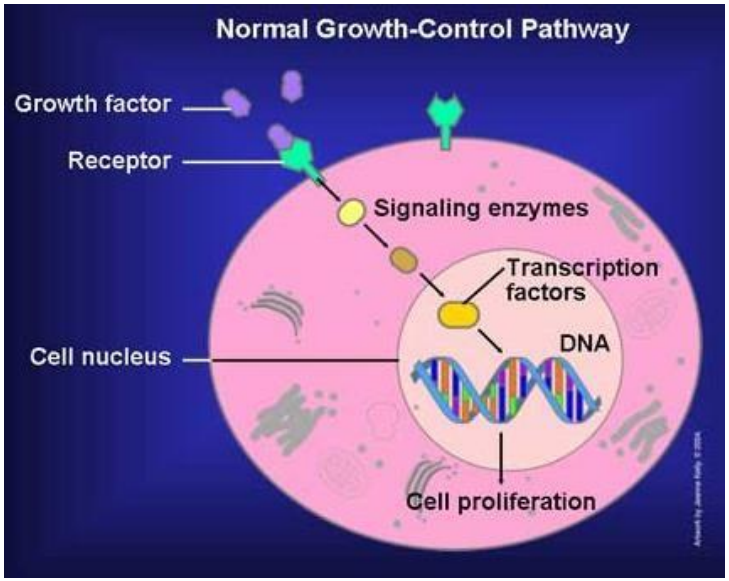
Growth factor signaling and oncogenes

Introduction

- One of the fundamental characteristics of cells is their ability to self-reproduce.
- Unregulated growth is a quintessential characteristic of cancer.
- Normally, cell division is only initiated in response to a signal from outside of the cell.
- An extracellular growth factor stimulates cell growth by transmitting a signal into the cell, and ultimately to the nucleus, to regulate gene expression in order to produce proteins that are essential for cell division.

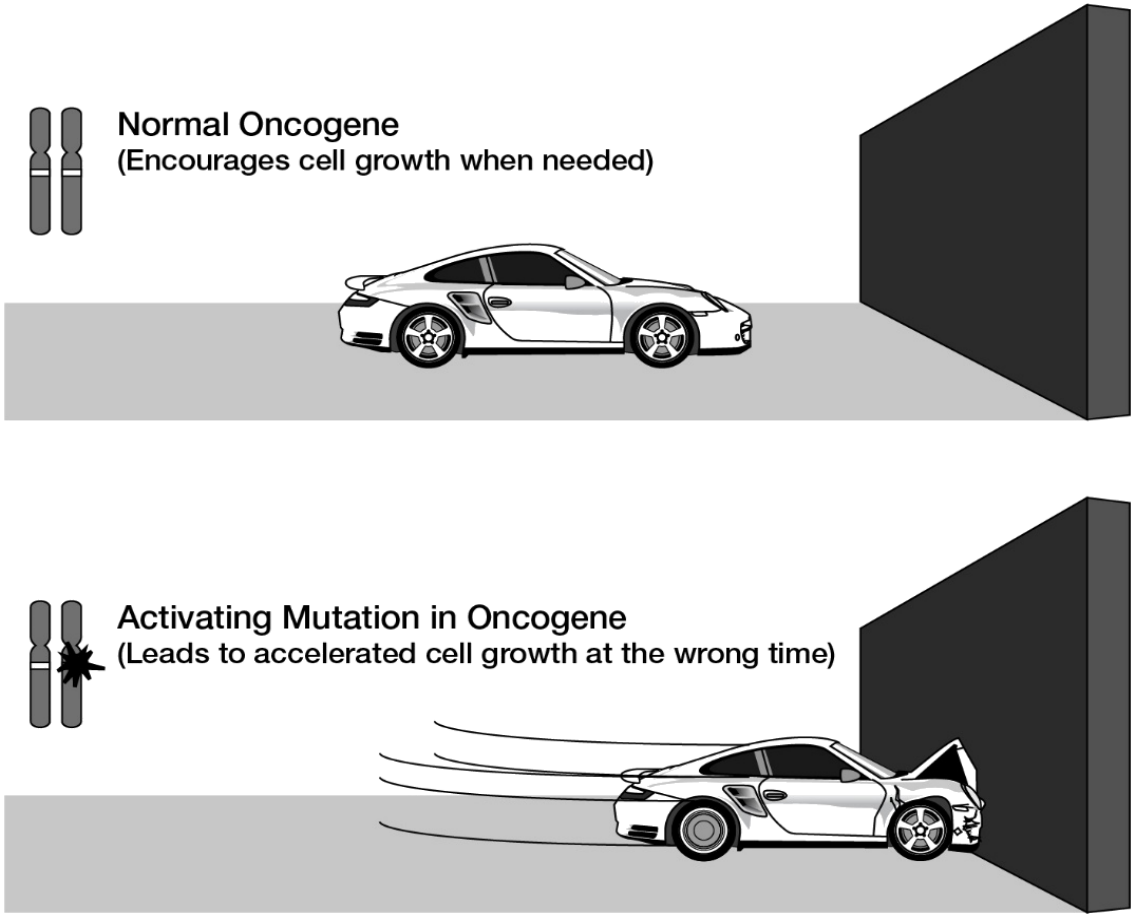
Function of the proto-oncogenes

- The proto-oncogenes would be involved in the basic essential functions of the cell related to control of cell proliferation and differentiation.
- Cells are stimulated by external signals which in turn stimulates intracellular signaling pathways, eventually leading to alterations in gene expression.



- **Mutations** in any of the genes result in their abnormal activation promoting cell growth in the absence of external stimuli and leads to malignant transformation.

Mutations in proto-oncogenes are typically dominant in nature, and the mutated version of a proto-oncogene is called an **oncogene**.

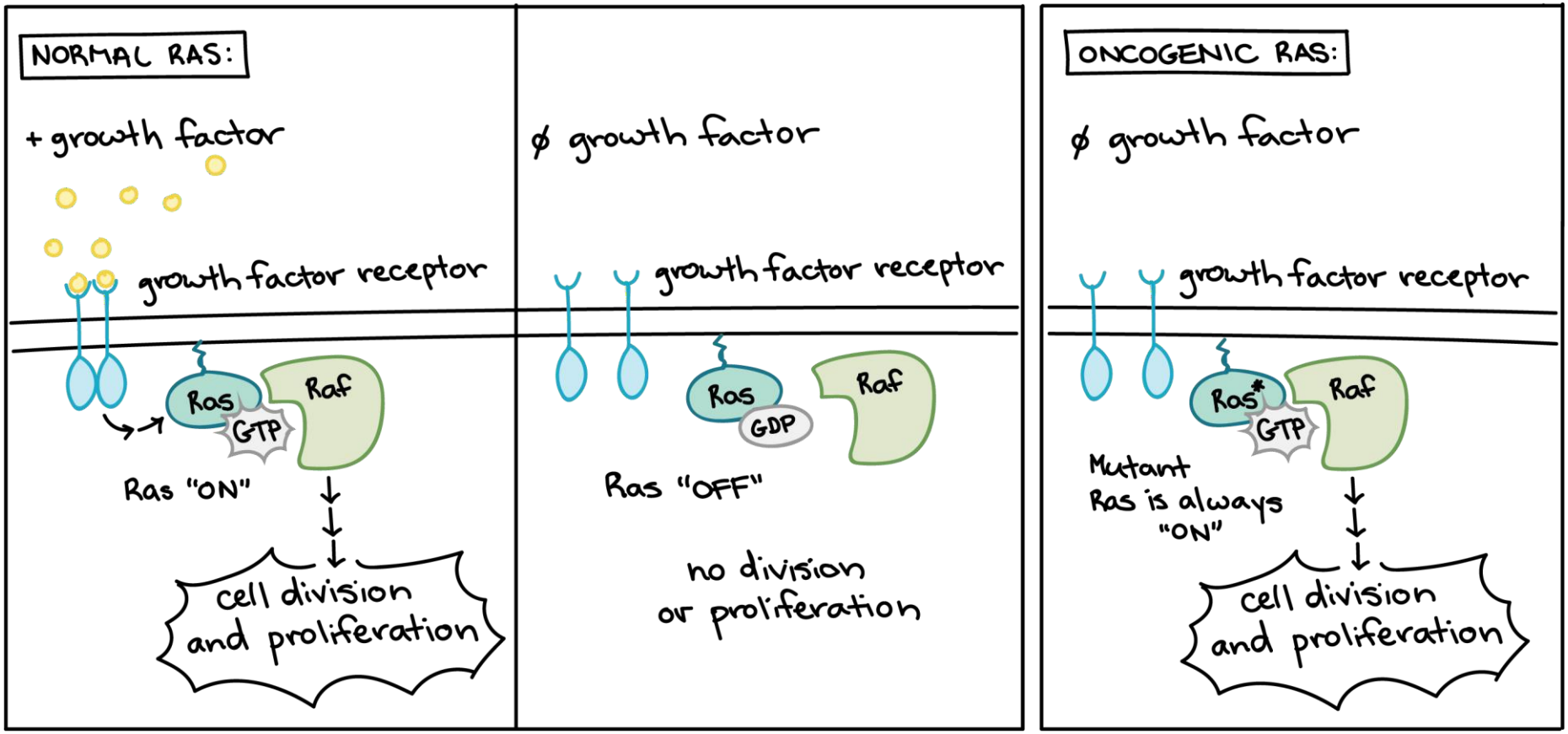


https://www.genome.gov/genetics-glossary/Oncogene

Mechanisms of oncogenic activation

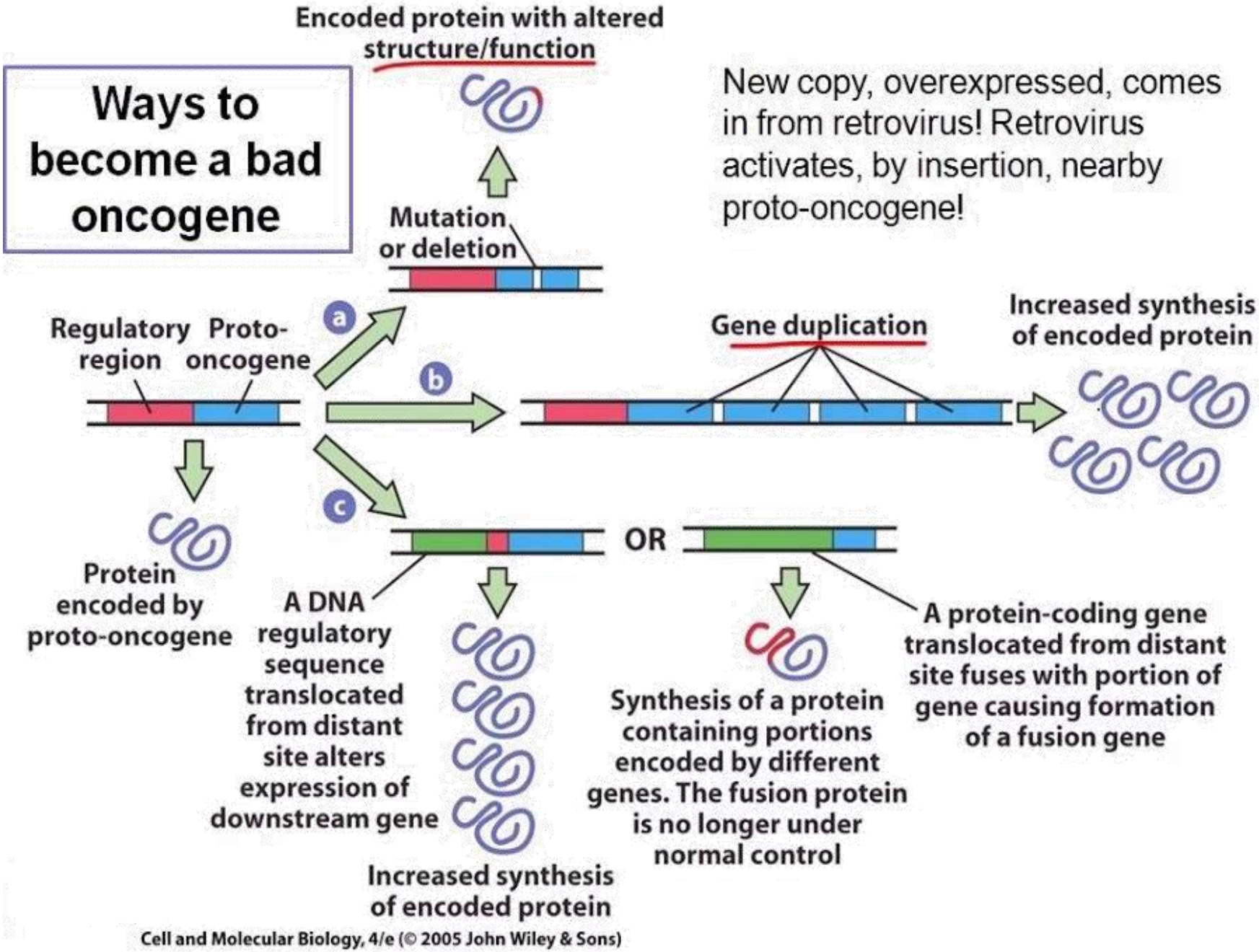
- The proto-oncogenes encode proteins that function to:
  - stimulate cell division,
  - inhibit cell differentiation, and
  - halt cell death

- The oncogenes, however:
  - exhibit increased production of proteins that lead to,
    - increased cell division,
    - decreased cell differentiation, and
    - inhibition of cell death; taken together, these phenotypes define cancer cells.
- Thus, oncogenes are currently a major molecular target for anti-cancer drug design.

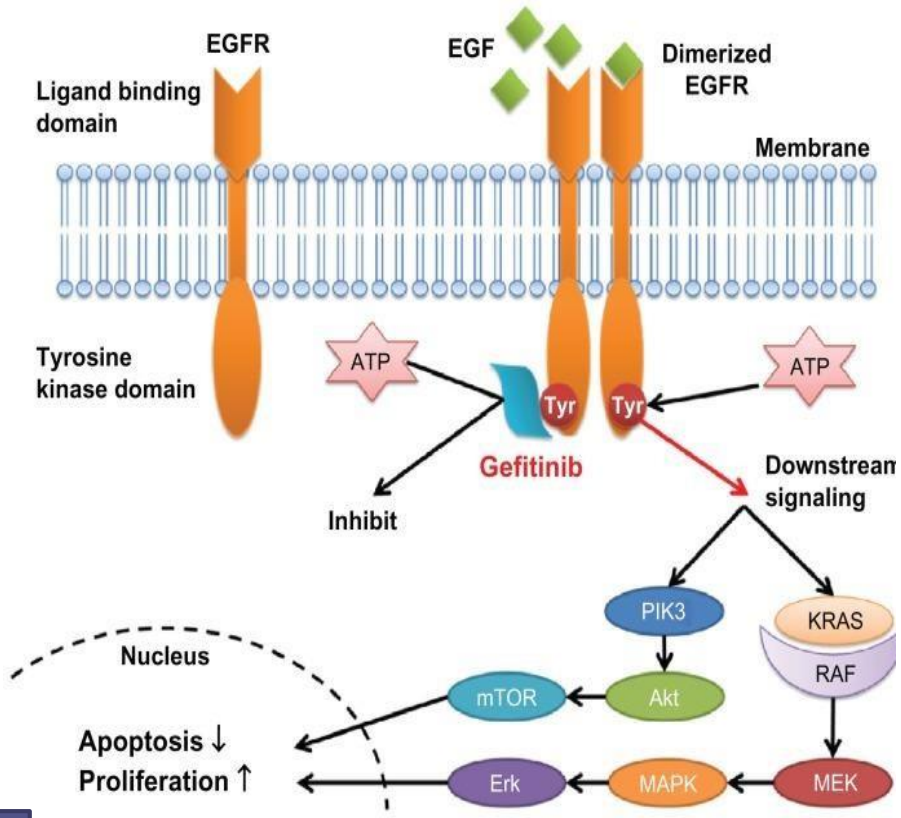

NORMAL RAS:
+ growth factor
growth factor receptor
Ras
GTP
Raf
Ras "ON"
cell division and proliferation
ø growth factor
growth factor receptor
Ras
GDP
Raf
Ras "OFF"
no division or proliferation
ONCOGENIC RAS:
ø growth factor
growth factor receptor
Ras*
GTP
Raf
Mutant Ras is always "ON"
cell division and proliferation

From Good to Bad: Proto-Oncogenes to Oncogenes

- Oncogenes arise as a result of mutations that increase the expression level or activity of a proto-oncogene.
- Underlying genetic mechanisms associated with oncogene activation include the following:
  1. Point mutations, deletions, or insertions that lead to a hyperactive gene product
  2. Point mutations, deletions, or insertions in the promoter region of a proto-oncogene that lead to increased transcription.
  3. Gene amplification events leading to extra chromosomal copies of a proto-oncogene
  4. Chromosomal translocation events that relocate a proto-oncogene to a new chromosomal site that leads to higher expression.
  5. Chromosomal translocations that lead to a fusion between a proto- oncogene and a second gene, which produces a fusion protein with oncogenic activity


Ways to become a bad oncogene
Encoded protein with altered structure/function
Mutation or deletion
New copy, overexpressed, comes in from retrovirus! Retrovirus activates, by insertion, nearby proto-oncogene!
Regulatory region
Proto-oncogene
a
b
c
Gene duplication
Increased synthesis of encoded protein
Protein encoded by proto-oncogene
A DNA regulatory sequence translocated from distant site alters expression of downstream gene
Increased synthesis of encoded protein
OR
Synthesis of a protein containing portions encoded by different genes. The fusion protein is no longer under normal control
A protein-coding gene translocated from distant site fuses with portion of gene causing formation of a fusion gene
Cell and Molecular Biology, 4/e (© 2005 John Wiley & Sons)

- **Tyrosine kinases** are a part of many cell functions, including cell signaling, growth, and division.
- These enzymes may be too active or found at high levels in some types of cancer cells, and **blocking them may help keep cancer cells from growing**.
- Some tyrosine kinase inhibitors are used to treat cancer.



Receptor tyrosine kinases (RTKs) have been identified as growth factor receptors and proto-oncogenes

- **What is the tyrosine kinase signaling pathway?**

- **How is it related to cancer?**
  - Receptor tyrosine kinases (RTKs) function as oncogene drivers in solid tumors through diverse mechanisms including mutation, amplification and autocrine/paracrine activation.

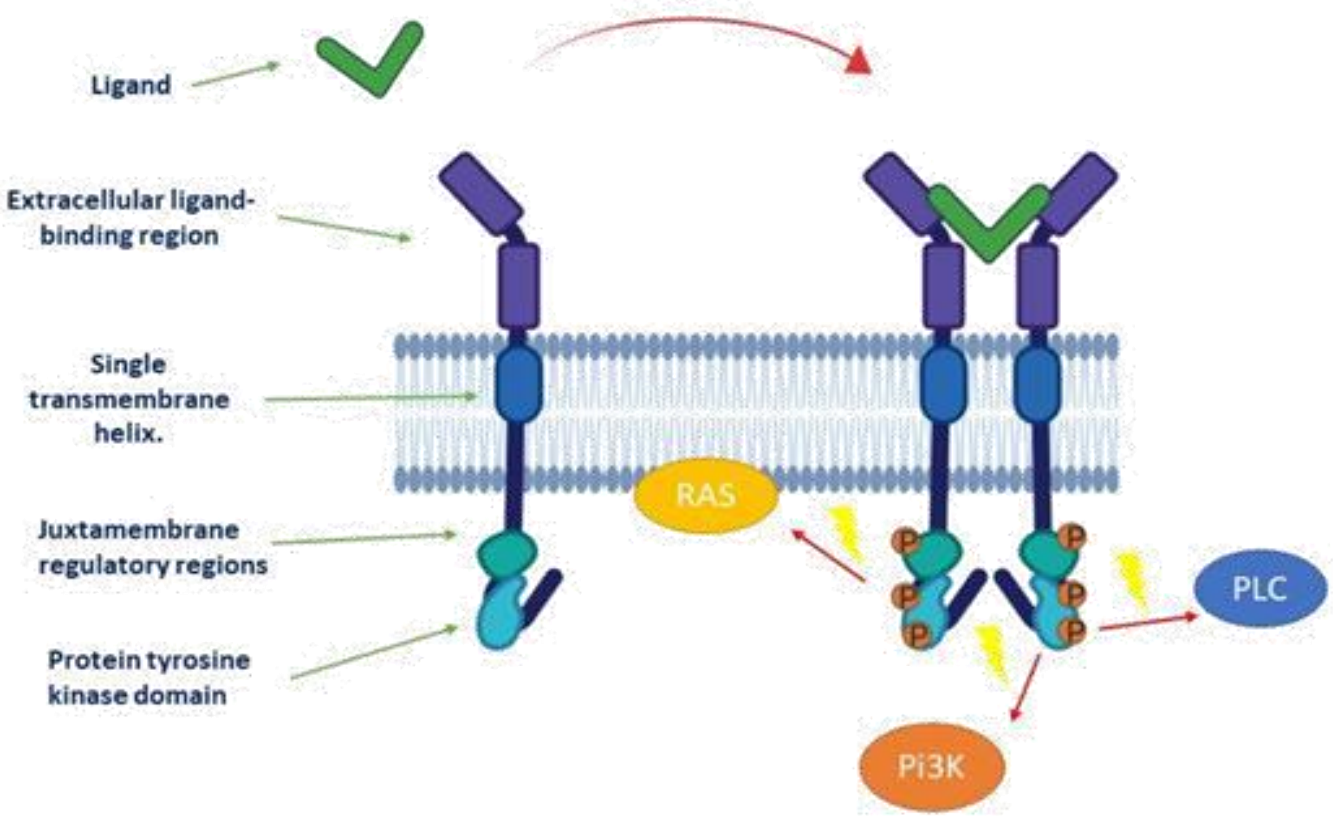
- Human cells contain ~60 RTKs, grouped into 20 subfamilies based on their domain architecture.
- All RTK subfamilies are characterized by four domains:
  - an extracellular ligand- binding domain,
  - a single transmembrane region and
  - an intracellular region consisting of the tyrosine kinase domain
  - and additional regulatory and protein interaction domains.
- Dysregulation of RTK signaling leads to many human diseases, especially cancer.

Activation of tyrosine kinase receptor.

Ligand binding stabilizes connections between monomeric receptors to form an active dimer, which in turn activates the intracellular kinase.

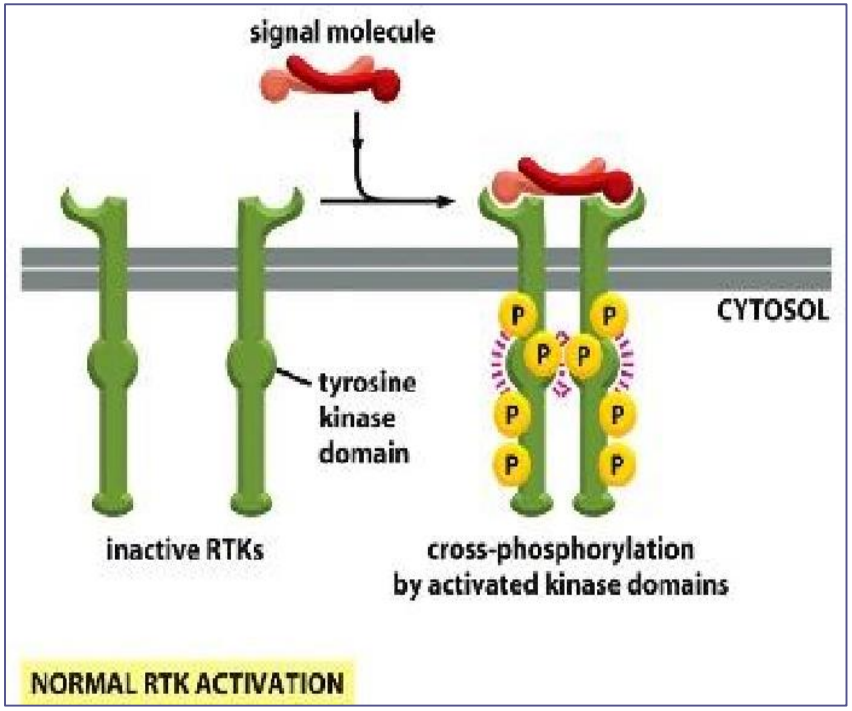
Three main effectors can be activated later:

phosphoinositide 3-kinase (Pi3K),
rat sarcoma (RAS), and
phospholipase C (PLC).



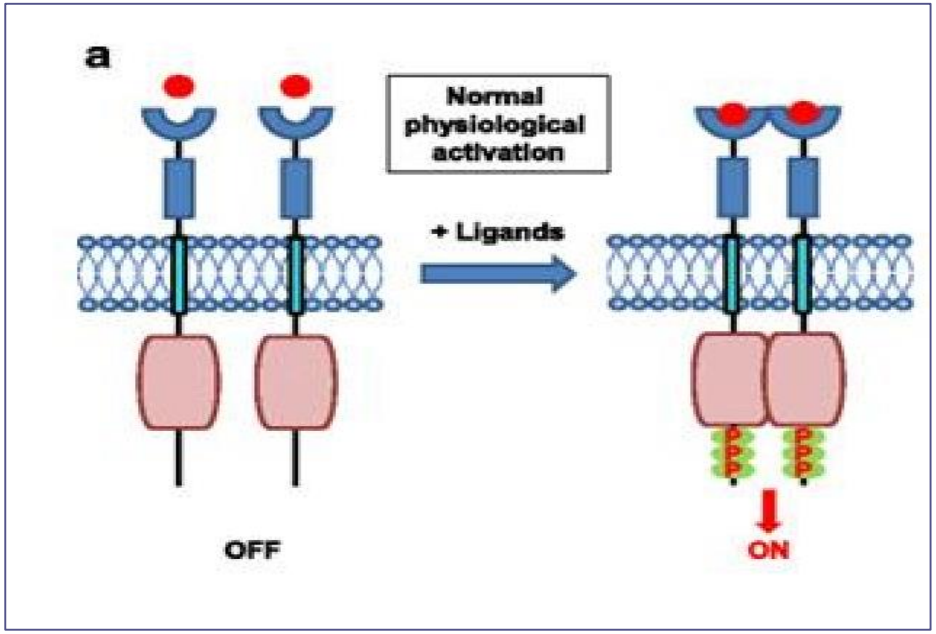
Mechanisms of RTK activation under normal physiologic conditions

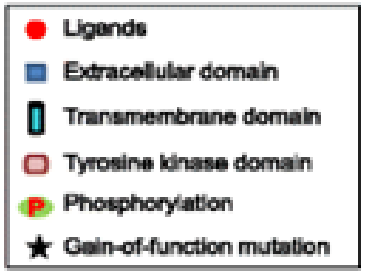
- RTKs are generally activated by receptor-specific ligands.
- Growth factor ligands bind to extracellular regions of RTKs, and the receptor is activated by ligand-induced receptor dimerization and/or oligomerization.
  - **A-** Schematic representation of RTK activation in normal physiology.



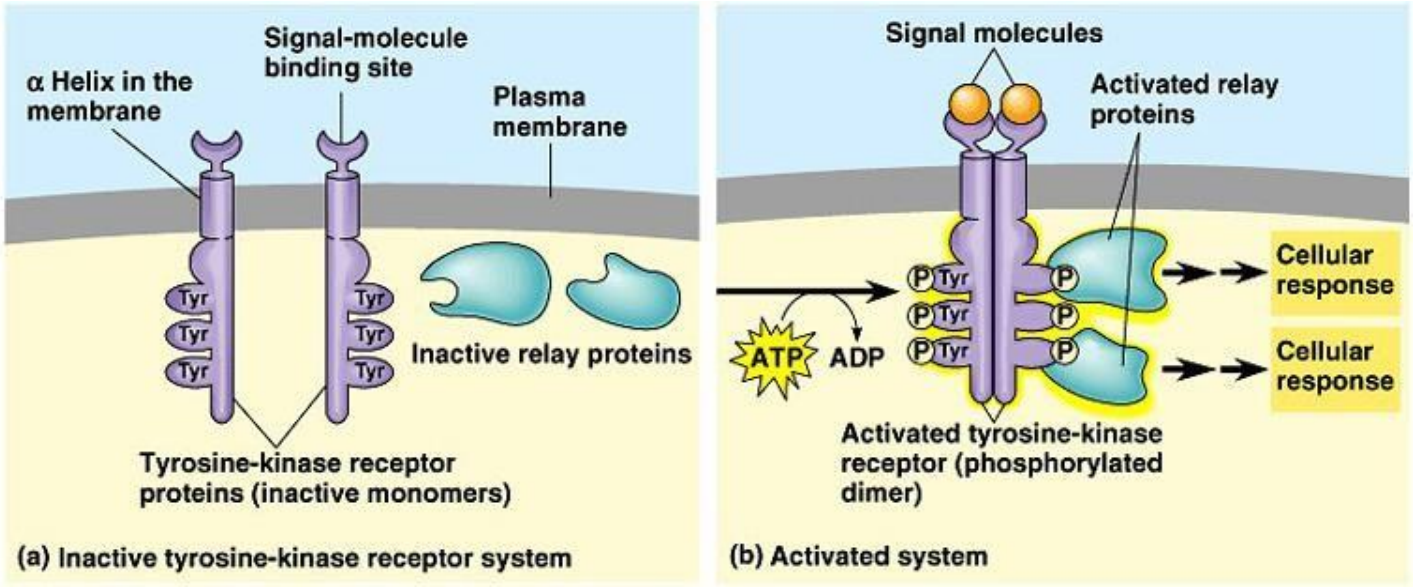
Mechanisms of RTK activation under normal physiologic conditions

- **A-** Schematic representation of RTK activation in normal physiology. RTKs are activated through formation of inter-molecular dimerization in the presence of ligands, resulting in kinase activation and phosphorylation of the receptor C-terminal tail.

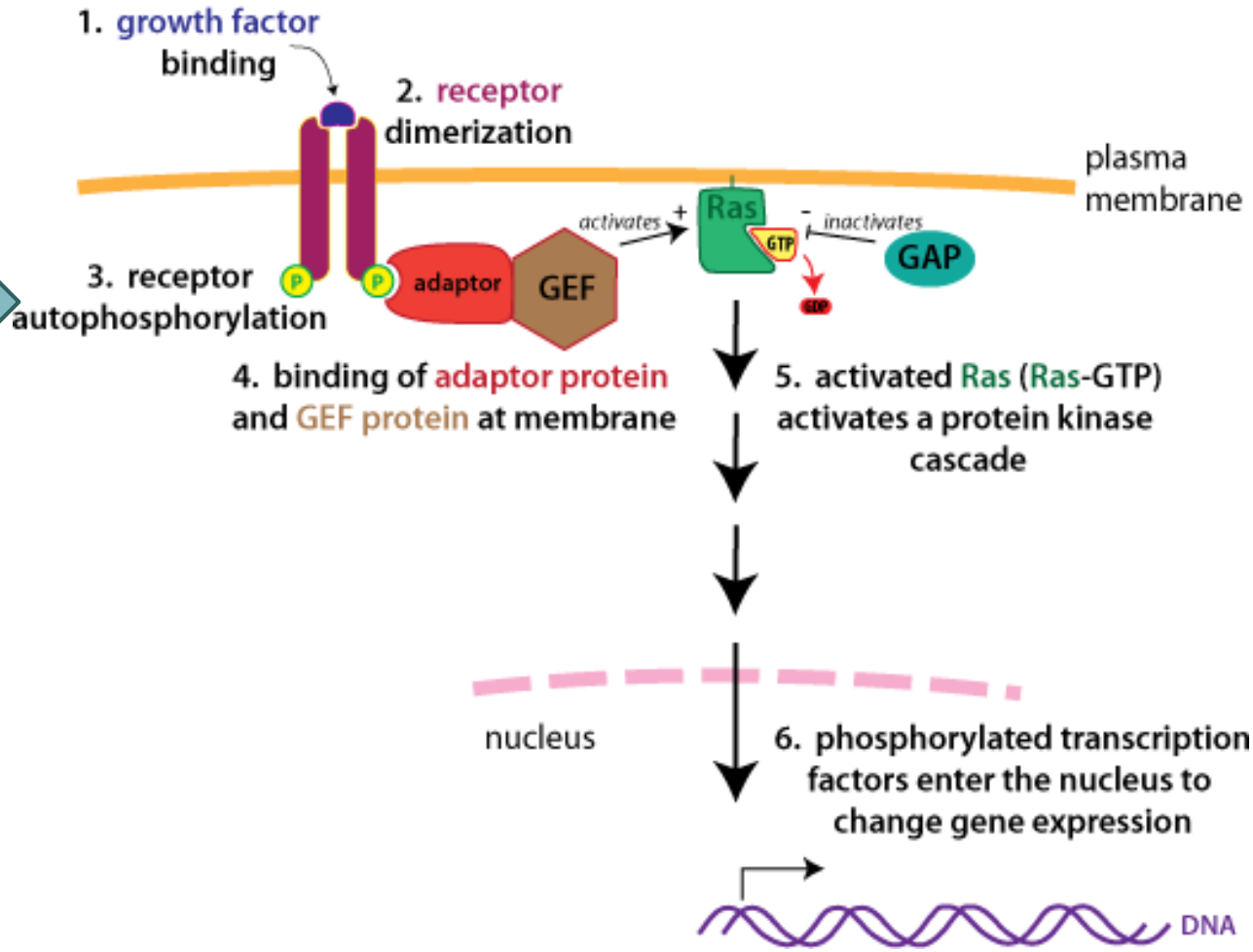




- For most RTKs, the resultant conformational changes enable *trans*-autophosphorylation of each TKD.
- Autophosphorylation of RTKs also recruits and activates a wide variety of downstream signaling proteins.
- These domains bind to specific phosphotyrosine residues within the receptor and engage downstream mediators that propagate critical cellular signaling pathways



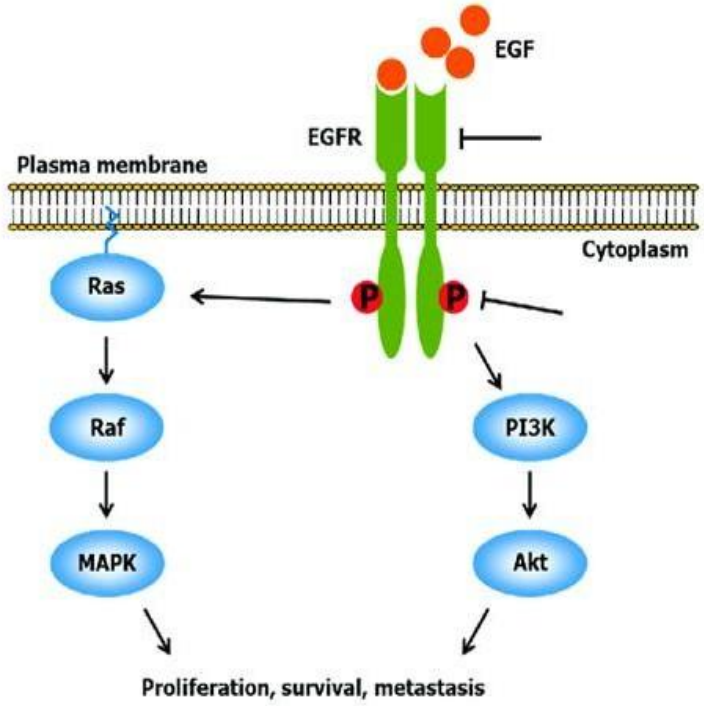
At this stage a signal from outside the cell has been transduced to inside the cell



- **Getting the signal from a growth factor outside the cell to inside the nucleus where gene expression is regulated requires several steps:**

1. binding of the growth factor to the receptor,
2. receptor dimerization,
3. autophosphorylation, activation of intracellular transducers (including the "star player" RAS) and a cascade of serine/threonine kinases
4. Regulation of transcription factors for gene expression

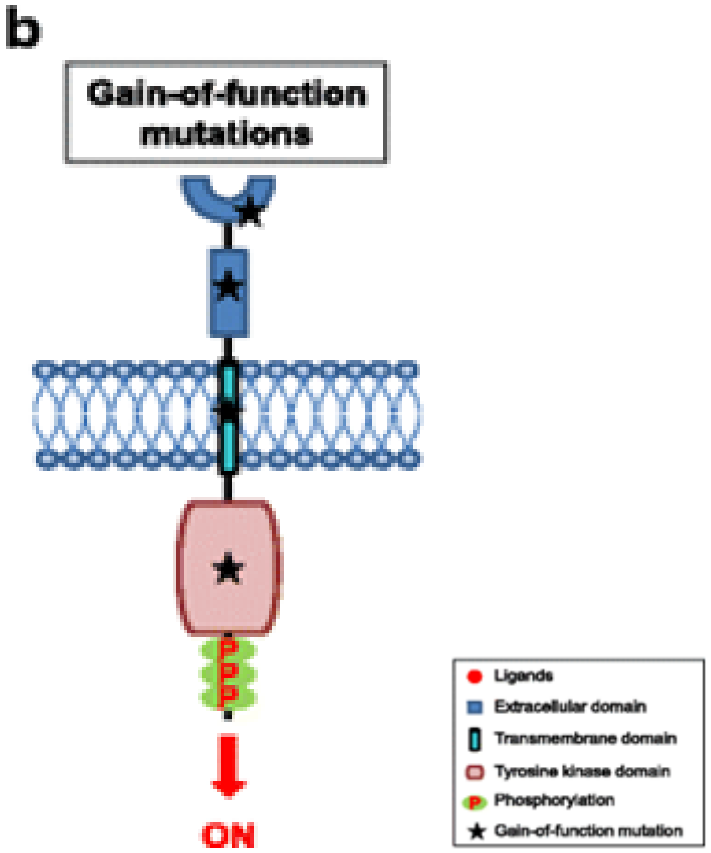
Each of the steps involved in the signal transduction pathway of EGF



Mechanisms of RTK activation under abnormal conditions

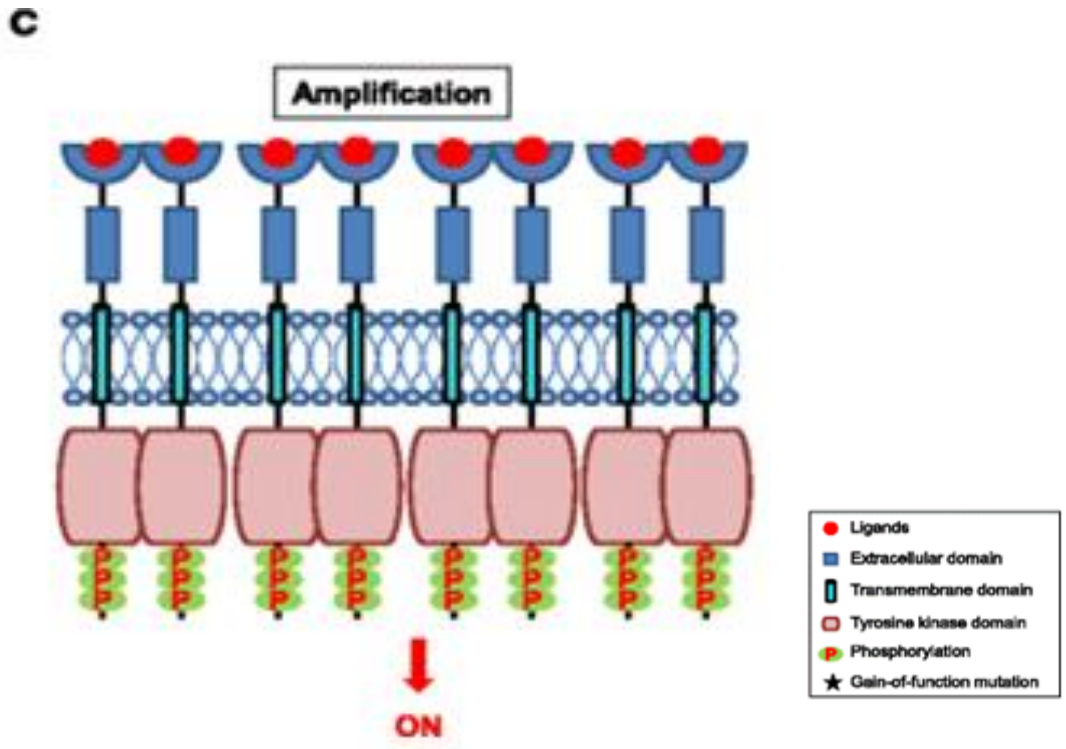
B- Schematic representation of potential gain-of-function mutations in the various subdomains of an RTK.

The mutations lead to constitutive activation of the RTK, typically in the absence of ligand.



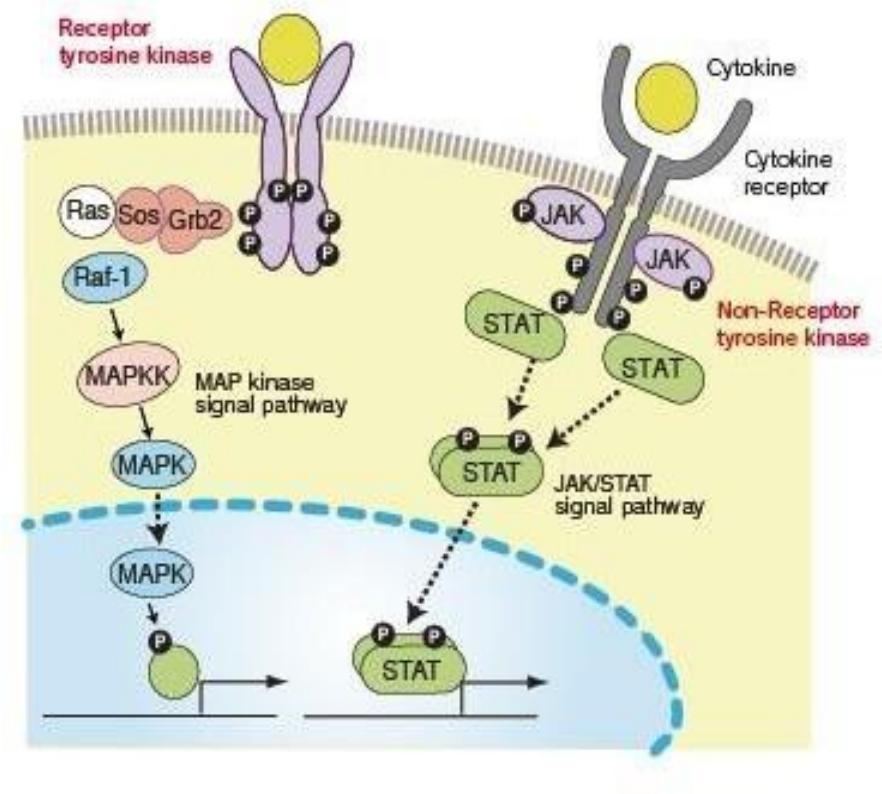
Mechanisms of RTK activation under abnormal conditions

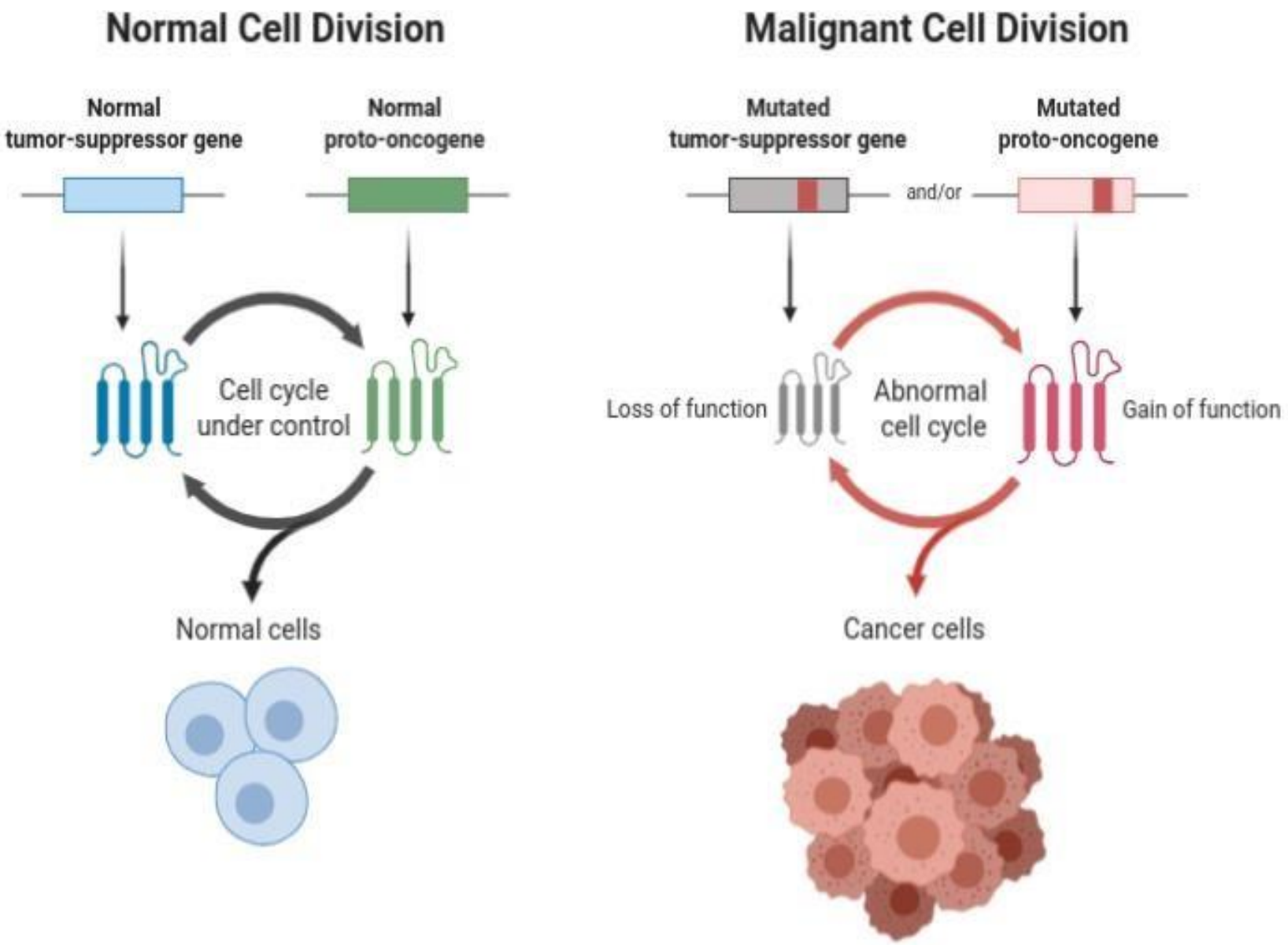
C- Overexpression of RTKs – often as a result of genomic amplification of the RTK gene - leads to increased local concentration of receptors



- **What is the difference between non receptor tyrosine kinase and receptor tyrosine kinase?**

- The key conceptual difference here is RTK has *intrinsic* TK activity and nRTK needs to recruit JAK to have kinase activity.




Normal Cell Division
Normal
tumor-suppressor gene
Normal
proto-oncogene
Cell cycle
under control
Normal cells
Malignant Cell Division
Mutated
tumor-suppressor gene
and/or
Mutated
proto-oncogene
Loss of function
Abnormal
cell cycle
Gain of function
Cancer cells