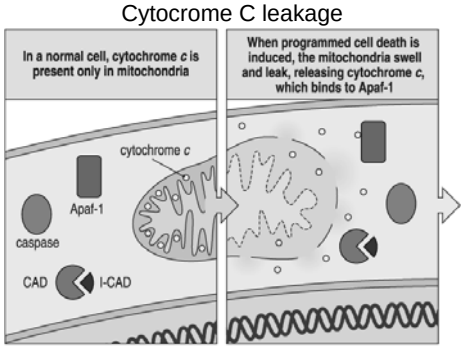


Figure 6-24 Immunobiology, 6/e. (© Garland Science 2005)

Fas - Fas ligand

Cytocrome C leakage



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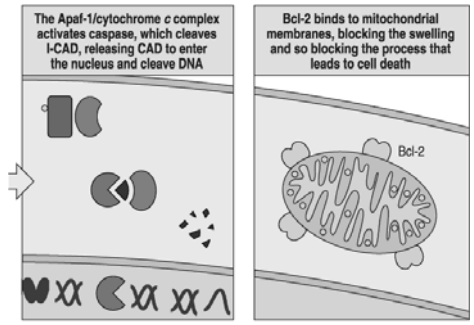

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