Neoplasia lecture 4

Tumors can survive more than expected compared to normal cells

HALLMARKS OF CANCER

They are able to affect the surrounding tissues and induce growth of blood vessels because of the increased tumors need of blood vessels , oxygen , nutrients to support their survival

- **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

Tumor cells have the ability to develop malignant characteristics, such as invasion and metastasis. A crucial aspect of their survival is their capacity to escape the immune system, which is primarily responsible for identifying and eliminating abnormal cells. Despite being inherently abnormal, tumor cells can effectively escape immune detection, enabling their continued survival and progression

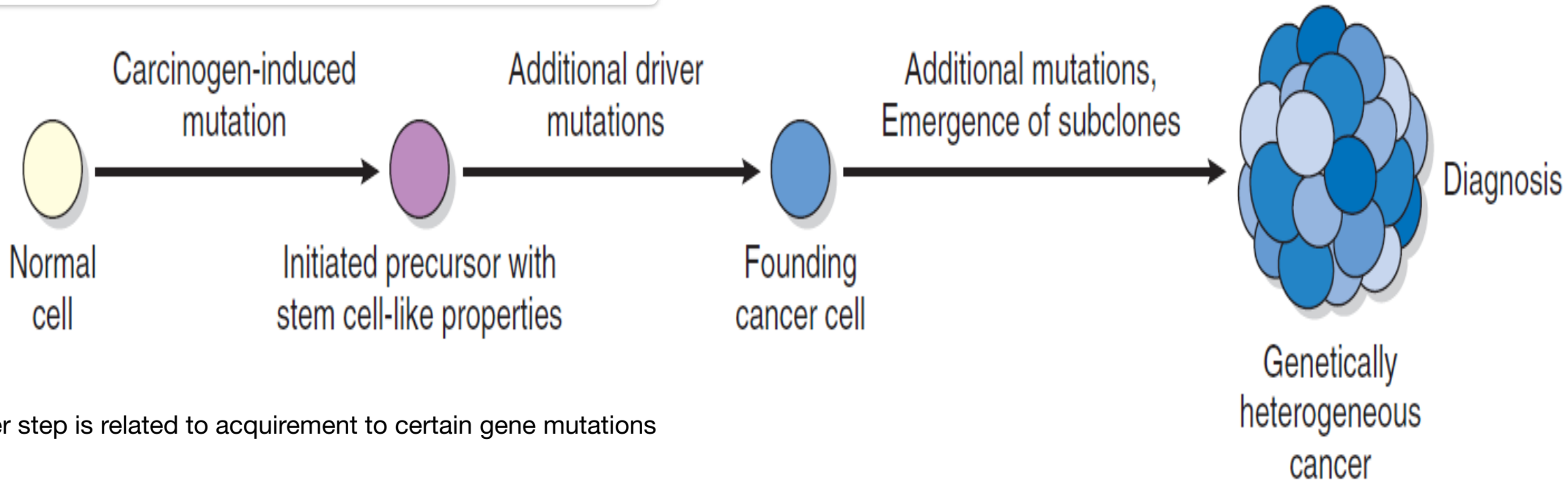
Further explanation

Cancer cells can bypass the need for external growth signals by producing their own or activating pathways that mimic these signals. This allows them to grow and divide uncontrollably, a hallmark of cancer.

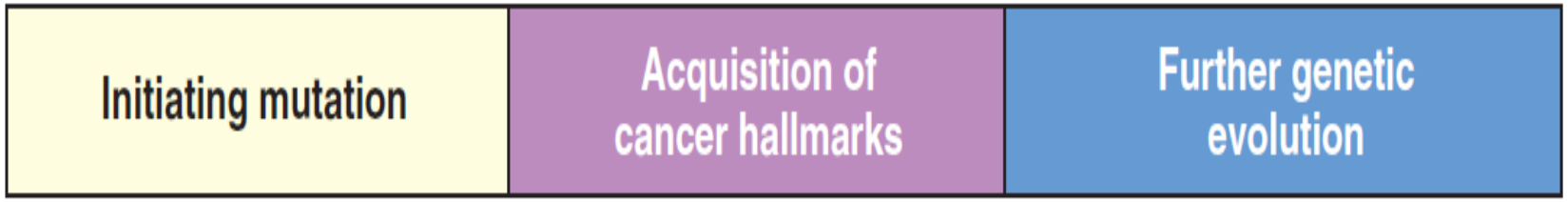
Cancer cells ignore signals that normally tell cells to stop growing. They do this by disabling or bypassing the pathways that control growth inhibition, allowing them to grow even when they shouldn't.

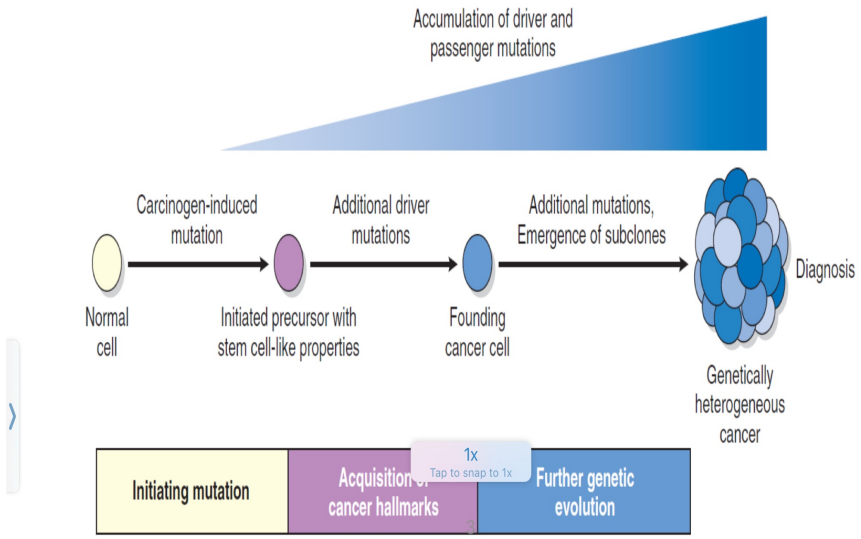
The development of cancer happens step by step(step wise faction). Some tumors grow quickly, while others take longer. This process starts when normal cells are exposed to carcinogens (cancer-causing substances) and acquire mutations in genes responsible for cell growth and division.

One mutation may lead to more mutations, known as promoters, which encourage the growth of abnormal cells. Over time, these cells gain more mutations and eventually develop all the characteristics needed to divide rapidly and survive. This leads to the formation of a mass of cells called a tumor, which can then be detected as clinical evidence of cancer



Ever step is related to acquirement to certain gene mutations





Further explanation for better understanding

1. **Normal Cell**: A healthy cell is exposed to carcinogens, which cause an initial mutation.
2. **Initiated Precursor Cell**: This cell gains stem cell-like properties, meaning it can survive longer and divide more.
3. **Additional Driver Mutations**: Over time, more key mutations accumulate in genes that control growth and survival. These are called "driver mutations" because they drive the cancer process.
4. **Founding Cancer Cell**: A cancer cell is formed, starting the tumor.
5. **Emergence of Subclones**: As the tumor grows, more mutations appear, creating genetically different groups (subclones) within the tumor.
6. **Genetically Heterogeneous Cancer**: By the time of diagnosis, the cancer is made up of many different cell types with varied mutations, making it harder to treat.

The bottom labels represent:

- **Initiating Mutation**: The first mutation that starts the process.
- **Acquisition of Cancer Hallmarks**: Cells gain abilities like uncontrolled growth and avoiding death.
- **Further Genetic Evolution**: Continuous mutations lead to more complex and diverse cancer cells.

Self-Sufficiency in Growth Signals

Cell in our body grow/ divide under certain control

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

Genes responsible for changes of tumor cells are
1- oncogen tumer
2- suppressor genes
3- repair genes
(All of these directly or indirectly will have some effect on cells growth)

Normally cells when divide need to receive signals

Steps of Normal cell proliferation

Usually present in matrix or induced by certain growth factors produced by other cells

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**

Normal cell proliferation involves a series of steps that begin when external signals bind to cell surface receptors. This binding triggers a cascade of signaling events that initiate changes on the inner surface of the cell membrane. These signals are then transduced through certain proteins in the inner leaflet of the membrane or through signaling pathways within the cytoplasm, which ultimately carry the message to the nucleus to initiate the cell cycle and division

When the signal reaches the nucleus, it activates nuclear proteins required for cell division. The activation of these proteins is tightly regulated to ensure proper cell cycle progression. This regulation is crucial, as the signaling pathways need to be carefully controlled, and inhibitors are in place to prevent the cell cycle from being activated continuously. Various genes are involved in controlling these signaling processes, ensuring that they are switched off once cell division is no longer needed.

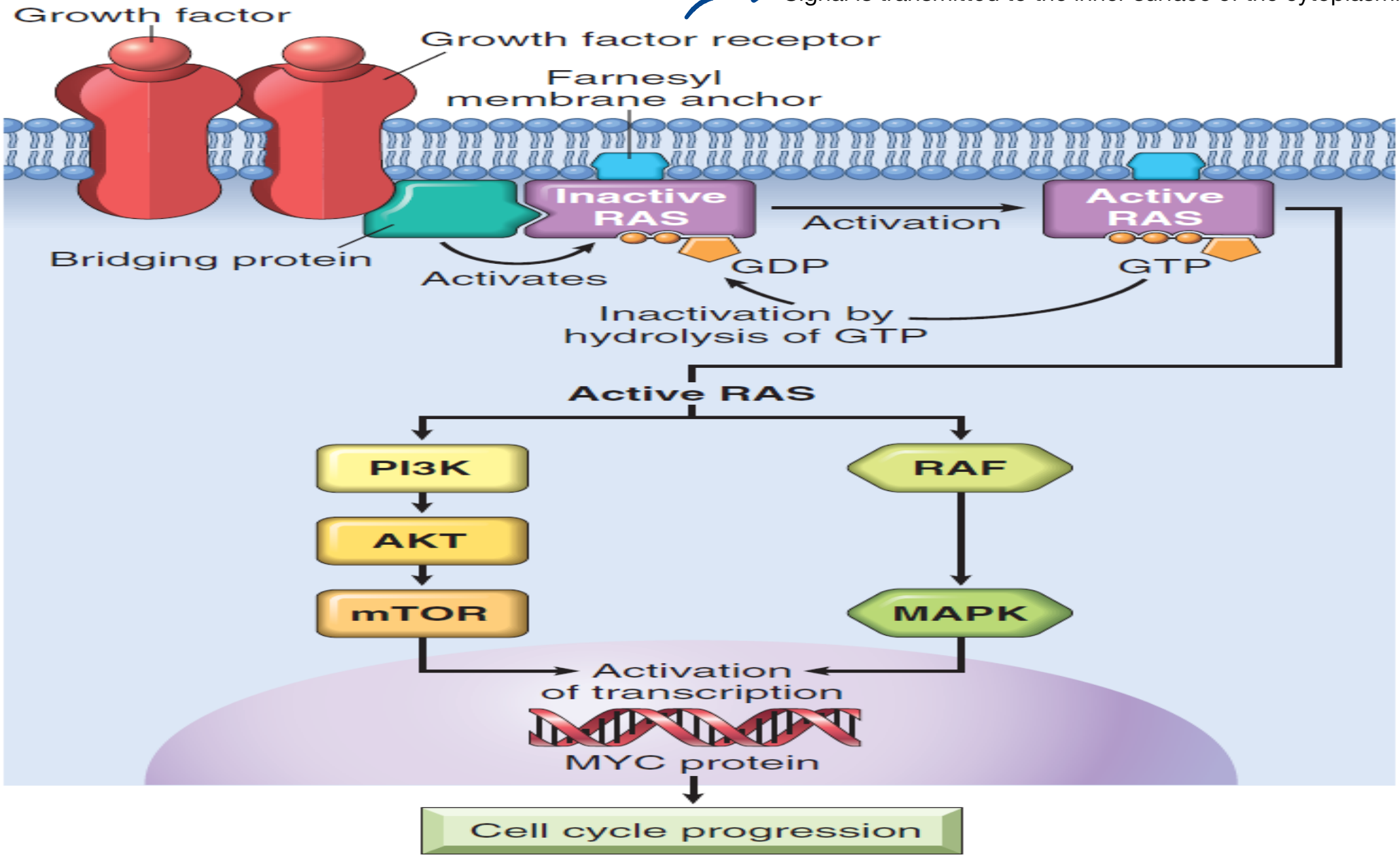
Cell division is highly controlled mechanism by different types of genes in order to prevent any unneeded growth or division

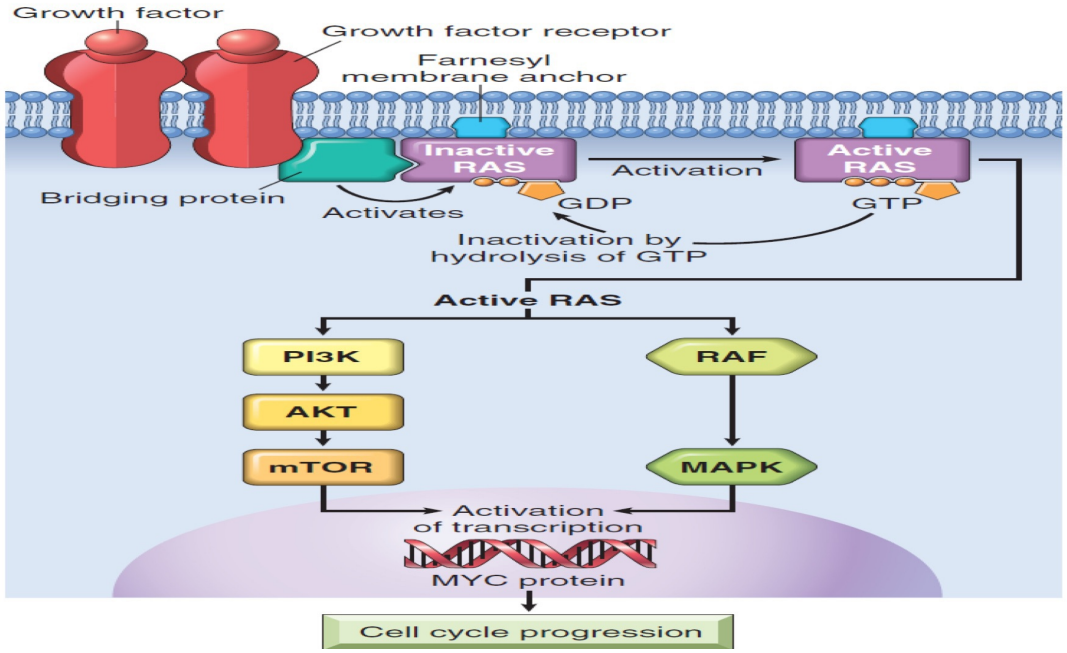
Dependent on other type of protein like cyclin dependent kinases which activates cyclins

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

Signal is transmitted to the inner surface of the cytoplasmic membrane





The most important one is RAS gene , once it's activated it initiates different pathways within the cytoplasm that end up carrying the massage to the nucleus (where there is different types of gens that should be stimulated in order to enter the cell cycle and divide

If we know what's the exact gene involved in cancer cells we might design a drug that antagonize the effect of that gene by this we might interfere with tumer cells growth
Nowadays we have some drugs that are used to target theses gens and to prevent the progression of tumor , it's affective but not widely used because it's targeted, only the tumors that have theses mutations are responsive , so we need to know more in prefer to design more drugs that targets mutations

All theses steps are involved in malignancy
Mutations of any gene . these steps are associated with increased signaling or over expression of gens

Gene mutations occur in all type of malignancy, although there are different types of gens , one of these gens must be Involved or seen in malignancy

From our book :

Fig. 6.18 Model for action of RAS. When a normal cell is stimulated through a growth factor receptor, inactive (GDP-bound) RAS is activated to a GTP-bound state. Activated RAS transduces proliferative signals to the nucleus along two pathways: the so-called "RAF/ERK/MAP kinase pathway" and the *PI3 kinase/AKT pathway. GDP,* Guanosine diphosphate; *GTP,* guanosine triphosphate; *MAP,* mitogen-activated protein; *PI3,* phosphatidylinositol-3.

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).**

Gene mutations in growth factors and growth factor receptors in tumor cells allow them to respond to growth factors produced by other cells. However, the more important aspect is their ability to respond to growth factors that are produced by the tumor cells themselves. Tumor cells are independent; they can produce the growth factors they need and respond to them. They do not need any other cell to stimulate their own growth, which is known as the paracrine effect

They are more sensitive to the same amount of growth factors than normal cells , they response more rapidly and more effectively to the same amount Even the receptors for growth factors are more sensitive and they can bind more efficiently

- **Autocrine signaling** occurs when a cell produces growth factors that it also responds to, effectively stimulating its own growth.
- **Paracrine signaling** refers to a situation where a cell produces growth factors that act on nearby cells, not the cell that produced them.

- **Some cancer cells acquire growth self-sufficiency by acquiring the ability to synthesize the same growth factors to which they are responsive.**
- **For example:** Glioblastoma > CNS tumer (Braun tumor) they secrete platelet derived growth factors (widely secreted growth factor) also they express on their surface platelets derived growth factors receptors
- **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.** Tumor cells might undergo stimulation by other cells to produce more growth factors

Growth Factor Receptors

Further explanation

Some growth factor receptors have an intrinsic **tyrosine kinase activity**, meaning that when a growth factor binds to the receptor, it automatically activates this enzyme activity within the receptor itself. This leads to a series of signals inside the cell, promoting growth and survival.

Other growth factor receptors, however, don't have this built-in enzyme activity. Instead, when the growth factor binds to these receptors, it triggers the activation of other proteins inside the cell that send signals to drive processes like cell growth or division.

- **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.**

Tumors may have abnormalities in growth factors receptors making them more sensitive to growth factors (intrinsic tyrosine kinase activity which is the stimulation of genes responsible for massage transduction for cytoplasm once receptors activates those kinases massage directly will be transmitted to the nucleus to initiate division

These receptors might get mutated by over expression and once they are over expressed there will follow continuous stimulation of kinases ,,,,,,,, continuous division

- **Many of the growth factor receptors function as oncoproteins when they are mutated or if they overexpressed.**

Further explanation for better understanding

Many growth factor receptors can become **oncoproteins** when they are mutated or overexpressed. An **oncoprotein** is a protein that, when altered, promotes cancer development.

- **Mutations** in growth factor receptors can cause them to be constantly active, even without the presence of growth factors. This leads to continuous signaling inside the cell, promoting uncontrolled cell growth and division, a hallmark of cancer.
- **Overexpression** occurs when there are too many copies of a growth factor receptor on the cell surface, making the cell overly sensitive to growth signals. This can result in excessive activation of the receptor and uncontrolled cell proliferation.

Both mutations and overexpression of growth factor receptors can disrupt normal cellular regulation, contributing to tumor development.

Yes, that's correct! **Oncoprotein receptors** refer to growth factor receptors that, when mutated or overexpressed, can **act without normal signaling control**. These receptors can become constitutively active, meaning they send growth signals continuously, even in the absence of their usual activating growth factors. This uncontrolled signaling promotes abnormal cell growth and division, which can contribute to the development of cancer. Essentially, these receptors act like "on" switches that can't be turned off, leading to unregulated cell proliferation.

Of 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 (Brain tumor), 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. Less frequently

HER2 has a drug that antagonize the effect of this mutation and is called HERCEPTIN, patients who have this mutation with Brest cancer benefit from drug and might suppress the tumor growth

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

Cytoplasmic signal transducer

- **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.**

Tyrosine kinase activity can be increased by two main mechanisms:

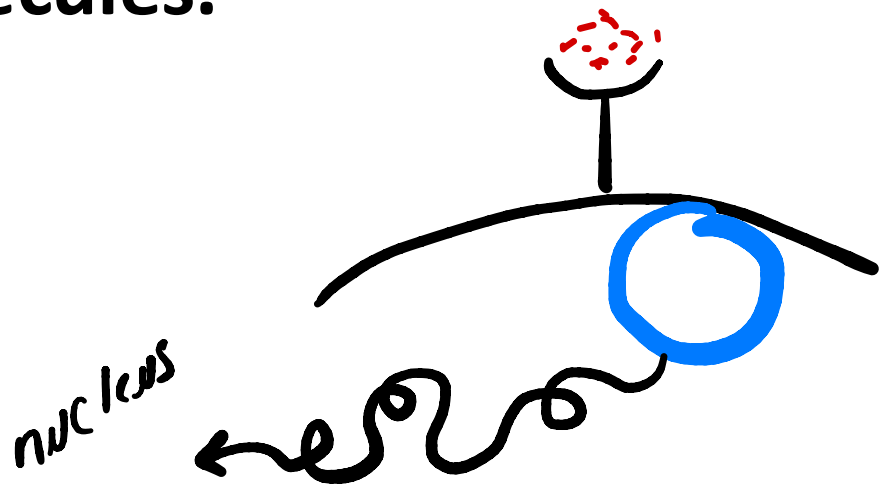
1. **Point mutations or small indels (insertions or deletions)**: These are tiny changes in the DNA sequence of the tyrosine kinase gene. They slightly alter the protein's structure, which can make the enzyme more active or harder to turn off. Think of it like a door hinge that gets stuck in the open position, keeping the pathway active.
2. **Gene rearrangements creating fusion genes**: Sometimes, parts of two different genes get combined, forming a "fusion gene." This new hybrid gene makes a chimeric protein, which is a tyrosine kinase stuck in an "always-on" mode. This abnormal activity can drive cell growth and division, contributing to diseases like cancer.

In both cases, the changes result in excessive tyrosine kinase signaling, disrupting normal cell behavior.

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.**

This process of signaling is very important because these proteins that bind to growth factors and pass the massage to the nucleus are important in many types of cancers



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

Usually tumors have one of them mutated

RAS

Normally Activation of RAS gene is shored lived, because we don't want continuous cell division
So this process is limited and highly controlled in order to prevent abnormal or excessive cell growth

- ***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]).

RAS - GTP complex > active form
RAS - GDP complex > inactive form

Dr explained

Approximately 30% of mutations in signal transduction pathways are related to the **RAS gene**. However, mutations can also occur in other genes that regulate or interact with RAS, leading to its activation. This means that patients with mutations in signal transduction pathways may not necessarily have a mutation directly in the RAS gene itself.

Each step in the signal transduction process involves multiple genes, and mutations in any of these genes can contribute to continuous, uncontrolled signaling. These mutations can disrupt the normal regulatory mechanisms, leading to excessive RAS activity and downstream effects, even in the absence of a direct RAS mutation. Thus, the dysregulation of the entire pathway, not just RAS, plays a critical role in disease progression.

- **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)

Normally When RAS gene is activated by binding of growth factor to its receptor, activation means acquiring one phosphate group this change the complex into RAS protein with guanicine triphosphate; this is a active form of RAS gene and it will send massages by series of different pathways

Guanosine triphosphatase is controlled by Guanosine triphosphatase activating protein that enhance the growth of enzyme , because an important process in the body must be controlled by different pathways , we don't want sth abnormal to happen

- **Active RAS is is short-lived because the activity of intrinsic guanosine triphosphatase (GTPase) activity**

  Leading to loss of one phosphate group which leads to inactivation of RAS gene
- **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.**

Any mutation is associated with loss of the inactivation leading to continuous stimulation to nucleus which happens in tumor

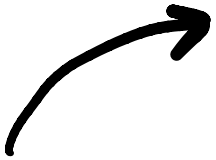
Once the signal reaches nucleus this will lead to activation of other group of gens that are called cyclines (nuclear genes once are stimulated the cell enters cell cycle and starts to divid

- **GEFs (Guanine Nucleotide Exchange Factors)**: Facilitate the release of GDP from Ras, allowing GTP to bind and activate Ras. Without GEFs, the activation of Ras would be inefficient.
- **GTP**: Functions as the "on switch" for Ras. Upon binding, it induces a conformational change in Ras, enabling it to interact with downstream effectors and transmit signals. GTP's high-energy phosphate bonds provide stability to the active state.
- **GTPase Activity (and GAPs - GTPase-Activating Proteins)**: GTPase activity hydrolyzes GTP into GDP, which turns Ras "off." GAPs accelerate this hydrolysis, ensuring that Ras signaling is temporary and tightly regulated.
- **GDP**: Marks the inactive state of Ras, resetting it until GEFs replace GDP with GTP during the next activation cycle.

- **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**

- **Activating Ras** = Exchange GDP for GTP.
- **Inactivating Ras** = Hydrolyze GTP into GDP.

RAS gene mutations are associated with point mutations (very limited mutations, change in one nucleic protein)

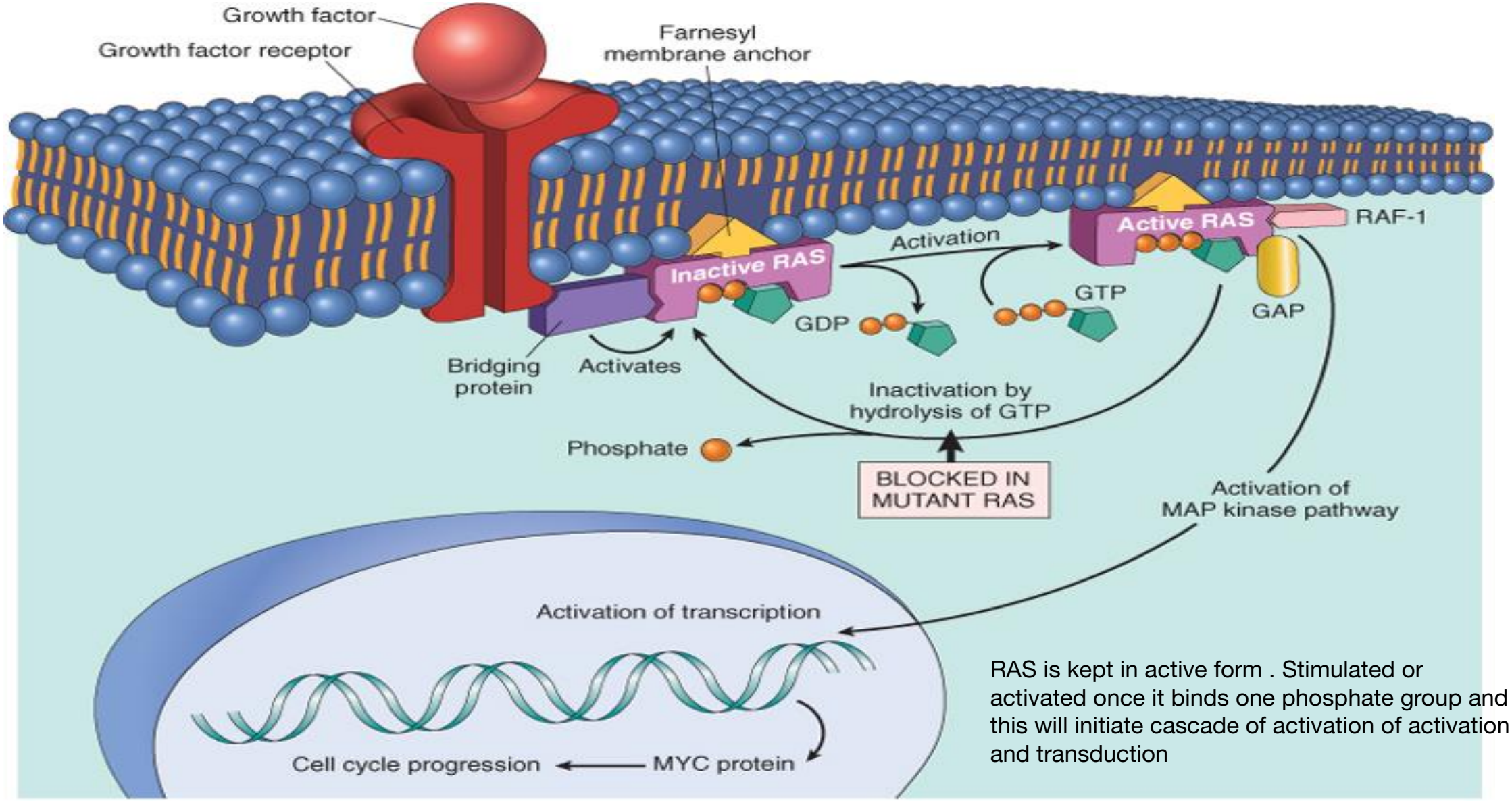


Ras is commonly activated by **point mutations** in specific amino acids that disrupt its normal function. These mutations typically occur in one of two critical regions:

1. **GTP Binding Pocket**: Mutations here affect how Ras binds GTP. These changes often result in Ras staying in its active, GTP-bound state for longer, as it becomes harder for the GTP to be hydrolyzed or replaced.
2. **Enzymatic Region for GTP Hydrolysis**: Mutations in this region hinder Ras's ability to hydrolyze GTP into GDP. This prevents Ras from switching off, keeping it perpetually active.

- **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



RAS is kept in active form . Stimulated or activated once it binds one phosphate group and this will initiate cascade of activation of activation and transduction

- **Examples**

Initially it's benign tumour but in these patient theses benign tumors will transform into malignancy

- Neurofibromatosis type 1

Gusnosine triphosphatase activating protein in 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

Neurofibromatosis Type 1 (NF1) and NF1 Mutation:

- **NF1 gene** codes for a protein called **neurofibromin**, which is a **GAP (GTPase-activating protein)**.
- Neurofibromin's job is to turn **Ras** off by accelerating the hydrolysis of GTP to GDP, switching Ras from its active form to its inactive form.
- When the **NF1 gene is mutated**, **neurofibromin** doesn't work properly, and Ras stays in its active form.
- This constant activation of Ras leads to uncontrolled cell growth and is one of the causes of **tumor formation** in NF1.

PTEN Mutation in Carcinomas and Leukemias:

- **PTEN** is a **tumor suppressor gene** that regulates the **PI3K/AKT pathway**, which is important for cell growth and survival.
- PTEN works by **inhibiting PI3K**, a protein that normally activates the AKT pathway.
- When PTEN is **mutated**, it can't suppress PI3K, leading to **increased activation of the AKT pathway**, which promotes cell survival, growth, and division.
- This mutation is commonly found in **carcinomas** (a type of cancer) and certain **leukemias**, contributing to the uncontrolled cell proliferation seen in these cancers.

In both cases, the mutations lead to **uncontrolled cell growth**, but through different pathways (Ras signaling for NF1 and PI3K/AKT for PTEN).

- *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**

There is a very characteristic tumor related to ABL gene mutation
Which is seen in chronic myeloid leukaemia , this leukaemia is characterised by having translocation of ABL gene from chromosome 9 to chromosome 22 this translocation of the gene causes complex of the gene that produce a continuous stimulation of of cell growth (Philadelphia chromosome)

95% of patients with chronic myeloid leukaemia have Philadelphia chromosome

There is a drug that antigonize the effect of this translocation (translocation of a gene will produce new protein)

Translocation of genes will produce new pro

- **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**

This gene when translocase to another side it might be stimulated due to the surrounding gens

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 gene is the most important one in malignancy

In order for cells to start dividing we need to activate nuclear gens

Because of their importance, their process of activation is complex

The **MYC translocation (8;14)** in **Burkitt lymphoma** is a genetic mutation where a part of the **MYC gene** on chromosome **8** is swapped with a part of the **immunoglobulin heavy chain (IgH) gene** on chromosome **14**.

This translocation results in the overexpression of the **MYC gene**, which is a **proto-oncogene** that regulates cell growth and division. Normally, MYC is tightly controlled, but when it is placed next to the IgH gene, it becomes highly active, leading to uncontrolled cell growth.

- **MYC activates several growth-promoting genes including cyclin-dependent kinases (CDKs)** Present in nucleus
- **Examples** 8> 14 characteristic finding of Burkitt lymphoma particularly the African type , even the acquired

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 Malignant tumor that occur in adrenals medulla

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

Very aggressive type of carcinoma

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**

462 are very essential type of kinases that are important in progression of cells in cell cycle

Cyclin dependent kinases are activated by the activated cyclin , cycline production and degradation occurs as pattern

For tumor cells to grow and to keep growing and dividing theses cycline and cycline dependent kinases and inhibitors should be mutated

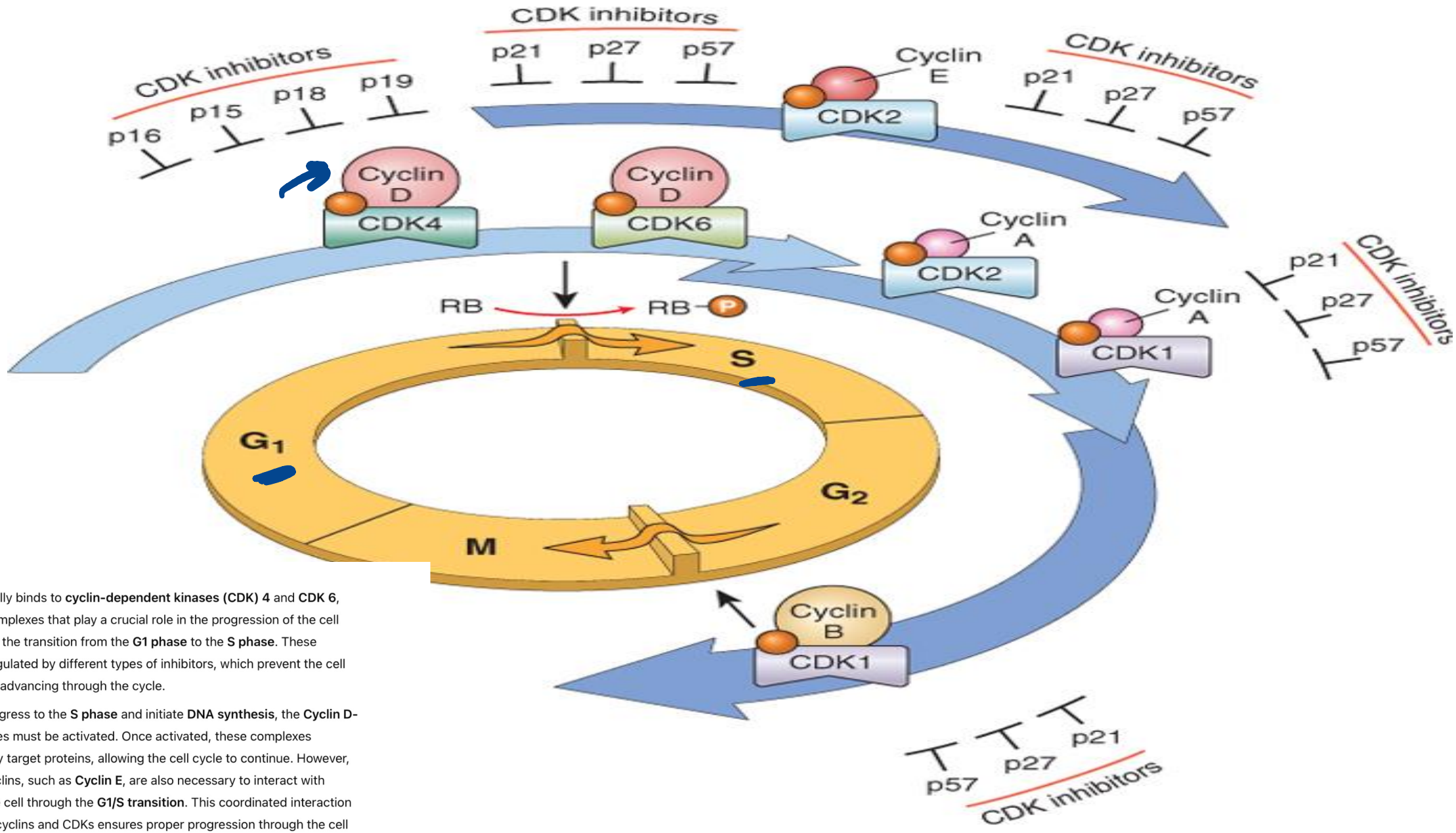
- ***CDK inhibitors*** **(CDKIs) exert negative control over the cell cycle**
- **Expression of these inhibitors is downregulated by mitogenic signaling pathways promoting the progression of the cell cycle.**

Cycline dependent kinases inhibitors are different types , some inhibitors can inhabit any form of cycline while others are selective

CDK inhibitors (CDKIs) are proteins that **slow down or stop** the cell cycle by inhibiting the activity of **cyclin-dependent kinases (CDKs)**. CDKs are essential for cell cycle progression, so when CDKIs are active, they prevent cells from moving forward in the cycle, ensuring proper regulation and preventing uncontrolled growth.

However, when cells receive **mitogenic signals** (signals that promote cell growth), these signals **downregulate** or reduce the expression of CDKIs. This decrease in CDKIs allows the cell cycle to progress more freely, leading to cell division and growth. Essentially, CDKIs act as brakes on the cell cycle, and mitogenic signals turn off these brakes to allow the cell to proceed through the cycle.

Once the DNA is synthesised and replicated the cell will divide producing cells that carry the same type of mutations



Cyclin D specifically binds to **cyclin-dependent kinases (CDK) 4** and **CDK 6**, forming active complexes that play a crucial role in the progression of the cell cycle, particularly the transition from the **G1 phase** to the **S phase**. These complexes are regulated by different types of inhibitors, which prevent the cell from prematurely advancing through the cycle.

For the cell to progress to the **S phase** and initiate **DNA synthesis**, the **Cyclin D-CDK4/6** complexes must be activated. Once activated, these complexes phosphorylate key target proteins, allowing the cell cycle to continue. However, other types of cyclins, such as **Cyclin E**, are also necessary to interact with **CDK2** to drive the cell through the **G1/S transition**. This coordinated interaction between various cyclins and CDKs ensures proper progression through the cell cycle and DNA replication.

FIG. 6.17 Role of cyclins, CDKs, and CDK inhibitors in regulating the cell cycle. *Shaded arrows* represent the phases of the cell cycle during which specific cyclin-CDK complexes are active. Cyclin D-CDK4, cyclin D-CDK6, and cyclin E-CDK2 promote passage through the G_1-S checkpoint by phosphorylating the RB protein (RB-P). Cyclin A-CDK2 and cyclin A-CDK1 are active in S phase. Cyclin B-CDK1 is essential for the transition from G_2 to M phase. Two families of CDK inhibitors can block the activity of CDKs and progression through the cell cycle. The inhibitors, p15, p16, p18, and p19, act on cyclin D-CDK4 and cyclin D-CDK6. Inhibitors belonging to the other family, p21, p27, and p57, can inhibit all CDKs. *CDK*, Cyclin dependent kinase.

genetic derangement is too severe to be repaired, the cells either undergo apoptosis or enter a nonreplicative state called *senescence*—primarily through p53-dependent mechanisms (see later).

Enforcing the cell-cycle checkpoints is the job of *CDK inhibitors (CDKIs)*; they accomplish this by modulating CDK-cyclin complex activity. Defective CDKI checkpoint proteins allow cells with damaged DNA to divide, resulting in mutated daughter cells at risk for malignant transformation. There are several different CDKIs:

- One family of CDKIs—composed of three proteins called p21, p27, and p57—broadly inhibits multiple CDKs
- Another family of CDKIs has selective effects on cyclin CDK4 and cyclin CDK6; these proteins are called p15, p16, p18, and p19

Book explanation

Dysregulation of the Cell Cycle in Cancer Cells. **Of the two main cell cycle checkpoints, the G1-S checkpoint is particularly likely to be lost in cancer cells.** Once cells pass through the G_1/S checkpoint, they are generally committed to undergo cell division, and thus cells with defects in this checkpoint proliferate excessively. Indeed, virtually all cancers appear to harbor genetic lesions that disable the G_1/S checkpoint, causing cells to continually reenter the S phase. For unclear reasons, particular lesions vary widely in frequency across tumor types, but they fall into two major categories.

- *Gain-of-function mutations involving CDK4 or D cyclins.* Changes increasing the expression of cyclin D or CDK4 are common events in neoplastic transformation. The cyclin D genes are overexpressed in many cancers, including those affecting the breast, esophagus, and liver, as well as a subset of lymphomas and plasma cell tumors. Amplification of the *CDK4* gene occurs in melanomas, sarcomas, and glioblastomas. Mutations affecting the genes encoding cyclins B and E and other CDKs also occur, but they are much less frequent than those affecting the genes encoding D cyclins and CDK4.

(4)

- *Loss-of-function mutations involving CDKIs.* CDKIs are disabled in many human malignancies, in which these factors act as tumor suppressors. For example, germline mutations of *CDKN2A*, a gene encoding the CDK inhibitor p16, are present in some familial melanomas and acquired deletion or epigenetic silencing of *CDKN2A* is seen in many gliomas, carcinomas, sarcomas, and leukemias.
- Loss of function mutations in *RB* (a tumor suppressor gene) is another oncogenic mechanism that disables the G_1S checkpoint (discussed below).

A final consideration of importance in a discussion of growth-promoting signals is that the increased production of oncoproteins does not, by itself, lead to sustained proliferation of cancer cells. There are two built-in mechanisms, cell senescence and apoptosis, that oppose oncogene-mediated cell growth. As discussed later, genes that regulate these two braking mechanisms must be disabled to allow the action of oncogenes to proceed unopposed.

- **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

Non selectively

Inhibitors exerts some negative control on in the progression of tumor cells , theses inhibitors are muted in tumour cells , some times mutation in theses inhibitors might be the most important factor in increasing cell division

- **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.

Part of tumours recognition tumours

In order to allow cells to enter cell cycle and to divide

- **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.**

In later stages in Timor we find out that tumour is very aggressive and is rapidly growing tumour due to many gene mutations required for there growth and survival

- **<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.

وفقكم الله لما يحبه ويرضى . ادعولنا يا دكاترة
واللهم صلّ وسلّم وبارك على سيدنا محمد
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