GENETICS OF CANCER

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Introduction

- Cancer is considered as the most common and severe problem of clinical medicine.

- Statistic shows:
  - Cancer in some form strikes over 1/3rd of the population.
  - Accounts for 20% of all deaths.
  - Is responsible for > 10% of total cost of medical care in developed countries.

- Cancer is not a single disease, but a name given to a variety of malignant tumours that have the same basic process of uncontrolled growth.

- Cell proliferation results in a mass (neoplasm or tumor) that invades neighbouring tissues (Cancer i.e. Crab) and may metastasize to more distant sites.

- Growth is autonomous, malignant and invariably fatal (if not treated).

- Early diagnosis and treatment are vital and help improve prognosis.

- Major aim of cancer research is to "detect and identify persons at increased risk of cancer development" i.e. Presymptomatic diagnosis

- Three forms of tumors exist. These are:

  - Sarcomas: Tumor has arisen in mesenchymal tissue.
  - Carcinomas: Tumor has arisen in epithelial tissue.
  - Hematopoietic and lymphoid malignancies: Tumor has arisen in the haematopoietic or lymphoid tissues.

  Further classification of tumors within each goup is based on the site, tissue type and degree of malignancy.

- Most cancers occur in later life (1 in 3 adults) however some occur in childhood (1 in 600).
- Aetiological factors in cancer:
  - Environmental factors
  - Genetic factors

  Some cancers are wholy environmental, others are multifactorial with both genetic and environmental aetiology.

<u>Environmental Factors</u>

e.g. `Industrial cancers' - prolonged exposure to carcinogenic chemicals;

- Skin cancer in tar workers.
- Bladder cancer in aniline dye workers.
- Angiosarcoma of liver in polyvinyl chloride (PVC) workers.
- Lung cancer in asbestos workers.

Genetic and Environmental Factors

- In several types of cancer both genetic and environmental factors play a role. Epidemiological studies show that breast cancer occurs in genetically susceptible individuals in presence of the environmental factors.

  - Higher incidence in:
    - Nulliparous women
    - Women who have a late first pregnancy
    - Women who have a later age of onset of menstruation
  - Higher incidence in N. America and W. Europe (8 times more) than in women of Japanese and Chinese origin.
    Risk of developing breast cancer increases with imigration from low to high risk area.
  - Gastric cancer:
    - Specific dietary and environmental substances (e.g. nitrates) are possible carcinogens.
    - 10 times more common in Japanese and Chinese than in Western Europe.

    Migration studies show that the risk of cancer development does not decrease on migration from high risk to low risk areas for 2-3 generations.

- Family studies:
  - Breast cancer: The risk of breast cancer in a first degree female relative of a women with breast cancer is 1.8-3 times higher than in general population.
  - Gastric cancer: First degree relative of patient with gastric cancer has 2.2 to 3 fold higher risk of developing gastric cancer.

- Twin studies:
  Concordance rate for breast cancer in twins are lower, suggesting importance of environmental factors.

- Disease association:
  Association between blood group A and gastric cancer has been shown (20% more risk).
  Chronic gastrics and pernicious anaemia patients have increased risk of gastric cancer (3-6 fold more risk).
- Biochemical factors:
  - Show acetylator status result in predisposition to bladder cancer.

- Viral factors:
  Certain viruses are tumor forming or oncogenic in humans
  - Tumor viruses
    e.g. papilloma virus, Epstein-Barr (EBV), cytomegalovirus (CMV), Hepatitis B virus
    These DNA tumor viruses are associated with certain types of human neoplasia.
  - RNA viruses (retroviruses) also cause cancer in animals (Table 1 and 2)

The Genetic Nature of Cancer

- Cancer is a genetic disease - New concept
- Approx. 5% cancer follow familial pattern
- Multifactorial in nature and have a significant genetic component.
- Some people are more susceptible to cancer due to some genetic defects that predispose to cancer.
- All cancers, even in the absence of any apparent inherited component is a result of mutation in somatic cells.
- Mutations that lead to cancer affect genes responsible for cell proliferation, cell development and other fundamental cellular activities, thus altering normal regulation and leading to un-controlled growth.
- Most malignancies are of single cell origin and cancer has a clonal nature.

Cancer Genes

- Two kinds:
  - Oncogenes - Facilitates malignant transformation.
  - Tumor suppressor genes - Block tumor development

These have opposite effect.

- Oncogenes:
  - Genes that affect normal cell growth and development. Derived from proto-oncogenes (Figure I).
  - Over 100 c-Onc genes known.
- Naming of oncogenes: Known by three letter abbreviations which reflect their origin and/or the type of tumor with which they are associated.

Relationship between c-onc and v-onc

- c-onc refers to a gene with oncogenic properties like the viral oncogenes, or v-onc. Retroviral oncogenes are thought to form through errors in the replication of the retrovirus genome following their integration at random sites into the host DNA. The result is a viral gene structurally similar to its cellular counterpart but is persistently different in its functions.

Conversion of proto-oncogenes to oncogenes:

- Increase in the absolute amount of proto-oncogene product or its production in inappropriate cell type:
  - Insertional mutagenesis: insertion of v-onc in close proximity to proto-oncogene: uncontrolled expression of cellular gene.
  - Gene amplification: Amplified segments of DNA are detected as 2 types of cytogenetic changes i.e. double minute (small accessory chromosomes) and homogenously staining regions (HSRs).
- Mutation in proto-oncogenes leading to oncogene formation.
  - Mutation in coding sequence.
    e.g. As proto-oncogenes are converted to oncogenes by point mutation.
  - Chromosomal translocation

e.g. chronic myeloid leukaemia translocation of material from long arm of ch.22 to ch. 9 and from ch. 9 to ch. 22
t (9;22) (q34:q11)
i.e. philadelphia chromosome.
This translocation transfers the cellular abl oncogene from ch 9 to a region of ch 22 known as break point cluster or bcr.
- Burkits lymphoma: involves translocation of the c-myc gene from long arm of ch. 8 on to ch. 14. (or from 2 to 22). Thus coming under the influence of the regulatory sequences of the immunoglobulin (1g) genes and are over expressed.

Function of oncogenes: Oncogenes are also classified according to the cellular location and their function in the signal transduction pathways.

- Growth factors:
  SIS (PDGF)
  Int (FGF-related)
  hst (FGF-related)
- Growth factor receptor. erb-B, erb B2, fm S, kit, sea, met etc.
- GTP binding proteins: N-ras, Ha-ras, ki-ras.
- Post receptor tyrosine kinases: src, abl, yes,

The gene products are capable of phosphorylation.

- Cytoplasmic oncogenes: mos, A-raf, B-raf.
  - Cytoplasmic gene products are part of signal transduction pathway.
- Nuclear oncogenes: fos, erb-A, myb, myc, N-myc, L-myc.
  - Encode proteins that are specific transcription factors and regulate gene expression.
- Apoptotic oncogenes: e.g. bcl-2
  - Cause increased growth and/or division or decreased cell death (apoptosis).

Tumor Suppessor Genes

- The products of these genes block abnormal growth and malignant transformation.
- They contribute to malignancy only when the function of both alleles is lost.
- Mutation in these genes are recessive.
- Referred to as anti-oncogene.
- The "Two-Hit" origin of cancer: the hypothesis was put forward by DeMars in 1960 and expanded further in 1971 by Knudson. "If a cell heterozygous to recessive germline mutation undergoes a second mutation, thus rendering the cell homozygous - this gives rise to a tumor".
  e.g. Retinoblastoma:
  Two mutations in the same retinal cell (Sporadic form) or one mutation in the germline and a second mutation in the retinal cell leads to retinoblastoma:
  Thus the tumor-suppressor gene is changed to oncogene.
  - The gene is located on chromosome 13 (13q14)
  - First mutations identified are point mutations (nonsense, frameshift or splicing errors). Generally C→ T transversions at CpG dinucleotide.

- This may occur through mitotic non-disjunction.
- Second mutation involves loss of part or whole Ch.13. This is referred to as "loss of heterozygocity"
  Thus, homozygocity for mutant allele.
- Loss of heterozygocity has been observed in a number of tumors (Table 3).

Examples of some tumor suppressor genes:

(i) The Rb gene:
- The Rb gene specifies a 4.7 kb transcript which encodes a nuclear protein, P105, which associates with DNA and is involved in the regulation of cell cycle. The gene product exists in a phosphorylated (active) or unphosphorylated (inactive) state. In the phosphorylated state it is associated with an unidentified nuclear factor and suppresses growth.
- RB gene is affected in familial retinoblastoma and in sporadic type of small-cell lung carcinoma.

(ii) p53
- The gene product is involved in cell cycle regulation.
- Over 50% of bladder, breast, colon and lung cancers have p53 mutations, which are generally in exons 5 to 10.
- In hepatocellular carcinoma the p53 mutations occur in "hot-spot". In codon 249 and is G $\rightarrow$ T mutation. May result from interaction with carcinogen aflotoxin B1 or hepatitis B virus.
- Mutation of a single allele could be sufficient to induce neoplastic transformation even when one copy of the normal allele remains.
- p53 mutation is common in Li-Fraumeni syndrome, a familial but rare syndrome; inherited as AD trait.

(iii) DCC gene i.e. Deleted in Colorectal Cancer.
- Allele loss on Ch 18q is seen in over 70% of colorectal carcinoma.

- DCC gene is expressed in normal colonic mucosa, but is either reduced or absent in colorectal carcinoma.
- In some cancers, somatic mutation in DCC may occur thus inhibiting gene expression.

(iv) WTI:

- The gene product is a zinc finger protein, which has DNA binding function. Mutations in WTI occur in familial Wilms tumor and in sporadic cases of lung cancer.

Familial Cancer

- Some cancers are inherited and their incidence is higher in relatives of patients than in the general population.
- Some even show Mendelian inheritance.
- Familial cancers are specific in terms of site, tissue involved and histological characteristics of tumor.
- This provides strong evidence that germline and somatic mutations both contribute to cancers.

Table 1: Viral Oncogenes

Virus	Species	Virus induced tumour	Oncogene	Map location of proto-oncogene	Biochemical property
• Signal transduction protein					
- Rous Sarcoma	Chicken	Sarcoma	Src	20q 12-13	protein kinase
- Abelson murine leukaemia virus	Mouse	Pre B-cell leukaemia	abl	9q 34	"
- Harvey murine sarcoma	Rat	Sarcoma	Ha-ras	11p 15.5	GTpase
• Nuclear DNA-Binding Protein					
- Avain myelocytomatosis	Chicken	Myelocytoma sarcoma	myc	8q24	Binds DNA
• Secreted Growth Factors					
- Simian Sarcoma	Monkey	Sarcoma	sis	22q 12.3-13.1	ß-chain of platelet-derived growth factor (PDGF)
• Growth Factor Cell Surface Receptor					
Avain erythroblastosis	Chicken	erythroleu-kaemia	erb-B	17q 21-22	Steroid receptor

Table 2: Oncogenic retroviruses host and associated tumors

Virus	Host	Tumor/Disease
Rous Sarcoma Virus	Chicken	Sarcoma
Avain Leukosis Virus	Chicken	Avain Leukaemia
Murine Sarcoma Virus	Mice	Sarcoma
Murine Leukaemia Virus	Mice	Leukaemia
Human T cell lympho trophic virus (HLTV)	Human	T-cell leukaemia
Human immune deficiency virus Type I (HIV-1)	Human	Kaposi sarcoma

Table 3: Loss of heterozygocity

Tumor	Sites of allele loss
Bladder carcinoma	11p
Breast cancer	3p, 7q, 11p, 13q, 16q, 17p, 17q
Colon cancer	5q, 17p, 18q, 22, others
Hepatocellular carcinoma	4q, 11p, 17p
Insulinoma	11
Osteosarcoma	13q
Pheochromocytoma	1p 22
Retinoblastoma	13q
Wilms tumor	11p

Figure 1