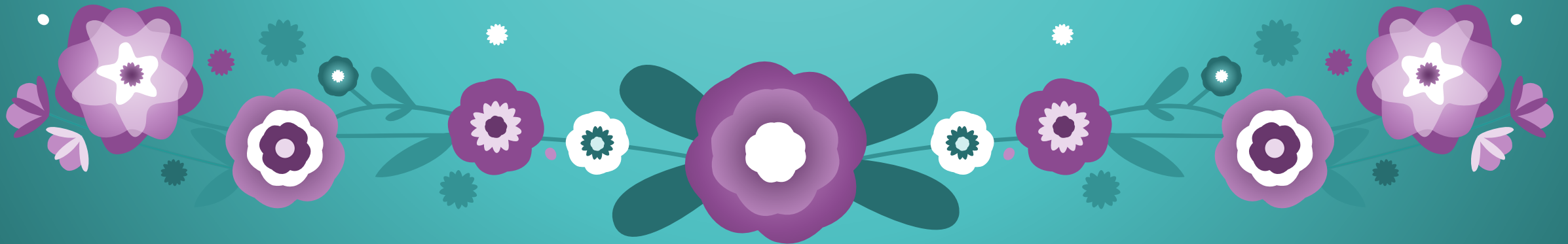


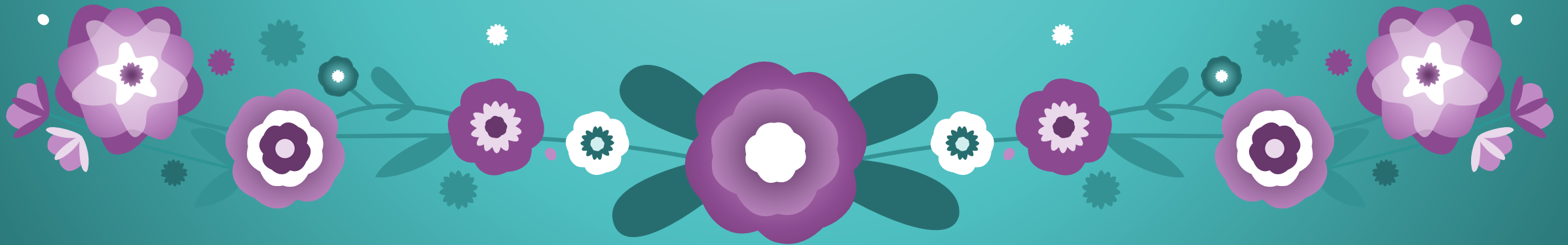
NEOPLASIA

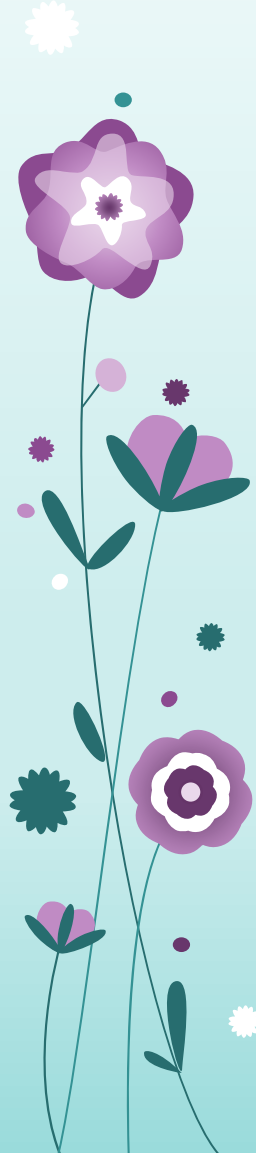
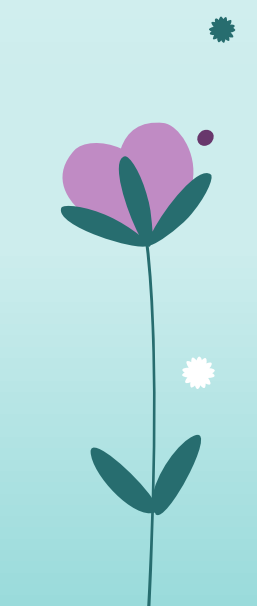
LEC. 6

Dr. Raghad Hanoon



Tumor immunity



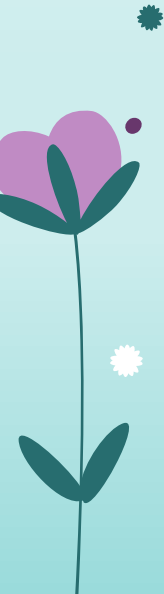
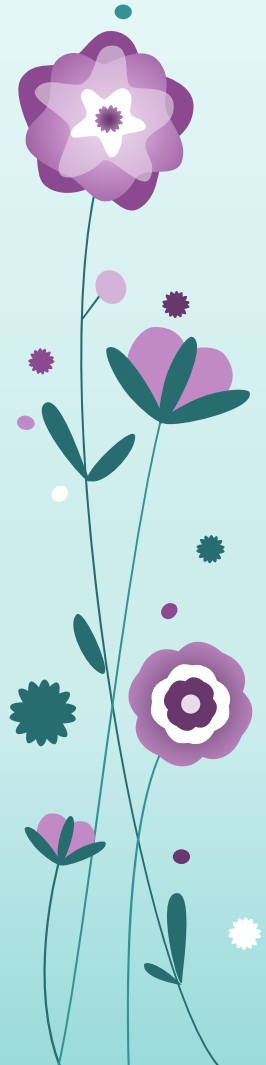
- 
- Malignant transformation is associated with complex genetic alterations, some of which may result in the **expression of proteins (antigens)** that are non-self by immune system.
 - ***Immune surveillance:*** refer to recognition & destruction of non-self-tumor cells by the immune system.
- 

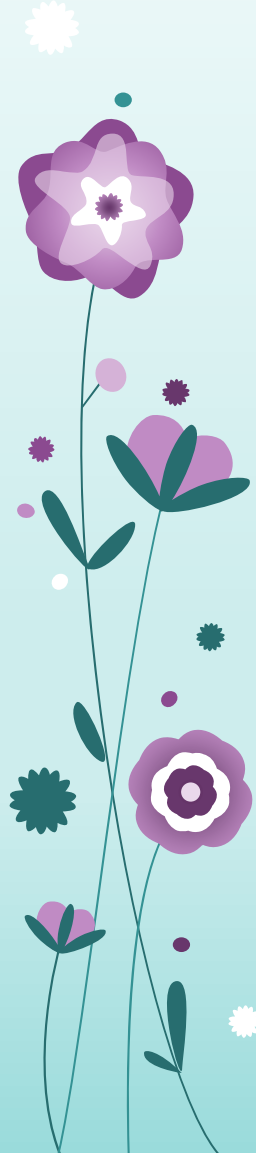
Tumor Antigens

- Antigens present on the tumors that *elicit the immune response*.
- **Classification of tumor antigens:**

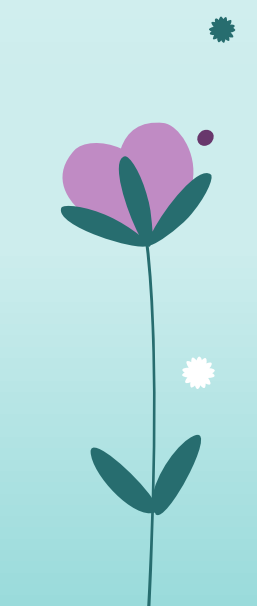
Initially, they were broadly classified into **two categories** based on their patterns of expression:

- 1. Tumor-specific antigens**, which are present only on tumor cells and not on any normal cells.
 - 2. Tumor-associated antigens**, which are present on tumor cells and also on some normal cells.
- This classification, however, is imperfect because many antigens thought to be tumor-specific turned out to be expressed by some normal cells as well.




- 
- The modern classification of tumor antigens **is based on their molecular structure and source:**

1. Products of mutated genes:

- Neoplastic transformation, as we have discussed, results from genetic alterations in proto-oncogenes and tumor suppressor genes or other mutated genes; these **mutated proteins represent antigens** that have **never been seen by the immune system** and thus can be **recognized as non-self**.
- 



2. Overexpressed or aberrantly expressed cellular proteins:

- Tumor antigens may be normal cellular proteins that are abnormally expressed in tumor cells and elicit immune responses.
 - One such antigen is **tyrosinase**, an enzyme involved in melanin biosynthesis that is **expressed only in normal melanocytes and melanomas**. The probable explanation is that tyrosinase is normally produced in such small amounts and in so few cells that it is not recognized by the immune system and fails to induce tolerance.
- 

3. Tumor antigens produced by oncogenic viruses:

- Oncogenic viruses (e.g.; HPV, EBV, HBV) produce proteins that are recognized as foreign by the immune system.

4. Oncofetal antigens:

- These are proteins that are **expressed at high levels on cancer cells and in normal developing (fetal) but not adult tissues.** The two most characterized oncofetal antigens are;

a. Carcinoembryonic antigen (CEA)

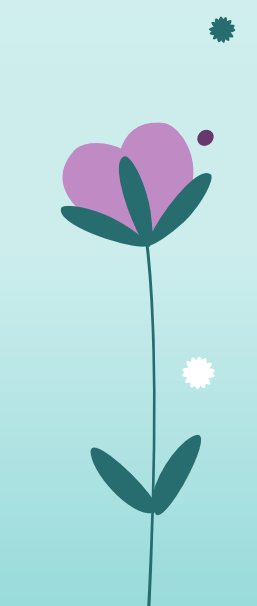
- GIT, pancreas, biliary system and breast cancer.

b. Alpha fetoprotein(AFP):

- hepatocellular carcinoma



5. Altered Cell Surface Glycolipids and Glycoproteins:

- Expression of higher than normal levels and abnormal forms of surface glycoproteins and glycolipids. These include;
 - **CA-125** - expressed on **ovarian carcinomas**
 - **CA-19-9**- expressed on **carcinoma in pancreas & biliary tract**
 - **MUC-1** - expressed on **breast carcinomas**
- 

6. Cell type-specific differentiation antigens:

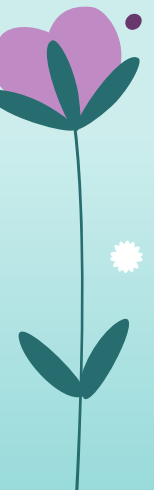
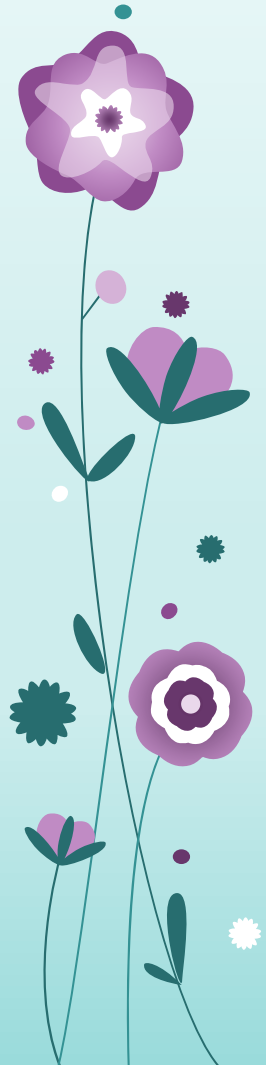
- Tumors express molecules that are normally present on the cells of origin, important for identifying the tissue of origin of tumors. These antigens are called **differentiation antigens** because they are specific for particular lineages or differentiation stages of various cell types.
- Typically, normal self-antigens, and therefore they do not induce immune responses in tumor-bearing hosts for example, *lymphomas* may be diagnosed as ***B-cell-derived tumors*** by the detection of surface markers characteristic of this lineage, such as ***CD10 and CD20***.

Effective Immune Responses to Tumor Antigens.

- Cell mediated immunity is the dominant antitumor mechanism.

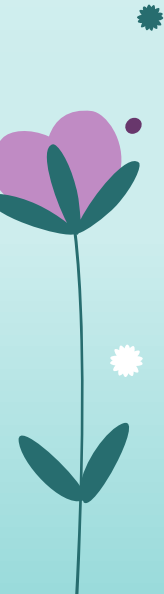
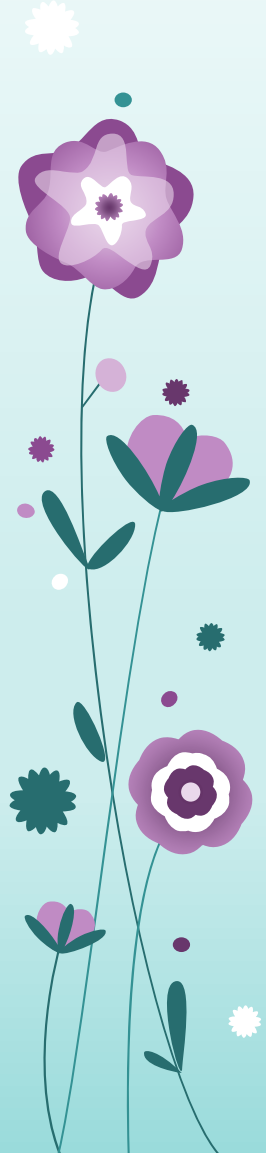
1. Cytotoxic T lymphocyte;

- CTLs are the major immune defense mechanism against tumors, recognize peptides derived from cytoplasmic proteins that are displayed bound to class I major histocompatibility complex (MHC) molecules.
- CTLs play a protective role against virus-associated neoplasms (e.g., EBV- and HPV-induced tumors)




2. *Natural killer cells*

- First line of defense against tumors.
- Are capable of destroying tumor cells without prior sensitization .
- After activation with IL-2, NK cells can lyse a wide range of human tumors. They recognize stress-induced antigens that are expressed on tumor cells and cells that have incurred DNA damage and are at risk for neoplastic transformation.





3. *Macrophage:*

- Activated macrophages exhibit cytotoxicity against tumor cells.
 - They may kill tumors by mechanisms similar to those used to kill microbes (e.g., production of reactive oxygen metabolites or by secretion of TNF).
 - T cells, NK cells, and macrophages may collaborate in antitumor reactivity. Interferon- γ , a cytokine secreted by T cells and NK cells, is a potent activator of macrophages.
- 

Immune Evasion by Cancers

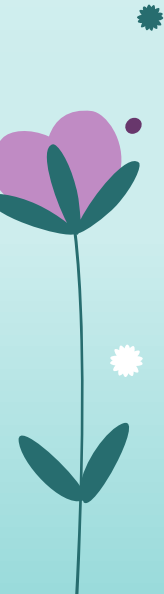
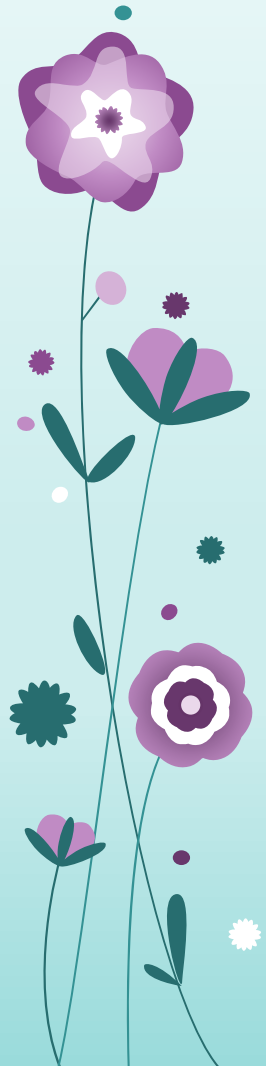
- Tumor cells must develop mechanisms to escape or evade the immune system. Several such mechanisms may be operative:

1. Selective outgrowth of antigen-negative variants:

- During tumor progression, strongly immunogenic subclones may be eliminated.

2. Loss or reduced expression of MHC molecules:

- Tumor cells may fail to express normal levels of HLA (human leukocytes antigens) class I molecules, thus escaping attack by cytotoxic T cells.

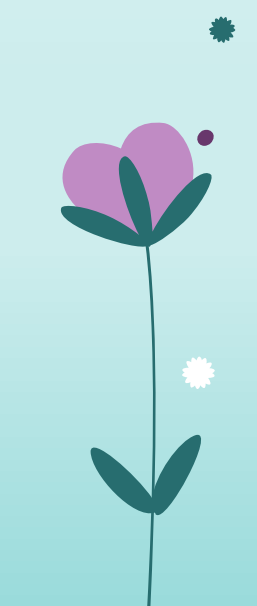




3. Lack of costimulation:

- Sensitization of T cells requires two signals, one by a foreign peptide presented by MHCI molecules and the other by costimulatory molecules.
- Although tumor cells may express peptide antigens with class I molecules, they often do not express costimulatory molecules.

4. Immunosuppression:

- Many oncogenic agents (e.g., chemicals and ionizing radiation) suppress host immune responses.
 - Tumors or tumor products also may be immunosuppressive, for example, **TGF- β** , secreted in large quantities by many tumors, is a **potent immunosuppressant**.
- 

5. Antigen masking:

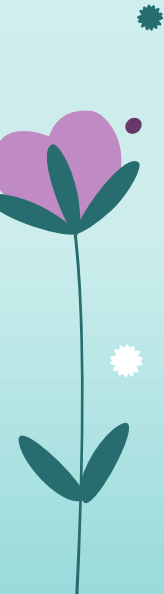
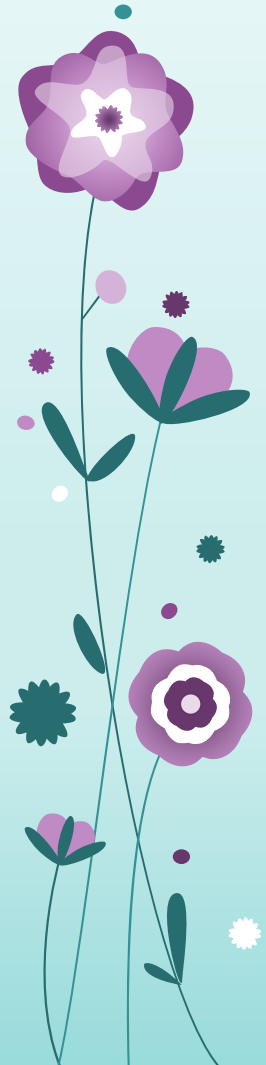
- The cell surface antigens of tumor cells may be hidden or masked from the immune system by glycocalyx molecules, such as sialic acid-containing mucopolysaccharides.

6. Apoptosis of cytotoxic T cells:

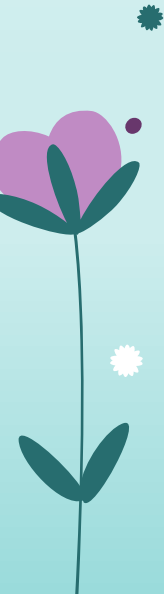
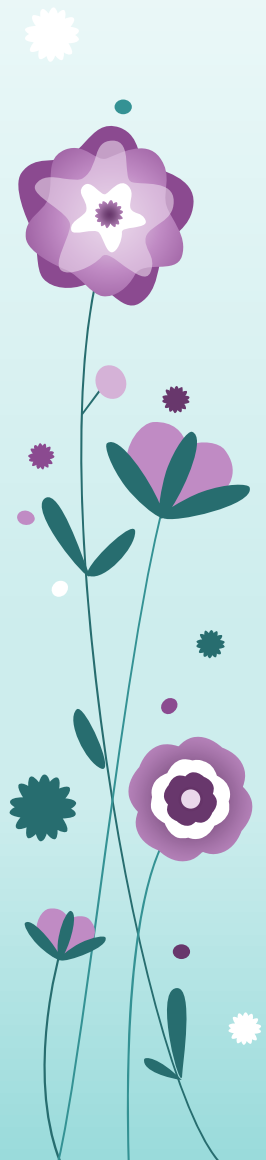
- Some melanomas and hepatocellular carcinomas **express FasL**. It has been postulated that these tumors kill Fas-expressing T lymphocytes that come in contact with them, thus eliminating tumor-specific T cells.

MicroRNAs and Cancer (miRNAs)

- Are noncoding, single-stranded RNAs, approximately 22 nucleotides in length, that function as negative regulators of genes. They mediate post-transcriptional gene silencing.
- Given that miRNAs control cell growth, differentiation, and cell survival, it is not surprising that they play a role in carcinogenesis.

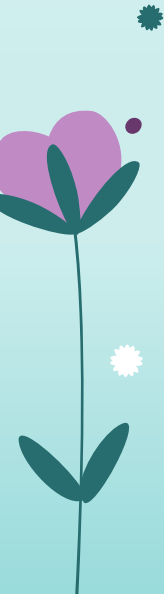
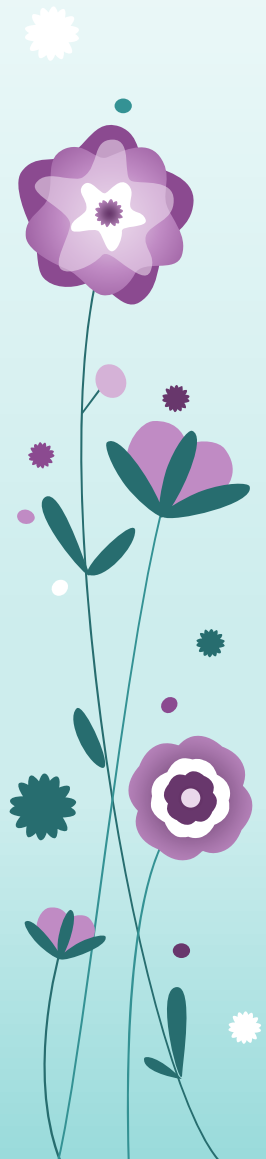


- miRNAs can participate in neoplastic transformation **either by** increasing the expression of oncogenes or by reducing the expression of tumor suppressor genes.
- Down-regulation or deletion of certain miRNAs in some **leukemias and lymphomas results in increased expression of BCL2**, the anti-apoptotic protein.
- miRNA-mediated **upregulation of RAS and MYC oncogenes - lung tumors and in certain B-cell leukemias**, respectively



Epigenetic basis of cancer

- Epigenetics refers to reversible, heritable changes in gene expression that occur without mutation.
- Such changes involve post-translational **modifications of histones and DNA methylation**, both of which affect gene expression.
- **In normal, differentiated cells**, the majority of the genome is not expressed. Some portions of the genome are silenced by DNA methylation and histone modifications.
- Cancer cells are characterized by a global DNA hypomethylation and selective promoter-localized hypermethylation.
- **Tumor suppressor genes** are sometimes silenced by hypermethylation of promoter sequences rather than mutation.



THANK YOU

