Pathology: Neoplasia

- Neoplasia - new growth

abnormal mass of tissue

uncoordinated with and exceeding growth of normal tissue

persists after cessation of stimuli

-Tumors/neoplasms/

2 basic types: benign, malignant/cancer/

-Basic components of tumors:

parenchyma - proliferating neoplastic cells, used for their nomen clature

stroma - supporting connective tissue and blood vesssels, for growth and evolution

-Neoplasm nomenclature:

histologic - mesenchym/epithelial

mesenchymal - benign/+oma/, malignant/+sarcoma

epithelial - benign/based on type/, malignant/+carcinoma/

teratoma - cancer of totipotent cells mostly found in gonads

choristoma - ectopic rest of tissue

hamartoma - native tissue with uncoordinated growth

- Identification of malignant and benign tumors based on

1. differentiation/anaplasia

2. rate of growth

3. invasivenes

4. metastasis

1. benign are more differentiated and mature than malignant due to their slow mitosis

malignant tumors form a discrete fibrous capsule which makes them easier for surgical removal except hemangioma and neurofibromas

malignant tumors histologically present as pleomorphic, hyperchro-matic, and hypermitotic

carcinoma in situ - epithelial cell cancer that has not yet invaded the basement membrane

2. malignant grow more rapidly than benign

3. invasivenes - tissue infiltration and destruction

malignant is more invasive than benign

4. metastasis - breaking of the primary tumor and wondering away

Pathology: Neoplasia (cont)

malignant are metastatic (except glioma and basal cell carcinoma) but benign aren't

metastasis is primary and invasivenes is secondary identification of malignancy

- metastatic/dissemination/ pathways

1. direct seeding(transcoelemic) - mostly peritoneal cavity

2. lympatic - most common for sarcoma

3. hematogenous - typical for carcinoma

mostly involves liver and lung (soil and seed phenomenon)

- cancer incidence can vary based on those factors

geographic - due to specific characterstics of that area

environment - nature of work places, sanity

age - most susceptible are above 55 years old, below 15 are susceptible to specific cancers also

- Genetic predisposition to cancer

1. autosomal dominant inherited cancer syndrome

familial retinoblastoma

2. defective DNA repair syndrome

ataxia telangectasia, xeroderma pigmentosa, bloom syndrome

3. familial cancers

high frequency occurence of cancer in a certain family with out a clearly defined pattern of transmission

characterized by

early age/juvenile/ onset

tomor arise in multiple close relatives

multiple or bilateral tumors

- non hereditary predisposition to cancer

non-neoplastic conditions (regenerative, dysplastic, hyperplastic) give way to malignancy

- cancer genes

fall under 4 classes

1. oncogenes overexpression from proto-oncognes

2. loss or dysfunction of tumor supressor genes by mutation

3. over expression of gene that prevent apoptosis

4. expression of genes that hide tumors from host immune system

- driver and passenger mutations

Pathology: Neoplasia (cont)

driver mutations contribute to cancer directly by acting on the cancer genes

passenger mutations are acquired and important in 2 ways

carcinogen associated damage the genome

provide genetic variation of tumor cells making selective therapy difficult

point mutation - activate or inactivate proteins of affected genes

gene rearengement - translocation and inversion caused cancer

e.g. philadelephia (ph) chromosome(leukemia), BCL2 B cell lymphoma 2(anti/pro apoptotic gene), myc gene(induce instablity in excess

deletion - may cause loss of tumor supressor gene

e.g. del13q14 gene - retinoblastoma, del17q13 (tp53) - multiple myeloma

gene amplification - lead to oncogens by over expression in two patterns

heterogenous staining regions, double minute

aneuploidy - chromosome number not multiple of haploid (23n)

increase oncogenes(myc) and decrease tumor supressors(tp53)

- MicroRNAs: inhibit gene expression post transcriptionally by repressing translation or cleaving mRNA

in case of tumor supressor gene their over activity leads to reduced tumor supressor protein

in case of oncogenes their inactivity potentiates occurence of cancer

- Epigenetic modification and cancer cells

epigenetic modification is reversible heritable gene expression changes without mutation

transcription is normally silenced by methylation and histone modification

but cancer cells have global DNA hypomethylation and slective promoter localized hypermethylation(tumor supressors)

- Carcinogenesis:

a multistep process that follows Darwinian selection(evolution)

result from accumulation of multiple genetic alteration leading to transformed phenotype and associated hallmarks

- 1.Hallmarks of cancer

1. self sustainability of growth factor

2. ignore growth inhibiting signal

3. evasion of apoptosis

4. angiogenesis

5. unlimited replicative potential

6. invasion and metastasis

7. evasion of immune surveilance

8. DNA repair defects

1. Gf sustainability: oncoproteins encoded by oncogens promote cell growth

cancer cells may produce Gf or induce others to do so

they have mutated or over expressed Gf receptors

mutation of signal transducing protein(ABL, RAS) genes gives them growth autonomy

nuclear transcription factors mutation of genes that regulate expression of growth promoting genes

2. insensitivity to gowth inhibitory signals

e.g. RB - governor of cell cycle mutation leads to uncontrolled growth

tp53 - guardian of genome eliminate neoplastic transformations by

-quiescence, -senescence, -apoptosis

tp53 is the most mutated human gene in human cancer

transforming growth factor beta pathway:

inhibit proliferation in endothelial, epithelial, hematopoietic cell

- Contact inhibtion NF2, and APC

is inhibition of cell proliferation because of cell to cell contact by transmembrane protein called Cadherin

epithelium maintained by E-Cadherin (E=epithelial) by 2 ways

a. NF2 gene - produce Neurofibromin 2 a tumor supressor

Neurofibromatosis 2 - hereditary NF2 gene mutation

b. binds with beta-catenin

3. Altered cellular metabolism:

cancer cells metabolism is different from normal cell metabolism because

- increased amount of glucose consumption than normal

- use of glycoltic pathway and convert it to lactose regardless of presence of oxygen to meet their rapid demand

- 1.Hallmarks of cancer (cont)

this phenomenon is called aerobic glycolysis or Warburg effect

4. evasion of apoptosis

cancer cells escape death because

- absence of tp53 gene which would normally kill them in that amount of stress and DNA defects

- over expression of anti-apoptotic members of BCL2 family e.g. follicular lymphoma

5. unlimited replicative potential

cancer cells upregulate telomerase enzyme which keeps telomeres(protective cap at the end of DNA) long enough for unlimited DNA replication hence achieving immortality

6. angiogenesis

cancer cells use neoangiogenesis for

- supply nutrient and oxygen

- stimulate neighboring tumor cell growth

- metastatic/dissemination/ pathway