CARCINOGENESIS: Genetic & Environmental factors

13/08/2018 15:08

OBJECTIVES
- Introduce concept of carcinogenesis (tumourigenesis)
- Understand non lethal mutation that immortalises cell
- Genetic factors that facilitate tumorigenesis
- Environmental factor in facilitating carcinogenesis

CARCINOGENESIS
- A large number of agents induce neoplastic transformation of cells in vitro and in experimental animals
- In man this has been noted through careful observation vs those noted to develop specific cancers

- Agents that are known to be carcinogenic are divided into
- I. Chemical carcinogens
- II. Ionizing radiation
- III. Oncogenic viruses
- IV. Genetic factors

General information
- Cancer is due to non lethal genetic mutations
- Damage may be induced through the environment i.e. chemical, radiation, viruses or may be inherited
- Tumours are monoclonal as seen in Women who are heterozygous for polymorphic X-linked markers e.g. glucose 6 phosphate dehydrogenase or x-linked restriction fragment length polymorphism

GENETIC DAMAGE
- it is a non lethal mutation
- acquired by action of environmental factors
- Once damage has occurred it leads to clonal proliferation (expansion).
- Regulator genes are divided into
  1. Growth promoting PROTOONCOGENES
  2. Growth inhibiting ANTIONCOGENES (suppressor)
  3. Cells regulating programmed cell death (apoptosis)

4. DNA repair genes

- These are the principle targets of genetic damage
- other important genes regulate the repair of damaged genes. Failure of this repair genes lead to mutations proliferating and a neoplastic proliferation.
- Carcinogenesis is a **multistep** process.
- The various phenotypic attributes and genetic characteristics are acquired in a stepwise fashion i.e. **Tumour progression**

ONCOGENES
- Oncogenes are cancer causing genes derived from protooncogenes (**c-onc**) which routinely promote normal growth and differentiation.
- They become oncogenes through viral induction e.t.c and code for oncoproteins that are not regulated by the normal regulatory systems, growth factors or external stimuli
- e.g. **Ras** oncogenes that lie along transduction pathway is most common in abnormality of dormant oncogenes in human tumours

Examples of Oncogenes
- **Growth factors** protooncogene- Sis(astro, osteo); hst-1 (ca stomach); int-2 (breast,bladder, melanomas)
- **Growth factor receptors**
- erb-B1 (sq cell ca)
- Erb-B2 (breast, lung, ovary, stomach)
- Erb-B3 (ca breast)
- **protein involved in signal transudation**
- Ras point mutation of GTP (Guanine Triphosphate) binding e.g. lung, colon, pancreas, leukemia

Sis encodes for PDGF
hst-1 encodes for FGF (fibroblast growth factor)

- Abl translocation of non receptor tyrosinase kinase (CML, ALL)
- **Nuclear regulating proteins**
- Myc- translocation e.g. Burkitt's lymphoma
- N-myc amplification (neuro, small cell ca lung)
- L-myc amplification (small cell ca)
- **Cell cycle regulators**
- cyclin D translocation of cyclins associated with mantle cell lym. Cd k4 amplification or point mutation (glioblastoma, melanoma, sarcoma

cMYC: Burkitt's lymphoma

ACTIVATION OF ONCOGENES
- I. Change in structure of gene that results in abnormal oncoprotein leading to aberrant function
- II. Changes in regulation of gene expression resulting inappropriate production of structurally abnormal growth promoting protein

- This is through **point mutation** e.g. Ras gene; **chromosomal rearrangements** i.e. translocations and inversions, ph chromosome t ch 9+22; **gene amplification** e.g. myc

CANCER SUPPRESSOR GENES
- Loss of these genes leads to cancers
- Expressed in homozygous state e.g.
- NF-1 neurofibromas, sarcomas
- NF-2 schwanommas, meningiomas
- APC familial polyposis coli,ca stomach, pancreas, melanoma

- Rb retino, osteo, ca breast, lung, colon
- BRCA-1/BRCA 2 breast, ovary
- WT- wilms tumour
- P53 found in most cancers. Gatekeeper against cancer. Molecular policeman (ch 17:p13.1)

Wims tumors: kidney tumors in paeds

GENES THAT REGULATE APOPTOSIS
- Genes that inhibit apoptosis lead to cancer formation e.g. bcl 2 -- lymphocyte accumulation in marrow and nodes
- P53 and c-myc

GENES REGULATING DNA REPAIR
- This are important in repairing damage caused by environmental factors e.g. ionizing radiation, chemicals and viruses. It also repairs damages that occurs spontaneously
- Importance of these gene is seen in those with hereditary mutation e.g. xeroderma pigmentosa, hereditary non polyposis colon cancer syndrome (LYNCH syndrome)

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is an autosomal dominant genetic condition that has a high risk of colon cancer as well as other cancers including endometrial cancer (second most common), ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin.

- These are non oncogenic and only allow other oncogenic mutations to progress.

MULTISTEP THEORY – MOLECULAR BASIS
- No single oncogene can fully transform cells in vitro.Together Ras and myc gene transform fibroblasts.(DNA transfection)
- Every human cancer analysed reveals multigenetic alterations i.e. activation of several oncogenes or activation of 2 or more suppressor genes

- The sequence in which the genes mutate have an effect
- Gene that regulate the initial step are called Gate Keeper genes e.g. apc,rb,nf -1. Those that affect genomic stability are care taker gene.
- Karyotypic changes in those tumours that are recognised help predict clinical outcomes

Epigenetic requlation of cancers
- Epigenetic mechanisms involve
  - aberrant DNA methylation
  - Histone modification thru acetylation, methylation and phosphorylation.
  - miRNA expression
- Areas targetted development in cancer chemotherapeutic treatment.

Tumour syndromes
- Retinoblastoma
- 40% familial with autosomal dorminant inheritance. Familial have 10,000 fold risk of getting Retinoblastoma. 60% sporadic.
- Born with defective Rb gene chromosome 13q14 (germline mutation) then acquires new mutation (second hit) that inactivates Rb gene.

40% familial; 60% sporadic

- develops tumour in infancy and often bilateral in 90%. Survivors develop second tumours e.g. osteosarcomas, rhabdomyosa, rhabdoid tumours.
- New mutations often unilateral disease and can be transmitted to offspings
- Retinoblastomas with MYC mutations are not inherited

…e.g. ostiosarcomas, rhabdomyosa, rhabdoid tumors etc

Colorectal carcinoma
- APC gene leads to FAP coli, Gardner syndrome, Turcot syndrome
- FAP have germ line mutation, present with multiple adenomatous polyp which progress to adenocarcinomas of colon
- Li Fraumeni syndrome with germ cell mutation of P53
- MENS 1and 2 and HNPCC (Lynch syndr)

-Gardner syndrome, also known as familial colorectal polyposis, is an autosomal dominant form of polyposis characterized by the presence of multiple polyps in the colon together with tumors outside the colon
-Turcot syndrome is a condition characterized by multiple adenomatous colon polyps, an increased risk of colorectal cancer , and an increased risk of brain cancer. It may be associated with familial adenomatous polyposis (FAP) or Lynch syndrome.
-Li-Fraumeni Syndrome (LFS) is an inherited familial predisposition to a wide range of certain, often rare, cancers. This is due to a change (mutation) in a tumor suppressor gene known as TP53.

- Defective DNA repair syndromes are autosomal recessive eg Xeroderma pigmentosum,
- Familial tumours present at early age of onset, are seen in 2 or more relatives, are multiple or bilateral. Siblings have a 2 to 3 times risk of getting the tumour.

Enviromental factors
- Cigarette smoking
- Alcohol abuse
- Viral e.g. HPV, Hep B and C
- Betel nut chewing
- Industrial pollution
- Dietary deficiencies
- Age and gender

THE END