



# NEOPLASIA 6

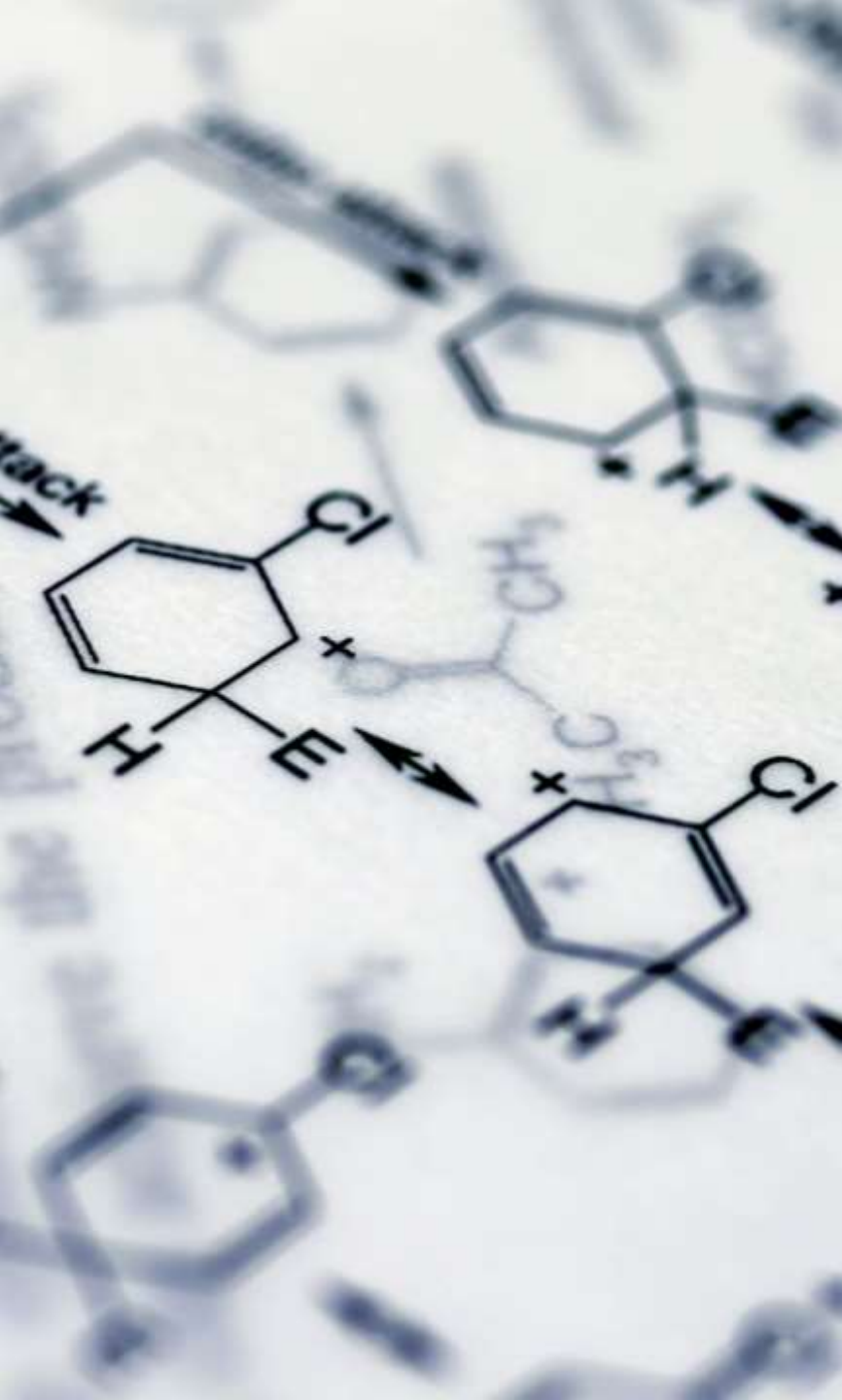
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▪ **ANATOMICAL PATHOLOGY**

MUTAH UNIVERSITY

SCHOOL OF MEDICINE- DEPARTMENT OF HISTOPATHOLOGY

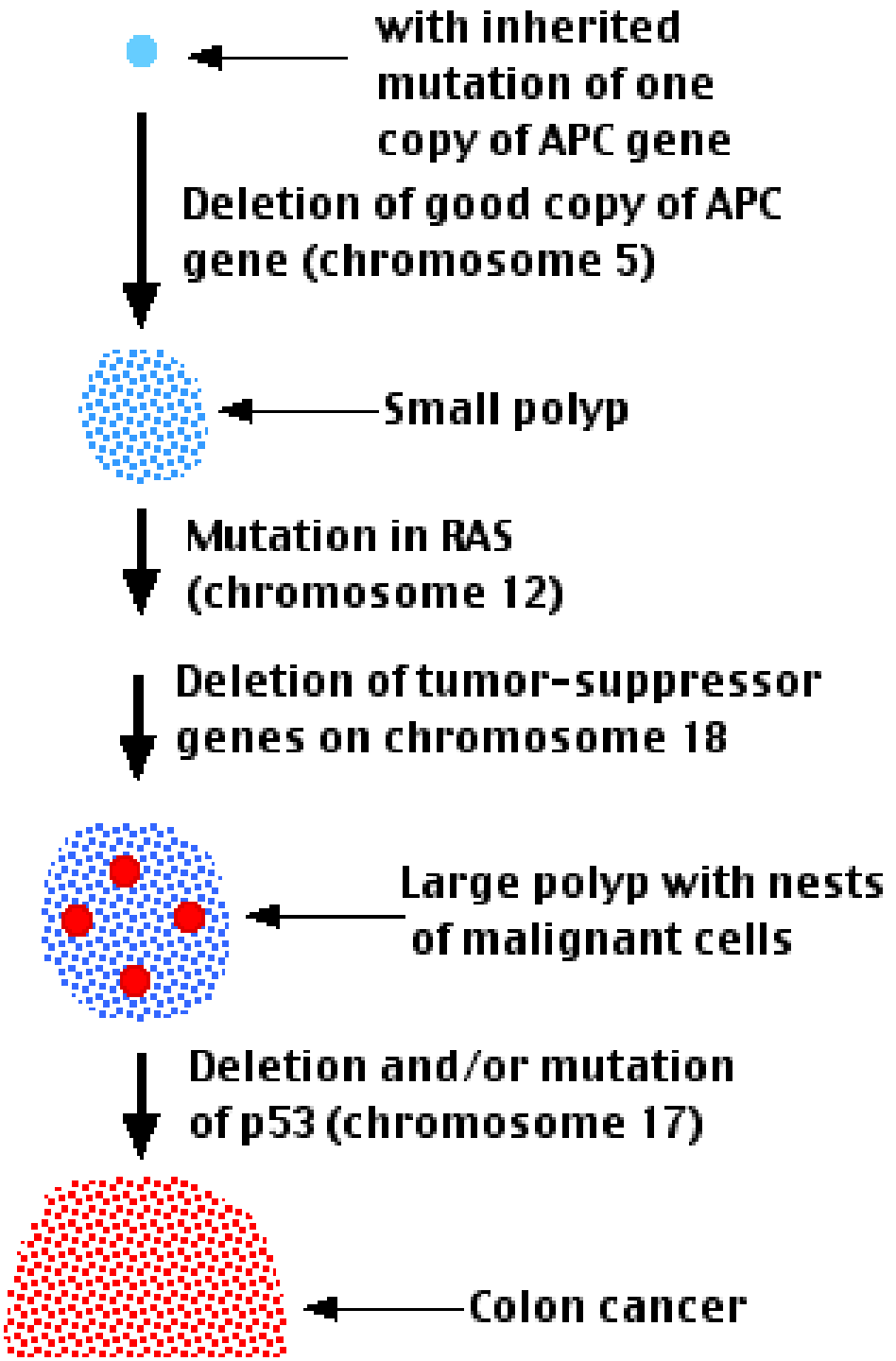
GENERAL PATHOLOGY LECTURES 2023



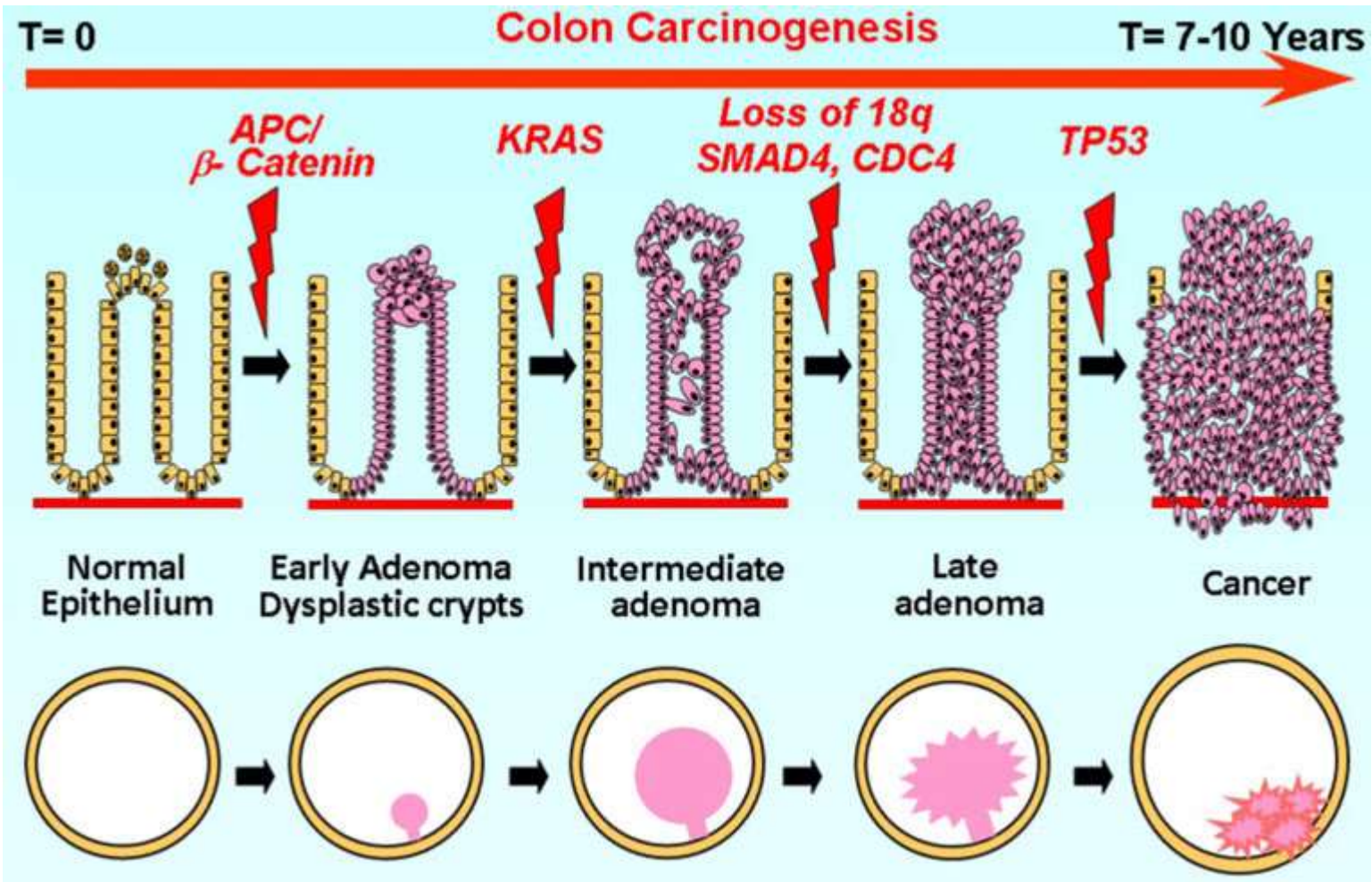
- List the main environmental causative agents of cancer.
- Understand the difference between direct and indirect acting chemical carcinogens.
- Understand the pathogenesis of cancer development due to several etiologic agents.



- Carcinogenesis, as we discussed in the previous lectures, results from one single clone that acquires certain mutations that allow this clone to proliferate rapidly.
- As the tumor mass grows, extra mutations occur that add certain phenotypes to this mass (subclones are formed).
- 8 phenotypic hallmarks are needed to sustain the tumor mass.
- These hallmarks are acquired via mutations.
- No single mutation is enough for the transformation of cells.
- Several mutations are needed to acquire the 8 hallmarks.
- One mutation might result in several hallmarks.



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- Note that in this example the patient is born with a defect in a tumor suppressor gene (APC), he acquires the second hit which results in some loss of sensitivity to growth inhibition.. So there is some proliferation resulting in polyp formation.
  - Next a mutation in RAS is acquired, so there is self-sufficiency in growth stimulation. This increases the likelihood of malignant transformation.
  - P53 mutation follows which ensures evasion of apoptosis.
  - P53 also affects autophagy and DNA repair.
  - Now we have a tumor that can proliferate and survive.. Other mutation can follow to acquire the rest of the hallmarks. It is now easy for these to occur because p53 mutations create a mutator phenotype that is susceptible to mutations.

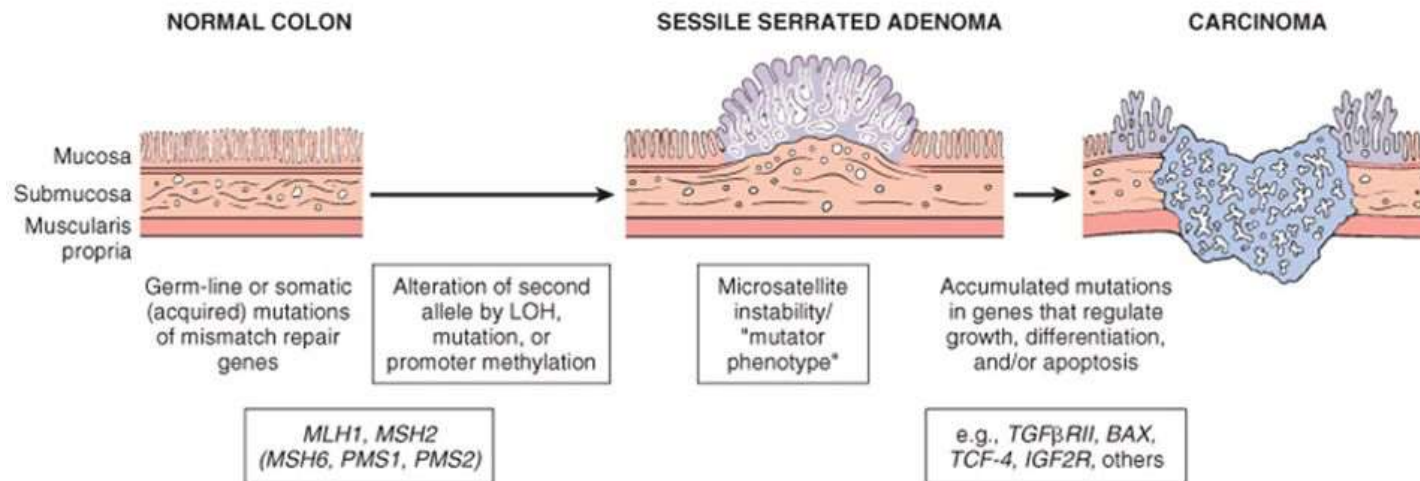


EXAMPLE: COLON CANCER.  
 NOTE THAT SEVERAL  
 MUTATIONS ARE NEEDED TO  
 DEVELOP CANCER. JUST GET  
 THE IDEA, DON'T MEMORIZE  
 THIS SEQUENCE!

# Carcinogenesis



- mismatch repair (microsatellite instability) pathway



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THIS IS ANOTHER POSSIBLE SEQUENCE OF COLORECTAL CARCINOMA. AGAIN WE NEED SEVERAL MUTATIONS TO ACQUIRE THE 8 HALLMARKS

SO: how do these mutations are acquired...  
what are the etiologic agents that can cause  
cancer???



This is the main topic of this lecture.

# ETIOLOGY OF CANCER

-Cancer can be caused by inherited or acquired mutations.

-We discussed many of the inherited mutations in the previous lectures.

-Environmental factors that cause mutations are mainly:

- Chemicals
- Radiation
- infections



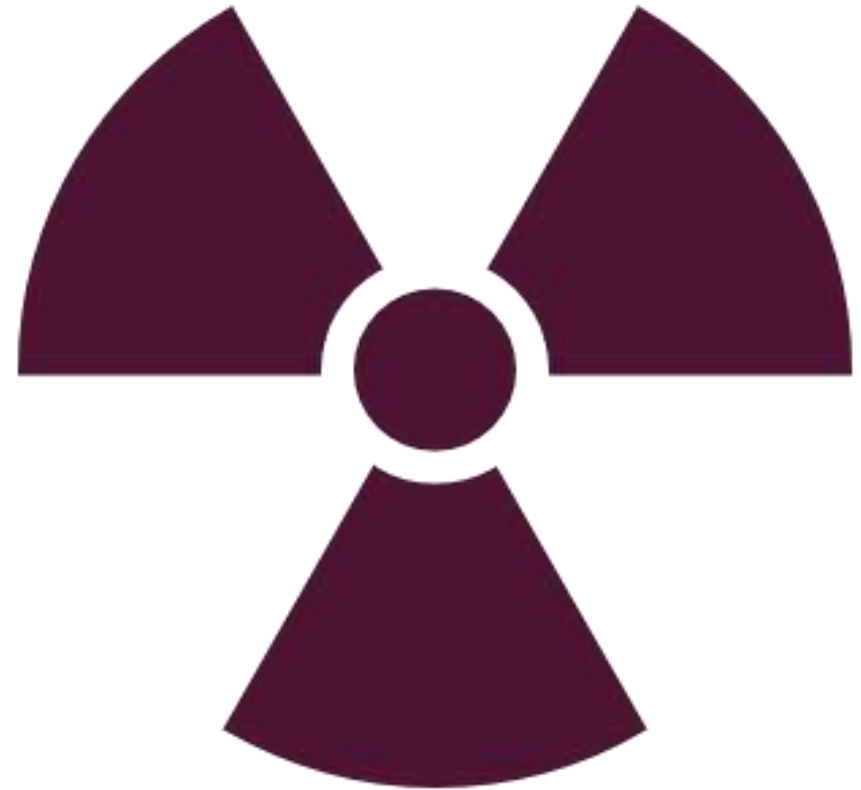
# CHEMICAL CARCINOGENESIS

- One of the first cancers linked to chemical carcinogens is scrotal squamous cell carcinoma
- Sir Percival Pott ..A London surgeon noted that scrotal cancer is common in Chimney Sweeps and he thought it is related to soot exposure.
- Danish Chimney Sweeps Guild ruled that its members bathe daily
- This reduced scrotal cancer. It is a very successful story about how to prevent cancer with lifestyle changes ( a daily bath in this instance!)
- So: chemicals can cause cancer



## CHEMICAL CARCINOGENS

- Chemicals cause cancer directly ( direct-acting agents) or by being converted to a carcinogenic metabolite ( indirect-acting agents)



# DIRECT ACTING AGENTS



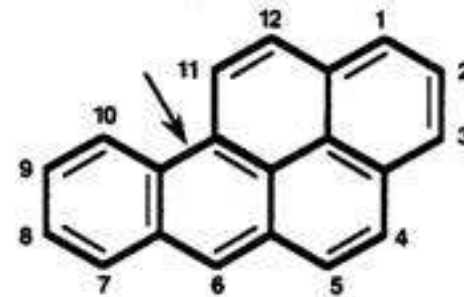
These are weak carcinogens that don't need metabolic conversion



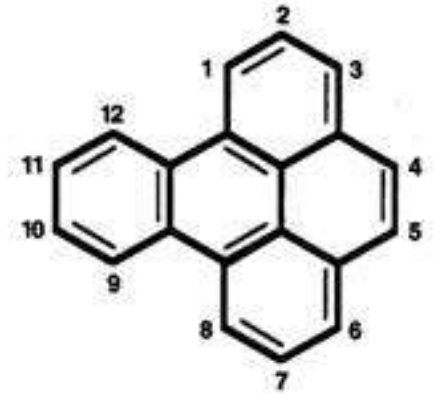
Examples: chemotherapy drugs (alkylating agents) can cause cancer, usually leukemia

# INDIRECT-ACTING AGENTS

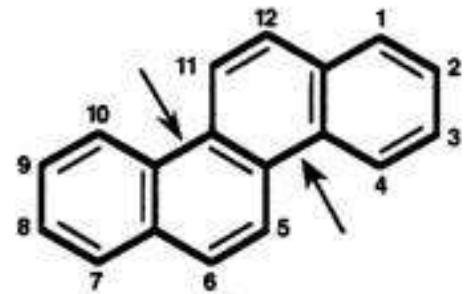
- These need metabolic conversion to become carcinogenic
- Example: polycyclic hydrocarbons which are present in fossil fuel



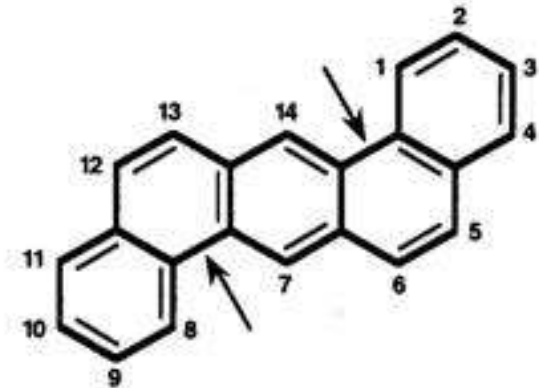
Benzo[a]pyrene



Benzo[e]pyrene



Chrysene



Dibenz[a,h]anthracene

## INDIRECT- ACTING AGENTS



Need metabolic conversion



This conversion is done by several enzymes mainly cytochrome p450 dependent monooxygenases



The genes encoding these enzymes are polymorphic



Certain polymorphisms in these enzymes increase risk of carcinogenesis

## INDIRECT- ACTING AGENTS

Benzo (a) pyrene is a polycyclic hydrocarbon present in cigarette smoke and can cause lung cancer

polycyclic hydrocarbons are also present in smoked meat. Produced from animal fat during broiling beef.

The main active product in polycyclic hydrocarbons is epoxides

Epoxides react with DNA, RNA and cellular proteins

## INDIRECT AGENTS

Aromatic amines and azo dyes. Example beta naphthalamine... increases bladder cancer in workers in the aniline dye and rubber industries.

Aflatoxin B .. Is a naturally occurring agent produced by aspergillus which is a fungus that grows on improperly stored grains and nuts. It increases incidence of hepatocellular carcinoma

Nitrites used as food preservatives can produce nitrosamines which are probably carcinogenic.. Linked to gastric cancer

# MECHANISMS OF ACTION OF CHEMICAL AGENTS



Chemical carcinogens have reactive electrophile group that form chemical adducts with DNA, RNA and proteins

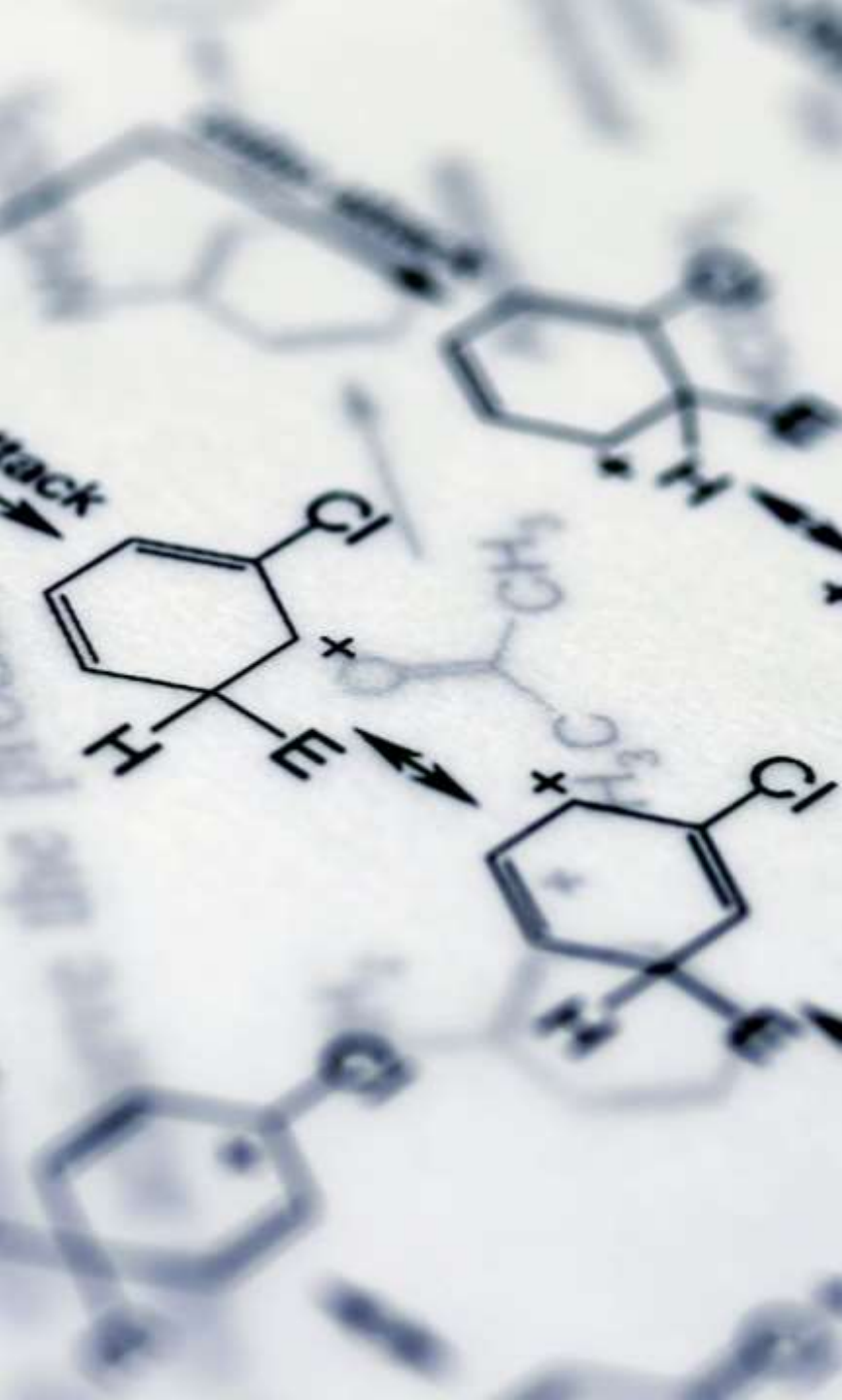


Any gene can be a target for chemicals.. But mostly mutated are RAS and TP53.



Aflatoxin causes TP53 mutation





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- Some chemical carcinogens are augmented by subsequent promoters (hormones, drugs, phenols)
  - The promoters are not carcinogenic by themselves.
  - Promoter effect has to come after the initiator (tumorigenic substance)
  - How do promoters work? They induce cell proliferation which causes clonal expansion of the mutated Cells.
  - These mutated cells now proliferate and accumulate additional mutations

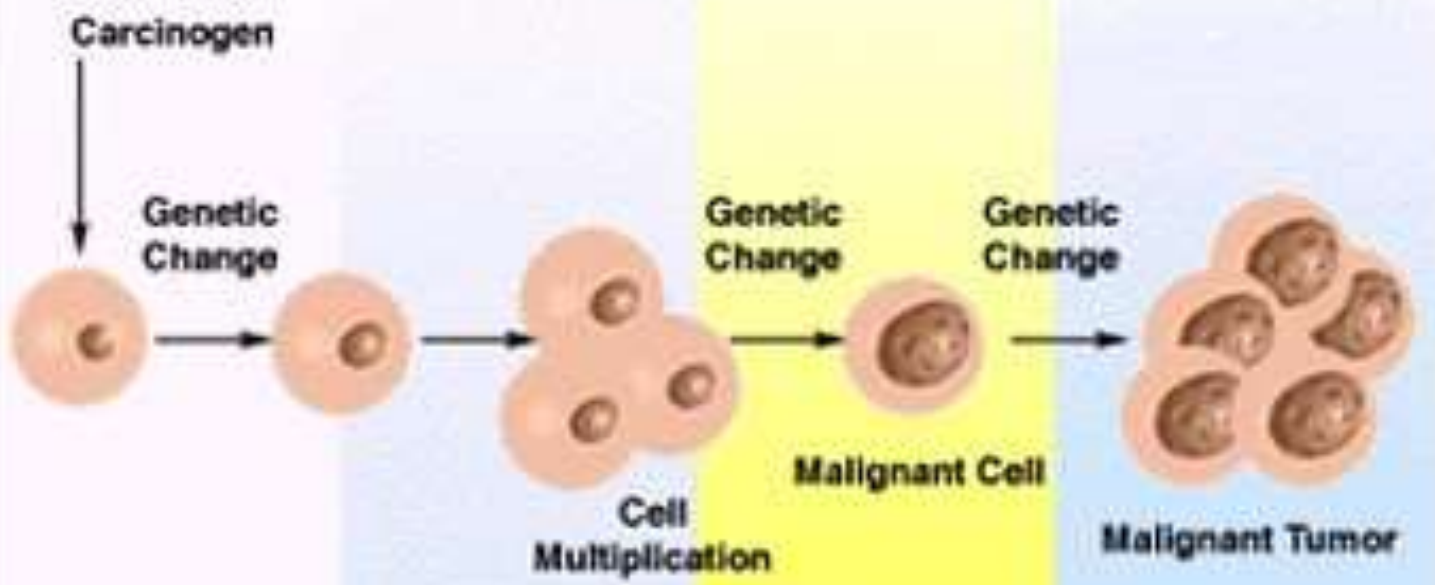
# CARCINOGENESIS

INITIATION

PROMOTION

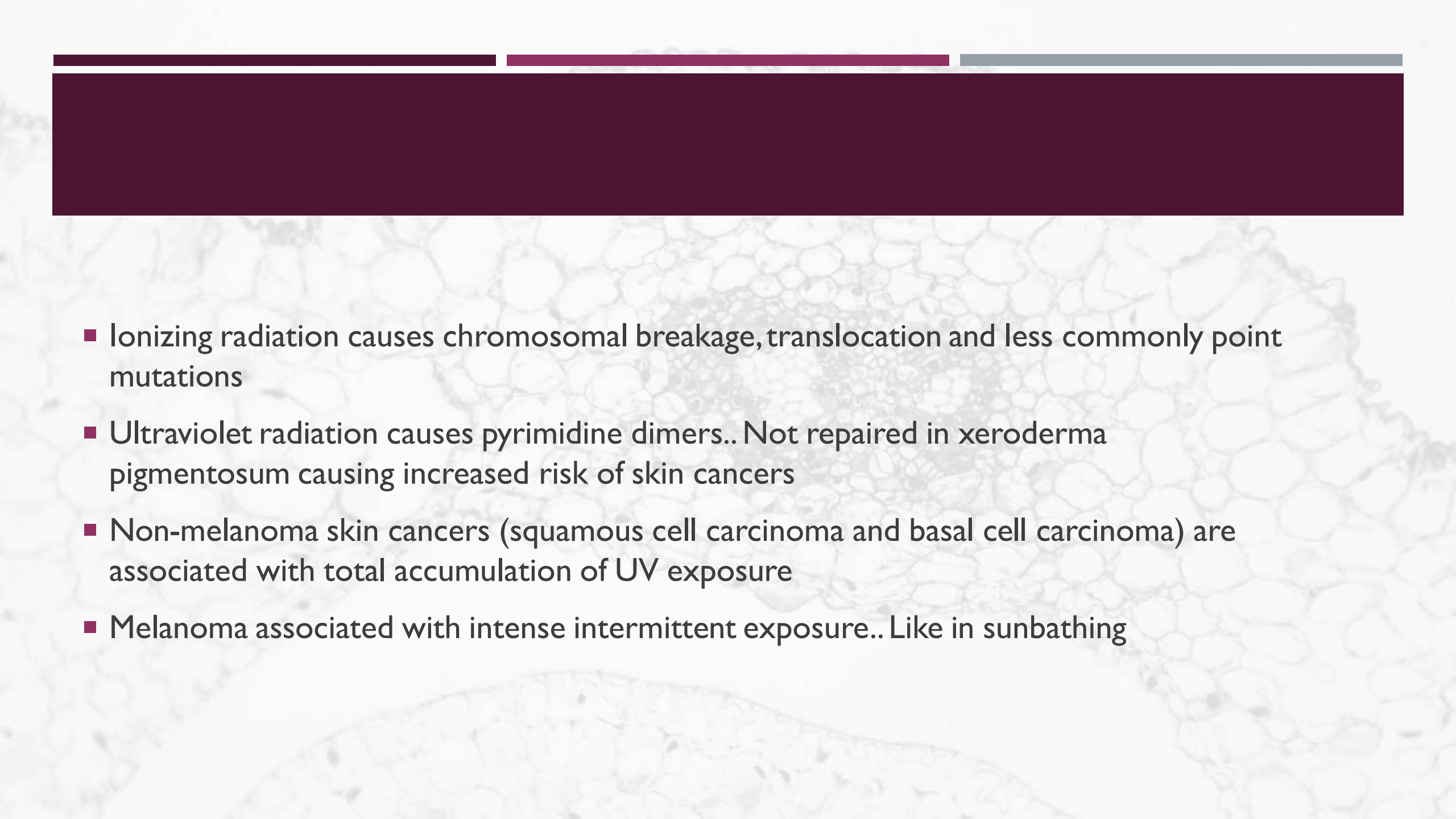
TRANSFORMATION

PROGRESSION



# RADIATION CARCINOGENESIS

- Miners of radioactive elements have 10 fold increase of lung cancer
- Survivors of atomic bombs in Hiroshima and Nagasaki .. Have increased incidence of leukemia... latent periods of 7 years. They also have an increased risk of thyroid, breast, colon and lung cancer
- Chernobyl nuclear power accident.. Also increased cancer
- Therapeutic radiotherapy of the head and neck can cause papillary thyroid cancer years later

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- Ionizing radiation causes chromosomal breakage, translocation and less commonly point mutations
  - Ultraviolet radiation causes pyrimidine dimers.. Not repaired in xeroderma pigmentosum causing increased risk of skin cancers
  - Non-melanoma skin cancers (squamous cell carcinoma and basal cell carcinoma) are associated with total accumulation of UV exposure
  - Melanoma associated with intense intermittent exposure.. Like in sunbathing

# VIRAL AND MICROBIAL CARCINOGENS



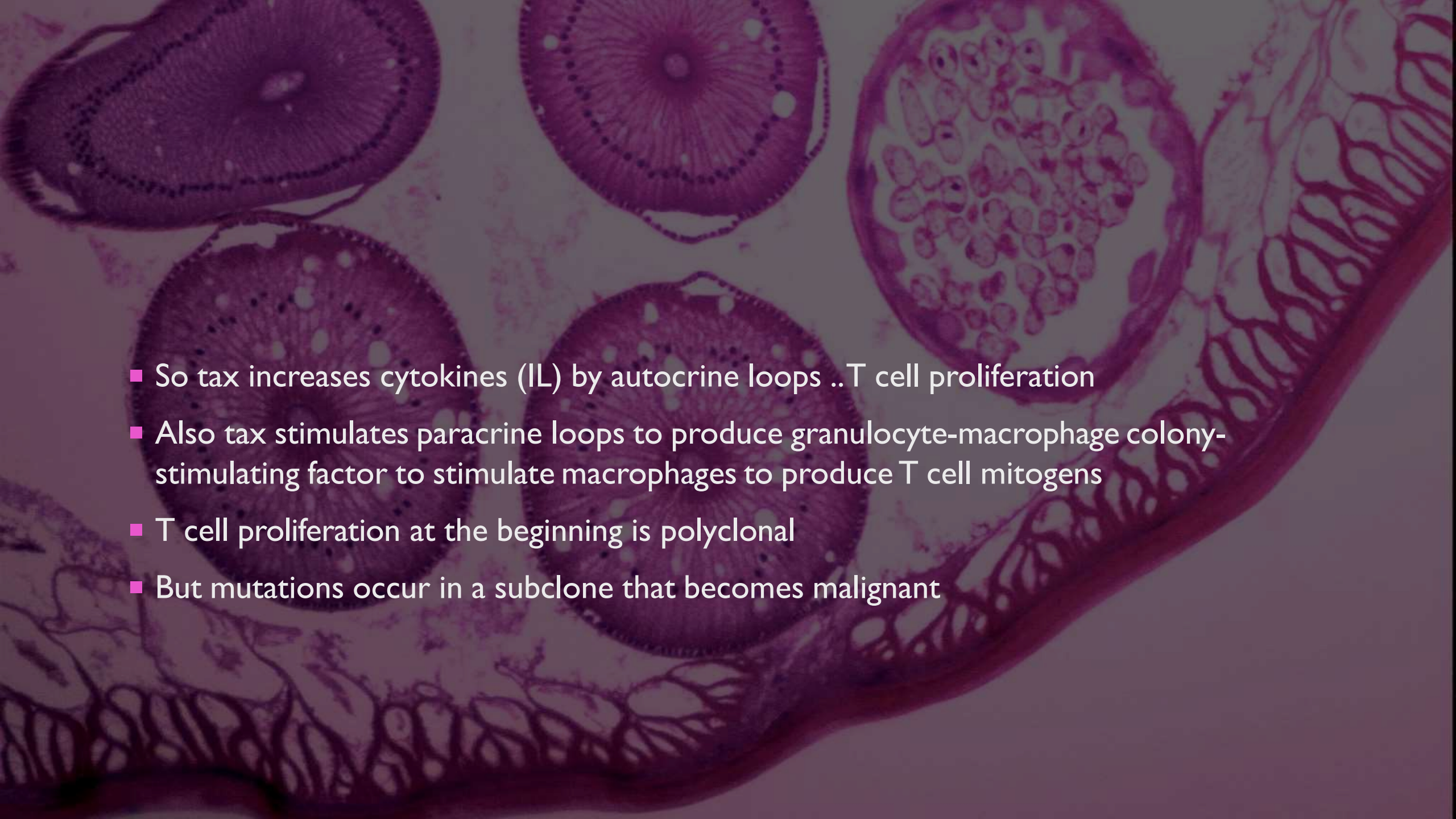
- Oncogenic RNA viruses: HTLV I
- Oncogenic DNA viruses: human papillomavirus, EBV, hepatitis B and C viruses
- Bacteria: H pylori

# HTLV I = HUMAN T LYMPHOCYTE VIRUS I

- A retrovirus involved in T cell lymphoma/ leukemia
- The virus is endemic in Japan and the Caribbean
- It targets CD4 T cells
- Transmitted sexually and through blood or breastfeeding
- Leukemia develops in 3- 5% of those infected after 20-50 years
- Very latent period. Suggests a multistep process of accumulation of multiple oncogenic mutations
- The virus does not encode an oncogene and is not integrated into a cellular oncogene

# HTLV I

- The viral genome contains a region called pX. This region contains several genes, one of them is TAX gene
- TAX protein, interacts with transcription factors like NF- $\kappa$ B, and can transform cells by:
  1. It interacts with transcription factors to activate the expression of cytokines (mainly IL 15) and cytokine receptors .. This creates autocrine signaling
  2. Also, TAX binds to and activates cyclins. So cell division
  3. TAX suppresses tumor suppressor genes like TP53 and p16(CDKN2A)

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- So tax increases cytokines (IL) by autocrine loops ..T cell proliferation
  - Also tax stimulates paracrine loops to produce granulocyte-macrophage colony-stimulating factor to stimulate macrophages to produce T cell mitogens
  - T cell proliferation at the beginning is polyclonal
  - But mutations occur in a subclone that becomes malignant



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## HPV = HUMAN PAPILLOMA VIRUS

- There are several types of HPV. Some produce benign warts (benign squamous cell papillomas), others cause cancer
- HPV 16 and 18 cause cancer. 16 and 18 are called high-risk HPV
- Cancers associated with HPV:
  - Squamous cell carcinoma of the cervix and anogenital region
  - Oropharyngeal carcinoma, especially those arising in the tonsils

# HPV

- Carcinogenic effect of HPV is related to two viral genes E7 and E6
- E7 binds RB protein and releases E2F
- E7 also inactivates CDKIs
- E6 binds to and degrades p53
  
- There are several HPV subtypes, some are high risk and others are low risk.
- High risk HPV are the ones linked to cancer.

## DIFFERENCES BETWEEN HIGH AND LOW RISK HPV TYPES

- E6 of high-risk HPV has a higher affinity to p53 than low-risk HPV. And E7 of high risk HPV has higher affinity to RB
- Low risk viral genes remain in nonintegrated episomes whereas high risk ones are integrated in cell genome causing overexpression of E6 AND E7
- Cells with integrated viral genome show genetic instability.

# HIGH RISK HPV

- Cells infected with high-risk HPV have decreased RB and p53 effect
- So: there is loss of tumor suppressor genes, inhibited apoptosis, no senescence, impaired DNA repair
- However, in experimental models HPV alone is not enough for transformation... a mutated oncogene is needed
- Importance of HPV in cervical cancer supported by protection of this cancer by anti-HPV vaccine

# EBV = EPSTEIN BARR VIRUS

- It Causes:
- Burkitt lymphoma
- B cell lymphomas especially in people with low immunity and HIV infection
- Hodgkin lymphoma
- Nasopharyngeal carcinoma
- T cell lymphomas
- Gastric carcinoma
- Natural killer lymphoma
- Sarcomas especially in the immunocompromized

# EBV

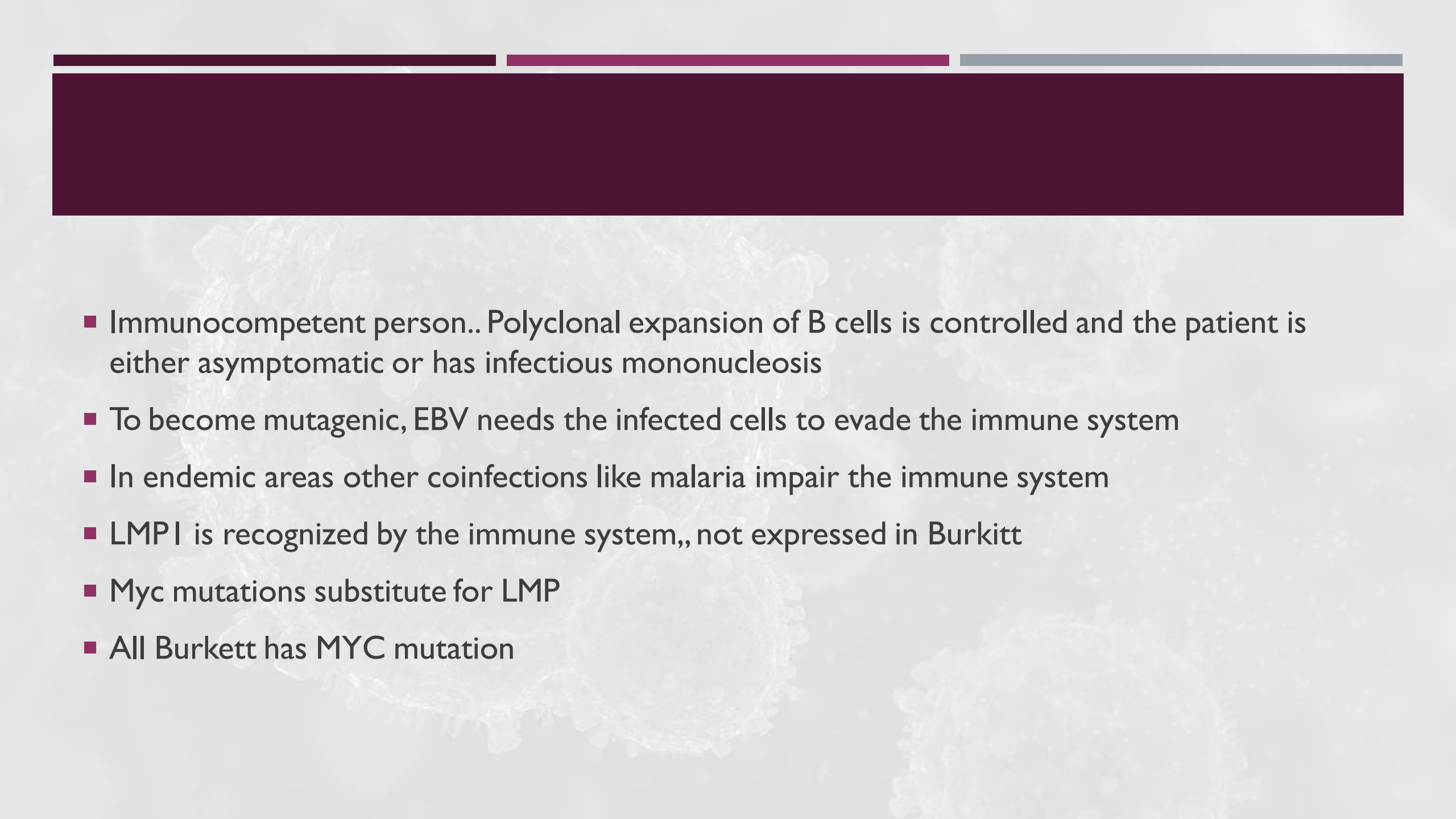
- EBV infects B lymphocytes by attaching to CD21 receptor
- This leads to polyclonal B cell proliferation
- One of the EBV genes = LMP I (latent membrane protein I) act as an oncogene
- LMP I promotes B cell proliferation through NF- $\kappa$ B and JAK/STAT pathways
- LMP I also activates BCL2.. So prevents apoptosis
- LMP also induces angiogenesis



EBNA2 IS ANOTHER EBV GENE THAT  
ACTIVATES CYCLIN D AND OTHER  
CELLULAR ONCOGENES



VIRAL CYTOKINES VIL 10 PREVENTS  
MACROPHAGES FROM ACTIVATING T  
CELLS AND KILLING VIRALLY  
INFECTED CELLS


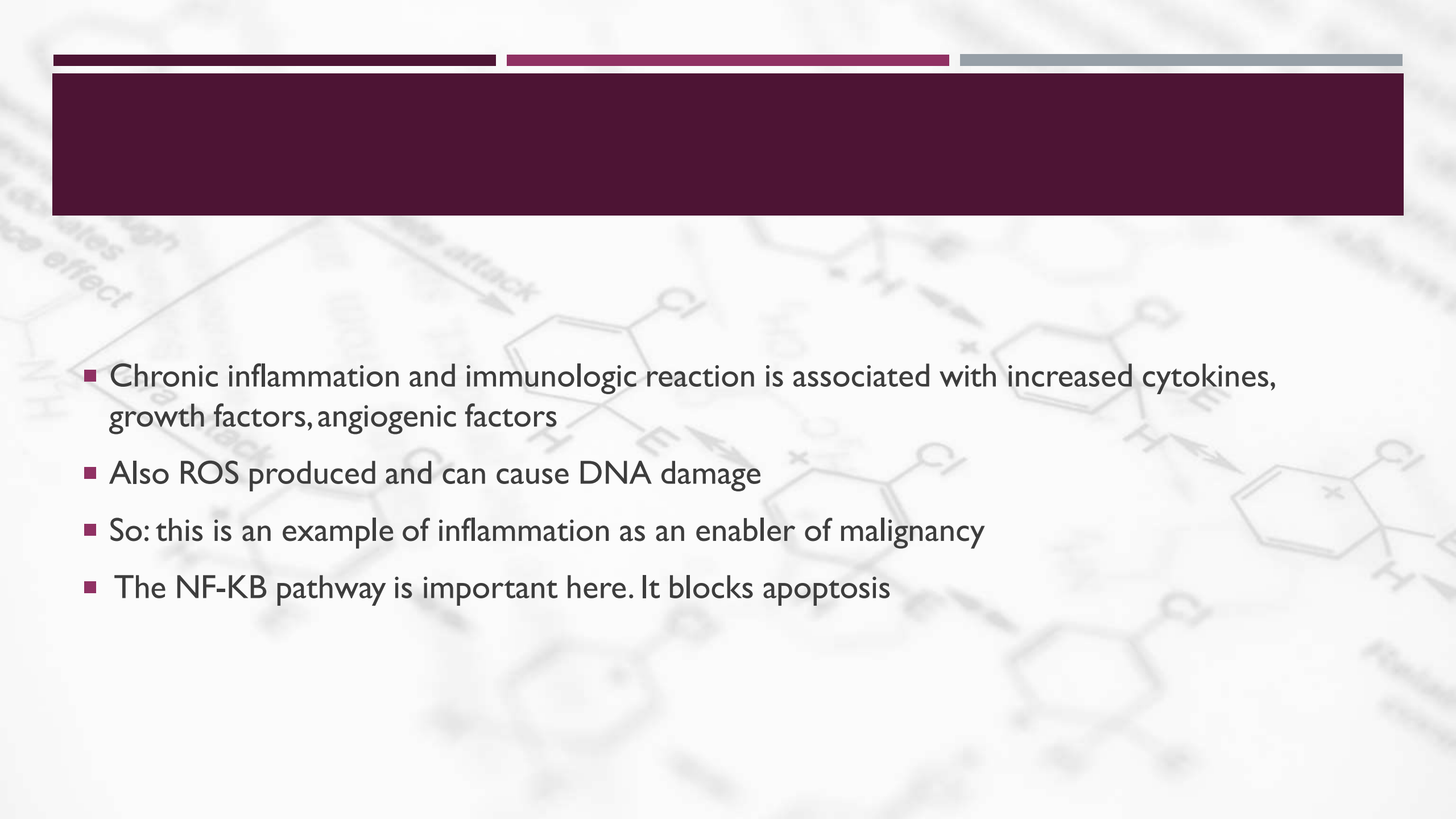
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- Immunocompetent person.. Polyclonal expansion of B cells is controlled and the patient is either asymptomatic or has infectious mononucleosis
  - To become mutagenic, EBV needs the infected cells to evade the immune system
  - In endemic areas other coinfections like malaria impair the immune system
  - LMPI is recognized by the immune system,, not expressed in Burkitt
  - Myc mutations substitute for LMP
  - All Burkitt has MYC mutation



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- People with T cell suppressed immunity ... LMP is expressed
  - Nasopharyngeal carcinoma. LMP is expressed
  - LMP induces angiogenic factors like VEGF, FGF, MMP9, AND COX 2

# HEPATITIS B AND C VIRUSES

- 70-85% of hepatocellular carcinomas are associated with B or C
- Hep B and C do not encode an oncogene
- Hep B genome is integrated into the hepatocyte genome but with no consistent pattern
- So how do they cause cancer? It's thought that the effect is multifactorial and related to immunologically mediated chronic inflammation with regeneration and genomic instability

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- Chronic inflammation and immunologic reaction is associated with increased cytokines, growth factors, angiogenic factors
  - Also ROS produced and can cause DNA damage
  - So: this is an example of inflammation as an enabler of malignancy
  - The NF-KB pathway is important here. It blocks apoptosis

## OTHER MECHANISMS



HBx gene in hep B can activate oncogenes



Viral genome integration probably plays a role in causing chromosomal rearrangements



Hep C core protein can also stimulate oncogenes

# HELICOBACTER PYLORI

Can cause gastric carcinoma and lymphoma (MALTOMA)

**H pylori cause cancer by inducing chronic inflammation**

Sequence: inflammation, atrophy, metaplasia, dysplasia, Cancer

This sequence needs decades to be completed and it occurs only in 3% of people with H pylori infection

H pylori also have genes that are tumorigenic like cagA= cytotoxic associated A which simulates growth factors

# HOW H PYLORI CAUSE LYMPHOMA



H pylori infection causes T cell activation that result in B cell proliferation which starts as polyclonal proliferation



Accumulation of mutation causes monoclonal expansion



Host genetic factors like polymorphisms in TNF and IL1 polymorphisms play a role in the susceptibility to develop MALTOMA



Early in the disease eradication of H pylori cures the lymphoma by removing antigenic cause of T cell proliferation

An aerial photograph of a multi-lane highway bridge spanning across a body of water. The water is a deep teal color with visible ripples. The bridge has several lanes in each direction, with a few vehicles visible. The text "THANK YOU" is overlaid in white, bold, sans-serif font on the left side of the image, preceded by a small teal square.

**THANK YOU**