

Lec 1 Neoplasia

Chromasomas → Non-neoplastic tumors (swelling) due to inflammation normal tissue that is translocated

Adenoma → 1. benign epithelium forming glands
2. neoplasm derived from glandular epithelium (tumors)

Hemangioma → Disorganized or Distorted tissue in its original place indigenous

Teratoma → Benign Tumor arising from totipotential germ cells forming any kind of cells

Papilloma → finger-like projections (benign epithelium)

Polyp → mass over mucosa, can be benign (malignant) or even non-neoplastic (inflammation) & its macroscopic gross

Epithelial Tissue ^{epithelium}
1. Squamous Cell
2. Urothelial
3. Glandular
Called Carcinoma

Mesenchymal & Soft Tissue → Stroma
Called Sarcoma
1. Bone → Osteosarcoma
2. Fibrous → Fibrosarcoma
3. Fat
4. Muscle
5. Cartilage

of Tumor Gland cells surrounding cavity & have secondary action
eg. Cholecystitis when Cholecyst Tumor

Very Very Important

Teratomas: Healthy tissue not in its original place
Healthy spleen tissue in liver tissue

Hemangiomas: Distorted tissue in its original place
Distorted liver tissue in liver tissue

Translocated Hemangiomas: Distorted tissue translocated to another site
distorted spleen tissue in liver tissue

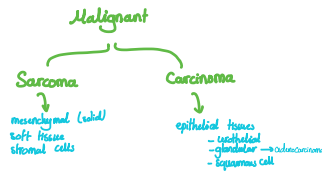
Epithelial cells → Carcinoma
Stromal cells → Sarcoma

Teratomas → benign, arising from more than 3 germ cell layers of the same type
Chorioncarcinos → non-neoplastic, organized proliferation of normal tissue, ectopic sites of knowledge, bleed heavily from

Tumors
Neoplastic → Specific Metabolism
NonNeoplastic → No metabolism
Chromasomas (ectopic Hemangioma)

Benign suffix except
-oma

- Lymphoma
- Melanoma
- Sarcoma
- Mesothelioma
- Multiple myeloma



Lec 3

* Oncogenes
1. RAS
2. ABL

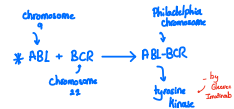
* Tumor Suppressor genes
1. RB → Genom
2. TP53 → Genom
3. TGF-β
4. p16
5. Contact Inhibition
6. APC

⇒ Translocation: haematogenic tumors & oncogenes
⇒ Deletions: non-haematogenic tumors & tumor suppressor genes

* Anaploidy

- 3 no. of chromosomes
- Mitotic checkpoint error

Epigenetic changes
Change gene expression through stimulating or inhibiting gene promoters

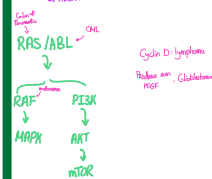


! Methylation = Silencing
↳ hypomethylation: ↑ oncogene expression
hypermethylation: ↓ tumor suppressor expression

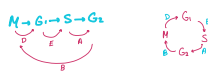
Methylation of microRNA
↓ : ↓ tumor suppressor gene
↓ : ↑ oncogene expression

Lec 4

Micro-environment by
1. Fibroblasts
2. Stromal cells
3. Epithelial



* CDKs: 1. enforcing checkpoints
2. delaying cell cycle



1. GF → tyrosinase
2. GF Receptors → tyrosinase (Cdk = phosphorylating kinase)
3. Signaling → RAS & RBL → PI3K → AKT → mTOR
4. TF → ME

Lec 2

more difference Human parent cell → more de-differentiation → worsen the malignancy

∴ Benign tumors are well differentiated resembles parent eg. Pituitary adenoma, lacrimal gland & can secrete hormones too

* Single most prognostic factor → Tumor Stage spread extent & metastasis
① Metastasis
② Local Invasion

Very Important Regulating Metastasis

- ① Doesn't metastasize → Basal cell carcinoma of skin
- ② Rarely metastasize → CNS tumours
- ③ Rapidly metastasize → Osteosarcoma

* Ovarian Cancer
ovarian cells arise through peritoneal cavity & 10% with metastatic deposits

⇒ Dysplasia = disordered, non-neoplastic, affecting only mucosa without underlying immature cells expansion

Lec 5

when hypophosphorylated RB inactivates E2F by

Tumor Suppressor Gene

1. RB → critical cycle
2. TP53 → critical cycle
3. TGF-β
4. APC
5. Contact inhibition

- ① sequestering E2F
- ② recruiting proteins that inhibit E2F promoter

results: no cyclin E formation thus cell trapped in G1 & can't cross G1/S checkpoint

RB binds to E2F inhibiting it from transactivating to cyclin E that allows cell passage from G1 to S

How RB is inactivated?

* RB is an oncoprotein! mostly all proteins are activated when phosphorylated except RB is inactivated when phosphorylated

↳ Cyclin D & CDK Complex phosphorylates RB inactivating RB allowing E2F transcription to cyclin E crossing G1/S checkpoint

* RB, Autosomal Dominant

Cont...

Stimulatory Signals → Deactivating RB by Hyperphosphorylation → Cell Division completed

Inhibitory Signals → Activating RB by Hypophosphorylation → Incomplete Cell Division

* Some oncogenes could cause RB hyperphosphorylation deactivating it causing continuous cell division resulting in cancer

→ Familial RB increased risk for other cancers:

- Osteosarcoma
- Soft-tissue Sarcoma

*** Tp53

- bound to MDM2 that destroys p53 after 20 min via ubiquitin proteasome
- when sensing damage ATM catalyzes post-translational modifications releasing MDM2 thus p53 has no longer life span if is activated

- Activated p53 transcribes:
 - Cell cycle arrest genes → CDKI
 - DNA repair genes → Repaired: ↑ MDM2 upregulation



mutant p53
 ↳ No cell cycle arrest
 ↳ No DNA repair
 ↳ No senescence
 ↳ No apoptosis
 ↳ expansion & additional mutations

- ⇒ Rare Li Fraumeni Syndrome inherit defective one allele & more disposition to cancer
- Breast Cancer
 - Sarcoma
 - Brain Tumors
 - Leukemia

RB → Osteosarcoma & Soft-tissue Sarcoma
 p53 → Sarcoma, Brain Tumor, Leukemia & Breast Cancer

Familial or Inherited

TGF-β

binds to receptor & transmits signals through SMAD4 to nucleus
 + CDKI
 - CDK4 & MYC

- Receptor: ① Colon ② Stomach ③ Endometrial
- SMAD: Pancreas
- mutations cause cancer in

E Cadherin

Loss: Invasive Lobular type

Present: Invasive Ductal Glandular type

Breast Carcinoma

contact inhibition by E-cadherin

glandular cluster in a colon stroma has E-cadherin

APC inhibits β-catenin by destruction
 ↳ part of WNT signaling
 ↳ stimulates TWIST & SLUG that decrease cadherin expression inhibiting contact inhibition
 ↳ increases Cyclin D1 & MYC transcription

Conclusion

- RB → E2F, Cyclin E, Cyclin D, CDK
- Tp53 → MDM2, ATM, CDKI, BAX, PUMA
- TGF-β → SMAD4, CDKI, CDK, MYC
- APC → β Catenin, TWIST, SLUG, Cadherin, Cyclin D1, MYC

Lec 6

IDH mutation is mostly found in:

- Acute myeloid leukemia
- Glioma
- Sarcoma

Autophagy

evaded in tumors but upregulated during stress

Stress in cancer cells means

↳ chemotherapy or ischemia

Lec 7

* Angiogenic factors secreted by:

- Pericythelial tumor cells
- Stroma
- Inflammatory Cells

stimulated by HIF-1α

VEGF: Tumor Cells or Macrophages

Protease: Tumor Cells or Stromal Cells

TSP-1: Fibroblasts (in response to tumor cells)

Releases FGF from ECM

* HIF-1α

Stimulates: VEGF production

Stimulated by: Hypoxia

destroyed by: VHL

thus Hypoxia prevents VHL from recognizing HIF-1α

Hypoxia → HIF-1α → VEGF

- by VHL

have suppressor gene (VHL)

Inherited defective gene (Randy) could cause

- Renal cell carcinoma
- Pheo Chromocytoma

Locomotion by

- Tumor-Derived Cytokines → attract cells
- Stromal cells secrete HGF, SCF
- Chemotactic Activity

Growth Factors → tumor

Cleavage products of matrix components

Tumor Dormancy

- Breast
- Prostate
- Melanoma

Cont...

Lec 7

Epithelial Markers → E-Cadherin
 Mesenchymal Markers → 1. Vimentin
 2. SMA Smooth muscle actin

Re-epithelial cells are more likely to invade & metastasize than epithelial cells

EMT
 epithelial cells

by
 1. TWIST
 2. SNAI2
 3. SNAIL

mesenchymal cells

thus
 ↓ E-Cadherin expression
 ↓ Vimentin & SMA expression

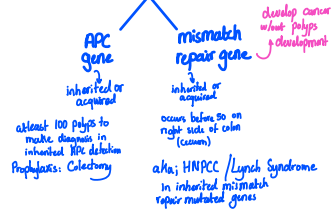
Local Invasion Extent

- Wall T
- ↓
- Mucosa & Submucosa T1
- ↓
- Muscularis Propria T2
- ↓
- Serosal fat & subserosa T3
- ↓
- Adjacent Structures T4

Lec 8

* Oncofetal antigens
 re-expressed in
 Colon & Liver Cancers
 eg: CEA & alpha-fetoprotein
Carcinoma embryonic antigen

Colon Cancer



⇒ Direct Interaction: Inflammatory & Tumor
 ⇒ Indirect Interaction: Inflammation & Resident Stromal

* Mismatch repair gene is mutated in HNPCC hereditary non-polyposis colon cancer syndrome
right side of colon called cecum
5 genes involved: MLH1, MSH2, MSH6, PMS2, EPCAM

* Nucleotide excision repair gene is mutated in Xeroderma pigmentosum causes skin cancer

* Recombination repair genes are mutated in autosomal recessive defects:
 ① Bloom's Syndrome → Cancer & Developmental defects
 ② Fanconi Anemia → Cancer & Anemia
 ③ Ataxia Telangiectasia → Cancer & Gait imbalance

Other DNA genes
 BRCA1 & BRCA2 → 50% of familial Breast Cancer & Rarely in Sporadic Breast Cancer
BRCA1 is ATM protein
one of gene mutated in Fanconi Anemia

Lec 9

* Direct Agents causing cancer eg:
 Alkylating agents such as chemo therapy could cause cancer like leukemia.

* Indirect Agents causing cancer

1. Polycyclic Hydrocarbons → Benz(a) Pyrene Lung Cancer
2. Aromatic Amines & Azo dyes → B. Naphthylamine Bladder Cancer
3. Aflatoxin B → Hepatocellular Carcinoma (T₂SE)
4. Nitrites → Nitrosamine Esophageal Cancer

Hiroshima & Nagasaki → Leukemia, Breast, Lung, Colon & Thyroid Cancer
 Head/Neck Radiotherapy → Papillary Thyroid Cancer
 Radioactive workers → Lung Cancer

Para Neoplastic Syndromes

- ① Cushing Syndrome
- ② Non-Bacterial Thrombotic Endocarditis
- ③ Hypercalcemia
- ④ Fingers Clubbing (mostly lung cancer)
 most common tumors associated: Breast, Lung & Hematologic Malignancies

