Chapter 18- Oncogenes, tumor suppressors & Cancer

- Previously we have talked about cancer which is an uncontrolled cell proliferation and we have discussed about the definition of benign , malignant, metastasis (organized process in which cells move from primary location to secondary location) , and angiogenesis (it is the ability of a cancer cell to make a new blood vessels to get nutrients and blood supply .
- Also we have talked about carcinogens :-
  A. Chemicals : any thing that react with DNA and lead to mutation .
  B. Radiation : energy hits DNA and breaks it.
  C. Viruses
- Most cancer patient have sporadic cancers not familial (Hereditary) .
- Accumulation of mutation (we need (4-7) mutation for full transformation to occur) happens in:

proto-oncogenes (up regulation causes accelerated proliferation)

TSG → (for tumor to happen you need to deactivate 2 gene)

- Bishop & Varmus are scientists that connected between retroviruses and oncogenes .
- Many of our oncogenes are carried in retroviruses, it enters the cell → integrate into DNA, so it passes on when the cell divide .
- There are 2 theories about viruses oncogenes :
  1. Millions of years ago, **viruses has the oncogens and they have passed it to us** .
  2. when the virus get out of the cell **it take the oncogen from our DNA with it** . (mostly)
  - When the viruses take the oncogene it acquires a survival advantage , by making it divide more faster thus it spread more
  -when a virus with an oncogene enters a cell, it will make it divide faster, so it will transcript the virus more.
  -Invasive(malignant) vs. noninvasive(benign)

Contact inhibition in vitro :

Non-cancerous cells form → mono layer growth.
Cancerous cells form→ multilayer growth.
.

*Chemical and physical DNA damage :-

#chemical :-

_ any chemical reacts with DNA is mutagenic ,it could be carcinogen .(it can affect the integrity of DNA molecule)

_ Ex. : 1. **Benzopyren** that it is found in cigarettes , when it inter the cell it attaches to its bases and causes point mutation that could lead to cancer if it was found in important region of DNA .

2. **Dimethylnitrozamine** :-

_ found in food preservative and fish

_it is a generous methyl donor (gives methyl group to the bases of the DNA mostly Guanine), it donate one methyl group to Guanine base where it become methylated Guanine , then in the <u>next round of replication</u> the methylated Guanine could be missed with adenosine(the polymerase will put T , and there will be a missense mutation or SNP. If it had happened in a non-coding region nothing will happen,but if it in an oncogene or tumor suppressor gene, it will cause transformation)

If this mutation was in coding region Ex. : in oncogens or TSG that will lead to transformation .

#physical carcinogens :-

_Radiation → ɣ rays has strong energy that reaches the bone and all the tissue of the body .

_UV → low energy wave length, which penetrate our body to skin cell and effect DNA of skin cells by causing thymine dimmers

- Mostly flexible

---

*Gain of function in proto-oncogens:-

- the increase in function could be due to :

a. <u>overexpression of gene</u> (increase of RNA copies to increase protein)

b. <u>sustains of activity</u> (of production).

c. <u>production at the wrong time</u> .

1) **Radiation or chemicals :** lead to mutation if it was in important areas of DNA, this will lead to problem .

- Proto-oncogenes could be mutated in the **promoter region** or the **coding region** .

A. **Promoter :** our Proto-oncogenes are made with <u>suboptimal activity</u> in the promoter and coding region, which means that they have weak promoter, or the coding region have SNP(single nucleotide polymorphism) to make protein with weak activity in order for a low division .

Ex. A promoter in GC BOX region , we change the sequences by changing some C base to A, to make the promoter less active and weaker, by that its ability to attract transcriptional factors will be less .

And when we change the A back to C by mutation, the promoter became stronger → more active gene (gain of function) .
Another example : A promoter in TATA BOX region , we change the sequences by changing some A base to C.

The strength or weakness of promoter is due to it sequence .

B. **In the coding region** : if the oncogene is an enzyme with active site (suboptimal)
The sequences will be a bit different in the gene level leading to a little change in the active site, to make its activity less, thus it will not cause increase division of the cell .

If a mutation occur in the area of the active site making it 100% active(optimal) → increase the activity of the enzyme .
Continuous activation of the enzyme ?
Happens by destroying the site of the enzyme which it uses it to inhebit its activity → Ex. In phosphorelation site when we add phosphate the enzyme will stop working , so if there was a mutation in place where the phosphate is added the enzyme will be always on .

2) **Gene amplification :** Her2/Neu , in breast cancer it is a weak gene with weak promoter at chromosome 17 in an inactive transcriptional region .

That is why it is always at low production , so when it is amplified for Ex. : from 2 weak gens to 4000 weak genes there effect will be stronger .. (مثل لما بنحط ضوئيين ضعاف بتكون القاعه مش كتير منوره , بس لما بنحط 50 ضوء ضعيف راح تكون القاعه منورة اكثر)

3) Translocation (gene rearrangement)
-by removing the proto-oncogene from an inactive area to an active one in another chromosome
- by removing the proto-oncogene from weak promoter and inserting it in a place where there is stronger promoter
-by fusing the proto-oncogene to another gene and making new protein(hybrid protein) more active than the previous one (Fusin gene)
Ex. : on chromosome 8 we have c-myc gene where it is transcriptional inactive , if a translocation happen and c-myc gene is moved to chromosome 14 in b-cell lymphocyte (it contain the immunoglobulin gene) c-myc will be activated with the immunoglobulin gene by **promoter proximity effect** : if a gene with a weak promoter enhance region is inserted next to a gene with strong promoter enhance region it will get activated .

Almost all lymphomas has translocation at chromosome 14 : Burkitt's lymphoma (8.14) , follicular lymphoma (t 14;18)
B-cells has immunoglobulin region at chromosome 14, and it is the most active place in its chromosomes.
not all translocations lead to cancer. Translocation to a locus with oncogene in it can cause cancer.
T 9;22(Chronic myeloid leukemia; ABL – go to BCR and attach to it making a new protein which is more active).

4) **Viruses :** integration in DNA occur by retroviruses **only** .(the doctor said that also some adenoviruses can)
-by inserting strong promoter next to the proto-oncogene
-by inserting the virus own oncogene: (viral myc –V-myc) it must be as our oncogene or with very very little difference .
-virus may make **<u>insertion mutagenesis</u>** if it inserts in the middle of a tumor suppressor gene.(so we loose the breaks).

---

*loss of function in antitumor genes :-

- is not enough to have mutation in proto-oncogene , there has to be a mutation in TSG (cell cycle regulators) as well .

Tumor suppressor genes =Anti tumor genes.

1) Repair enzyme : if cell fail to repair the damage (mismatch), or to stops at check points of cell cycle if there was a damage the cell activates apoptosis .

-Repair enzyme mechanism : Ex. : Mismatch repair gene (MMRs,found in HNCPP), BRCA1 and BRCA2 found in familial breast cancer .

Normally familial cancers happen in tumor suppressors. When an embryo inherit an oncogene, it will be aggressive and the embryo will die early)

-Most cancer with familial origin are breast and colon cancer

Why only these cells are affected ?? because the mutated TSG is only expressed in these cells.

-10% of colon and breast cancer are familial , that means the patient is affected in early age (20-30 years) , because they are born with one of the TSG copy mutated , and when the other copy get mutated (90% chance it will get mutated) that will lead to cancer .

-So people with relatives having breast cancer usually have prophylactic treatment by having mastectomy .

1. Why familial cancer having mutation in TSG and not oncogene ? because if there is mutation in the oncogene it will be aggressive and the cancer will happen at the embryonic stage and the patient will not survive long enough to pass the mutation
2. Why BRCA1& BRCA2 only happens in overy and breast ? Because these tissues are the only one that depends on these genes and uses them.

2)Tumor suppressors/cell cycle inhibitors: Proteins that work in cell cycle and at check points EX:P53

3)Genes that stimulate apoptosis could be considered TSG. And genes that prevent apoptosis are considered oncogenes.

- **Oncogenes**: their job is to control the division of the cell not to cause cancer.
- Most of our cells do not divide most of the time, only if it had a signal.

Ex. Skin cells divide slowly, but when there is a cut the cells will divide faster then usual. How? The cut will drive platelets that will release GF called platelets derived growth factors (PDGF is secreted by all cells of the body, But first was discovered in platelets that's why it is called PDGF) which will interact with PDGF receptor leading to activation of signal transduction proteins (proteins that transfer signals from cytosol to nucleus)making the cell divide by cell cycle proteins.

How do we stimulate cell cycle proteins? By activating its genes through transcriptional factors.

Growth factor →Receptor -→ signal transduction → nucleus (activation of TF) → production of cell cycle proteins(regulators of cell cycle) → division of the cell

Every step → proto-oncogene → if it is mutated→ oncogenes
-if any of these steps get mutated, this will lead to independent of the cell to regulate process which will lead to cancer. (Ex: over expression or tumor inactivation)

- each step has a regulator of its own (TSG) which inactivate the step.

<u>1-Growth Factor and Growth Factor receptors</u> : PDGF and PDGFr, EGF and EGFr (include Her2\Nu)

Mutations could happen in this step by :

-increases in GF quantity. -increase in receptor number.

- mutation in the receptor leads to continuously active receptor without binding to the GF → always active.

Ex: mutation made it independent upstream, and it continues to bind to the target protein , giving continuous signal downstream
myc → transcription factor →(t8;14) in burkitts lymphoma → it work on its own(more active)
PDGF/ PGDF-R was first discovered in platelets, but it is present in other cells and stimulate its division.

2-signal transduction proteins : Ras, Raf …..
-they transmit signal from cell surface to the nucleus .

- Ras : is an important oncogene because it is found in almost all solid tumors (lung,breast,colon)
  it's a G-protein
  ras is activated when it take GTP.
  it goes and activate RAF
- Ras/ Raf or MAPK Pathway:

Ras → Raf (MAPKKK) → MEK (MAPKK) → MAPK → activate transcriptional factors.(MYC)

(Ras,Raf,MEK,MAPK) are all activated by phosphorylation, So they are Kinases.

- If one of these steps got mutated, for example by adding phosphate to Raf and never removing it, this will lead to sustained activation.

RAS has a GTPase Domain→ (GTP→GDP +iP) , but to start its action it need activation of this domain by NF-1

If there is a mutation in the NF-1 binding domain , or if there is a mutation in GTPase domain → this will cause continuous activation.

NF-1 = tumor suppressor (negative regulator)

3- Transcriptional Factors :these are responsible for activation of cell cycle proteins.Ex:myc

Which transcription factor is oncogenic : cell cycle activators

If there was a mutation in myc, the cell will become Growth Factor independent, and there is no need for any previous step (GF,GFr ,transduction signal) for it to divide.

The doctor said we need to memorize the following from slid 246 :

- Growth factors : PDGF (NOT sis), EGF
- Growth factor receptors : PDGFr , EGFr(erb-B1--erb-B2(her2\neu)) HERSEPTIN (drug) block the EGF-R/ rhe HER2
- Signal transduction proteins : ras(In most of solid tumors its under the HER-2 ; so some cancers that contain mutated only Her-2/EGF-R can be blocked by a drug but if he also has another mutation in RAS , he wont benefit from the drug) , abl (found in CML “leukemia” and L, it is the 4^{th} step of transduction, it is used in a drug called Gleevec (work on BCR- ABL complex ,, it is invented by Novartis Company) that prevent ATP from entering the molecule and attaching that phosphate to it and that will lead to stopping the activation)
- Transcription factors : myc
- Apoptosis regulators : Bcl-2
- Cell cycle regulators : cyclen D , CDK4

Done by; Dana Mubarak