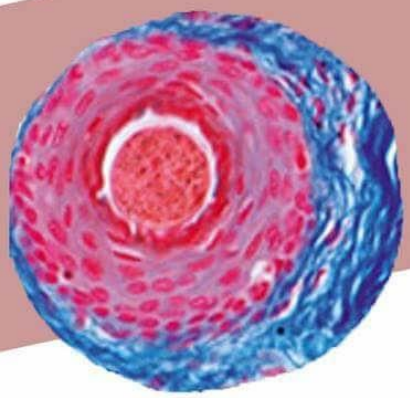
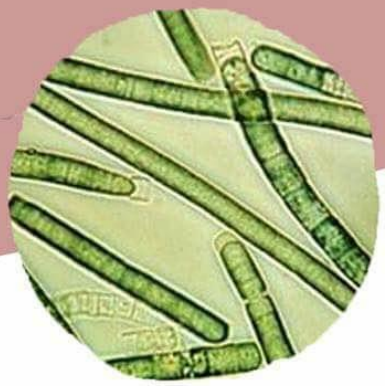
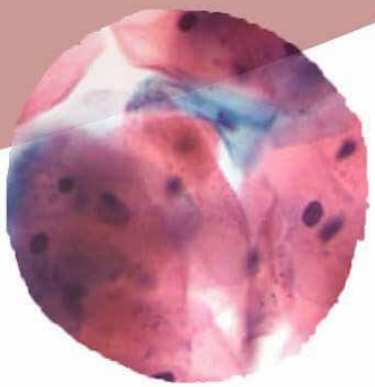
INTRODUCTION TO PATHOLOGY

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Sheet# 22

SHEET 22 PATHOLOGY (Dr Mazin - record 22)

ETIOLOGY OF CANCER
(Why cancer occurs ?!)

>>Etiology of cancers is divided into **3 major categories : Radiation** (nuclear reactions, bombs, earthquakes, power plants, UV etc…) , **Microbial** (microorganisms) and wide variety of **Chemical causes** of cancers.

1. CHEMICAL :-

***Q :**Do you know what is Chimney Sweeps ? >>Somebody who sweep chimneys (المدخنة) .

When wood was the major fuel for heating homes, there is going to be accumulation of soot and other combustible materials in the chimney. If you left it alone, it will cause risks and the chimney will get blocked and kills everybody in the house because of accumulation of carbon monoxide. This guy (Chimney Sweeps) will go around the chimneys offering their services to sweep the chimneys (get out all of the soot).

The picture in the slide 28 is a guy who covered with soot from top to bottom. They are not black people. This guy never bath. They were constantly covered by soot from top to bottom.

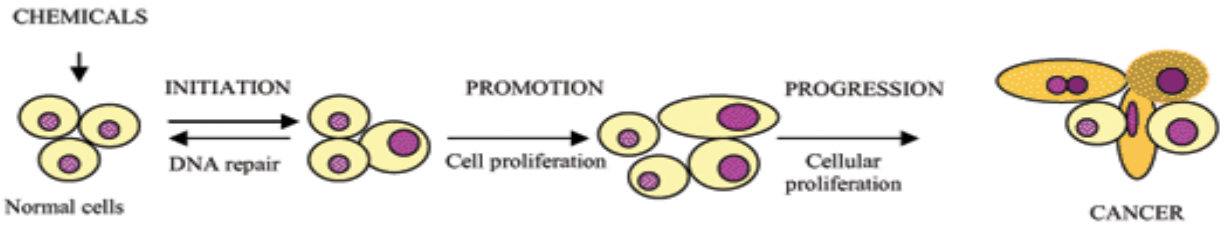
One particular surgeon at that time discovered that this chimney sweeps had higher risk of getting scrotal cancers than anybody else in general population. His deduction at that time because of their job and he correctly attributed this in chimney sweeps at that time to chronic exposure to soot . There are a lot of chemical carcinogens that comes out of burnt wood with soot . So, they are mandated to bath because they get bath once a week or once a month. As they were mandated, the risks and incidences of scrotal cancers drop dramatically.

Now, chemical carcinogens are divided into **2 major categories**: **Direct** (do not need metabolism) , and **Indirect** acting carcinogens (those that need metabolism). Examples of chemical that can directly acting on cells are : mercury and those that can indirectly acting on cells (damage it) such as CCL4. The systems that can metabolize both of them are cytochrome P450 : they can be carcinogenic or metabolized to become carcinogenic. Polymorphism of P450 can have different effects on each individual. Somebody who have an over active of cytochrome P450 systems, when they are exposed to indirect carcinogen, they will be worse because they are going to metabolize the chemical carcinogens more and producing the carcinogenic materials.

For direct acting carcinogenic materials, they steal electrons. The example of these direct acting chemical carcinogens are **Alkylating agents**. As an example, in certain types of lymphomas, when you give the alkylating agents to treat only to induce leukemia. The worst part is some of these alkylating agents that are not normally used in lymphoma (they usually used in treating cancers, chronic inflammatory disease, etc..) and unfortunately leukemia in patients who never have cancer before. These chemical drugs are the last option after going through all another drugs in treating patients and they are only used in certain cases because the risk is so high. It doesn't mean majority of patients will end up

with leukimia but there are cases like these (about 1% of population). But, when you treat patients, you are not only look at the chance something happening, you will look at the severity as well.

Now , chemical carcinogens typically are initiators. They start prolong , but they do not continue the prolong . So, there is a whole initiation progression pathway for most cancers where the first cell is transformed to another (the entry of carcinogenic materials) and there is a continuation of that initiation event. So, you need proliferation and so on. Typically these are going to be controlled by other things inside your body like hormones or different types of chemicals that are not carcinogenic materials by itself but they can induce collateral effect.



>>For example, COX2 (cyclooxygenase 2) is over expressed (in rectal cancers). Over expression of COX2 itself is not carcinogenic and does not induce cancers. They has to be first in transforming event and then COX2 will induce progression of that cancers (cannot induce initiation). (*_*)

2. <u>RADIATION</u> :-

Don't forget it is not only UV light, nuclear power plants and nuclear events (Hiroshima Nagasaki, etc..) depleted uranium in neighbour countries but also medical staffs exposed into radiation in the hospital as well. When there are massive dose of radiation, the patch on the clothes will turn from green into black.

So, people who work in radiation department (eg : doing x-ray) will get exposed. Although they stand behind the walls, or just wearing safety aprons but they still can get chance of exposing to radiation. It is an occupational hazards.

Again , a cardiologist will do catheterization. They go through the catheter up into the heart and inject a dye and see how that dye distribute especially in the coronary arteries. They observe the dye by x-rays!!

In any cases , radiation damages typically induces either chromosomal breakages , translocations or , less frequently, point mutations during proliferation . The most common effects are chromosomal breakages. Now, after Hiroshima and Nagasaki, there was a lot of leukemias and lymphomas but some tumor incidence didn't change. The thing that change was the aggressiveness of these tumors. The death from the tumors increase but the incidence did not change . The cells that are mostly affected are typically rapidly replicated cells , and this is the base of radiotherapy . Radiotherapy try to target the most rapidly replicated cells in that region . Long term >> low dosage can decrease the risk of

most types , but short term may cause more side effects to the nearby cells even to die or harmful damage to the cells.

As we know, UV radiation can induce damages and the pathway needed to treat the damage is by nucleotide incision repair. If you have an inherited abnormality in these pathway, you will end up with xeroderma pigmentosum. That's why UV radiation can cause skin cancers. Two major types of skin cancers that we are worry about are melanoma skin cancers and non-melanoma skin cancers. Depending on the type of UV radiation, you will get one or the another. If you are exposed to sun, like sun tanning and so on and don't put sunblock, you are at a higher risk to get melanomas skin cancer. Meanwhile, people who are exposed to sun always (lifelong) but not intense, they are mostly going to get squamous cell carcinoma. Those people are people who works under sun such as builders.

The risk of getting for lighter skin people is higher than darker skin because no melanin **(Fair skin)**. No melanin means no protection against the UV radiation. The **geographical location** also plays a role in getting skin cancers. For example, if you are a lighter skin person (fair skin) living in northern Sweden (where they get 2 hours of sunlight in a year), you will reduce the risk of getting skin cancers ,but if you are in the middle of Africa then the risk to get skin cancer increase. The **personal habit** also determine the risk of getting skin cancers (eg : cover up, wearing sunblocks daily, etc..)

3. MICROBIAL (Viruses & Bacteria) :-

>> We will start with **viruses.**

>> Viruses are divided into **2 categories** : DNA & RNA.

- RNA viruses (HTLV-1) :

HTLV-1 is a retrovirus. A retrovirus is a virus that has RNA genome and for replication process, it has to reverse transcription itself from RNA to DNA and then to recreate the RNA genome back. The protein is called reverse transcriptase.
HTLV-1 is very similar to HIV in targeting specific type of cells (t-cell / t-helper cells / CD4 positive cells). And for HTLV-1 which target those cells, 3-5% of patients that receive this infection will end up with t-cell leukemia. It is a very small percentage but it is a worrying event to end up with leukemia from a viral infection. These virus, just like HIV is transmitted through sexual but unlike HIV, it also can be transmitted through blood and breastfeeding. The other thing about HTLV-1 is they have long latency (20 – 50yrs). You get infection today but 20 years later you will get leukemia. So, this means HTLV-1 is a latent virus and need other events to induce leukemia. They cannot cause leukemia alone make it doesn't happen immediately . It is a multistep process !

The virus doesn't have oncogene . HTLV-1 produces a certain protein called **TAX**. This protein inhibits the function of P53 so, no apoptosis, no repair of mutations , no senescence and accumulation of mutations occur. TAX also activates certain cyclins and inhibits the cyclin dependent kinase inhibitor specifically P16. So, proliferation occurs, no apoptosis, no senescence and accumulation of mutations. It's quite a few of hallmarks

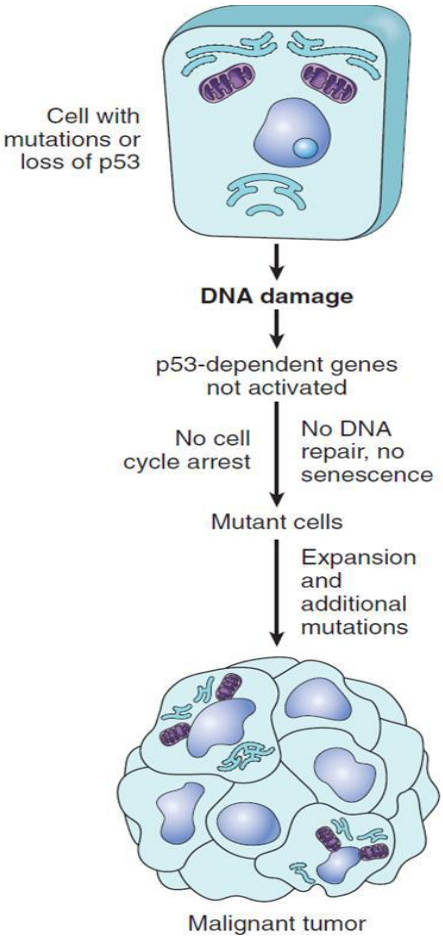
right there. As it turns out, if you take TAX alone, it is necessary and sufficient to induce cancer, but it takes particular time to do.

<u>*NOTE :</u> Not only this virus induces TAX, HTLV-1 also induces T-cells to produce **IL 2 , IL 15** and their receptors, which then further stimulates macrophages and macrophages are stimulated by some other T-cells that produce other cytokines and colony-stimulating factors that then result in proliferation of T-cells and then you get polyclonal T-cells proliferation rather than starting with monoclonal T-cells and end up with heterogeneous groups of cells (extraordinary).

<u>* **Remember :-** **TAX** is a viral encoded protein but it's not an oncogene.(So Be Careful)</u>

>> Why that happens ?

The virus is not going to transform one cell but it's going to transform the whole cells. So, if it infect one gene of CD4 T-cell, it's going to affect the whole bunch of the genes CD4 T-cells and some of the CD4 T-cells will start proliferating and producing polyclonal proliferation because multiple viruses infecting many cells . Eventually, because P53 is not active and we have stimulate that proliferation, there is going to be a mutation that turns out from T-cell proliferation to T-cell leukemia. From that polyclonal T-cell proliferating cells, they are going to emerge into a malignant clonal, a monoclonal growth of T-cells that become a T-cell leukemia.



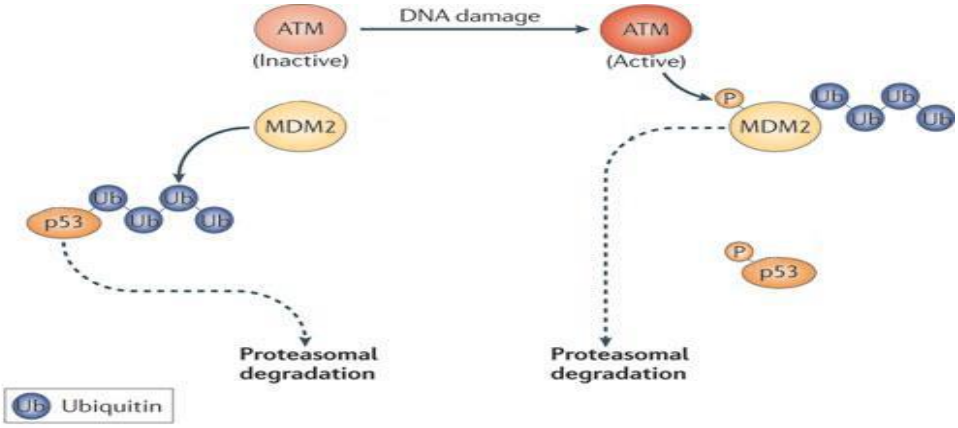
HTLV-1 are in endemic region. If you end up in Japan or in Caribbean, then you need to be worried about HTLV-1 (regardless the gender). When you do receive the patients with a T-cell leukemia, you should check the patients for HTLV-1 to make sure they know that they are affected by the virus and not spread to somebody else.

- **HPV (DNA Virus) :**

Human Papilloma Virus (HPV) . There are several subtypes of HPV. There are subtypes 1, 2, 4 and 7 which produce <u>warts</u> (benign squamous papillomas). They don't cause malignant tumors. They are induced by the infection with agents. Subtypes 6 and 11 produce <u>warts on genital areas</u>. They are benign and not malignant too. However, subtypes 16 and 18 can induce squamous papillomas on the cervix and the anogenital region thus become <u>squamous cell carcinoma</u> (SCC) . These subtypes (16 & 18) produce a particular different form of two viral proteins : E6 and E7.

E6 and E7 are produced by all of these subtypes (all HPV) but for these two subtypes in particular (16 & 18) , it is more active. So, E7 inhibits , directly bind to Rb (retinoblastoma) and allow the E2F to be released, enter the cell cycle and initiation. E7 also inhibits the cyclin dependent kinase inhibitors, P21 and P27. Now, as it turns out, the reason why E7 from subtypes 16 and 18 can do this while as the other one cannot is the E7 protein from these subtypes has a considerably a higher affinity to Rb than another subtypes that cannot induce cancer. Protein is different and it binds differently to Rb.

E6 on the other hand mediates enhances P53 proteosomal degradation. Again, the subtypes 16 and 18 have an E6 protein that is considerably more avidly binding to P53 than another subtypes. So, no P53, no apoptosis, no senescence, no checking on DNA damage and inducing a mutated phenotype.



Now, as it turns out, when you get HPV infection, either it can remain in circular form, proliferate and you will end up with mild infections or the genome opens up. The problem is that when the genome opens up from its circular genome into linear, it integrates into the autocellular DNA. Notice that the integration site that we are worry about is the site that opens up on the viral genome. They are regulators on E6 and E7. When the viral genome is circular, E6 and E7 are not produced at a very high rate. When the regulators are broken and the DNA is inserted, E6 and E7 are now massively over produced. They are over expressed.

E6 and E7 are not sufficient to produce cancers. So, there has to be another causes/effect that produce cancers typically a Ras mutation. So, this bring us to the whole point of necessity and sufficiency. First one we said is not an oncogene but it is necessary and sufficient. You take the TAX alone and put it into the cells, so you can transform the cells. If you put E6 and E7 you will make them immortal but they will not become malignant unless you induce cellular mutation.

>>Necessity and Sufficiency

Oxygen is necessary to live. You cannot live without oxygen but oxygen alone is not sufficient for you to survive. You need water, food and shelter to live. Also pouring freezing water on your friend is sufficient to wake him up but it is not necessary . That is the difference between necessity and sufficiency .

- **EBV (a DNA virus) :**

The common names disease for EBV virus are : Herpesvirus and Mono . This frequently occur in western society in college students because they have many connections in their daily life . EBV is the first virus linked to human tumor specifically Burrkit lymphoma. Translocation occur from MYC(a gene) of one chromosome to the next can cause Burrkit lymphoma . So, turns out EBV can also induce Burrkit lymphoma.

EBV not only can induce T-cell lymphoma but they also can induce T and natural killer cell (NK cell) lymphoma and some carcinoma & sarcoma. EBV can be seen in two places; Africa and South East Asia (SEA) but despite being dominant in these two places, they are not produce the same type of tumors. In Africa, it induces Burrkit lymphoma. In South East Asia it induces Nasopharyngeal Carcinoma. Two very different diseases.

>> Why that T-cells that affect the Africa but epithelial cells that affect the SEA?

Africa is an endemic also for malaria. Malaria can affect your immune system thereby allowing EBV to replicate uncontrollably and induce Burrkit lymphoma. Now, there are two ways for the virus to infect the cells, either through CD21 or in epithelial cells through integrins.

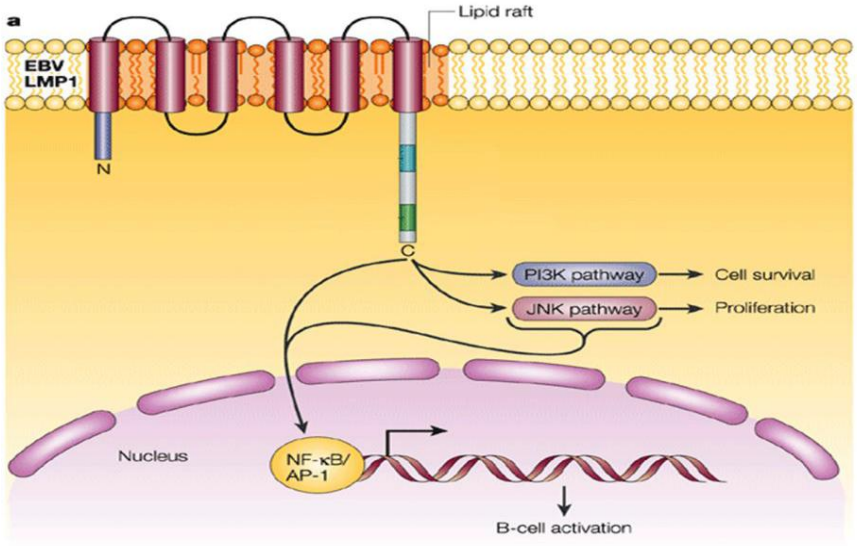
In either cases, you will end up with viral DNA gene being injected into the nucleus, where it becomes episomes, a circular piece of DNA attached to the host chromosomes. Now, one of two things can happen, either the virus goes into latent. Viral latency is to be differentiated from disease latency. **HIV** has a long latent period but that doesn't mean the virus is latent but the disease is latent.

Virus is actually still active. There is a constant fight going on between the HIV virus and the immune systems and eventually when the virus goes out, the disease becomes active, turn into AIDS patients.

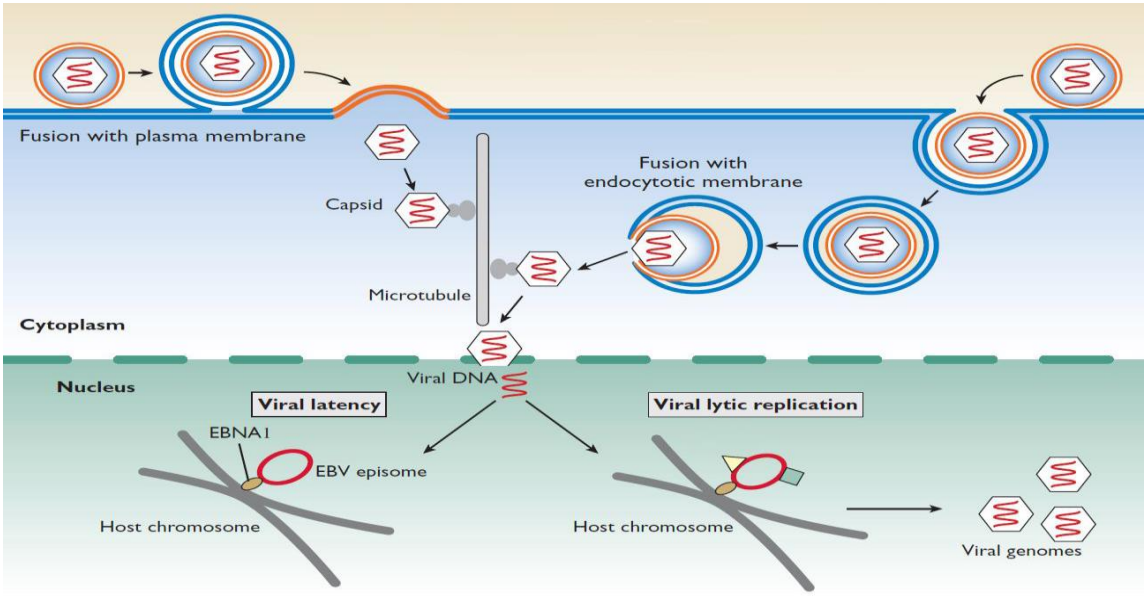
In this case, the virus is truly latent. There is no lytic reaction and replication of the virus. If the virus does activate its certain genes, it ends up killing the cells. The reason we worry about is, it actually does have an oncogene called LMP1. LMP1 is also very

antigenic. If LMP1 is expressed on the T cells or epithelial cells, it will be defected by your immune systems (because it is a surface proteins) and those cells will be killed off. Once you look into Burrkit lymphoma's patients, its sporadic areas, who have an EBV infection, you will not find LMP1 expression but you will find MYC translocation. However, if you look into Burrkit lymphoma in endemic region such as Africa, you will frequently find LMP1 being transcribed and a MYC translocation.

So, LMP1 mimics B cell receptors called CD40, a family of TNF and this particular receptor rather than inducing apoptosis, it actually inhibits the apoptosis by activating Bcl2. It induces the cells survival and induce progression through the JAK/STAT pathway. Another protein is called EBNA2 (which is not a viral oncogene), it does help in proliferation and increase production of cyclin D and proto-oncogene called SRC .



In the primary infection, if there is an LMP1, these cells are going to be detected and killed off and there is going to be no consequences. This patients typically will have infectious polynucleosis and have all type of symptoms and go through this disease ande there will be no consequences . The only time where they are going to be a long term consequences is if the virus escaped the immune systems, does not express LMP1 and later on, it can become reactive. The main thing for the Burrkit lymphoma and MYC translocation to occur is escaped from immunity.



<<NO ESCAPE FROM IMMUNITY, NO CANCER.>>

Immunosuppressed patients behave in different way. There is no immune selection pressure on the cells that are infected with EBV. This means, the cells that are infected by EBV are not going to be killed off and end up with a lympho-proliferative disease that is not quite cancer makes translocation in hazard location and proliferation that because LMP1 alone is not enough to induce the cancer . You can easily treat this patient by transplantation.

There is another protein that this virus produced, which is vIL10. vIL10 is a major inhibitory interleukin . It turns off inflammation. As it turns out, EBV produce a very similar molecule to human IL10. When the virus at some point, way back in the past, infected the cells and integrated its DNA into that cells, rather than taking its own DNA when leaving , it produces its vIL10 . Not particular virus became superior to other viruses , and when vIL10 was pirated from the host genome , this viral cytokine can prevent macrophages and monocytes from activating T cells and killing virally infected cells .

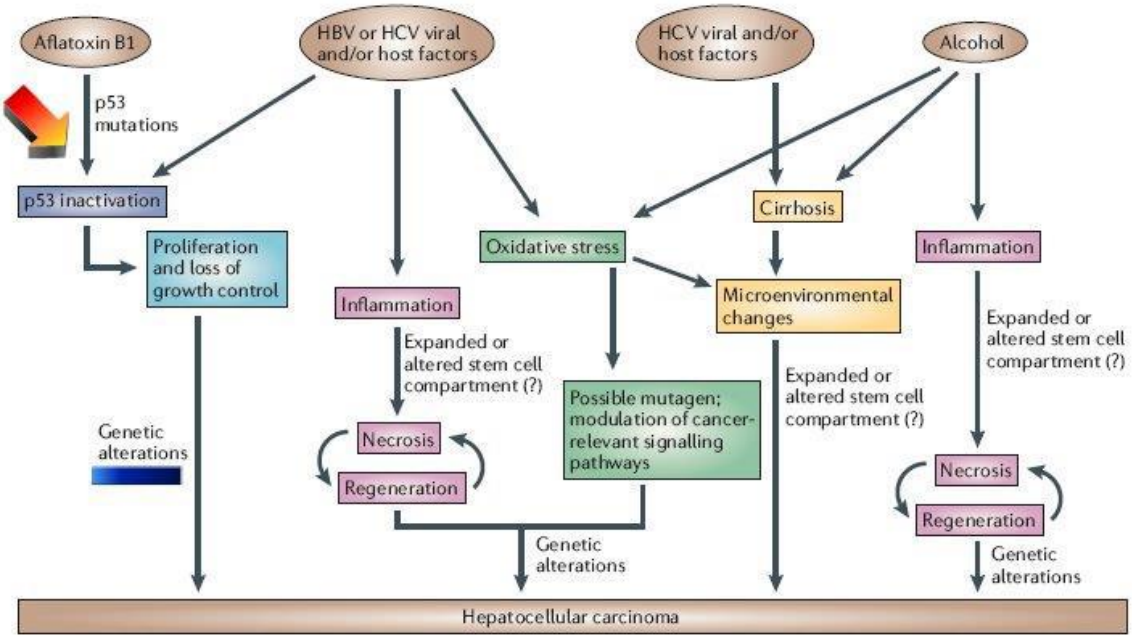
- Hepatitis B and hepatitis C virus :

The major mechanism on how the hepatitis B and C virus can induce liver cancer is by inducing chronic inflammation (hepatocellular carcinoma). Inflammation has lots of species , cytokines, growth factors, anginogenesis and so on. Cells are going to proliferate and will end up with one cell will turn into a cancer cell. Hereby we end up with hepatocellular carcinoma. These doesn't mean that Hep B and C do not have any particular role. There are certain proteins like HBx in Hep B and Hep C core proteins that can turn off and turn

on certain pro growth pathway . They are not oncogenes in another cells and integration of the viral genome is not result in transformation.

In Epidemiology, there is one region of the world that rather than have breast cancer as the most common cancers, they have hepatocellular carcinoma as the most common cancers. Aflatoxin is a carcinogenic toxin that produce by fungi and can effect nuts and maize and it turns out that particular region does not store them really well and end up with toxin production. That's why they end up with hepatocellular carcinoma.

*If you notice, alcohol have some effects on the liver which is why cirrhosis also is a risk factor for hepatocelular carcinoma.



- **Helicobactor pylori :**

H.pylori is a bacteria that associated with gastric ulcers. It can induce a chronic inflammatory condition which is called gastritis. Chronic inflammation, cytokines, growth factors, ECM degradation products and ROS can end up leading to gastro adenocarcinomas through gastritis, metaplasia and dysplasia pathway. It also induce another type of cancer called MALT lymphomas. It looks very much like lymph mucosal cells but it is at the wrong place.

As is turns out, certain polymorphisms in IL 1 ,TNF-alpha receptors and the ligands create spouses this lymphoid population to become lymphomas especially when H-Pylori present . Again H-pylori in not present in the organism , its oncogene CagA (Cytotoxin-Associated A gene) is injected into the gastric epithelial cells where it has a variety of effects .

>> NEVER GIVE UP . JUST WAKE UP EARLY , STAND FROM YOUR BED AND BE SURE YOU WILL DO IT <<

/ Enjoy :)

~ nabilamunierah ~