Charting New Horizons in Education

Neoplasia III

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Pathology

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MOLECULAR BASIS OF CANCER

- **Carcinogenesis is a multistep process.**
- The attributes of malignancy (e.g., invasiveness, excessive growth, escape from the immune system, etc.) are acquired, a process called tumor progression. At the genetic level, progression results from accumulation of successive mutations

- Although tumors begin as monoclonal proliferations, by the time they are clinically evident, they are extremely heterogeneous

- **Certain fundamental changes in cell physiology contribute to development of the malignant phenotype:**

1. Self-sufficiency in growth signals (proliferation without external stimuli).
2. Insensitivity to growth-inhibitory signals.
3. Evasion of apoptosis.
4. Defects in DNA repair.
5. Limitless replicative potential (related to telomere maintenance).
6. Sustained angiogenesis to provide adequate nutrition and waste removal.
7. Ability to invade and metastasize.
8. Ability to escape immune recognition and regulation.

Oncogenes

- Normally: our cells have **proto-oncogenes** → These cause cell proliferation in a **regulated manner.**
- If the proto-oncogenes are mutated or overexpressed: they are called **oncogenes**
- Proto-oncogenes encode for proteins: proto-oncoproteins, or oncoproteins
- These oncoproteins include: transcription factors, growth regulating proteins, proteins involved in cell survival.

Oncogenes

- Oncogenes cause overexpression of proteins involved in cell growth.

- If one **allele is mutated or overexpressed:** there will be increase in the growth proteins, which is enough to increase cell growth → mutations of oncogenes act in a dominant manner .
- Important oncogenes: RAS and ABL

HOW ONCOGENES OVEREXPRESSED?

1. Point mutation resulting in activation
2. Amplification : increased number of copies of the oncogenes
3. Translocations
4. Epigenetic modification

HOW ONCOGENES OVEREXPRESSED?

- Cancer is characterized by proliferation in the absence of growth promoting signals.
- Oncogenes are genes that promote autonomous cell growth in cancer cells; their unmutated normal counterparts are proto-oncogenes.
- Proteins encoded by proto-oncogenes may function as growth factors or their receptors, transcription factors, or cell cycle components.
- Oncoproteins are the protein products of oncogenes; they resemble the normal products of proto-oncogenes except that they lack normal regulatory elements, and their synthesis may be independent of normal growth stimuli.

PROTO-ONCOGENES

- Proto-oncogenes normally stimulate growth in a controlled manner.
- If they are mutated, they cause uncontrolled growth (cancer)
- Mutations convert proto-oncogenes into constitutively active oncogenes that endow the cell with growth self sufficiency.

PROTO-ONCOGENES

- Tumor suppressor genes counteract the function of oncogenes.
- If they are inhibited by a mutation, cells can proliferate without the "braking" effect of the tumor suppressor genes.

GENETIC DAMAGES IN NEOPLASMS

- Five types of regulatory genes are mainly affected:

1. Growth promoting proto-oncogenes
2. Growth inhibiting tumor suppressor genes
3. Genes that regulate apoptosis
4. Genes involved in DNA repair.
5. Genes that regulate interactions between tumor cells and host cells. → Particularly important are genes that enhance or inhibit recognition of tumors cells by the host immune system.

TUMOR SUPPRESSOR GENES

- They normally inhibit cell growth
- If mutated or lost: loss of growth inhibition → so tumors occur.
- Both alleles need to be lost or mutated for the tumors to develop.
- Because if only one allele is lost , the other can compensate → So they are recessive genes
- In some cases loss of one allele is enough for transformation → haploinsufficiency

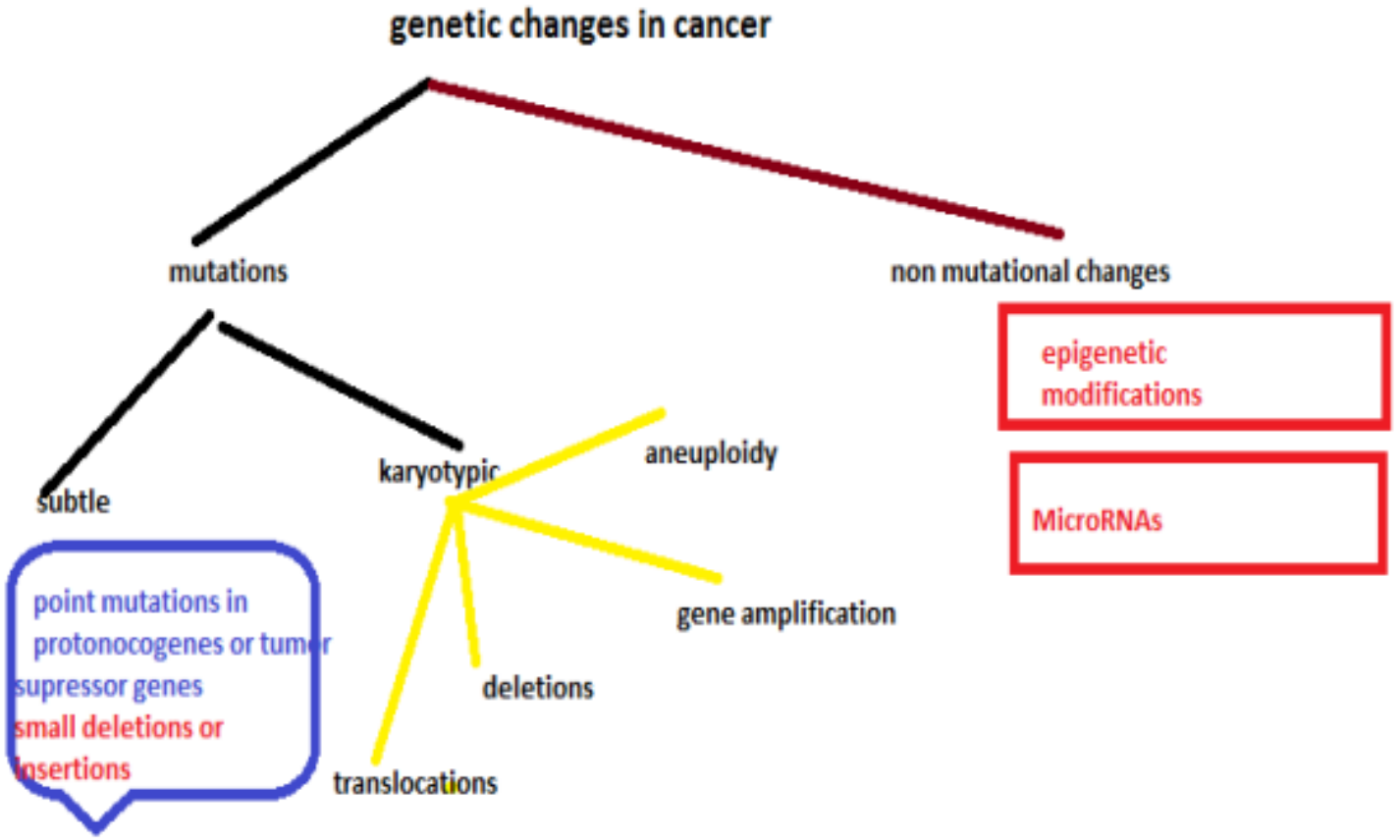
- Most important examples:

1. RB gene (retinoblastoma gene) → Governor: controls growth and puts a brake in cellular proliferation
2. TP53 gene → guardian of the genome → sense genetic damage.

- So if there is damage it causes cessation of proliferation or if the damage cannot be repaired it causes apoptosis.

Mechanisms of damage

- WE NOW KNOW THE TYPES OF GENES THAT SHOULD BE DAMAGED FOR CANCER TO OCCUR.
- BUT HOW THEY ARE DAMAGED?



Point mutations

- These are single changes in nucleotides
- Point mutations that stimulate an oncogene or inhibit both alleles of a tumor suppressor gene can result in cancer.

BALANCED TRANSLOCATIONS

- Translocations can cause cancer if they increase expression of a protooncogene.
- This can happen by two mechanisms:

1. Removing the proto-oncogene from its normal, regulated locus to a new position where it becomes under influence of a highly active promoter.
2. Translocation forms a new fusion gene that encodes a novel protein.

TRANSLOCATIONS

- **Occur mainly in hematogenous neoplasms; why?**
- Because lymphoid cells make DNA breaks during antibody or T cell receptor recombination. (loads of cutting and rearrangements of the genes → so there is more chance that a gene that was cut will be “pasted “ in a new locus!

TRANSLOCATIONS

- In the upper example, the translocation created a new gene ABL-BCR from fusion of two genes (ABL and BCR). This created a new tyrosine kinase that can activate cell proliferation resulting in leukemia.

- In the other example in the pic, the translocation moved the MYC oncogene to a new locus (near the IG gene) that increased expression of the MYC gene resulting in increased cell proliferation

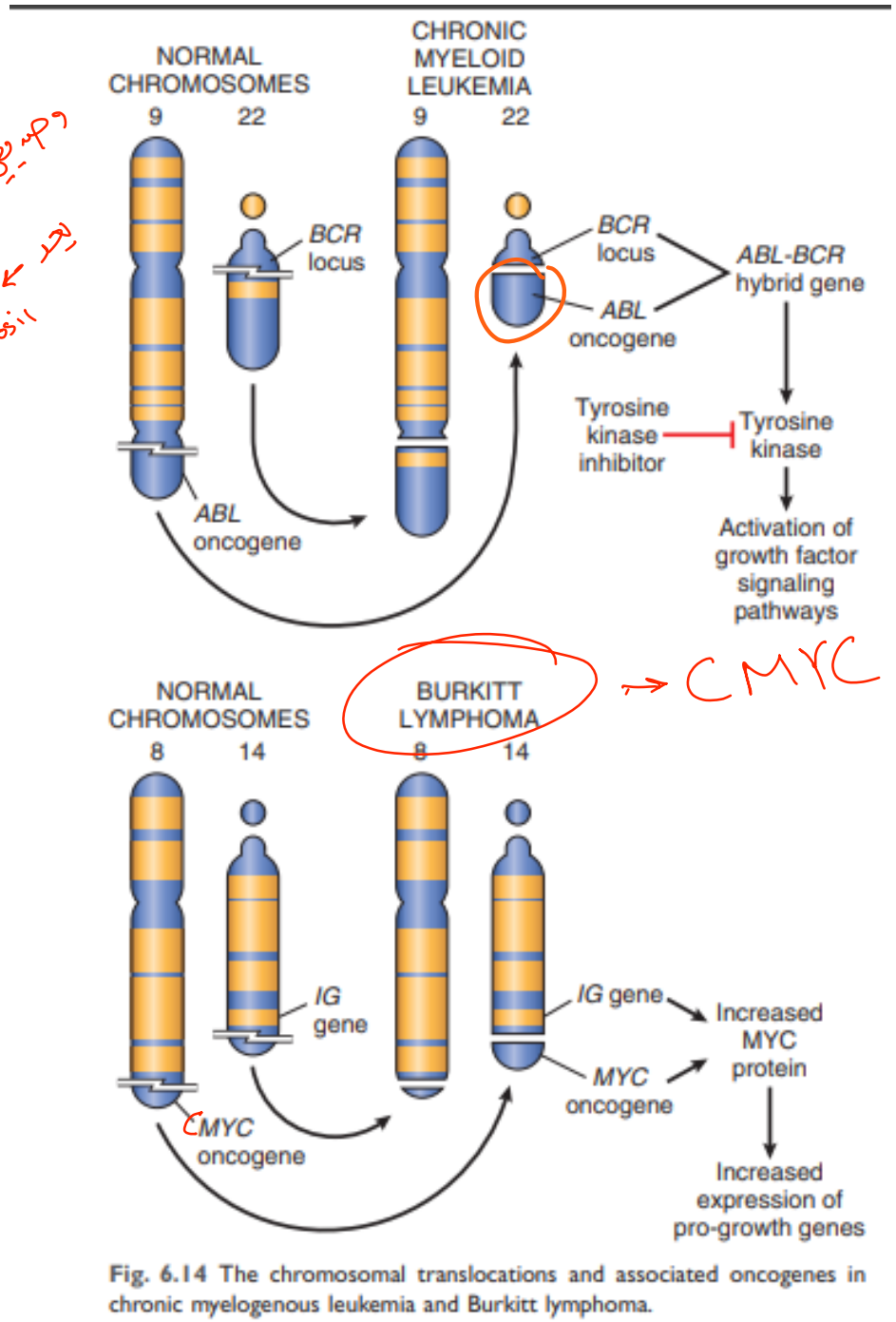
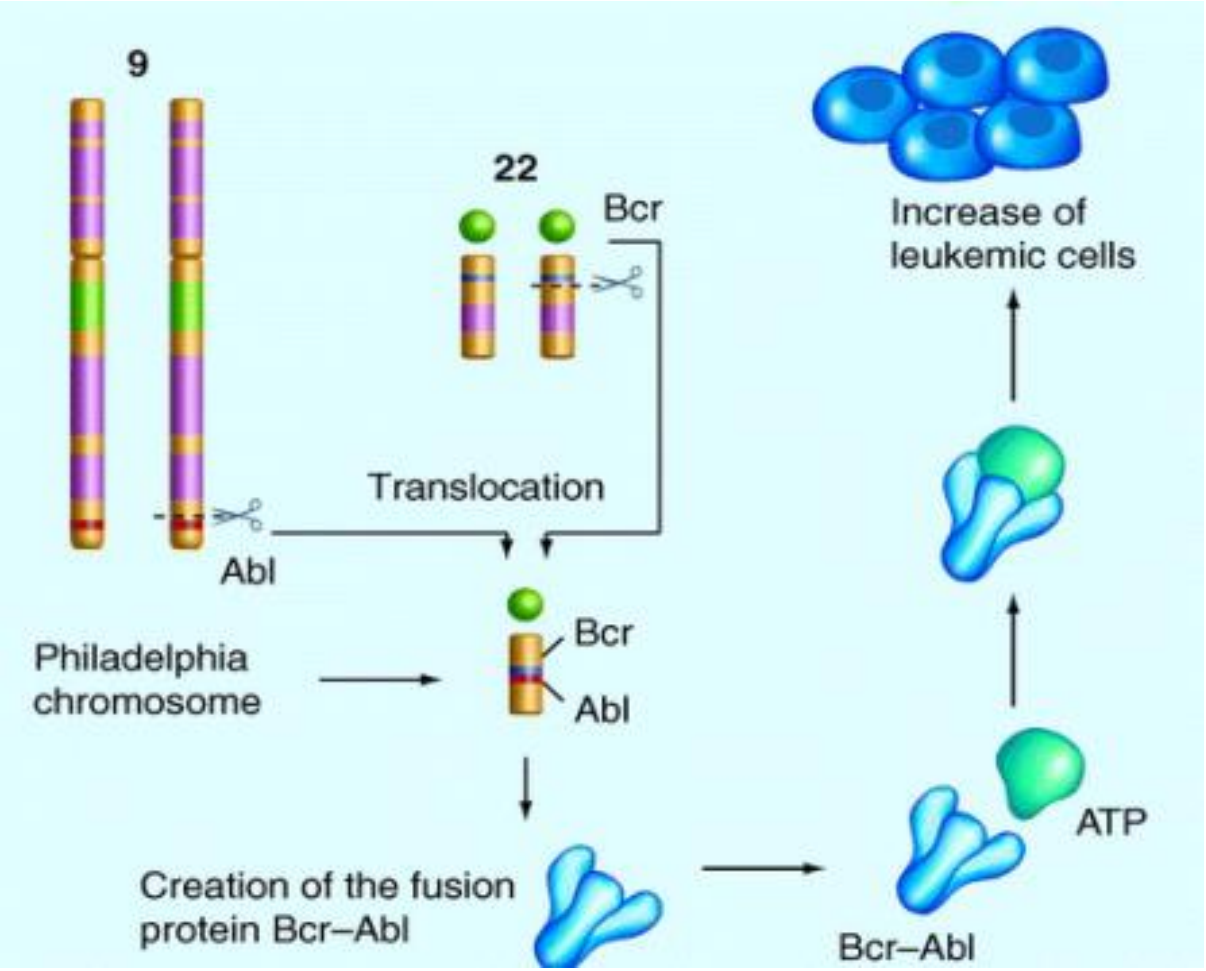


Fig. 6.14 The chromosomal translocations and associated oncogenes in chronic myelogenous leukemia and Burkitt lymphoma.

TRANSLOCATIONS

- PHILADELPHIA CHROMOSOME: AN EXAMPLE OF A TRANSLOCATION CAUSING A NEW PROTEIN (A KINASE) THAT INCREASES CELL PROLIFERATION



GENE AMPLIFICATIONS

- Proto-oncogenes can be amplified and overexpressed → Converted to oncogenes.
- This is seen in karyotyping as two patterns:

1. **Homogenously stained region (HSR)** = increased copies of the gene present within the chromosome
2. **Double minutes:** extra copies of the gene separated from the chromosome.

GENE AMPLIFICATIONS

Neuroblastoma
NMYC

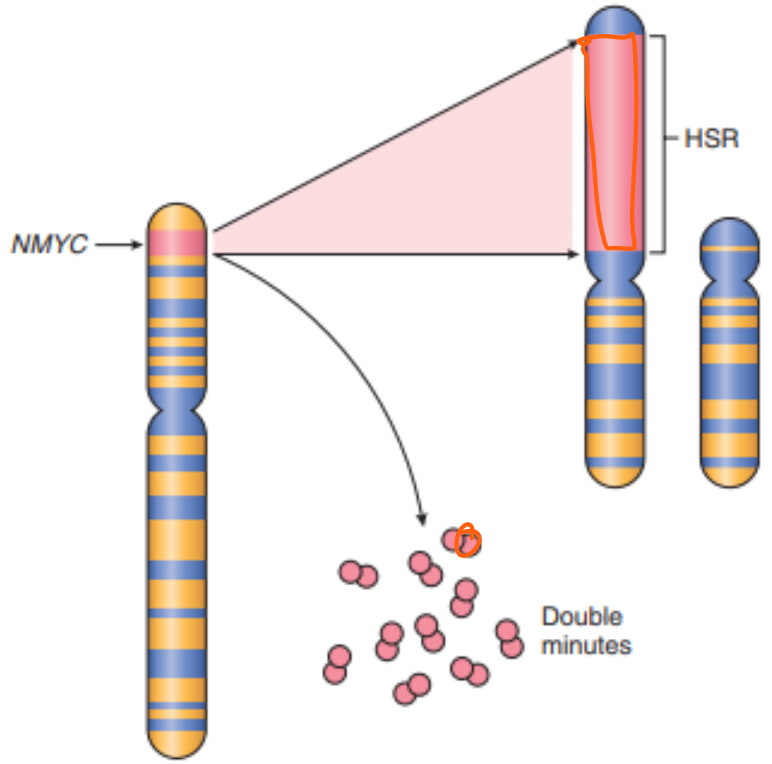


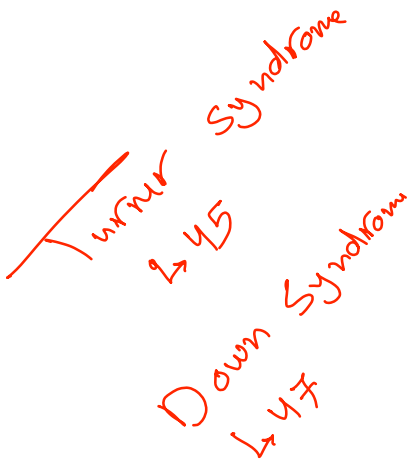
Fig. 6.15 Amplification of the *NMYC* gene in human neuroblastoma. The *NMYC* gene, present normally on chromosome 2p, becomes amplified and is seen either as extrachromosomal double minutes or as a chromosomally integrated homogeneous-staining region (HSR). The integration involves other autosomes, such as 4, 9, or 13. *(Modified from Brodeur GM, Seeger RC, Sather H, et al: Clinical implications of oncogene activation in human neuroblastomas. Cancer 58:541, 1986. Reprinted by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.)*

DELETIONS

- More in **non-hematopoietic solid tumors**
- Second most common karyotypic abnormality.
- Result in loss of tumor suppressor genes
- 2 copies of the tumor suppressor gene need to be lost, usually one by point mutation and another by deletion

ANEUPLOIDY

- = number of chromosomes not multiple of the haploid state (23).
- Result from errors of the mitotic checkpoint



Epigenetics

- Epigenetics are reversible, heritable changes in gene expression that occur without mutation.

- Epigenetic mutations: functionally relevant changes to the genome that do not involve a change in the nucleotide sequence.
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- Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence.

EPIGENETIC MODIFICATIONS

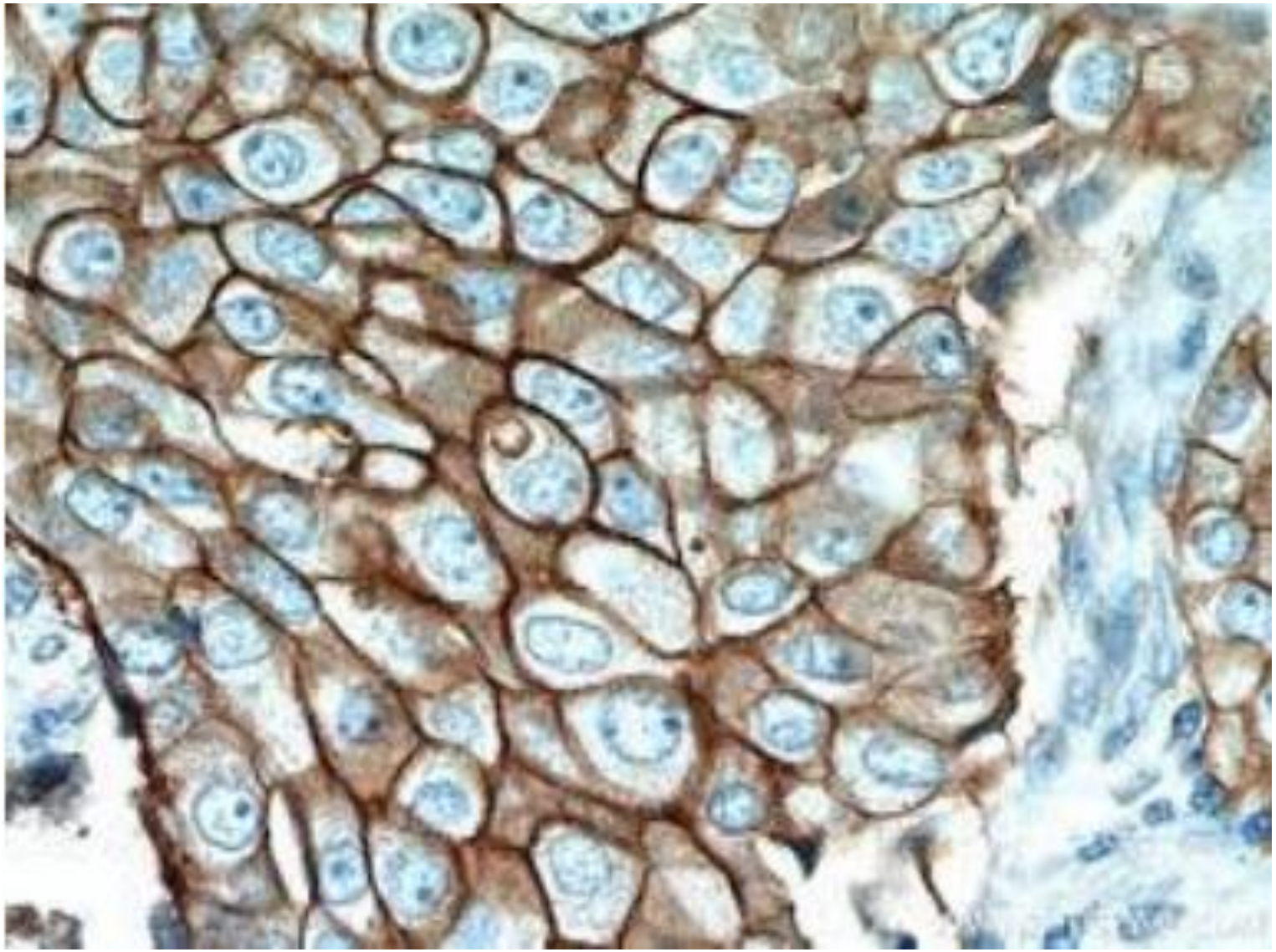
- Reversible, heritable changes in gene expression without mutation.
- Two types: Histone modifications and DNA methylation.

EPIGENETICS AND CANCER

- Gene expression is silenced by DNA methylation= more methyl groups lead to more silencing.
- In cancer cells:

1. Global DNA hypo methylation: increases expression of genes → Also causes chromosomal instability
2. Selective promoter hyper methylation of tumor suppressor genes: silenced

CASE STUDY: APPLICATION OF TODAY'S LECTURE



«Wherever the art of medicine is loved,
there is also a love of humanity.»

- Hippocrates-

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