BIOCHEMISTRY OF CANCER. (4 mark)

Cancer is defined as a disturbance of growth, characterized by excessive proliferation of cells without apparent relation to physiological demands of the organs involved.

→ Cancer cells are characterized by 3 properties:

1. Immortalization - unrestricted control of growth.
2. Invasion of local tissues.
3. Spread or metastasis to other parts of the body.

Etiology of cancer:

Multifactorial.

genetic factors
Hormonal "
metabolic "
physical "
Environmental "
chemical "

Molecular basis of carcinogenesis.

- **Carcinogenesis:** Process by which normal cells are transformed to cancer cells.
- Important hallmark. Uncontrolled cell division.

3 stages - Initiation, promotion, progression.

Mutagens:
Any substance which increase rate of mutation can also enhance rate of incidence of cancer.

promoters: carcinogen produces a mutation but promotes growth factor for uninhibited cell division.

carcinogens
physical, chemicals or biological agents which can cause cancer are called carcinogens.

→ All the carcinogens are mutagens.

Physical agents:
UV rays, X rays, gamma rays
↓
cause damage to DNA.
or
formation of free radicals in tissues - molecular damage.

Chemicals
introduced into the body by means of -

occupation - aniline, asbestos.
Diet - aflatoxins, food additives, colouring agents.
Lifestyle - tobacco smoking, chewing - benzopyrene.
MC - Methyl cholanthrene - powerful.

—

- polycyclic aromatic hydrocarbons.
  ↳ benzopyrene, cholanthrene, DMBA.
- Aromatic amines.
  ↳ N-Methyl-4-aminoazobenzene. (MAB)
- Nitroso compounds-
  Dimethyl nitrosamine.
- Natural compounds.
  Aflatoxins.

→ Transformation by oncogenic virus.

Virus.	Abbreviation	Associated human diseases.
Epstein - Barr virus.	EBV.	Burkitt's lymphoma (BL), Nasopharyngeal carcinoma.
Human papilloma virus.	HPV.	Uterine cervical carcinoma.
Hepatitis B virus.	HBV.	Hepatoma

Biological carcinogens / oncogenic viruses.

→ Some viruses are carcinogenic
→ Oncogenic virus may be a RNA or a DNA virus.

Anticarcinogens.
Any substance that retards cell transformation / promotion.
eg: Vit A, carotenoids, Vit E, Vit C.
→ Curcumin, Flavonoids.

→ Phenolic compounds in fruits (like grapes, strawberries, walnuts).

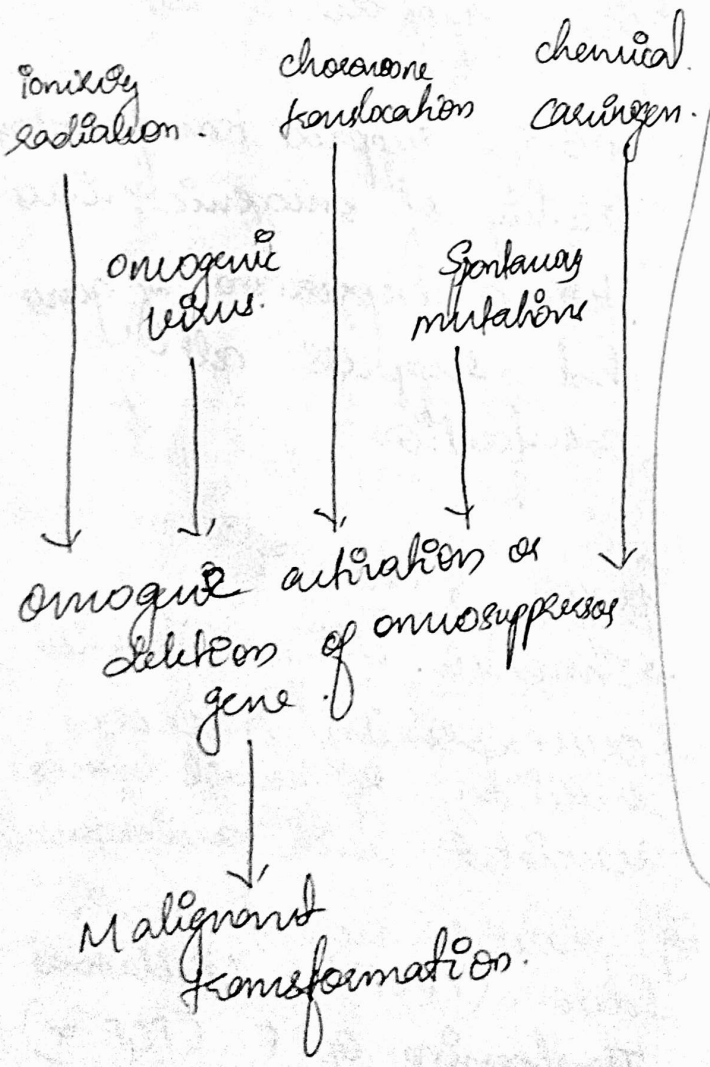
→ Tubers, beans, leafy vegetables.

→ Low protein, low fat diet, good fibre content

→ Green tea

Cancerous transformation due to changes in function of 2 classes of genes.

- Oncogene.
- Onosuppressor genes.



Oncogenes.

Oncogene: genes capable of producing cancer.

proto oncogene: oncogene present in normal cells.

→ Important regulatory genes of the cell.

→ May be connected to oncogene due to

- Environmental factors
- Inherited mutations

Eg: src – Rous sarcoma in chicken

ras – rat sarcoma.

erb-B – erythroblastosis virus in chicken.

Sis – simian sarcoma in monkey.

Proto oncogene activation by various means.

→ point mutation
→ gene amplification
→ gene translocation
→ insertion of a viral promotes / enhancer.

→ Eg:

Onosuppressor genes / tumour suppressor genes / anticoncogenes.

→ Genes which normally protect the individual cell from developing a cancer.

Mutation / abnormality (deletion) of these genes may result in cancer.

eg: p53.
Retinoblastoma gene (RB.

Name	Abbreviation.
Retinoblastoma	RB.
Wilm's tumor	WT.
Familial adenomatous polyposis	→ FAP.
Deleted in colon cancer	→ DCC.
Gene for protein 53	p53.
Familial breast cancer	BRCA

Onosuppressor gene - RB.

RB - governs cell proliferation

→ RB gene expressed to form Rb protein. (p105)
Mol. wt. 105kg.

→ Rb protein - suppress cell proliferation.

Mutation - both allele of RB gene deleted - cause Retinoblastoma.

Onosuppressor gene p53

Guardian genome or Molecular policeman.

→ Gene encodes p53, phosphoprotein (Mol wt - 53kd)

→ It blocks the cells with damaged DNA by triggering blocking of cell division, until damage is repaired.

→ If damage is severe, p53 triggers apoptosis of cell.

→ p53 - suppress transformation ability of oncogenic virus.
Activate expression of gene that suppress cell proliferation.

Growth factor.

→ Stimulate cell proliferation

→ Overexpression / increased secretion of growth factors, associated with carcinogenesis

Eg: platelet derived growth factor. (PDGF) - Glioblastoma
Transforming G.F. (TGF α)
↳ Sarcoma.

Epidermal growth factor EGF.
TGF α, TGF β.
PDGF → wound healing.

Normal cell vs cancer cell.

Normal cell	Cancer cell
contact inhibition.	cancer cells continue to grow.
cells are of equal size and shape.	cancer cells are of different size and shapes.
Nucleus small	nucleus is larger & darker.
Normal number of chromosome.	Abnormal no. of chromosome

Tumour Immunology:

Tumor specific antigens (TSA)
→ occur only in tumour cells.
→ can be abnormal product of cancerous / mutated oncogene.
Eg: Ras protein.

Tumour associated antigens (TAA)
→ occur only in both healthy and tumor cells.
eg: ⇒ oncofetal antigens (AFP, CEA)

Tumor Markers.
→ Also called tumor index substances.
→ are factors released from the tumor cells which could be detected in blood and therefore indicate the presence of tumor in the body.
→ Some are specific for one type of cancer, while others are seen in several cancers.

Ideal tumor marker
- Highly specific (detect in only 1 tumor type)
- Highly sensitive.
- Non detectable in physiological or benign disease state
- Long lead time : sufficient time for alteration of natural course of disease.

Uses of tumor marker
→ for follow up of cancer & to monitor the efficiency of therapy & also to detect recurrence of tumor.
→ for screening & early

detection of cancer.
→ diagnosing cancer.
→ for assessing the prognosis of cancer.

common tumor markers.

Name	Serum level increased in
Oncofetal proteins.	
AFP.	Hepatoma.
CEA.	Colorectal
Tumor associated antigens / Carbohydrate antigens.	
CA125	• Epithelial ovarian cancer
CA19-9.	• carcinoma of pancreas.
Enzymes.	
ALP.	• Bone secondaries.
ACP. (Glandular)	• Lung, Seminoma
PSA	• Prostate cancer.
PAP	• Prostate cancer.
NSE.	• Nervous system tumours.
Hormone:	
β-HCg.	• Choriocarcinoma
calcitonin	• Medullary thyroid Ca.

Tissue catabolic product.
Hydroxy proline

Bone metastasis

Serum proteins.
Ig
Bence jones protein

• Multiple myeloma

Receptor tumour markers:
Estrogen receptor.
Progesterone receptor
HER2

• carcinoma breast, uterus

Breast cancer.
→ At the time of diagnosis, breast cancer tissue should be tested for estrogen & progesterone receptors, HER2 antigen.
→ Response to hormone therapy in early or advanced breast cancer.
→ May be used to determine prognosis.
→ Serum markers such as CA 15-3 & CA 27.29.

Biochemical basis of cancer therapy.
* Surgery
* Radiotherapy.
* chemotherapy.

Anticancer drugs:

(1) Methotrexate
MOA: Folic acid analog (competitive inhibitor of DHFR)

(2) 6-mercaptopurine.
MOA: purine analog. (inhibit conversion of IMP to AMP)

(3) 5-Fluorouracil.
MOA: pyramidine analog (inhibit thymidylate synthase)

(4) Mitomycin
MOA: Intercalation of DNA strands.

(5)

(6).

Targeted therapy in cancer.

(1) Small molecule drugs.
Eg: In breast, lung, colorectal carcinoma.

(2) Monoclonal antibodies
eg: In breast cancer, chronic lymphoid leukemia.

Name	Used against the cancer.
1.	
2.	
3.	
4.	

Apoptosis

programmed cell death.
→ Seen mass falling of leaves.
→ Many organisms exhibit this process. It is a natural biochemical process.
→ Required in developmental process and to maintain homeostasis

Characteristic changes during apoptosis are:
(1) Nuclear shrinkage.
(2) chromatin condensation.
(3) Membrane blebbing
(4) Skip ladder pattern of DNA during electrophoresis.
(7)

Apoptosis mediating genes/ Suicidal genes/ Nonsuppressor genes.

- P^{53}
- Rb
- c-fos.

→ Apoptosis protecting genes: bcl2.

Apoptotic pathways:

- Extrinsic pathway (extrinsic pathway).
- Intrinsic pathway. (intrinsic mitochondrial pathway)
- Common pathway.

→ 3 phases of apoptosis
initiation
regulation
execution.

EXTRINSIC.

TNF & FAS → death ligand.

TNF-R & FAS → receptors.

they bind → pathway activated

these receptors have domain that ~~adapt~~ acquire some adaptor proteins → TRADD & FADD.

They bind to procaspase 8 and form DISC.

Death inducing signalling complex → DISC

↓

initiates caspase 8. (initiator caspase)

INTRINSIC PATHWAY

Oxidative stress, DNA damage, hypoxia

↓

triggers mitochondria

↓

↑ed mitochondrial permeability leading to release of cytochrome C into the cytosol.

↓

formation of apoptosome (consists of cyt. C, procaspase 9 and adaptor APAF-1)

↓

activated initiator caspase 9.

COMMON PATHWAY

these 2 initiator caspases will converge with caspase 3, then 6, then 7 (executioner caspases)

↓

Endonuclear activation
degradation of DNA
nuclear fragmentation.
cytoplasmic condensation.
protease activation
degradation of cytoskeleton

↓

formation of apoptotic bodies

caspase cascade

final effector mechanism of cell death is through the activation of caspases - cysteinyl aspartate specific proteases

caspases 1 to 10 are identified.

cell cycle.

Period between 2 mitotic divisions in a somatic cell.

phase of cell cycle are:
G_1 phase (gap 1)
S phase (synthesis)
G_2 phase (gap-2)
M phase (mitosis)

M phase (Mitotic phase)
Period where cell divides.

Interphase: period b/w end of M phase & beginning of next mitosis

diagram

Phases of cell cycle

G_1 phase: Protein & RNA content increases
duration: 12 hours.

S phase: DNA synthesized (once) DNA content doubles & replicated completely
duration: about 6-8 hours

G_2 phase: cytoplasmic enlargement, DNA repair, histones produced.
Duration: about 4-5 hrs

Total cell cycle duration: 20 - 22 hours.

Regulation of Cell cycle.

→ 4 no. of check points regulate cell cycle.

3 check point.
- G_1 S transition
- S phase.
- G_2 M transition.

Regulated by.
- cyclins (4) - A, B, D & E
- kinases (5) → 1, 2, 4, 5 & 6.
cyclin dependent kinase

UV

↓

ATM released

↓

CHK 1 kinase activated

↓

CDC 25 inactivated

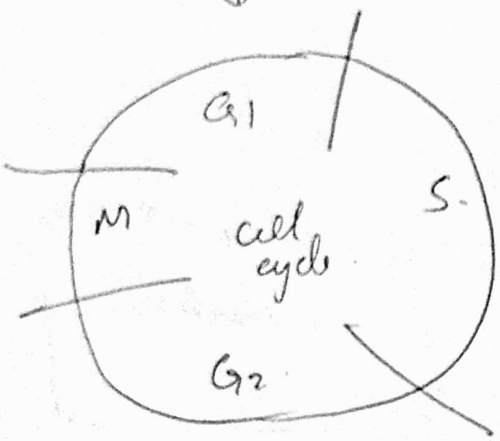
↓

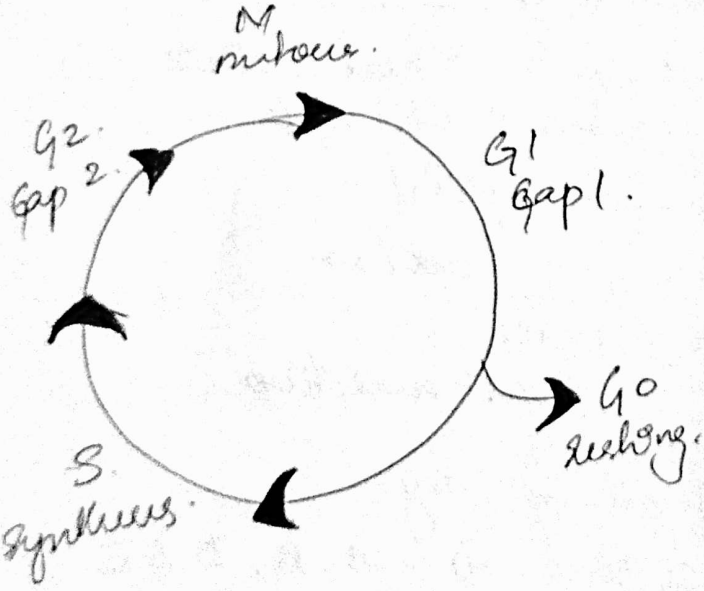
cyclin CDK$_2$ active.

↓

G1 - S checkpoint released

↓





with age - related diseases

→ all physiological processes

Biochemistry of aging

Aging - natural phenomenon

- Geriatric / Gerontology: medical branch dealing