PATHOLOGY

Medical Committee
The University of Jordan

SHEET

SlIDE

Lecture Number: 22

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- Before we start (revision of the previous Lecture)

-hallmarks of cancer we covered:

1) Limitless replicative potential:

- In normal cells, which lack expression of telomerase, the shortened telomeres generated by cell division eventually inactivate cell cycle checkpoints, leading to senescence and placing a limit on the number of divisions a cell may undergo.
- In cells that have disabled checkpoints, DNA repair pathways are inappropriately activated by shortened telomeres, leading to massive chromosomal instability and mitotic crisis.
- Tumor cells reactivate telomerase, thus staving off mitotic catastrophe and achieving immortality.

2) Development of sustained Angiogenesis:

- Vascularization of tumors is essential for their growth and is controlled by the balance between angiogenic and antiangiogenic factors that are produced by tumor and stromal cells.
- Hypoxia triggers angiogenesis through the actions of HIF1α on the transcription of the pro-angiogenic factor VEGF. Because of its ability to degrade HIF-1α and thereby prevent angiogenesis, VHL acts as a tumor suppressor. Inheritance of germ line mutations of VHL causes VHL syndrome, characterized by the development of a variety of tumors.
- Many other factors regulate angiogenesis; for example, p53 induces synthesis of the angiogenesis inhibitor TSP-1.

3) Ability to invade and metastasize :

- Ability to invade tissues, a hallmark of malignancy, occurs in four steps: loosening of cell–cell contacts, degradation of ECM, attachment to novel ECM components, and migration of tumor cells.
- Cell–cell contacts are lost by the inactivation of E-cadherin through a variety of pathways.
- Basement membrane and interstitial matrix degradation is mediated by proteolytic enzymes secreted by tumor cells and stromal cells, such as MMPs and cathepsins.

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- Proteolytic enzymes also release growth factors sequestered in the ECM and generate chemotactic and angiogenic fragments from cleavage of ECM glycoproteins.
- The metastatic site of many tumors can be predicted by the location of the primary tumor. Many tumors arrest in the first capillary bed they encounter (lung and liver, most commonly).
- Some tumors show organ tropism, probably due to activation of adhesion or chemokine receptors whose ligands are expressed by endothelial cells at the metastatic site.

Those are summaries from the book.

Now, Let's start today's lecture :

This lecture will cover two new hall marks of cancer:

1)Reprogramming Energy Metabolism

2)Evasion of the Immune System

it will discuss Genomic Instability as an Enabler of Malignancy .Also we'll cover the Tumor-Promoting Inflammation as Enabler of Malignancy .and Finally we'll talk about Multistep Carcinogenesis and Cancer Progression.

I added only the important figures from the slides. I highly suggest you check their figures so they'll help you understanding what the doctor is talking about.

New Hallmarks of Cancer

1)Reprogramming Energy Metabolism:

Embryo Cells and Cancer Cells:

So, how cancer cells produce so many other cells?

If we look at the embryo, the normal proliferating cells of the embryo, we'll find that they are also very fast replicating because they are creating a whole new organs .Cancer cells are also rapidly growing cells and they adopt the same mechanisms that the embryo fast proliferating cells use in order to replicate and reproduce themselves. When we are talking about reprogramming energy metabolism, we can think of it as if cancer cells

dedifferentiated into an earlier state of cell life (i.e. embryonic state of cells) in order to be able to adapt the same mechanisms of proliferation as those of the embryonic cells.

Energy metabolism mode of normal cells

What do the normal cells do with glucose?

They start off the glycolysis >> And the end result of glycolysis, which is pyruvate, is then moved to the Krebs cycle or the TCA cycle which produces the majority of your ATP.

Energy metabolism mode of rapidly growing cells and cancer cells

Rapidly replicating cells adopt a mode of energy metabolism called the "Warburg effect" , For its discoverer "Otto Warburg," a German scientist presented in time of Nazism (النازية).he got the Nobel prize in 1931 but not for describing the Warburg effect ,as the book mentions, but for the discovery of the nature and mode of action of the respiratory enzyme. He described Warburg's effect later on in the 1940's.

Now, what's Warburg Effect?

When Cells that have adequate oxygenation and they do not use that oxygen for producing ATP out of glucose i.e. they're notably don't have an active Krebs cycle or TCA cycle . They use glycolysis only .

Because you don't only use alot of energy to replicate the cell, You also want to create new membranes ,new organelles, new proteins,etc. all of these requires carbon backbones , we are a carbon based organisms. but, Where do we get carbon from ? Nutrition, obviously - glucose.

So what the cells do, in order to replicate so fast and produce new organelles ,is changing their metabolism from what differentiated cells do . In fast replicating cells and in cancer cells , pyruvate is actually shunted toward synthetic pathways other than oxidative phosphorylation. So, if we want to use that pyruvate to synthesize molecules, lipids and organelles, we no longer send it through the TCA cycle or the Krebs cycle.

Which means for each molecule of glucose, how many ATP are we producing?

Two, our book mentions two. USMLE references sometimes mention 4 or 5 or 6 or 7. Depends on how you calculate it .If you are talking purely about ATP > it's two. If you are talking about produced NAD, NADPH, etc. depending on which calculation do you use. Each one of those may produce two or four or six, depending on the underlined mechanism.

NOTE: when we are talking about number of ATP the professor doesn't care about how many ATP are produced during glycolysis. But you might want to be aware of that if you want to apply for USMLE. Because some of the questions ask how many ATP is produced for glucose molecule and they are asking about NAD and NADPH.

So, these cells now are producing two ATP molecules out of one glucose molecule instead of 36 molecules, which's not an enough amount. As a result, these cells are going to be very "glucose hungry", which means that they're going to uptake alot of glucose to produce the required amount of ATP and send off the pyruvate needed down the synthetic pathways.

Growth Factors Stimulation and Glucose Metabolism

- As we mentioned in previous lectures, PI3K , AKT and RAS are Proto-oncogenes. pi3K/AKT downstream, RAS and other growth factors can activate the enzyme responsible for the glycolytic part of glucose metabolism because they favor cell growth.
- However, PTEN opposes them. It is a tumor suppressor which means that it doesn't favor cell growth. So it'll inhibit glycolytic pathway. So if you inactivate PTEN you activate glycolytic pathway.
- Tyrosine kinases (oncogenes) can also block the last steps in the pyruvate into the TCA cycle.
- TP53 is also a tumor suppressor.
- So, if you're activating oncogenic pathways and you are inhibiting these tumor suppressor pathways, you are essentially turning off aerobic phosphorylation. you are preventing TCA cycle from functioning and you are sending pyruvate down synthetic pathways .
- So, oncogenes and tumor suppressor also affect the uptake of glucose into the cells.
- There's a sentence in the book says :
  "it is now becoming clear that oncogenes and tumor supressors that favors cell growth, such as TP53 ,PTEN and Akt (an intermediate in RAS signaling) stimulate glucose uptake by affecting glucose transport proteins and favor aerobic glycolysis". Which is WRONG.
  This sentence fits Akt which is a growth factor and it is the opposite for the tumor supressors , TP53 and PTEN which doesn't favor cell growth , doesn't favor aerobic glycolysis and doesn't stimulate glucose uptake.CORRECT IT .
- Remember : for neoplasm to occur ,tumor suppressor genes are inhibited and proto-oncogenes are activated.

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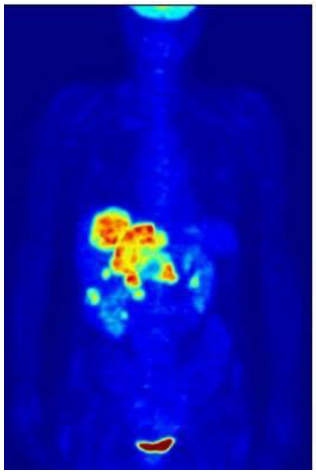
Applications

- Diagnosing Cancers

Because this is common to alot of cancers if not all of cancers:" cancers are very glucose hungry" .if you give glucose that is non-metabolizable, i.e. it looks like glucose but your synthetic pathway cannot break it up, and you add some kinetic techniques to detect it "like PET scanning (Positron Emission Tomography: an imaging test that uses a radioactive substance called a tracer to look for disease in the body.the organs where this radiolabeled substance is accumulating will appear lightened) , in this case you are using radiolable glucose what is going to show up tissues that really uptake alot of glucose(appers lightened),those tissues –glucose hungry tissues- will show where neoplasm metastasized.

Note that you have to ignore the accumulation of glucose in the gallbladder because this metabolites that were going to be excreted to the renals. The brain also uses a lot of glucose so you can ignore that too. Everything else you can't ignore . this figure show a colo-rectal cancer that has metastasized to the liver .



Because we understand how cancer cells Regulate their metabolism differently we'll be able to create new diagnostic techniques to detect where these 'glucose hungry' cells are .

- Treatment of Cancers

In addition, because this is common to so many cancers, there is now an active area of research of how can we shut down this pathway and prevent these cells from producing ATP and the synthetic molecules they require for rapid growth.

So, This is Reprogramming of energy metabolism.
SIMPLE ENOUGH?? Yess
Let's REVISE

✓ Both Embryo Cells and Cancer Cells: 1)rapidly growing 2) undifferentiated

- ✓ normal cells: start off the glycolysis>> pyruvate is then moved to the Krebs cycle to produce the majority of our ATP.
- ✓ rapid growth cells and cancer cells adopt "Warburg effect" ,When they have adequate oxygenation and they do not use that oxygen for producing ATP out of glucose, They use glycolysis only ,then pyruvate is shunted toward synthetic pathways other than oxidative phosphorylation. these cells are going to be very "glucose hungry", they're going to uptake alot of glucose.
- ✓ PI3K,AKT,RAS, Tyrosine Kinases >> Proto-oncogenes >> favor cell growth .
- ✓ PTEN , TP53 >> tumor suppressors >> don't favor cell growth .
- ✓ When you activate oncogenic pathways and inhibit tumor suppressor pathways>>you turn off aerobic phosphorylation and shunt pyruvate to other synthetic pathways.
- ✓ With glucose that is non metabolizable and PET scan you can detect where the tumor had metastasized with ignoring gallbladder and brain.
- ✓ If we found a way to shut down this pathway and prevent these cells from producing ATP and the synthetic molecules they require for rapid growth we may be able to cure cancer.

2)Evading Immune System

There's a whole lecture about this but we are going to give a preview only.
We have mentioned before that if a cell get into the blood stream it needs to avoid being detected by our immune system. Or even when a tumor is in its place (in-situ) you always have inflammatory cells that are circulating in your body and at a certain blood level that if they detect an abnormal microbe or an abnormal cell which is not supposed to be there your immune system should kill it.

Immunocompromised & Immunocompetent

Immunocompetent >> a person whose immune system is able to produce a normal immune response.

Immunocompromised >> a person who has an immunodeficiency ,Like HIV patients. They may have Atypical cancers (cancers when they're still young, or cancers that are very rare).

However, most cancers happening in immuno competent people because there are immunocompetent people a lot more than there are immunocompromised people.

Cancer cells and immune system

Typically, if a cancer cell has an abnormal antigen (either an excess of antigens or as mutated antigen) that is presented on the surface of the cell, using the Major Histocompatibility Complex proteins (MHC), T cells will recognize this abnormal antigen and will kill these cells.

So, the cancer cells produces an excess of antigens that is normal, or an abnormal antigen presented on the surface of the cancer cell, and T cells recognize this as foreign, then Cancer cell killed and problem is solved.

Selective Pressure and Evolution and cancer Antigens

If we put ourselves in the cancer cells' shoes we'll find that immune system is a major selective pressure. "Selective pressure means any reason for organisms with certain phenotypes to have either a survival benefit or disadvantage"-Education Poetal.

Selective pressure leads to evolution by driving natural selection. in case of cancer cells they either adapt or die. Cells that are presented later(survived) have essentially adapted. But how did they adapt? They stopped producing those particular antigens because foreign cells that produce antigens are killed off by the immune system.

Cells that don't produce their antigen survive so this is a survival mechanism.

Mutations in the MHC class I proteins, that present antigens, will not allow antigens to be presented to T cells anymore.

Also, helping cancer cells in the evasion of immune system , the mass of these antigens.a lot of cancers have a very thick glycocalyx , a very thick coating of sugars, on their proteins. Which prevents recognition of the T cells for any antigen that is present.

Some cells actually actively growth inhibit the immune system.TGF-β as we said is an immune suppresser, so if cells produced excess of it , it is going to inhibit T cells.

Cells also can KILL T cells. FasL is the death receptor ligand which reduces apoptosis, if you have abnormal FasL binded to T cells it is going to kill it off.

Also, another mechanism which we have mentioned before in relation to metastasis is "Embolus" ,the outer layer superficial and the inner layer is what survive and evade the immune system.

These are several mechanisms that are used by cancer cells to avoid immune system.

So, This is Evasion of Immune System.
SIMPLE ENOUGH?? Yess
Let's REVISE

- ✓ Immunocompromised patients may have Atypical cancers (cancers when they're still young ,or cancers that are very rare).
- ✓ cancer cells produces an excess of antigens that is normal, or an abnormal antigen presented on the surface of the cancer cell, and T cells recognize Antigens presented by MHC, then Cancer cell is killed .
- ✓ Cancer cell evade immune system by: stopping producing particular antigens, mutations in MHC class I proteins, the very thick glycocalyx of its antigens, inhibit growth of T-cells (excess production of the immune suppresser TGF-β ,killing T cells by abnormal FasL binding to it or by Embolus,the outer layer superficial and the inner layer is what survive and evade the immune system.

Now, let's start with the Genomic Instability as an Enabler of Malignancy.

Genomic Instability as an Enabler of Malignancy

Accumulation of Mutations

How do we accumulate mutations?

We have mentioned two mechanism:
1) P53 mutator phenotype.
2) tolemerase during the cell cycle will start bridge-fusion breakage cycle

DNA Repair Mechanisms

Various things cause damage to DNA. Either removing bases, creating cross links between strands , same strand ,or you single strand break ,or the double strand break ,or during replication they get an error.
Whatever the reason is , if that error is detected there are various mechanisms of repair processes .

We have previously mentioned one repair process, which is, the repair process of last resort , during the bridge fusion breakage cycle >> the non-homologous end joining NHEJ , a type of recombination repair .

Other Mechanisms of DNA repair:

1. Basic excision repair
2. Nucleotide excision repair
3. Mismatch repair
4. Homologous recombination

We will talk about each one of these using examples of inherited cancer syndromes.

First: Mismatch repair

What's mismatch repair?

The parental strands are methylated

You opened them up for replication

You copied them

The whole created new strands are not methylated (not yet anyway)

Remember that: Methylation is heretible , and what we mean with heritable is that the methylation ,in addition to the sequence, is also eventually copied into the new daughter strands .
However, before that happens, if there is an abnormal base pair match, it will be detected by mismatch repair and cut out and then recopying the parental strand and end up with the proper sequence.

There are Multiple proteins in mismatch repair, they're five genes .they're directly related, if one is mutated it'll inhibit the trancription of the other four . (not important as the doctor said)

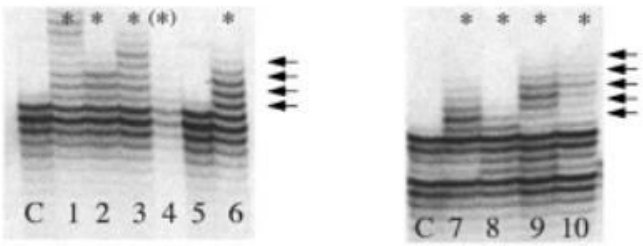
If one of these genes are mutated, you'll get what is called **Hereditary Nonpolyposis Colorectal Cancer Syndrome** .

Hereditary Nonpolyposis Colorectal Cancer Syndrome .

These patients get cancer in the colon but, in contrast to FAP patients(Familial Adimonatous Polyposis),they don't have polyps. Also, typically, these cancers are right

colon predisposed.
Now, if you remember what we said about P53 , is it has a mutator phenotype.it isn't directly responsible for proliferation or inhibiting of antiproliferation pathways or inhibition of apoptosis .It is just there to produce more mutations (genomic instability).
Same as P53, a mutator phenotype can result in TGF-β type2 receptor mutations and BAX mutations in those patients.
So what's the TGF-β pathway?
Inhibition of proliferation. so, if you inhibit an inhibitor or you mutate part of that pathway you induce proliferation .
What's BAX ?
proapoptotic channel that allow cytochrome c to leak out.

Microsatellites
Microsatellites are small (1-6) nucleotide repeats, that could be coding or non-coding, that are unique to each individual.
This's what we use for DNA fingerprinting , which we use to define parents of a child or who killed someone using parts of the killer body that was found at where they found the killed person.
If you look at your cells in general, and you do a DNA fingerprinting, all of your cells should look the same. If you DON'T have DNA mismatch repair, you will get what's called "Microsatellite instability", i.e. either expansion of these microsatellites or deletion of the microsatellites.
So if you run cells from the same individual (cancer cells) and they didn't look the same this is called microsatellite instability. Because mismatch repair genes are responsible for keeping those microsatellite intact as well.



Second: Nucleotide Excision repair
disease caused: Xeroderma Pigmentosum (autosomal recessive)

Xeroderma means dry skin, pigmentosum means pigmented skin.
These patients have very high sensitivity to UV. UV can cross link creating pyramidine bridges, that will result in an intrastrand cross-link that need to be repaired by Nucleotide excision repair pathway. Patients with Xeroderma Pigmentosum have an abnormality in

the genes responsible for nucleotide excision repair. Those patients because they're exposed to sun they get frequent skin cancers.

Third : Homologous recombination repair

Remember you have two alleles for each gene. If you have a complete double strand break in one of the alleles where you can't use the other strand to fix the first strand What do you do?

You go to the other allele and you copy off the other allele and you either end up with a hybrid allele which resemble the original allele or each one is separated .there are various enzymes that are responsible for homologous repair.

It may cause:

a) Ataxia-Talengectasia

ATM protein which activates P53, and when P53 is activated we can fix the whole stranded breaks, is mutated in those patients.

Those patient has cerebral ataxia along with an increased propensity to certain metastasis during the time of cell mutation and cancers.

b) bloom syndrome

Sensitive to ionizing radiation, patients have developmental defects that break unique facial features. They have narrow faces, long faces and very common in Ashkanaji-Jews.

c) Fanconi anemia

sensitive to DNA cross- linking reagents. Some of these are actually used as therapies. Cyclophosphonamide is a DNA cross linking reagent it is used in chemotherapy , it is also a product of mustard gas which is used in chemical warfare.

there's one more pathway that we are **not going to say a word about it .mutations in **BRCA1** and **BRCA2** you have to read from the book and you are going to be asked about it .

Cancers Resulting From Mutations Induced by Regulated Genomic Instability: Lymphoid Neoplasms.

Last mechanism in accumulating genomic instability. remember when we said that the translocations are common in Lymphoid cells (T and Bcells) because they have regulated genomic instability . 84 genes produce 10^16 antibodies.

VDJ recombination (Variable, Diversity and Joining regions recombination), the original

gene found in B cells and T cells because we use it for both antibodies and T cell receptor. You will get variable recombination of these different genes to produce antibodies and receptors.
Because we are specifically making double stranded breaks and joining these regions- the joining may not be accurate as well - there is a potential here for mutations and translocations.

Our book also mentions two proteins: RAG1 and RAG2 , they're responsible for creating these hair pins that bring two distant locations then they're joined together to produce the new antibody or the immune T cell receptor.

As the new antibody or the immune T cell receptor matures, mature B cells or T cells express a specialized enzyme called Activation-Induced Cytosine Deaminase (AID). It removes an amino group from Cytosine turning it into Uracil(which takes the place of Thymine in RNA. So,if you look at it ,it could be mistaken for a Thymine-recognized as Thymine-) .if you change the Cytosine to what looks like the Thymine (it's actually U) ,DNA repair mechanisms will either change that G-C basepair into T-A basepair or it will return back to the G-C basepair and no harm is done. But this is a common mechanism used in activating lymphocytes to produce Somatic hypermutation. i.e.this enzyme discriminately turns all C's to U's and then some of those will be mutated some of them will not . this's really useful in producing antibodies because you produce additional variability in antibodies in addition to the different recombination done by the VDJ. It can also class switch where homologous recombination is used to combine regions and you switch from the IgM to the IgG or sometimes G conversion can occur where recombination from the other allele is used to fix mutation in the first allele and there's no guarantee that the other allele doesn't have its own mutation either.

So, This is Genomic Instability as an Enabler of Malignancy.
SIMPLE ENOUGH?? Yess
Let's REVISE

- ✓ Mechanisms of DNA repair: Basic excision repair,Nucleotide excision repair,Mismatch repair and Homologous recombination.
- ✓ Mismatch repair :
  - When the parental strands are methylated, you copied them but the whole created new strands are not methylated . Methylation is heretible.
  - Causes Hereditary Nonpolyposis Corectal Cancer Syndrome .mutated phenotype causes TGF-βtype2 receptor mutations and BAX mutations.

- Microsatellites are small (1-6) nucleotide repeats, that could be coding or non-coding, that are unique to each individual. used for DNA fingerprinting .all of cells of an individual should look the same. If you dont have a DNA mismatch repair, you will get what's called "Microsatellite instability", either expansion of these microsatellites or deletion of the microsatellites, because damage to the microsatellites is no longer repaired.

✓ Nucleotide Excision repair :
- disease caused: Xeroderma Pigmentosum: UV can cross link creating pyramidine bridge, that will result in intrastrand cross-link , frequent skin cancers.

✓ Homologous recombination repair :
- Diseases:
  - Ataxia-Talengectasia: ATM protein which activates P53, and when P53 is activated we can fix the whole stranded breaks, is mutated in those patients. cerebral ataxia along with an increase metastasis during the time of cell mutation and cancer.
  - bloom syndrome : sensitive to ionizing radiation, patients have developmental defects that break unique facial features(narrow faces, long faces), very common in jews.
  - Fanconi anemia: sensitive to DNA cross- linking agents. Some of these are actually used as therapies. Cyclophosphonamide is a DNA cross linking reagent it is used in chemotherapy it is also a product of mustard gas which is used in chemical warfare.

✓ Cancers Resulting From Mutations Induced by Regulated Genomic Instability : Lymphoid Neoplasms.
- RAG1 and RAG2 break distant regions then join them together
- VDJ recombination (Variable, Diversity and Joining regions recombination).
- Additional variability is achieved by AID enzyme , activate hypermutations , used in Ig class switching

Now Let's start with Tumor-Promoting Inflammation as Enabler of Malignancy .

Tumor-Promoting Inflammation as Enabler of Malignancy.

Chronic Inflammation and Carcinogenesis

When you have an injury, inflammation will start ,you bring neutrophils and macrophages along with other WBCs. we can induce angiogenesis and proliferation ,and inhibit apoptosis for repair.

Now imagine, this inflammation goes on and on and on. what it is going to do? It'll increase proliferation , inhibit apotosis ,affect differentiation and induce angiogenesis .All of these are really good for cancer and bad for you. That's why chronic inflammation patients who have (Barrett esophagitis, ulcerative colitis, H. pylori gastritis, HIV, Hepatitis B and C and chronic Pancreatitis) chronic inflammatory condition **ongoing** have an increased risk to have various cancers especially cancers of where that inflammation goes on .

Now, cancer itself whether through stromal or parenchymal effects, because we know it is usually a combination of both will also induce inflammatory cells to come in.

Now, if you remember from the previous lecture what happens when you degrade ECM? You increase chemotactic ; they'll not only direct the direction of cancer cells and normally they will bring WBC. Now, the white blood cells including neutrophils produce **cyclooxygenase** and **reactive oxygen species** which can damage DNA ,proteins , and cause mutations .

Growth Factors and chronic inflammation and carcinogenesis

As we mentioned before, growth factors induce cells to survive, proliferate, migrate and differentiate. And inhibit apoptosis .All of these are good for repair bad for you in the long run. Also, as we mentioned before, reactive oxygen species degrade proteins and cause mutations, Another complicated problem .If you break down protein that is a tumor supressor protein –and this is not genetic change ,it is a change in protein level- you'll increase carcinogenesis because you inhibited an inhibitor which is an activation. One of the tumor supressor genes that can be affected by chronic inflammation is the **PTEN** tumor supressor gene .

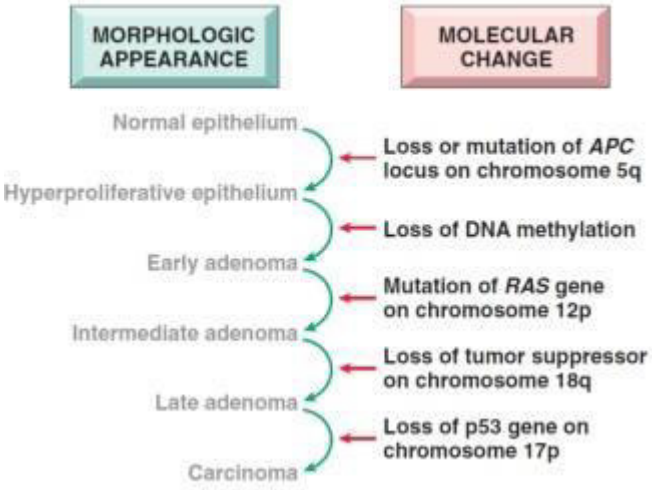
So, This is Tumor-Promoting Inflammation as Enabler of Malignancy .
SIMPLE ENOUGH? Yess
Let's REVISE

- ✓ Patients who have (Barrett esophagitis,ulcerative colitis, H pylory gastritis , HIV , Hepatitis B and C and chronic Pancreatitis)chronic inflammatory condition on going have an increased risk to have various cancers especially cancers of where that inflammation goes on .
- ✓ White blood cells including neutrophils produce cyclooxegenase and reactive oxygen species which can damage DNA ,proteins , and cause mutations .If it break down protein that is a tumor supressor protein it'll increase carcinogenesis. One of the tumor supressor genes that can be affected by chronic inflammation is PTEN .

Carcinogenesis is a multistep process

Clinical Example

The Adenoma Carcinoma pathway for Colon Cancer.



At the beginning loss of APC will occur. Destruction of APC will free β-catenin making it active, it'll cause an increase in the expression of Myc. gene which is responsible for activating genes responsible for producing cyclins that help CDK to phosphorylate Rb and allow continuing of DNA replication and cell cycle. Also, increase the expression of E-cadherin regulators (TWIST / SLUG / SNAIL) and will cause lack of adhesion between adjacent cells.

Then, Loss of DNA methylation will occur. Hypomethylation will cause an increased expression of various genes that is normally suppressed and genomic instability .

After that, there will be a Mutation in RAS gene. RAS gene is an oncogene, when mutated it will be constantly active causing proliferation...etc.

There's another tumor suppressor that the book is vague about , called Deleted Colorectal Carcinoma (DCC) .

Then, there will be a loss of a tumor suppressor. if you deleted a tumor suppressor what is going to happen? Inhibition of inhibitor is activation .

Finally, loss of P53 .which means you won't be able to fix DNA damage and mutations are going to accumulate. You are not going to be able to send cells down apoptotic pathway and you are going to induce bridge-fusion break cycle.

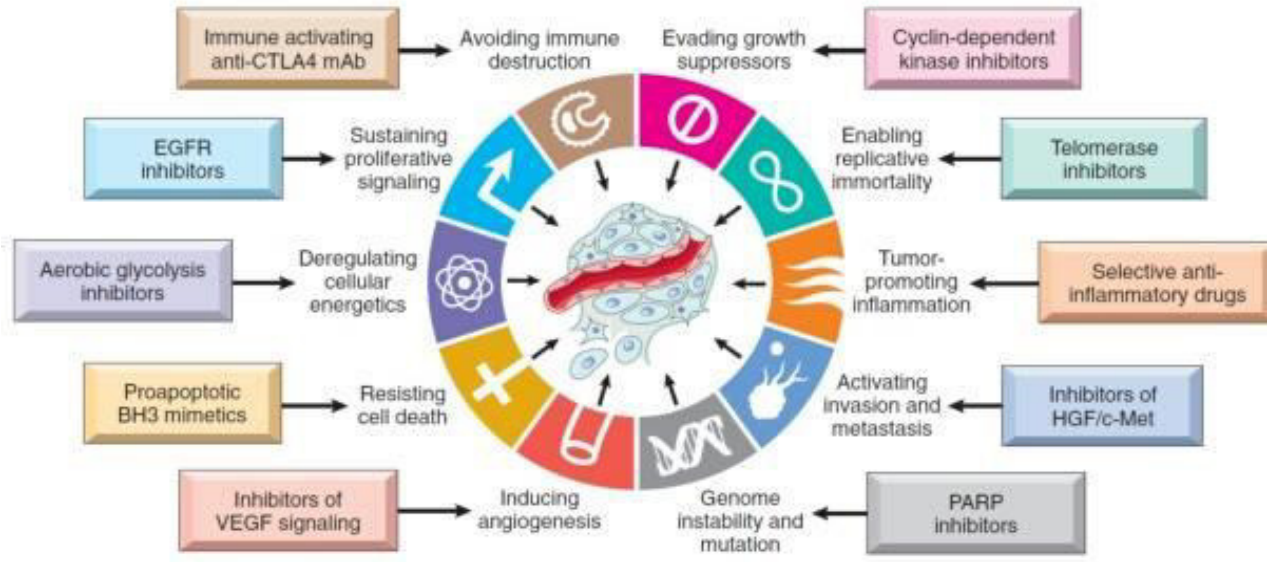
So, This is carcinogenesis is a multistep process.
SIMPLE ENOUGH? Yess
Let's REVISE

✓ In The Adenoma Carcinoma pathway for Colon Cancer:

- loss of APC>> β-catenin is active >> increase in the expression of Myc. Gene>> activating genes responsible for producing cyclins that help CDK to phosphorylate Rb and allow continuing of DNA replication and cell cycle.
- Loss of DNA methylation >> Hypomethylation>> increase expression of various genes that is normally suppressed and genomic instability.
- Mutation in RAS gene.
- Loss of a tumor suppressor like (DCC).
- Loss of P53 >>won't be able to fix DNA damage and mutations are going to accumulate. you are not going to be able to send cells down apoptopic pathway and you are going to induce bridge fusion break cycle.

Hallmarks concluded

Knowing all of these hallmarks help us in treating, especially with new treatments . We have to know what's going on.



- inhibit CDK , inhibit the cell cycle.
- inhibit the telomerase >>you'll drive the cell to senescence because telomeres get shorter

- Anti-inflammatory drugs >> remember when we said that COX-2 is over expressed in certain cancers so you have to inhibit it.
- Inhibitors of the HGF or the HGF receptor (c-Met) >>HGF as we mentioned when it is over expressed it'll cause migration (e.g. glioblastomas).
- PARP inhibitors>> they are not mentioned in our book but they included them here : Parp is a sensor of single stranded breaks, it is important to repair single stranded breaks. And if you allow the cell to replicate with those breaks you are going to produce a double stranded breaks which are usually repaired by homologous recombination. One of the pathways responsible of homologous recombination the BRC-A, part in the book that we have to read about . So cells that have abnormal BRC-A and you inhibit PARP you are going to induce double stranded breaks which can't be repaired and you are killing those cells,specifically cells that have the abnormal BRC-A.
- Inhibitors of the VEGF signaling >> inhibit cell angiogenesis and a lot of pathways that are responsible for carcinogenesis .
- BH3 mimetics >> which are sensor proteins , they're proapoptotic .so if you mimic them you are activating apoptosis.
- Aerobic glycolysis inhibitors (recently discussed).
- EGFR inhibitors >> this is one of the receptors of tyrosine kinases that we mentioned that could be over expressed or mutated where it is independent of the ligand, if you inhibited that tyrosine kinase receptor that induces growth - you inhibit growth .
- CTLA4 >>induces inhibition of T cells ,it is responsible for T cells becoming accustomed to a particular antigen that they see over and over and over again.. so some cancer cells inappropriately produce CTLA4 which inhibits T-cells preventing them from being able to recognize the antigens on the cancer cells .. so by giving patients ANTI-CTLA4 monoclonal antibodies (mAb) , we are destroying the produced CTLA4 and thus preventing its inhibition of the T-cells , allowing the T-cells to once again recognize the cancer cells and active immunity will destroy the cancerous cells. This is currently being used in melanoma treatment.

ولاثنين من أصدقائي أقول على مدخل الليل:"
إن كان لا بُدَّ من حُلُم ، فليكُنْ
مثلنا ... وبسيطاً
كأنْ : نَتَعَشَّى معاً بعد يَوْمَيْنِ
نحن الثلاثة ،
مُحْتَفلين بصدق النبوءة في حُلْمنا
وبأنَّ الثلاثة لم ينقصوا واحداً

منذ يومين ،
فلنحتفل بسوناتا القمرْ
وتسامُح موتٍ رآنا معاً سعداء
"! فغضَّ النظرْ

Thanks go to My sister ,Majd and My friend ,Reem For helping me in this sheet

Good Luck

Raya Abdalhameed Al-Majali