Neoplasia

Lec 1

Tumors
Neoplastic → Specific Mutations
NonNeoplastic → No mutations
↳ Choristomas (ectopic / heterotopia)

- **Choristomas** → Non-neoplastic tumors (swelling) due to inflammation; normal tissue that is translocated (appearance: normal, location: abnormal)
  - ectopic tissue, congenital proliferation, heterotopia, normal-looking
- **Adenoma** → 1. benign epithelium forming glands 2. neoplasm (tumor) derived from glandular epithelium
- **Hamartoma** → Disorganized or Destructed tissue in its original place indigenous
- **Teratoma** → Benign Tumor arising from totipotential germ cells forming any kind of cells (mixed tumor more than 1 kind of tissues)
- **Papilloma** → finger-like projections (benign epithelium)
- **Polyp** → mass over mucosa, can be benign/malignant (GIT) or even non-neoplastic (inflammation) & it's macroscopic gross

Benign → suffix -oma
except
1. Lymphoma
2. Melanoma 
3. Seminoma
4. Mesothelioma (cells lining cavity of organ)
5. Multiple myeloma (plasma cells cancers)

Epithelial Tissue (very important) → called Carcinoma
1. Squamous Cell
2. Urothelial
3. Glandular

Mesenchymal (solid) & Soft Tissue ⟶ Stroma → called Sarcoma
1. Bone → Osteosarcoma
2. Fibrous → Fibrosarcoma
3. Fat
4. Muscle
5. Cartilage

Malignant
- Sarcoma → mesenchymal (solid), soft tissue, stromal cells
- Carcinoma → epithelial tissues
  - urothelial
  - glandular → adenocarcinoma
  - squamous cell

* True Gland: cells surrounding cavity & have secretory action
eg: Colonic Glands aka; Daisy Flower

Very Very Important
- Teratoma: Healthy tissue not in its original site — healthy spleen tissue in liver tissue
- Hamartoma: Destructed tissue in its original site — damaged liver tissue in liver
- Translocated Hamartoma: Destructed tissue translocated to another site — destructed spleen tissue in liver tissue

⚠ Epithelial cells → Carcinoma
Stromal cells → Sarcoma

- *Teratoma (mixed tumor) →
  - tumors arising from ovaries & testes
  - show tissue components from 3 germ cells lines & diff. tissue types
- *Choristomas →
  - non-neoplastic
  - Congenital proliferation of normal tissue in abnormal location
  - ectopic tissue & heterotopia
  - Normal-Looking tissue

Lec 2

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

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

*Single most prognostic factor ⟶ Tumor Stage (spread extent & metastasize)
1. Metastasis
2. Local Invasion

Very Important Regarding Metastasis
1. Doesn't metastasize → Basal cell carcinoma of skin
2. Rarely metastasizes → CNS tumors
3. Rapidly metastasize → Osteosarcoma

** Ovarian Cancer (& Appendix) — seeding through body cavities: tumor cells move through peritoneal cavity & fill it with metastatic deposits

⇒ Dysplasia
- disorded, non-neoplastic, affecting only mucosa without underlying tissue
- immature cells expansion

Lec 3

* Onco genes
1. RAS
2. ABL

* Tumor Suppressor genes
1. RB → Governer
2. TP-53 → Guardian
3. TGF-β
5. Contact Inhibition
6. APC

⇒ Translocation : haematogenic tumors & oncogenes (+ amplification)
⇒ Deletions : non-haematogenic tumors & tumor suppressor genes → 2 mutations: 1 by deletion, 1 by point

** Anaploidy
- ↑ no. of chromosomes
- Mitotic Checkpoint error

Epigenetic changes → change gene expression (& not DNA sequence) through stimulating or inhibiting gene promoters

* ABL (chromosome 9) + BCR (chromosome 22) ⟶ ABL-BCR (Philadelphia chromosome) → tyrosine kinase (by Gleevec & Imatinab)

⚠ Methylation = Silencing
- hypomethylation: ↑ oncogene expression
- hypermethylation: ↓ tumor suppressor expression

Methylation & microRNA
- ↑ : ↓ tumor suppressor gene
- ↓ : ↑ oncogene expression

Lec 4

Microenvironment by
1. Pericytes
2. stromal cells
3. fibroblasts

RAS (Colon & Pancreatic) / ABL (CML)
- RAF (melanoma) → MAPK
- PI3K → AKT → mTOR

Cyclin D: lymphoma
Produce own PDGF : Glioblastoma

** CDKI :
1. enhacing checkpoints
2. delaying cell cycle

1. GF → eg: glioblastoma
2. GF Receptors → hyperresponsive (no.↑) or morphology change (always active)
3. Signaling → RAS & ABL < RAF → MAPK; PI3K → AKT → mTOR
4. TF → MYC

Lec 5

Tumor Suppressor Gene
1. RB → external signals
2. Tp53 → internal signals
3. TGF-β
4. APC
5. Contact inhibition

RB → binds to E2F (transcription gene) inhibiting (inactivating it) it from transcriptioning to cylin E that allows cell passage from G1 to S

* RB in an exception! (Chromosome 13)
mostly all proteins are activated when phosphorylated except RB is inactivated when phosphorylated

** RB: Autosomal Dominant ← Two Hit Hypothesis (Familial)

when hypophosphorylated RB inactivates E2F by
1. Sequestering E2F
2. recruiting proteins that inhibit E2F promotor

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

How RB is inactivated?
↳ Cyclin D & CDK Complex phosphorylated RB inactivating RB allowing E2F transcription to cyclin E crossing G1/S checkpoint

Cont...

Stimulatory Signals → Deactivating RB by Hyperphosphorylation → Cell Division completed

Inhibitory Signals → Activating RB by Hypophosphorylation → Incomplete Cell Division

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

→ Familial RB
increased risk for other Cancers:
1. Osteosarcoma
2. Soft-tissue Sarcoma

* Tp53
- bound to MDM2 that destructs p53 after 20 mins via ubiquitin proteasome
- when sensing damage ATM catalyzes post-translational modifications releasing MDM2 thus p53 has no longer life span & is activated
- Activated p53 transcribes:
  1. Cell cycle arrest genes → CDKI (preventing: 1. Cyclins & CDK 2. RB phosphorylation / inactivation)
  2. DNA repair genes
     - Repaired: ↑ MDM2 upregulation
     - Unrepaired
       - Apoptosis → BAX & PUMA
       - Senescense → CDKI (global chromatin changes causing permanent gene expression change)

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
1. Breast Carcinoma
2. Sarcoma
3. Brain Tumors
4. Leukemia

∴ RB → Osteosarcoma & Soft-tissue Sarcoma
p53 → Sarcoma, Brain Tumor, Leukemia & Breast Carcinoma
→ Familial or Inherited

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

Receptor: 1. Colon 88%, 2. Stomach, 3. Endometrial (mutation causes cancer in)
SMAD: Pancreas 100% (mutation cause cancer in)

E Cadherin (tumor cells appear in absence of protein (Ecadherin is lost) non-cohesive)
Loss: Invasive Lobular type
Present: Invasive Ductal Glandular type
→ Breast Carcinoma
(tumor cells form glandular structure (E-Cadherin is present) cohesive)
glandular structure is a cohesive structure has E-Cadherin

contact inhibition by 1. E-Cadherin 2. Merlin

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:
1. Acute myeloid leukemia
2. Glioma
3. Sarcoma

Autophagy
→ evaded in tumors but upregulated during stress

stress in cancer cells means
↳ chemotherapy or ischemia

Lec 7

* Angiogenic factors secreted by:
1. Parenchymal tumor cells
2. Stroma
3. Inflammatory Cells

(Stimulated by HIF-1α hypoxia inducible factor)
VEGF: Tumor Cells or Macrophages
Protease: Tumor Cells or Stromal Cells → Releases FGF from ECM
TSP-1: Fibroblasts (in response to tumor cells) (induced by p53)

* HIF-1α
Stimulates: VEGF production
Stimulated by: Hypoxia
destructed by: VHL (an oxygen sensor)
thus Hypoxia prevents VHL from recognizing HIF-1α

Hypoxia → HIF-1α → VEGF
- by VHL

(tumor suppressor gene) VHL
Inherited defective gene (Rarely) could cause
1. Renal cell carcinoma
2. Pheochromocytoma

Locomotion by
1. Tumor-Derived Cytokines → autocrine motility factor
2. Stromal cells secrete HGF (hepatocyte growth factor) & SCF (motility factor)
3. Chemotaxis Activity (motility stimulation)
   - Growth Factors (motility stimulation)
   - Cleavage products of matrix components

Tumor Dormancy
1. Breast
2. Prostate
3. Melanoma

Cont...

Lec 7

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

* mesenchymal cells are more able to invade & metastasize than epithelial cells

EMT

epithelial cells → (by 1. TWIST 2. SNUG 3. SNAIL) → mesenchymal cells

thus
↓ E Cadherin expression
↑ Vimentin & sma expression

Local Invasion Extent

- Wall (Carcinoma in situ) — T
- ↓ Mucosa & Submucosa — T1
- ↓ Muscularis Propria — T2
- ↓ Serosal fat subserosa — T3
- ↓ Adjascent Structures — T4

Lec 8

* Oncofetal antigens
↳ re-expressed in Colon & Liver Cancers

eg: CEA (Carcino embryonic antigen) & alpha- fetoprotein

Colon Cancer

APC gene
↳ inherited or acquired
atleast 100 polyps to make diagnosis in inherited APC detection
Prophylaxis: Colectomy

mismatch repair gene (→ develop cancer w/out polyps development)
↳ inherited or acquired
occurs before 50 on right side of colon (cecum)
aka; HNPCC / Lynch Syndrome
In inherited mismatch repair mutated genes

⟹ Direct Interaction: Inflammatory & Tumor
⟹ InDirect Interaction: Inflammatory & Resident Stromal

* Mismatch repair gene is mutated in HNPCC hereditary non polyposis colorectal cancer syndrome
  - right side of colon called cecum
  - 1 gene: inherited defective
  - 1 gene: acquired defective

* Nucleotide excision repair gene is mutated in xeroderma pigmentosum (repairs nucleotide cross-linking upon exposure to uv light)
  - 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 & BRCA 2 → 50% of familial Breast Cancer & Rarely in Sporadic Breast Cancer
- BRCA1 ↳ linked to ATM protein
- BRCA 2 ↳ one of genes 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 (→ have reactive electrophile group)
  1. Polycyclic Hydrocarbons ⤳ Benzo (a) pyrene : Lung Cancer
  2. Aromatic Amines & Azo dyes ⤳ β- Naphthalamine : Bladder Cancer
  3. Aflatoxin B ⤳ Hepatocellular Carcinoma (Tp53)
  4. Nitrites ⟶ nitrosamine ↳ Gastric Cancer

Hiroshima & Nigasaki → 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

Hypercalcemia
↓
1. PTHrP
2. TGF-α → activate osteoclasts
3. TNF & IL-1