Molecular basis of cancer

(Cancer critical gene)

Dividing cell proliferation or, to sensitivity to differentiation and apoptosis. These genes may be involved in following process:-

1. cell cycle progression (eg Rb, myc)
2. Differentiation process (eg Hh, Apc)
3. DNA repair (eg Atm, Brca)
4. cell Death (eg Bcl2)

Critical Cancer gene of two types:-

(i) Proto oncogene — gain of function mutation, dominant gene

(ii) Tumor Supressor gene: — loss of function mutation, recessive gene.

Proto oncogene:-

Prot^s of Proto oncogene participates in various metabolic processes like regulation of cell cycle, cell to cell signalling, TF and intracellular signal transduction.

Examples of Proto oncogenes and nature of their products:-

Name	Nature of gene products
Myc, Fos, Jun	Synthesis of TFs.
Src, abl	Synthesis of Tyrosin kinase.
K-ras	Synthesis of GTPase.
Sis	Synthesis of platelate derived Growth factor.
erbB	" Epidermal Growth factor

Proto oncogenes in cell can change into an oncogene by many conceivable modes:—

(I) Point Mutation:

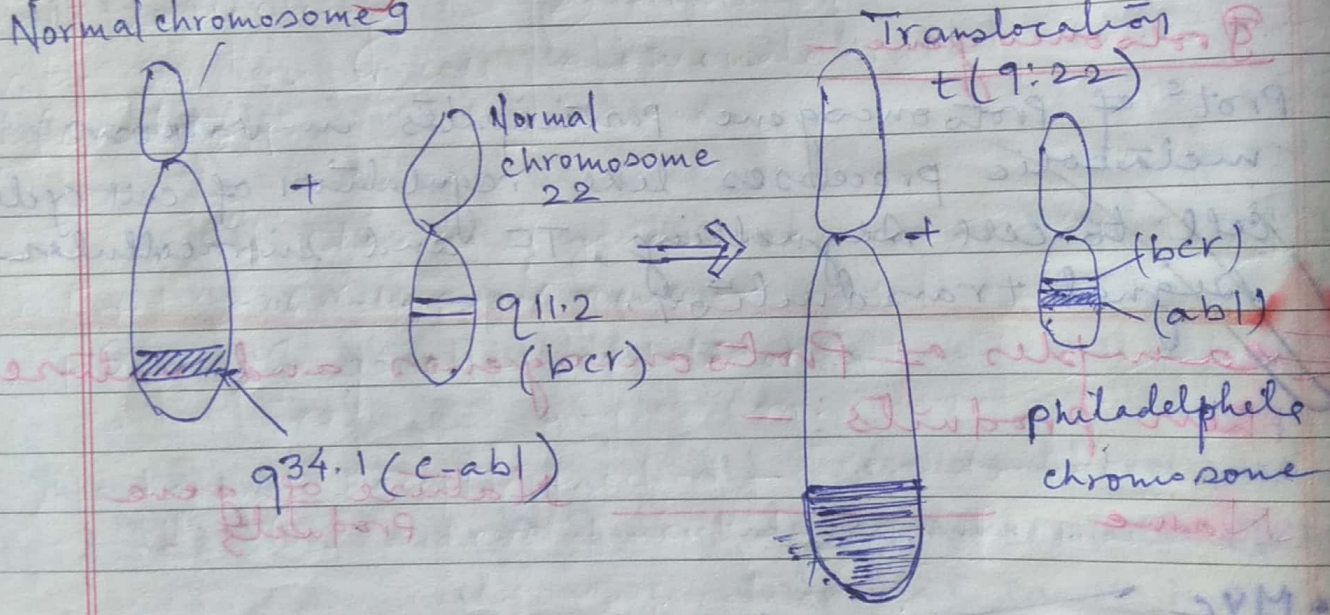
→ ras oncogenes not present in normal cell

→ ras oncogenes present in tumor cell due to point mutation resulting in single a.a substitution at critical ~~condition~~ position.

(II) Chromosomal translocation:

→ Over expression of proto-oncogene causes chromosomal translocation.

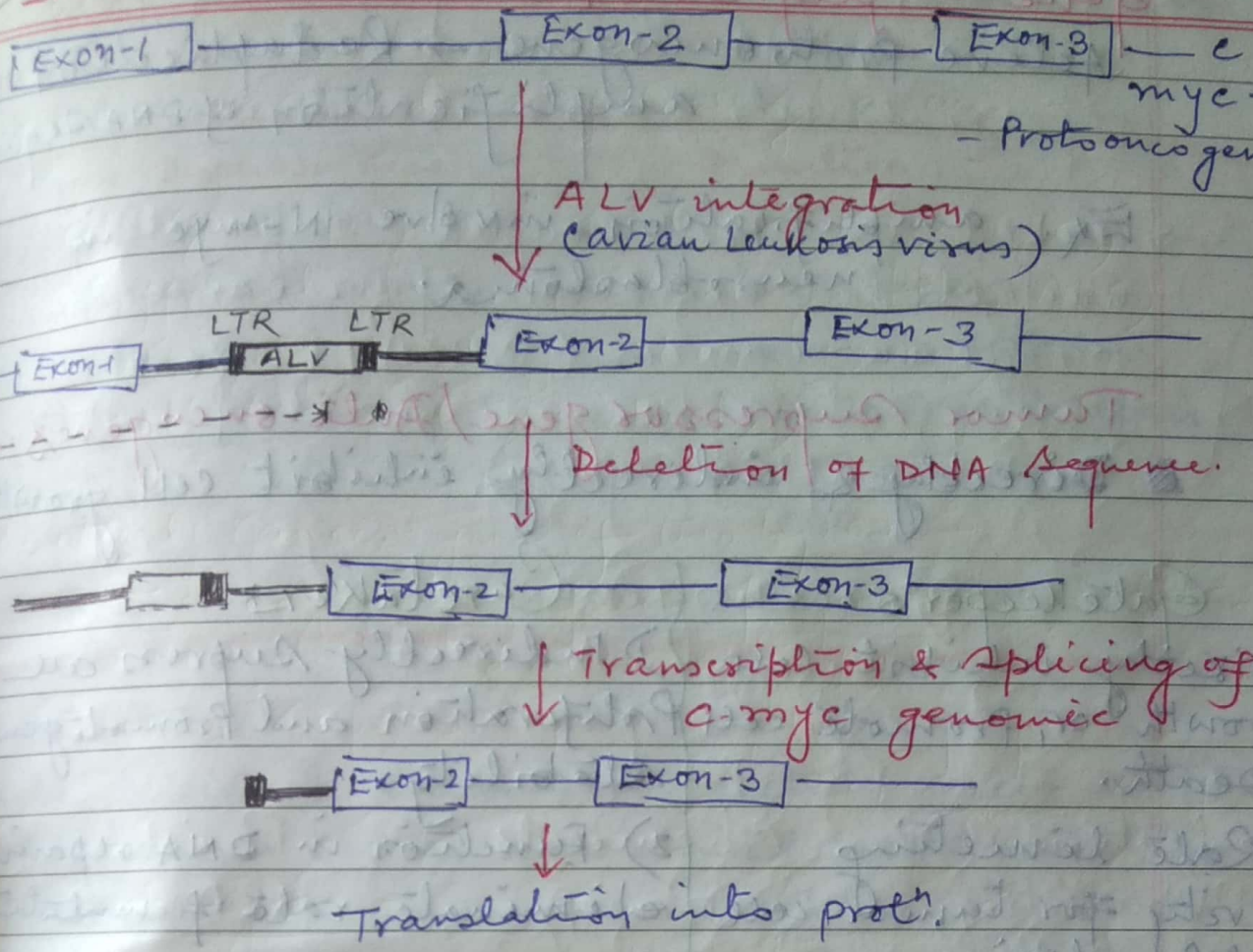
eg. Burkitt's Lymphoma



Example of specific chromosome aberration and associated cancer:—

Cancer	chromosomal alteration
(I) Chronic myelogenous leukemia	Translocation (9, 22)
(II) Acute Myelogenous leukemia	– Translocation (8; 21)
(III) Retinoblastoma	– Deletion (13q)
(IV) Wilms tumor	——— Deletion (11p)

Insertional activation :-



Activation of the c-myc oncogene as a consequence of ALV integration. In a normal cell, the three exons of the c-myc gene are normally spliced into mRNA that can translated into the c-myc protn. (only exon-2 & exon-3 actually coded for the protn). When ALV integrates into c-myc locus (usually b/w exon 1 & 2), the presence of the LTR sequences, in the sequence in the transcript results in increased expression of the myc protn, which is harmful to the cell. The integration of ALV is often followed by deletion of portions of viral sequences, leaving one of the LTRs intact. Insertion of ALV increases synthesis of c-myc.

Gene amplification –

Active Proto oncogene → Reduplication & amplification of DNA sequences.

Ex. - amplification involve N-myc in neuroblastoma

Tumor Supressor gene / Anti-oncogenes :–

- Directly & indirectly inhibit cell growth :–

Gatekeeper's	Caretakers
1) Directly inhibit cell growth or, promote cell Death.	1) Indirectly Supress cell Proliferation and Promote genetic Stability.
2) Rate limiting activity for tumor cell Proliferation	2) Function in DNA repair if eliminate rate of mutation.

Five broad classes of genes are generally grouped into tumor Supressor gene :–

(1) p16 & Rb gene :– regulate or inhibits cell cycle progression.

(2) Hedgehog Receptor patched :– encode receptors or, developmental signals that inhibits cell proliferation.

(3) p53 gene :– check point control prot^n. arrest the cell cycle if DNA is damaged

(4) Gene promotes apoptosis.

(5) Gene encodes enzymes that participates in DNA repair.

Example of tumor Supressor genes and their functions.

	Tumor Supressor gene	Function.
(1)	BRCA-1	TFs
(2)	BRCA-2	DNA repair
(3)	CDK-4	cyclin D-kinase.
(4)	hMLH1	DNA mismatch repair.
(5)	NF-1	GTPase
(6)	p53	TFs.
(7)	Rb	cell cycle check point.

Importance of p53 gene:-

→ Well studied encode polypeptide, acts as TFs.
→ 50% human cancer associated with mutation in p53 gene.
→ It plays role in maintenance of genomic stability during mitotic proliferation.
→ It arrests cell at G1-S boundary & affects the G2 checkpoint.
→ It plays in DNA damage repair.
→ It promotes apoptosis of the cells.

Importance of DNA damage repair:-

- Alteration in DNA damage repair systems causes no. of human cancer.
→ Bloom Syndrome is associated caused by mutation in helicase gene.
(Mutation is caused due to ↑se chromosomal breaks and chromatic exchange).

→ Mutation in any one of several genes or prot^{n} involved in nucleotide excision repair, which causes Xeroderma pigmentosum.

→ Defect in Trc^{n} coupled component of nucleotide excision repair causes breast & Ovarian cancer (BRCA1 (Breast cancer prot 1) has been implicated with Trc^{n} coupled repair).

Carcinogenesis :-

Tumor promoter gene

- Radiations
  Ex. UV radiation, Y-rays, B-rays
- Chemicals
  Ex. Benzopyrene, Benzene.
- Biological
  Ex- Oncoviruses

Chemicals:
- Direct acting Carcinogen
  Act without metabolic activation
- Indirect acting Carcinogen
  act with metabolic activation.

Example:— Aflatoxin.

→ Aflatoxin activated into 2,3 and caused mutation in p^{53} gene.

→ Aflatoxin, mycotoxin produced by Aspergillus flavus, A. parasiticas; most exclusive liver cancer carcinogen.

Aflatoxin consists → difurofuran ring system (fused) → coumarin moiety (with methoxy group) (attached) → benzene ring

chemical modified by liver enzyme → linked G residue in DNA

Induces G-T transversion

- Benzene → Leukemia
- Arsenic → Lung & skin cancer
- Cadmium → Prostate cancer
- Radon → Lung cancer
- Asbestos → Lung & GIT
- Vinyl chloride → angiosarcoma & liver cancer.

Oncovirus / tumor virus.

Transformed normal cell into oncogenic state

DNA containing oncovirus

1. Hepatitis B-Virus (Liver cancer).
2. Papilloma virus (cervical & other anogenital cancer.
3. Epstein Barr Virus. (Burkitt's lymphoma & nasopharyngeal carcinoma)
4. Kaposi's sarcoma associated herpesvirus (Kaposi's sarcoma)

- Papillovirus uses two viral prot^n. E6 & E7 and bind with p53 & Rb respectively.
- Adenovirus uses E1A & E1B prot^n and bind with Rb and p53 respectively.

RNA Containing oncovirus.

1. HTLV-1 Virus (Human T-Cell lymphotrophic virus-1) adult T cell Leukemia/ lymphoma.
2. HTLV-2 (Hairy cell Leukemia)
3. Simian Virus 40 (Non-Hodgkin's lymphoma)

NOTE:-
- 1st oncovirus was found in Rous sarcoma virus designated as the Src oncogene.
- Oncogene carried out by Rous sarcoma virus is called- V-Src and the protooncogene related to it in cellular genome C-Src.

(Oncogene is the virus is not the oncogene but it replicate with host cell then causes Cancer.)