Molecular basis of tumours -2

Carcinogens

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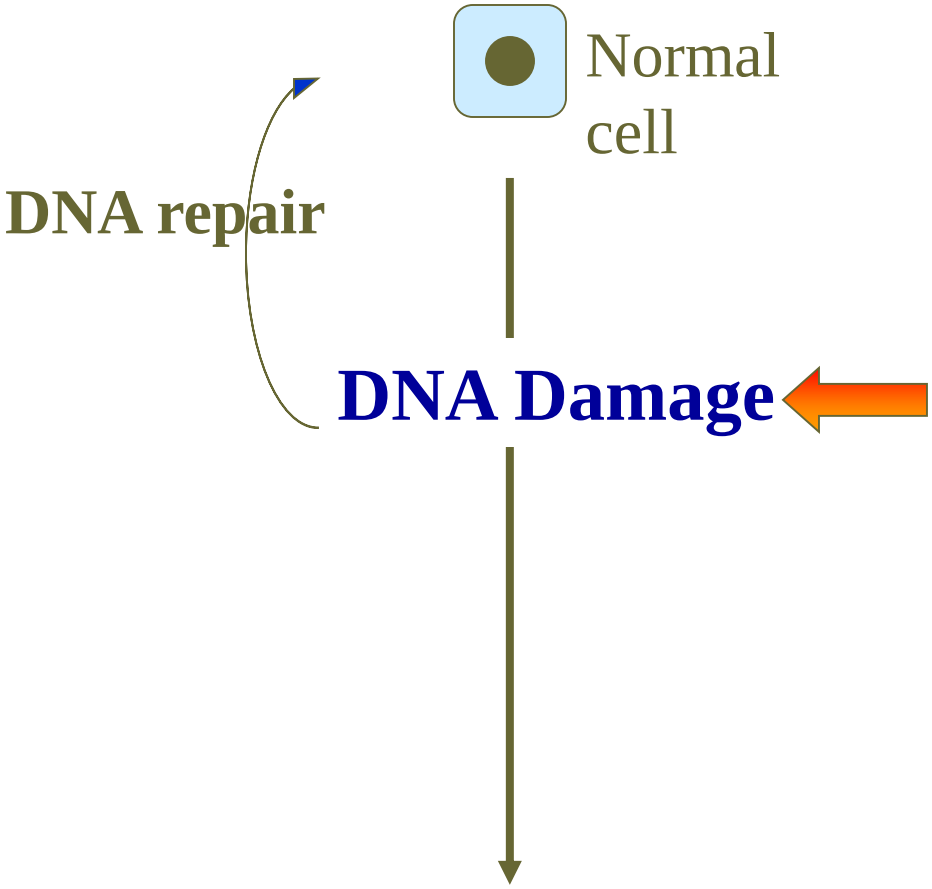
- More than 200 years ago Sir Percival Pott (1714 – 1788) an English Surgeon correctly attributed scrotal skin cancer in chimney sweepers to chronic exposure to soot
- First scientist to demonstrate that a cancer may be caused by an environmental carcinogen.
- Since that time hundreds of chemicals have been identified to be carcinogens

Objectives

- Define the major groups of carcinogens
- Mechanism of action of chemical carcinogens
- Know the terms- initiator, promoter, complete and incomplete carcinogens, direct and indirect carcinogens
- Some examples of chemical carcinogens and the tumours they produce
- Viruses that cause tumours
- Mechanism of action of radiation carcinogens
- now examples for each of these

Carcinogens

- A carcinogen is an agent known or suspected to participate in the causation of cancer.
- These agents are known as carcinogenic/ oncogenic.
- Ultimate site of action of carcinogens is mainly the DNA.
- Carcinogens are therefore mutagenic.



carcinogens

- **Acquired /environmental - 85%**
  - Chemical
  - Microbial agents
  - Radiation
- **Inherited**

An Abnormal protein, which **allow the cell to become a tumour cell**

- Carcinogenesis is a multistep process.
- More than one carcinogen may be required to produce a single tumour.
- Once the process of carcinogenesis is started, the presence of carcinogen is not required to continue the process.
- ‘hit-and–run’ theory

How do we identify carcinogens?

- Epidemiological studies
- Assessment of occupational risks
- Direct accidental exposure
- Laboratory studies on animals
- Transforming effects of cell cultures
- **Mutagenicity** testing in bacteria

Think about examples.....

Major categories of environmental carcinogens

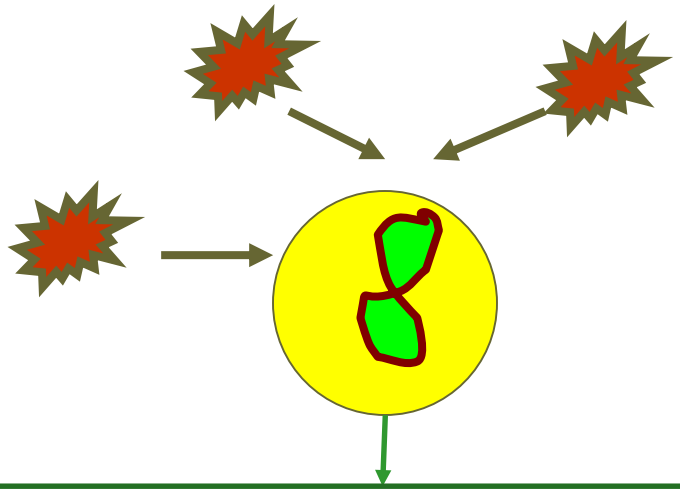
- Chemicals
- Microbial agents
  - Mainly viruses
  - Bacteria, fungi and parasites
- Radiation energy
  - Ionizing radiation
  - Nonionizing radiation
- Other
  - Hormones

Chemical carcinogenesis

- Cancer induction by chemicals can be broadly divided into 2 steps
  - Initiation
  - Promotion

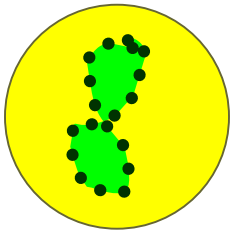
Chemical carcinogenesis

Exposure of a cell to an **initiator** (carcinogen)



Rapid
Irreversible

Permanent damage to the DNA



At least one cycle of proliferation to keep the damage permanent

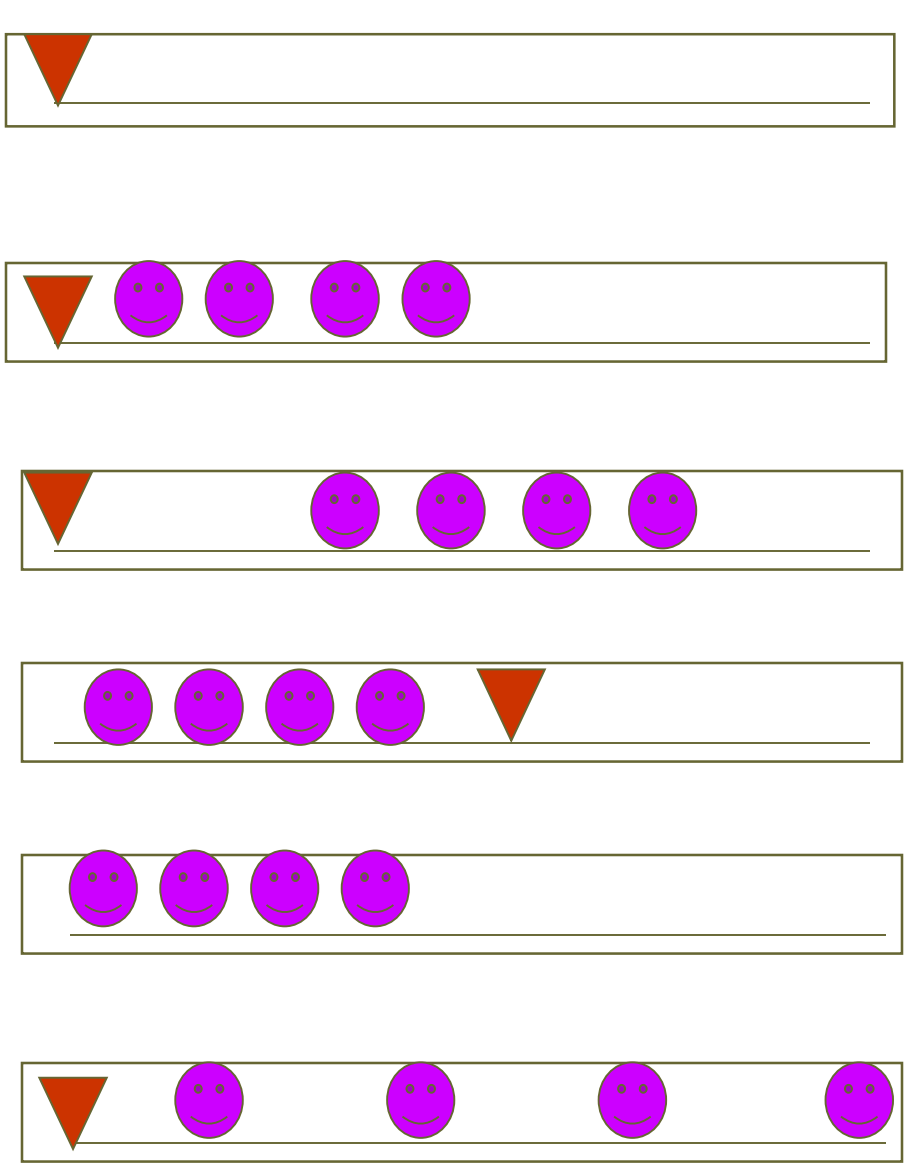
However initiation alone is not sufficient for tumour formation

Chemical carcinogenesis

Promotion

- Promotors can induce tumours in initiated cells
- Promotors are non tumourogenic by themselves
- The cellular changes they make are reversible
- Promotors should be applied after the initiator
- The promotors lead to proliferation and clonal expansion of the initiated/mutated cell forming a malignant tumour

Initiation and promotion of carcinogenesis



Chemical carcinogens

Complete carcinogens

Capable of causing initiation and promotion both

Incomplete carcinogens

Capable of initiation only

Chemicals that initiate carcinogenesis

Direct acting

- Do not require metabolic conversion for their carcinogenicity

  Eg; alkylating agents – anticancer drug Cyclophosphamide

Indirect acting- procarcinogens

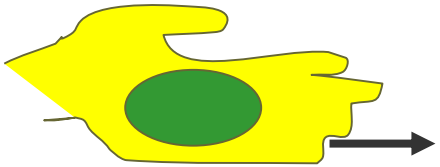
- Needs in-vivo metabolic activation to produce ultimate carcinogen, capable of transforming cells

Eg: polycyclic hydrocarbons, benzo pyrens, aromatic amines

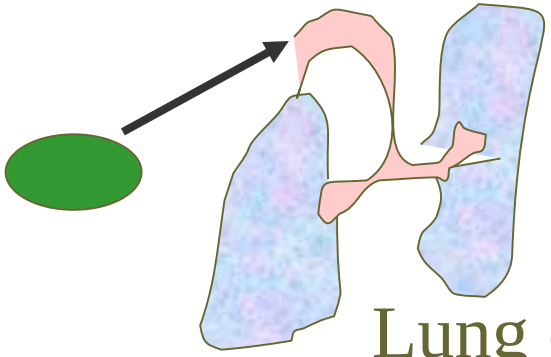
Indirect acting /procarcinogens

- If the enzyme needed for metabolic conversion is available at the site of entry of procarcinogen, the tumour will occur at the site of entry.

- Poly cyclic aromatic hydrocarbons



Skin cancer



Lung cancer

- Dietary nitrates $\xrightarrow[\text{bacteria}]{\text{Gut}}$ Nitrosamine

Read on different chemical carcinogens and their mechanism of action and the tumours they cause

Some chemicals associated with human cancer

Chemical	Occurrence	Tumour
Alkylating agents	chemotherapy	leukaemias
Asbestos	insulation	mesotheliomas
Benzene	solvents	Leukaemias
Nickel	mining	Lung cancer
Nitrosamine	dietary	Gastric cancer
Polycyclic hydrocarbons	Incomplete burning of organic material	Lung, bladder cancer etc..
Vinyl chloride	PVC	Angiosarcoma-liver

Polycyclic aromatic hydrocarbons

- First chemical carcinogens to be intensively studied
- A procarcinogen & requires hydroxylation to become ultimate carcinogen
- Hydroxylating enzymes are ubiquitous in human tissues
  - Skin cancer among painters
  - Lung , bladder cancer in smokers
- Many cancers are associated with PCAH, commonest is the lung cancer
- Many carcinogenic compounds are found in tobacco, commonest is 3,4 benzpyrene

Aromatic amines

- Used in rubber and dye industry
- Needs hydroxylation in the liver
- ß naphthylamine ⟶ 1-OH-2-naphthalamine
- Immediately conjugated with glucuronic acid in the liver , masking the carcinogenic effect
- However in the urinary tract decongugation occur by the enzyme glucuronidase
- Exposure of the urothelium to carcinogen
- Cancer of urothelium

Nitrosamines

- Dietary nitrates and nitrites and gastrointestinal cancer
- Used in fertilizers, food additives

Microbial carcinogenesis

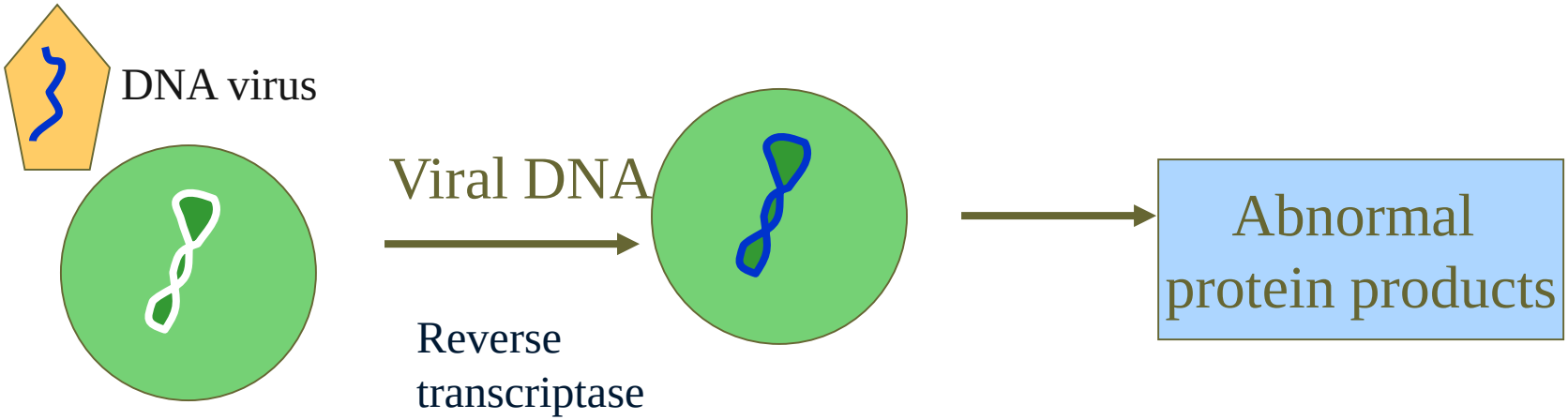
- Viruses
  - RNA viruses
  - DNA viruses
- Bacteria
- Fungi
- Parasites

Viral Oncogenesis

- Protooncogenes → viral oncogenes

Activation by oncogenic viruses

(v oncs)



Viral Oncogenesis

- Some viruses act indirectly by causing tissue destruction leading to increased cellular proliferation
  - Eg; hepatitis C virus

Oncogenic DNA viruses

- Epstein-Barr virus
- Hepatitis B virus
- Human Papilloma Virus (HPV)
- Human Herpes Virus 8 (HHV 8) / Kaposi Sarcoma Herpes Virus KSHV

Epstein-Barr Virus

- EBV infects B lymphocytes and possibly epithelial cells of nasopharynx
- EBV infected B cells are immortalized.
- EBV gene, latent membrane protein-1(LMP-1) act as an oncogene and causes autonomous proliferation of B lymphocytes
- LMP-1 also inhibits apoptosis by activating Bcl-2
- Causation of B cell lymphomas

Epstein-Barr Virus

- Implicated in the pathogenesis of
  - Burkitt lymphoma
  - B cell lymphomas in immunocompromized patients
  - Nasopharyngeal carcinomas
  - Rare T cell lymphomas

Read on EBV and cancer

Hepatitis B Virus

- Strong association between HBV and hepatocellular carcinoma
- Chronic liver cell infection leads to compensatory proliferation of hepatocytes
- Many cytokines, growth factors, chemokines , reactive oxygen species are produced by activated immune cells
- These cause mutagenesis

read

Human papillomavirus

- There are many subtypes of HPV
- Some types (1,2,4,7) cause benign squamous papillomas (warts)
- High risk HPVs-(16 & 18)
  - Squamous cell carcinoma of cervix and ano-genital region
- High-risk HPV types express oncogenic proteins
  - Inactivation of tumour suppressor genes
  - Activates cyclins
  - Inhibits apotosis
  - Combat cellular senescence

Read more

Oncogenic RNA viruses

- Human T cell Leukaemia Virus - type 1 (HTLV 1)

  -T cell leukaemia/ lymphoma
- Hepatitis C virus

  -hepatocellular carcinoma

Other microorganisms implicated in carcinogenesis

Bacteria

- ***Helicobacter pylori*** -gastric lymphoma
  -gastric carcinoma

Fungi

- **Aflatoxin producing *Aspergillus flavus***
  -Hepatocellular carcinoma
- ***Parasites***
  - ***Schistosoma*** **-Bladder cancer**
  - ***Clonorchis sinensis*** **- cholangiocarcinoma**

Radiation carcinogenesis

- UV rays of sunlight
- Ionizing electromagnetic or particulate radiation

Ultraviolet rays

- UVB light damages DNA by forming Pyramidine dimers
- These are repaired by nucleotide excision repair pathway
- With excessive sun exposure the NER pathway is overwhelmed
- Cells with defective DNA are propergated
- High risk of skin cancer in people with defective DNA repair genes
  - Xeroderma pigmentosum

Ultraviolet rays

- Increased incidence of
  - Squamous cell carcinoma of skin
  - Basal cell carcinoma of skin
  - Melanoma of skin
- Degree of risk depends on
  - type of UV rays
  - Intensity of exposure
  - Protective melanin barrier

Ionizing radiation

- Causes chromosomal breakage, translocations & point mutations
- Electromagnetic -x rays, ɤ rays
- Particulate – α particles,β particles, protons & neutrons
- Vulnerability of various human tissue to radiation are different
  - Most frequent- leukaemias and thyroid cancer
  - Intermediate -Breast, lung & salivary gland cancer
  - Skin and GI tract cancers are rare

Ionizing radiation and cancer

- Radiology workers
- Mining of radioactive substances
- Military exposure – Hiroshima & Nagasaki in 1945
- Accidental exposures- Chernobyl accident
- Therapeutic exposure

Hormones as carcinogens

- Oestragens – endometrial and breast cancer
- Androgens and anabolic steroids- hepatocellular cancer

Read on

- Genetic predisposition of cancer
- Familial cancer syndromes
- Familial cancers

Summary…..

Percenatge of understanding …

- 10% ????
- 10-25% ??
- 25-50%????
- 50-75%????
- >75