Slide 1

BIOCHEMISTRY OF CANCER

Oncology – deals with the etiology, diagnosis, treatment, prevention & research aspects of cancer.

Slide 2

LEARNING OBJECTIVE

- *ETIOLOGY OF CANCER*
- *MOLECULAR BASIS OF CARCINOGENESIS*
- *ONCOGENES*
- *ONCOSUPPRESSOR GENES*
- *CELL CYCLE*
- *APOPTOSIS*
- *TUMOUR MARKERS*
- *BIOCHEMICAL BASIS OF CANCER THERAPY*

1-role of chemical carcinogens,radn,virus in carcinogenesis
2-intiation,promotion
3,4-role in carcinogenesis
5-defn,clasfcn,clnc signfcnc
6-role of alkyltng agnt,antimetabolite,antibiotic,recpt blokrs,radiothrpy,monoclonal abs

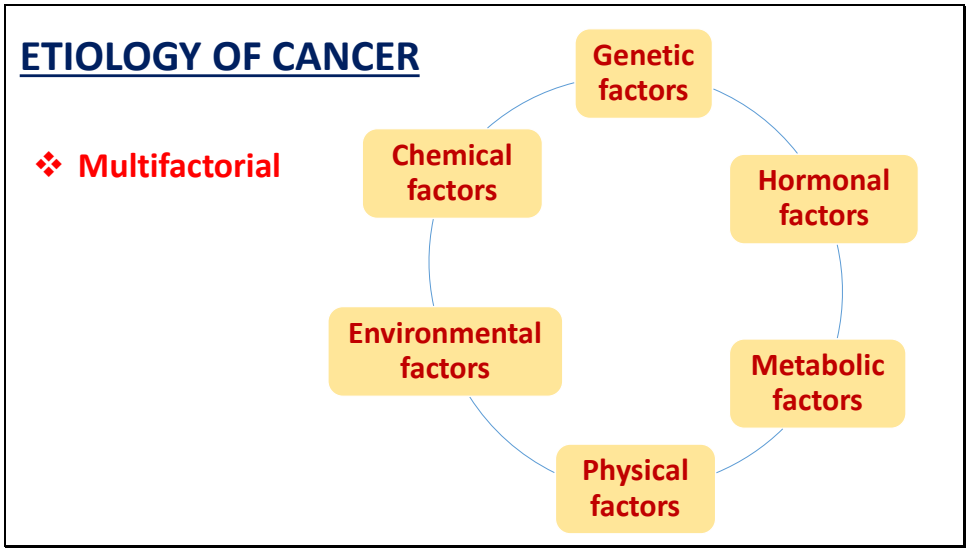
Slide 3

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

❖Cancer cells are characterized by 3 properties:

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

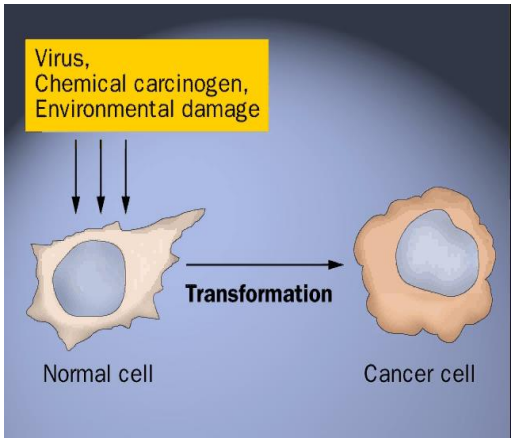
Slide 4



All cancers originate from an aberrant cell which goes on to multiply and produce a tumor mass.
Oral cavity,upper git-common ca in males [ind],female-breast & cervix

Slide 5

MOLECULAR BASIS OF CARCINOGENESIS



- ***Carcinogenesis:***

Process by which normal cells are transformed to cancer cells.

- ***Important hallmark:***

Uncontrolled Cell Division

Multiple events lead to this-include mutan,epigenetic events,abnml cell divsn.a balace b/n cell prolfrn & progrmd cell death maintained,it is lost in cancer.

❑Non lethal genetic damage lies at the heart of carcinogenesis .

❑ The principal targets of genetic damage

Oncogenes

- Tumor suppressor genes
- DNA mismatch repair genes
- Genes involved in apoptosis

Carcinogenesis is a **multistep process .**

Slide 6

- **3 Stages – Intiation ,Promotion,progression**
- **Mutagens**:

  any substance which increase rate of mutation can also enhance rate of incidence of cancer

- **Promoters** : carcinogen produces a mutation, but promoter gives drive for unchecked cell division.

Earlier 2 hit hypothesis,but now-multiple mutn rather than[1-2 mutn] needed.envrnmntal factors-carcinogen,radn ,errors in dna replcn,failure of dna repair respnsble for carcngns.successive mutn lead to ca-somatic mutan theory of carcinogenesis.ca can also due to abn chrm nos.also due to oxdtve stress by ros.contribute totumour heterogeneity. Benzopyrene applcn to skin doesn't produce ca,croton oil applcn doesn't lead to to skin ca,but when benzpyrn applcn followed by croton oil,tumor devlpd.here croton oil is promtr.the biological history of tumor shows progrsn of malgncy.

Slide 7

CARCINOGENS

❖ ***Physical, chemical 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

UV rays, X-rays, gamma rays are mutagenic.
These rays cause damage to DNA by altering the bases of DNA.
X-rays and gamma rays lead to formation of free radicals in tissues. These free radicals will interact with DNA and other molecules and may cause molecular damage

Slide 8

- **CHEMICALS**:
  - introduced into the body by means of
- *Occupation – aniline, asbestos*
- *Diet – aflatoxins, food additives, colouring agents*
- *Lifestyle – tobacco smoking ,chewing– benzopyrene*
- *Methyl cholanthrene -powerful*

TABLE 42.1 Some chemical carcinogens.

Polycyclic aromatic hydrocarbons	Benzopyrenes, Cholanthrenes, Dimethyl-benzanthracene (DMBA)
Aromatic amines	N-Methyl-4-aminoazobenzene (MAB)
Nitroso compounds	Dimethyl nitrosamine
Natural compounds	Aflatoxins

Wide variety of compounds are carcinogenic. Polycyclic aromatic hydrocarbons, Aromatic amines, Nitrosamine, various drugs, inorganic compounds like As, Be, Cd, Chr, Asbestos etc
They may bind covalently to cellular macromolecules- DNA, RNA and Proteins.
Covalent interaction with DNA results in damage of DNA and cause mutation of genes.
Some of the chemicals as such are not carcinogenic (Procarcinogens); but can be converted to carcinogenic catabolites by the action of Cyt P_{450}

Slide 9

BIOLOGICAL CARCINOGENS/ ONCOGENIC VIRUS

- Some viruses are carcinogenic.
- Oncogenic virus may be a RNA or a DNA virus
- Transformation by oncogenic virus

TABLE 42.3 Human oncogenic viruses.

Virus	*Abbreviation*	*Associated human disease*
Epstein-Barr virus	EBV	Burkitt's lymphoma (BL); Nasopharyngeal carcinoma (NPC)
Human papilloma virus	HPV	Uterine cervical carcinoma
Hepatitis B virus	HBV	Hepatoma

Eg. Human Papilloma virus, SV_{40}, Epstein Barr Virus (Burkitt's lymphoma, Nasopharyngeal cancer), Hepatitis B virus, retrovirus C and B etcThey may carry Oncogenes and when these are introduced to host cell, protooncogenes of the host cells will be stimulated to get expressed continuously resulting in uncontrolled cell

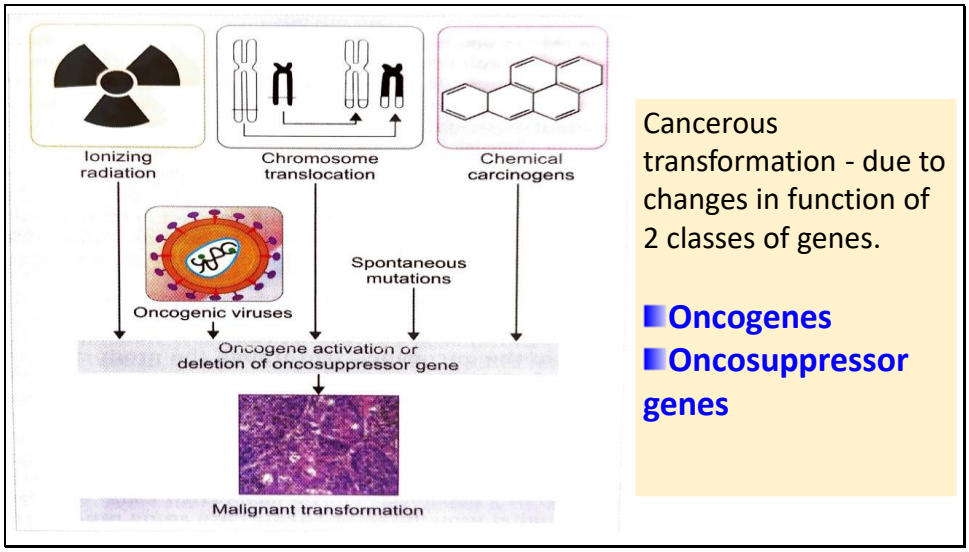
Slide 10

ANTIMUTAGENS

- **Any substance that interfere with tumor promotion**. Eg :
  - ***Vitamin A & Carotenoids, Vitamin E, Vitamin C***
  - ***Curcumin , Flavonoids***
  - ***Phenolic compounds in fruits [like grapes,strawberries,walnuts]***
  - ***Tubers,beans,leafy vegetables***
- **Low protein,low fat diet,good fiber content**
- **Green tea**

Vit c-antioxdnt,prvntdamage by free rad,vit c given to persons working with aniline prvntd prdn of new ca.curcumin-in turmeric prevent mutn.good fiber beneficial.green tea –effective for chemicaly induced mutn

Slide 11



cancerous transformation or uncontrolled proliferation of cells are due to changes in the function of 2 classes of genes.

*Oncogenes
*Tumor suppressor genes

Slide 12

ONCOGENES

➢**Oncogenes:** genes capable of producing cancer.

➢**Proto-oncogenes:** Oncogenes present in normal cells

- *Important* ***regulatory genes*** *of the cell.*
- *May be* ***converted to oncogenes***

due to: ***Environmental factors*** *[chemicals, radiation ,viruses].*
Inherited mutations

• Ex: ***src*** - Rous sarcoma in chicken
ras - rat sarcoma
erb-B - erythroblastosis virus in chicken
sis - simian sarcoma virus in monkey

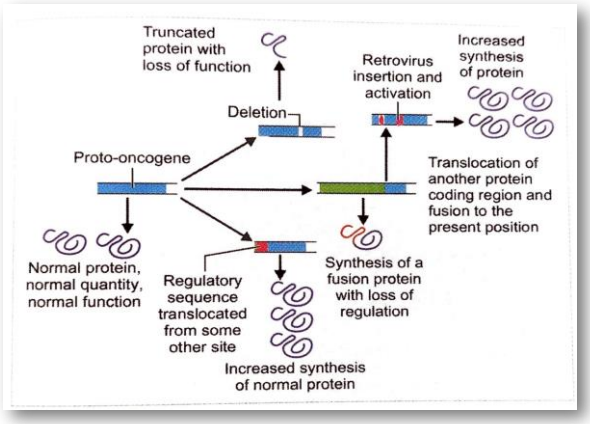
. Oncogenes – mutated proto-oncogenes that promote autonomous cell growth .
Proto - oncogenes – normal cellular genes whose products promotes cellular proliferationThey are part of normal pathway by which cells are stimulated to divide in response to external signals. These genes were first isolated from viruses. Products of most of the protooncogenes are growth factors which generally cause mitosis & differentiation of target cells.
Protooncogenes are transformed to oncogenes by mutation or when an extra oncogene is inserted by viral infection.
Then they produce continuous expression resulting in uncontrolled activity and malignant transformation

Oncoproteins - Proteins encoded by oncogenes .

➢They are devoid of regulatory elements .
➢ Promotes cell growth in the absence of normal growth promoting signals.

Slide 13

PROTO ONCOGENE ACTIVATION BY VARIOUS MEANS



- **Point mutation**
- **Gene amplification**
- **Gene translocation**
- **Insertion of a viral promoter/enhancer**

More than 80 protooncogenes are isolated

These are under the control of regulatory genes & expressed only when they are required

Slide 14

TABLE 42.4 Some cellular oncogenes.

Oncogene	*Virus carrying the gene*	*Oncogene product*	*Subcellular localization of the oncogene product*
Abl	Abelson leukemia virus in mouse	Tyrosine kinase	Plasma membrane
erb-B	Erythroblastosis virus in chicken	Receptor for epidermal growth factor (EGFR)	Membrane
Myc	Myelocytoma virus in chicken	DNA-binding protein	Nucleus
sis	Simian sarcoma virus in monkey	Platelet-derived growth factor (PDGF)	Membrane
Ras	Rat sarcoma	GTPase	Cytoplasm

Slide 15

ONCOSUPPRESSOR GENES / TUMOR SUPPRESSOR GENES/ANTIONCOGENES

- **Genes ,which normally protect the individual cell from developing a cancer.**
- Mutation / abnormality [deleted]of these genes may result in cancer**.**
- **Examples : *p53***
  Retinoblastoma gene (*RB)*

Slide 16

TABLE 42.5 Important oncosuppressor genes.

Name of the oncosuppressor	*Abbreviation*
Retinoblastoma	RB
Wilms' tumor	WT
Familial adenomatous polyposis	FAP
Deleted in colon cancer	DCC
Gene for protein-53	p53
Familial breast cancer	BRCA

Slide 17

ONCO SUPPRESSOR GENE- *RB*

- RB-Governor of Proliferation
- *RB* gene expressed to form Rb protein.[p105], (M.wt-105kd)
- Rb protein –suppress cell proliferation
- Mutation -both allele of RB gene deleted - causes Retinoblastoma

First and prototypic, tumor suppressor gene discovered-Located on Chr 13q14*RB* was discovered by studying a rare disease,- retinoblastoma.
Rb protein –suppress cell proliferation,prevent activity of various oncogenes. Mutation of this gene causes Retinoblastoma – a tumor seen in children

Rb protein (M.wt-105kd) is a part of mechanism that ensures the completion of G_1 phase before the cell enters to S phase.Knudsons two hit hypothesis

Slide 18

ONCO SUPPRESSOR GENE – *P53*

- '**Guardian genome' or 'Molecular policeman**'.
- Gene encodes p53, Phosphoprotein [M.wt -53kd]
- It blocks cells with damaged DNA – by triggering blocking of cell division,until damage is repaired.
- If damage is severe ,p53 trigger apoptosis of cell.
- p53- Suppress transformation ability of oncogenic virus

  Activate expression of genes that suppress cell proliferation.

A short arm of chr 17 –deleted in varous ca-this region contain an oncsuprsr gene p53. containing 375 aa
So called asGene encodes p53, Phosphoprotein [M.wt -53kd]. It acts on the nucleus and regulates certain genes involved in cell division
Normal functional p53- suppress transformation ability of oncogenic virus
activate expression of genes that suppress cell proliferation

Slide 19

GROWTH FACTOR

- Stimulate Cell proliferation .
- Overexpression / increased secretion of growth factors, associated with carcinogenesis.
- Eg: - Platelet-derived Growth Factor (PDGF)- Glioblastomas

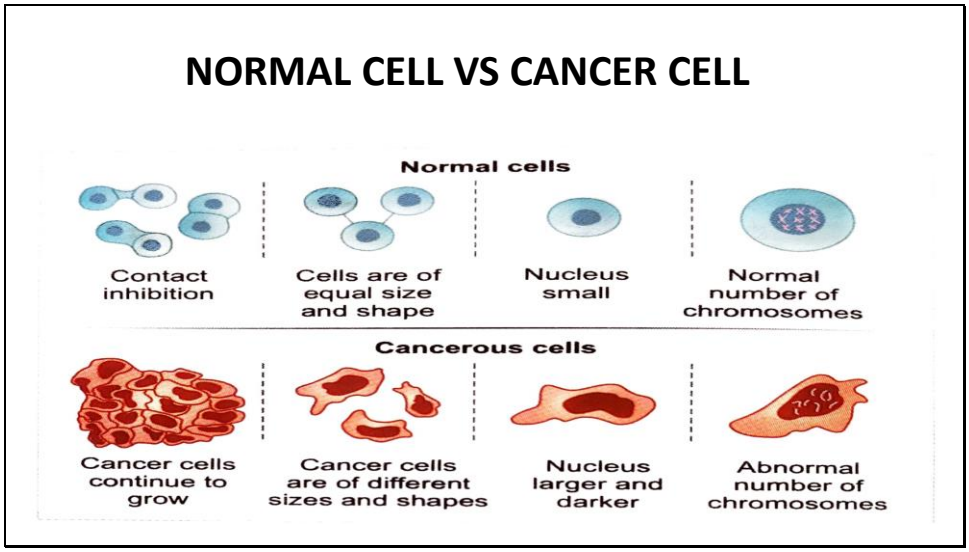
  Transforming Growth Factor A (TGF- α) - Sarcomas

- Acquire the ability to synthesize the same growth factors to which they are responsive, creating an autocrine loopGlioblastomas express platelet-derived growth factor (PDGF)
- Sarcomas overexpress transforming growth factor α (TGF- α)

Slide 20

Growth factor	Abbreviation	Produced by	Function
Epidermal growth factor	EGF	Fibroblasts, submaxillary gland	Stimulates epidermal and epithelial cells
Transforming growth factor-beta	TGF-β	Platelets, placenta	Inhibition of fibroblasts
Platelet-derived growth factor	PDGF	Platelets	Accelerates wound healing
Nerve growth factor	NGF	Submaxillary gland	Growth of sensory neurons
Erythropoietin	EP	Kidney	Stimulates erythropoiesis
Granulocyte colony-stimulating factor	GCSF	Endothelial cells and fibroblasts	Stimulates granulocytes
Monocyte colony-stimulating factor	MCSF	Endothelial cells	Stimulates monocytes
Tumor necrosis factor alpha	TNF-α	Monocyte	Necrosis of tumor cells, proliferation of leukocytes

Slide 21



1]TUMOUR KINETICS,-MORE NO CELLIN DIVIDING PHASE,2]DOUBLING TIME; TIME TAKEN TO DOUBLE ITS MASS
LIFESPAN- IMMORTAL,FN OF APOPTOSIS LOST[DUE TO INCREASED & PERSSTNT ACTIVITY OF TELOMERASE.
3] MALIGNANT TRANSFORMATION-MULTILAYERED APPEARTHAN NORMAL MONOLAYER.4]CONTACT INHIBITION-GROWTH OF NORMAL CELL INHBTD BY CONTACT WITH OTHER CELLSOF SAME KIND,BUT CA CELLSNOT SUBJECT TO SUCH CONTACT INHIBITION
BIOCHEMICAL CHANGES,METAB ALTRN IN CA CELLS,
METASTASIS & SECONDARIES
Cancer cachexia-rdn in body wt,resulting predomntly from loss of skeletal muscle& adiopose tissue.angiogenesis-cells attract blood vessel to grow & feed tissue .normal process,benign to malignant transform-angiogens step.

Slide 22

TUMOR IMMUNOLOGY

Slide 23

TUMOR ANTIGENS

Tumor specific antigens [TSA]

- Occur only in tumor cells
- Can be abnormal product of oncovirus/mutated oncogenes.
- Eg: Ras Protein

Tumor Associated antigens [TSA]

- Occur only in both healthy & tumor cells
- Eg: oncofetal antigens[AFP,CEA]

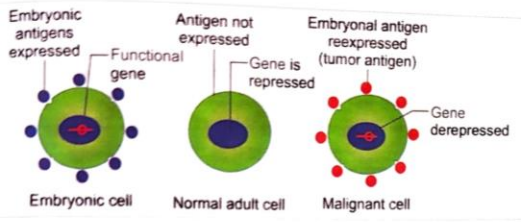


Fig. 42.21: Oncofetal antigen

Tumors may express tumor antigens that are recognized by the immune system & may induce an immune response.tsa-can be pdts of oncovirus

Slide 24

TUMOR MARKERS

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

There are several biochemical tests which help in diagnosis and management of cancer. Are substances usually proteins , that are produced by the body in response to caner growth or by the cancer tissue itself
Many cancers are associated with abnormal production of proteins, enzymes, hormones etc. which can be measured in plasma or serum. These molecules are called Tumor markers which are specific for cancer of a particular tissueDetected in higher than normal amounts in the blood , urine or body tissues.
.

Slide 25

IDEAL TUMOR MARKER ???

- **Highly specific** : detectable in only one tumor type
- **Highly sensitive** : Non detectable in physiological or benign disease state
- **Long lead time** : Sufficient time for alteration of natural course of disease

Slide 26

USES OF TUMOR MARKERS

- ❑For follow-up of cancer & to monitor the effectiveness of therapy & also to detect recurrence of tumor
- ❑For Screening and Early Detection of Cancer
- ❑Diagnosing Cancer
- ❑For assessing the prognosis of cancer

For localisation of cancer, **Determining the Prognosis (Outlook) for Certain Cancers, Determining the Effectiveness of Cancer Treatment, Detecting Recurrent Cancer**

Slide 27

COMMON TUMOR MARKERS

Name	Serum level increased in
Oncofetal proteins Alpha feto protein[**AFP**] Carcino embryonic antigen (**CEA**)	**Hepatoma**, germ cell cancer **Colorectal**, lung & gastrointestinal cancers
Tumor associated antigens /Carbohydrate Antigens • **CA125** • CA19-9	• Epithelial ovarian cancer • Carcinoma pancreas
Tissue Antigens • Tissue polypeptide antigen	• General cancer load

AFP-Homologous to albumin
Fetal albumin [serve thefunctions of albumin in fetal life]
Increased in : hepatocellular carcinoma, pregnancy with fetal malformationd of neural tube
elevated CEA level -before surgery indicate worse prognosis.
If all cancer has been removed, CEA should return to normal levels in about 4 to 6 weeks.
After treatment, CEA measurement every 3 to 6 months should be considered to help early diagnosis of recurrence.

Ca 125-Epithelial ovarian cancer Any adenocarcinoma with advanced stage . **Physiological conditionsMenstruation Pregnancy** Clinical applications
Its measurement in postmenopausal women with pelvic masses helps to differentiate malignant from benign d

Slide 28

Enzymes • Alkaline phosphatase [**ALP**] • Placental type ALP • Prostate specific antigen **PSA** • PAP • NSE	• Bone secondaries • Lung,Seminoma • Prostate cancer • Prostate cancer • Nervous system tumors
Hormones • Beta human chorionic gonadotropin [**beta-Hcg**] • Calcitonin • ACTH • VIP • VMA • Hydroxyindole acetic acid	• Choriocarcinoma • Medullary thyroid Ca • Lung oat cell Ca • Apudomas • Pheochromocytoma • Carcinoid Syndrome

CEA in non-small cell lung

NSE in small cell lung cancerProstatic acid phosphatase,neuron specific enolas
Its measurement in postmenopausal women with pelvic masses helps to differentiate malignant from benign diseases

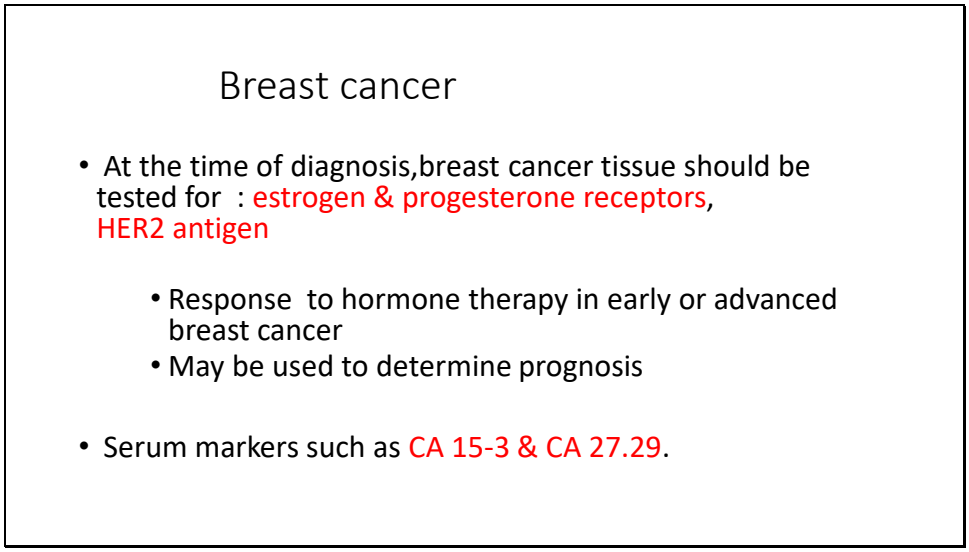
- hCG can exist in multiple forms

Intact 2-chain peptide
To maintain progesterone production by the corpus luteum during early pregnancyFree alpha and beta chains
Various degradation products
Benign prostatic hypertrophy (BPH)Acute and chronic prostatitisUTIUrinary retention.Diagnosis of prostate cancer.Determining prognosis Surveillance following diagnosisMonitoring**Benign conditions** Benign prostatic hypertrophy

Slide 29

Tissue catabolic product Hydroxy proline	Bone metastasis
Serum proteins **Ig** Bence jones proteins [urine]	**Multiple myeloma**
Receptor tumor markers **Estrogen receptor [ER]** **Progesterone receptor [PR]** **HER2/neu[erbB2 or EGFR2]**	 **Carcinoma breast,uterus** **Carcinoma breast**

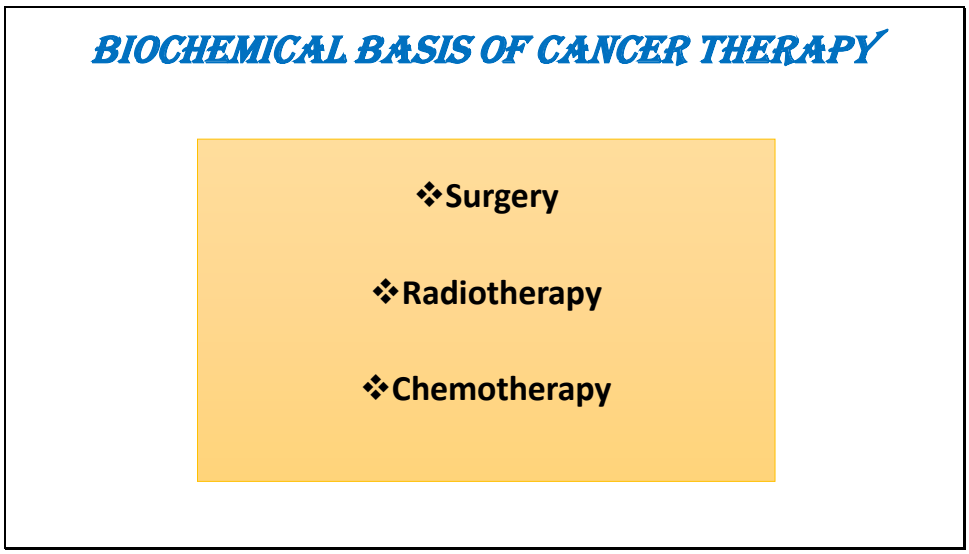
Slide 30



At the time of diagnosis, breast cancer tissue should be tested for estrogen & progesterone receptors, as well as HER2 antigenHer – 2 :

For the identification of patients who may be treated with Trastuzumab in the metastatic setting and to identify patients that may be eligible for clinical trials Blood levels should go down if cancer responds to treatment and rise if disease progresses

Slide 31



Surgery & radiOTHERAPY –prime modlty trtmnt in all solid tumors.chemo-in leuk,lymphoma,other disseminated malignancyeffectiveness of cytotoxic derug directly proprnl to no.of ca cells.

Slide 32

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 : pyrimidine analog[inhibit thymidylate synthase]

4] **Mitomycin**
MOA: intercalation with DNA strands

Slide 33

TABLE 42.9 Common anticancer drugs.

Name	*Type*	*Mode of action*
Methotrexate	Folic acid analog	Competitive inhibitor of dihydrofolate reductase. THFA is required for nucleotide synthesis
6-mercaptopurine	Purine analog	Inhibits the conversion of IMP to AMP
6-thioguanine	Purine analog	Inhibits synthesis of purine nucleotides
5-fluorouracil	Pyrimidine analog	Inhibits thymidylate synthase
Cyclophosphamide	Alkylating agent	Cross linking of bases of DNA; inhibition of strand separation
Mitomycin C	Antibiotic	Cross bridges are formed between DNA base pairs
Actinomycin D	Antibiotic	Intercalates with guanine bases of DNA; prevents transcription
Vincristine and Vinblastine	Alkaloids from Vinca rosea	Interferes with assembly of cytoskeleton and inhibits Stathmokinesis (spindle movement)
Adriamycin	Anthracyclines	Topoisomerase mediated breaks in DNA
Etoposide	Podophyllo-toxin	Stabilizes topoisomerase-II-DNA cleavage complexes
Cisplatin	Platinum compound	Forms intrastrand DNA adducts
Taxanes	Apoptosis inducer	Inhibits mitotic spindle formation; used in carcinoma breast

Slide 34

TARGETED THERAPY IN CANCER

- 1]Small molecule drugs:
- Eg :in breast,lung,colorectal carcinoma

- 2]Monoclonal antibodies
- Eg :in breast cancer,CLL

1]they can enter cells &act on intracellular targets
2]new innovation- moa-ab mark ca cell make it easier for immune systm to attack.,block growth receptors

Slide 35

TABLE 42.10 Monoclonal antibodies used as anticancer agents.

Name	*Target*	*Used against the cancer*
Alemtuzumab	CD52 on B cells	B cell CLL
Bevacizumab	VEGF	Colorectal, solid tumors of kidney
Blinatumomab	CD19	B cell ALL
Cetuximab	KRas	Colorectal, head and neck
Daratumumab	CD38	Multiple myeloma
Dinutuximab	Disialoganglioside GD2	Pediatric neuroblastoma
Elotuzumab	SLAMF7	Multiple myeloma
Panitumumab	EGFR	Colorectal cancer
Imatinib	Tyrosine kinase	CML
Ipilimumab	CTLA-4	Metastatic melanoma
Lapatinib	Tyrosine kinase	Carcinoma breast
Nivolumab	PD-1	Metastatic melanoma, non-small cell lung carcinoma
Ofatumumab	CD20	CLL
Olaratumab	PDGFRA	Soft tissue sarcoma
Panitumumab	EGFR	Colorectal cancer
Pembrolizumab	PD-1	Metastatic melanoma
Rituximab	CD20	NHL, CLL, B cell leukemia
Sorafenib	VEGF	Renal cell cancer, hepatocellular carcinoma
Trastuzumab (Herceptin)	HER-2/neu (EGFR2, c-erb-B2)	Breast cancer

(ALL: acute lymphoblastic leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; EGFR: epithelial growth factor receptor; NHL: non-Hodgkin's lymphoma; PDGFRA: platelet derived growth factor receptor alpha; VEGF: vascular endothelial growth factor.)

Slide 36

APOPTOSIS

Slide 37

APOPTOSIS- PROGRAMMED CELL DEATH

- Term means “falling off leaves”
- Many organisms exhibit a process of programmed cell death called **apoptosis**.
- A natural biochemical process.
- Required in developmental processes & also to maintain homeostasis of a whole organism.

Many organisms exhibit a process of programmed cell death called **apoptosis.** A natural biochemical process of cell deathDuring development in the growing embryo, tissues present at one stage must be removed as development proceeds -
As new cells are generated, old , damaged & imperfect cells has to be removed for the health of the organism.
- for example, the "webbing" that humans have between fingers at a certain point in fetal life.

Characteristic changes during apoptosis are:

- Nuclear Shrinkage
- Chromatin condensation
- Membrane blebbing
- Step ladder pattern of DNA during electrophoresis.

Slide 39

- ***Apoptosis mediating genes / suicidal genes/ oncosuppressor genes*** :

❖ P53
❖ Rb
❖ c-fos

- ***Apoptosis protecting genes*** :

❖bcl2

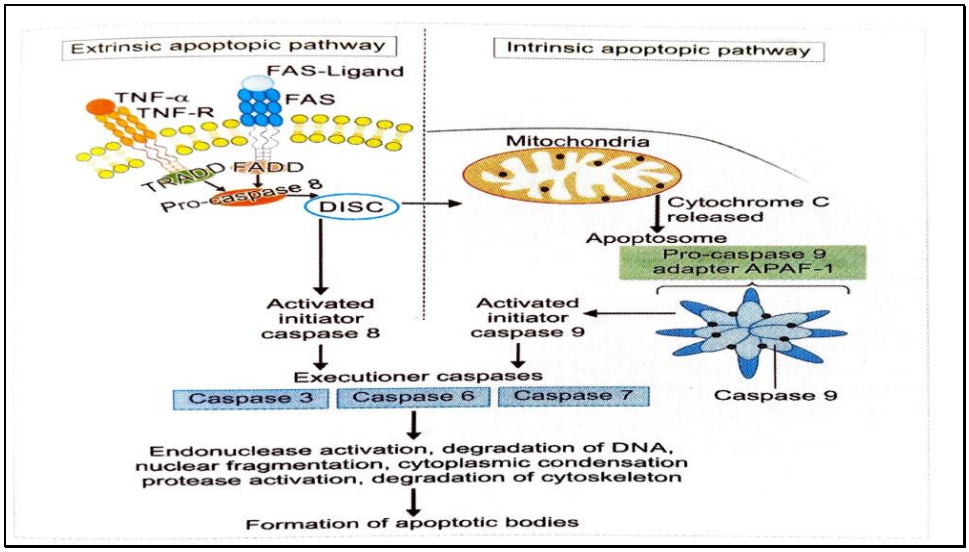
Stress,other stimuli activate cell surface receptors,a cascade of activation take place.

Slide 40

- **Apoptosis pathways** :
  - **Extrinsic pathway [extrinsic death receptor pathway]**
  - **Intrinsic pathway [intrinsic mitochondrial pathway**
  - **Common pathway**
- **3 phases of apoptosis**:
  - Intiation ,regulation & execution

Intiation-triggers

Slide 41



. Apoptosis pw- extrn&intrns-result in programd cell death.when cell at rest,proapoptotic Bax&bak remain inactive.exrtrnsc death receptor pw-intiated by binding death ligand[TNF,Fas L] TO A death recptr[TNFR1,Fas].THESE DEATH RECEPTRS HAVE intacellular death domain,THAT RECRUY adaptor protein.[TRADD-TNF ASSOC DETH DOMAIN,FADD] & CASPASE 8,WHN DETH RECPTR BIND DEATH DOMAIN BINDNG SITE FOR ADAPTR PROT EXPOSED.Ligand receptor adptr prot complex[DISC-death inducing signalingcomplex]intiate ,activate casp8[intr]'
INTRNSC PW: intd within cell,factors-hypoxia,dna damage,oxdtv stress,-trigger intn of mitochndrl pw-result in incrsd mitocndrl permeability.relese cytochromec to cytosol.other apoptotic factors-apop incng factor[AIF].-COPMLEX APOPTOSOME[cyt c ,Apaf-1 & caspase] FORMED activate caspase 3 .
Common pw-casp 9-upstream caspof intr pw,casp8-that of extrnsc pw.
Both pw converge to casp3 –which cleave other casp seqnly.

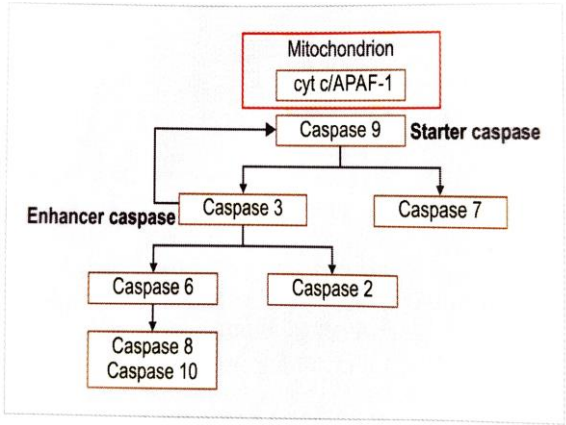
Slide 42

Apoptosis- Caspase cascade

- Final effector mechanism of cell death is through the activation of :

  Caspases- Cysteinyl Aspartate Specific Proteases.

- Caspases 1 to 10 are identified



Caspases are present as zymogens, acitvated one by one. The **caspases** are proteases that cleave the carboxyl side of aspartate (c-asp-ase)

Caspases 1 to 10 are identified – named in the order of their discovery.
First one to be activated is Caspase 9- Initiator
Final one is Caspase 3(effector/executioner) .cas9-a substrate for cas-3'
Casp3-activate cas-6,8,10,these hydrolyses the target proteins.
Activates Caspase activated DNAse which cleaves the cellular genome – death by several cuts

Slide 43

CELL CYCLE

Slide 44

➢ **Cell Cycle** : Period between 2 mitotic divisions in a somatic cell.

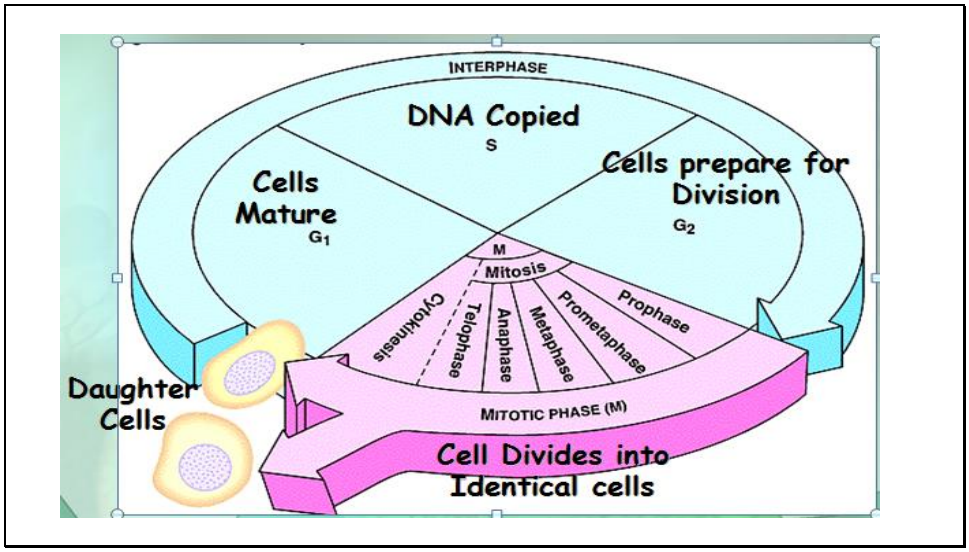
➢Phases of cell cycle are:

- **G_1 Phase [gap-1]**
- **S Phase [synthesis]**
- **G_2 Phase [gap-2]**
- **M Phase [mitosis]**

M Phase (Mitotic Phase)- *Period when the cell divides.*
Interphase- *period between end of M phase & beginning of next mitosis.*

In human it lasts for about 18-24 hours. Under microscope, 2 visible phases of cell cycle are
M Phase (Mitotic Phase)- *Period when the cell divides.*
Interphase- *Extended period of synthesis and growth*

Slide 45


INTERPHASE
DNA Copied
S
Cells prepare for Division
G2
Cells Mature
G1
M
Mitosis
Cytokinesis
Telophase
Anaphase
Metaphase
Prometaphase
Prophase
MITOTIC PHASE (M)
Daughter Cells
Cell Divides into Identical cells

Slide 46

PHASES OF CELL CYCLE

G_1 Phase : Proteins and RNAs content increases
Duration – about 12hrs

S Phase : DNA synthesized[once], DNA content doubles,is replicated completely .
Duration – about 6-8 hrs

G_2 Phase- cytoplasmic enlargement,DNA repair,histones produced
Duration – about 4-5 hrs

Total cell cycle duration : 20-22 hours

G_1 Phase : Cells are released from M phaseto a Gap phase during which Proteins and RNAs are synthesized - 6-12hrs

S Phase :This phase starts with initiation of synthesis of the DNA and lasts till DNA is replicated completely – 6-8 hrs

G_2 Phase: Gap Phase between S phase and M Phase - Condensation of DNA to Chromosome.At the end of this phase cell contains 2 diploid sets of chromosomes - 4-5 hrs

M Phase:

- **Nuclear envelope dissolves.**
- **Cell organized to mitotic spindle.**
- **Chromosome segregates into 2 diploid sets**
- **Cell divides into 2 daughter cells**

Slide 47

REGULATION OF CELL CYCLE

• A number of check points are there which regulates the cell cycle.

3 Check Points

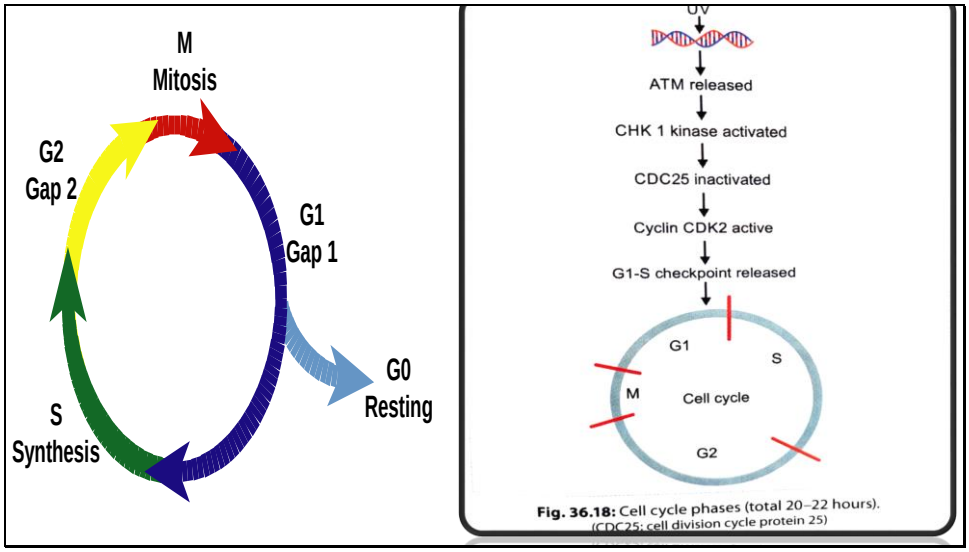
• G1S transition
• S Phase
• G2M transition

Regulated by

• Cyclins (4) – A, B, D & E
• Cyclin dependent Kinases(5) – 1, 2, 4, 5 & 6

Cell will embarks on its division cycle only if it is assured that it can successfully complete the act. Cell cycle is completed within 20-22 hours in normal cell .
In normal adult tissues, only 1% of the cells are in dividing state, rest of the cell in quiescent state.Cells will ignore the stop signals and continues to prolifera
phaseMany of the cancer causing viruses and cancer causing genes are capable of alleviating or disrupting the apparent restriction that normally controls the entry of mammalian cells from G1 to S phases

Slide 48



G_1/S checkpoint is most critical primary decision point. if cell receives "GO" signal, it divides. if cell does not receive signal, it exits cycle &
switches to G_0 phase.

G_0 phase non-dividing, differentiated statemost human cells in G_0 phase

The **G2/M DNA damage checkpoint** prevents the cell from entering mitosis (M phase) if the genome is damaged

The **M checkpoint** is where the attachment of the spindle fibres to the centromeres is assessed. Only if this is correct can mitosis proceed. Failure to attach spindle fibres

correctly would lead to failure to separate chromosomes

Cyclins activate specific CDK proteins which phosphorylate specific regulatory substrates.

CDK2- Cyclin E complex directs the cells in G_1 phase to enter S phase

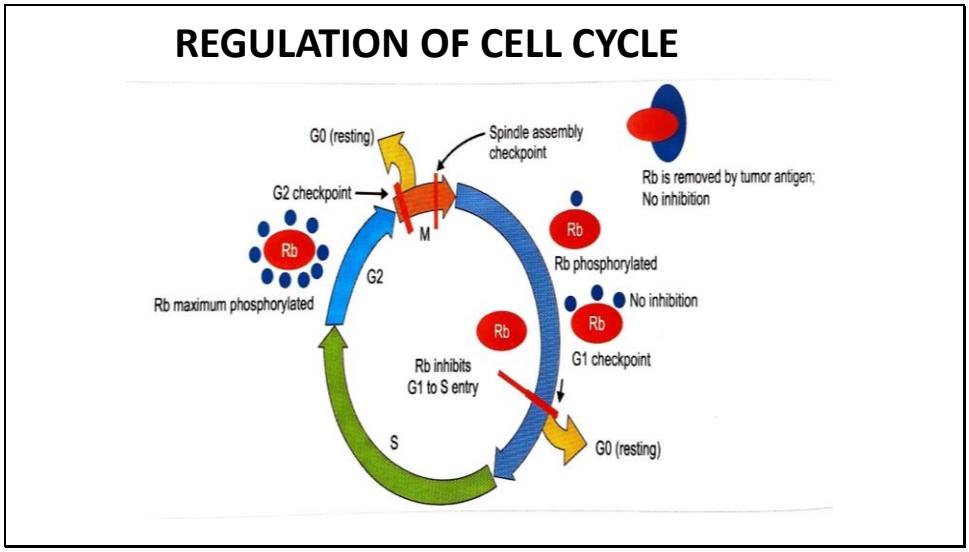
CDK-2 complexed with Cyclin A pushes the cells to complete S phase.

CDK1, Cyclins A and B makes the cells to complete the G2 phase and enter in to M phase. M Phase promoting Factor (MPF) pushes the cell to mitosis

At the end of G_2, p34 is activated and phosphorylates many substrates leading to chromosome condensation.

At the end of M Phase, MPF becomes inactive by cyclin degradation

Slide 49


REGULATION OF CELL CYCLE
G0 (resting)
Spindle assembly checkpoint
Rb is removed by tumor antigen; No inhibition
G2 checkpoint
M
Rb
Rb phosphorylated
Rb maximum phosphorylated
G2
No inhibition
Rb
Rb
G1 checkpoint
Rb inhibits G1 to S entry
S
G0 (resting)

Slide 50

BIOCHEMISTRY OF AGING

The word ageing does not give a good feeling to most of us because of problems and diseases associated with ageing.

Healthy and active ageing is a process to achieve physical, mental and social well being throughout one's life particularly in the later years.

Slide 51

- Aging –natural phenomenon
- **Geriatrics / Gerontology :**

  medical branch dealing with age-related diseases.
- All physiological process decline as age advances.

Ageing is a process of gradual ,progressive and generalized impairment of functions resulting in the loss of adaptive response to stress and increasing the risk of diseases
Differ in individual-due to diff in lifestyle,diet,disease,genetics etc

Slide 52

TABLE 43.2 Significant changes occurring in the body during aging.

Change during aging	*Clinical manifestation*
Sarcopenia	Loss of muscle mass
Osteopenia	Osteoporosis
Oxidative stress	Accumulation of age pigment, lipid peroxidation
Decreased antioxidant status	Type 2 diabetes mellitus, Coronary artery disease
Increased insulin resistance	Diabetes mellitus
Glycation of proteins	Accumulation of AGE in tissues
Loss of subcutaneous fat	Wrinkles
Loss of elasticity of collagen	Stiffening of joints and tissues

Cellular theories of aging

- ***G.Hayflick limit theory***
- ***Mutation theory***
- ***Error catastrophe theory***
- ***Free radical reaction theory***
- ***Pacemaker theory***

Slide 54

- ***G.Hayflick limit theory***
- Cultured human fibroblast double only a limited number of times before they lose their capacity to divide and finally die

- ***Mutation theory***
- As person grows older,his genetic material[DNA] deteriorated,caused by accumulated errors in replication.leads to aging.

No of cell divsn of cultrd cell roughly related to age of cell donor,longevity of species

Slide 55

- ***Error catastrophe theory***
- Accumulation of errors in aminoacid sequence in proteins,result in mistakes in protein synthesis & consequently cell death.

- ***Free radical reaction theory***
- It says free radicals generated will lead to deterioration of lipids,other body substance, cause aging.

- ***Pacemaker theory***
- Ageing is caused in part by progressive breakdown in immunological system

Esp that effect enzms needed for prot synths.as age progress,a decline in immune system.,alo prodn of autoantibody

Slide 56

- ***Telomerase***
- Declining activity of telomerase – another cause of senescence
- ***Mutations in mitochondrial DNA***

-due to free radicals,oxidative stress

Whenever the cells divide, telomeres are shortened leading to cellular damage associated with aging, which can be rebuild by an immortalizing enzyme i.e telomerase, an enzyme found only in genetic cells .It appears to repair and replace telomeres that controls the life span of dividing cells .malignancy-continuous exprsn of telomerase

Slide 57

- **CRISPR TECHNOLOGY TO REVERSE AGE**

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Slide 58