Genetics & molecular biology

◉ Sheet ○ Slide

Number:	36
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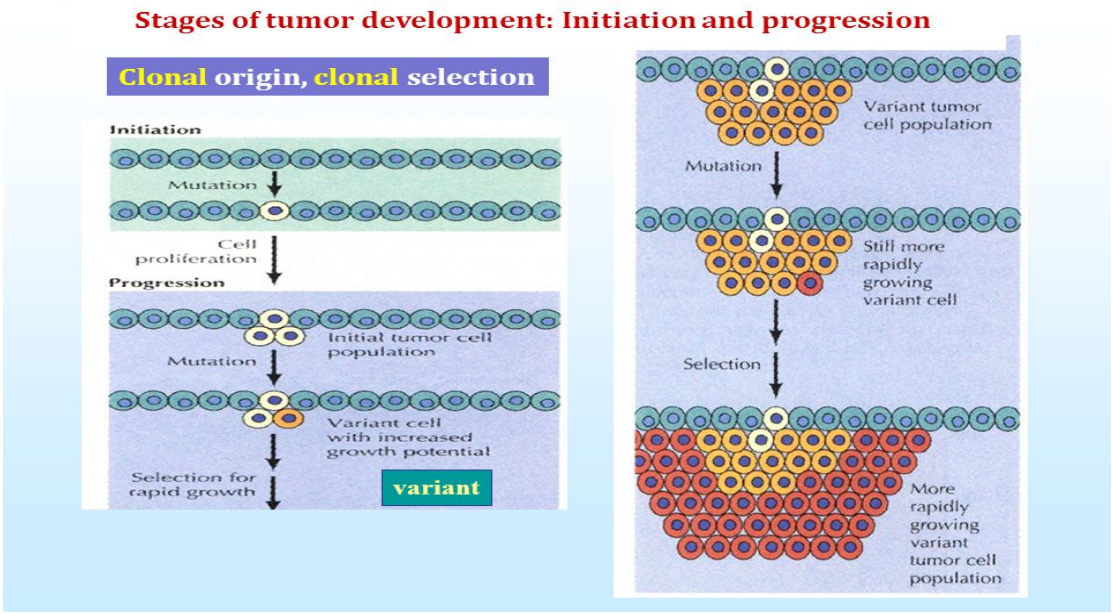
Cancer

- ⇨ It is unregulated and uncontrolled growth of cells which have features of malignancy.
- ⇨ It's a multistep process, involves accumulation of mutations and needs time. The final mass (tumour mass) is composed of heterogeneous cells because they acquire different mutations, so they don't necessarily have the same genes.



How does cancer develop?

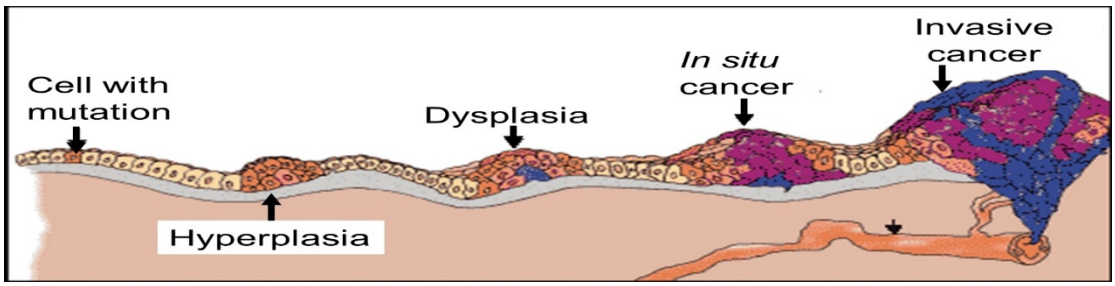
1- Cells normally proliferate in a well-regulated manner called cell cycle.

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, tumour 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.



Carcinogens

Environmental causes of cancer (carcinogens) are divided into:

A. Initiators:

- *They induce genetic mutations that result in malignant cells.*
- *E.g.: long exposure to radiation (UV light, X-ray), and certain types of viruses*.

B. Promoters:

- *They don't initiate cancer, but aid in its progression.*
- *E.g.: toxins like alpha toxin, hormones like Oestrogens (used to treat some diseases that are related to postmenopausal period like osteoporosis, especially in females), pathogens like some species of viruses and bacteria (Helicobacter pylori), and certain chemicals.*
- *They 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, for example:

a) *Patients with HPV infection (especially type 16 and 18) are at very high risk of developing cervical cancer.*
b) *Hepatitis B patients have higher chance of developing liver cancer than Hepatitis C patients.*
c) *Retroviruses are associated with certain types of leukaemia (T-cell leukaemia).*
d) *Herpes virus is linked to Burkett's lymphoma and Kaposi's sarcoma.*

Cellular features of cancer

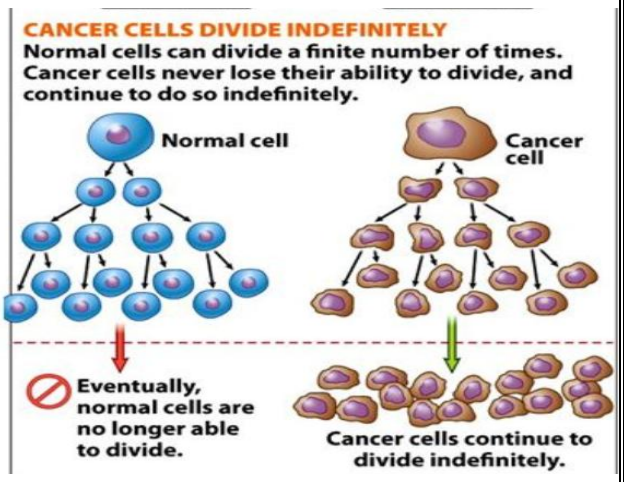
What are the differences between a normal cell and a cancer cell?

1) **Clonal origin:** the malignant tumour starts from a single cell that proliferates to make a population inside the normal tissue.
2) **Accumulated Mutations:** which give malignancy features to the population of cells.
3) **Uncontrolled 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).

Cancer cells don't reach senility, due to Telomerase activity that keep the high growth rate in the cells.

Telomeres are (noncoding) nucleotides that cap the two ends of chromosomes to preserve the genetic material of these chromosomes. As the normal cell divides, the telomeres become shorter. When telomeres become too short, cell division stops. (That doesn't happen in the case of cancer). 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.

Autocrine signalling 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.

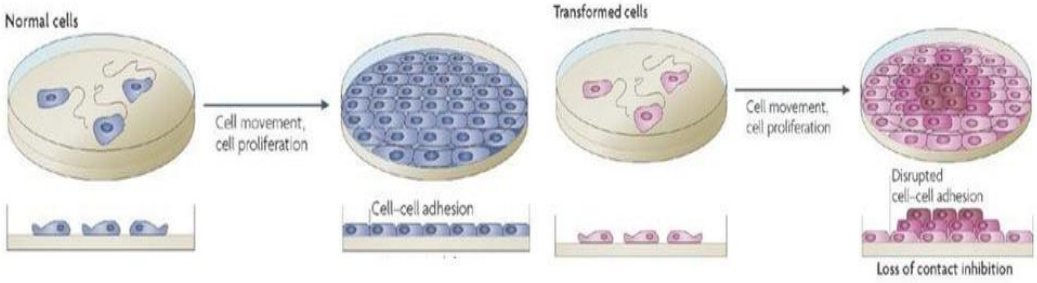


4) Loss of contact inhibition:

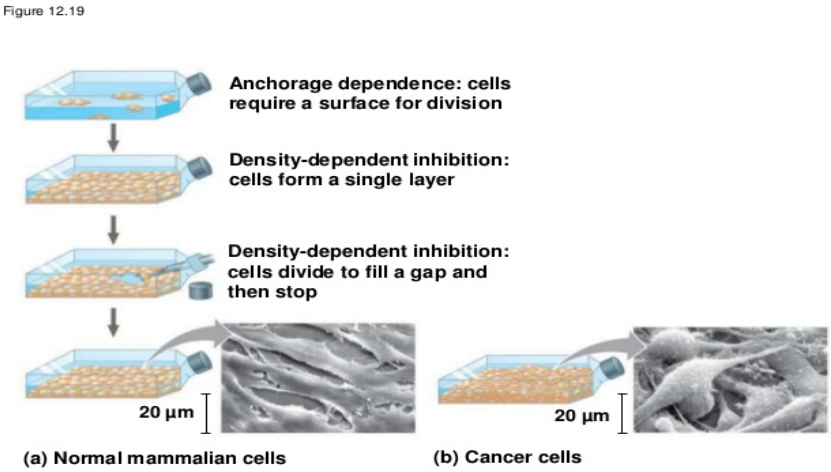
Cancer cells lose contact with other cells or with the extracellular matrix, so they can easily detach and metastasize through blood vessels or lymphatic system.

Normal cells grow in a plate, they 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.

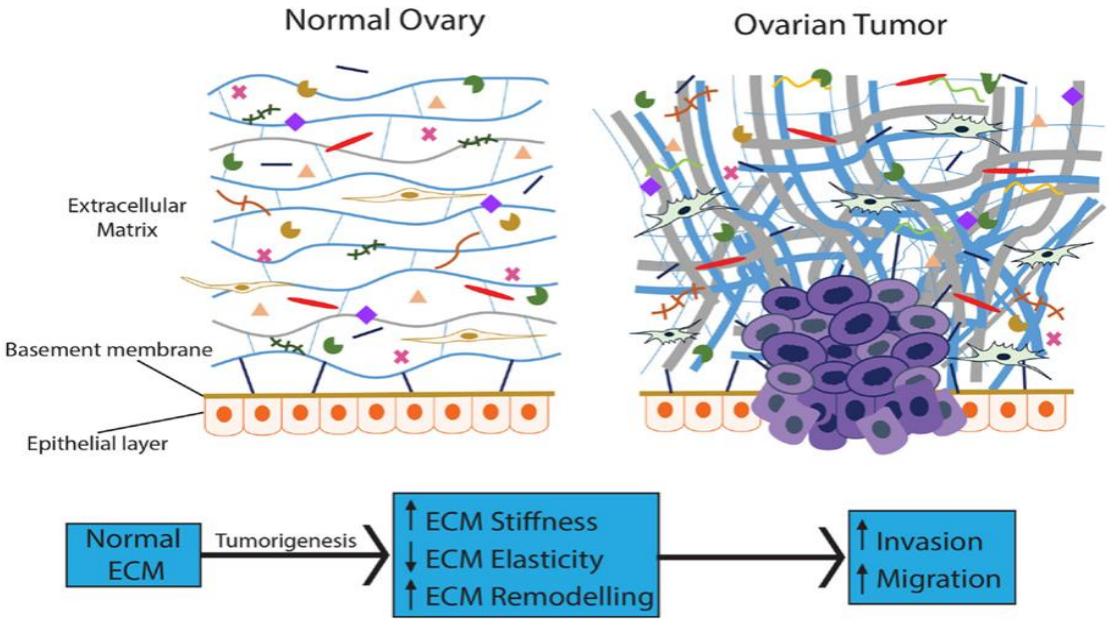


5) Loss of density-dependent inhibition



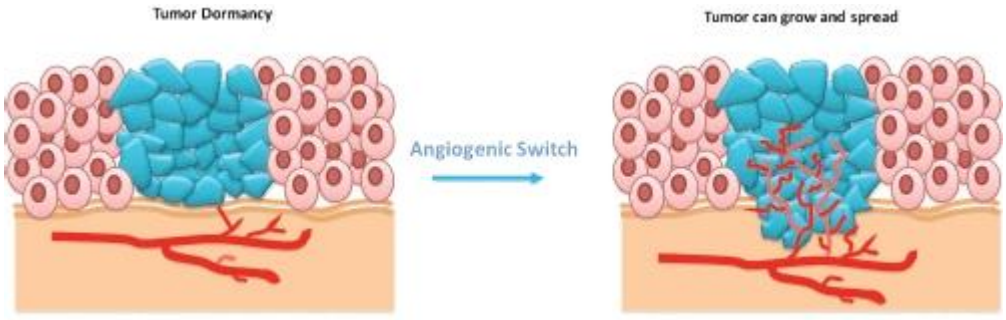
6) Invasiveness

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 invasion is followed by metastasis.



7) Angiogenesis

Cancer cells form their own blood vessels by secretion of VEGF (Vascular Endothelial Growth Factor). More blood vessels ➔ more blood supply (O2 and nutrients) to cancer cells ➔ more proliferation of cancer cells.



8) 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. This feature can cause chemotherapy resistance.

9) 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.

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).

Mutations in proto-oncogenes

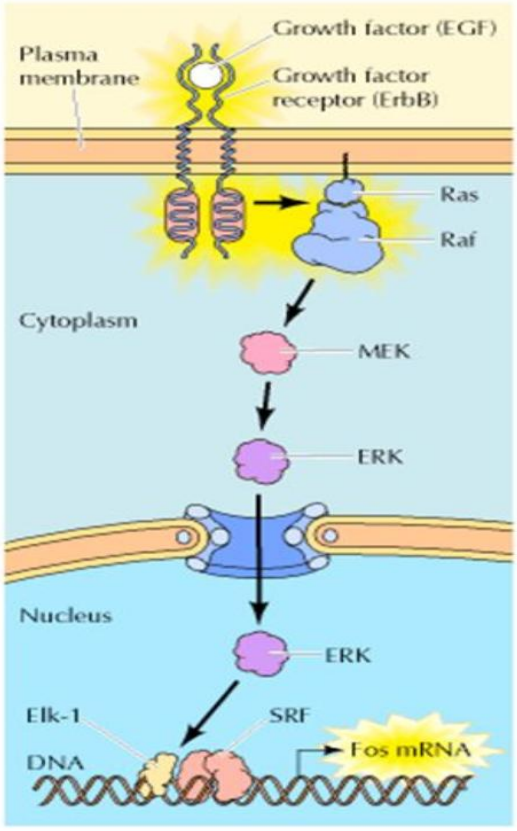
Proto-oncogenes are normal genes that are translated into proteins to stimulate cell cycle (activate proliferation) in a controlled manner. If one of these genes gets mutated in a way that makes the cell divide continuously, it becomes an oncogene.

Tumour suppressor genes: are normal genes that are translated into proteins to inhibit the cell cycle (decrease proliferation). If one of these genes are mutated, the cell can proliferate continuously without inhibition.

(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).

Oncogenes and signal transduction

- Any change (mutation) that causes over activity in genes that code for a signalling pathway might produce an oncogene.
- *For example: 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.*
- RAF gene is a proto-oncogene, its protein is a kinase. Kinases have catalytic domains and regulatory domains. If the control of the regulatory domain is lost, the kinase



Proteins with known oncogenic potential are highlighted with a yellow glow

(catalytic domain) will become active all the time ➔ becomes oncogene.

Oncogenes and transducers

- A single nucleotide change, which alters codon 12 from GGC (Gly) to GTC (Val), is responsible for the tumorigenic activity of the rasH oncogene.
- The mutation maintains the RAS proteins constitutively in the active GTP-bound conformation.

Oncogenes and viruses

- Assume that we have viral-induced cancer in which the mutated gene codes for a kinase. 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.

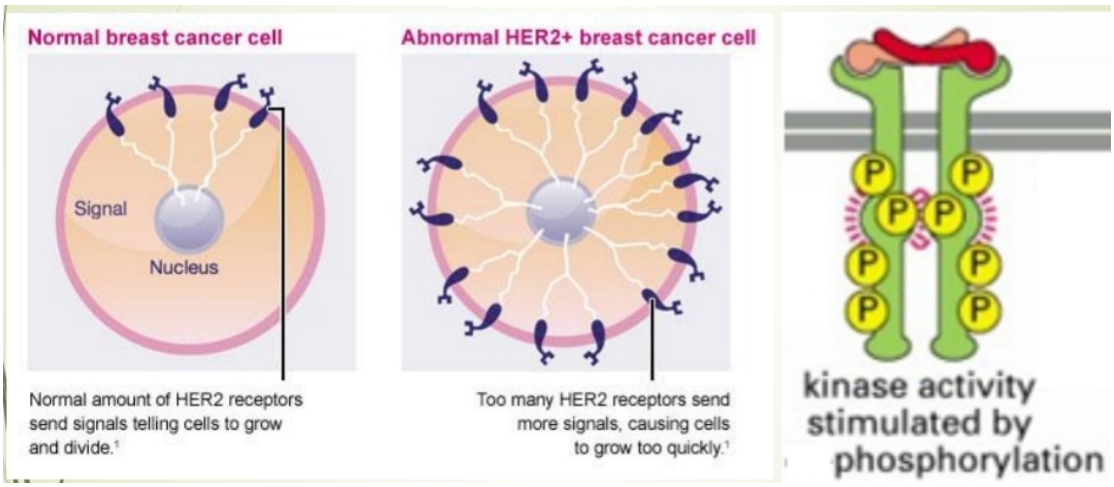
Oncogene	Virus
abl	Abelson leukemia
akt	AKT8 virus
erbA	Avian erythroblastosis-ES4
erbB	Avian erythroblastosis-ES4
raf	3611 murine sarcoma
rasH	Harvey sarcoma
rasK	Kirsten sarcoma
src	Rous sarcoma

- 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 (leukaemia).

- Mutations that include AKT, ERBA and ERBB genes results in avian erythroblastosis. (ERBA AND ERBB encode for receptor tyrosine kinases).
- Mutations in RAF, RAS (in all its subtypes; rash, Rask ...), and SCC cause different types of sarcoma.

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 (constitutively active), but both lead to the same outcome.



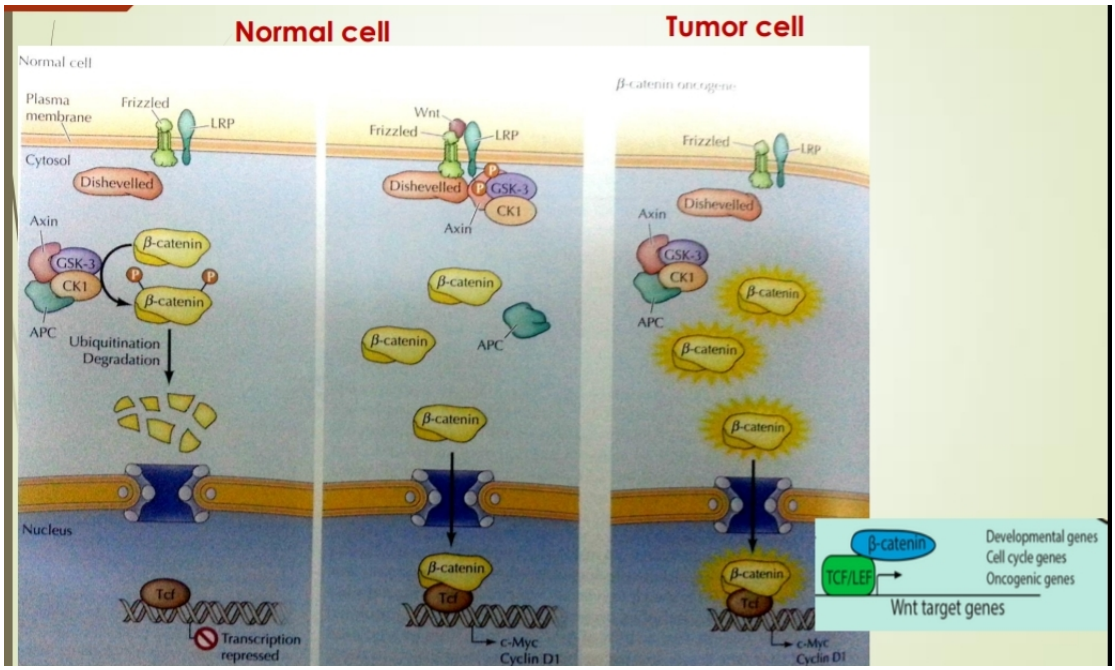
Oncogenes and transcription factors

An example here is β-Catenin in WNT signalling 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.

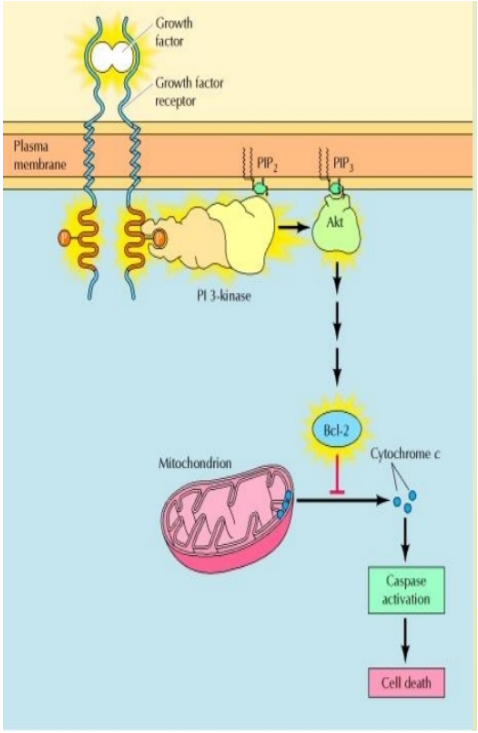
[Target genes are mainly developmental, cell cycle regulators, and proto-oncogenes]

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 signalling 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 favours 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 leukaemia.

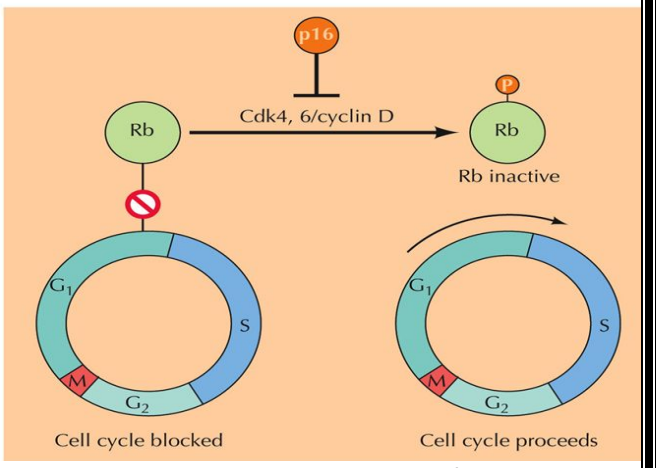
Mutations in tumour suppressor genes

Tumour suppressor genes: are normal genes that are translated into proteins to inhibit the cell cycle (decrease proliferation). If one of these genes are mutated, the cell can proliferate continuously without inhibition.

1) PTEN is a lipid phosphatase that dephosphorylates PIP3 into PIP2. PIP3 is important for AKT, so PTEN acts as tumours 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).

2) Rb is a tumour suppressor gene, in normal cell its protein binds to E2F and prevents it from functioning (E2F function as transcription factor).

INHIBITION OF CELL CYCLE PROGRESSION BY RB AND P1



Mutations that cause deletion of Rb gene, lead to increased cell cycle progression and tumour formation, due to continuous activation of E2F.

3) P53 – as a tumour 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.

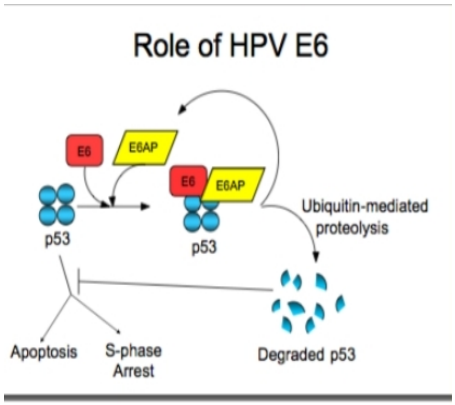
Viruses and tumour suppressor genes

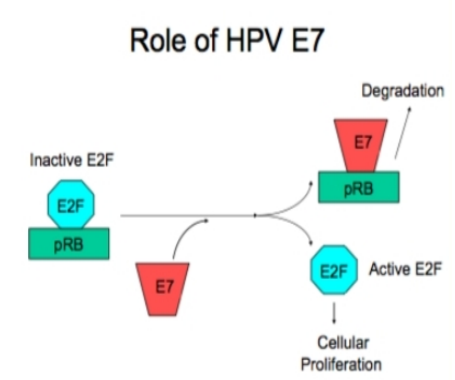
Human papillomavirus and cervical cancer

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 tumour suppressor any more (it is considered mutated). This leads to more activation of cell cycle and less apoptosis.

E7: it binds to RB, 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).

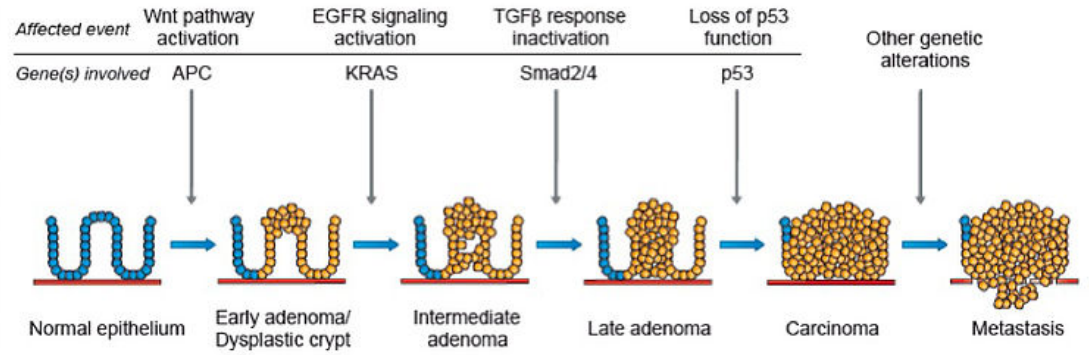




At the end, it is important to understand that cancer is multistep process that results – despite the sequence of mutations appearance – in formation of heterogeneous group of malignant cells that are equipped with weapons of immortality and high proliferative capacity.

The multistep genetic model for the formation of colorectal cancer

a- Inactivation of TSGs and the activation of oncogenes leading to dysfunctional pathways.
b- Accumulation of mutations in a sequential manner, with mutations of some genes preceding that of others.
c- Mutation in WNT pathway in the epithelial cells of intestine, that causes over activation of beta-catenin. That leads to formation of dysplastic population (early adenoma).
d- Activation of EGFR (tyrosine kinase receptor), leads to the activation of RAS pathway (kRAS), which results in intermediate adenoma.
e- Inactivation of TGF-beta pathway, leads to activation of Smad2/4.
f- Loss of p53 function (tumour suppressor gene), leads to carcinoma.
g- Other mutations and alterations are involved.



⇨ Molecular diagnostics is used to find the specific treatment for each cancer patient depending on the mutations that they have.
⇨ Resistance for cancer drugs can develop, due to continuous accumulation of mutations in the tumour cells.