Subject neoplasia "2" Date No.

① Differentiation and anaplasia → loss of structural and functional differentiation of normal cells backward formation
↓ (Dedifferentiation)
to what extent the neoplasia resemble the parenchymal

anaplasia → 100% malignant
benign → 100% differentiation
differen. → maybe benign or malignant

* Anaplastic cells characteristics "PLATN"
→ pleomorphism
→ loss of polarity
→ Atypical mitosis tripolar, quadripolar
→ Tumor giant cell formation
→ Nuclear abnormalities (4)
- hyperchromatism
- variation in nuclear size + shape
- prominent single or multi nucleoli
- enlargment of nuclei
↑ N/C ration
↳ keyword for anaplasia

* Dysplasia "precancerous lesions"
non-neoplastic disorderly proliferation
it may convert to cancer & predict malignancy

How to recognize it?
① loss of uniformity
② loss of architectural orientation

characteristics:
→ pleomorphis
→ hyperchromatic nuclei

* Side note: cells either
① tumor stem cell
② dedifferentiated mature cells

* Side note: loss of differentiation in tumor cells it lead to (dysplasia)

carcinoma in situ: worst stage of dysplasia involve entire thickning of epithelium
→ may lead to invasive cancer

NOTEBOOK

② local invasion → distinguishes cancer from benign

benign: cohesive, localized, encapsulated

* even if it's not encapsulated it is still benign → leiomyoma

smooth muscle benign tumor

growth of cancer contains 3

① infiltration ② invasion

③ distruction of tissue

* cancer: 2 types

① distant

② local

③ Metastasis: spread of tumor to physically discontinuous areas

from primary site (secondary implant)

↑ anaplastic + ↑ size of primary neoplasm = ↑ mets

* cancer can penetrate (disseminate) into:

① lymphatics → carcinomas ② hematogenous → sarcoma (like bone, muscle...)

③ seeding into body cavities

* first lymph node to recieve lymph flow from primary tumor: sentinel lymph node

* lung + liver most common secondary sites in hematogenous

leiomyoma (benign)	(malignant) leiomyosarcoma
small, slow growing, non mets	large, rapid growing, mets
non invasive, differentiated (well demarcated)	local invasive, poorly differ. (necrosis, hemorrhage)

Subject Date No. 2

③ epidemiology

Study of cancer in population and its origin

factors &

1) environmental Diet, smoking, alcohol, infectious agent, reproductive history (HPV, Hepatitis C)

2) age ↑ age → ↑ frequency of cancer & breast or endometrium cancer

① decline in the immune system

② accumulation of somatic mutation

3) acquired predisposing conditions (chronic infection, precancerous lesion)

A) chronic inflammation Inflammatory bowel disease and colorectal carcinoma

B) immunodeficiency may lead to virus-induced cancers

C) precursor Lesions epithelial differentiation may lead to carcinoma → metaplasia dysplasia

endometrial hyperplasia and dysplasia → endometrial carcinoma

Squamous metaplasia and dysplasia → lung carcinoma

keratoplakia (oral cavity, vulva, penis) → squamous cell carcinoma

villous adenoma of the colon → colorectal carcinoma

4) cancer genes → mutations maybe inherited or acquired by the environment by germline

Types & (4)

① proto-oncogene stimulate cell growth → gain of function "oncogene"

② TSG prevent uncontrolled growth → loss of function

③ genes regulate apoptosis prevent cell death → gain of function

④ genes regulate host-tumor interaction → loss of function

NOTEBOOK

Subject neoplasia "3" Date No.

① point mutation change in one nucleotide in DNA causing gain or loss of function → (A) point mutation in RAS & proto oncogene to oncogene
(B) point mutation in TP53 & loss of TSG function

② gene regulation chromosomal translocation or inversion
(mostly associated with mesenchymal, hematopoietic neoplasms)
here we activate proto oncogene to oncogene by two ways &-

(A) move the gene from its normal location to a promoter/enhancer
cause two cancer types &
① Burkitt lymphoma T(8;14) on myc gene
② follicular lymphoma T(14;18) on BCL2 gene

(B) create fusion genes encode weird chimeric proteins
causing & chronic myeloid leukemia T(9;22) ABL & BCR genes
→ create Ph chromosome

③ deletion loss of tumor suppressor gene function
causes & ① retinoblastoma RB gene on 13q14
② loss of TSG TP53 gene on 17p

④ gene amplification overexpression and hyperactivity of normal proteins proto → oncogene
causes & ① HER2 gene → breast cancer
② NMYC gene → neuroblastoma (poor prognosis)
present on 2p → ① extrachromosomal double minutes
② homogeneous staining region HSR

⑤ aneuploidy missing or extra chromosome / not a multiple of haploid state
in human → 23

Subject Date No. 13

RB protien :

① DNA-binding protien ② works as a point of integration for diverse signals

③ regulate G1/S phase → Before DNA replication happens

promote cell cycle progression

④ Diverse signals : inactivate RB → hyperphosphorylation

activate RB → hyperphosphorylation

Block cell cycle progression

* DNA replication in S phase :-

inactivation (phosphorylation) of RB → E2F release →

activate cyclin D-CDK4 / cyclin D-CDK6 / cyclin E-CDK2

→ DNA replication occurs

phosphorylase → add phosphate

phosphatase → remove phosphate

carcinogenesis : multi step process result from accumulation of multi mutations give rise to transformed phenotype

tumor progression : cancer become more aggresive and require greater malignant potential how? they aquire more mutation with time they become less responsive to therapy.

Subject Hallmark of cancer 8 Date No.

① Self-sufficiency in growth signals (proto oncogene → oncogene)

1 growth factor → cancer secret its own growth factor
stromal cells secret growth factors
ex: glioblastoma produce PDGF + PDGF receptor

2) growth factor receptor → its mutated or overexpressed so we call it oncoprotien. ex: EGF in glioblastoma, epithelial tumer in head + neck squamous cells carcinoma in lung

3) downstream signal-Transducing proteins → mutation in signaling pathway ex: ABL, RAS oncoproteins

4) nuclear transcription factors → continuous stimulation lead to expression of growth-promoting factor. ex: MYC mutation

② Insensitivity to growth inhibitory signals & TSG

① RB in cell cycle it's a TSG
retinoblastoma 60% sporadic, The remain autosomal dominant
loss of normal RB lead: retinoblastoma, breast cancer, bladder cancer
small cell cancer in lung

Sporadic	autosomal
- two mutations are required - both of normal alleles of RB must be mutated	- children inhert one defective copy of RB gene and the other is normal

NOTEBOOK

② TP53 → guardian of the genome

p53 transcription factor protein → work neoplastic transformation

By 3 ways : ① apoptosis ② senescence ③ quiescence

* it maintain the integrity of genome / central monitor of internal stress

- healthy non-stressed cells p53 associated with MDM2 have short half life 20M

So, there is two ways for cancer to act :

① loss of function mutation in p53

② gain of function mutation in MDM2

mutation in p53 causes (LFS)

stress : mutagens, carcinogens, ionizing radiation

③ TGF-β → inhibitor of proliferation

seen in epithelial, endothelial, hematopoitic cell

mutation of TGF-β seen in cancers : endometrium

colon, pancreas, stomach

④ contact inhibition : normal cells stop proliferation after forming confluent monolayer By E-cadherin

in cancer → loss of E-cadherin expression → advanced stage of cancer

③ altered cellular metabolism

① warburg effect (AKA: aerobic glycolysis)

↑ glucose take up ↑ conversion to lactose By fermentation via glycolytic pathway

* PET Scanning expose glucose hungry tumors

aerobic glycolysis → 2 ATP from 1 glucose

oxidative phosph. → 36 ATP from 1 glucose

→ causes rapid dividing of tumor cells.

② Autophagy

normal cells & in case of sever nutrient deficiency.

cell arrest + cannabalize its own self

Tumor cells & can live under marginal enviromental conditions

- consider autophagy deranged →

→ may use it in severe nutrient deprivation

to be dormant in metabolic hibernation

③ oncometabolism

mutation in enzymes of Krebs cycle → IDH enzyme mutation

→ produce 2-HG (prototypical oncometabolite)

this mutation seen & sarcoma, gliomas, cholangiocarcinoma

acut myeloid leukemia

* chronic myeloid leukemia

has to do with forming Ph. chromosome

Date No.

④ evasion of cell death by acquired mutation disable the key components of the intrinsic pathway

loss of function : TP53
prevent upregulation of PUMA (pro-apoptotic BH3 from P53)
→ cell survive stress and DNA damage

gain of function : BCL2
overexpression of BCL2 (anti-apoptotic)
cause follicular lymphoma

⑤ limitless replicative potential
normal cells after 70 doubling → senescence because of telomeres shortening at the end of chromosome

cancer cells → limitless by telomere maintenance
① lengthening telomeres
② upregulation of the enzyme telomerase

eroded telomeres → double stranded DNA breaks
it will lead to arrest by TP53 + RB

mutation in TP53 + RB causes limitless replication
causes homologous end-joining pathway

NOTEBOOK

⑥ Sustained angiogenesis most important hallmark

dual effect on tumor growth

① perfusion supplies with needed oxygen and nutrients

② helps with mets

new vessels not normal → dilated, leaky, haphazard
appear in angiogram

they are formed by angiogenesis promoters

① gain of function → bFGF

② loss of function → inhibitors & endostatin, angiostatin

factor affect angiogenesis:

Ⓐ hypoxia → HIF 1α & oxygen sensitive transcription factor → activate VEGF

Ⓑ mutation in TSG and oncogene

normally P53 stimulation + antiangiogenesis thrombospondin-1
repress angiogenesis repress VEGF

But cancers causes mutation in them, so it ~~#~~ allow more environment ~~#~~ for angiogenesis