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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
How the recognition of an stimuli effects changes on the cell?

Signals Alter Cell behavior

Response
– Cell activation
– Cell death
– Cell secretion

Cytotoxic T cell

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<th>virus</th>
<th>APC</th>
<th>CTL</th>
<th>CD8+</th>
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Cell killing

Cytokines

Signal transduction:
“Conversion of signal from one form to another”

Extracellular signal “tickles” receptor

• Signal activates intracellular biochemical cascades
• Activation of transcription factors
• Expression (or repression) of genes
• Changes on behavior of cell
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

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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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
  - Immobilize 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

Adaptor molecules

- Phosphorylation creates binding sites for other molecules.

Adaptor molecules = bridges

Phosphorylation creates a SH2 binding domain

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

Phospholipase C-γ (PLC-γ)

- Phosphatidylinositol-bisphosphate (PIP2)
- Diacylglycerol (DAG)
- Inositol triphosphate (IP3)

IP3 opens Ca2+ channels that allow entry from ER.
Ca2+ 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

Small G proteins like Ras are active when they bind GTP
Small G proteins cleave bound GTP to GDP, becoming inactive
Guanine-nucleotide exchange factors (GEFs) displace GDP from small G proteins and allow GTP to bind

Fig 6.6 © 2001 Garland Science
Protein tyrosine kinases

Activation of GTP-binding proteins

Membrane phospholipid

Catabolism (PLC)

MAP & Jun Kinases

Ca++; Protein kinase C

Regulatory sequences

Expression of proteins (cytokines, receptors, etc.)

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-based activation motifs (ITAMS)
Receptor structure

Immunoreceptor tyrosine-based activation motifs (ITAMs)

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

Phosphorylation of ITAMs on B-cell receptor tails by Src-family kinases

Signaling: Protein phosphorylation initiates signaling cascade
Other signaling pathways

- Cytokines
- Toll Like Receptors
- Fas-Fas ligand
- Apaf1 activation
Cytocrome C leakage

In a normal cell, cytocrome C is present only in mitochondria.

When programmed cell death is induced, the mitochondria swell and leak, releasing cytocrome C, which binds to Apaf-1.

The Apaf-1/cytocrome C complex activates caspase, which cleaves I-CHD, releasing CHD to enter the nucleus and cleave DNA.

Bcl-2 binds to mitochondrial membranes, blocking the swelling and so blocking the process that leads to cell death.

Lecture slides index:
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