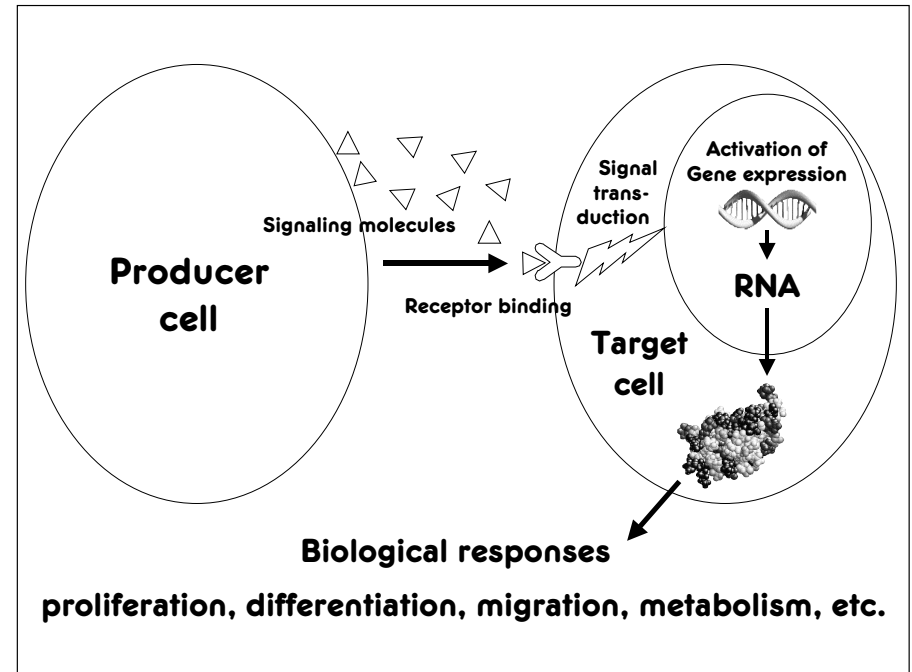


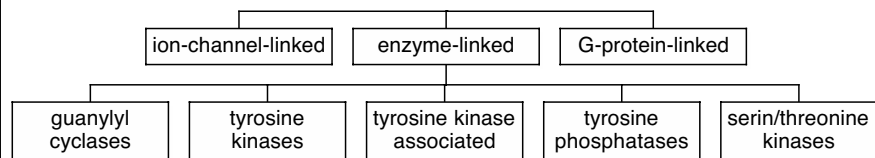
Tyrosine kinases

<http://msbl.helsinki.fi/tkseminar>

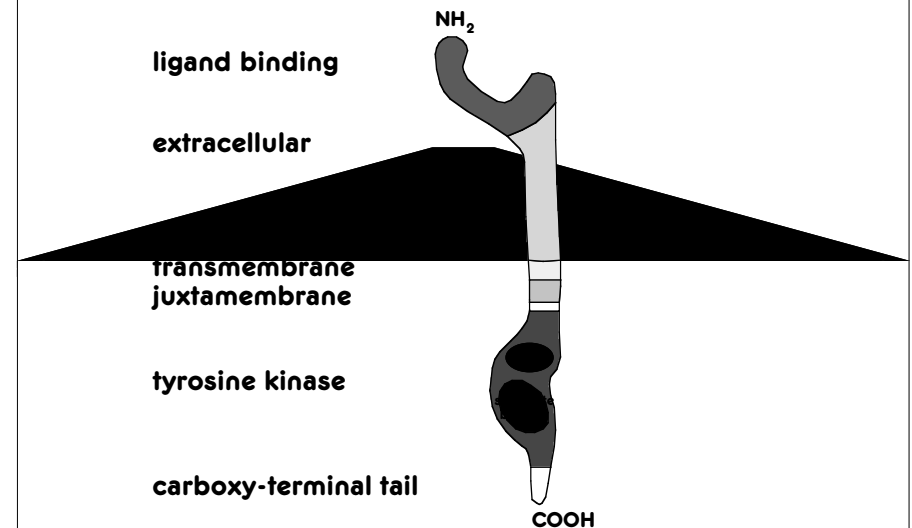
Michael Jeltsch

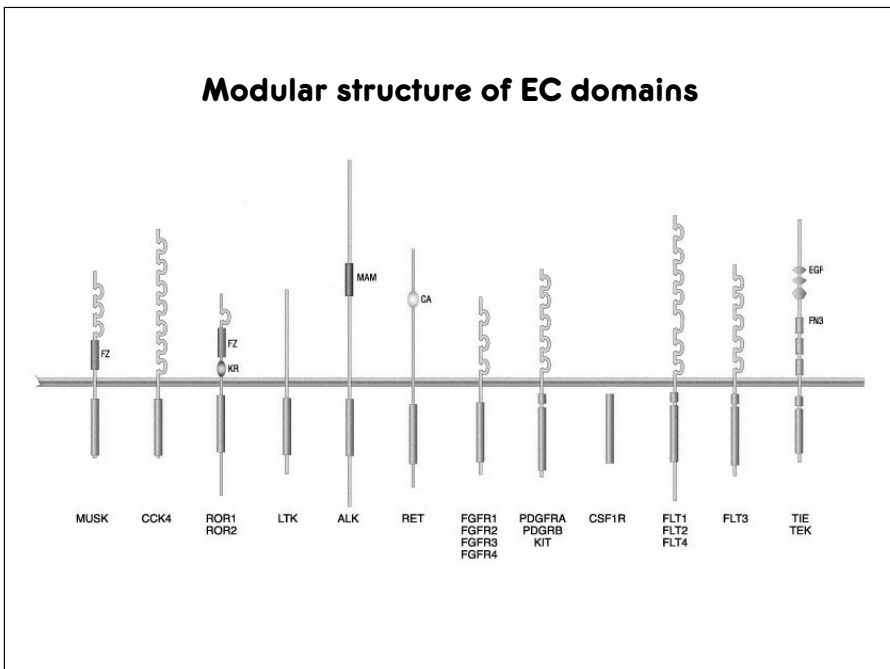
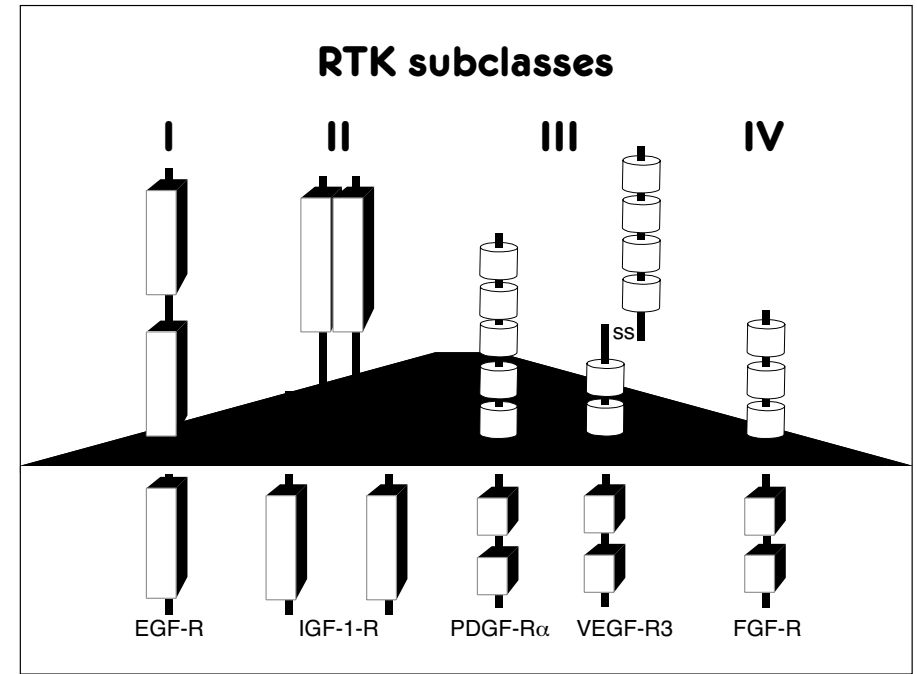


Cell surface receptors



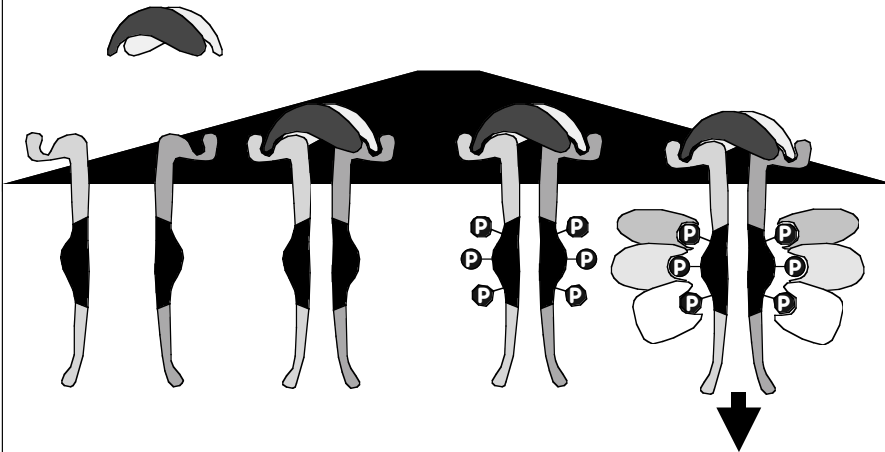
Receptor Tyrosine Kinases





- ### RTK ligands
- Cytokines (EGF, FGF, CSF-1, insulin)
 - Membrane-bound proteins (eprhins)
 - Extracellular matrix components (HSPGs)
 - Some RTKs need two ligands for activation

Signaling through an RTK



Dimerization or oligomerization

- Bivalent ligand
(e.g. VEGF, PDGF)
- Ligand-induced conformational change
(probably EGF)
- Intracomplex conformational change
(e.g. insulin)

Transmembrane signal transfer

- Exact mechanism unknown
- Same or similar mechanism for all RTKs (evidence from hybrid receptors)

Autophosphorylation

- Specific Tyr residues, usually outside the tyrosine kinase domain (juxtamembrane domain, cytoplasmic tail, kinase insert)
- Purposes:
 - Regulation of tyrosine kinase activity
 - Recruitment of signaling molecules

Signaling proteins are modular molecules

SH2	PTB	SH3	PH/FYVE	PZB	WW
-----	-----	-----	---------	-----	----

- SH2 (Src-homology 2)
- PTB (phosphotyrosine binding)
- SH3 (Src-homology 3)
- PH (pleckstrin homology)/FYVE
- PDZ
- WW

SH2 (Src-homology 2)/ PTB (phosphotyrosine binding)

- Bind to PY (and sometimes Y)
- Specificity is achieved through the context
- SH2: 1-6 amino acids C-terminal to PY
- PTB: 3-5 amino acids N-terminal to PY (or Y)

SH3 (Src-homology 3)

- Binds to proline motif PXXP

WW

- Binds to proline motif PXPX

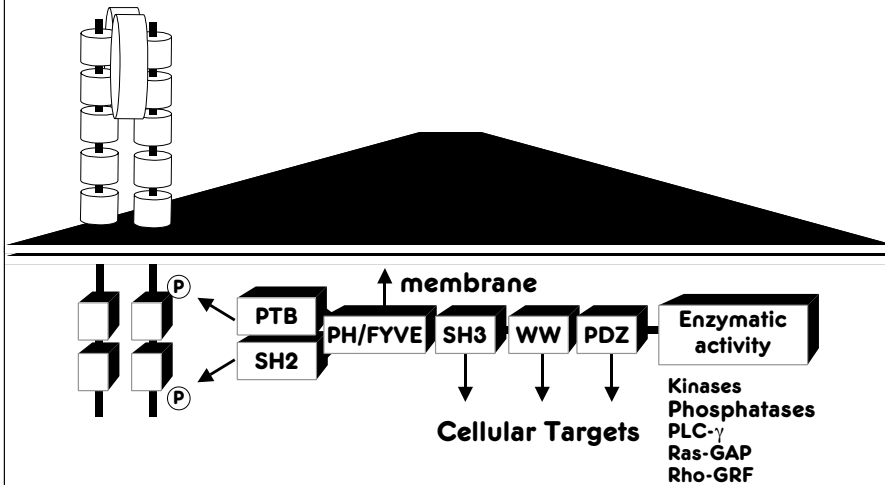
PH (pleckstrin homology)/FYVE

- PH domain binds to phosphoinositides (membrane-localization)
- FYVE domain binds specifically PtdIns-3-P

PDZ (PSD-95, DDLP, ZP1)

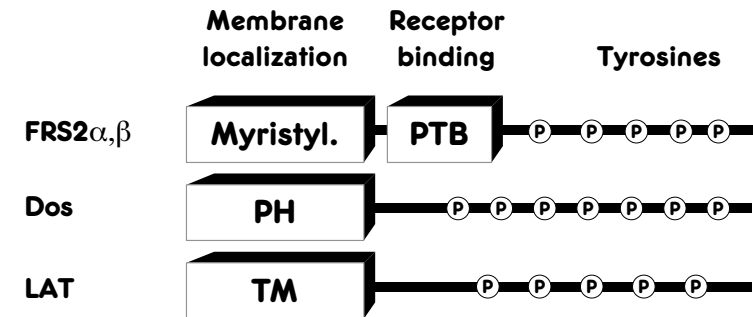
- Bind to hydrophobic C-terminal stretches of target proteins

Assembly of a specific signaling complex



Docking proteins

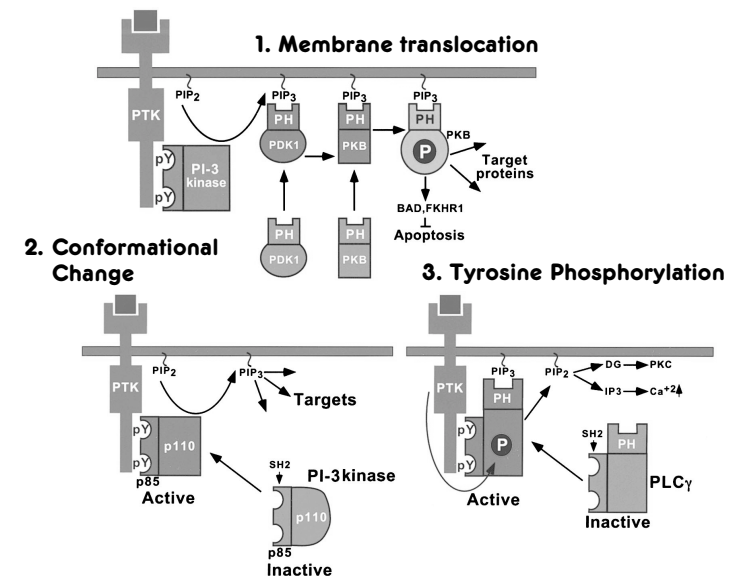
Indirect recruitment is the main recruitment method for some receptors (insulin receptor, FGF receptors)



Topics in activation of effector proteins

1. Activation by Membrane Translocation
2. Activation by a Conformational Change
3. Activation by Tyrosine Phosphorylation

Activation of signaling molecules: PDGF receptor



Intracellular Signaling Pathways

The diagram illustrates the following signaling pathways:

- STAT Pathway:** Receptor tail phosphorylates STAT, leading to a transcription factor.
- PLCγ Pathway:** Receptor tail activates PLCγ, which produces IP₃ and DG, leading to Ca²⁺ release and activation of CaMKPKC, which then acts as a transcription factor.
- PI-3K Pathway:** Receptor tail activates PI-3K, which produces Rac, leading to NADPH Synth. and H₂O₂ production. H₂O₂ activates PTP, which in turn activates the receptor tail.
- Ras Pathway:** Receptor tail activates Ras, which activates MAPK, which then acts as a transcription factor.
- Cdc42 Pathway:** Receptor tail activates Cdc42, which activates JNK, which then acts as a transcription factor.
- PI-3K/PKB Pathway:** Receptor tail activates PI-3K, which activates PDK1, which activates PKB. PKB then activates S6-K and GSK-3, which inhibit apoptosis.

The diagram also shows that the receptor tail can directly activate transcription factors.

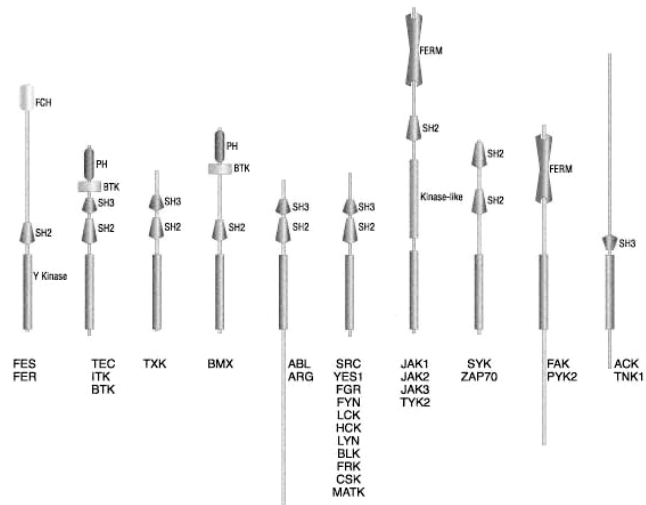
Signal Termination

The diagram illustrates the termination of a signal transduction pathway. A transmembrane receptor is shown with an extracellular domain, a transmembrane domain, and an intracellular domain. The intracellular domain is phosphorylated (P) and is the target of several regulatory proteins: PKC, PTP, and another PTP. Ubiquitin (Ub) is shown attached to the intracellular domain, leading to endocytosis and degradation. A cbl protein is also shown, which is phosphorylated and interacts with the receptor. A double-headed arrow indicates a reversible interaction between the receptor and another protein. A small square is shown above the receptor, and a larger square is shown below it, indicating a transition or state change.

- **Ligand-induced oligomerization or conformational change**
- **Autophosphorylation/crossphosphorylation**
- **Recruitment of signaling molecules to phosphorylated tyrosines (“signaling complexes”)**
- **Termination of Signaling (endocytosis)**

Intracellular vs. Transmembrane Receptor Tyrosine Kinases: Phylogenetic tree of tyrosine kinases

Cytoplasmic Tyrosine Kinases

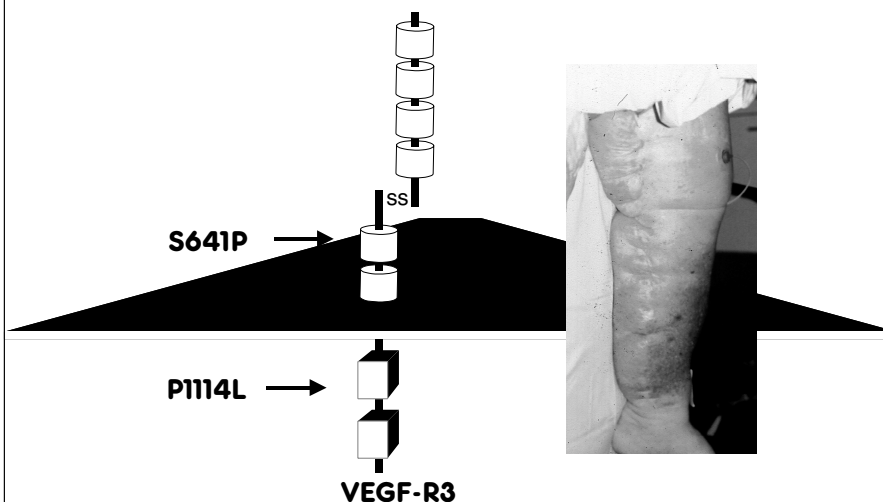


Tyrosine kinase-derived oncogenes

oncogene	retrovirus	cellular counterpart
v-src	Rous sarcoma	c-src
v-erbB	avian erythroblastosis	EGF receptor
v-fms	McDonough feline sarcoma	CSF-1 receptor
v-kit	feline sarcoma	SCF receptor
v-abl	Abelson murine leukemia	c-abl
v-sis	simian sarcoma	PDGF

Dominant Negative Receptors:

VEGFR-3 mutations in hereditary lymphedema



Further reading

Schlessinger, J. (2000): Cell Signaling by Receptor Tyrosine Kinases. *Cell*, Vol. 103, 211-225.