Oncology

Desmoplasia - Term used for prodn of abundant collagenous stroma by the parenchymal cells.
- It leads to excessive fibrosis in tumor due to formation of an abundant collagenous stroma.

eg:- In Serous Carcinoma of breast

METASTASIS:

» Spread of tumor by invasion in such a way that discontinuous secondary tumor mass/masses are formed at the site of lodgement away from primary site.

» most reliable feature of a malignant tumor

» All malignant tumors metastasise except two.

1. Gliomas of CNS
2. Basal cell Carcinoma of the skin.

Routes

1. Hematogenous spread
2. Lymphatic "
3. Transcoelomic "

Sarcoma - blood spread
Carcinoma - lymphatics

1) Lymphatic Spread — 1st Lymph node - Sentinel lymph node

↳ Carcinoma.

↳ The pattern of L.N. involvement follows the natural routes of lymphatic drainage producing regional nodal metastasis.

→ The 1st node in a regional lymphatics that receives lymph flow from the primary tumor is called Sentinal lymph node.

→ Sentinal L.N. is useful in breast cancer, vulvar cancer and melanoma.

1st used by Gould.

→ Skip metastasis

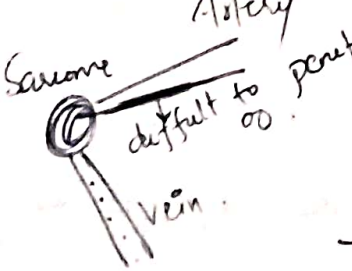
→ On the L.N - tumor cells lodge 1st in Subcapsular Sinus.

VIRCHOW's L.N → nodal metastasis to left supraclavicular L.N from cancers of abdominal organs eg: cancer of stomach, colon & Gall bladder.

2) Haematogenous Route:

↳ Common route for Sarcoma.

↳ Veins are more commonly involved than Arteries because veins have thinner walls that can be penetrated readily (As - Thicker)



→ most common (2°s) are seen in Liver

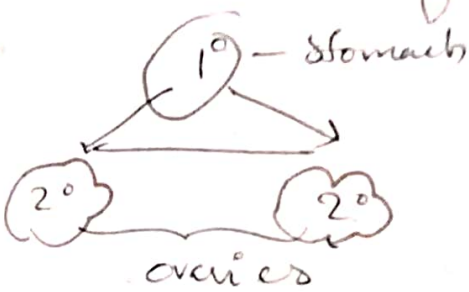
→ 2nd " " " " " " lung

due to Portal circulation.

due to Caval circulation.

3. Transcoelomic Spread.

(i) Direct seeding on into body cavities or surface
↳ Seen by tumors



ii) Spread via CSF
↳ Malignant tumors of the ependyma & leptomeninges → spread → via CSF → metastases at other sites in CNS.

iii) Implantation → by surgeon's scalpel.

Proto-oncogenes:
↳ Normal genes required for cell proliferation.
↳ Discovered by Harold Varmus & Michael Bishop

Protooncogenes
↓ MUTATION → Point mutation.
→ chromosomal translocations
→ gene amplification.
Oncogenes.
↓
Oncogenic protein

5 classes
↳ Growth factors eg: PDGF-β, TGF-α, FGF, c-MET
↳ Receptor for GFs eg: EGF-R, C-KIT-R, RET-R, FMS-like
↳ Cytoplasmic sign Transduction Proteins - Mutated RAS, ABL-BCR
↳ Nuclear transcription factors - C-MYC, N-MYC, L-MYC
↳ Cell Cycle regulatory proteins - Cyclin D, Cyclin E, CDK4

RAS gene: → most common gene to get mutated.
→ RAS protein is signal transducing protein

2 scenarios.

Normally

∴ RAS binded with

GDP (inactive)

GTP (active)

Mutation

↓

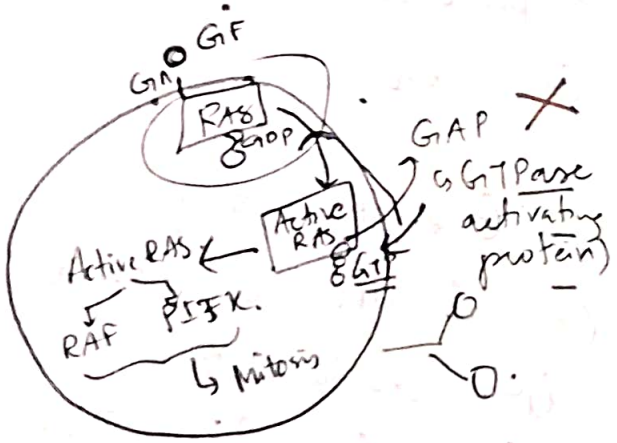
GAP (mutated)

↓

Activated RAS

↓

Uncontrolled mitosis.



Examples

K-RAS - Colon, lung pancreatic tumors.

N-RAS - Melanoma, blood tumors (AML)

H-RAS - Bladder & kidney tumors.

ABL-BCR hybrid gene.

↳ have tyrosine kinase activity

↳ 9 & 22 → philadelphia chromosome. eg: CML

↳ translocation t(9;22)

↓

Target therapy

↳ Imitinib

↳ ABL-9

↳ BCR-22

Tumor Suppressor gene.

↳ These are the genes whose products downregulate the cell cycle and thus apply brakes to cellular proliferation. Chr-17 p 13

Gene	Associated tumours
1. RB	RetinoBlastoma, Osteosarcoma
2. p53 (TP53)	Most human cancers, common in Ca lung, head and neck, colon, breast.
3. TGF-β & its receptors	Ca pancreas, colon, stomach
4. APC & β-catenin proteins	Ca colon
5. Others	
i BRCA 1 & 2	Ca breast, ovary
ii VHL	Renal cell carcinoma
iii WT 1 & 2	Wilms tumors
iv NF 1 and 2	Neurofibromatosis type 1 & 2.

RB gene

Is present on chrom. no (13) (13q14)

Cwhite eye reflection
retinal tumor.

I

Growth Inhibitors

↓

Activates CDK inhibitors and inactivates cyclins and CDKs

↓

Hypophosphorylation of RB

↓

RB becomes active

↓

forming an inactive complex with transcription factor EF-2

↓

blocks cell division (no mitosis)

II

Growth factors

↓

Activates cyclins & CDKs

↓

Hyperphosphorylation of RB

↓

RB becomes inactive

↓

Dislocation of RB from transcription factor EF2

↓

Cell division (mitosis)

III

Mutation

↓

Permanent inactivation of RB

↓

Permanent dislocation of RB from transcription factor EF 2

↓

Abnormal cell division (mitosis)

↓

Cancer.

p53 gene:-

- ↳ located on chrom 17.
- ↳ Guardian of genome
- ↳ Molecular policeman
- ↳ tumor suppressor gene as well as DNA repair gene

Li-Fraumeni syndrome -
Inherit 1 mutant p53 allele
↳ other may inactivate normal allele
↳ 73% with sarcoma, breast cancer, leukemia, brain tumors.

UV radiation (DNA damage)

↓

p53 accumulate in cell

- p21 (Brake) → ↓ Cell cycle arrest
- GADD 45 (mechanic) → ↓ DNA repair
  - → Growth arrest & DNA damage.
  - successful → ↓ MDM-3 → ↓ Degradation of p53
  - Unsuccessful → ↓ BAX → ↓ Apoptosis

Cells with mutation / loss of p53

↓

DNA damage

↓

p53 dependent genes not activated

↓

No cell cycle repair / arrest

No DNA repair

↓

Mutant cells → Expansion & additional mutations

↓

Cancer.