

Neoplasia ✓

Formation of new and abnormal growth of tissue is called neoplasia.

There are two type of neoplasia

Benign Tumor
Malignant Tumor

neoplasia have 2 cell
tumor parenchyma
Reactive stroma

Benign Tumor

Differentiation ✓

Well differentiated

Area

Remain localize

Anaplasia ✓

No anaplasia

Metastasis ✓

No metastasis

Growth ✓

slow growth Rate

Capsule ✓

enclose in capsule

size ✓

small size

Malignant Tumor

Un differentiated

invade and penetrate in surrounding Tissue

Anaplasia present (loss of mature cell or tissue)

Metastized to regional lymph node

Fast growth Rate

Capsule never present

large size **niceday**



Date: (2) -

Suffix ✓

Suffix oma

Suffix carcinoma

harmful ✓

No

harmful

Margins ✓

Margins are expansile

Margins are infiltrate.

Invasion ✓

No invasion occur

Invasion occur

example.

Fibroma

Fibrosarcoma

Benign cell

Malignant cell

① -

Well differentiated cell. resemble to normal cell

Undifferentiated cell not resemble e-normal cell

② -

Uncommon Mitosis / Normal

Common Mitosis. / abnormal

③ -

✓ distributed chromatin

✓ Clumped chromatin

④ -

✓ dec

↑ N/C Ratio ↓

⑤ -

cell not infiltrate

cell infiltrate

⑥ -

✓ organised

No

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✓
Diploid

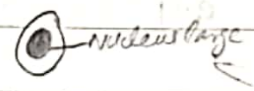
⑦-

Range of ploidy

Slow Growth

⑧-

Rapid



Mixed Tumor :-

→ Tumor contain epithelium component with in myxoid stroma that may contain island of cartilage or bone

* More than one cell type → derive from 1 germ cell layer eg salivary gland

Teratoma :-

* More than one neoplastic cell type derived from more than 1 germ cell layer

e.g. arise from totipotent cells

→ Totipotent cell of gonads.

Hamartomas :-

* Benign tumor

* made up of mature but disorganized

cells of tissue

* excessive cellular growth

e.g. :-

Pulmonary chondroid hamartomas

hepatoma
melanoma
seminoma
lymphoma

Date: (4)

Choristoma :-

* Normal cell in wrong location

not true tumor / ectopic focus of normal tissue (heterotopia)

e.g

Pancreatic choristoma in liver.

4 Type of Gene.

↑ Growth Gene

TGF, FGF, PDGF, CDK4
EGF, MYC

↓ Inhibitory Gene

APC, P53 - Rb gene
BRCA1

↑ Repair Gene. defect

BRCA1, 2
MSH2, 6, MLH1

↑ Apoptotic gene

BAX
BAK gene

Carcinoma

Malignant tumor
originated by epithelial cells

adenocarcinoma

Sarcoma

Malignant tumor
originated by mesenchyma

liposarcoma

fibrosarcoma

Differentiation :-

“ Neoplastic parenchymal cells resemble the normal parenchymal cells both morphologically and functionally ”

Anaplasia

“ Lack of differentiation is called Anaplasia (Malignancy) ”

- In malignant tumor lack of differentiation
- but in some tumor - ① well differentiation
- ② functionally malignant

example :-

Squamous cell carcinoma

- ① - Well differentiated
- ② - but functionally malignant

Characteristic

Morphologic change :-

① - Pleomorphism :-

- ① - Variation in size and shape
- ② - Tumor giant cell with single huge polymorphic nucleus
- ③ - other have 2 - or more hyperchromatic nuclei



نواة الشلال

②- Nuclear Morphology:-



- ①- Nuclei large
- ②- N/C ratio is 1:1
- ③- normally N/C ratio 1:4, 1:6.
- ④- Nucleus shape - Variable
- Irregular
- ⑤- chromatin is clumped and coarse
- ⑥- Darkly stained
- ⑦- hyperchromatic

③- Mitosis:-

Mes

①. Atypical mitotic figures.

tripolar	} spindles
quadrupolar	
Multipolar	

④- Loss of polarity:-

- ①- Orientation is disturbed
- ②- Nuclei haphazard.
- ③- Large mass of tumor cell
grow in an anarchic fashion

⑤- Other Growth -

- ①- For Rapid growth tumor Require blood supply.
- ②- less blood supply
- ③- Growing tumor Grow e- large central area of ischemic Necrosis.

① - Well differentiated Sq-cell carcinoma produced Keratin

② - hepatocellular carcinoma secretes bile

Give Rise of Paraneoplastic Syndrome

③ - Bronchogenic carcinoma may produce (Corticotropin, Parathyroid-like hormone, Insulin, Glucagon)

Metaplasia

① - ✓

Reversible replacement of one differentiated cell type with another mature cell type

Conversion in cell type

② -

Reversible Process

③ - ✓

Don't lead to cancer

④ - ✓

Mature cell development

⑤ -

MCO's Occure in various type of tissue/cell

⑥ - ✓

Dysplasia

development of abnormal type of cell within tissue

OR Disorderd cellular development

change in phenotype of cells

Irreversible Process

May cause cancer

Disorderd cellular development

only in epithelium

⑦- ✓

Not all Metaplasia is dysplasia

all dysplasia occur in metaplastic epithelium

⑧-

Sq. cell epithelium Replace by glandular epithelium which is good for high acidity

have . enlarge nuclei
High N/c ratio.
↑ mitotic figures
Pleomorphism-

⑨- ✓



MCDs

①- Dysplasia full involve in

thickness of epithelium
Pre Invasive but lesion does not penetrate
also called Basemend Membrane
Carcinoma in situ

②-

~~Invasive~~ → Invasive → Tumor cell breach bacemnt Membrane

Hyperplasia

①-

Increase no. of cells
Proliferation of cells

②-

Organ enlarge

③-

due to stress
chronic inflammation
hormonal dysfunction

④-

endometrial hyperplasia

Metaplasia

Replacement of one differentiated cell type with other mature cell type

No

due to Physiological change
Smoking

Mass

Barrett's oesophagus

Metastasis:-

Define:-

spread of tumor to sites that are physically discontinuous to with primary tumor

benign tumor not metastize.

All malignant tumor can metastized

Example gliomas. and carcinoma

of skin invade early but rarely metastized

- Invasion mean tumor invade in surrounding cell.
- Metastatic tumor move at other organ by

↓
Pathways

Name

Three method.

① - Seeding within body cavity and surface

①. It occurs when neoplasms invade a natural body cavity or surface

Example:-

- ① - Lung cancer may cover pleural cavity
- ② - Ovarian cancer cover peritoneal cavity
- ③ - colon cancer invade pericolic adipose tissue.

② - Lymphatic Spread:-

Cancer transport by lymphatics

Example:-

① -

In breast

- ① - carcinoma arise in upper outer quadrant related to axillary lymph node
- ② - cancer of inner quadrant spread e- intral mammary artery which enter in lymphatic system both drain in supraclavical node.

Lower axilla
↳ Scapular
central node
axillary node

② -

Lungs:-

- ① - arise in respiratory passage and metastized first at bronchial lymph node then tracheobronchial and hilar node

8 Hematogenous Spread:-

carcinoma spread e- blood verrele
 Artery have thick wall are less
 readily penetrated than vein

Clonal expansion
 Growth angiogenesis
 ↓ Transformation

Metastatic subclone
 ↓ Growth

Adhesion and
 invasion of basement
 Membrane
 ↓ B.M invasion

passing through
 ECMatrix
 ↓ Intravasation

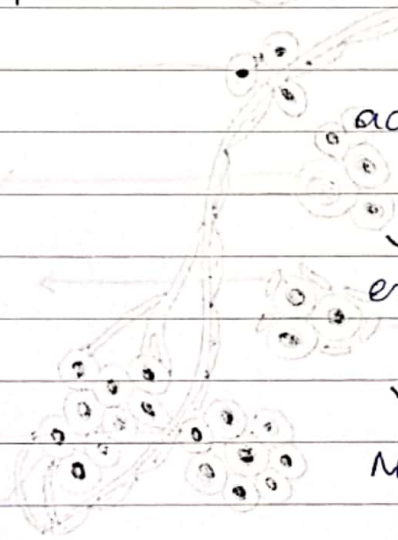
Invasion

Interaction e- host
 Lymphoid cells

↓ embolization

Tumor cell embolus

↓ adhesion



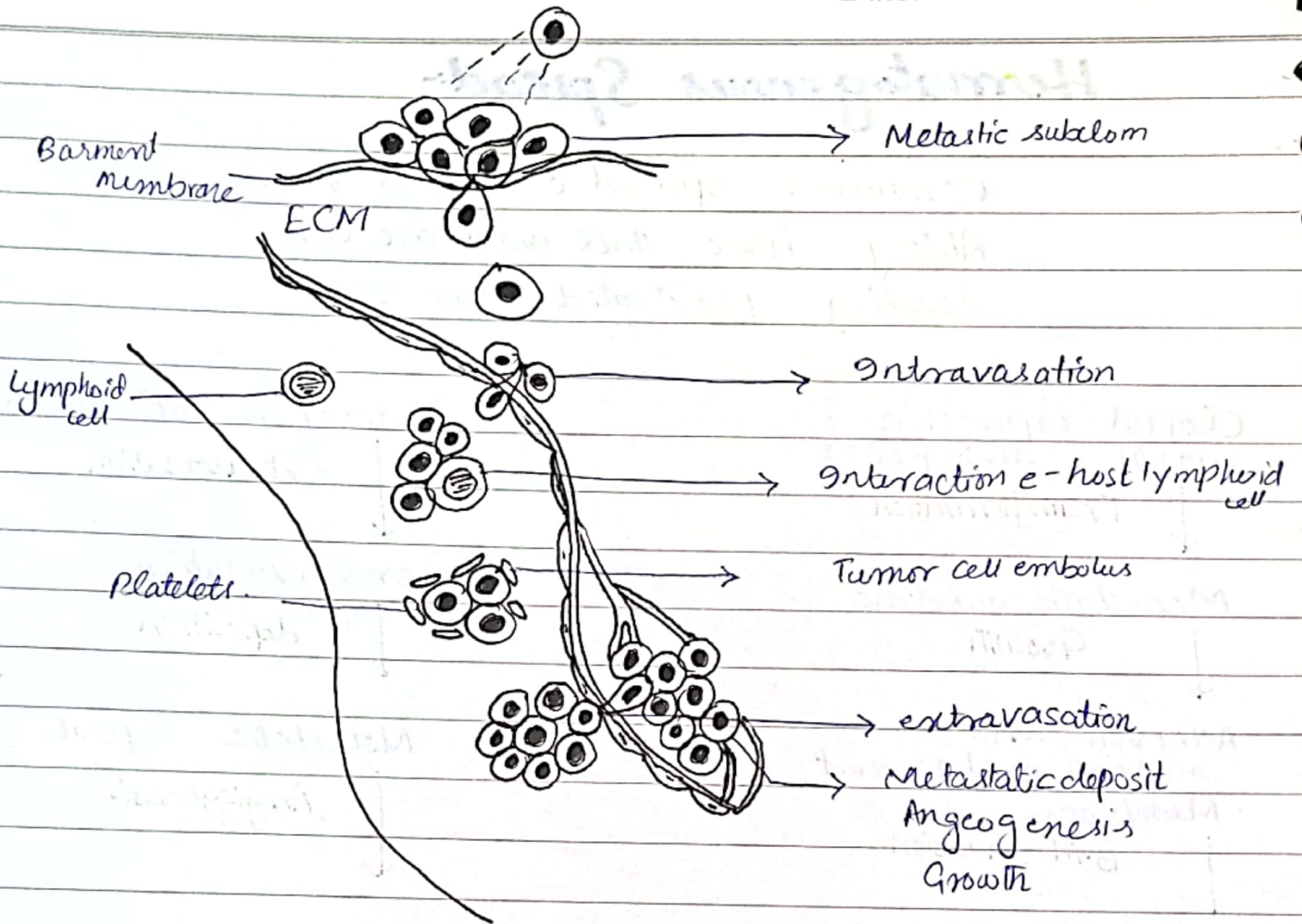
adhesion to B-Membrane
 ↓ extravasation

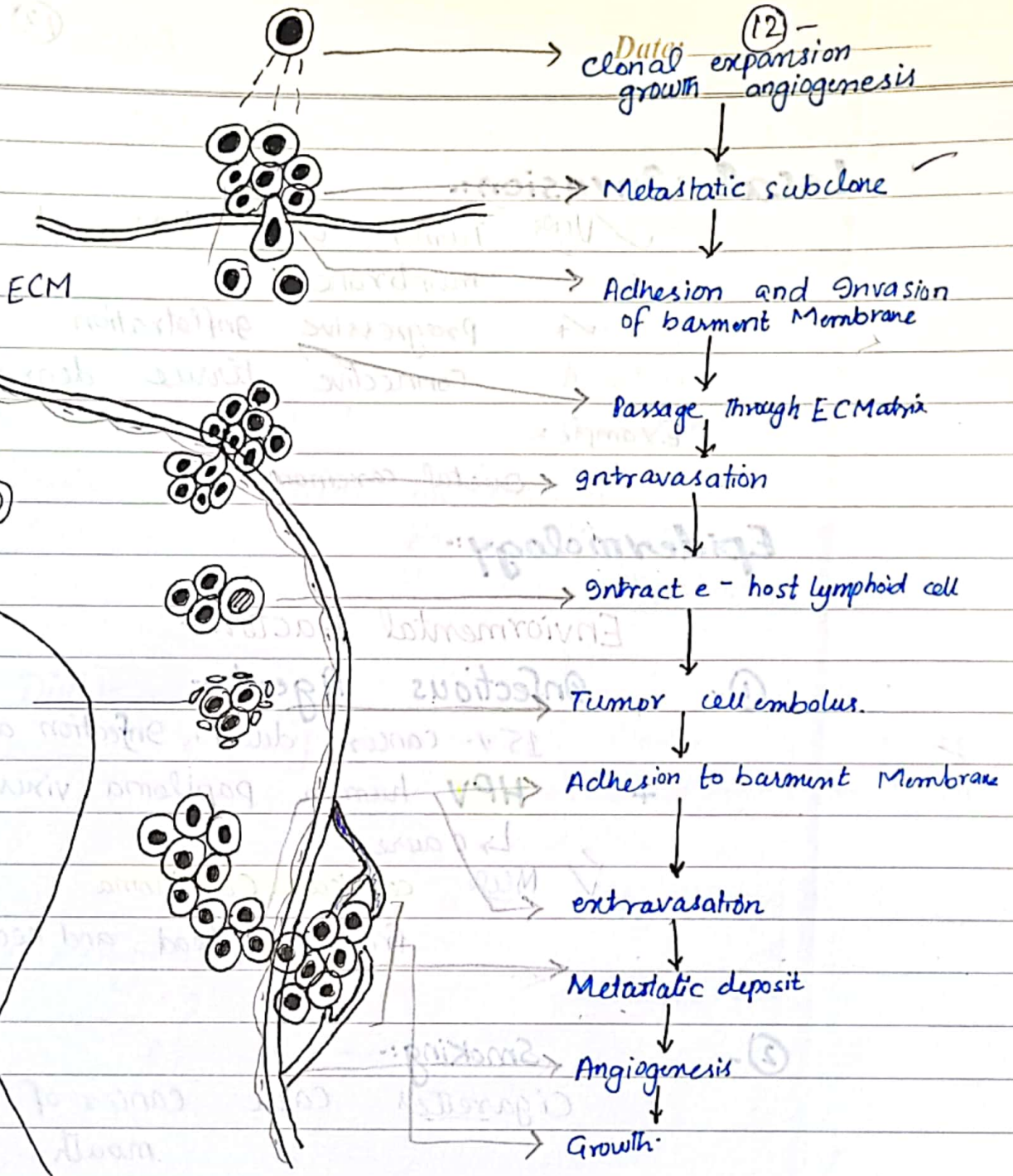
extravasation
 ↓ deposition

Metastatic deposit
 ↓ Angiogenesis

Angiogenesis
 ↓ Growth

Growth





Steps

Local Invasion:-

- ✓ Cells Tumor cross basement membrane
- ✓ progressive infiltration
- Connective tissue degradation

Example:-

Ductal carcinoma

Epidermology:-

Environmental Factors:-

①- Infectious Agents:-

15% cancer due to infection agent

+ HPV human papilloma virus.

↳ cause

✓ Cells cervical carcinoma

fraction of head and neck cancers

②- Smoking:-

Cigarettes cause cancer of

- mouth
- pharynx
- oesophagus
- Larynx
- Pancreas
- bladder

90% cancer

③- Alcohol Consumption:-

- Increase Risk of carcinoma ✓
- oropharynx ✓
- larynx ✓
- esophagus ✓
- hepatocellular ✓
- chirophosis ✓

• Tobacco inc Risk of cancer of airways digestive tract.

④- Diet:-

dietary factor cause cancer of colorectal prostate breast ✓

⑤- Obesity:-

52% men] ↑ Weight
62% Women	

due to obesity cancer

14% in men

20% in Women.

⑥- Reproductive history:-

estrogen and progesteron level cause cancer of breast endometrium

⑦- Environmental Carcinogens:-

Agents	Uses	organ Cancer
Arsenic Arsenic Comp	Component of alloy, electrical herbicidal, fungicidal	Lungs. Carcinoma → skin carcinoma
Asbestos/ silica	floor tiles, fire, heat friction resistances	Asbestosis Sillicosis → esophageal, Gastric colon
Beryllium Beryllium Comp	Metal alloy, Nuclear Reactor Missile fuel	
Chromium Chromium Comp	Metal alloy, paints, pigments Preservatives	
Nickel comp.	Welding, ferrous alloy Welding Nickel plating	→ oropharyngeal carcinoma.
Radon	Minerals contain Uranium.	
Vinyl chloride Aromatic Amides Carbamate	Refrigerant, adhesive for plastics Pressurized containers	Hepatic angiosarcoma
cadmium comp	Phosphorus compound, metal plating used in batteries and alloys. Coatings.	Prostate carcinoma

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Diseases

Agent

Neoplasm.

Asbestosis ✓
silicosis

silica

Lung Carcinoma.

Inflammatory ✓
bowel disease

colorectal " ✓

Lichen sclerosis ✓

Sq-cell carcinoma

Pancreatitis ✓

Alcoholism

Pancreatic Carcinoma

chronic cholecystitis ✓

Bile acid

Gallbladder Cancer

bacteria

Gall stones

Barrett oesophagus ✓

esophageal carcinoma

liver flukes

ulcer

MALT lymphoma /
Helicobacter pylori

MALT lymphoma

hepatitis ✓

hepatitis B/C

hepatocellular Carci

Osteomyelitis

Bacterial infec

Carcinoma
sinus

cervicitis

Papilloma virus

Cervical
carcinoma

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chronic cystitis	Schistosomiasis	Bladder Carcinoma
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Age:-

①- Most cancer b/w ages of 55 and 75

②- In children - Young than 15 year.

Leukemia

Tumor of CNS

Lymphoma

Soft tissue

Bone

Sarcomas.

Carcinogenic Agent :-

A substance capable of causing cancer in living tissue.

Main Classes :-

Chemical agent] cause cancer on human
Physical "	
Microbial "	
] cause cancer on Animal and human

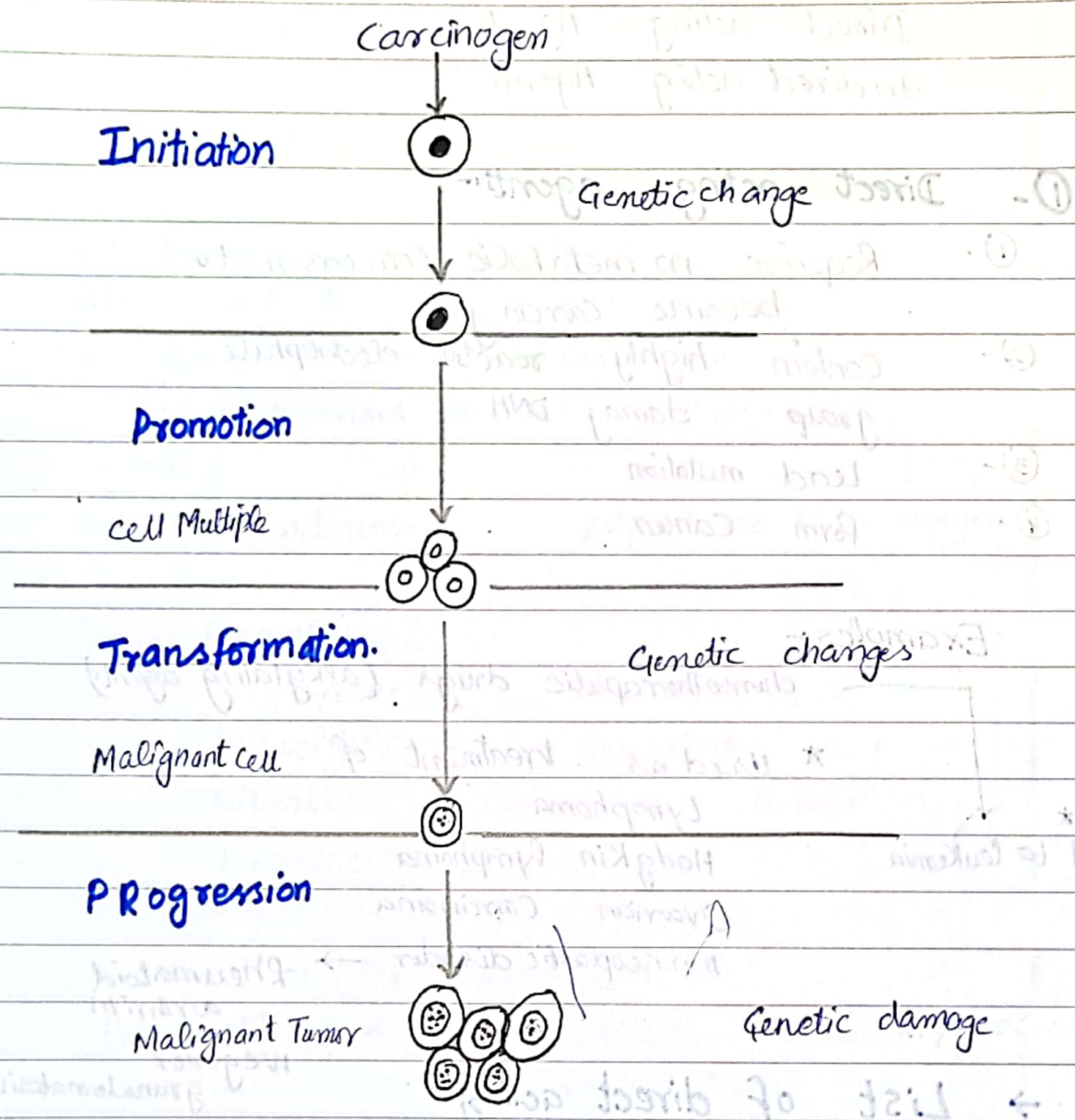
Carcinogenesis :-

Transformation of normal to neoplastic cell is caused by both exogenous and endogenous factor. include chemical - Physical agent, viruses, activation of cancer promoting gene, inhibition of cancer suppressing genes.

Phases of Carcinogenesis.

- ①- Initiation
- ②- promotion
- ③- Transformation
- ④- Progression

Steps of Carcinogenesis



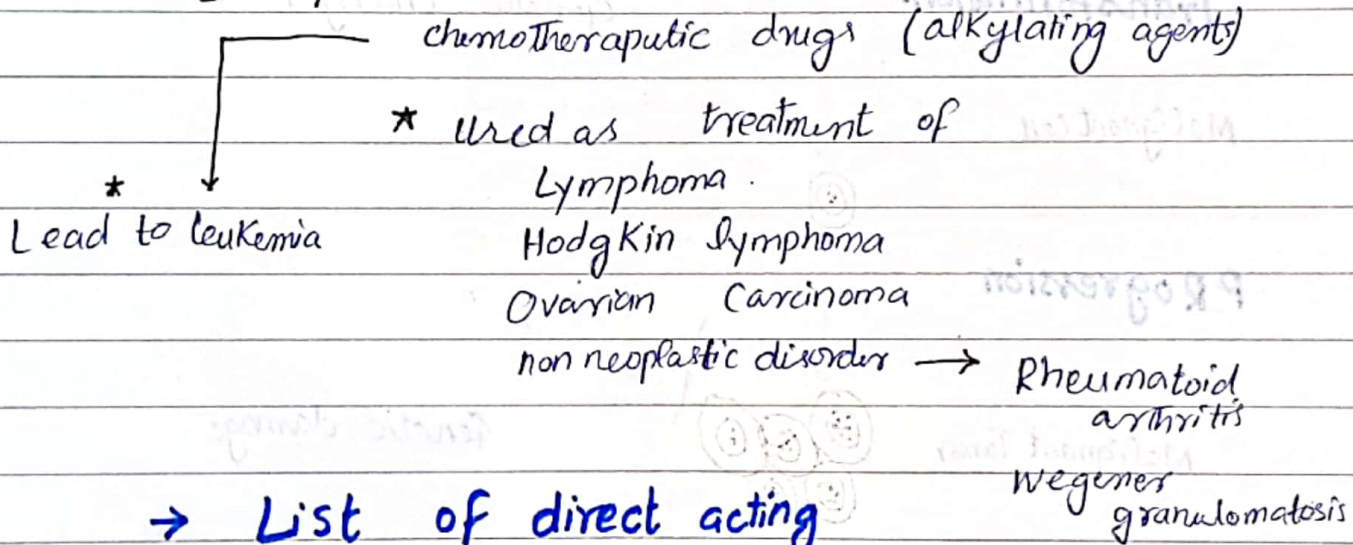
Chemical Carcinogenesis:-

- Direct acting Agents
- Indirect acting Agents

①- Direct acting agents:-

- ①- Require no metabolic conversion to become carcinogens
- ②- Contain highly reactive electrophile group damage DNA
- ③- Lead mutation
- ④- Form Cancer

Examples:-



→ List of direct acting Carcinogenesis :-

Alkylating Agents:-

- * Cyclophosphamide
- chlorambucil
- * Nitrosoureas

B-propionolactone

Dimethyl sulfate *

Diepoxy butane

→ Anti cancer drugs

Acylating Agents- :
Acetyl imidazole
Dimethyl carbamyl chloride

②- In directing acting agents-

- ①- Require metabolic activation ✓
- ②- Convert to ultimate carcinogen
- ③- Conversion to ultimate carcinogen require endogenous metabolic pathway.

E.g

Endogenous enzyme

Cytochrome P450 oxygenase

-AOM

Example

- Benzopyrene , Alfa-toxic B1
- Fungicides , Insecticides
- Nitrates , Aromatic amines
- Azo-dyes

List of In direct agents:-

Polycyclic and Heterocyclic Aromatic Hydrocarbons:-

3 Methyl cholanthrene

7,12 Dimethyl benz (a) anthracene

Benz (a) anthracene

Benzo (a) pyrene

Aromatic Amines, Amides, Azodyes:-

- ✓ B-naphthylamine
- ✓ Benzidine
- 2 Acetyl aminofluorene.

Natural Plants:-

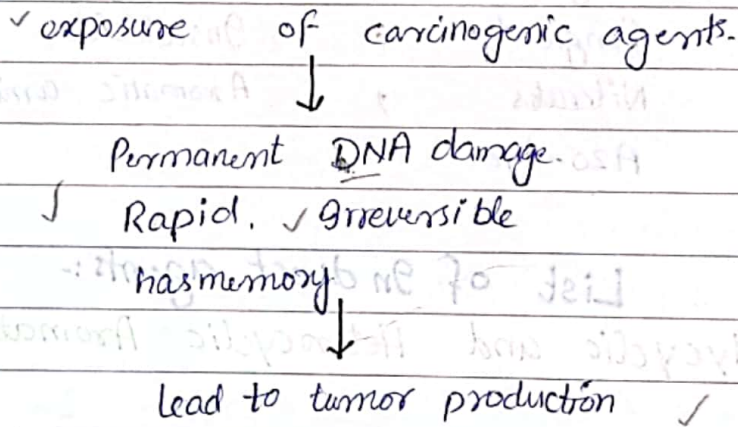
- ✓ Aflatoxin B₁
- ✓ Cyanin
- ✓ Sufale
- Betel nuts

Others

- Nitroamines
- ✓ Amines
- ✓ Vinyl chloride
- ✓ Nickel,
- Insecticide/fungicides

MOA:-

Initiation:-



highly reactive electrophile ✓

(DNA, RNA, Protein RAS, P53) damage
cause nonlethal damage to DNA
can't be repaired ✓

Initiation

Carcinogen

electrophilic intermediate

Binding to DNA

adduct formation

Permanent DNA cell lesion. initiate cell.

Cell proliferate

altered differentiation

Pre neoplastic clone

Proliferation:

Malignant Neoplasm

Detoxification

Excretion

Detoxification

Normal cell

Cell death

Additional mutation

Promotion:-

- ①. induce initiated cell ✓
- ②. Not tumorigenic ✓
- ③. Dnt damage DNA ✓
- ④. are Reversible
- ⑤. Promotor dnt give rise to tumor directly.

②- Physical Agents

Radiation:-

- Ionizing Radiation**
- X-rays
 - Gamma rays
 - Particulate Radiation
 - alpha
 - Beta
 - Protons
 - Neutrons
 - Cosmic Radi

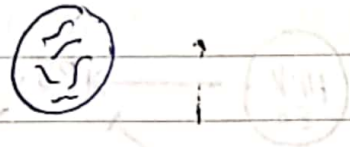
UV-Radiation:-

- A. Not exposed due to ozone layer
- B] Most heavy potent.
- C]

Ionizing Radiation:-

- ①. Cause Chromosome breakage
- ②. Translocation
- ③. Less frequently
- ④. Point Mutation

- 5) Double strand DNA damage
- 6) Genome instability
- 7) Favours Carcinogenesis
- 8) Single strand DNA break
- 9) Fragmentation.



UV-light:-

- cause formation of pyrimidine dimers.
- can be repaired by nucleotide pathway
- skin cancer result
- [Squamous cell cancer
Basal cell cancer
Melanoma] skin
- Xeroderma pigmentosum.

Microbial carcinogen:-

Type:-

- 1) RNA oncogene Virus ✓
- 2) DNA oncogene Virus ✓
- 3) Helicobacter pylori

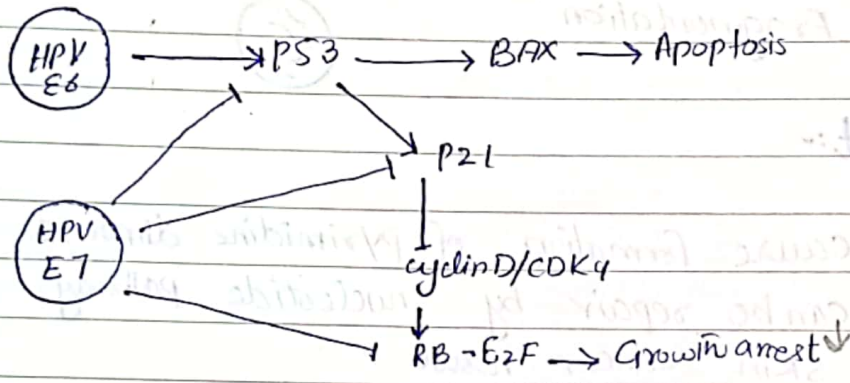
DNA oncogene:-

Human Papilloma Virus HPV

HPV
EBV
HBV

- HPV 1, 2, 4, 7. cause benign squamous cell papilloma ✓
- HPV 16, 18 - 80% squamous dysplasia
cervical cancer ✓
cancer in situ.

- HPV 16, 18 has E6, E7 protein
 ↓ degrade PS3 gene ↓ form Rb gene under phosphorylated.



Epstein Barr viruses:- (EBV)

- Burkitt Lymphoma
- B-cell Lymphoma
- Hodgkin Disease
- Nasopharyngeal Carcinoma

Translocation

Hepatitis B Viruses (HBV):-

- HBV Cause liver cancer

Hepatitis B

↓
DNA viruses

↓
DNA damage

↓
cause hepatic T cell lymphocytic viruses. Lymphoma

②- RNA oncogenic viruses:-

①- Acute transforming viruses:-

- have viral oncogene (src, abl, myb)
- directly transform human oncogene

ATV

STV

②- Slow transforming viruses:-

- Not have viral oncogene
- may insert near to human oncogene and make them overexpressed now (HTLV-1) *

can cause cancer.

③- Helicobacter pylori:-

- L → cancer cause bacteria
- cause Gastric adenocarcinoma
- Gastric Lymphoma
- contain (GAGA) *

Hallmarks of Cancer:-

Cancer related genes in the context of several fundamental changes, which dictate the malignant phenotype is called hallmarks of cancer.

- ①- Self sufficiency in Growth signals.
- ②- Insensitivity in Growth inhibitory signals.
- ③- Altered cellular metabolism
- ④- Evasion of apoptosis.
- ⑤- Limitless replicative potential (Immortality)
- ⑥- Sustained angiogenesis.
- ⑦- Ability to invade and metastasize
- ⑧- Ability to evade host immune Response

①- Self sufficiency in Growth signals:-

- * Tumors have the capacity to proliferate without external stimuli usually as a consequence of oncogene activation

Steps:-

Growth factor

TGF α
FGF3
PDGF- β

↓
Specific Receptor on cell Membrane

EGFR
PDGF
ALK receptor

↓
Activation of Receptor

↓
Activate signal Transduction protein

RAS
GTP binding

↓
Transmission of signals (2nd messenger
3- cascade)

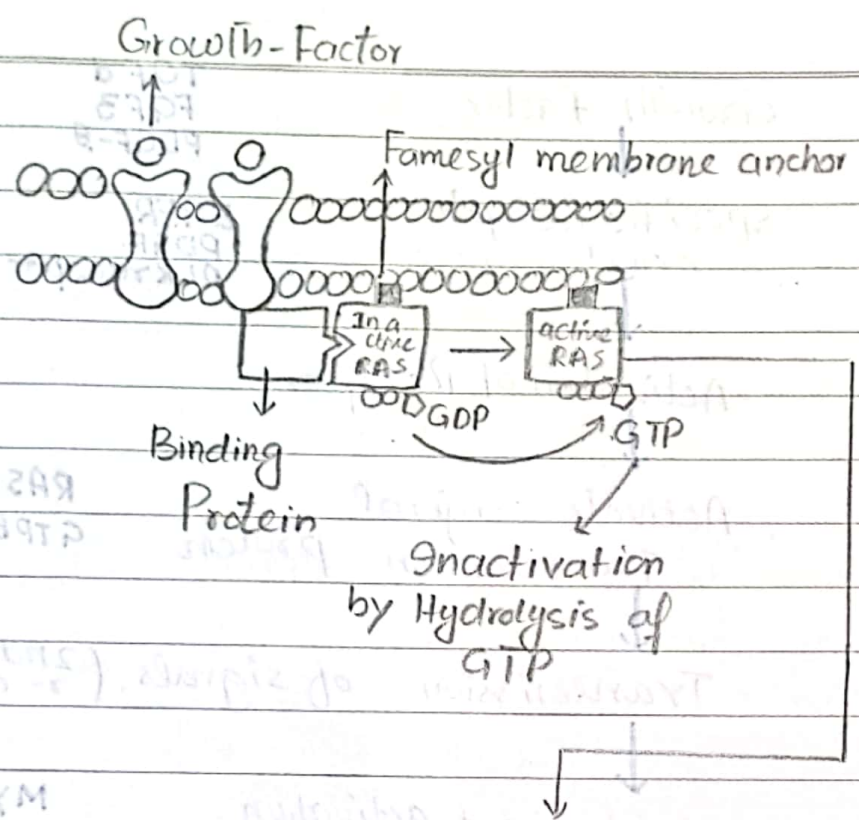
↓
Induction + activation
of nuclear regulatory factor

MYC

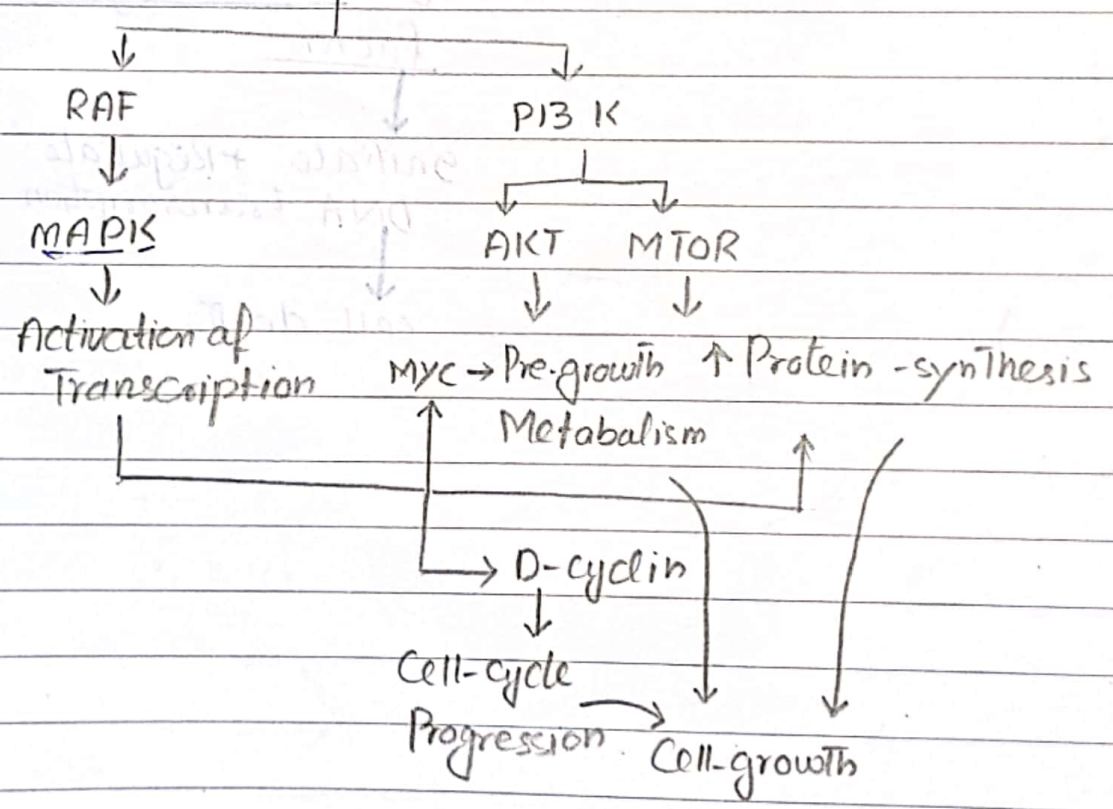
↓
Initiate + Regulate (cell cycle)
DNA transcription

↓
cell death.

cyclins
CDK4



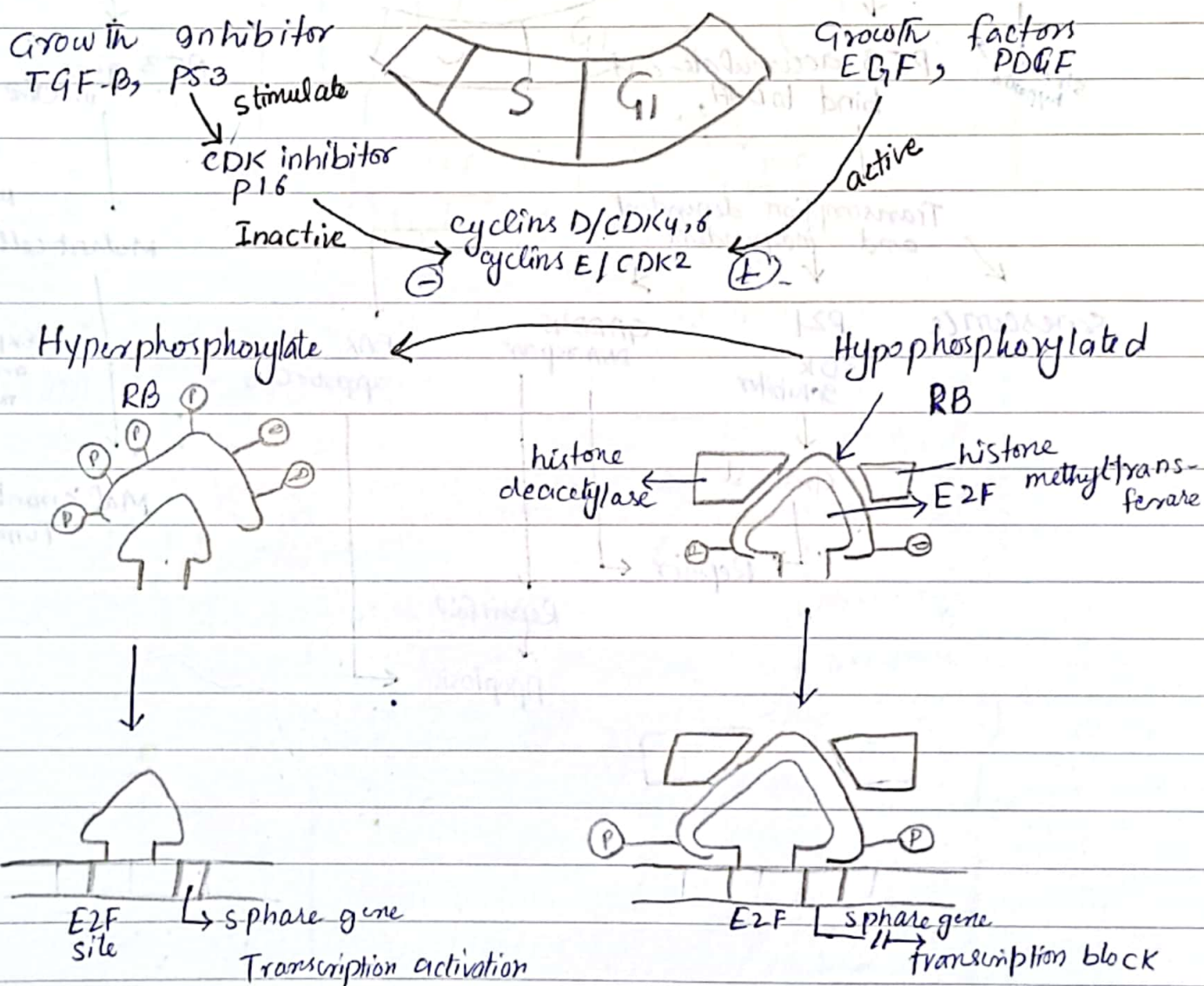
Active RAS



Insensitivity to growth-inhibitory signals:-

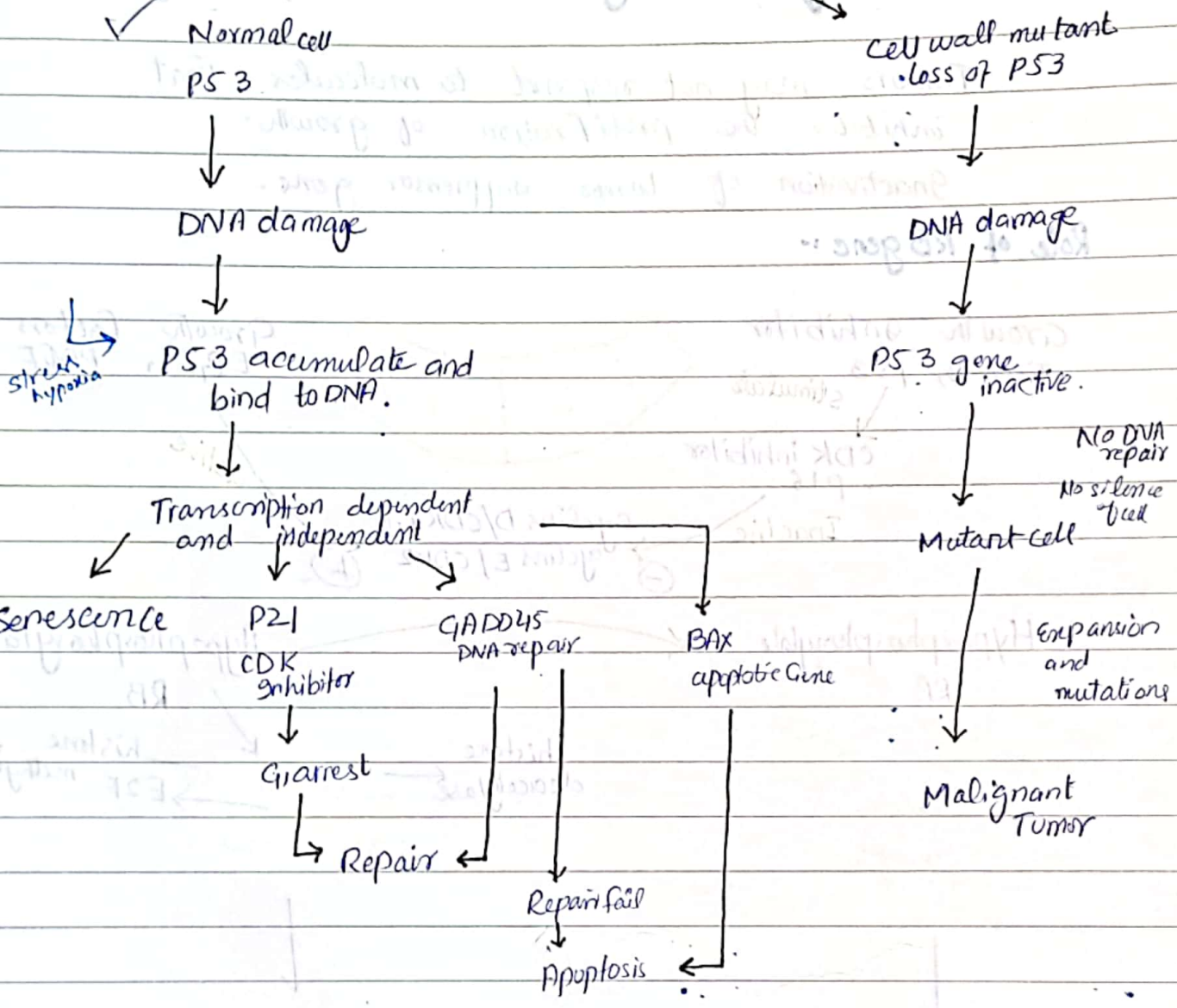
Tumors may not respond to molecules that inhibits the proliferation of growth-
Inactivation of tumor suppressor gene.

Role of RB gene:-



Roll of P53:-

Gonizing Radiation / UV
carcinogens.

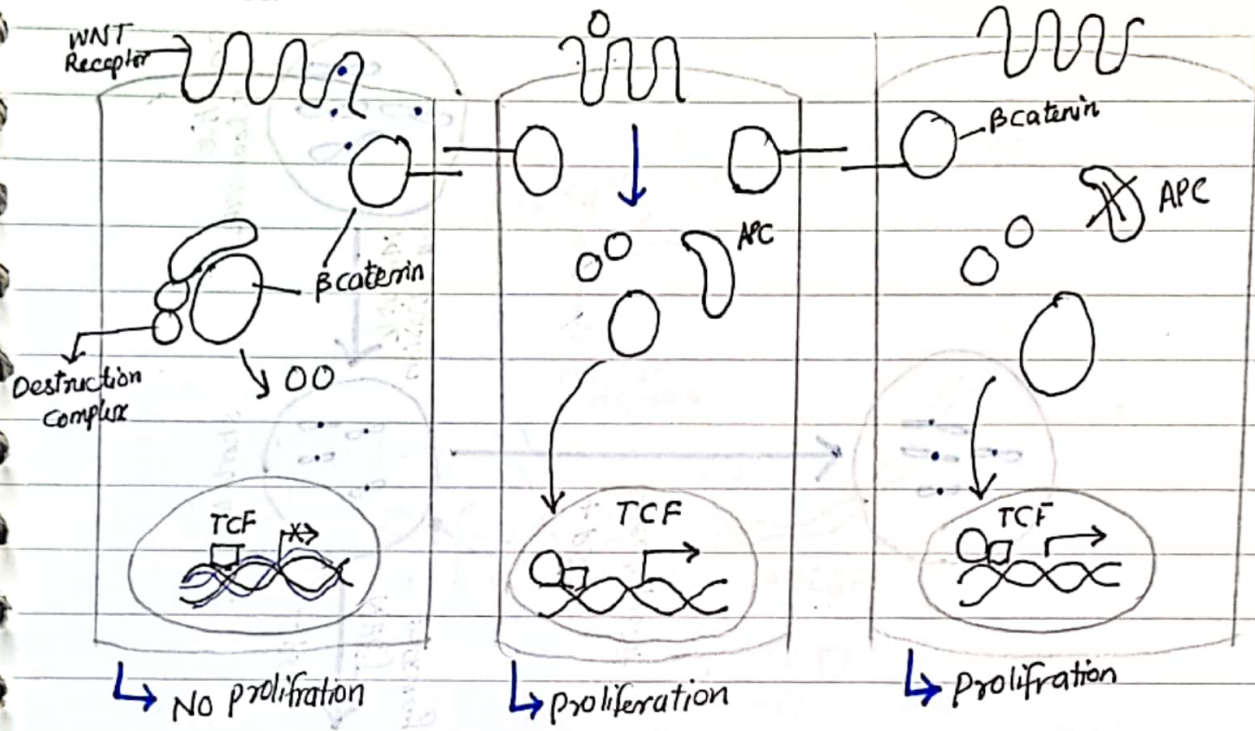


APC:-

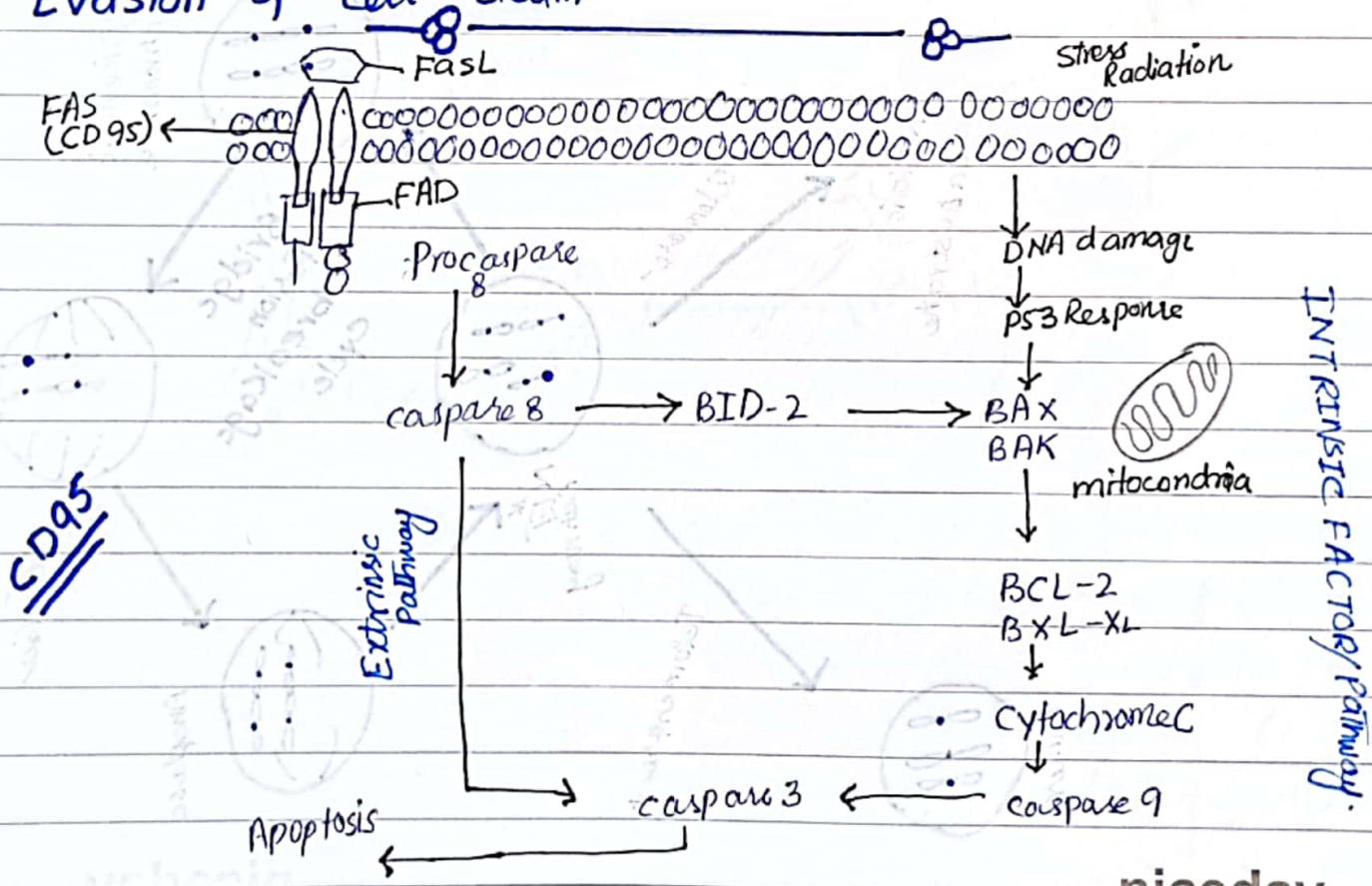
Resting cell

WNT Stimulate

Tumor cell with mutated APC

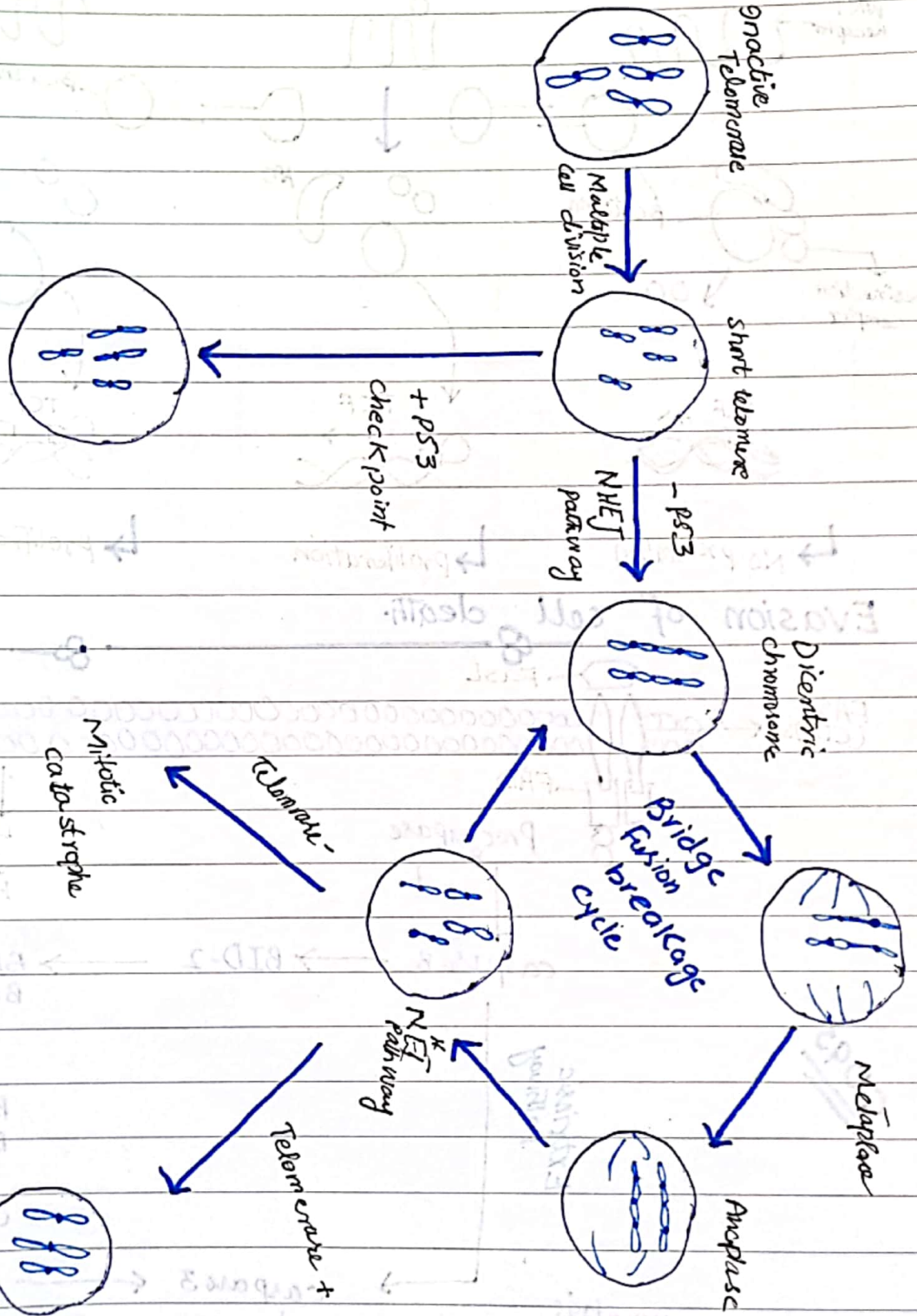


Evasion of cell death.



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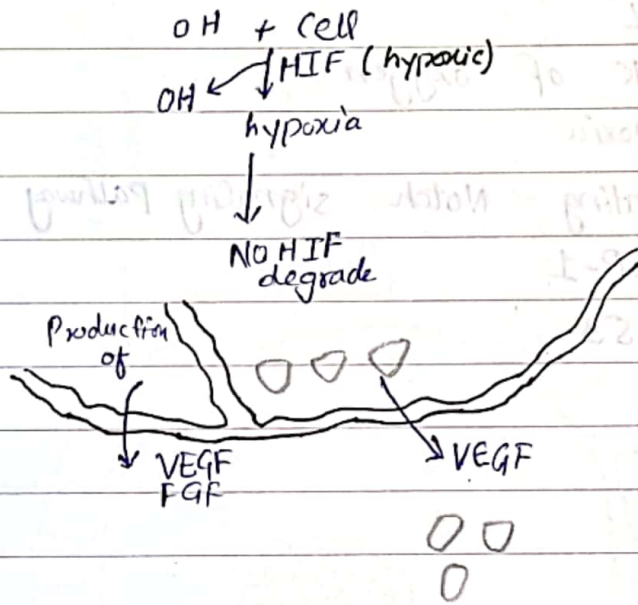
Limitless Replicative Potential :-



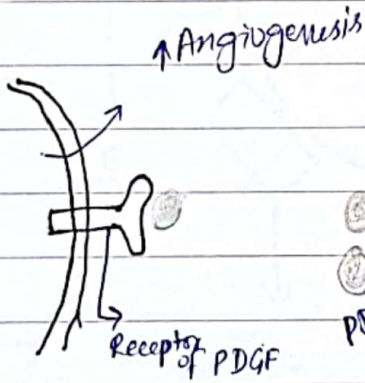
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Sustained Angiogenesis:-

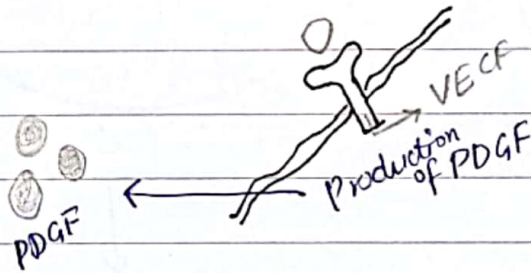
Normoxia
Normal cell + O₂



③ -
Pericyte cell



② -
Endothelial cell



Factors effect on Angiogenesis:-

- ①- ↑ Angiogenic factor FGF, VEGF
- ②- ↓ Angiogenic inhibitor
- ③- ↓ VHL
- ④- ↑ Lack of oxygen
- ⑤- Hypoxia
- ⑥- Activating Notch signaling pathway
- ⑦- ↓ TSP-1
- ⑧- ↓ P-53

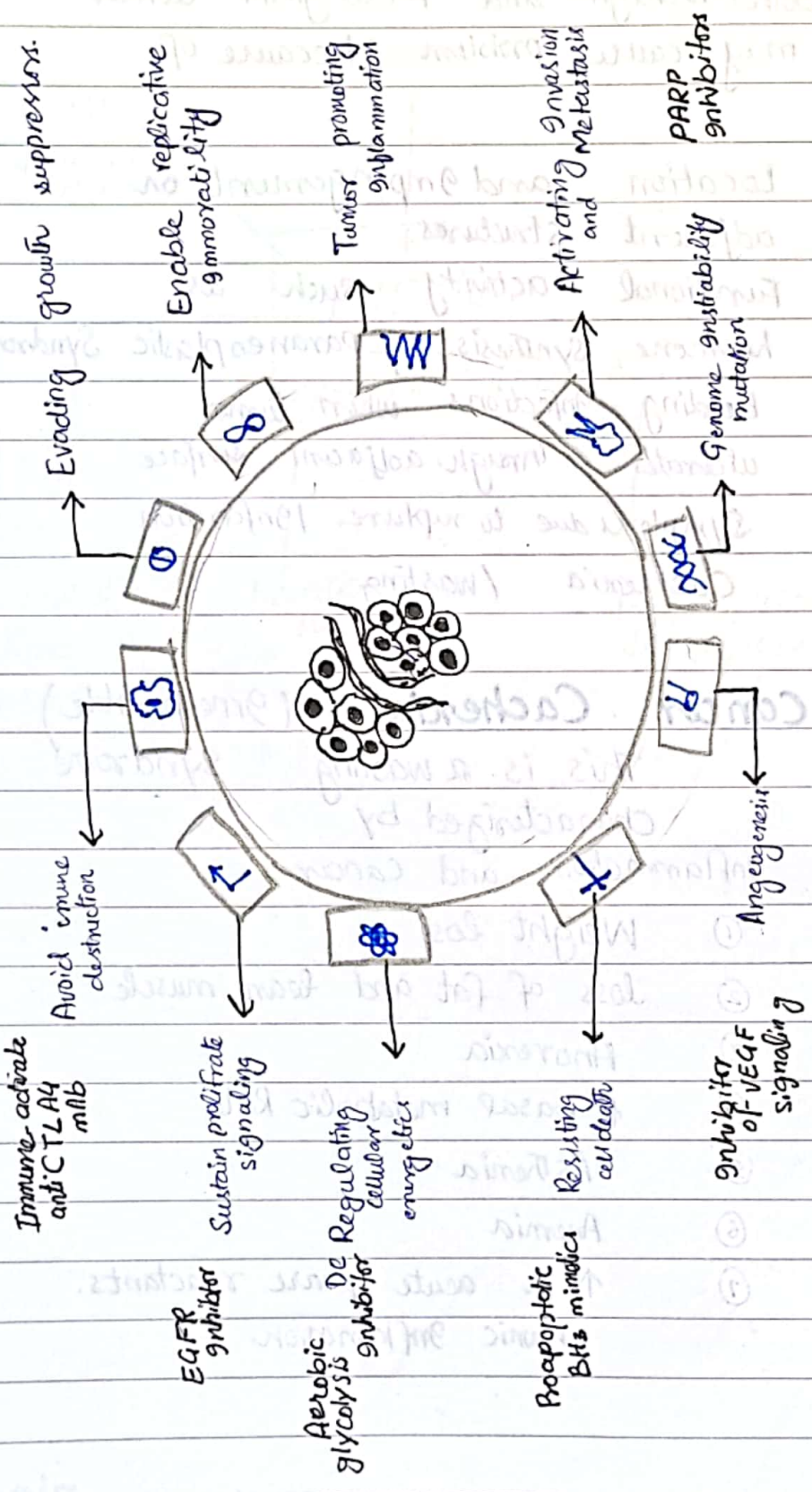
Cyclin-dependent Kinase inhibitors

Telomerase inhibitors

Anti-inflammatory drugs

Inhibitors of HGF/c Met

Poly ADP-ribose polymerase



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Clinical Aspects Of Neoplasia :-

both benign and malignant tumour may cause problem because of

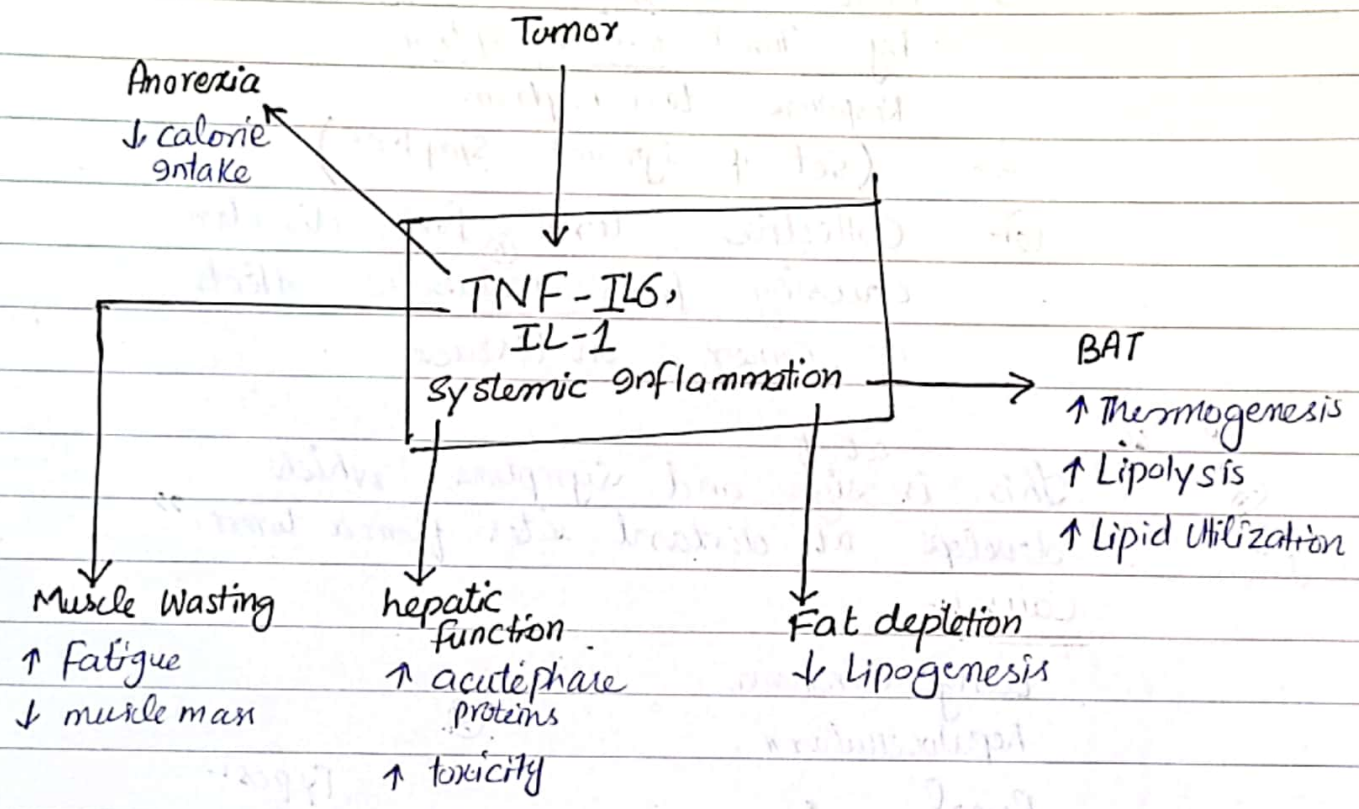
- ①- Location and impingement on adjacent structures.
- ② Functional activity such as hormone synthesis // Paraneoplastic Syndrome
- ③ Bleeding - Infections when tumour ulcerates through adjacent surface.
- ④ Symptoms due to rupture / infarction
- ⑤ Cachexia / Wasting

Cancer Cachexia (Irreversible)

This is a wasting syndrome characterized by

Due to chronic inflammation and cancer

- ① Weight loss
- ② loss of fat and lean muscle
- ③ Anorexia
- ④ ↑ basal metabolic Rate
- ⑤ Asthenia
- ⑥ Anemia
- ⑦ ↑ in acute phase reactants.
Chronic Inflammation



Paraneoplastic Syndromes:-

Heterogenous Group of disorders

- ①- Rare disorders^① that trigger^② by altered immune system Response to a neoplasm.
- ②- (Set of sign and symptoms.)
- ③- Collective term^③ for disorders causing from metabolic affects of cancer on tissues

✓ Define ④.

66

This is set of sign and symptoms which develops at distant sites from a tumor "

Causes:-

Lung Carcinoma
 hepatocellular "
 Renal "
 Leukemia
 Breast Cancer
 Ovarian "
 Gastric
 Neural "

⑤

Types:-

Endocrine
 Hematological
 Neuromuscular

Symptoms:-

Ataxia
 encephalitis.
 numbness. / Nephropathy
 myoclonus

Syndromes

Cancer

Causal Mechanism

Endocrinopathies:-

✓ Cushing synd.

- Lung carcinoma
pancreatic "

ACTH

✓ Hypercalcaemia

Sq. cell carcinoma of lung
breast "
Renal "

Parathyroid hormone
TGF- α
TNF
IL1

J Hypoglycemia

Ovarian carcinoma
Fibrosarcoma

insuline

Polycythemia:-

Renal carcinoma
hepatocellular "

Erythropoietin

Nerve / Muscle Syndromes:-

Myasthenia ✓

Bronchogenic carcinoma

Immuneologic

CNS defect ✓

Breast carcinoma

Dermatologic

✓ Acanthosis Nigricans

Gastric carcinoma
Lung "
uterine "

"

Deratomyositis

Breast carcinoma

"

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Hematologic Changes

Venous Thrombosis ✓	Pancreatic carcinoma	Tumor product
Non bacterial Thrombotic	Advanced Cancer	hypercoagulation
Red cell aplasia	Thymic Neoplasms	

Others :-

Nephrotic Syndrome	Cancers	Tumor antigens
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Laboratory Diagnosis of Cancer :-

several method for diagnose cancer:-

- ① - Biopsy/excision
Tissue Removed
- ② - Fine-needle aspiration.
- ③ - Cytologic smears.

- ④ CT scan
- ⑤ bone scan
- ⑥ MRI
- ⑦ PET
- ⑧ Ultrasound
- ⑨ X-ray
- ⑩ CBC

Tumor Markers :-

* tumor associated enzyme, hormone etc present ^② in blood can be used for detection of ^③ cancer.

* useful in determining the effectiveness of therapy
biomark found in blood / urine.

CBC test

④ " ① -

This is a substance produced by cancer or some time benign condition "

- ④ Protein
- antigen
- Mucin
- isoenzyme
- cell free DNA

Tumor Markers

Hormones:-

- HCG ✓ →
- Calcitonin ✓ →
- Catecholamine
- Ectopic hormones

*✓ Oncofetal Antigens:-

- α-Fetoprotein ✓
- Carcinoembryonic Antigen →

- Liver cell, germ cells, testis cancer.
- Carcinoma of colon, Pancreas, lung, stomach, heart

Enzyme:-

- Prostatic acid phosphatase ✓ →
- Neuron specific enolase

- Prostate cancer
- lung cancer.

Specific protein.

Immunoglobulins:- ✓

- Prostate specific antigen ✓ →

- Multiple Myeloma
- prostate cancer

Glycoprotein:-

- CA 125 ✓ →

- CA-19-9

- CA-15-3

- Ovarian Cancer

- Colon Cancer, Pancreatic

- Breast cancer

Tumor Type:-

- ✓ Testicular, Trophoblastic
- ✓ Medullary Carcinoma Thyroid
- Pheochromocytoma

Cell free DNA

TP53, APC, RAS in stool / serum

Colon cancer

TP53, RAS mutant in " "

Pancreatic "

TP53 RAS in sputum, and serum

Lung "

TP53 mutants in urine

Bladder "