Neoplasia lecture 4

HALLMARKS OF CANCER

- **The hallmarks of cancer:**

1• Self-sufficiency in growth signals

2• Insensitivity to growth-inhibitory signals

3• Altered cellular metabolism

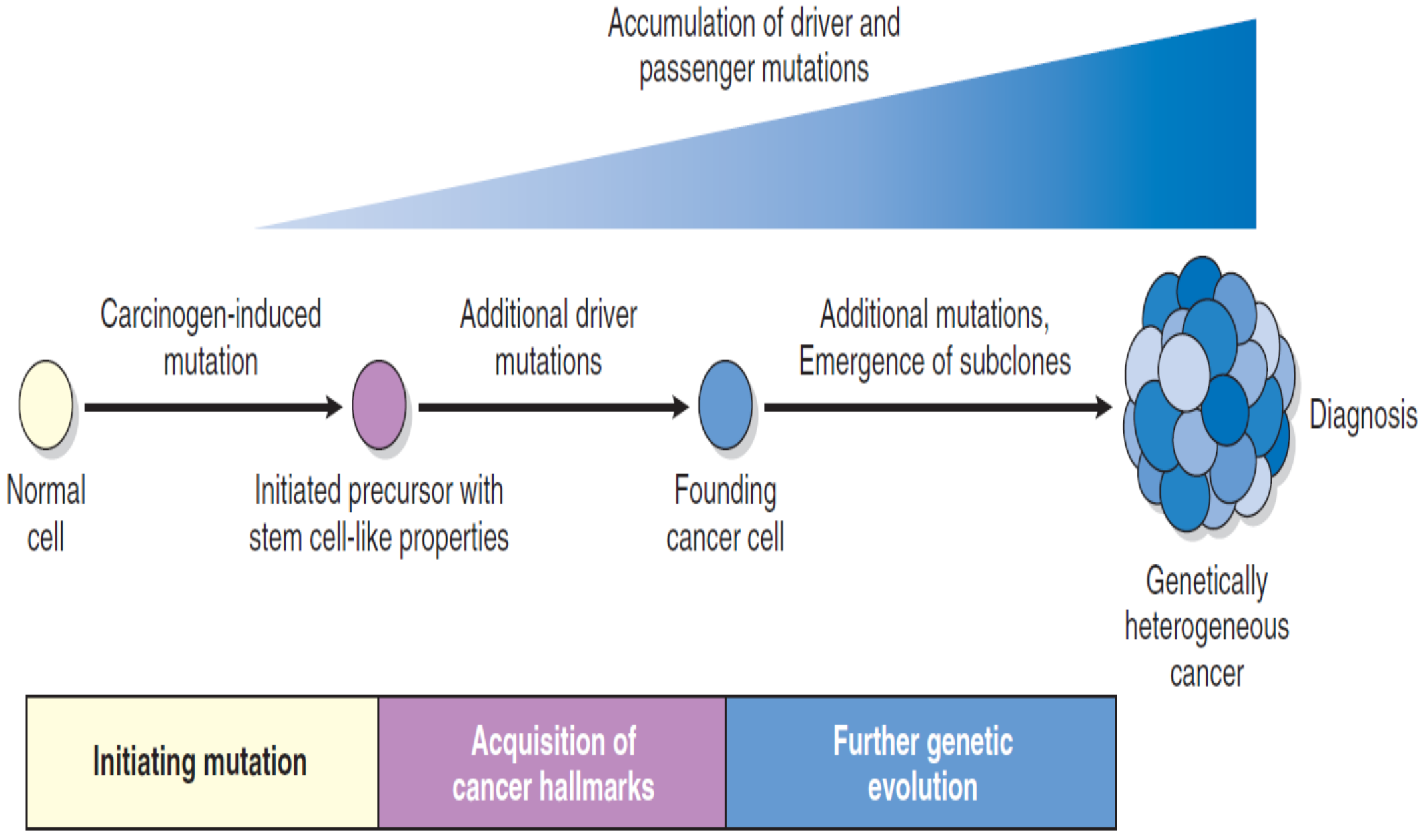
4• Evasion of apoptosis

5• Limitless replicative potential (immortality)

6• Sustained angiogenesis

7• Invasion and metastasis

8• Evasion of immune surveillance


Accumulation of driver and passenger mutations
Carcinogen-induced mutation
Additional driver mutations
Additional mutations, Emergence of subclones
Diagnosis
Normal cell
Initiated precursor with stem cell-like properties
Founding cancer cell
Genetically heterogeneous cancer
Initiating mutation
Acquisition of cancer hallmarks
Further genetic evolution

Self-Sufficiency in Growth Signals

- **It stems from gain-of-function mutations that convert proto-oncogenes to oncogenes.**
- **Oncogenes encode proteins called *oncoproteins* that promote cell growth even in the absence of normal growth-promoting signals.**

Steps of Normal cell proliferation

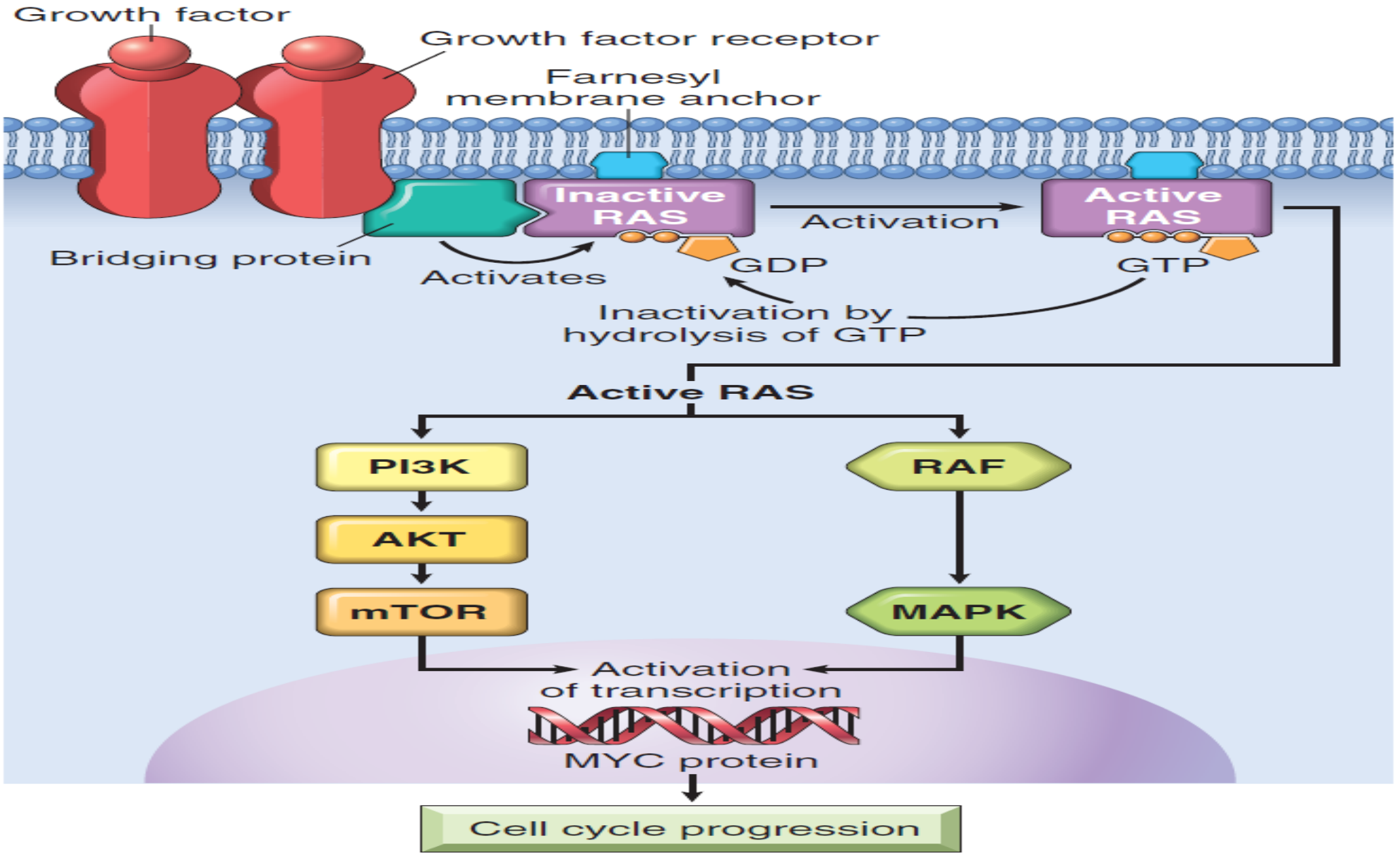
1. Binding of a growth factor to its specific receptor on the cell membrane

2. Transient and limited activation of the growth factor receptor, which in turn activates several signal transducing proteins on the inner leaflet of the plasma membrane

3. Transmission of the transduced signal across the cytosol to the nucleus by second messengers or a cascade of signal transduction molecules

4. Induction and activation of nuclear regulatory factors that initiate and regulate DNA transcription and the biosynthesis of other cellular components that are needed for cell division, such as organelles, membrane components, and ribosomes

5. Entry and progression of the cell into the cell cycle, resulting ultimately in cell division


Growth factor
Growth factor receptor
Farnesyl
membrane anchor
Inactive
RAS
Activation
Active
RAS
Bridging protein
Activates
GDP
GTP
Inactivation by
hydrolysis of GTP
Active RAS
PI3K
AKT
mTOR
RAF
MAPK
Activation
of transcription
MYC protein
Cell cycle progression

Growth Factors

- **Cancers may secrete their own growth factors or induce stromal cells to produce growth factors in the tumor microenvironment.**
- **Most soluble growth factors are made by one cell type and act on a neighboring cell to stimulate proliferation (paracrine action).**

- **Some cancer cells acquire growth self-sufficiency by acquiring the ability to synthesize the same growth factors to which they are responsive.**
- **For example:**
- **Many glioblastomas secrete platelet-derived growth factor (PDGF) and express the PDGF receptor**
- **Many sarcomas make both transforming growth factor-α (TGF-α) and its receptor.**
- **In some cases, tumor cells send signals to activate normal cells in the supporting stroma to produce growth factors that promote tumor growth.**

Growth Factor Receptors

- **Some growth factor receptors have an intrinsic tyrosine kinase activity that is activated by growth factor binding while others signal by stimulating the activity of downstream proteins.**
- **Many of the growth factor receptors function as oncoproteins when they are mutated or if they overexpressed.**

- **Examples:**
- Epidermal growth factor (EGF) receptor family.
- ERBB1 is overexpressed in 80% of squamous cell carcinomas of the lung, 50% or more of glioblastomas, and 80-100% of epithelial tumors of the head and neck
- HER2 (ERBB2) is amplified in approximately 20% of breast cancers and in a smaller fraction of adenocarcinomas of the lung, ovary, stomach, and salivary glands.

- **These tumors are exquisitely sensitive to the mitogenic effects of small amounts of growth factors.**
- **HER2 is significant in treatment**

- **Tyrosine kinase activity is stimulated by point mutations or small indels that lead to subtle but functionally important changes in protein structure, or gene rearrangements that create fusion genes encoding chimeric receptors.**
- **Examples**

Leukemias, lymphomas, and certain forms of sarcoma.

Downstream Signal-Transducing Proteins

- **The signaling proteins that couple growth factor receptors to their nuclear targets are activated by ligand binding to growth factor receptors.**
- **The signals are transmitted to the nucleus through various signal transduction molecules.**

- **Two important oncoproteins in the category of signaling molecules are Present:**
- **1. RAS**
- **2. ABL**

RAS

- ***RAS* is the most commonly mutated oncogene in human tumors.**
- **Approximately 30% of all human tumors contain mutated *RAS* genes, and the frequency is even higher in some specific cancers (e.g., pancreatic adenocarcinoma)**
- RAS is a member of a family of small G proteins that bind guanosine triphosphate [GTP] and guanosine diphosphate [GDP]).

- **Signaling by RAS involves the following sequential steps:**

- Normally RAS flips back and forth between an excited signal transmitting state and a quiescent state

- RAS is inactive when bound to GDP

- Stimulation of cells by growth factors such as EGF and PDGF leads to exchange of GDP for GTP and subsequent conformational changes that activate RAS (RAS-GTP)

- **Active RAS is is short-lived because the activity of intrinsic guanosine triphosphatase (GTPase) activity**
- **RAS hydrolyzes GTP to GDP releasing a phosphate group and returning the protein to its quiescent GDP bound state.**
- **The GTPase activity of activated RAS is magnified dramatically by a family of GTPase-activating proteins (GAPs)**
- **GAPs act as molecular brakes that prevent uncontrolled RAS activation by favoring hydrolysis of GTP to GDP.**

- **Activated RAS stimulates downstream regulators of proliferation**

by several interconnected pathways that converge on

the nucleus and alter the expression of genes that regulate

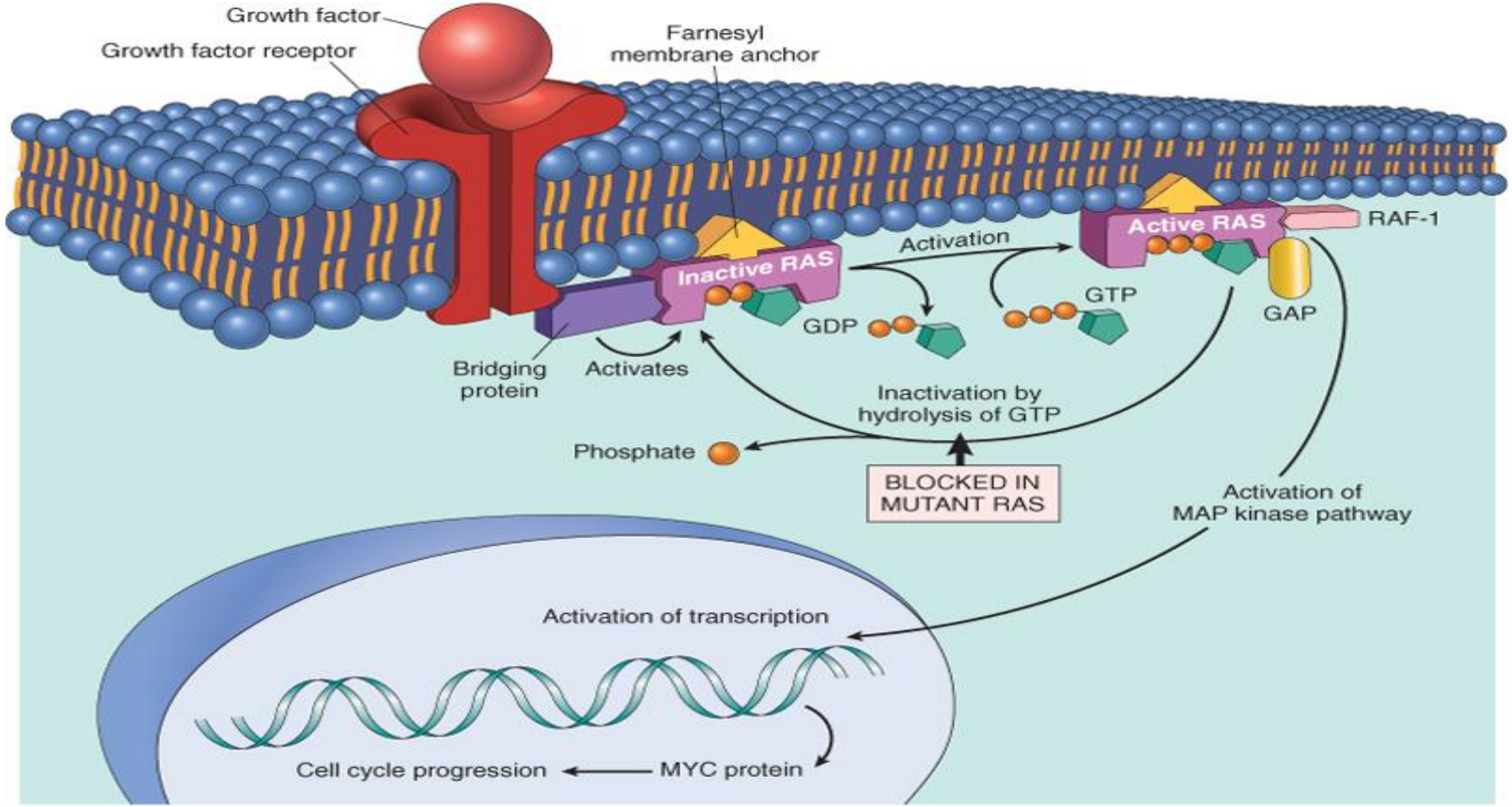
growth such as MYC.

- **For example, BRAF, which lies in the so-called “RAF/ERK/MAP kinase pathway” is mutated in more than 60% of melanomas and is associated with unregulated cell proliferation**

- **RAS most commonly is activated by point mutations in amino acid residues that are either within the GTP binding pocket or in the enzymatic region that carries out GTP hydrolysis.**
- **Both kinds of mutations interfere with breakdown of GTP which is essential to inactivate RAS.**
- **RAS is thus trapped in its activated, GTP-bound form and the cell is forced into a continuously proliferating state.**
- **Activating mutations in RAS can be mimicked by loss-of function**

  GAPs leading to a failure to simulate GTP hydrolysis and traping RAS in

  active state


Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
RAF-1
GTP
GDP
GAP
Bridging protein
Activates
Inactivation by hydrolysis of GTP
Phosphate
BLOCKED IN MUTANT RAS
Activation of MAP kinase pathway
Activation of transcription
Cell cycle progression
MYC protein

- **Examples**

- Neurofibromatosis type 1

  the GAP neurofibromin-1 (NF1) is mutated

- A tumor suppressor gene called PTEN which is a negative inhibitor of PI3 kinase is frequently mutated in carcinomas and certain leukemias

- *ABL*

- **The ABL proto-oncoprotein has tyrosine kinase activity that is controlled by internal negative regulatory domains**
- **In chronic myeloid leukemia and certain acute leukemias a part of the *ABL* gene is translocated from its normal site on chromosome 9 to chromosome 22 forming Philadelphia (Ph) chromosome**

- **This fusion gene encodes as BCR-ABL hybrid protein that has a tyrosine kinase activity.**
- **The BCR-ABL protein activates all of the signals is a potent stimulator of cell growth.**
- **Imatinib mesylate (Gleevec) is BCR-ABL kinase inhibitors that has a dramatic clinical response in patients with chronic myeloid leukemia**

Nuclear Transcription Factors

- **Mutated RAS or ABL results in inappropriate and continuous stimulation of nuclear transcription factors that drive the expression of growth-promoting nuclear genes**
- ***MYC, MYB, JUN, FOS,* and *REL* oncogenes, function as transcription factors that regulate the expression of growth-promoting genes, such as cyclins**
- **MYC is involved most commonly in human tumors**

- **MYC activates several growth-promoting genes including cyclin-dependent kinases (CDKs)**
- **Examples**

***1. MYC translocation* (8;14) in Burkitt lymphoma, a highly aggressive B-cell tumor.**

***2. MYC* also is amplified in breast, colon, lung, and many other cancers**

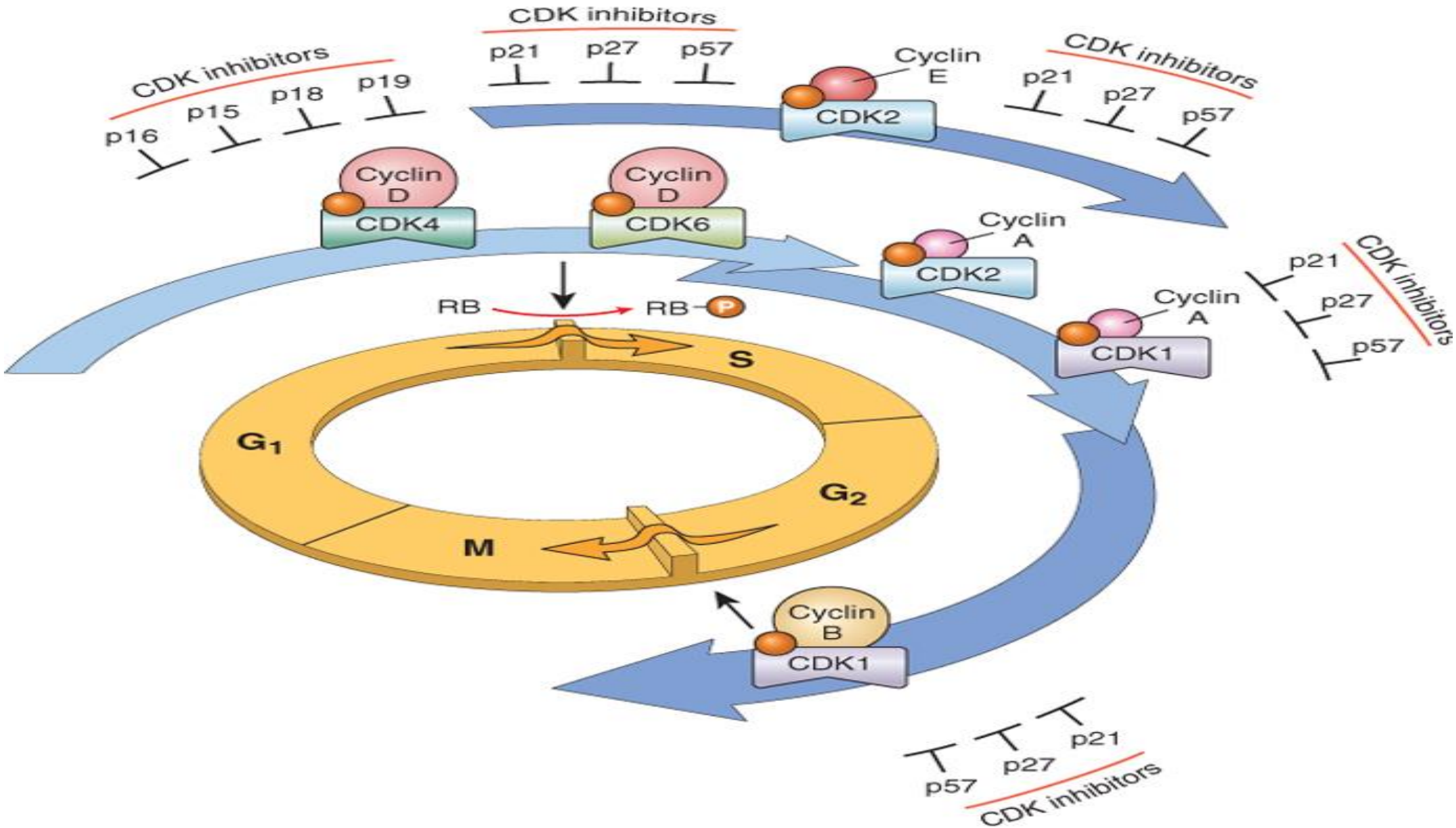
3. *NMYC gene* is amplified in neuroblastoma

***4. LMYC* gene is amplified in small cell carcinoma of lung**

Cyclins and Cyclin-Dependent Kinases

- **Progression of cells through the cell cycle is controlled by *cyclin-dependent kinases* (CDKs)**
- **CDKs are activated by binding to *cyclins***
- **Cyclins are characterized by cyclic nature of production and degradation**

- ***CDK inhibitors*** **(CDKIs) exert negative control over the cell cycle**
- **Expression of these inhibitors is downregulated by mitogenic signaling pathways promoting the progression of the cell cycle.**


CDK inhibitors
p16
p15
p18
p19
CDK inhibitors
p21
p27
p57
Cyclin
E
CDK2
CDK inhibitors
p21
p27
p57
Cyclin
D
CDK4
Cyclin
D
CDK6
Cyclin
A
CDK2
RB
RB
P
S
G1
G2
M
Cyclin
A
CDK1
CDK inhibitors
p21
p27
p57
Cyclin
B
CDK1
p57
p27
p21
CDK inhibitors

- **The CDK-cyclin complexes phosphorylate crucial target proteins that drive the cell through the cell cycle.**
- **On completion of this task, cyclin levels decline rapidly.**
- **More than 15 cyclins have been identified; cyclins D, E, A, and B appear sequentially during the cell cycle and bind to one or more CDK**.

- **Mishaps affecting the expression of cyclin D or CDK4 seem to be a common event in neoplastic transformation.**
- **The cyclin D genes are overexpressed in many cancers, including those affecting the breast, esophagus, liver, and a subset of lymphomas.**

- **Amplification of the *CDK4* gene occurs in melanomas, sarcomas, and glioblastomas.**

- **Mutations affecting cyclin B and cyclin E and other CDKs also occur, but they are much less frequent than those affecting cyclin D/CDK4.**

- **While cyclins arouse the CDKs**
- **CDK inhibitors (CDKIs) silence the CDKs and exert negative control over the cell cycle**
- **One family of CDKIs, composed of three proteins :**
- **1- p21 [CDKN1A]**
- **2-p27 [CDKN1B]**
- **3-p57 [CDKN1C]**

inhibits the CDKs broadly

- **The other family of CDKIs has selective effects on cyclin D/CDK4 and cyclin D/CDK6.**
- **The four members of this family :**
- **1-p15 [CDKN2B]**
- **2-p16 [CDKN2A]**
- **3-p18 [CDKN2C]**
- **4-p19 [CDKN2D]**

are sometimes called INK4 (A-D) proteins.

- **Expression of these inhibitors is down-regulated by mitogenic signaling pathways, thus promoting the progression of the cell cycle.**
- **E.g**
- **p27 [CDKN1B], a CDKI that inhibits cyclin E, is expressed throughout G_1.**
- **Mitogenic signals inhibit p27 relieving inhibition of cyclin E-CDK2 and thus allowing the cell cycle to proceed.**
- **The CDKIs are frequently mutated or otherwise silenced in many human malignancies.**

- **<u>Examples</u>**
- **Germ-line mutations of p16(*CDKN2A)* are associated with 25% of melanoma.**
- **Acquired deletion or inactivation of p16(*CDKN2A)* is seen in:**

1. 75% of pancreatic carcinomas

2. 40% to 70% of glioblastomas

3. 50% of esophageal cancers

4. 20% of non-small-cell lung carcinomas, soft tissue sarcomas, and bladder cancers.