Sheet 21

Carcinogens Agents

this sheet will answer this Question→ WHAT CAUSE CANCER ?
Before we start answering this Q we must know the difference between **Causation and correlation ,** Causation indicates that one event is the result of the occurrence of the other event, while correlation does not imply that.it does not indicate that the change in one variable is the cause of the change in the values of the other variable.
when we study cancer we need to determine if that certain carcinogens agent is causative or correlated to a certain cancer.

Carcingous agents are from different families :

- ✓ Chemicals
- ✓ Physical agents (radiations)
- ✓ Bacterial agents
- ✓ Viruses

Chemical carcinogens agents

example: soot (السخام) , soot have (polycyclic hydrocarbons) that result from burning of fossil fuels.
In the past chimney sweep(منظف المداخن ، روميو) used to have massive risk to develop scrotal skin cancer.
Note : polycyclic hydrocarbons are also present in cigarettes along with another 200 type of carcinogens (it is the DEATH STICK)

There are two major groups of chemicals: (exactly as in the cell injury lectures) [Direct , Indirect]

- ✓ <u>Direct acting chemicals</u>.
  Considerably these are weak; they induce DNA cross linking (as we are talking for the most part about mutations).
  The main example that you need to know about in direct acting chemicals is: **alkylating agents**

figure1 (group of chemotherapeutic agents>>DRUGS), these chemotherapeutic agents while you are treating a certain cancer, can induce –sadly leukemia among other cancers.

So you only give a patient one kind of chemotherapy for them to turn around and come back with different types of cancers. What is even worse is that some of these alkylating agents can be used in patients that are non cancer patients, patients who have rheumatoid arthritis or Wegner granulomatosis (autoimmune diseases where they are refractory for all the stranded treatments). That means: if you prescribe alkylating agents to these patients you MUST Prescribe them carefully

you must ask ur-self (how old is this patient? am I really increasing their risk of dying because of leukemia? or they are old enough that it shouldn't be a problem?)

Note :Patients should be fully informed / aware of the risk of any drug they receive,

(in this case patients should be informed there is increased risk of leukemia from using these agents, you must tell him that u can turn around from a non cancer patient to a cancer patient from the type of treatment you give them.)

The effect of alkylated agents is crosslinking of the DNA.(circled) notice that the cross-linking could be :

A: Interstrand (between 2 stands)

B:Intrastrand (at the same strand)

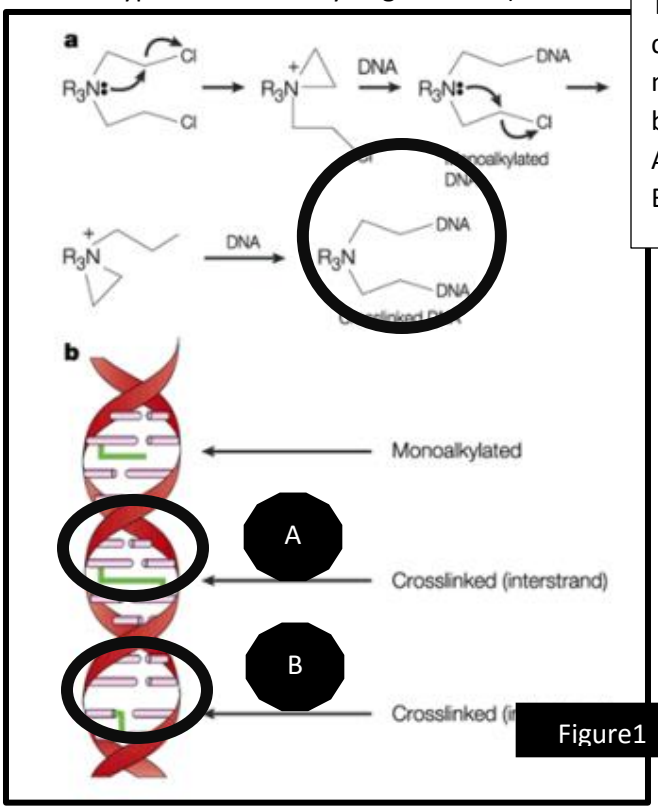


Figure1

- ✓ Indirect i.e. chemicals that require metabolism by p450 system to become toxic (in this case, carcinogenic).

So, if you have a mutation in one gene of polymorphism in your p450 system which increases your p450 activity, you are in a higher risk of getting cancer from these carcinogenic agents.

Note :Most of chemical carcinogens cause random mutation, but SOME have characteristic mutation ,example: Polycyclic hydrocarbons (like in cigarette) are the main example here, from burning of fossil fuels and breathe, lead to lung cancer and other.

another example is Aflatoxin, natural agent; produce by molds " Aspergillus" : grow on improperly stored grains, seeds & nuts.. when you ingested > Aflatoxin can create very characteristic TP53 mutation -give abnormal p53 phenotype- develop to hepatocellular carcinoma... if you remember the map in sheet 1 which was all red except some regions in green, where they ingest a lots of nuts and have TP53 mutation & hepatocellular carcinoma..

Note: TP53 is the gene, P53 is the protein

Initiators Vs promoters figure2

Chemicals could either be initiators or promoters , to understand this you must recall the difference between : necessary and sufficient factors (الضروري و الكافي)
necessary : is important to the process , the process can not happen without it. But it does not indicate that if only this factor is present solely then the process will occur.
sufficient : the process can happen even if this factor was solely there.

- ✓ Initiators :
  they start transformation, the carcinogenic process.. can NOT produce cancer without promoters... they are typically Carcinogens (so initiators are necessary but not sufficient)

- ✓ Promoters : can NOT induce cancer, but they enhance the carcinogenic process....

  Note: promoters are not necessarily to be carcinogenic they might be physiologic (growth factors, COX2 -see in colon cancer-, inflammation, hormones.. All can be promoters)
  promoters are typically things that induce the cell's proliferation..
  they simply provide the best environment for cancer to occur like endometrial hyperplasia it is the right fertile ground for cancer, because you already induced proliferation, and there's a higher chance of accumulating mutations..because you are going in the cell cycle again and again.
  So estrogen –here- can be considered as promoter. But it is not an initiator, it is not going to cause transformation, it is going to induce proliferation so it is a promoter. It is not going to give you a mutation.

NOTE : we said that cancer is rare, so for cancer to occur with these "physiological promoters" You have to be exposed to these promoters frequently or continuously. These promoters move the cancer along; induce proliferation to propagate this initial transformation and to allow further mutations to accumulate.

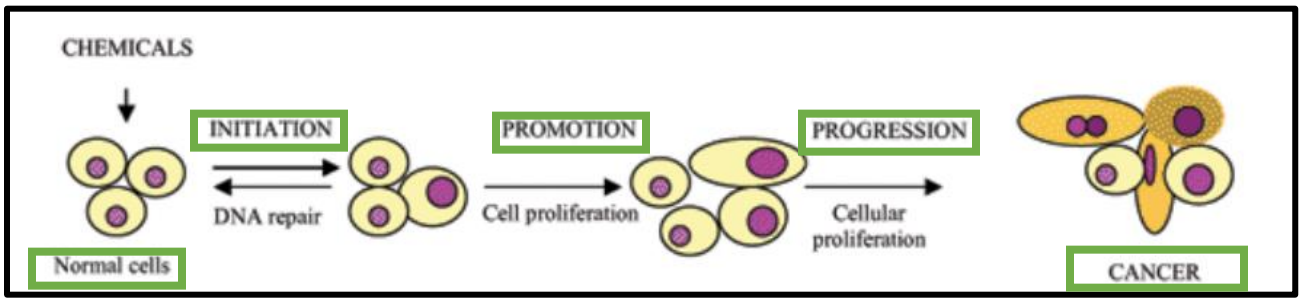


Figure 2: cancer needs initiators and promotors to occur..
after exposed to chemicals the transformation to cancerous cells begin.. the transformation process needs Initiators , promoters and progression to be accomplished
Notice how the first step is reversible

Physical carcinogens (Radiation):

nuclear radiations are carcinogens , here are some evidences:

- ✓ after nuclear pomp in Hiroshima and Nagasaki myeloid leukemia jumped massively in Japan. So
- ✓ After Toronto (power plant in the prior Soviet Union): various cancers and childhood leukemia jumped massively.
- ✓ In Neighboring Iraq where they had dumped / used lots of depleted uranium, it is called depleted uranium but it is not truly depleted, and there were several studies that have proven a link between areas that were comparted with depleted uranium and a massive increase in childhood developmental abnormalities, and childhood cancers

This radiation will cause DNA damage, chromosomal breaks, translocations and -less frequently- point mutations.

X-rays
when you send a patient to get an X-ray or CT scan, you need to realize that this radiation can induce DNA damage. That is why when people work in the Xray department they wear special bagets (they are usually green) and when they turn black they no longer can work in the department for that year, they have exceeded their yearly quota of radiation.

UV radiation: causes pyrimidine dimers -skin cancer
Recall From last sheet !
Which repair pathway do we use to get rid of pyrimidine dimers?
- Nucleotide excision repair pathway. Why not mismatch repair pathway?
- Because we are talking about UV radiation in cells that are not necessarily in replication, So they could use the mismatch repair pathway if they -the cells- were replicating and UV radiation causes problem (if it is a replicating cell).
** If you have lost both alleles of a gene responsible for the nucleotide excision repair pathway, what disease do you have?
- Xeroderma pigmentosa (dry pigmented skin) + being at a higher risk of skin cancer.
So that means: if you are exposed to UV radiation your nucleotide excision repair pathway will take care of the mutations that UV radiation induces. However, as you get older, your nucleotide excision repair pathway will become less efficient, if you are exposed to a lot of sun, your pathway is not going to be able to keep up with all the damage that occurs. So, if you are exposed to a lot of UV radiation, over a period of life time, you are in a considerably higher risk of getting non-melanoma skin cancer (squamous cell carcinoma and basal cell carcinoma). We were talking about accumulated exposure /life time exposure to UV (the major group: daily workers).

But people who get intense intermittent -sever episodic- exposure to UV radiation (sun bathers/ whether in the beach or going to a tanning salon), for some reason that we do not fully understand, get melanoma skin cancer rather than nonmelanoma skin cancer (basal cell carcinoma or squamous cell carcinoma)
The risks of skin cancers are:
1. Fair skin: the lighter you are the higher the risk. The darker you are, the lower the risk. Why? Melanin is what protects your cells from UV radiation. So if you have melanin you are more protected. You don't have melanin: less protected, so, make sure you wear a sun screen if you are out in the sun for a long period of time.

2. Geography: If you are of Netherlandic origin and you moved to Africa, you are in considerably higher risk. If you are of British descent and moved to Australia, you are in considerably higher risk. But if you are a native of Australia, or you are a native of Africa, you are more likely to be dark skinned. Throughout evolution people who lived in these regions accumulated more and more melanin over generations, or so goes the theory.

So, fair skin PLUS geography. Inuit (native of Alaska/ They do not see much sun)

3. Personal habits: if you have the habit of going to a tanning salon, if you have the habit of staying in sun without wearing proper sun protection, if you have the habit of going sun bathing in a beach: you are in a higher risk of getting cancer.

Microbial carcinogens : (1-4 viral , #5 bacterial)

1

Retrovirus HTLV1

Retrovirus is a RNA virus with reverse transcriptase activity (it can reverse its RNA genome to DNA) this virus is endemic in Japan & Caribbean
[HTLV1] virus is similar to HIV -also a retrovirus- in its **tropism** i.e. it attacks the same cells that HIV attacks: CD4 positive T cells (T helper cells).
- Transmitted by sex/ blood/ breast feeding

- Only 3-5% of infected population end in T cell leukemia or lymphoma after a long latent period (20-50 yrs)after multi step process ..

CD4+ cells and HTLV1 virus

last time we talked about the cytotoxic T lymphocytes " CD8 positive T cells".
- CD4 positive cells are the traffic police; they produce cytokines, interleukins and tell other cells what to do. However, in the absence of policeà chaos, your immune system is compromised.
That is why in HIV when your CD4 drops below certain count you are immunocompromised, you now acquired immunodeficiency syndrome.
In case of HTLV1, this virus attacks the CD4 positive cells and induces their proliferation.
Note: HTLV-1 does not have a viral oncogene -part of the viral gene mimics an pro-oncogene that human already have. The problem with that would affect cell-cell interaction, affect the cell cycle or affect transcription.

What TAX Do?

Inhibit tumor suppressors (P53 & cyclin dependent kinase inhibitors (p16/CDKN2A))
Induce oncogenes (cyclins +cyclin dependent kinase)

HTLV1 and Tax protein figure3
- How does HTLV1 induce cancer?
-by Tax protein :
There is a protein called Tax, it inhibits p53 function, inhibit apoptosis & induce a mutator phenotype. Tax also stimulates cyclins and cyclin dependent kinases , while inhibiting cyclin dependent kinase inhibitors (p16/CDKN2A).
Collectively what does that mean?
these changes will Induce autocrine and paracrine effects on T cells (indicated in figure4)
autocrine: : T cells start producing cytokines/interleukins and their receptors "autocrine signaling loops", so IL-2 and IL-15 in addition to their receptors.
Paracrine : it produces GM-CSF which induces other cells -macrophages- to produce T cell mitogens, growth factors, stimulating angiogenesis... further pushing these cells to proliferate
what hallmarks are we talking about?
Growth, Evasion of death and Genomic Instability

-Therefore TAX protein is necessary and sufficient for transformation
explanation:
Necessary = if you don't have TAX, you will NOT produce cancer
Sufficient = in absence of all other prote[illegible]n for transformation

Figure3

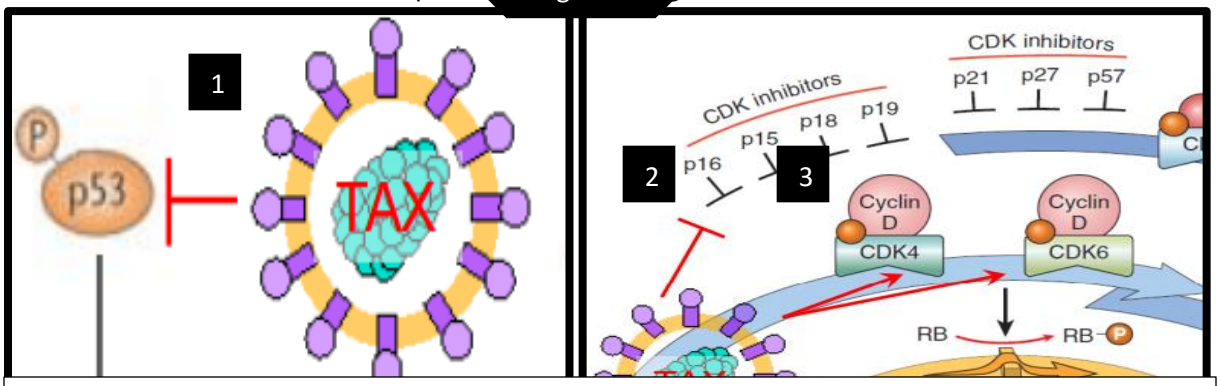


Figure3: Tax protein induce cancer by
1: inhibiting P53 protein
2: inhibit Cyclin dependent kinase inhibitors
3: stimulate cyclin D activity>>proliferation is induced

the tumors –here- are Polyclonal in Origin: figure4
One more thing that you need to know about viruses induced tumors, like HTLV1:
They start up- rather than the other cancers we talked about- as polyclonal, why?

Because the virus infect more than one cell (different cells that have different mutations in the beginning)
as you progress, one cell get an advantage over the other cells because it accumulated a new mutation t[illegible]3 or induces cyclin D or over expresses MYC,, etc. Th[illegible]
know about.

Figure4

1

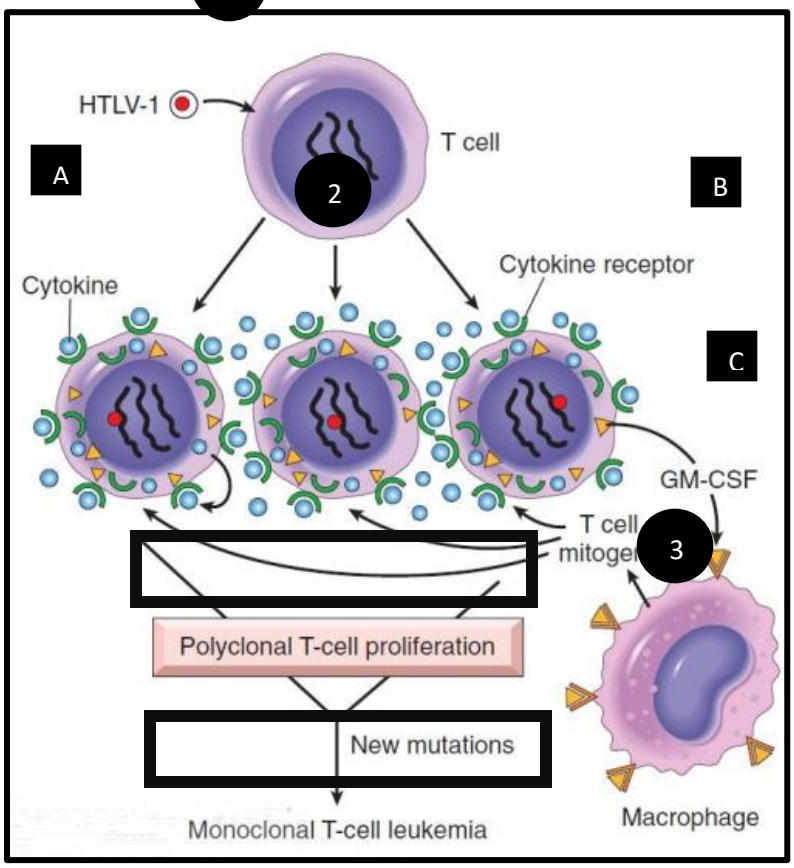


Figure4: cancer induced by HTLV-1 is initially polyclonal then it turns into monoclonal by natural selection. (squares)

Autocrine Vs Paracrine effects :
1 : HTLV-1 invade a T cell >>this induce mutations
2 : Autocrine effect among T cells characterized by production of cytokines (A) and cytokines receptors (B)
3: paracrine effect of Tcells characterized by production of GM-CSF (c) which stimulate macrophages >>this support the overall carcinogenic process

2

HPV (Human Papilloma virus)

There are subtypes for HPV:

- ✓ 1, 2, 4, and 7 will produce warts (benign squamous papilloma) with very very low risk of tran
- ✓ sformation
- ✓ 6, 11 will produce genital warts.
- ✓ The most important types are type 16 and 18 as they will produce squamous cell carcinoma of the cervix and the anogenital region with very high carcinogenic potential.
  These are the subtypes that are included in the vaccine against HPV to prevent squamous cell carcinoma of the cervix.

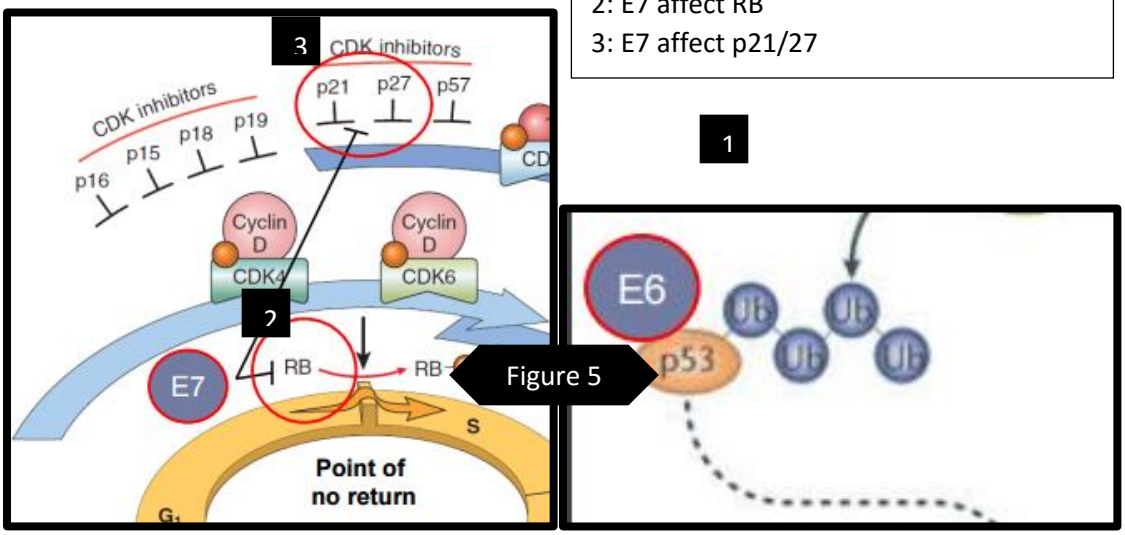
What exactly happen ?
it's all about E6 and E7 protiens figure5
E7 inhibits RB function, and allows E2F to be released and that will increase cyclin E for the cell to

continue through the S check point, also inhibit the non-specific CDKIs like p21 p27, allowing cell to proliferate.

E6 mediate/ stimulate the ubiquitin degradation of p53, again, E6 from 16 and 18 subtypes has a higher affinity for p53 compared to other HPV subtypes.

[so E6>>P53, E7>>RB +p21/27]

Figure 5: in HPV
1: E6 affect P53
2: E7 affect RB
3: E7 affect p21/27



here's a Q that must arise :

All subtypes of HPV produce E6 and E7, so why 16 and 18 are carcinogenic while the others are not?

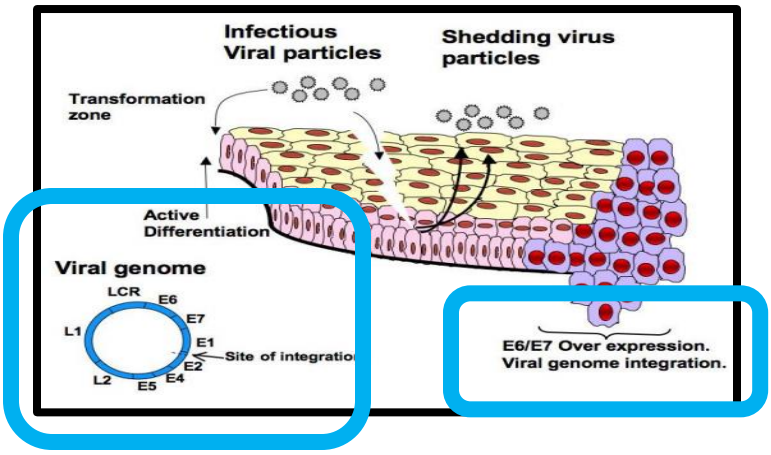
- E6 and E7 from the 16 and 18 subtypes are more active.
- So, for E7: the E7 that comes from strains 16 and 18 has a higher affinity for RB than the strains that do not induce cancers. -

Note: E6 and E7 are generally not expressed initially at the viral infection; sometimes the virus genome remains separate, stays as a circular piece of the DNA that is replicated along with your DNA.

when will they be expressed ?

Figure6

duced/ over expressed when viral genome integr



read this paragraph from the Book

Of interest , in benign warts the HPV genome do not integrate into the host genome while in cancer the HPV genome is randomly integrated into the host genome. Integration interrupts the viral DNA resulting in overexpression of the oncoproteins E6, E7 ..

furthermore cells in which the viral genome has integrated show significantly more genomic instability .

What hallmarks of cancer HPV do induce :
- E6 and E7 leads to the hallmarks of cancer that we have just mentioned: Genomic instability, loss of sensitivity to growth inhibitory signals from CDKIs, you induce transition of the cell cycle because you have inactivated RB. so by this These cells are now transformed.
Note :This is not inevitable, only a small percentage of patients who have HPV end up with cancer, it is also a process that takes a long time and it is a multi step process and E6 and E7 in their own are not enough/ insufficient to induce cancer (there are other steps are required to induce cancer). Usually you'll see RAS mutation associated with that tumor.
so again and again , cancer is rare –relatively-

Back to Necessity and Sufficiency

- ✓ Tax is necessary and sufficient, if you do not have Tax, you can't induce T cell leukemia and lymphoma. If you have Tax alone and nothing else, it is sufficient to induce that cancer.
- ✓ E6 and E7 are not sufficient in their own

* If u didn't understand yet what do we mean by these terms check figure7

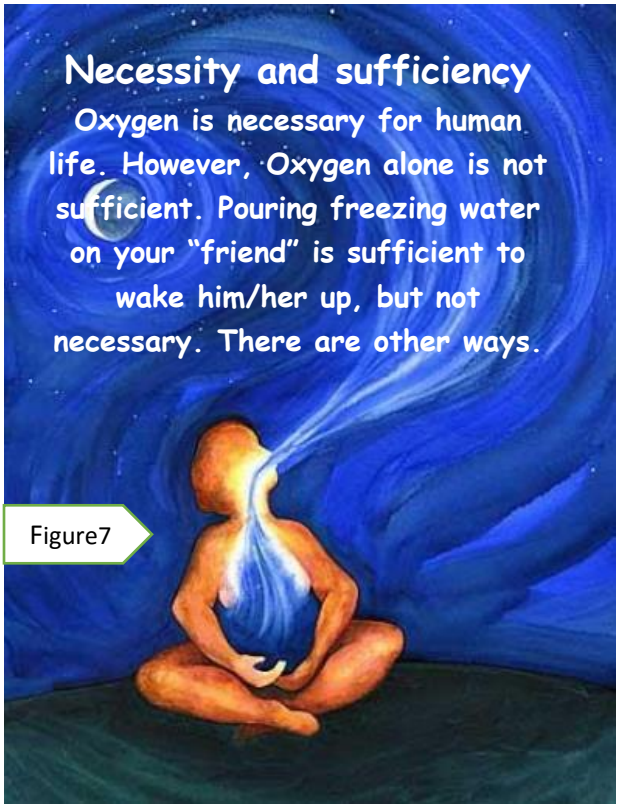


Figure7

EBV is the first virus that was associated with cancer (Burkitt lymphoma)

3 EBV (Epstein Bar Virus)

It causes infectious mononucleosis (the kissing disease) which transmitted with saliva.
if someone got the virus there are 2 scenarios :

- ✓ In **immunocompetent person :** the infected cells start replicating >> the immune system identifies those cells>>kill them off >>end up disease.

- ✓ **immunocompromised patients** : the immune system can not kill those cells and a wide variety of sarcomas, carcinomas, T, B and natural killers cells lymphomas.
  Note : In the immunocompetent it can induce cancer but rarely.

Generally:

What happen in EBV-induced-Burkitt lymphomas ?
commonly a translocation >> t(14;18) translocation >> We are putting MYC gene in the front of the very active promoter of the immunoglobulin's heavy chains >> this lead to **MYC over expression**.

Note : experimentally You can in low frequently find EBV genome in some of these Burkitt lymphoma patients, but MYC is what is driving the cancer.

Now let' s dig in : (referred to the book the sheet is missy)
let's state some facts first , explanations are followed:

- ✓ Burkitt lymphoma is endemic in certain parts of Africa and is sporadic elsewhere.
- ✓ In endemic places , if u test any patient >> most likely u are going to find EBV genome.
- ✓ In regions of the world in which Burkitt lymphoma is endemic >>you will also find that malaria is endemic .. along with other infections that impair immune competence and allow B cell proliferation.
- ✓ In immunological normal persons the patients either remain asymptomatic or experience a self-limiting episodes of infectious mononucleosis.
- ✓ Evasion of the immune system seems to be key step in EBV related oncogenesis.

Explanations and Transformations :

the primary transformation in Burkitt lymphoma (induced by EBV) is related to B cells proliferation and **LMP1** gene.
what happens ?
B cell excessive proliferation !
How? Figure8

1) EBV uses CD21 receptor to attach to and infect B cell (CD21= a complement system receptor)
2) LMP1 (latent membrane protein 1) is an oncogene that get activated in response to this "attachment" >> this activation lead to B cell proliferation.

How does LMP1 induce b cell proliferation ? figure9

- ✓ By activating signaling pathways such as NF-KB and JAK/STAT
- ✓ These pathway mimic B cell activation by B cell surface molecule CD40 (a TNF receptor)

Overall activating these pathways will :

- ✓ Induce b cell proliferation
- ✓ Inhibit apoptosis. How ?
  LMP1 prevent apoptosis by activating BCL2 gene .
  بهذا يكون الفايروس أظهر ذكاءً فذّاً ؛ إذ عمل على تكثير الخلايا التي يمكنه مهاجمتها قبل أي شيء.
- ✓ More and more proliferation by **EBNA2** EBV-encoded protein
  what this protein does that it :
  [1] activate cyclin D
  [2] activate src family of proto-oncogenes (similar to RAS)
- ✓ Preventing macrophages and monoytes from activating T cells and killing virally infected cells .
  this is achived by viral cytokines [vIL-10] **this viral interleukin (IL) is very similar to our interleukins (IL) –it is very similar to a degree that it can inhibit our macrophages from doing their work.. as if it is a human IL , IS IT ?

VIL-10 of EBV and evolution

EBV hijacked/pirated/took bit of our DNA i.e. some time in the evolutionary period of this virus, when it was packaging its DNA into a new viron, a bit of our DNA went to this packaging and this virus started to express vIL-10. # This is a random act, It didn't go and look for IL10 gene. It packaged what it found So, this new strain of virus (in the past) is now a considerably higher advantage comparing to the other viruses because it can evade the immune system, which is why it is now the dominant strain virus, it contains vIL-10.

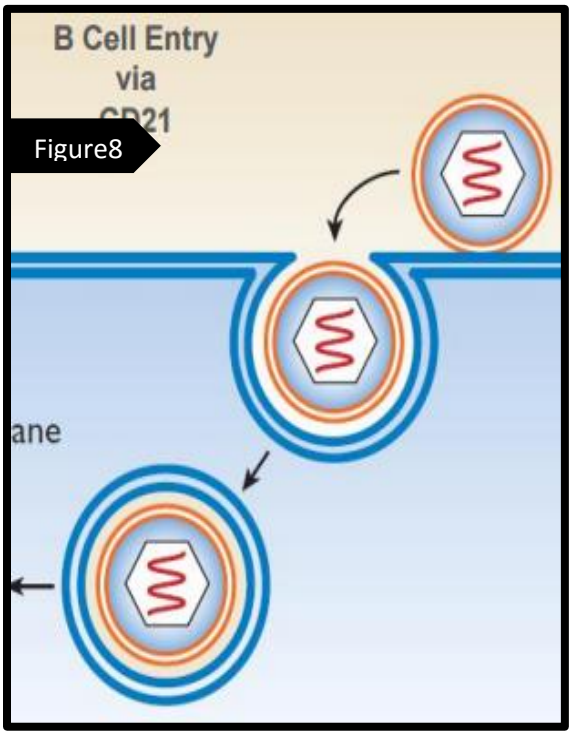
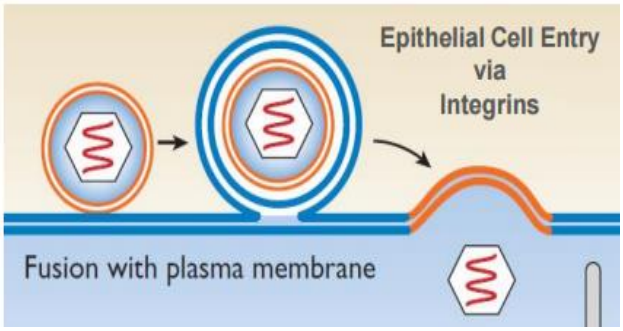


Figure 8 represent the entry of EBV via CD21 receptor..
followed by activation of LMP1 >>B cell proliferation (not shown)

note in In epithelial cells, although the book says it is unclear, there is new data that says it enters by integrins to the epithelial cell.



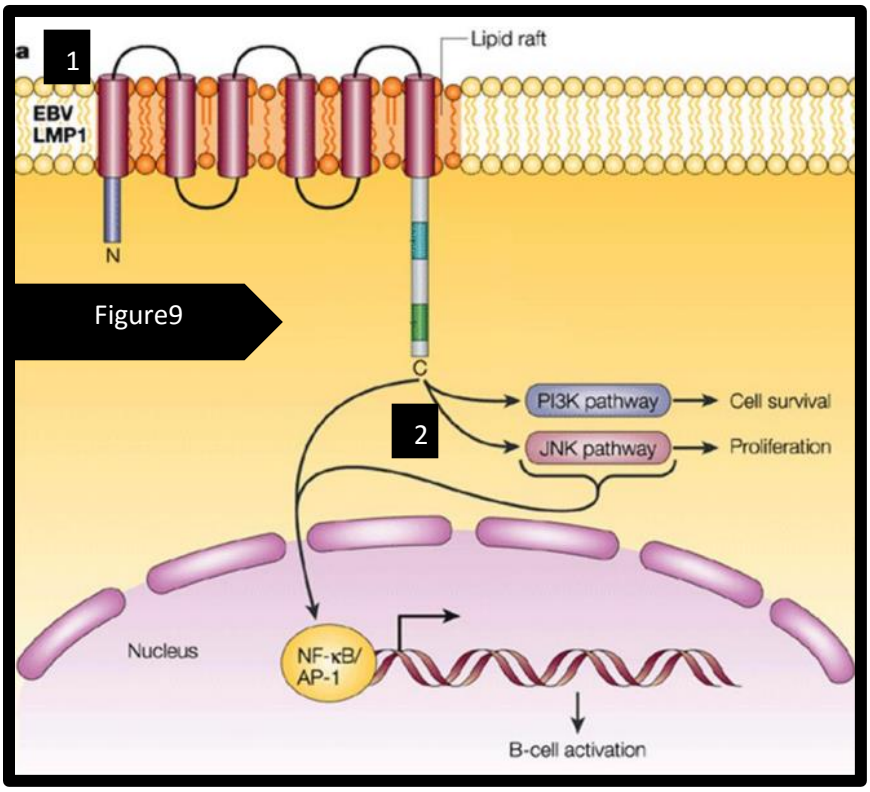


Figure9

1: EBV activate a membrane protein LMP1
2: this activation lead to activation of several pathways that induce B cell proliferation , survival and survival (do not memorize these pathways from this figure , stick to text)

To be safe , Now just re-read what is written in our sheet about this virus ☺

4 Hepatitis B and Hepatitis C viruses

Fairly simple mechanism.. figure10
The main theory : **Necrosis and regeneration**
this relay on the fact that Hepatocytes are stable but regenerative cells.
If you induce inflammation and you induce necrosis you are going to induce regeneration.

where is the risk ?
inflammatory by-products (ROS, ECM degradation products, angiogenesis, growth factors, etc) that are going to induce proliferation and potentially ROS will induce mutations.
So you have the cycle of inflammation, necrosis, regeneration that increases your chances of **hepatocellular carcinomas.**

Although neither of these viruses have oncogenes, some viroproteins like HBx in Hepatitis B can induce certain cytokines and cell cycle cyclins production that also induce proliferation.

There are two other things here:

1) Alcohol works in a very similar way.
2) Aflatoxin (a chemical carcinogen) Remember that big red map (in lecture 2 of neoplasia) where everywhere in the world there was breast cancer except in South West Asia there was hepatocellular carcinoma, aflatoxin is the cause.
   Aflatoxin is a toxin produced from the Aspergillus mold and this mold grows on nuts and improperly stored seeds, they consume a lot of these improperly stored nuts and thisinduces a characteristic **p53 mutation**. If you find this particular mutation you can immediately identify aflatoxin as the cause of this hepatocellular carcinoma.

   So in addition to inducing inflammation, regeneration and repair, you are also stamping out p53 activity through a mutation.

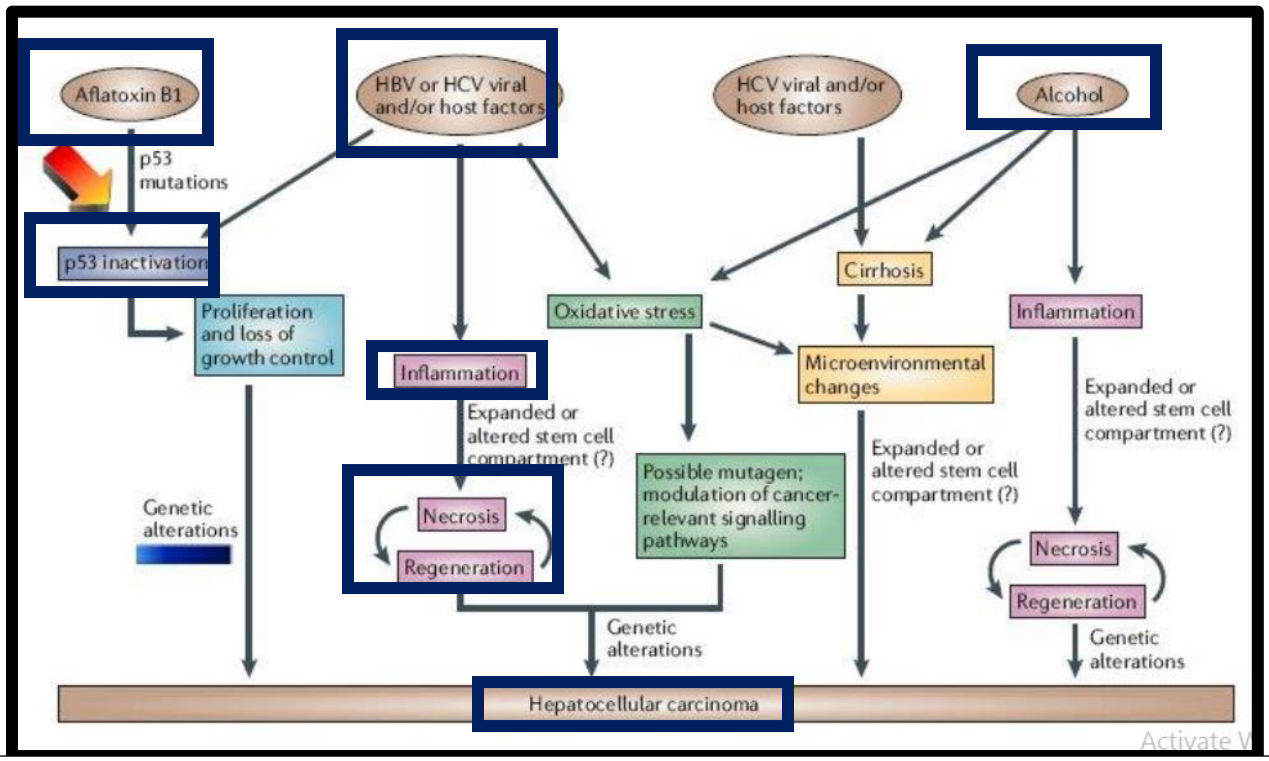


Figure 10 : Hepatocellular carcinoma induced by HBV / HCV
Notice the cycles of necrosis and regeneration , the inflammation , the influence of alcohol , and aflatoxin B1 that induce P53 mutation .

5 H. Pylori bacteria

H pylori infection is chronic , and can induce through multiple steps :

- ✓ Ulcers
- ✓ Gastritis
- ✓ Atrophy
- ✓ metaplasia (we know metaplasia is not good if stayed for too long)
- ✓ dyspasia
- ✓ **gastric adenocarcinoma**.
- ✓ **MALT lymphoma** (discussed below) **figure11**

Remember

H. Pylori produce ALKALINE media around it. If you have a patient with H. Pylori, this H. Pylori needs to be eradicated,, or you're increasing the risk for gastric adenocarcinoma
Another tumor that this bacterium can produce is called MALT lymphoma. It is like any other lymphoma but when you look to it under the microscope it looks like mucosa-associated lymphoid tissue.(recall GI)

In this case "after chronic gastritis" because the bacterium is inducing inflammation, now inflammatory cells proliferate and induce mutations in lymphoid cells of GI .

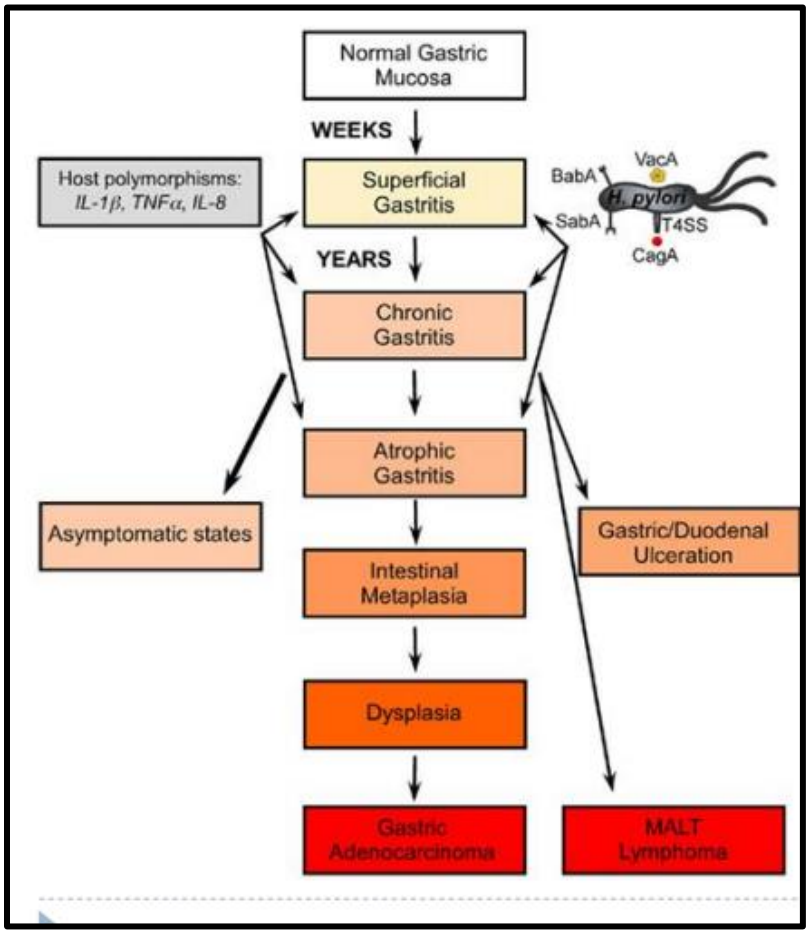


Figure 11 : follow up the pathogenesis and notice the outcomes .

Now revise ur-self with these clips from the Book

SUMMARY

Chemical Carcinogens

- Chemical carcinogens have highly reactive electrophile groups that directly damage DNA, leading to mutations and eventually cancer.
- Direct-acting agents do not require metabolic conversion to become carcinogenic, while indirect-acting agents are not active until converted to an ultimate carcinogen by endogenous metabolic pathways. Hence, polymorphisms of endogenous enzymes such as cytochrome P-450 may influence carcinogenesis.
- After exposure of a cell to a mutagen or an initiator, tumorigenesis can be enhanced by exposure to promoters, which stimulate proliferation of the mutated cells.
- Examples of human carcinogens are direct-acting agents (e.g., alkylating agents used for chemotherapy), indirect-acting agents (e.g., benzopyrene, azo dyes, aflatoxin), and promoters or agents that cause hyperplasia of endometrium or regenerative activity in the liver.

SUMMARY

Oncogenic DNA Viruses

- HPV is associated with benign warts, as well as cervical cancer.
- The oncogenicity of HPV is related to the expression of two viral oncoproteins, E6 and E7; they bind to Rb and p53, respectively, neutralizing their function.
- E6 and E7 from high-risk strains of HPV (which give rise to cancers) have higher affinity for their targets than do E6 and E7 from low-risk strains of HPV (which give rise to benign warts).
- EBV is implicated in the pathogenesis of Burkitt lymphomas, lymphomas in immunosuppressed patients (HIV infection or organ transplant recipients), some forms of Hodgkin lymphoma, uncommon T cell and NK cell tumors, nasopharyngeal carcinoma, a subset of gastric carcinoma, and rarely sarcomas.
- Certain EBV gene products contribute to oncogenesis by stimulating a normal B cell proliferation pathway. Concomitant compromise of immune competence allows sustained B cell proliferation, leading eventually to development of lymphoma, with occurrence of additional mutations such as t(8;14) leading to activation of the *MYC* gene.

SUMMARY

Radiation Carcinogenesis

- Ionizing radiation causes chromosome breakage, translocations, and, less frequently, point mutations, leading to genetic damage and carcinogenesis.
- UV rays induce the formation of pyrimidine dimers within DNA, leading to mutations. Therefore, UV rays can give rise to squamous cell carcinomas and melanomas of the skin.

SUMMARY

Oncogenic RNA Viruses

- HTLV-I causes a T cell leukemia that is endemic in Japan and the Caribbean.
- The HTLV-I genome encodes a viral TAX protein, which turns on genes for cytokines and their receptors in infected T cells. This sets up autocrine and paracrine signaling loops that stimulate T cell proliferation. Although this proliferation initially is polyclonal, the proliferating T cells are at increased risk for secondary mutations that lead to the outgrowth of a monoclonal leukemia.

SUMMARY

Hepatitis B and Hepatitis C Viruses

- Between 70% and 85% of hepatocellular carcinomas worldwide are due to infection with HBV or HCV.
- The oncogenic effects of HBV and HCV are multifactorial, but the dominant effect seems to be immunologically mediated chronic inflammation, with hepatocellular injury, stimulation of hepatocyte proliferation, and production of reactive oxygen species that can damage DNA.
- The HBx protein of HBV and the HCV core protein can activate a variety of signal transduction pathways that also may contribute to carcinogenesis.

SUMMARY

Helicobacter pylori

- *H. pylori* infection has been implicated in both gastric adenocarcinoma and MALT lymphoma.
- The mechanism of *H. pylori*–induced gastric cancers is multifactorial, including immunologically mediated chronic inflammation, stimulation of gastric cell proliferation, and production of reactive oxygen species that damage DNA. *H. pylori* pathogenicity genes, such as *CagA*, also may contribute by stimulating growth factor pathways.
- It is thought that *H. pylori* infection leads to polyclonal B cell proliferations and that eventually a monoclonal B cell tumor (MALT lymphoma) emerges as a result of accumulation of mutations.