بسم الله الرحمن الرحيم

CYTOLOGY

MID – Lecture 15

The Biology of Cancer Cells

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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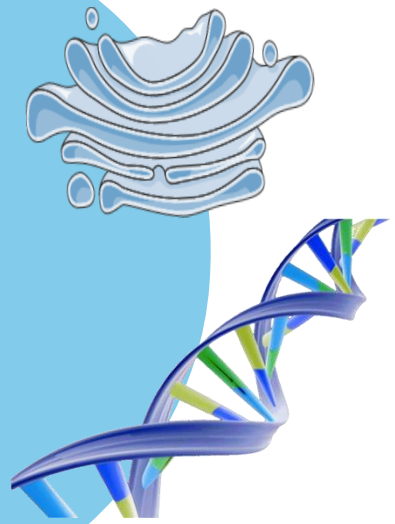

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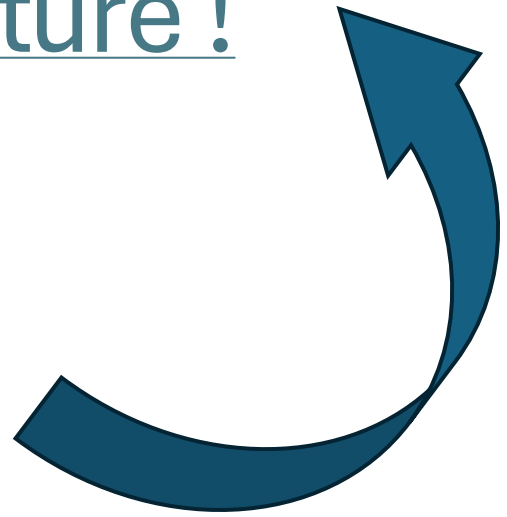
Quiz for the previous lecture !



بسم الله الرحمن الرحيم

اللهم افتح علي فتوح العارفين، اللهم لا سهل إلا ما جعلته سهلا وأنت تجعل الحزن إذا ما شئت سهلا

Lecture 11:
The Biology of Cancer Cells

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School of Medicine

Second year, first semester, 2024-2025

قال صلى الله عليه وسلم من رأى مبتلى فقال: الحمد لله الذي عافاني مما ابتلاك به وفضلني على كثير ممن خلق تفضيلا، لم يصبه ذلك البلاء.

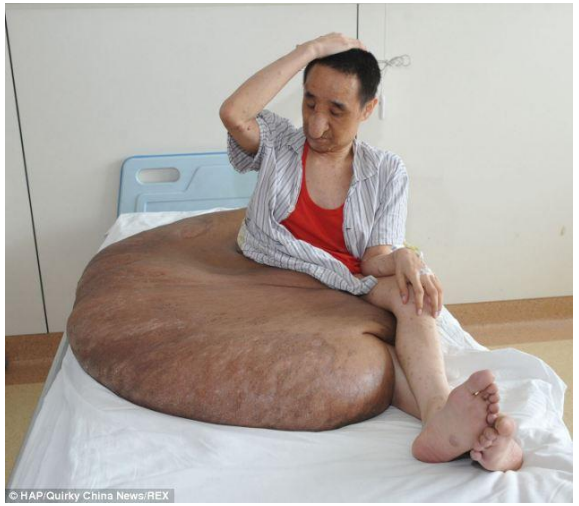
What is cancer?

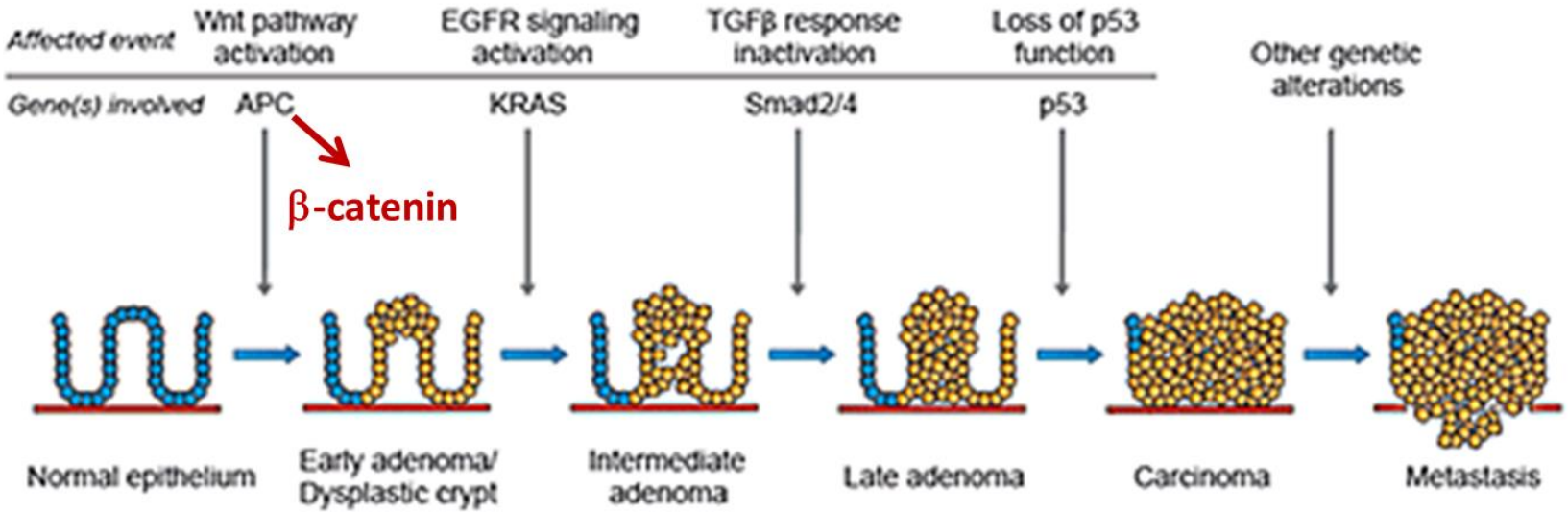
- A tumor is any abnormal proliferation of cells.(mass of cells that have a potential to become cancer)
  - A benign tumor is confined to its original location. Cluster of cells in certain place
  - A malignant tumor (cancer) when it invades surrounding tissue and spreads throughout the body via the circulatory or lymphatic systems (metastasis).

Benign can become

- Cancer develops from a multistep process involving mutation with progressively increasing capacity for proliferation, survival, invasion, and metastasis.

  - The way cancer develops is complex and depend on cancer type, and even within same cancer there are different mutations.
  - KEY term : The cancer develops as a result of accumulation of mutations.
  - It is a multistep process and each step requires a certain types of mutations, these mutations provide the cancer cell the ability to proliferate, invade and metastasize





Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759-767.

This is an old idea developed by feron and vogelstein from John Hopkins University

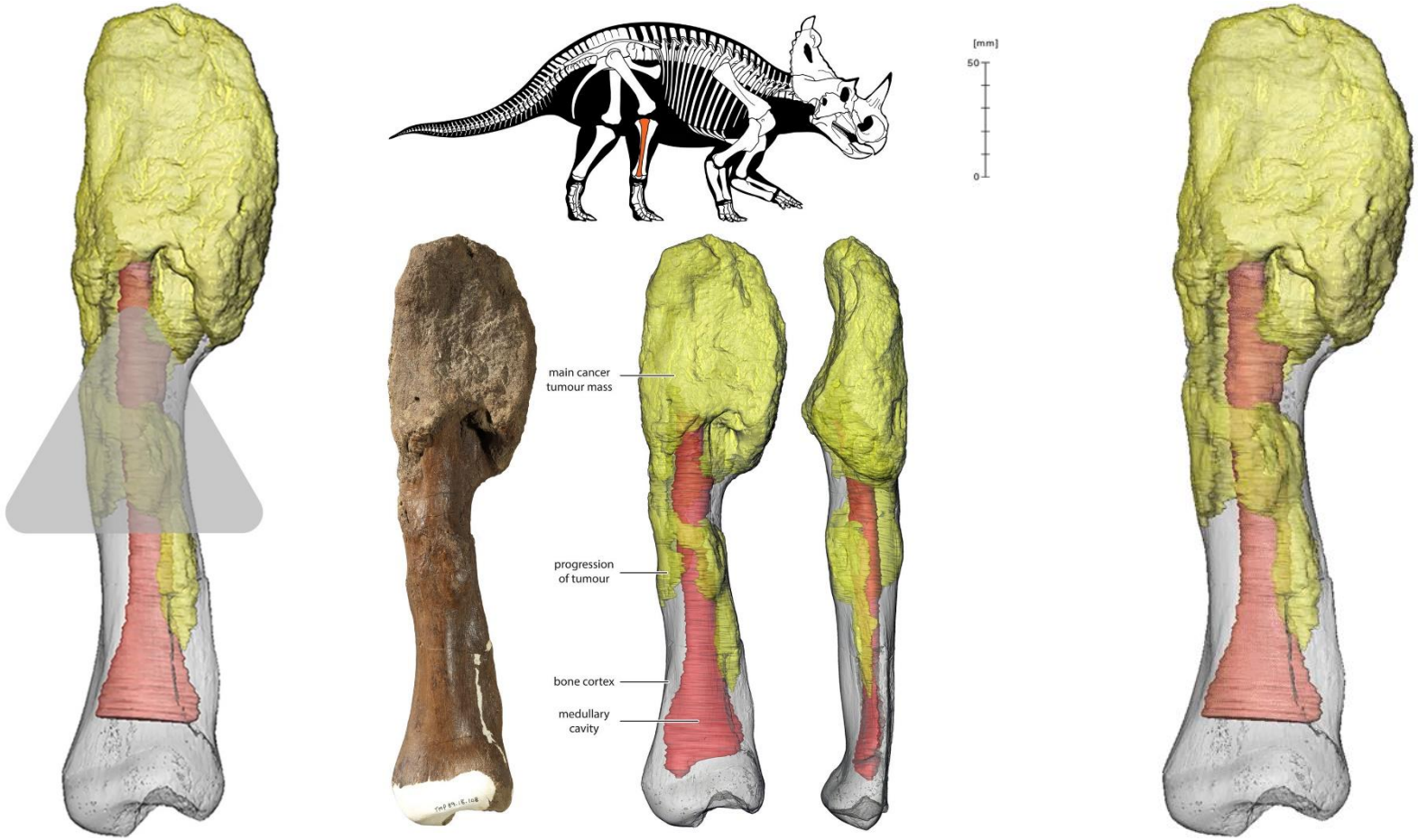
- They said In order for colorectal cancer to develop, it go through several biological stages ,each stage require a certain mutation .

Examples
*mutation in B catenin Pathway result in development of adenoma benign .
*mutation in kRAS oncogene resulting in uncontrollable proliferation of cells .
* mutation of p53 results in development of carcinoma and Invasive cells and metastasis.

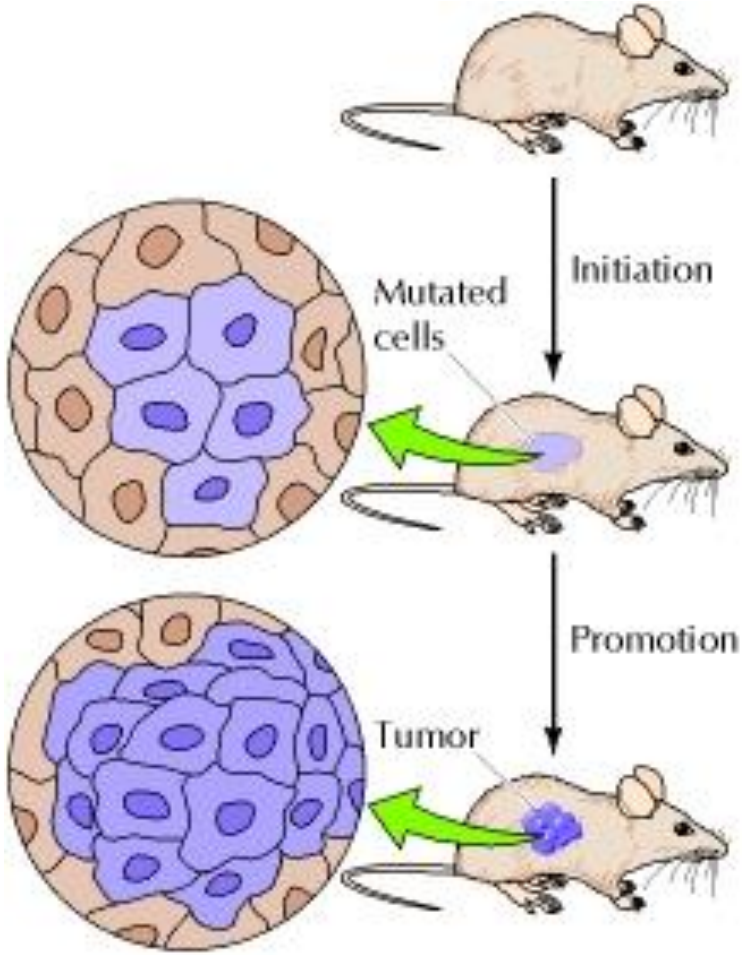
So the idea is Accumulation-of mutations

Cancer is old. Cancer was discovered in bones of dinosaurs.

Doctors diagnose advanced cancer—in a dinosaur
https://www.science.org/content/article/doctors-diagnose-advanced-cancer-dinosaur



The theory behind the molecular causes of cancer



The basic idea behind how cells become cancers is that they are exposed to carcinogens and there are two types of them

- Carcinogens (substances that cause cancer) are:

1. Initiators: factors that induce genetic mutations.
   Making cells susceptible to become tumor
   - Radiation, pathogens Viruses and chemical carcinogens

> ➢ But being exposed to initiator isn't enough in order to become malignant or aggressive cells have to be exposed to promoter

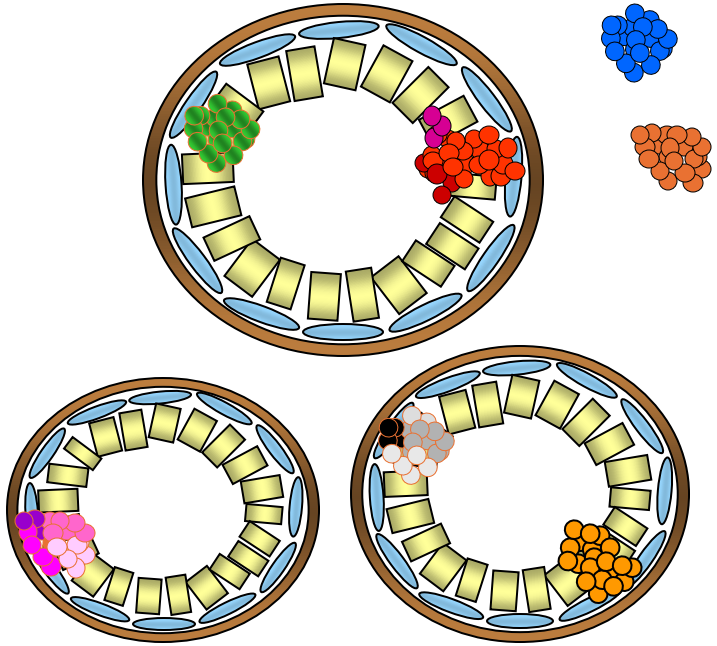
2. Promoters: stimulate cell proliferation that leads to accumulation of mutations. Some of these mutations are random and some can confer a selective advantage to the cell to become cancer , such as more rapid growth and resistance to therapy, Some may become mesechymel like or invasive …
   - Examples: Chemicals, hormones (estrogens) ,pathogens, smoking estrogens can promote mammary cells , breast cells cancer in women.

Why are those who smoke have a higher probability to develop cancecr ?

➢ Because chemicals in smoking are both initiators and promoters

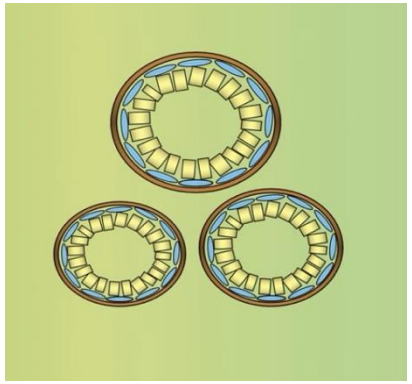
So cancer need an initiatior then promoter

Cancer is clonal and heterogeneous

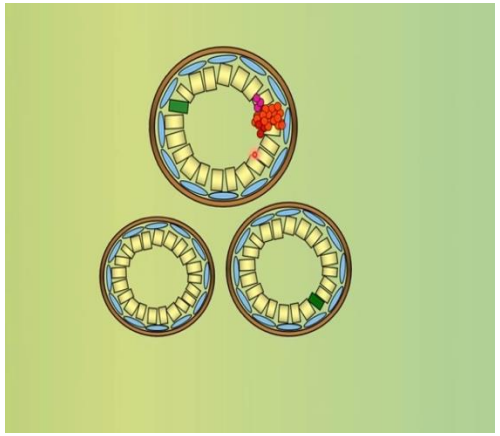


Cancer is clonal and heterogeneous

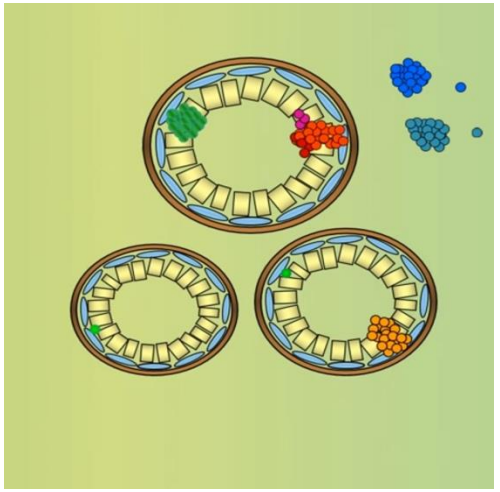
① first we have a normal cell suppose It is a mammary gland(normal breast cells), mutation can take place in different type of cells by being exposed to intiator or by chance



② Some of cells grow uncontrollably, they will accumulate mutations creating a heterogenous mass of cells [different cells].

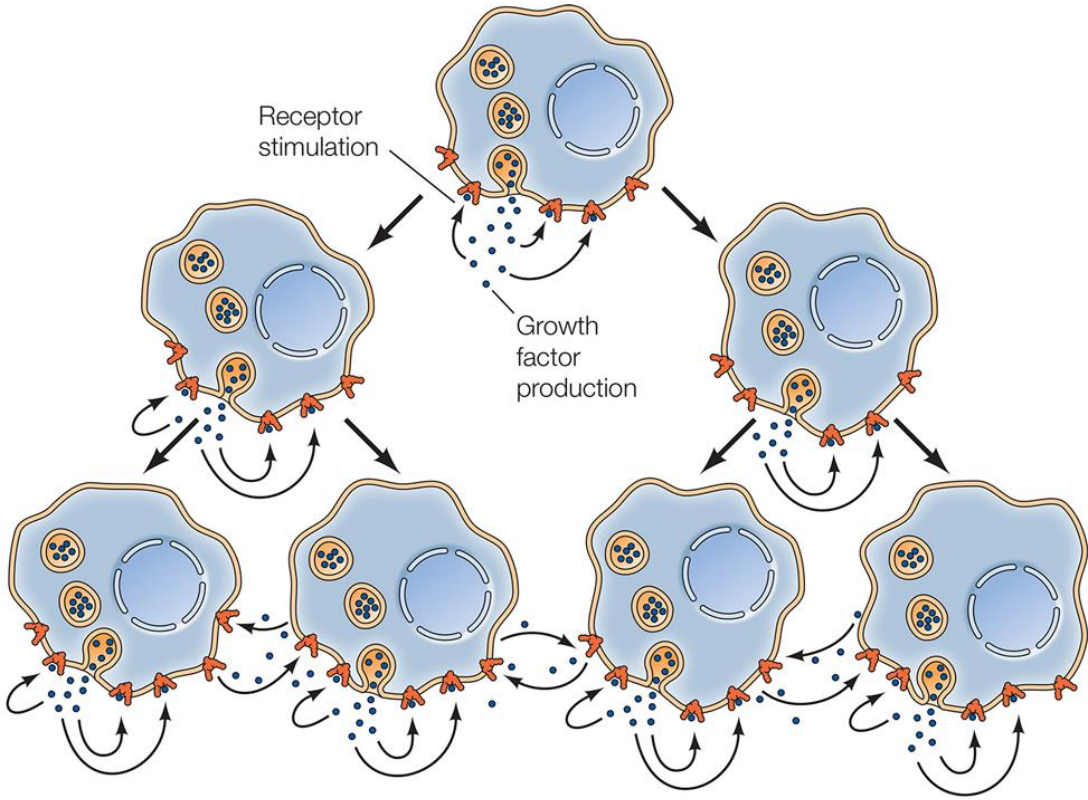


③ eventually, they can metastasize, means that they can go somewhere else and develop tumor mass in other places ,this is actually the main cause of death (spreading of cancer cells to other sites) and it is not really from the formation of tumors.



Features of cancer (1)

- Clonality
  - they develop from single (certain)cell and then these cells form tumors and enventually cancers
- Uncontrolled proliferation
  - keep on growing, sometimes it takes years to develop
- Accumulation of genetic mutations
  - Key feature
- Autocrine growth stimulation
  - Some of cancer cell secrete growth factors that act on the cells themselves stimulating the proliferation .



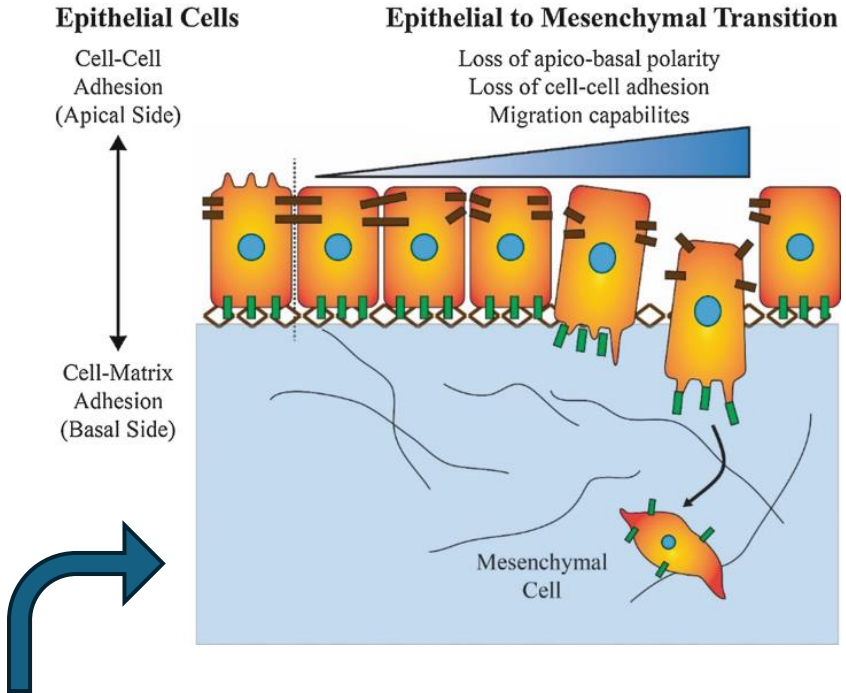
Features of cancer (2)

- Reduced cell-cell contact and altered cell-matrix adhesion — Like adherence and tight junctions

Because of:

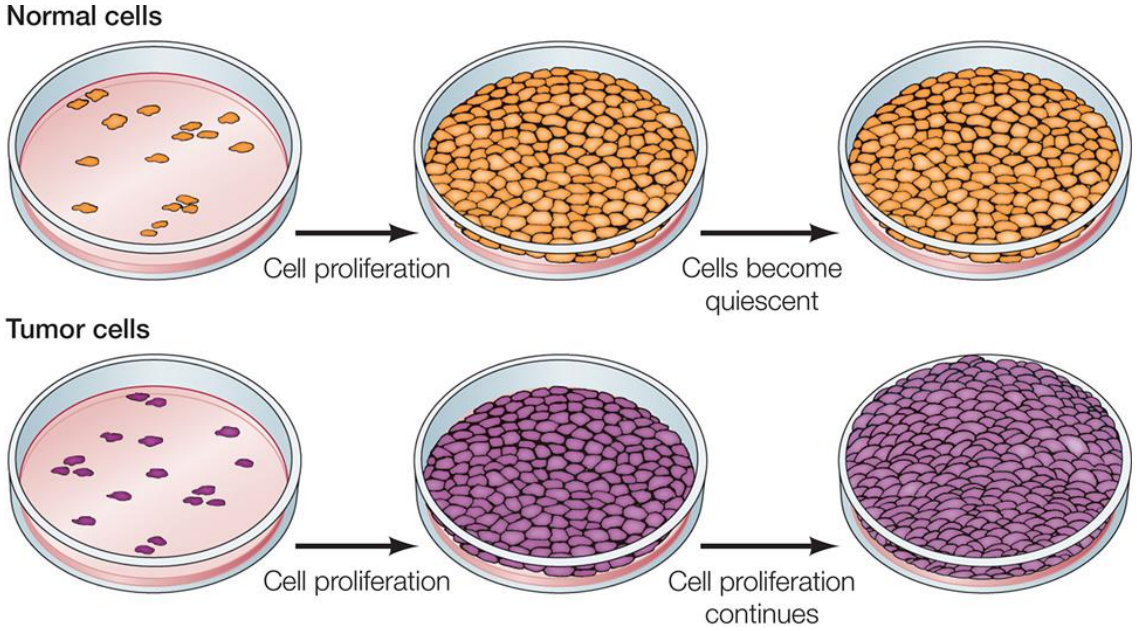
  - Loss of E-cadherin ➢ They become mesechymel
  - Dysregulation of integrins ➢ develop and express different types of integrins that allow cells to adhere to different matrix proteins ,for example: instead of laminin they adhere to collagen

- Invasiveness and extracellular proteolysis



- What happens then is that cells migrate, invade or move from original site through tissues reaching blood vessels, then they can spread
- As they move they can adhere to diff type of proteins and form focal adhesions with them.
- Proteolysis = they will degrade matrix proteins(to enable them to move).

- **Loss** of density-dependent **inhibition** and contact **inhibition**



- **Density dependent Inhibition:**
  normal cells grow and when they reach a certain density they stop growing (density dependent inhibition) but cancer cells do not stop (loss of this inhibition).

- **Contact inhibition:**
  Cells when contact each other they stop growing, eg: when you have an injury on your skin cells proliferate to close the injury, normal cells stops growing once they touch each other, but cancer cannot they keep piling up.

قال رسول الله صلى الله عليه وسلم : العين حق . زاد مسلم : ولو كان شيء سابق القدر سبقته العين

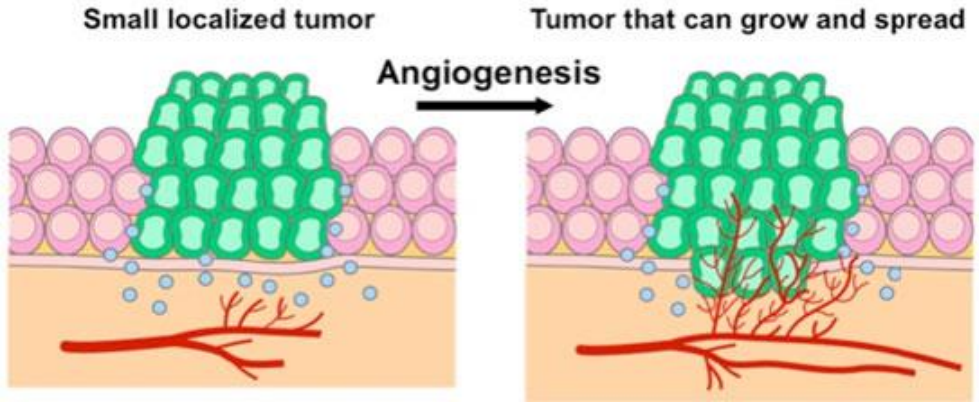
Features of cancer (3)

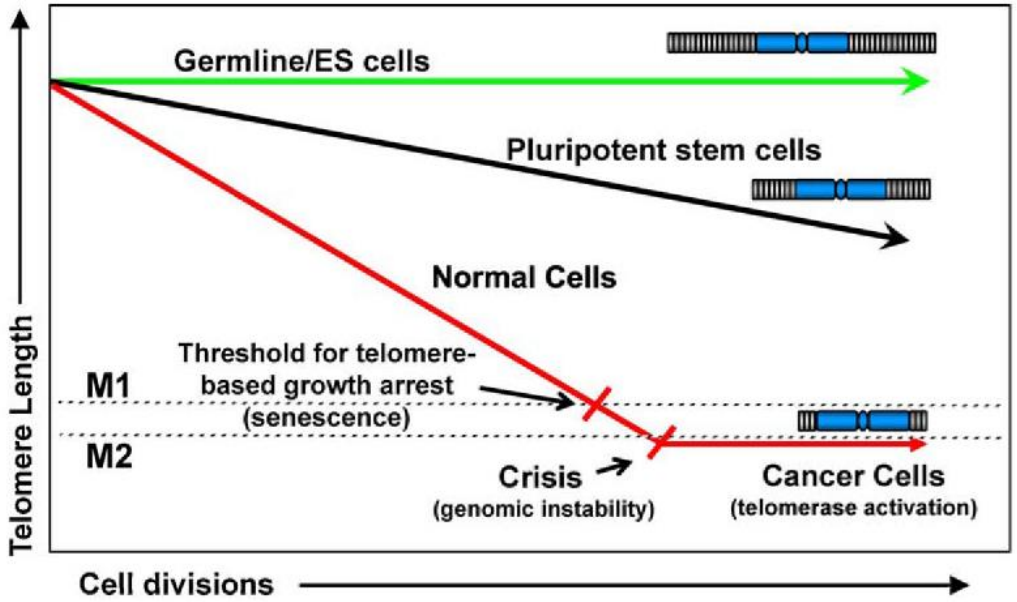
- Ability to induce Angiogenesis
- Loss of differentiation
- Loss of apoptotic capability
- Expression of telomerase enzyme

Genesis :creation
Angio:bloodvessels
➢ To feed themselves and reach blood easily and spread.

➢ So they keep growing

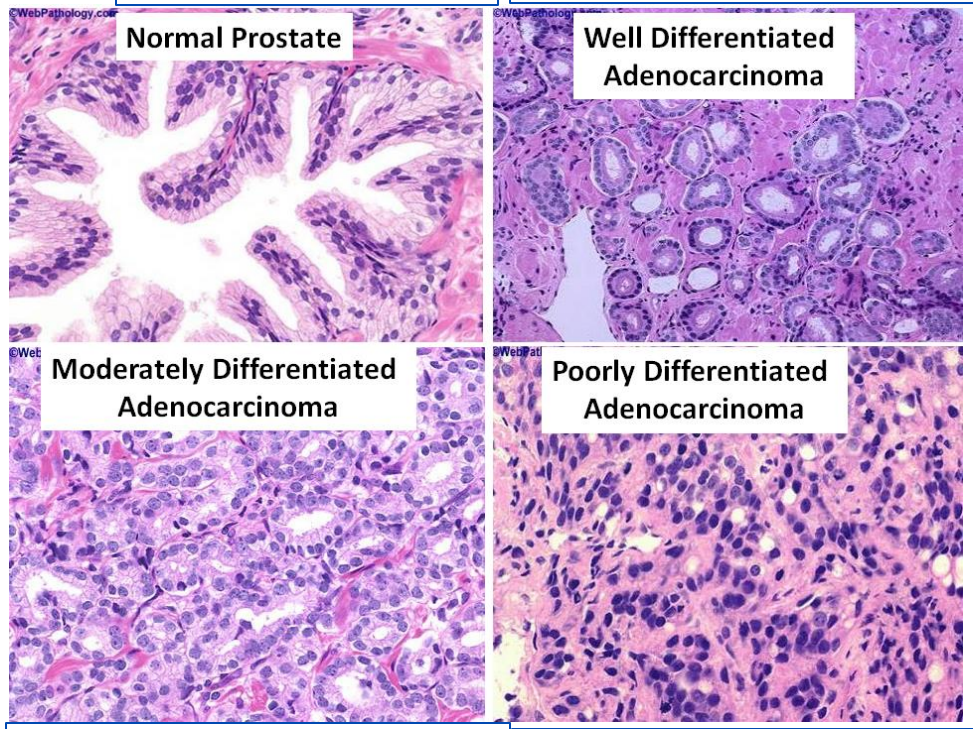
➢ Allowing them to stay alive





Well differentiated, functional

The Normal cells have lost their differentiation and loss their structure.
Carcinoma means cancer



losing the differentiation further

Losing differentiation all together

Inducers of cancer



- Genetics ➢ Mutations in DNA
- Viruses
- Bacteria ➢ Helicobacterio pylori (causes gastric cancer , cancer in stomach that cause hyperacidity and ulcers).
- Radiation
- Chemicals ➢ Like in cigarettes
- Environment ➢ Sunlight
- Epigenetics
- Stress ➢ Some say that stress may cause cancer by manipulating and changing immune system and ability to eradicate ubnormal cells including cancer cells.
- Magic and sorcery
- Envy and the evil eye

Oncogenes and tumor suppressor genes

Oncogene Gain of function

- A gene capable of inducing one or more characteristics of cancer cells when activated.
  - These genes normally exist in our cells,when it is normal It is called proto-oncogenee
- A proto-oncogene: a normal cell gene that can be converted into an oncogene.
  - It can cause cancer if it gets over activated

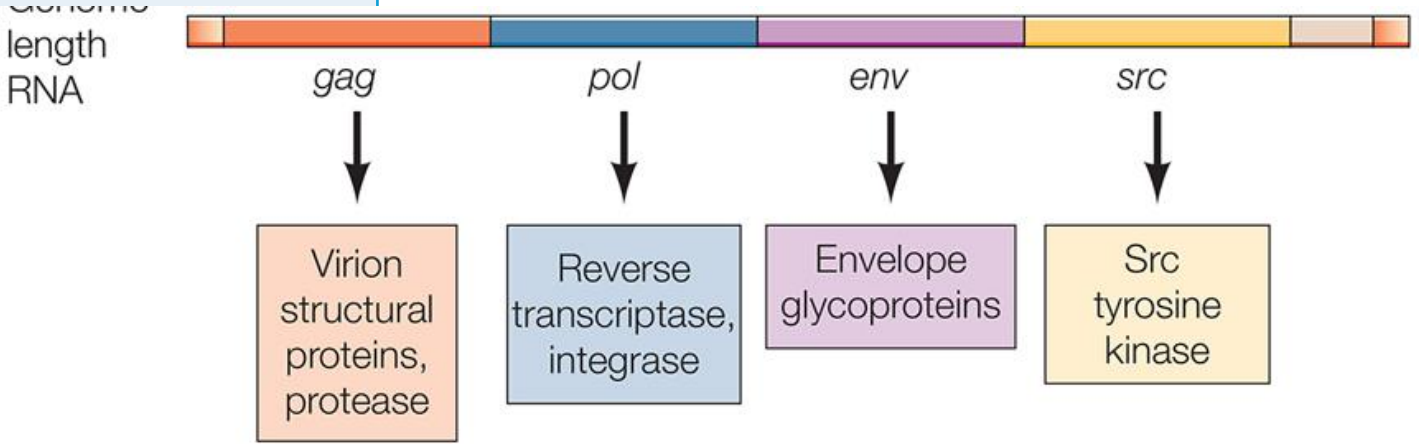
Tumor suppressor gene (TSG) Loss of function

- A gene whose inactivation leads to tumor development.
  - Genes that are needed to control cells from overgrowing and proliferating, keep number of cells limited but once they lose function you cells will get out of control

Some of oncogenes are originated from viruses and these viruses infect our normal cells ,these can cause cancer.

Viral oncogenes

Oncogene	Virus
abl	Abelson leukemia
akt	**AKT8 virus**
erbA	Avian erythroblastosis-ES4
erbB	Avian erythroblastosis-ES4
raf	**3611 murine sarcoma**
rasH	**Harvey sarcoma**
rasK	**Kirsten sarcoma**
src	**Rous sarcoma**



Those genes originally come from viruses also they exist in our DNA, when they are mutated in our DNA they can cause cancer.

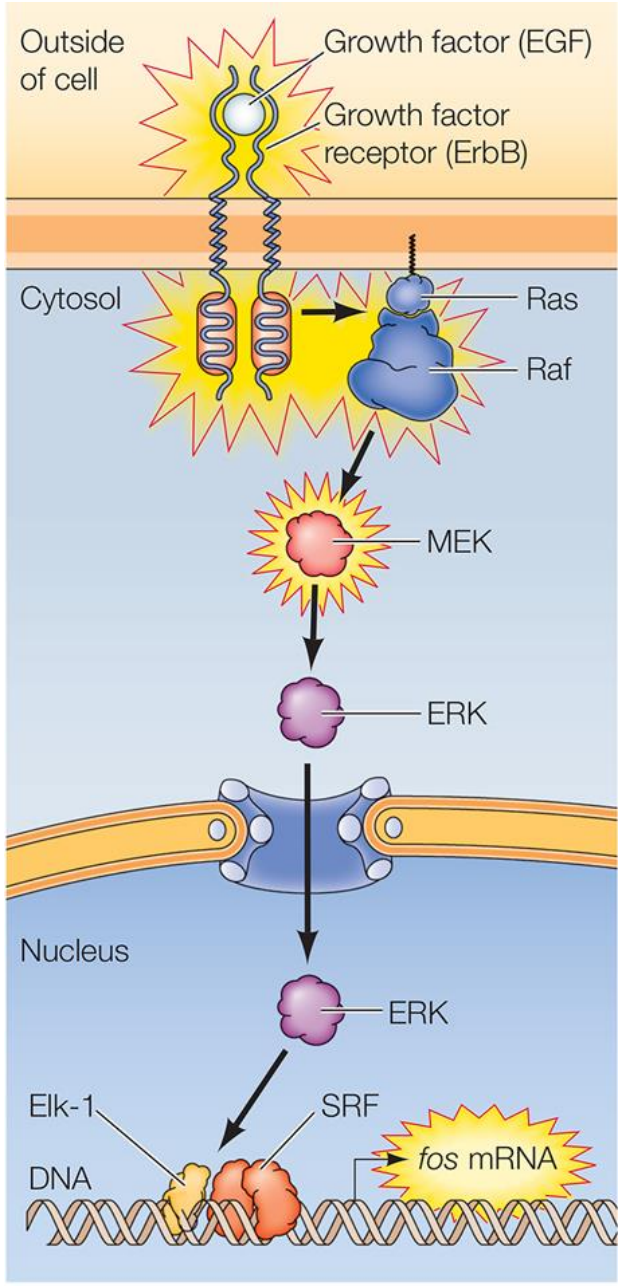
- If these viruses infect our cells they may become cancerous

Oncogenes and signal transduction

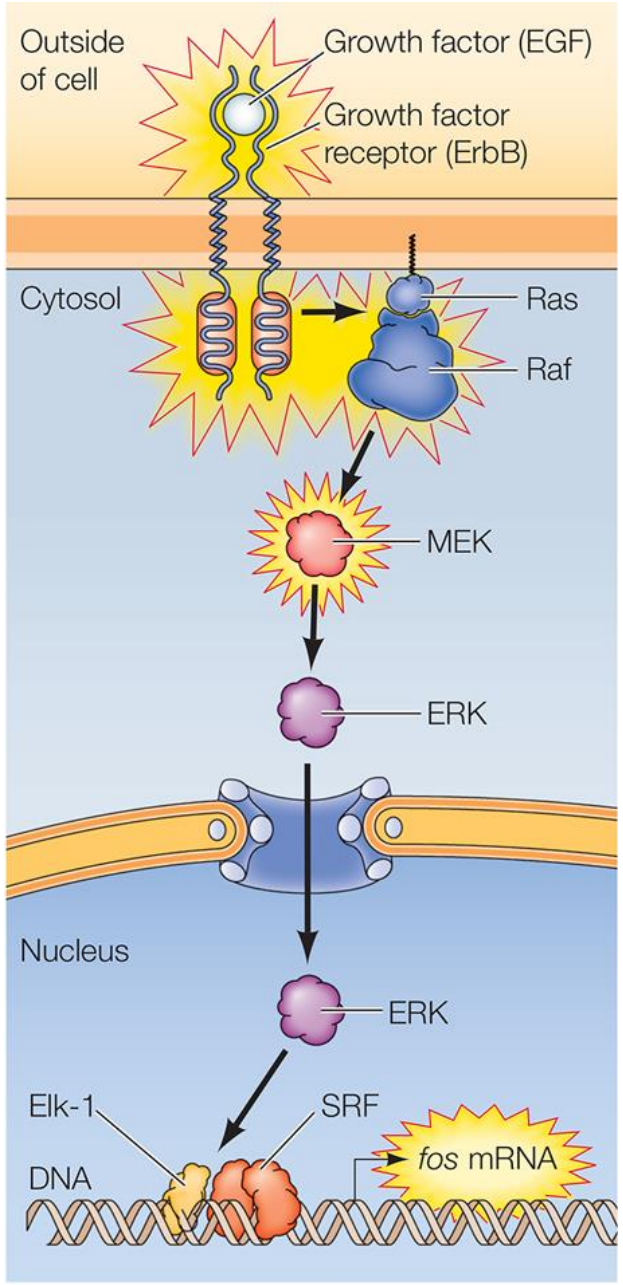
* Oncogenic proteins can include any proteins in signaling pathways that stimulate cell growth

- Oncogenic proteins act as:
  - Growth factors (e.g., EGF)
  - Growth factor receptors (e.g., ErbB)
  - Intracellular signaling molecules (Ras and Raf)
  - Transcription factors (e.g., fos)

Any of these intermediates can be mutated and cause cancer.



Picture explained in the next slide :)



*Growth factors bind to their receptors, triggering the signal transduction cascade.
This is exemplified by the Ras/Raf/MAPK pathway:
activated Ras will activate Raf → activates MEK → activates ERK. ERK then translocates to the nucleus, inducing the expression of certain genes that stimulate cell growth

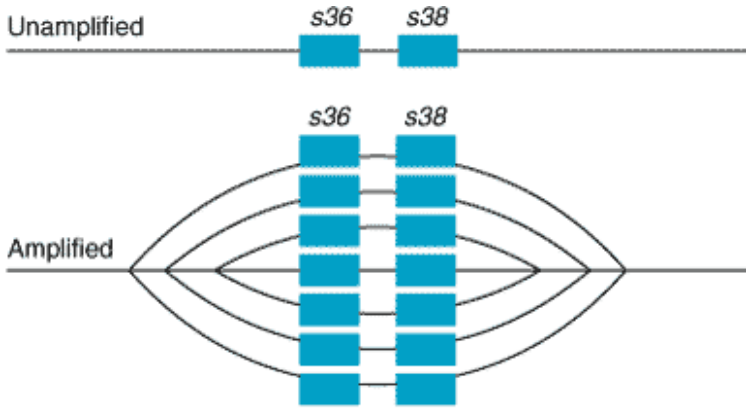
Mutation in any of these factors that would cause **overactivation** of these proteins causes cancer.
Overproduction of growth factors leads to over receptor stimulation.
Mutations in receptors lock them in an active state, which continually stimulates the signal transduction pathway.
Mutations in Ras or effectors can also contribute to cancer development & the overstimulation of cell growth.

﴿وَآتاكُم مِن كُلِّ ما سَأَلتُموهُ وَإِن تَعُدّوا نِعمَتَ اللَّهِ لا تُحصوها...﴾
اللهم إنا نحمدك على كل نعمك ونستغفرك من جميع الذنوب والخطايا ونتوب إليك

Let's talk about few examples of mutated oncogenic proteins:

Oncogenic receptors

Gene amplification

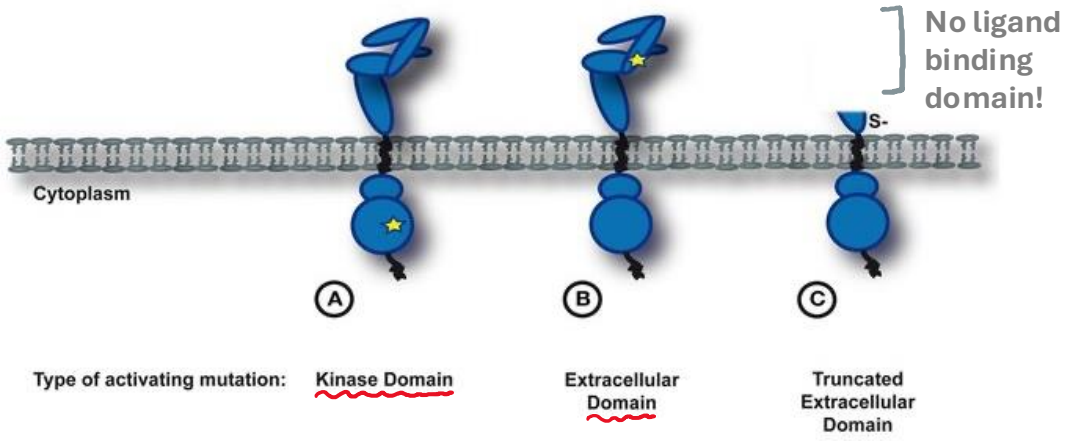


Epidermal growth factor (EGF) receptors are expressed in small numbers on normal mammary (breast) cells membrane .
In Gene amplification –→One gene copy that produces the HER2 receptor (human epidermal growth factor),
due to **gene amplification** you would have multiple copies of this DNA(this gene) by an unknown mechanism , this stimulates overexpression of these receptors (large numbers of receptors)on the cell's surface, making the cell more sensitive to growth factors.
In turn, causing uncontrollable cell growth → mutation accumulation → cancer, eventually.

Oncogenic receptors

The receptor cannot interact with its ligand (GFs) normally, so it becomes independent of the GFs' presence. In some cases, the receptors self-assemble to allow themselves to dimerize and activate the signal transduction pathway; **autonomous activation.** This is also applicable to deletion mutations (cytosolic domains).

Activating mutations



In addition to gene amplification, mutations also occur in the A)kinase domains, B)ligand-binding domains (extra cellular domain) or C)deletion mutations. **Ligand-binding domain** mutations cause the receptor to be independent of growth factors. **Deletion mutations removes** the ligand-binding domains; however, the cytosolic domain is still present, and it can activate in the absence of growth factors.

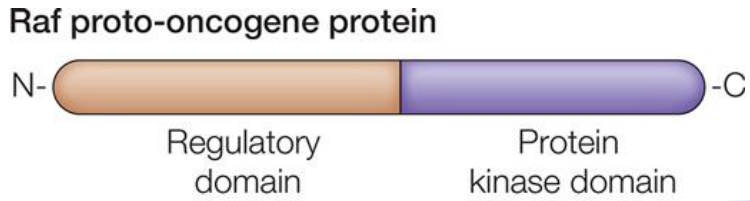
Drug called Herceptin (trastuzumab) is a monoclonal antibody that binds to HER2 and blocks it. Signaling pathway becomes inactivated.
It is used for the treatment of metastatic breast cancers that express elevated levels of ErbB-2.

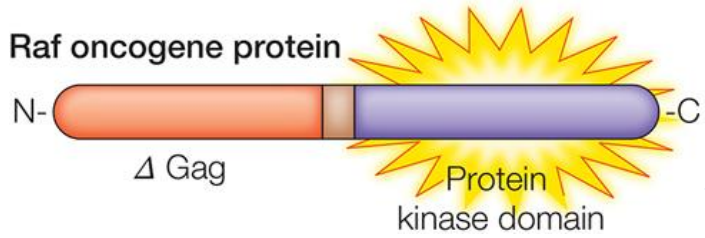
Refer to the 1st reference to see a helpful video :)

Mutation in transducers & effectors can cause cancer.

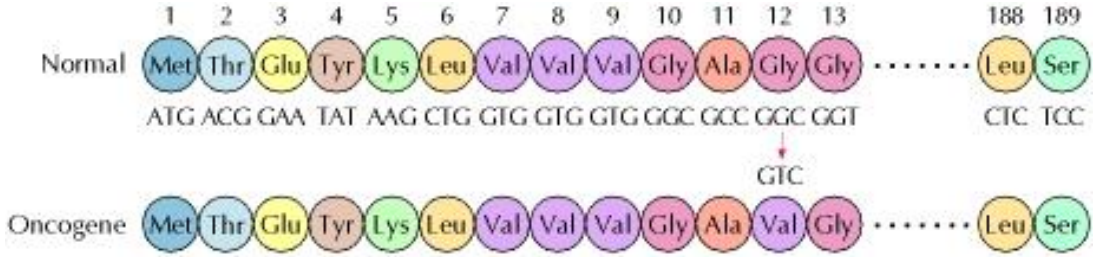
Oncogenes: transducers and effectors

- A single nucleotide change, which alters amino acid 12 from Gly to Val, is responsible for the tumorigenic activity of the Ras (mutation in RAS oncogene). Resulted in production of an overactive RAS , Even in the absence of a ligand & an active receptor.
  - The mutation maintains the Ras proteins constitutively in the active GTP-bound conformation. No GTP hydrolysis so RAS active all the time ..
- Raf becomes an oncogene when Val600 is converted to glu. Results in an overactive Raf activates MRK, then ERK, etc.
  - Also, the loss of the regulatory domain of Raf converts it to an oncogene.





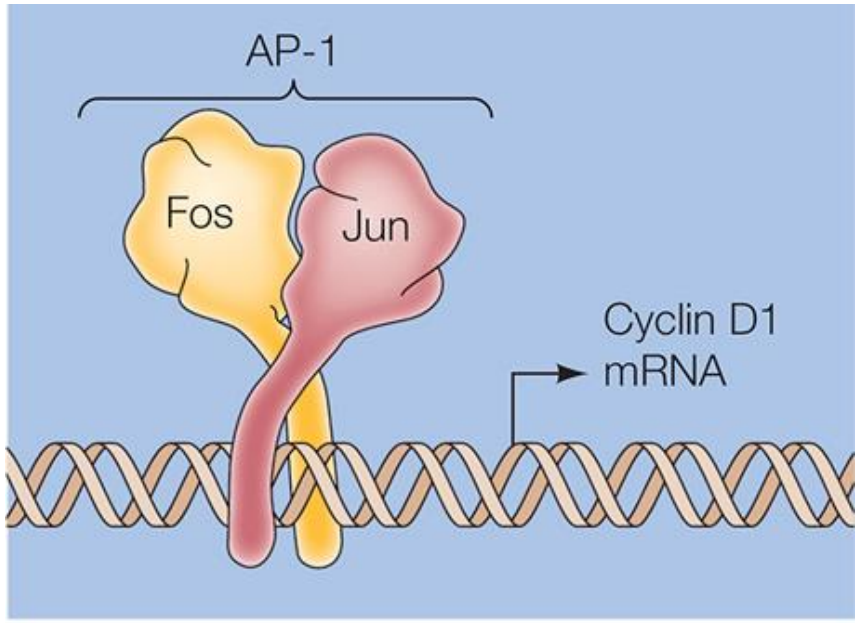
To jog your memory: a domain is a functional 3D structure that is a part of a protein and folds independently of the rest of the protein.



Raf has two domains: a regulatory domain and a kinase domain.
A mutation in the **regulatory domain** (deletion of regulatory domain) causes its **kinase domain** to become independent of the regulatory domain →This causes persistent activation of the kinase domain.

The alterations in amino acids (Gly→ Val, Val600) are not required :)

Oncogenes and transcription factors



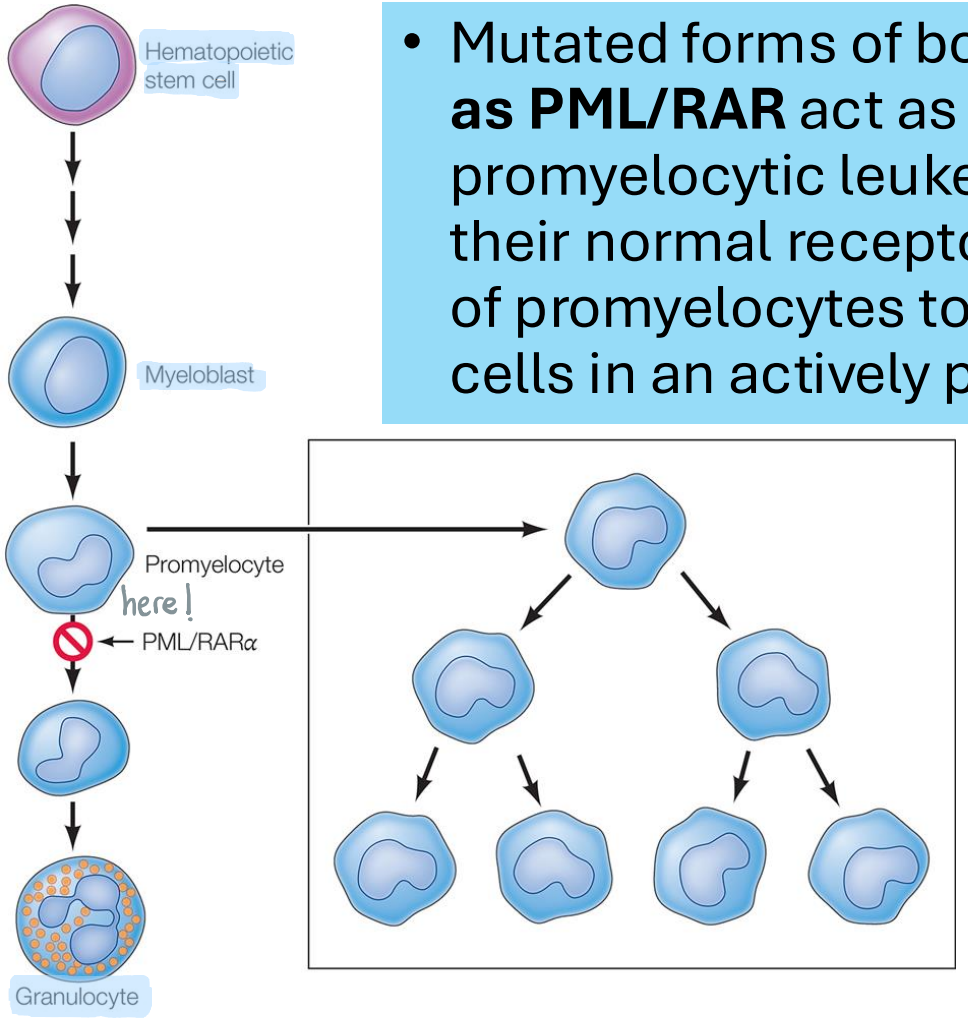
- (Another transcription factors) **Fos and jun** can become oncogenic as transcription factors that induce the expression of cyclin D1, which is a proto-oncogene itself, as well as its partners Cdk4 and Cdk6.

Mutation in Fos and jun →result in over expression in cyclin D1 which activate cdk4/cdk6 , Leads to the production of cyclin E, promoting the cell's progression through the cell cycle.

Differentiation may also be affected

Oncogenes and differentiation

The normal RARα receptor is important for the differentiation of hematopoietic cells, **PML** is a normal protein, but in APL, it becomes fused with **RARα** to form the **PML/RARα fusion protein**, which blocks differentiation and promotes leukemia by preventing the normal differentiation signals from taking effect.



- Mutated forms of both **the retinoic acid receptor known as PML/RAR** act as oncogene proteins in human acute promyelocytic leukemia by interfering with the action of their normal receptor, thereby blocking cell differentiation of promyelocytes to granulocytes, and maintaining the cells in an actively proliferating state.

As previously mentioned, when cells differentiate, they typically lose the ability to proliferate.

← In this example, a mutation diverts the differentiation pathway, resulting in a state of constant cell division , keeping proliferation .

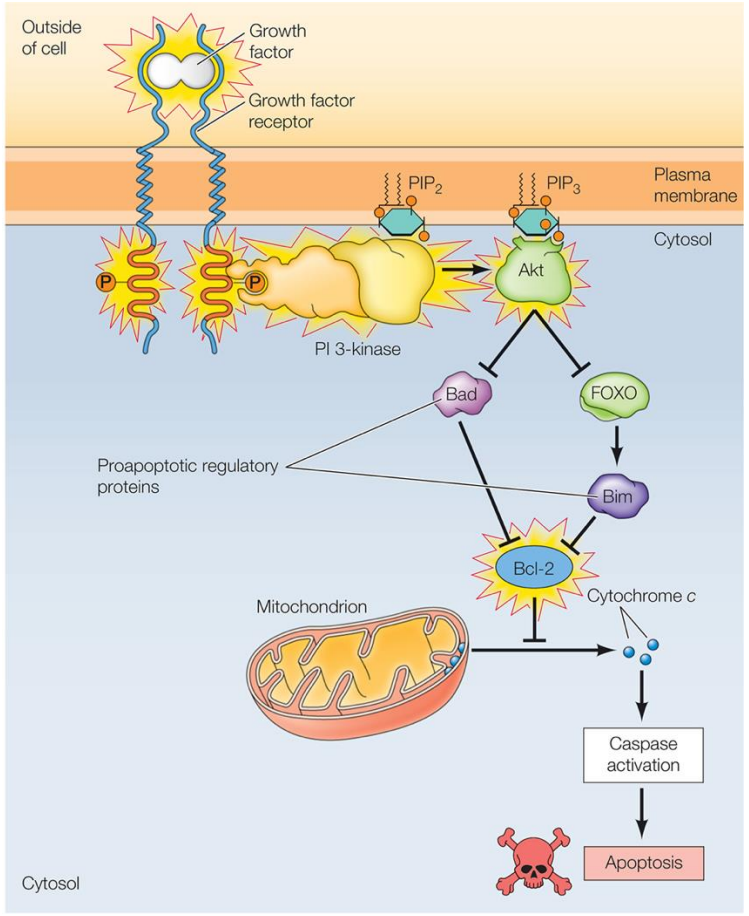
This is why some researchers believe that perhaps the stimulation of cells to differentiate instead of proliferating is a better strategy for the treatment of certain cancers.

Oncogenes and cell survival

Apoptosis is blocked (cells are prevented from dying)

- The Akt pathway promotes cell survival (don't die anymore- apoptosis inhibition) by inhibiting pro-apoptotic proteins and inducing anti-apoptotic proteins.
- The genes encoding PI 3-kinase, Akt, and the anti-apoptotic Bcl-2 can act as oncogenes.

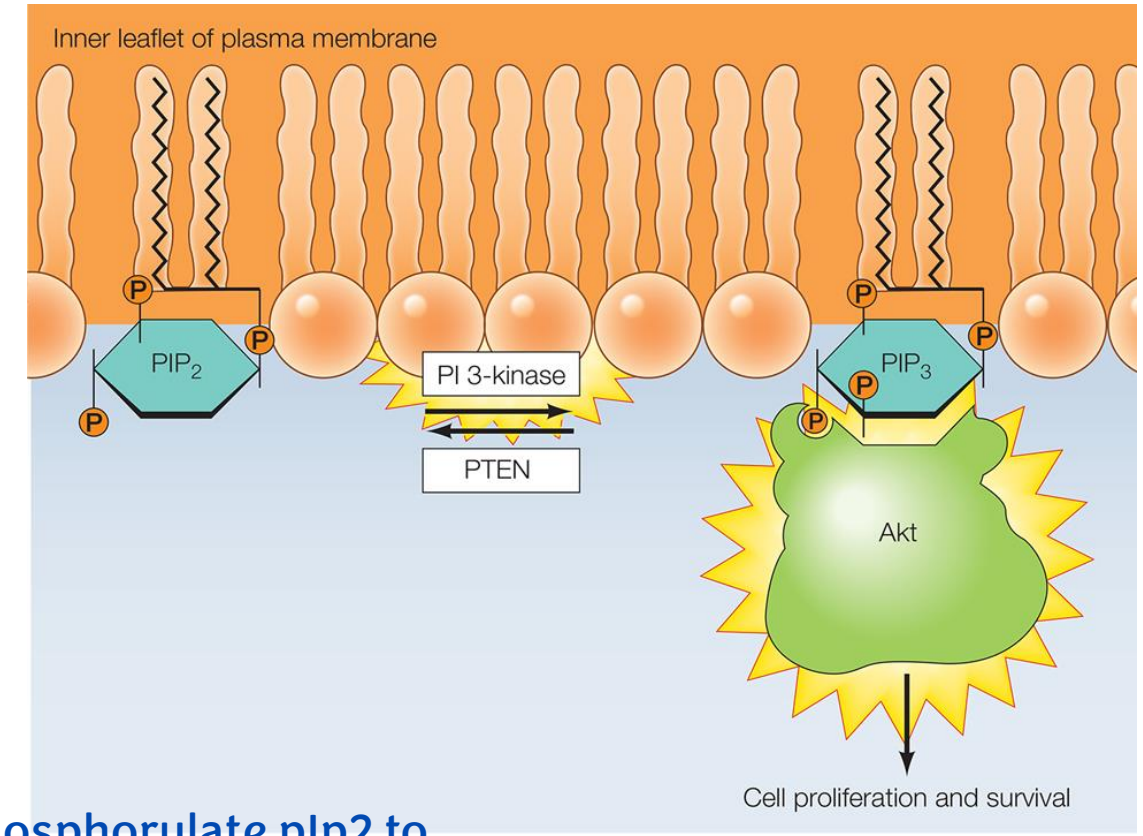
Mutations in the PI 3-kinase are common in breast and other types of cancer.
· pro-apoptotic protein = proteins that promote apoptosis .



Tumor Suppressor Genes

TSG and proliferation and survival

- The tumor suppressor protein PTEN is a lipid phosphatase that dephosphorylates PIP3 into PIP2.
- It counters the action of the oncogenes PI 3-kinase and Akt, which promote cell survival.

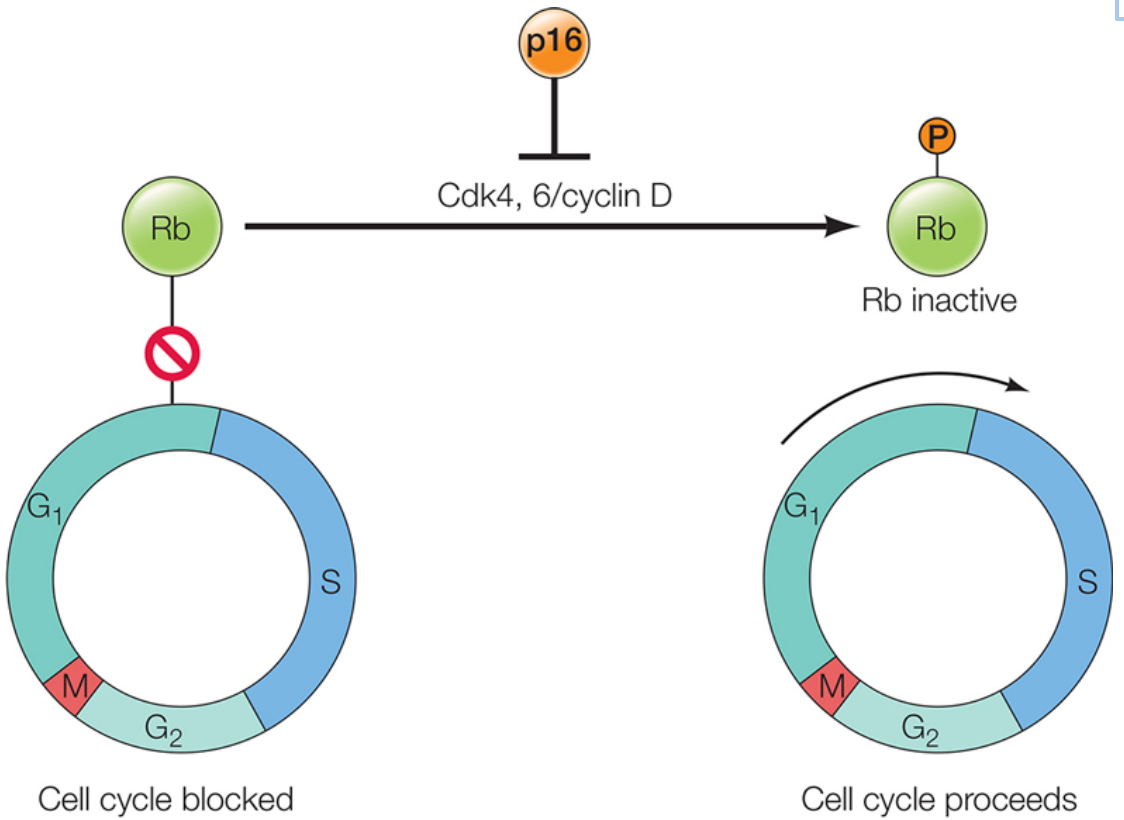


Mutation in PI 3-kinase pathways and Akt can result in overactive signal transduction pathways, leading to increased cell survival and proliferation.

PTEN (mutation in TSG) counteracts PI 3-kinase which phosphorylate pIp2 to pIp3 resulting in activation of AKT .
PTEN counteracts by dephosphorylates PIP3 into PIP2, so that Akt is not activated anymore. Accordingly, PTEN mutations cause an overactive Akt and consequently, cell proliferation and survival (mainly).

Mutation in genes that regulate cell cycle as :

TSG and cell cycle



Mutations in the cyclin D gene and the retinoblastoma (Rb) gene can disrupt the regulation of the cell cycle, leading to uncontrolled cell division.

- Cdk4/cyclin D complexes promote passage through the restriction point by phosphorylating and inactivating Rb. the Cdk4/cyclin D complex **inactivates Rb** through phosphorylation, allowing the cell to progress through the restriction point and move forward in the cell cycle.
- Inactivation of Rb results in increased cell cycle progression and tumor formation.

Mutations in the cell cycle inhibitors, such as p15, p16, p21, p27, can cause retinoblastoma and cancer.

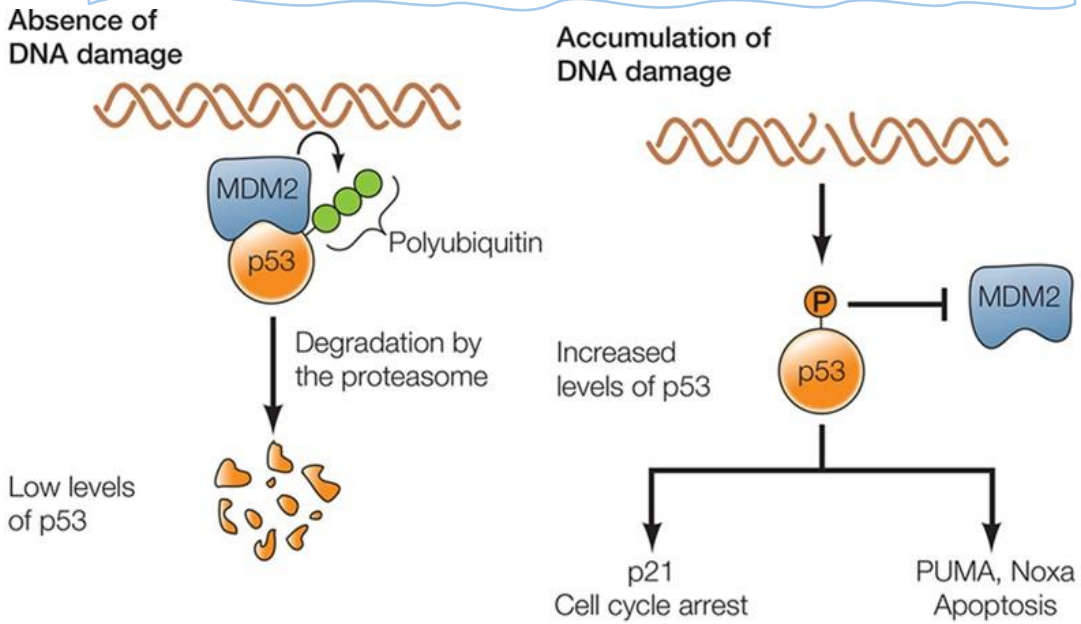
اللهم أعني على الدراسة ولا تجعل قلبي يمل منها وكن معي في كل لحظة ووفقني لما تحب وترضى، اللهم لا تجعل الدرجات أكبر همي ومبلغ علمي ورضني بما قضيت لي

Role of p53

Mutations in p53 are crucial in the formation of cancer.
50% of cancers are cause by mutations in the p53 gene.

- p53 is required for both cell cycle arrest and apoptosis induced by DNA damage.
- In the absence of DNA damage, p53 is ubiquitinated and degraded by the proteasome keeping p53 levels low.

Mutation in DNA will activate ATM/ATR , resulting in phosphorylation in p53 so p53 induce apoptosis on cell cycle block



- Accumulation of DNA damage results in p53 its phosphorylation, which inhibits ubiquitination, resulting in increased p53 levels, causing: **Executed by ATM/ATR**
  - Cell cycle arrest via induction of the Cdk inhibitor p21,
  - Apoptosis by induction of the proapoptotic Bcl-2 family members.

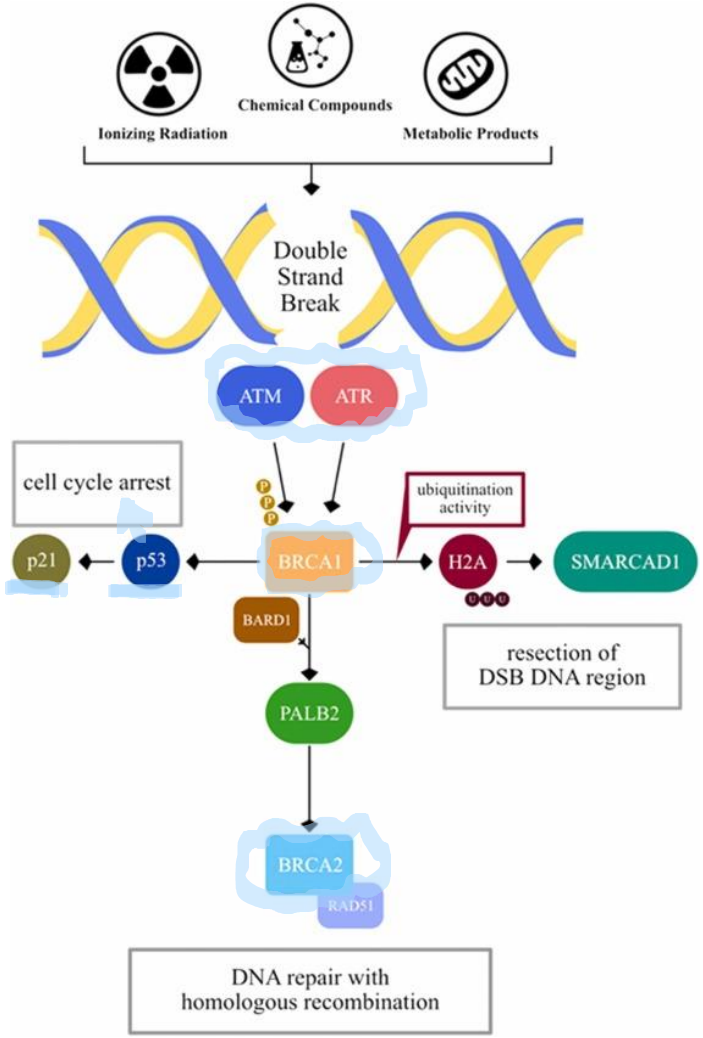
اللهم إني أعوذ بك من الهم والحزن، وأعوذ بك من العجز والكسل و الجبن و البخل

TSG and genomic integrity

BREast CAncer genes 1 & 2

- Like ATM, BRCA1 and BRCA2 are **stability genes since** that maintain the integrity of the genome from DNA breaks these gene will be activated by ATM/ATR and both BRCA1 and BRCA2 can involve in DNA repair .
- DNA Double Strand Breaks (DSBs) are detected by ATM and ATR, which phosphorylate target proteins that activate BRCA1 to initiate DNA repair either directly or by activating BRCA2. Both genes can repair DNA.
- BRCA1 also activates p53 to arrest cell cycle progression through p21. Alternatively, if DNA repair is not possible, the cell undergoes apoptosis.
- Mutations of BRCA1 and BRCA2 are responsible for hereditary breast and ovarian cancers.

These genes are familial-- tend to run in families.



We can observe a connection between the different signal transduction pathways and molecular mechanisms in the cell. سبحان الله {كُلَّ شَيْءٍ خَلَقْنَاهُ بِقَدَرٍ}

A mechanism of viral carcinogenesis

Viruses can cause cancer by introducing oncogenes or inhibiting the function of TSG.

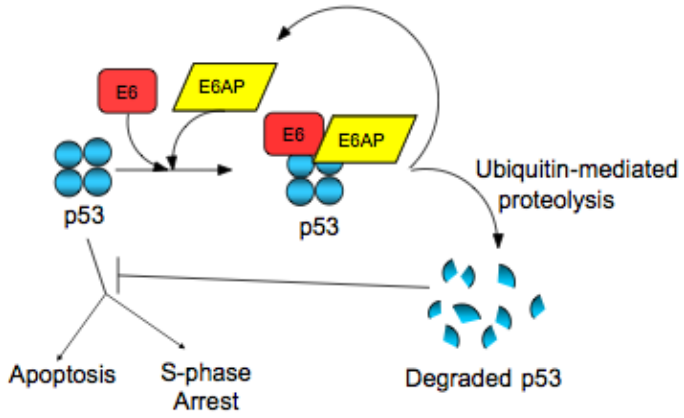
★Can cause cervical cancer in women.

- The E6 and E7 proteins of the human papillomavirus (HPV) block the function of the cellular p53 and Rb proteins, respectively.

Even if the cells have mutations in their DNA, p53 cannot function or stop the cell from growing, nor can the DNA be repaired.

E6 stimulates the degradation of p53 by proteolysis.

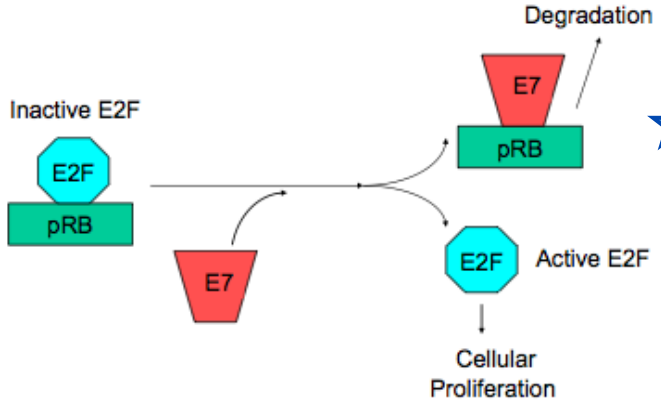
Role of HPV E6



Stops cells from undergoing the cell cycle.

E7 binds to Rb blocking its function.

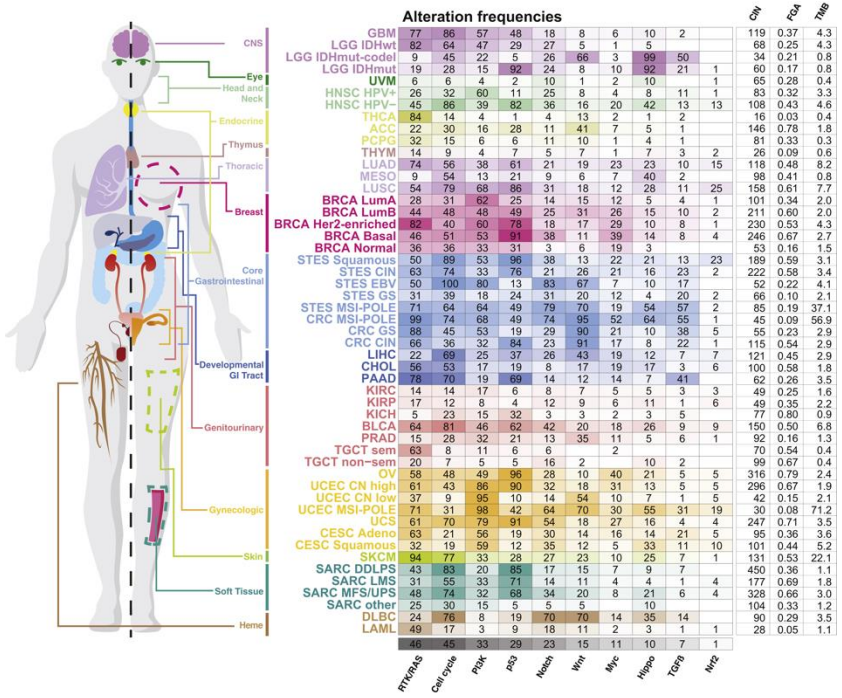
Role of HPV E7



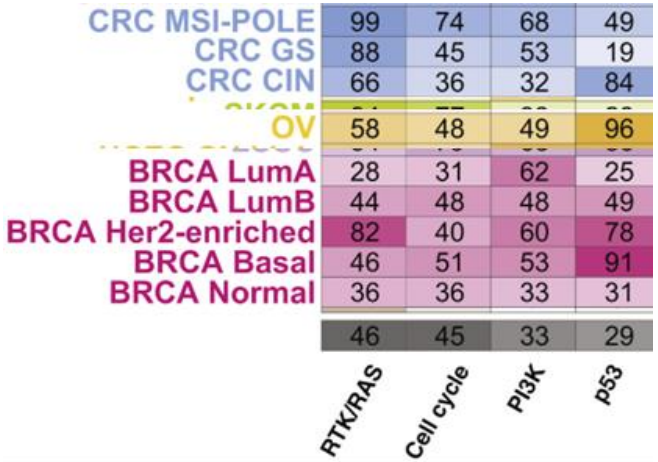
★Cervical cancer rates have decreased in Western countries following the introduction of the HPV vaccine, which has helped reduce cases over the past 10–15 years. In general, cervical cancer is less common in the Middle East (due to cultural/Islamic practices), but recent years have seen a rise in cases. As a result, governments are increasingly advocating for the HPV vaccine for women.

{يَقُولُونَ هَلْ لَنَا مِنَ الْأَمْرِ مِنْ شَيْءٍ قُلْ إِنَّ الْأَمْرَ كُلَّهُ لِلَّهِ..}

Mutations are cancer-specific.



- A subset of oncogenes (RTK and Ras), tumor suppressor genes (p53), and signaling pathways (RTK, PI3K) are involved in cancer types and cancer-specific subtypes.



·Cancer can be caused by mutations in different genes, which affect different signaling pathways.
·However, it seems that some pathways are cancer **type** and **subtype-specific**. Breast cancer has many subtypes and is not just one type of BRCA. Each subtype can carry certain types of mutations and may have overactive/downregulated **specific** signal transduction pathways and genes.
·For example, RTK and Ras mutations are common in colorectal cancer. p53, PI 3-kinase, and cell cycle protein mutations are all common in specific cancers.
These mutations are <u>not</u> random(causing certain cancer) .

Oncogenic Signaling Pathways in The Cancer Genome Atlas
https://www.cell.com/cell/fulltext/S0092-8674%2818%2930359-3

Summary

1. Cancer Basics

- Definition: Abnormal proliferation of cells.
- Tumor Types:
- Benign: Non-invasive, remains localized.
- Malignant (Cancer): Invasive, spreads via blood/lymph.

2. Molecular Causes of Cancer

- Carcinogens:
- Initiators: Cause genetic mutations (e.g., radiation, chemicals).
- Promoters: Stimulate cell proliferation, increasing mutation risk (e.g., hormones, smoking).
- Inducers:
- Genetics: Inherited mutations.
- Viruses: HPV, EBV cause oncogenic mutations.
- Bacteria: Infections like H. pylori.
- Environmental Factors: Radiation, chemicals, stress.

3. Cancer Cell Characteristics

- Uncontrolled Proliferation: Clonal and heterogenous.
- Invasiveness: Ability to spread through tissues.
- Loss of Growth Regulation:
- Density-Dependent Inhibition: Lost in cancer cells.
- Loss of Apoptosis: Cells evade programmed cell death.
- Angiogenesis: Formation of new blood vessels for tumor growth.
- Telomerase Expression: Enables limitless cell division.

4. Key Cancer Genes

- Oncogenes: Mutated or overactive genes that drive cancer (e.g., Ras, Myc).
- Types:
- Growth factors and receptors.
- Intracellular signaling proteins (e.g., Ras, Raf).
- Transcription factors (e.g., Fos, Jun).
- Tumor Suppressor Genes (TSG): Genes that prevent tumor formation.
- Examples: p53 (cell cycle control), Rb (cell cycle inhibition), BRCA1/2 (DNA repair).

5. Mechanisms of Oncogenic Mutations

- Activating Mutations: Mutations that maintain active signaling (e.g., Ras mutations).
- Gene Amplification: Multiple copies of oncogenes (e.g., HER2).
- Epigenetic Changes: Silencing of TSGs, activating oncogenes.
- Viral Oncogenes: Viral proteins (e.g., HPV E6 and E7) inactivate TSGs like p53 and Rb.

6. Tumor Suppressor Mechanisms

- p53: Prevents cell cycle progression with DNA damage.
- RB: Regulates the cell cycle, suppressing uncontrolled growth.
- BRCA1/2: Maintain genomic stability by aiding DNA repair.

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. HER2 Gene Overexpression & Mutations 0:13-1:38

﴿...وَمَن يَتَّقِ اللَّهَ يَجعَل لَهُ مَخرَجًا ۝ وَيَرزُقهُ مِن حَيثُ لا يَحتَسِبُ وَمَن يَتَوَكَّل عَلَى اللَّهِ فَهُوَ حَسبُهُ إِنَّ اللَّهَ بالِغُ أَمرِهِ قَد جَعَلَ اللَّهُ لِكُلِّ شَيءٍ قَدرًا﴾

اللَّهُمَّ لَكَ الْحَمْدُ كُلُّهُ، اللَّهُمَّ لَا قَابِضَ لِمَا بَسَطْتَ، وَلَا بَاسِطَ لِمَا قَبَضْتَ، وَلَا هَادِيَ لِمَا أَضْلَلْتَ، وَلَا مُضِلَّ لِمَنْ هَدَيْتَ، وَلَا مُعْطِيَ لِمَا مَنَعْتَ، وَلَا مَانِعَ لِمَا أَعْطَيْتَ، وَلَا مُقَرِّبَ لِمَا بَاعَدْتَ، وَلَا مُبَاعِدَ لِمَا قَرَّبْتَ، اللَّهُمَّ ابْسُطْ عَلَيْنَا مِنْ بَرَكَاتِكَ وَرَحْمَتِكَ وَفَضْلِكَ وَرِزْقِكَ، اللَّهُمَّ إِنِّي أَسْأَلُكَ النَّعِيمَ الْمُقِيمَ الَّذِي لَا يَحُولُ وَلَا يَزُولُ، اللَّهُمَّ إِنِّي أَسْأَلُكَ النَّعِيمَ يَوْمَ الْعَيْلَةِ، وَالْأَمْنَ يَوْمَ الْخَوْفِ، اللَّهُمَّ إِنِّي عَائِذٌ بِكَ مِنْ شَرِّ مَا أَعْطَيْتَنَا وَشَرِّ مَا مَنَعْتَ، اللَّهُمَّ حَبِّبْ إِلَيْنَا الْإِيمَانَ وَزَيِّنْهُ فِي قُلُوبِنَا، وَكَرِّهْ إِلَيْنَا الْكُفْرَ وَالْفُسُوقَ وَالْعِصْيَانَ، وَاجْعَلْنَا مِنَ الرَّاشِدِينَ، اللَّهُمَّ تَوَفَّنَا مُسْلِمِينَ، وَأَحْيِنَا مُسْلِمِينَ، وَأَلْحِقْنَا بِالصَّالِحِينَ غَيْرَ خَزَايَا وَلَا مَفْتُونِينَ، اللَّهُمَّ قَاتِلِ الْكَفَرَةَ الَّذِينَ يُكَذِّبُونَ رُسُلَكَ، وَيَصُدُّونَ عَنْ سَبِيلِكَ، وَاجْعَلْ عَلَيْهِمْ رِجْزَكَ وَعَذَابَكَ، اللَّهُمَّ قَاتِلِ الْكَفَرَةَ الَّذِينَ أُوتُوا الْكِتَابَ إِلَهَ الْحَقِّ