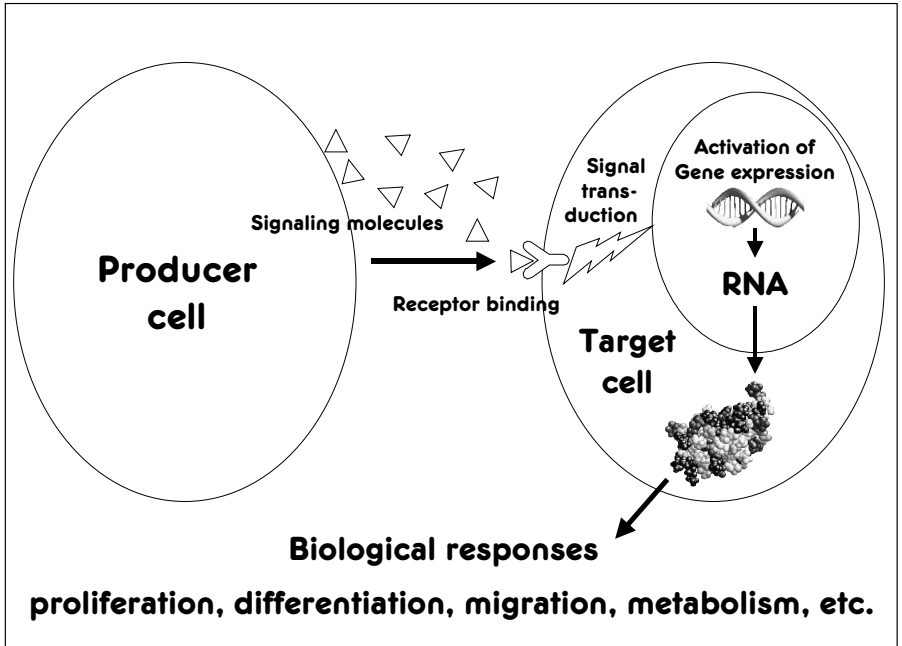
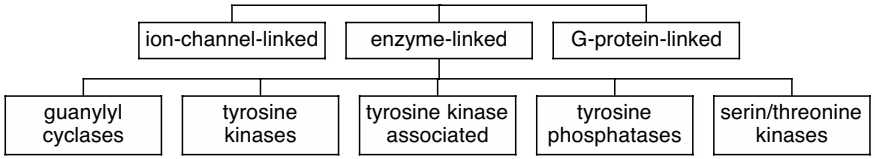
Tyrosine kinases

http://msbl.helsinki.fi/tkseminar

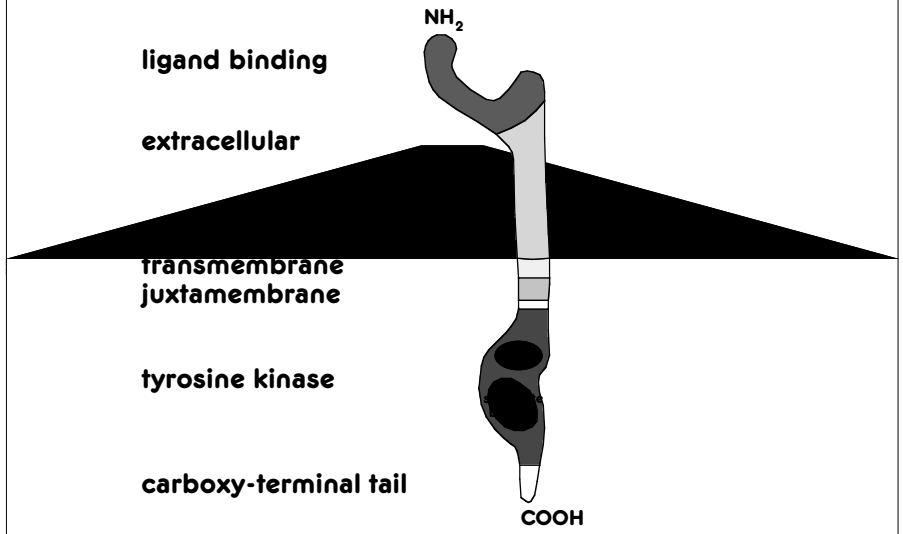
Michael Jeltsch

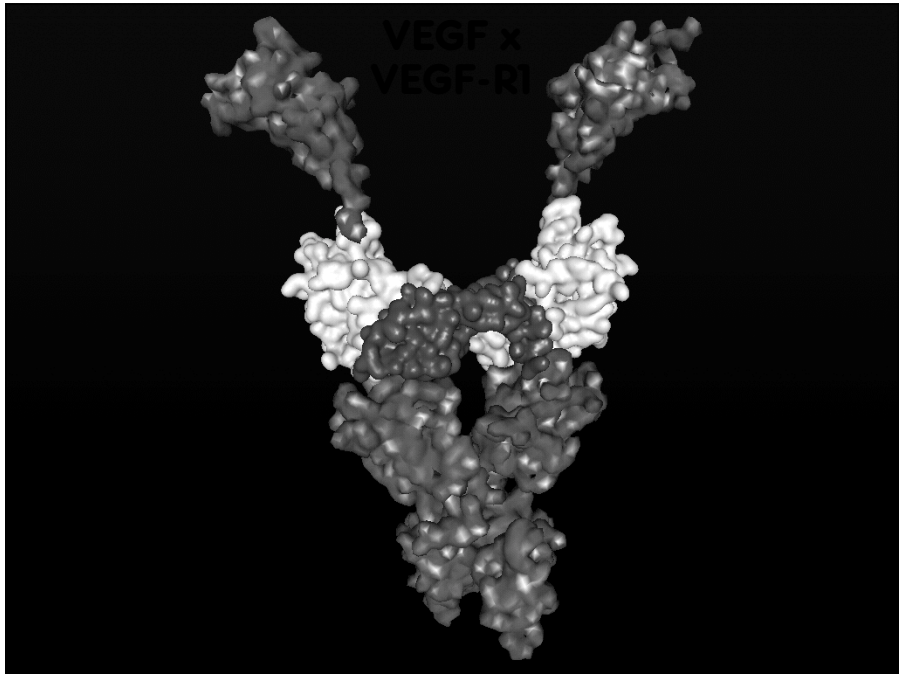


Cell surface receptors

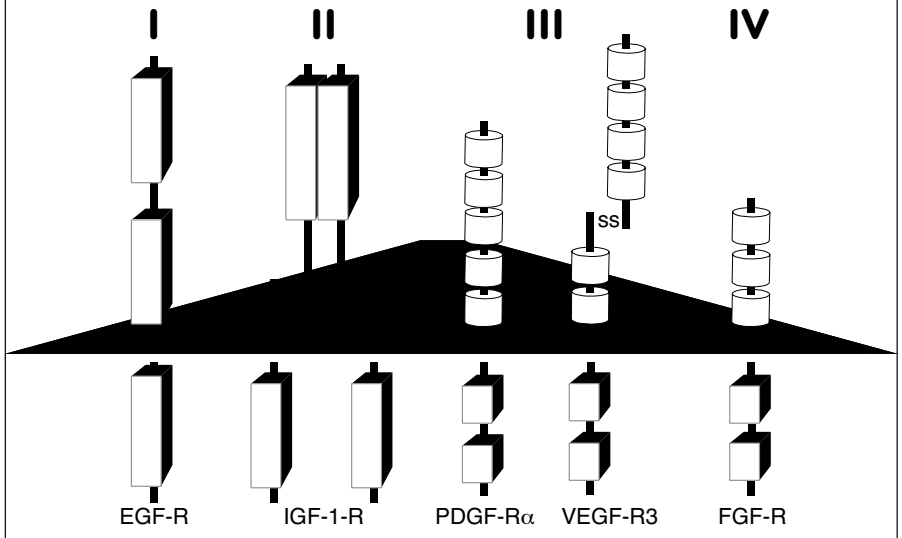


Receptor Tyrosine Kinases

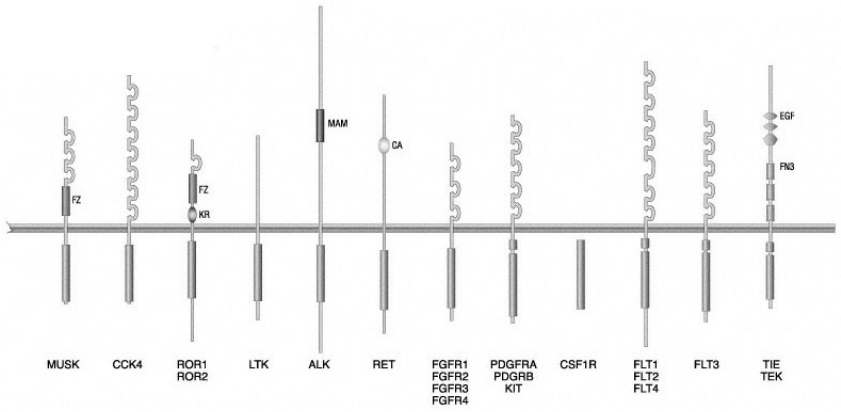




RTK subclasses



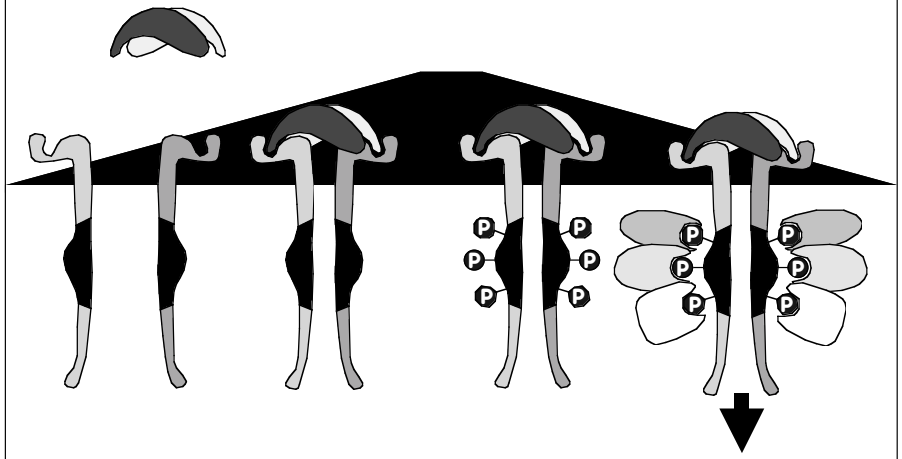
Modular structure of EC domains



RTK ligands

- Cytokines (EGF, FGF, CSF-1, insulin)
- Membrane-bound proteins (ephrins)
- 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)

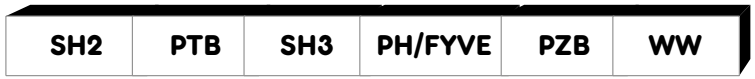
Transmembrane signal transfer

- 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 (Src-homolgy 2)
- PTB (phosphotyrosine binding)
- SH3 (Src-homolgy 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 aids N-terminal to PY (or Y)

SH3 (Src-homology 3)

- Binds to proline motif PXXP

WW

- Binds to proline motif PXPX

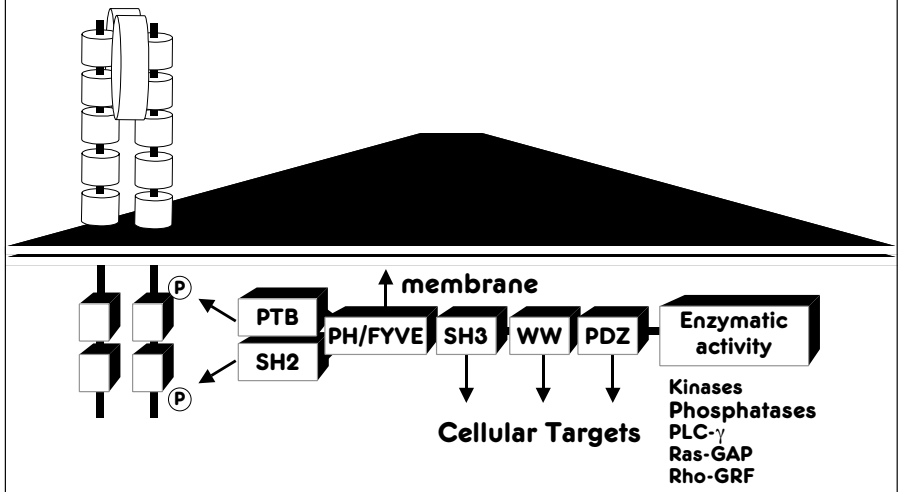
PH (pleckstrin homology)/FYVE

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

PDZ (PSD-95, DDLP, ZP1)

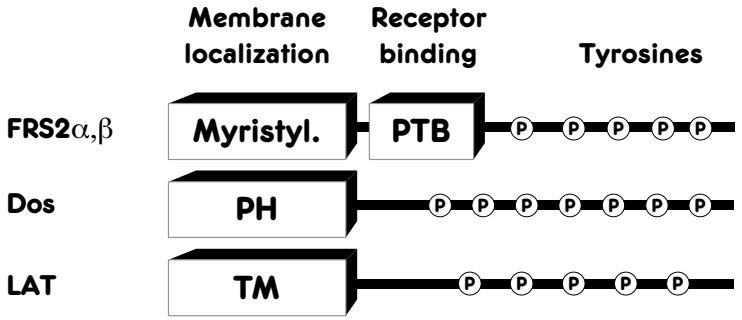
- Bind to hydrophobic C-terminal strtches of target proteins

Assembly of a specific signaling complex



Docking proteins

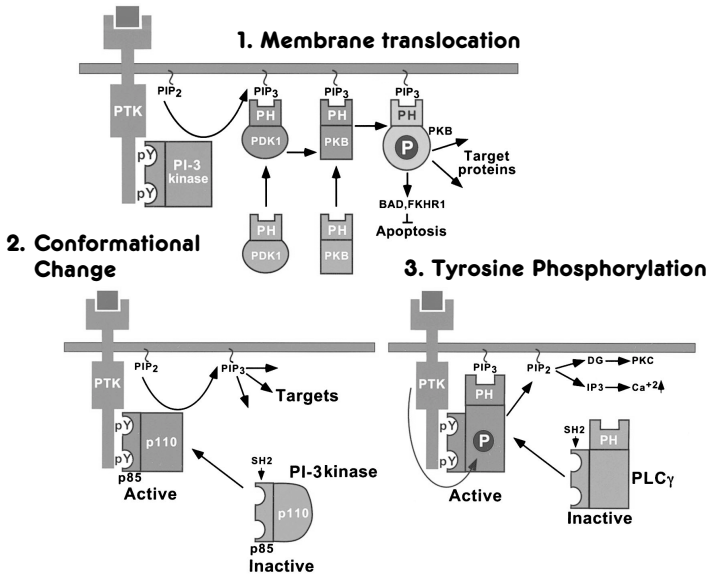
Indirect recruitment is the main recruitment method for some receptors (insulin receptor, FGF receptors)



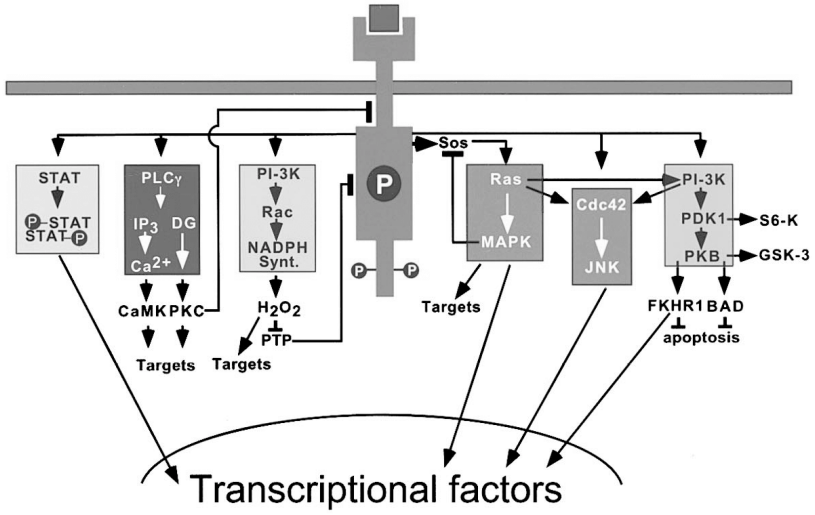
Topics in activation of effector proteins

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

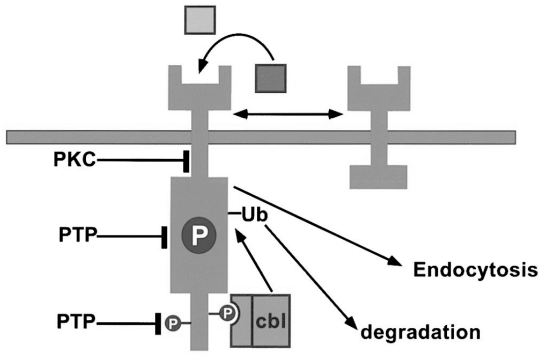
Activation of signaling molecules: PDGF receptor



Intracellular Signaling Pathways

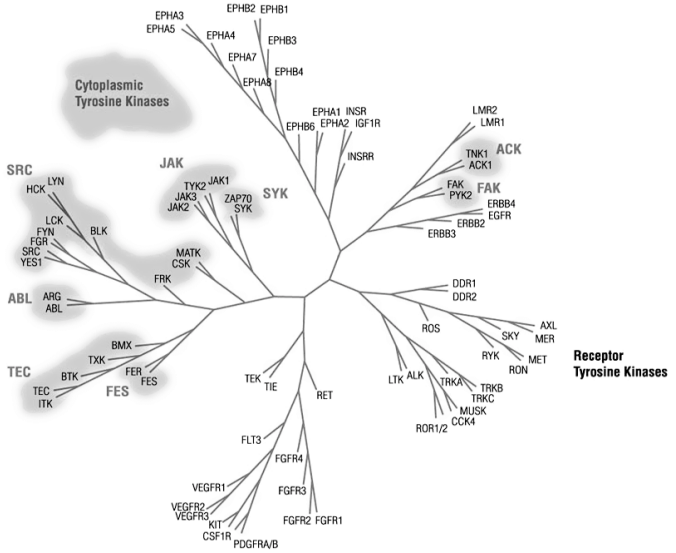


Signal Termination

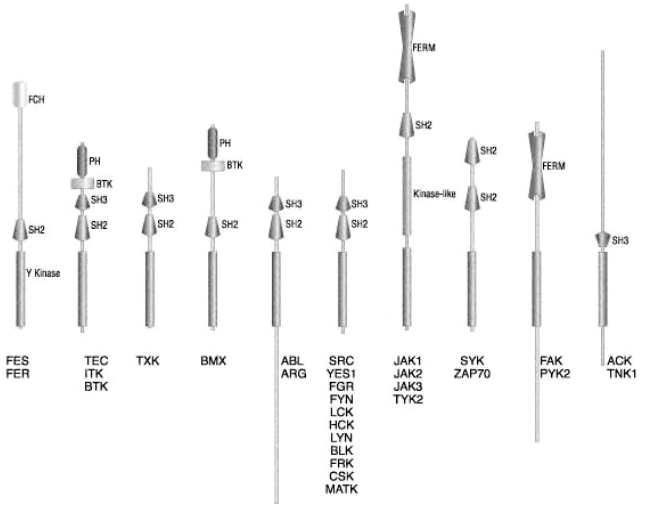


- Ligand-induced oligomerization or conformational change
- Autophosphorylation/crossphosphorylation
- Recruitment of signaling molecules to phosphorylated tyrosines ("signaling complexes")
- Termination of Signaling (endocytosis)

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



Cytoplasmic Tyrosine Kinases

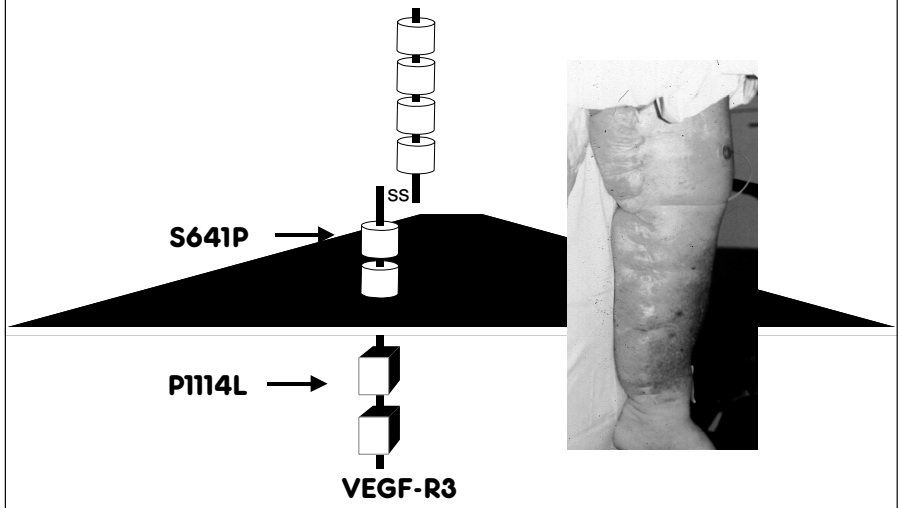


Tyrosine kinase-derived oncogenes

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.