VIRAL ONCOGENES.

dysfunction (OG).

Viruses that causes tx are called oncogenic viruses.

Carcinogenic agents

- Chemical carcinogens
- Microbial carcinogens
  - Virus
  - Bacteria Hypylori
- radiation

Oncogenic viruses

- RNA virus
  - HTLV-1
  - Hep C.V.
- DNA virus
  - HPV
    - Merkel cell polyoma virus
  - EBV
  - HBV
  - HHV 8
    - Human Herpes Virus-8.

HTLV-1 - retrovirus

Target for neoplastic transformation → CD4+ T cell. It has CD4+ T cell Tropism

Tumours caused → adult T cell leukemia/Lymphoma.

- long latency - (20-50 years)
- mode - sexual, blood products Breast feeding.

Mechanism of Oncogenesis.

- It affects CD4+ T cells
- It does not have a classical oncogene.
- Instead, it uses two viral regulatory proteins - Tax & HBZ

Tax protein {Tax gene}

activates

↓

NF-KB pathway.

promote T cell proliferation & survival.

- Macrophages

by GM CSF release from CD4+ T cells.

↓

macrophages produce T cell mitogens

↓

polyclonal prolif of T cells.

No need.

Inactivates

↓

① p53 & Rb tumour suppressors

no control on cell cycle.

↓

↑ risk of dvlping mutations & genomic instability in dividing T cells.

② DNA repair pathways

causes genomic instability.

End result

- accumulation of mutations and chromosomal abnormalities.

↓

monoclonal Neoplastic proliferation of CD4+ T cells

↓

adult T cell leukemia.

HPV

High risk HPV. - 16, 18, 31, 33.

↓

HPV genome integrates to host genome

↓

genomic instability - malignancy.

Low risk HPV - 6, 11

HPV genome remains in non-integrated episomal form

↓

benign warts.

Cell affected : Squamous epithelial cells on

Infection → Immature squamous cell-poly

replication → maturing, non-proliferative SC

Tsc caused

Squamous cell carcinoma of vulva, vagina, cervix, anogenital regi

adenocarcinoma cervix

oropharyngeal cancers - tonsil.

Mechanism

- HPV genome

↓

Integrates into Host's genome

↓

over expression of viral genes E_6 & E_7 - oncogenes.

↓

oncoproteins: E_6, E_7

HPV virus.

Integrate into host genome.

Overexpression of:
viral oncogenes: E_6, E_7 and
viral oncoproteins: E_6, E_7.

E_6

- degradation of P_{53} gene → Inhibition of P_{53} gene.
- upregulation of Telomerase by (+) TERT; catalytic subunit of telomerase → Immortalization

E_7

- (−) p21 → leads to ↑ CDK4/cyclin D complex.
- binds to RB & inactivates it; so, (−) RB gene {phosphorylation}
- (−) RB – E2F
- release of inhibitory effect on cell cycle.
- G1 – S phase checkpoint

Explanation.

- cyclin D – CDK4 complex
- phosphorylates RB gene.
- Unphosphorylated RB gene complex with E_2 → Un-RB-E2F
- phosphorylation → release of E_2F
- free E_2F (+) transcription of S phase genes.
- p21 binds & (−) CDK4 – cyclin D complex
- so (−) of p21 → CDK4 – cyclin D (−) RB.

Done wrote

- E_7 directly binds to unphosphorylated RB and prevents it from binding to E2F → free E_2F.

effects.

* inactivation of tumour supressor genes
* activation of cell cycle & ↑ cell proliferation.
* Genomic Instability
* Immortalization.
* activate cyclins.

NOTE:

Infection by HPV is not enough for malignancy. It only causes Immortalization.

co transfection + Environment factors
with mutated Ras gene
↓
FULL MALIGNANT TRANSFORMATION

EBV Impt

Cells affected : B cells

↓

causes Immortalization of B cells.

Cancers produced: ** (t 8;14) **

1. African form of Burkitt Lymphoma.
2. Subset of Hodgkin's lymphoma.
3. rare form of T cell lymphoma.
4. NK cell lymphoma.
5. Nasopharyngeal carcinoma *
6. B cell lymphoma in Immunocompromised.
7. Gastric Carcinoma.

Mechanism

EBV infects B lymphocytes by binding to

↓

CD 21 receptor

- lytic infection {minority people}
  - ↓ death of infected cells.
  - ↓ release of virions
  - ↓ infection of other B cells.
- latent infection. {majority}
  - ↓ virus becomes latent inside B cell.
  - ↓ Immortalization of B lymphocytes. ("hallmark" of EBV infection)

Molecular Basis of B-cell Immortalization.

(1) LMP-1 viral Oncogene.

latent membrane protein-1

- activates
  - ↓ NF-kβ & JAK/STAT pathway
- ~~prevents apoptosis by~~ activating - Bcl_2
  - ↓ prevents apoptosis

↓

promote B cell survival & proliferati

(2) EBNA2 gene.

↓

stimulates.

↓

cyclin D & SRC family protooncogene

(3) Viral cytokine vIL-10.

↓

supresses activation of T cells by macrophages

EBV Induced Burkitt's Lymphoma

Initially, EBV infects B cells via ~~BRLF~~ / CD21 receptor.

↓

latent infection with EBV.

↓

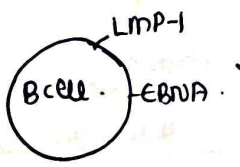
Immortalization of B cells with polyclonal B cell expansion.

↓

they express LMP-1, EBNA

- minority.
  - ↓
  - Escape cytotoxic T cells.
  - ↓
  - they get mutations
  - t (8; 14)
  - myc translocation.
  - ↓
  - Burkitt's lymphoma.
  - ↓
  - endemic in Africa, new guinea.
- majority.
  - ↓
  - they get killed by EBV Ag specific cytotoxic T cells.
  - ↓
  - B cell growth is controlled in immunocompetent.

B cells - EBV transformed



polyclonally activated B cell. (EBV transformed)

mutation. t 8;14

Burkitt's lymphoma cells

Hepatitis B & C.

HBV is m/c ass. with HCC.

Chronic viral infection.

↓

hepatocyte injury.

↓

activate immune cells.

- GF (cytokines, chemokines.)
  - ↓
  - regeneration.
  - ↓
  - ↑ cell survival
  - ↑ tissue remodeling
  - ↑ Angiogenesis.
- ROS production.
  - ↓
  - Mutagenic & Genotoxic.
- ④ NF-κβ
  - ↓
  - Blocks apoptosis
  - ↓
  - allows hepatocytes with DNA damage to survive.

HBV directly causes HCC by. ①

↓

④ TFs and several signal transduction pathways.

viral integration into host genome ②

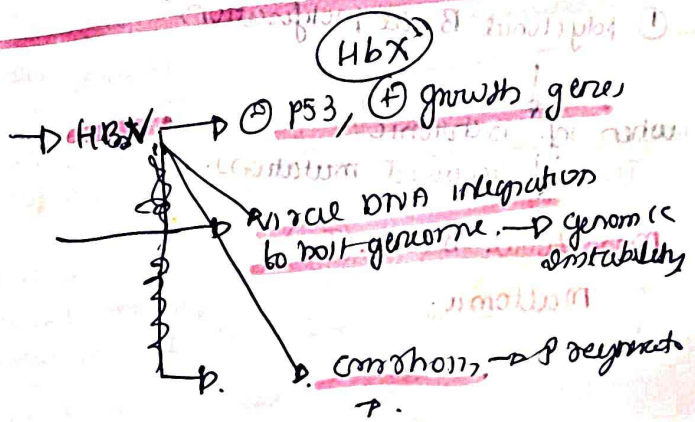
↓

can alter Tc suppressor gene. &

④ oncogenesis

↓

HCC.



H. pylori

Causes: Gastric adenocarcinoma (1)

Gastric Lymphomas (2)
↳ MALT lymphoma
ie, Maltoma.

Virulence factors → Cag A
Vac A

Gastric Adeno Ca.

- takes decades to happen & causes sl.

chronic gastritis.
↓
gastric atrophy
↓
Intestinal metaplasia.
↓
dysplasia
↓
Cancer.

Gastric lymphoma.

B cell origin {maltoma}

H. pylori infection
↓
⊕ Hpylori reactive T cell.
↓
⊕ polyclonal B cell proliferation
↓
when inf. is chronic
↓ acquired mutations.
monoclonal B-cell (Tx)
↓
maltoma.

parasites

Schistosomiasis — SCC of urinary bladder.

clonorchis sinensis — Cholangio ca, pancreatic Ca, HCC

opisthorchis sinensis — cholangeo Ca.

Fasciola Hepatica — "

Fungi

Aspergillus - Aflatoxin B_1 - HCC.
flavus.