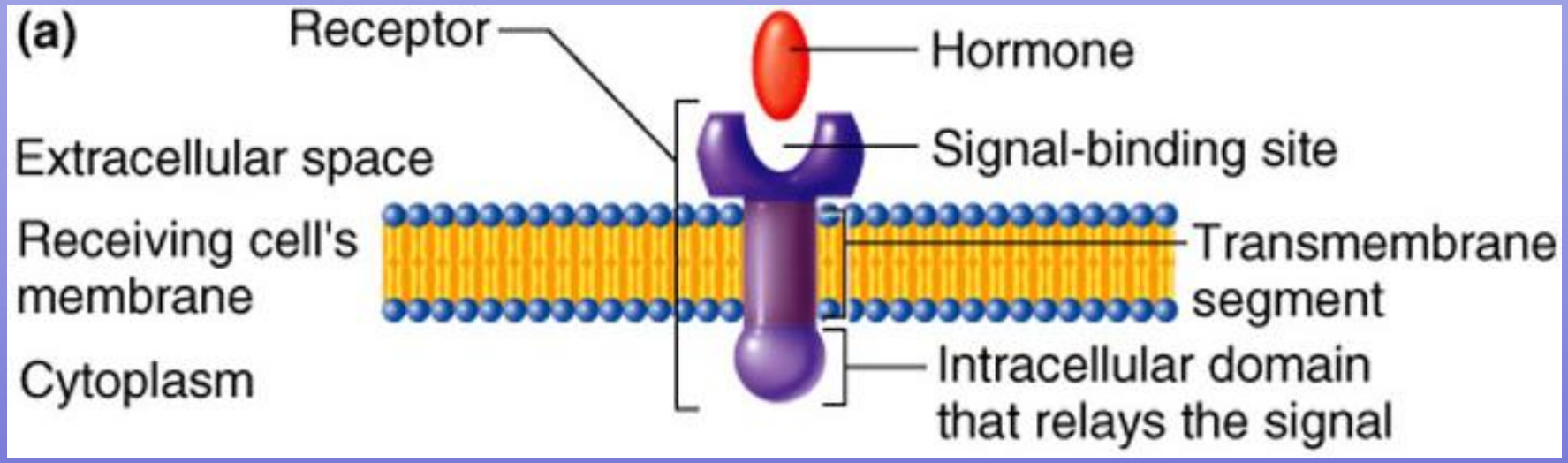
Growth factor signalling and oncogenes

Cell Cycle Control is through the effects of growth factors which interact with membrane-bound glycoprotein receptors that transduce the message via a series of intracellular signals that promote or inhibit the expression of specific genes.

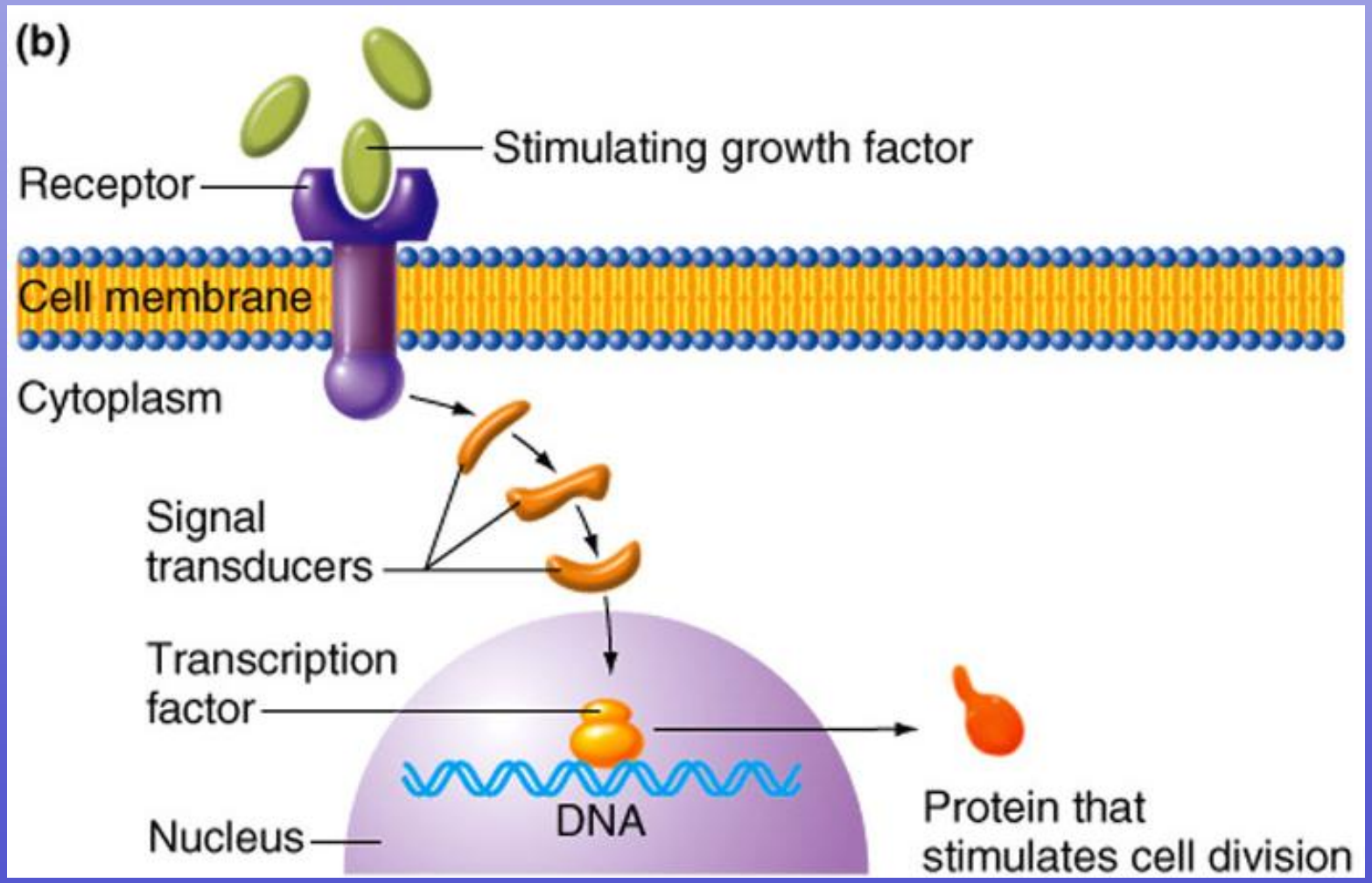
Molecular components of each signaling system



- Growth factors – hormones and cell-bound signals that stimulation or inhibit cell proliferation
- Receptors – membrane bound proteins that accept signals
  - signal-binding site
  - transmembrane segment
  - intracellular domain

Fig. 18.15 a

Signal transducers relay messages and transcription factors activate expression of genes



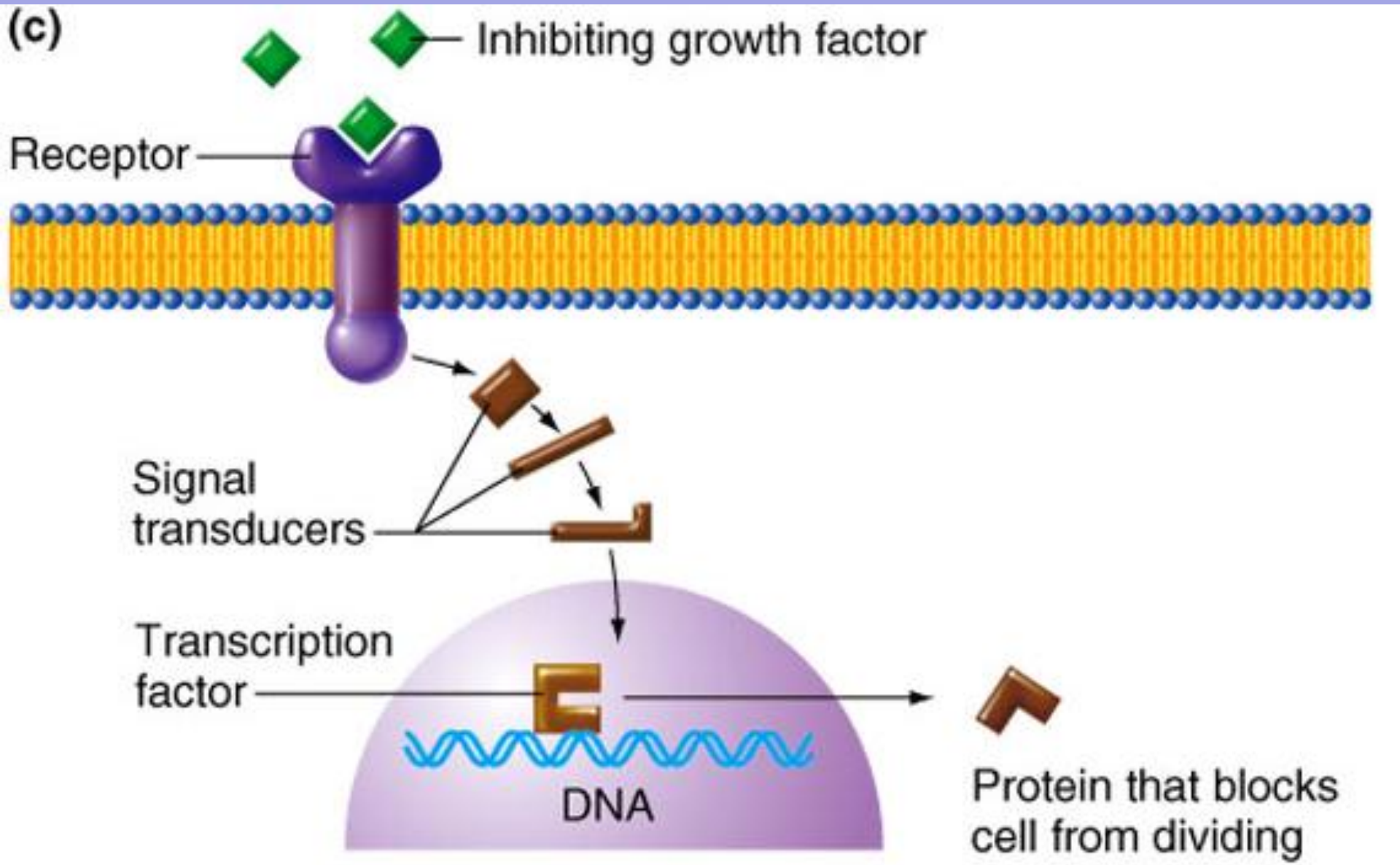
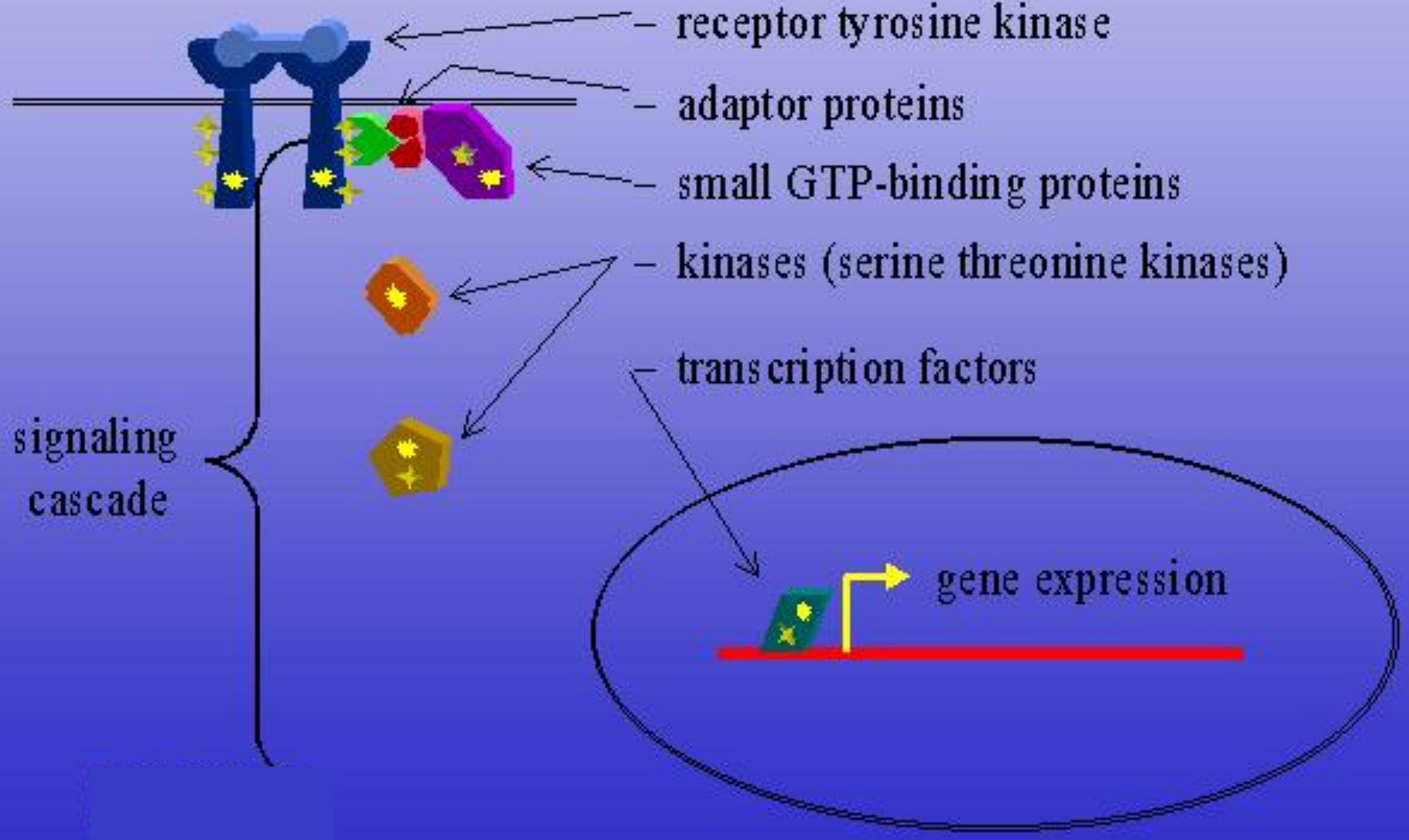

(c)
Inhibiting growth factor
Receptor
Signal transducers
Transcription factor
DNA
Protein that blocks cell from dividing

Fig. 18.15 c

Growth factor signaling and oncogenes

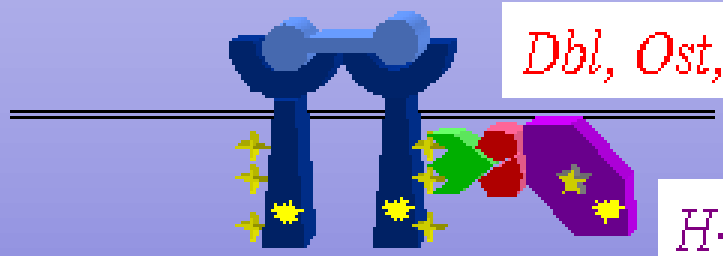
- The signaling cascade consists of a network of interacting proteins
- these proteins are:



There are many oncogenes

v-sis, int 2, KS3, HST, int-1

EGFR, v-fms, v-kit, v-ros, MET, TRK, NEU, RET, sea



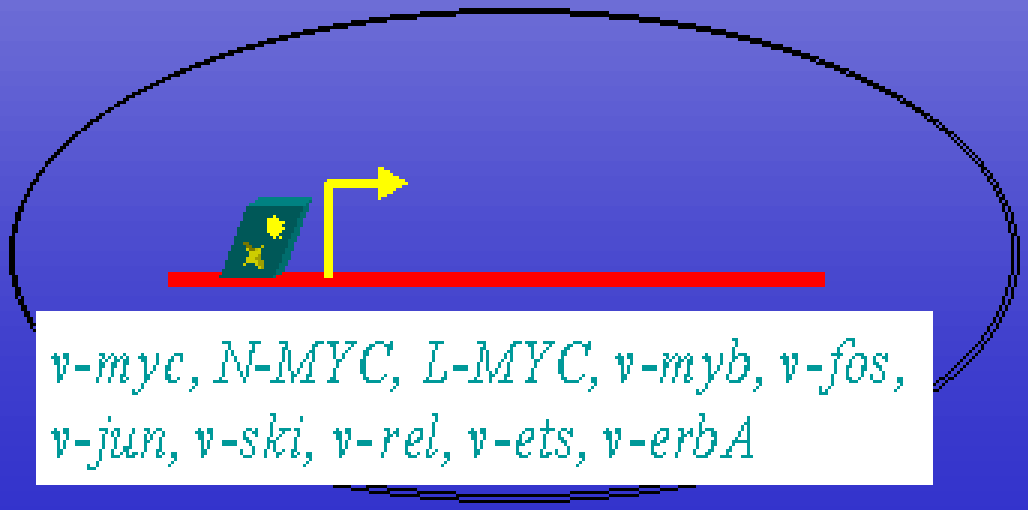
Dbl, Ost, Tiam-1, Vav, Lbc

H-RAS, K-RAS, N-RAS, gsp, gip

v-crk

SRC, v-yes, v-fgr, v-fps, v-fes, BCR/ABL,ros

v-mos, v-raf, pim-1, cot (ser/thr)

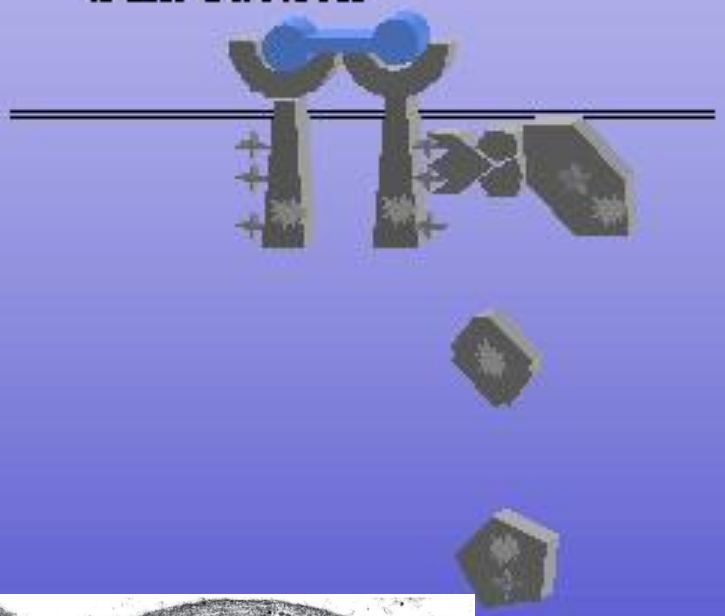


v-myc, N-MYC, L-MYC, v-myb, v-fos, v-jun, v-ski, v-rel, v-ets, v-erbA

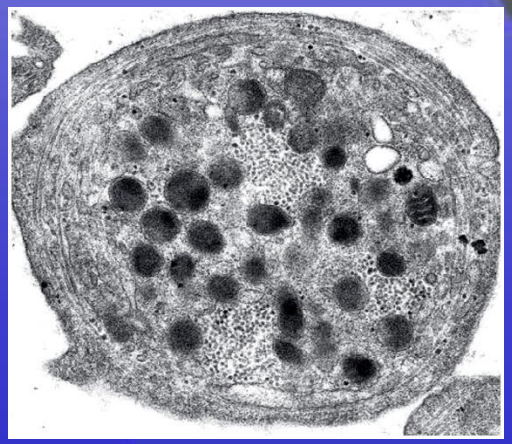
v-sis

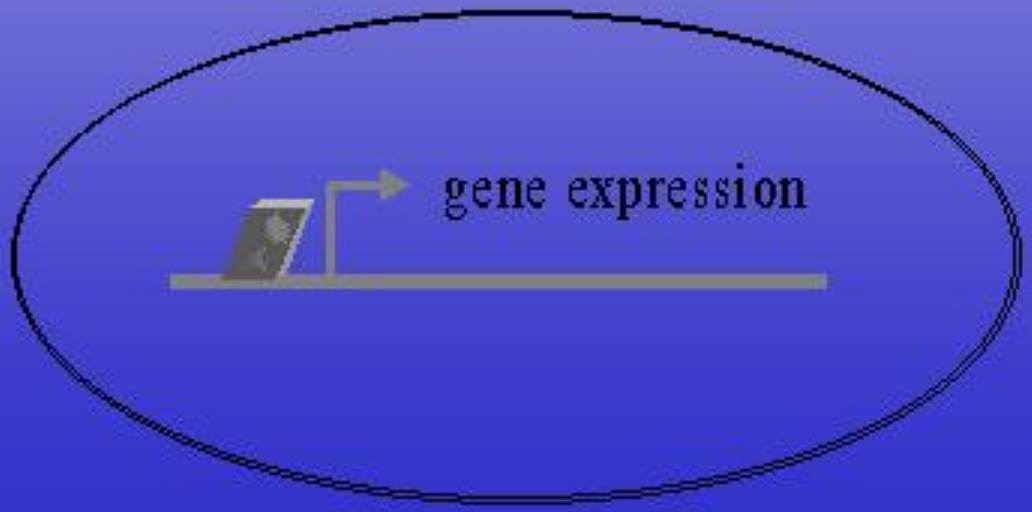
Growth factors

- overexpression by viral transduction



- c-sis is the cellular protooncogene encoding PDGF-B chain growth factor.
- v-sis is a virally encoded oncogene. Cells that are infected with viruses carrying v-sis overproduce PDGF like growth factors, causing constitutive growth stimulation
- c-sis can also become overexpressed in some tumors in the absence of viral involvement
- occurs in sarcomas and astrocytomas



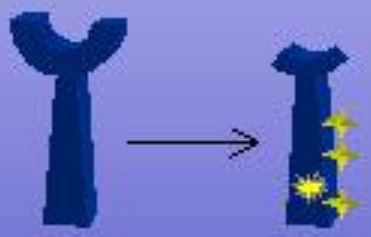


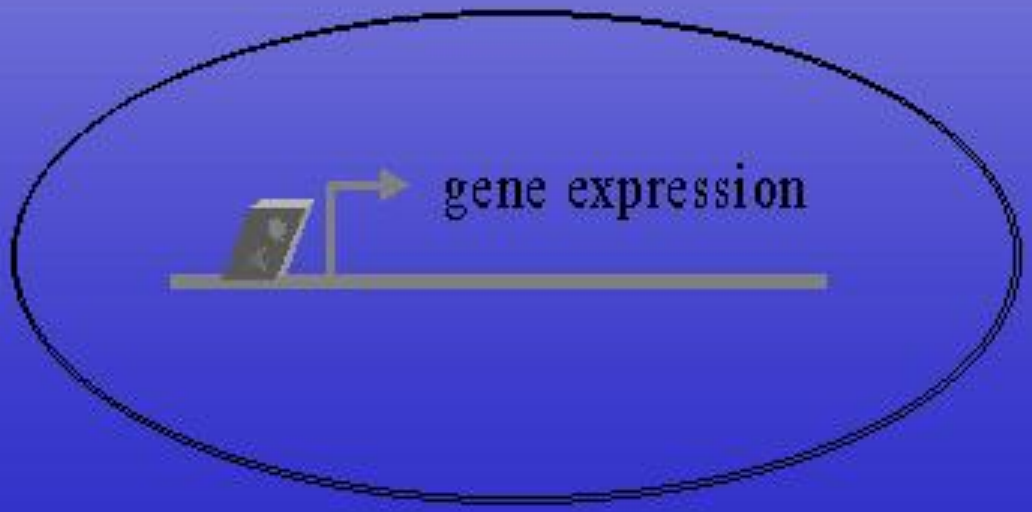
Δ-EGFR

Growth factor receptor

- intragenic deletion mutation

- a deletion mutation eliminates exons 2 to 7 in the extracellular domain, leading to ligand-independent activity
- this oncogene is also often amplified, and occurs in astrocytoma IV/glioblastoma multiforme





Mutations in GF receptor can cause ligand-independent activation

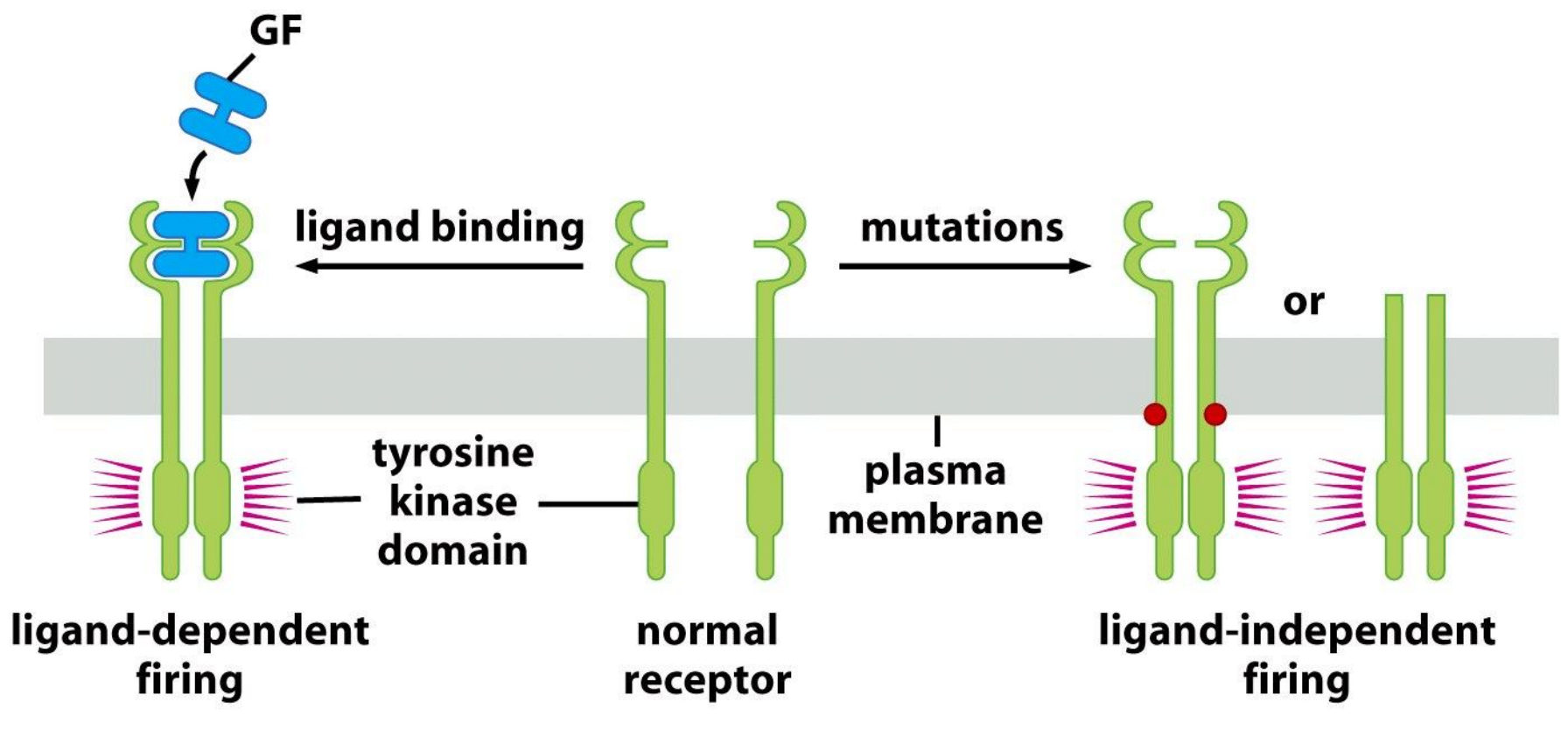


Figure 5.12a *The Biology of Cancer* (© Garland Science 2007)

Other growth factor receptors

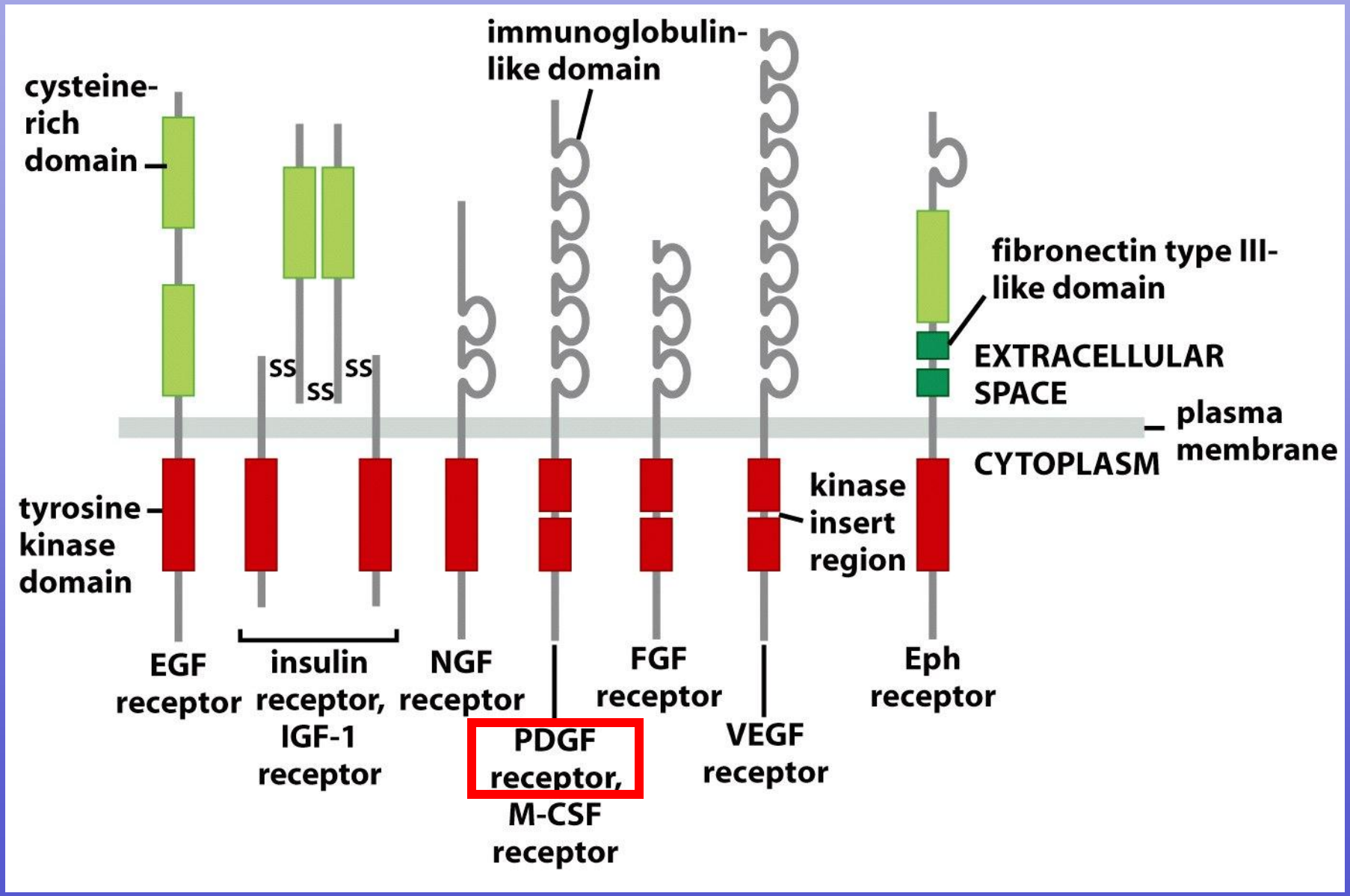
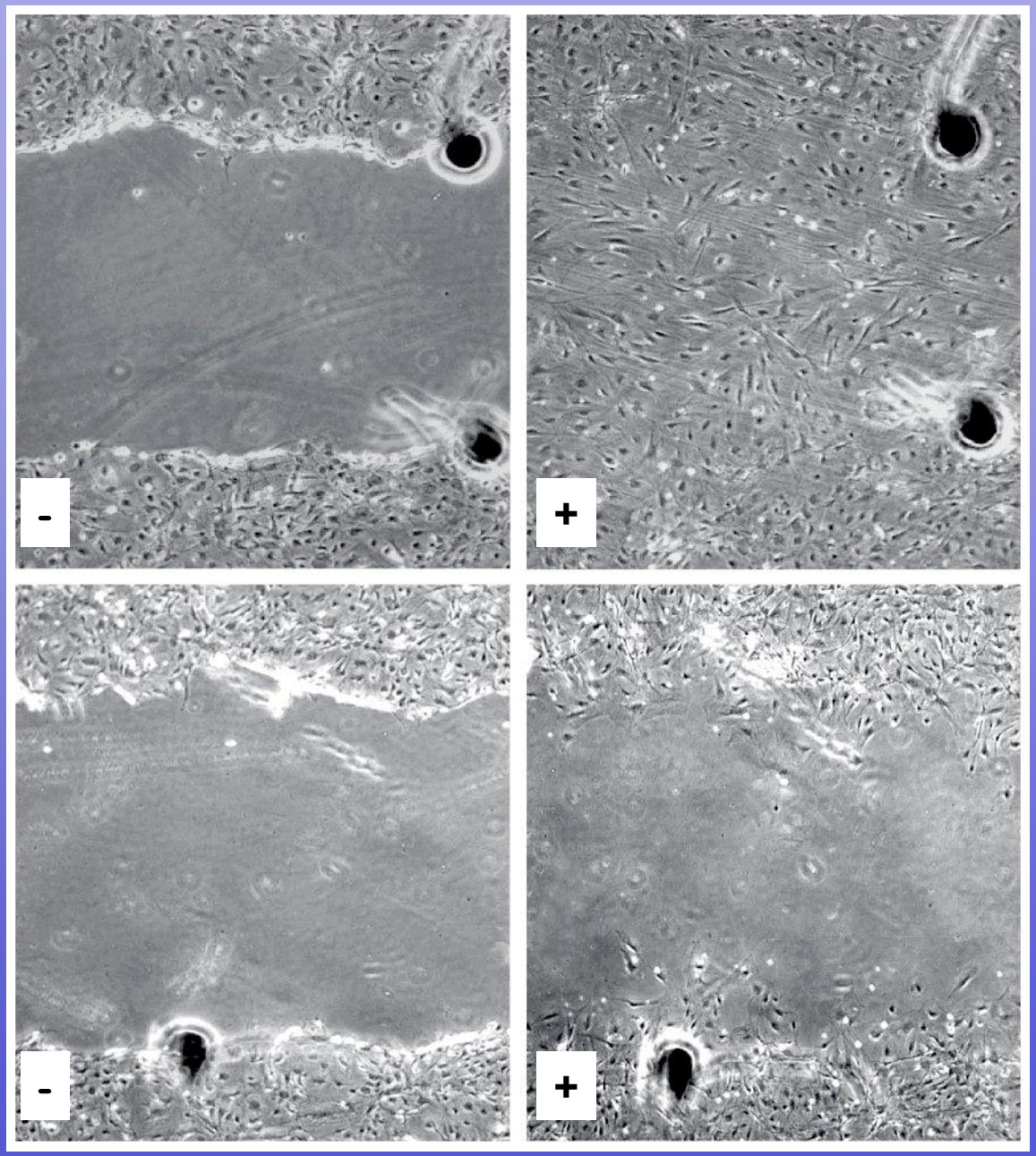


Figure 5.10 *The Biology of Cancer* (© Garland Science 2007)



Normal fibroblasts

+/- PDGF

PDGF receptor negative fibroblasts

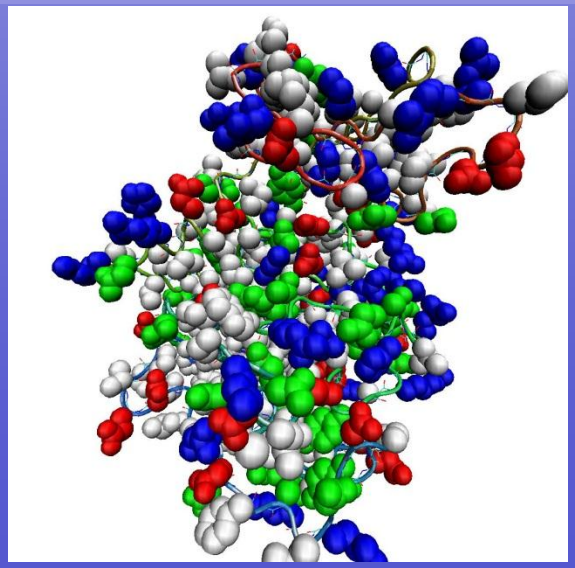
+/- PDGF

Figure 5.4a *The Biology of Cancer* (© Garland Science 2007)

c-crk (cell cycle related kinase)

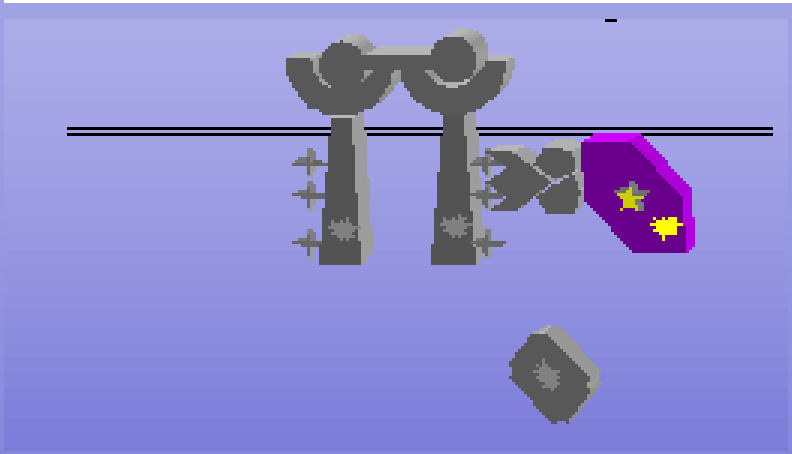
- **Adaptor proteins**
- overexpression by viral transduction

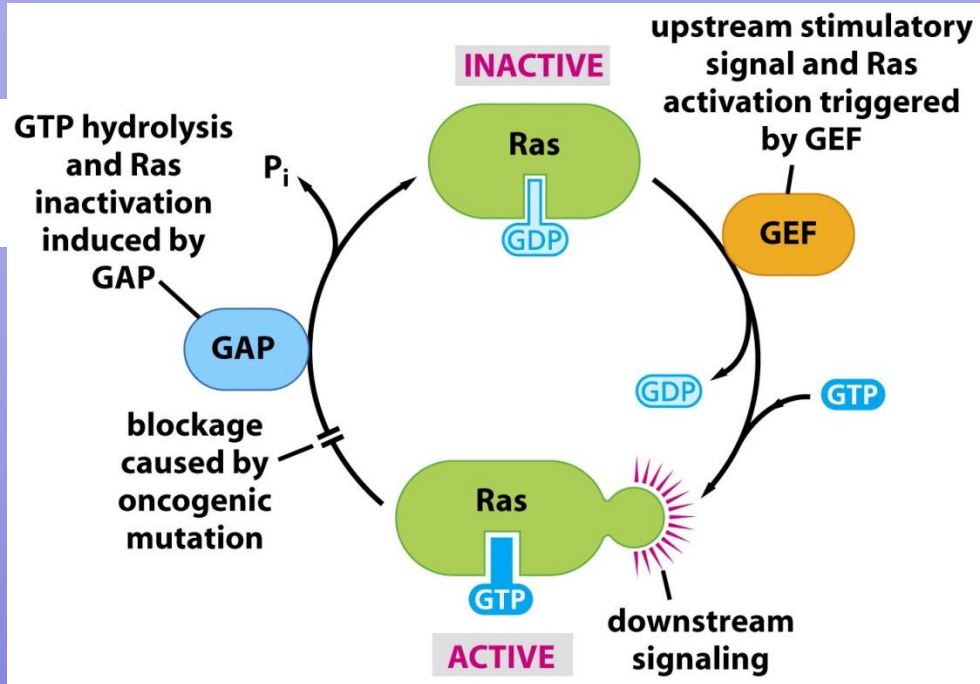
- The crk protein contains only SH3 and SH2 domains:
  - SH2 domains bind phosphorylated tyrosine residues
  - SH3 domains bind proline rich sequences in ligand proteins
- it functions to bring substrate proteins to tyrosine kinase receptors



Ras

Small GTP-binding signalling molecule





Guanine nucleotide exchange factor (GEF) - activation by GDP to GTP

GTPase activation proteins (GAP) - inactivation by GDP to GTP

- Various viral forms identified:
  - v-Ha-ras
  - v-Ki-ras
  - N-ras
- chemical carcinogenesis results in characteristic mutations at residues 12, 13, 59 and 61.

V-ras or mutated ras has lost the ability to interact with accessory proteins and are either GEF independent or GAP insensitive (GTP state)