Genetics
& Cell biology

◉ Sheet ○ Slides

Number

14

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Cancer

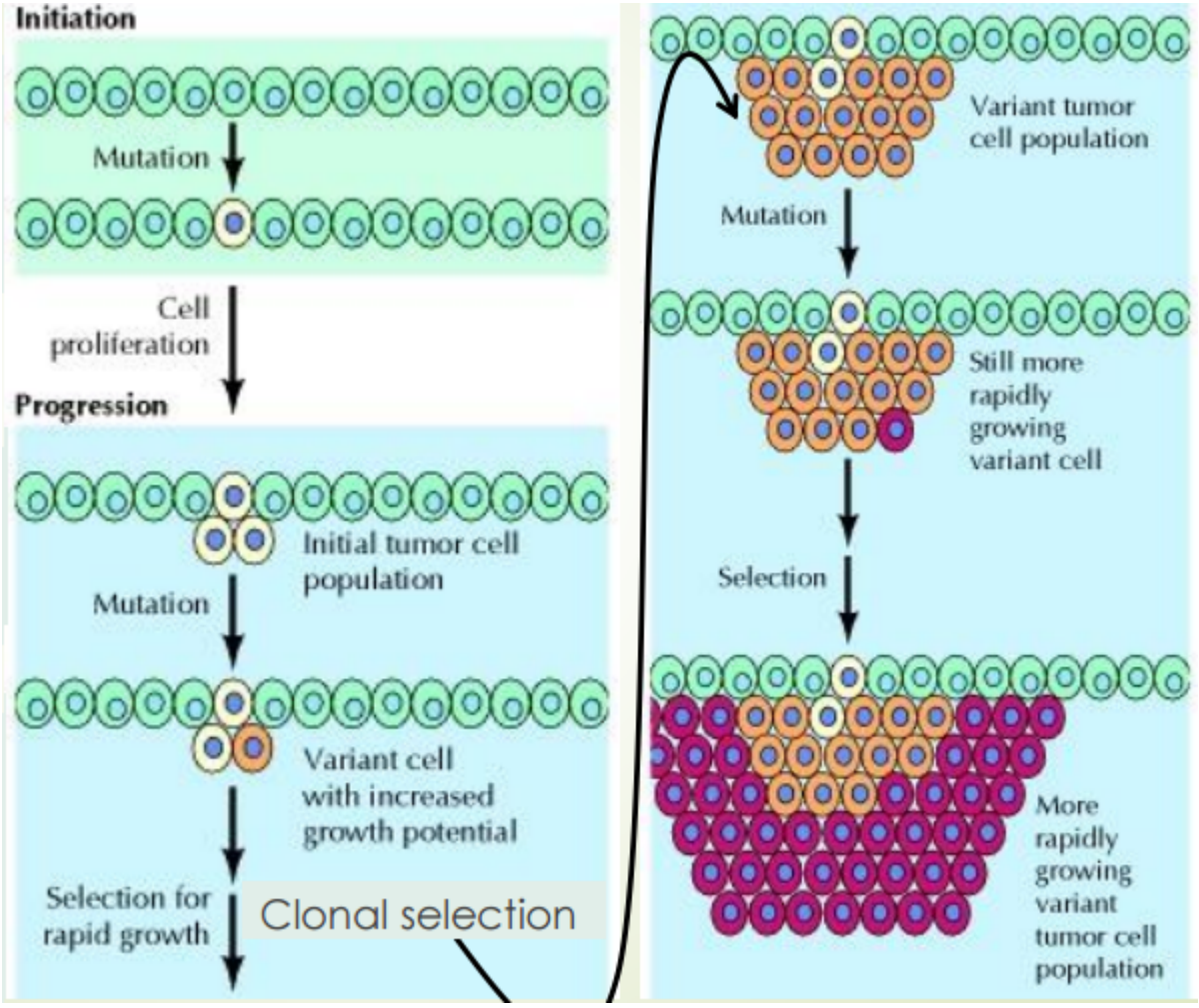
This is not a new topic for you since we've discussed cancer previously in the pathology course. In this lecture, we are going to review some points, discover new details about cellular changes in cancer, and link it to cell biology.

What is cancer??

It is unregulated (uncontrolled) growth of cells and tissues. As they grow, they overwhelm the normal cells and take their nutrients, so we start to lose the function at that site.

How does cancer develop??

There are many theories that explain cancer development and progress; the most accepted one is the theory of *accumulation of mutations in a multistep process*:



1- Cells normally proliferate in a well-regulated manner called cell cycle.
2- Throughout life, people are exposed to many factors (radiation, chemicals, viruses…etc.) that may cause mutations in some cells (*acquired mutations*).
3- These mutations might be in a gene that is involved in cell cycle regulation: cyclins, cyclin-dependent kinases, transcription factors, tumor suppressor genes, and proto-oncogenes. A mutation in any of these genes that results in loss of control over the gene might lead to loss of control and disruption of cell cycle.
4- As a result of the mutation (and the disrupted cell cycle), mutated cells start to proliferate rapidly in an uncontrolled manner. (One single mutation is sufficient for this step).
5- The increased proliferation and decreased regulation of the cell increase the chance of developing new mutations in some cells. More mutations result in more proliferation. Now, we have more than one population of cells each with different types of mutations; some have one mutation, others have two .. etc., and they continue to proliferate at the same time. The ones with more mutations in them ➔ proliferate faster.
6- With time, cells acquire more and more mutations, and the final mass (tumor mass) id composed of ***heterogeneous*** cells. Meaning, cells of the same tumor *don't* necessarily have the same genes (the same mutations).

Environmental causes of cancer (carcinogens) are divided into:

Initiators: induce genetic mutations; mentioned above in point 2.

Promoters: don't initiate cancer, but they aid in its progression. For example, hormones like *Estrogens* (used to treat some diseases like osteoporosis, especially in females) may increase the chance of developing cancer. Other examples include pathogens like some species of viruses and bacteria (Helicobacter pylori) and some types of chemicals. Those factors may increase the chance of developing cancer, BUT THEY STILL DON'T INITIATE CANCER. Some viral infections are linked to specific cancers as listed in the table below:

TABLE 18.2 Tumor Viruses

Virus family	Human tumors	Genome size (kb)
DNA Genomes		
Hepatitis B viruses	Liver cancer	3
SV40 and polyomavirus	None	5
Papillomaviruses	Cervical carcinoma	8
Adenoviruses	None	35
Herpesviruses	Burkitt's lymphoma, nasopharyngeal carcinoma, Kaposi's sarcoma	100–200
RNA Genomes		
Hepatitis C virus	Liver cancer	10
Retroviruses	Adult T-cell leukemia	9–10

These viruses either have a *direct* effect by causing the cancer or *indirect* effect by increasing the risk of it; so patients that got infected with a certain virus have *high risk* of developing a certain cancer.

Note: the correlation between HPV and cervical carcinoma is high; there is *direct* effect (cause effect) relationship between them.
Note: Hepatitis B patients have higher chance of developing liver cancer than Hepatitis C patients, *but* the chance of cancer development is relatively low for both of them; *indirect effect.*

Retroviruses are associated with certain types of leukemia (T-cell leukemia). Herpes virus is linked to burkitt's lymphoma and kaposi's sarcoma.

Cellular features of cancer:

What are the differences between a normal cell and a cancer cell?

1- **Unlimited proliferation:** under the microscope, we can see a group of cells that differ from others in their abnormal shape and arrangement. Their disarrangement is due to the high rate of growth and proliferation (so consequently, their number is high).
   Why do cancer cells have increased growth rate (higher proliferation)?
   Because of *many* factors like ➔ *Telomerase* activity: Telomeres are extra (noncoding) nucleotides that cap the two ends of chromosomes to preserve the genetic material of these chromosomes. As the cell divides, the telomeres become shorter. When telomeres become too short, cell division stops.
   Eternal youth can be achieved if we could preserve the length of telomeres. This can be done by using cancer cell as a model since they changed their telomerase activity to preserve telomeres' length and divide endlessly.
2- Cancer cells accumulate **genetic mutations.**
3- Cancer cells **lose contact** with other cells or with the extracellular matrix, so they can easily detach and **metastasize** through blood vessels or lymphatic system.
4- **Autocrine signaling** is very active in cancer cells; they produce growth factors that increase their own growth. Meaning, they have receptors for these growth factors in which binding of the growth factor to these receptors will auto-stimulate the proliferation of these cells.
5- **Loss of contact inhibition:** When normal cells are grown in a plate, they're going to proliferate until they fill the plate with a *one-cell-thick* layer. This happens because cell growth is inhibited once one cell touches another. Thus, they DON'T grow above each other.

In case of cancer cells, this regulatory mechanism is lost ➔ Even if they touch each other, their growth doesn't stop; they grow above each other forming many layers of cells.

6- **Loss of density-dependent inhibition**

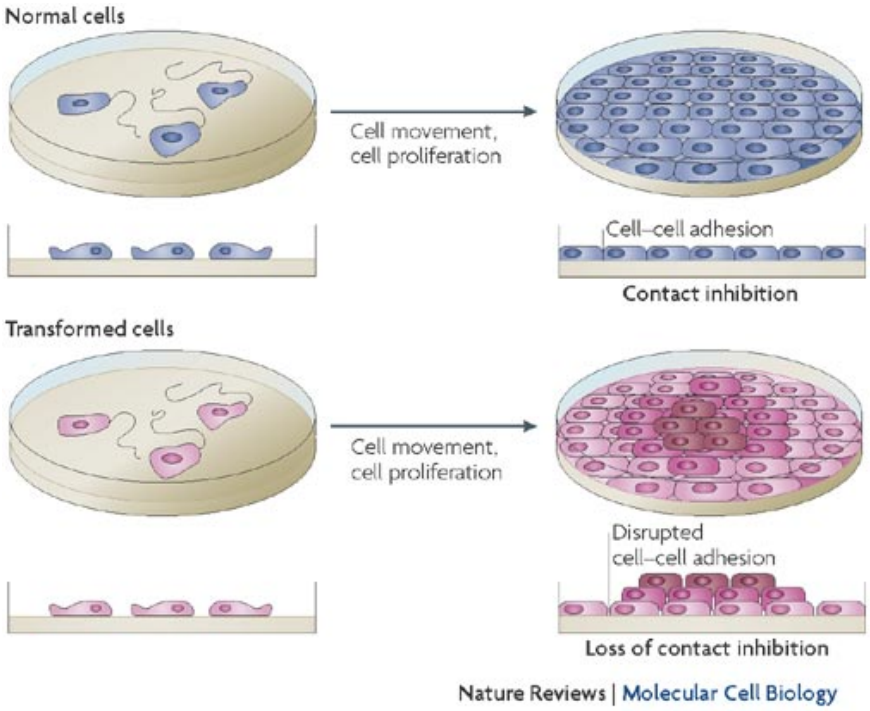


Figure showing difference between:

- Normal cells which have contact inhibition.

- And cancer cells which lost contact inhibition.

7- **Invasiveness:** when cancer cells first grow and form a population, they are still surrounded (trapped) by a membrane in a localized region. With continuous growth and addition of mutations, some cells become more aggressive and start to secrete **proteases**. These proteases digest the extracellular matrix allowing cancer cells to invade the surrounding tissue; this is called **Carcinoma in situ**. Carcinoma in situ: local invasiveness without reaching blood stream or lymphatic system. It is caused by overproduction of proteases from cancer cells.

8- **Angiogenesis:** Cancer cells form their own blood vessels by secretion of VEGF (Vascular Endothelial Growth Factor). More blood vessels ➔ more blood supply and nutrients to cancer cells ➔ more growth and division of cancer cells.

9- **Loss of apoptotic capability:** When normal cells sense damage in their DNA, they stop growing (cell senescence). If the damage is more severe, they target apoptosis (cell suicides). Cancer cells, on the other hand, don't end up with senescence or apoptosis even though they have many mutations and a lot of DNA damage.

10- **Lack of differentiation:** The difference between stem cells (undifferentiated cells) and fully differentiated cells is that stem cells have much higher ability to divide.

For example, osteocytes and myocytes (fully-differentiated) almost have no proliferation ability, whereas osteoblasts and myoblasts (mesenchymal stem cells) have good proliferative activity.

Note: there is also a type of cells called *progenitor cells*. They are like stem cells but more specific. They have a tendency to differentiate into a specific type of cells (target cells).

In case of cancer, locking of cells in an early stage of differentiation preserves their ability to divide repeatedly. That's why cancers that have undifferentiated cells are considered more *aggressive* than cancers that have differentiated cells (so yes we can find a cancer with well-differentiated cancer cells)

Oncogenes and tumor suppressor genes:

Minutes [00:00-10:00]

Any gene of ours that has a role at some point in the regulation of cell division is called **proto-oncogene** as long as it is functioning normally in a controlled manner. If this gene gets mutated in a way that makes the cell divide continuously, it becomes an **oncogene**. (In the case of cancer, genes that stimulate cell growth will be over activated whereas genes that stimulate cell death or inhibition of growth, like *p53,* will be suppressed).

Example: assume that we have viral-induced cancer in which the mutated gene codes for a kinase. Kinases have catalytic domains and regulatory domains. If the control of the regulatory domain is lost, the kinase (catalytic domain) will become active all the time. What happens is that once the virus *randomly* integrates its gene into the cellular genome, it might insert its sequence in the gene that codes for the kinase and, specifically, that which codes for the *regulatory domain*. If it does, the regulatory domain is lost, and the kinase becomes constitutively active. This will transform the proto-oncogene to oncogene ➔ leading to 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

Note: *ABL and BCR genes* are present each in different chromosome, but both code for kinases. A translocation mutation between them produce Philadelphia chromosome which codes for an intrinsically over active kinase. This translocation leads to cancer (leukemia). Other types include akt and erb A and B. The last two encode for receptor tyrosine kinases, and their mutation results in Avian erythroblastosis. Mutations in Raf, Ras (in all its subtyopes; RasH, Rask ..), and Scc cause different types of sarcoma.

Human papilloma virus and cervical cancer:

This is just a selected example of viral-induced cancer to discuss *how a virus induces cancer*. (It was selected due to the high correlation between HPV and cervical cancer):

As any virus, HPV infects a cell, goes inside, and starts to use cellular machinery to produce viral proteins. Two important HPV proteins:

E6: it activates degradation of p53, so p53 is not functioning as tumor suppressor any more (it is considered mutated). This leads to more activation of cell cycle and less apoptosis.

E7: it binds to RB. RB is tumor suppressor; it normally binds to E2F and prevents it from functioning (E2F function as transcription factor). When E7 binds to RB, E2F is free and can bind and activate the expression of genes that activate cell cycle (cyclins and cyclin-dependent kinases).

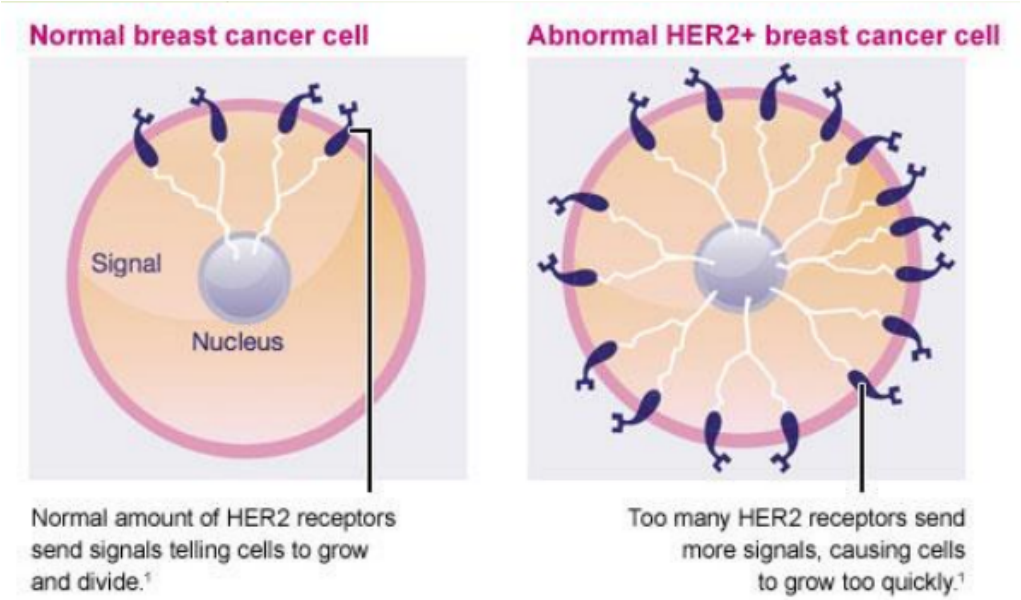
Oncogenes and signal transduction:

Any change (mutation) that causes over activity in genes that code for a signaling pathway may produce an oncogene. Examples: a permanently binding *ligand*, a constitutively stimulated *receptor*, a permanently *2nd messenger* in its active conformation, and an over-activated *transcription factor* ➔ they all results from oncogene mutations.

Note that a proto-oncogene codes for normal proteins (ligand, receptor, transcription factor… etc.), while an oncogene codes for the *abnormal ones*.

Oncogenes and receptors:

A cancer cell, in addition to having mutated receptors that are constitutively active, can also over express the receptors on its surface. In the case of receptor overexpression, the chance of receiving the signal is much higher; meaning that the cell becomes very sensitive to this signal, and the signal is hugely *amplified* intracellularly. The over expressed receptor might be normal or abnormal (intrinsically active), but both lead to the same outcome.



Mutations that transform a proto-oncogene into an oncogene can be as minimal as *single nucleotide substitution*. If it results in a silent mutation, no problem will occur. Also, for the substitution to cause harmful effect, it **doesn't necessarily** change the codon of a nonpolar amino acid into a polar one. Changing one nonpolar amino acid into another nonpolar one can produce a great effect on the final protein (the same happens when changing one basic amino acid to another, or one acidic amino acid to another).

Example: CFTR (Cystic Fibrosis Transmembrane-conductance Regulator) functions as a channel for chloride ions. The mutation in this gene only substitutes one nonpolar amino acid with another nonpolar amino acid, but results in **cystic fibrosis**. Similar mutations transform RAS into an oncogene which leads to cancer development.

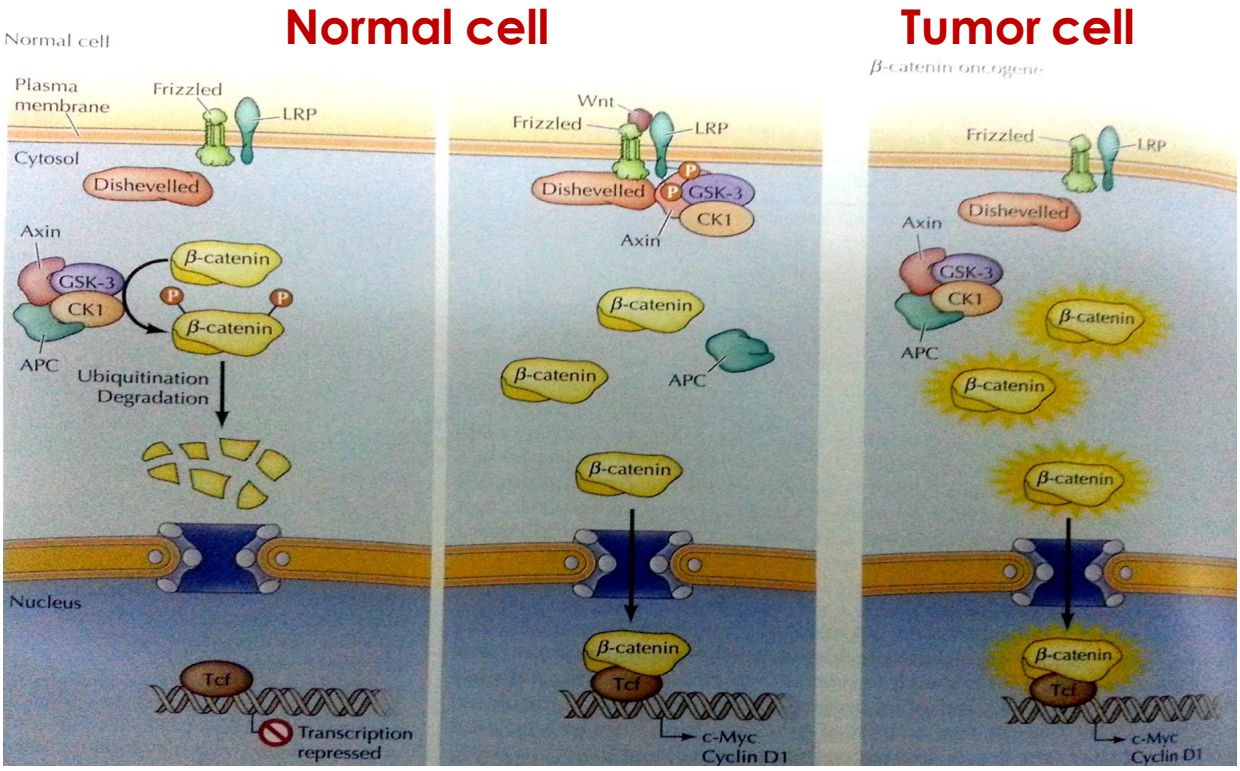
Oncogenes and transcription factors:

An example here is **β-Catenin** in Wnt signaling pathway:

In Normal cells: when Wnt is not binding, β-Catenin is bound to a complex called "destruction complex", this complex (contains **APC)** destroys β-Catenin. When Wnt is bound, APC dissociates from the complex, so β-Catenin is not destroyed and is able, as a transcription factor, to enter the nucleus where it binds and activates target genes.

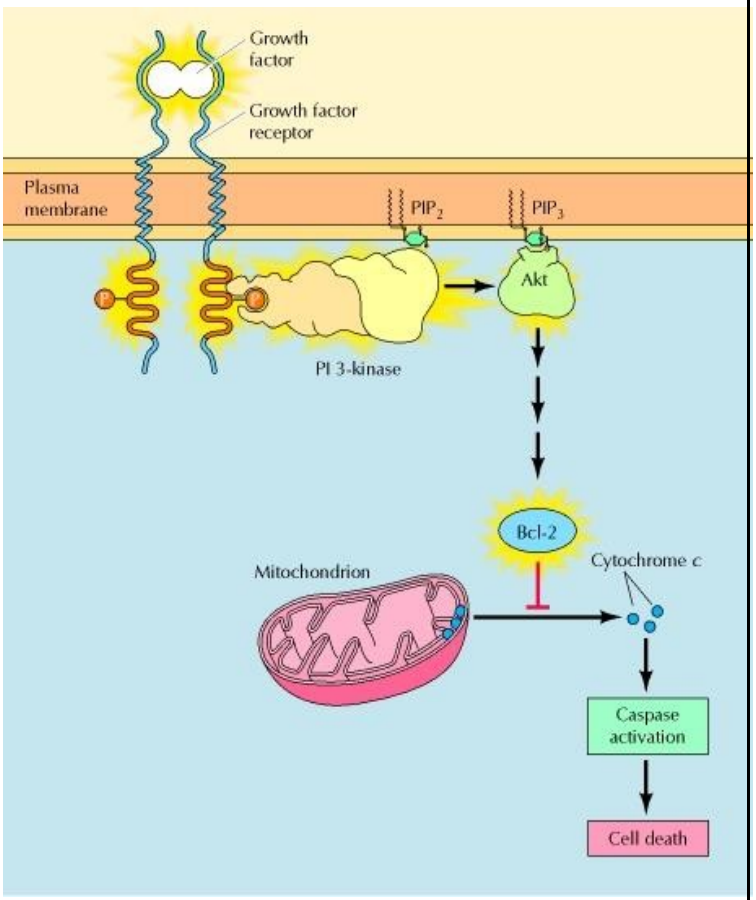
[Target genes are mainly developmental, cell cycle regulators, and oncogenes]

In cancer cells: one of the proteins from the destruction complex is mutated so that the complex dissociates even if Wnt is not bound, this leaves β-Catenin active all the time ➔ promoting cancer development.



Oncogenes and cell survival and proliferation:

PI3 kinase pathway and RAS-Raf-MEK-ERK pathway are main signaling pathways in controlling cell survival. In PI3 pathway, there are many targets for AKT protein like Bcl-2 family of proteins (some proteins of this family are pro-apoptotic while others are anti-apoptotic). Pro-apoptotic members are inhibited by AKT, so IP3 pathway favors cell growth by providing an escape from apoptosis for mutated (cancer) cells. PI3 is widely studied to be targeted by drugs while AKT is not because it acts as a hub; meaning that it is involved in many interconnected pathways which makes it hard to target it for therapy.

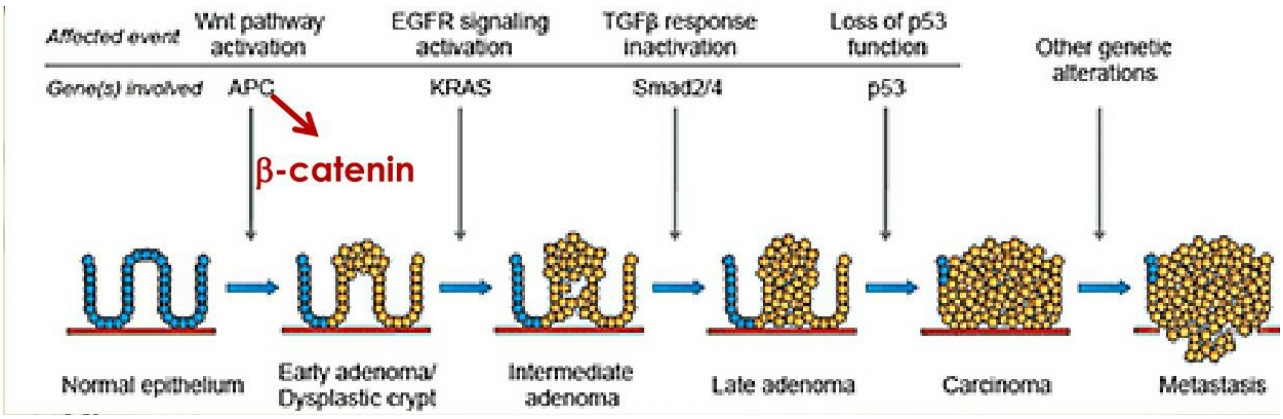


Oncogenes and differentiation: ErbA (thyroid hormone receptor) and retinoic acid receptor (PML/RARα) lock the cell at an early stage of differentiation; they don't allow the completion of cell differentiation. Thus, they preserve the proliferative ability of the cell; thereby, promoting acute promyelocytic leukemia.

Mutations in tumor suppressor genes:

- PTEN is a lipid phosphatase that dephosphorylates PIP3 into PIP2. PIP3 is important for AKT, so PTEN acts as tumor suppressor by opposing the action of PI3 kinase; thereby, inhibiting growth and proliferation. That's why PTEN mutations are associated with certain types of cancer (mutations that delete PTEN)
- Mutations that cause deletion of Rb gene, a gene that inhibits progression past the restriction point in G_1 and is controlled by CDK4/Cyclin D complexes[1], also lead to increased cell cycle progression and tumor formation.
- P53 – as a tumor suppressor that is activated by ATM that detects damages in DNA– activates P21 and BAX. This leads to cell cycle arrest or apoptosis in case of DNA damage. Loss of P53 means continuous growth despite the huge damage and loss of DNA integrity.

At the end, it is important to understand that cancer is multistep process that results – despite the sequence of mutations appearance – in formation of heterogeneous group of malignant cells that are equipped with weapons of immortality and high proliferative capacity, the following is one possible sequence of mutation:



[1] Cdk4/cyclin D complexes promote passage through the restriction point by phosphorylating and inactivating Rb.