

Neoplasia 2023/2024

lecture 3

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ILOS

- 1. List types of genes mutated or altered during carcinogenesis.
- 2. Differentiate between oncogenes and tumor suppressor genes.
- 3. Understand the mutational and non mutational genetic changes responsible for carcinogenesis.

INTRO

- In this lecture we will start discussing how neoplasms, mainly malignant ones, occur.
- As you know cancer is caused by mutations and DNA changes.. But not any mutation will cause cancer.
- In this lecture we will take a broad look at the types of DNA changes that can cause cancer and in the coming lectures we will discuss specific mutations in detail.

Molecular basis of cancer

- Neoplasms are caused by nonlethal, genetic damage, which causes uncontrolled cellular proliferation.
- Nonlethal: so cells can still multiply!
- Genetic damage: mutations or non-mutational damages (details later in this lecture)
- Uncontrolled proliferation... not all genetic damages produce tumors, they only do so if they result in a *crazy* cell that can multiply continuously in an uncontrolled, uninhibited fashion!

Tumor clonality

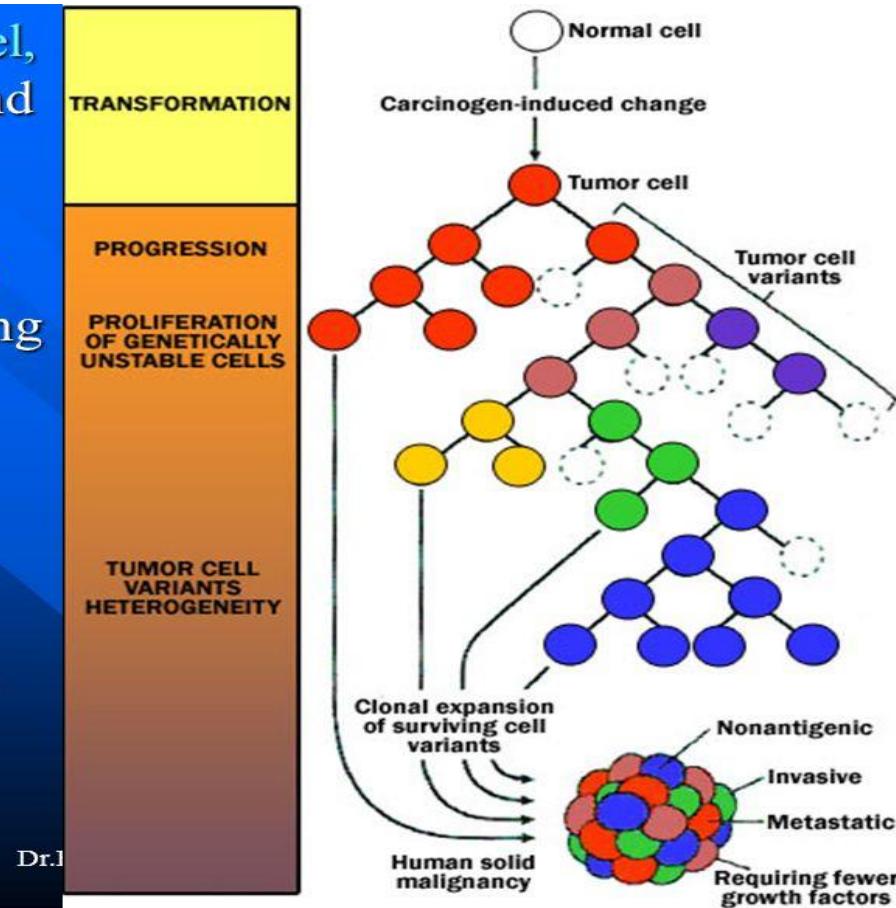
- Because tumor cells originate from one single genetically damaged *crazy* cell, they are clonal
- What does a clone mean?.. Refer to lecture 2!
- Note: tumors start as a clone, but with time they acquire several mutations in some of the cells.. They become heterogeneous. This is because some cells develop mutations that make them acquire characteristics like: ability to invade, to metastasize.. etc

Tumor clonality

- So: malignant cells originate from one single transformed cell that acquires a mutation allowing it to proliferate in an uncontrolled manner.
- This cell keeps proliferating forming a clone.
- But the proliferating cells acquire additional mutations, that help the tumor mass to grow further or to avoid death, or to metastasize ..etc.
- Each cell with a new mutation proliferates forming a **sub-clone**.
- The end result is a tumor mass where each cell has the original mutation in the parent cell plus extra mutations that differ between the sub-clones.

Carcinogenesis is a multistep process

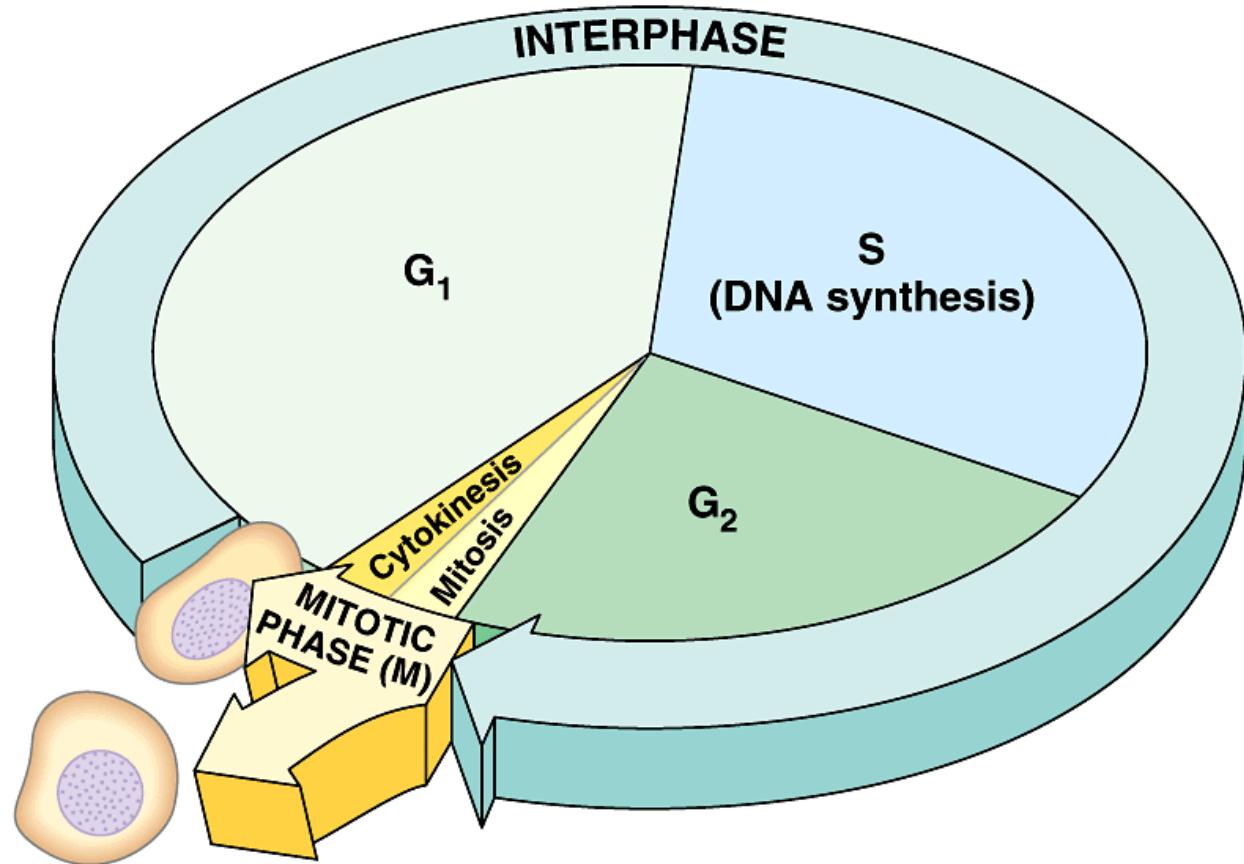
- At the **molecular level**, tumor progression and heterogeneity result from **multiple mutations** generating **subclones** with varying abilities to grow, invade, metastasize, and resist therapy .
- During progression, tumor cells are subjected to immune and nonimmune selection pressures.



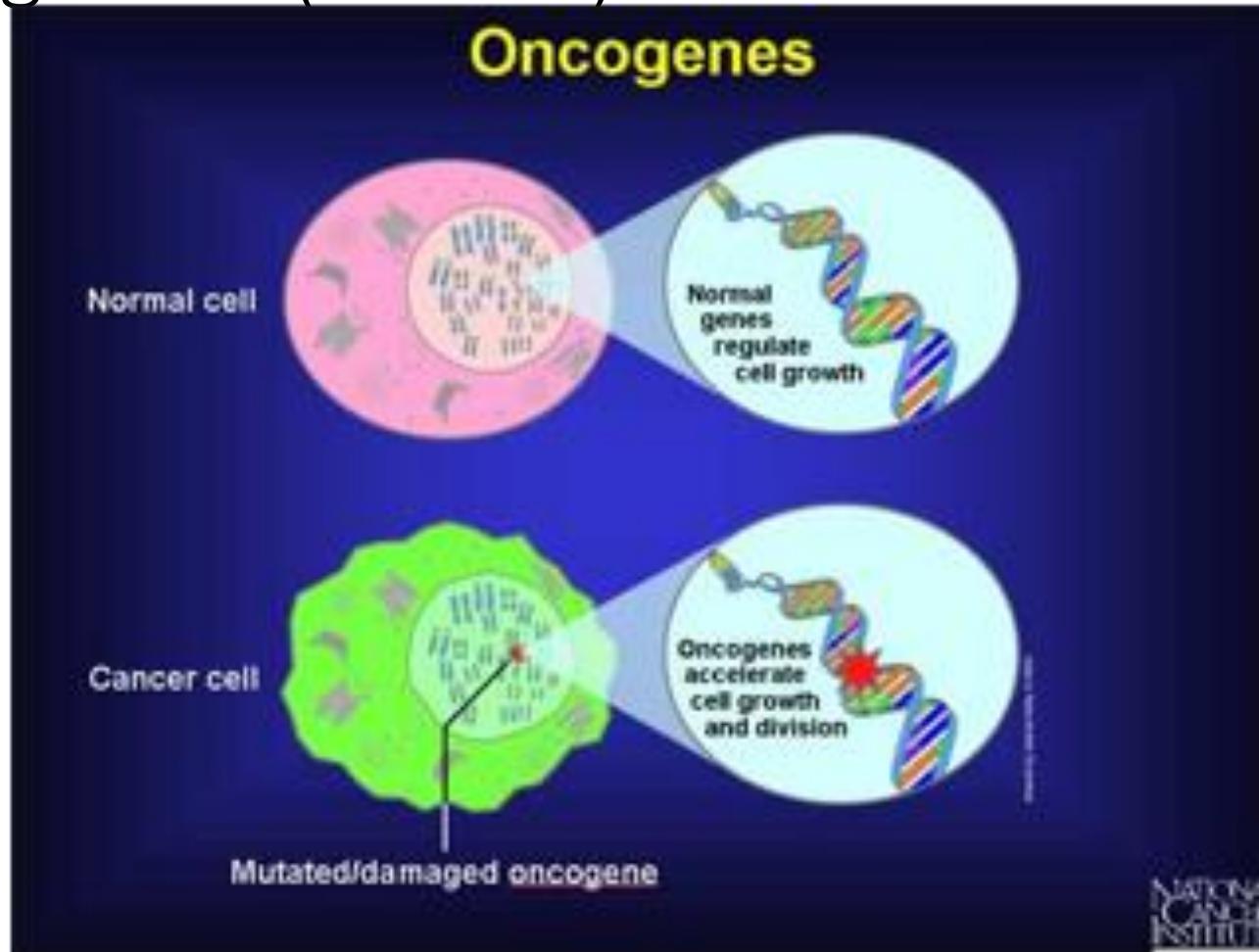
What are the genetic damages that can transform cells?

- For a genetic damage to transform a cell, it has to cause uncontrolled proliferation.
- The majority of our cells proliferate continuously. This proliferation is regulated by certain genes. There is a balance between genes that stimulate growth and those inhibiting it. Loss of this balance can cause uncontrolled proliferation.
- So : for cancer to occur there is stimulation of genes that cause cell proliferation, or downregulation of genes that inhibit proliferation.

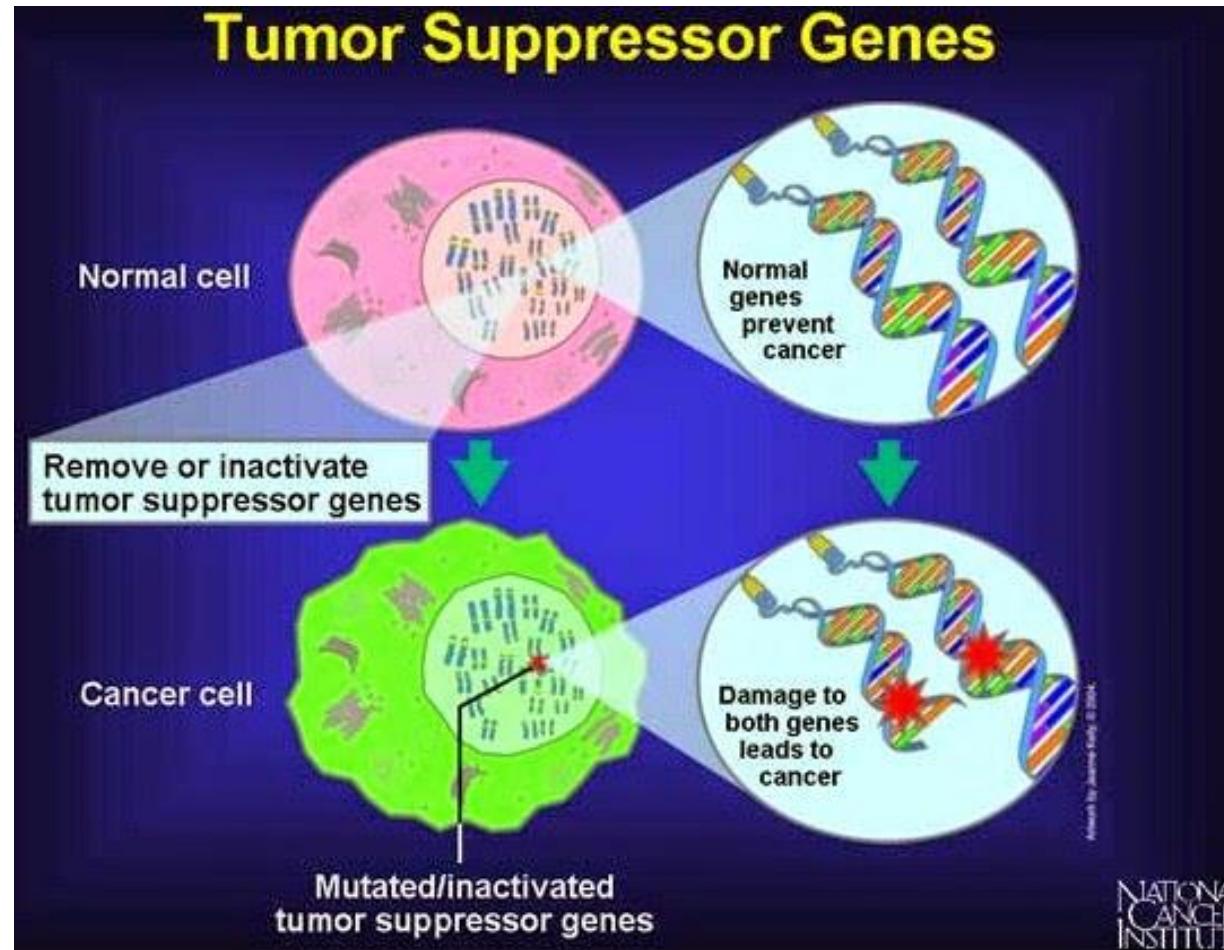
Cell cycle is regulated by a balance between growth stimulating genes = **protooncogenes** and growth inhibiting genes= **tumor suppressor genes**.



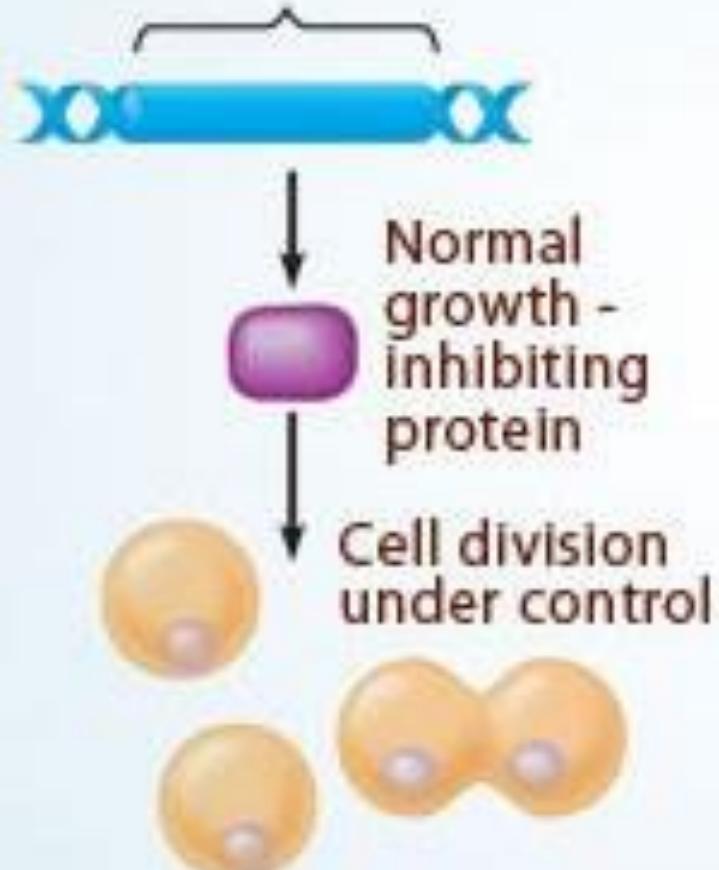
Proto-oncogenes normally stimulate growth in a controlled manner. If they are mutated, they cause uncontrolled growth (cancer)



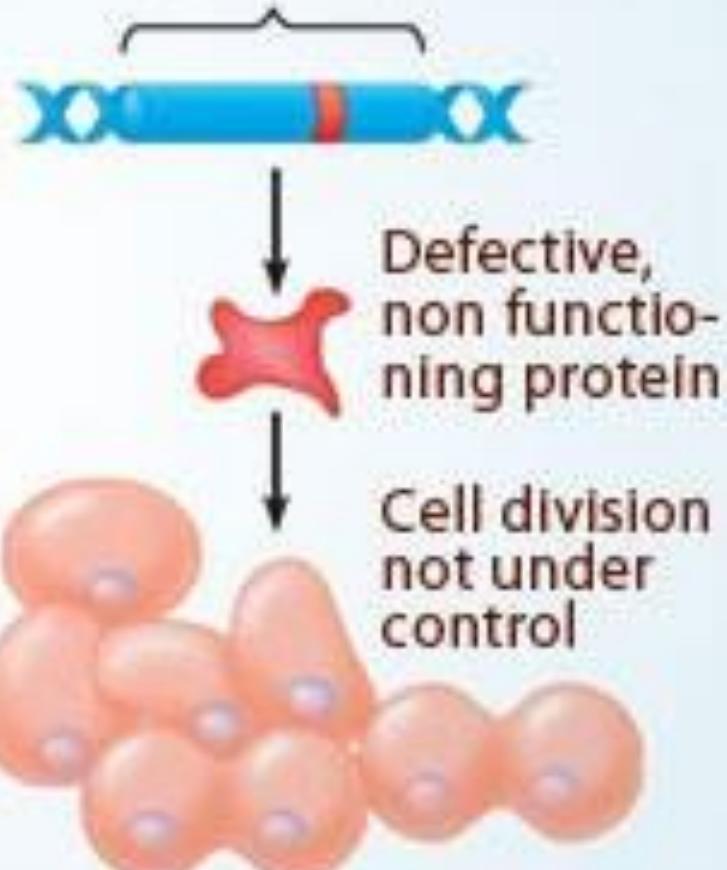
Tumor suppressor genes counteract the function of the oncogenes. If they are inhibited by a mutation, then cells can proliferate without this “braking” effect of the tumor suppressor genes.



Tumor-suppressor gene



Mutated tumor-suppressor gene



Other genes involved in cancer

- Besides oncogenes and tumor suppressor genes, there are other types of genes that are involved in transforming cells:
- - Genes that regulate apoptosis: these are very important because if the damaged cell dies by apoptosis, then no proliferation is possible. So, these genes are frequently mutated in cancers to keep cells alive and block apoptotic messages.
- - DNA repair genes also play a role in carcinogenesis. If DNA damages are repaired, then no cancer will occur. If DNA repair genes become nonfunctioning, then there is a chance of DNA damages to accumulate in cells.
- Genes that affect the interaction between tumour cells and host cells (surrounding normal cells) also play a role in carcinogenesis.. Especially genes which affect **immune response of the host to cancer cells**.

Genetic damages in neoplasms

So: 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.

note

- Normal genes that cause cell proliferation are traditionally called: proto-oncogenes.
- When they are mutated, they are called oncogenes.

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
- So 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
- Details will follow . Don't worry

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 these are **recessive** mutations (two mutations in two alleles are needed for cancer to occur)

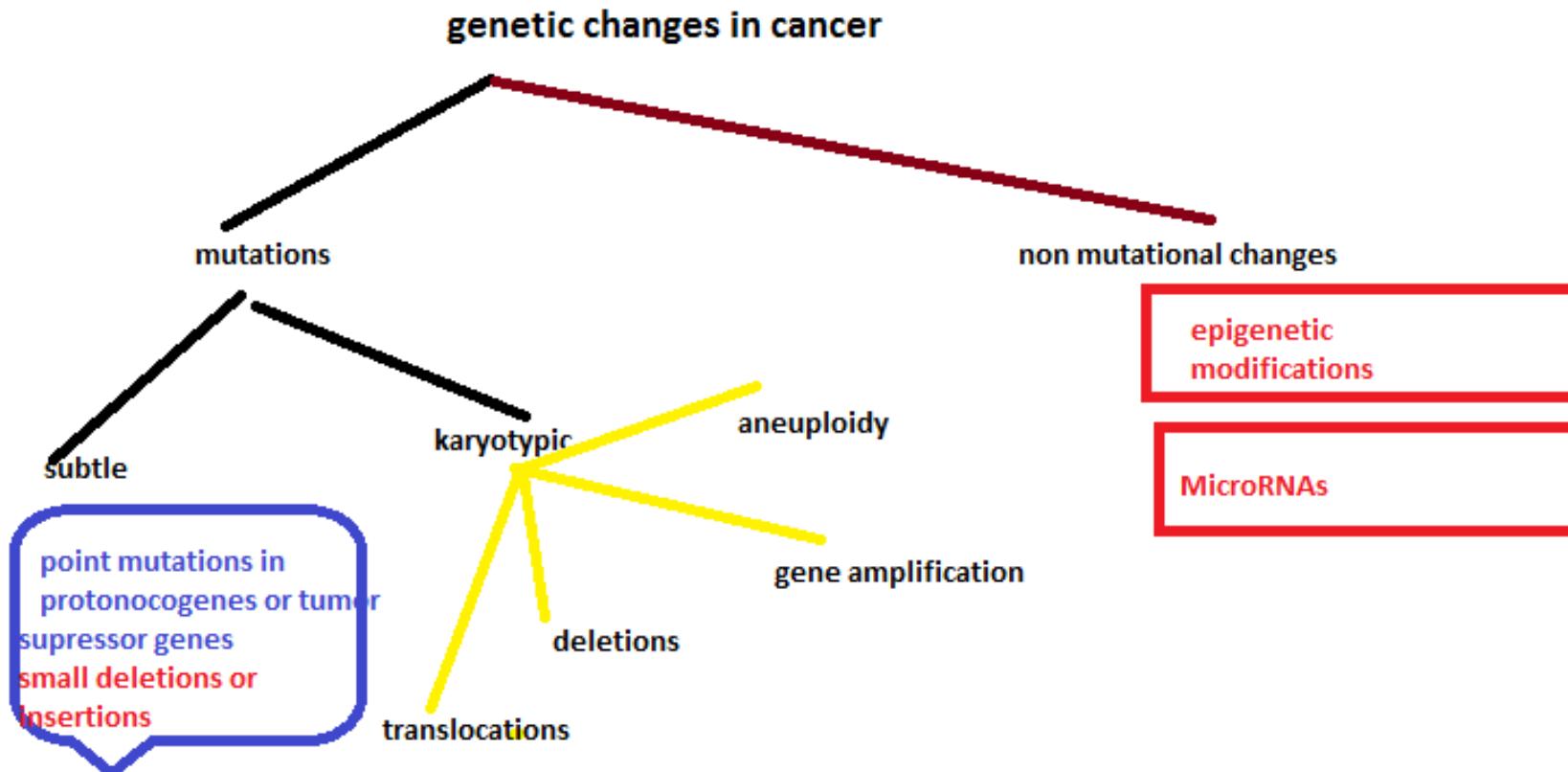
Tumor suppressor genes

- Most important examples:
- 1. RB gene(retinoblastoma gene) .. Called the Governor of the genome: controls growth and puts a brake in cellular proliferation
- 2. TP53 gene ... guardian of the genome... it senses genetic damage. So if there is damage it causes cessation of proliferation or if the damage cannot be repaired it causes apoptosis.

Genetic lesions in cancer

- We now know the types of genes that should be damaged for cancer to occur. But how they are damaged?
- They can be damaged by Mutational or non-mutational damages.
- **Mutations:** 1. subtle: point mutations, insertions, point deletions :or 2. large, karyotypic change: translocations, large deletions, gene amplification, aneuploidy
- **Non mutational:** MicroRNAs and epigenetic modifications

Genetic lesions in cancer



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 proto-oncogene.**
- 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 (new) protein.

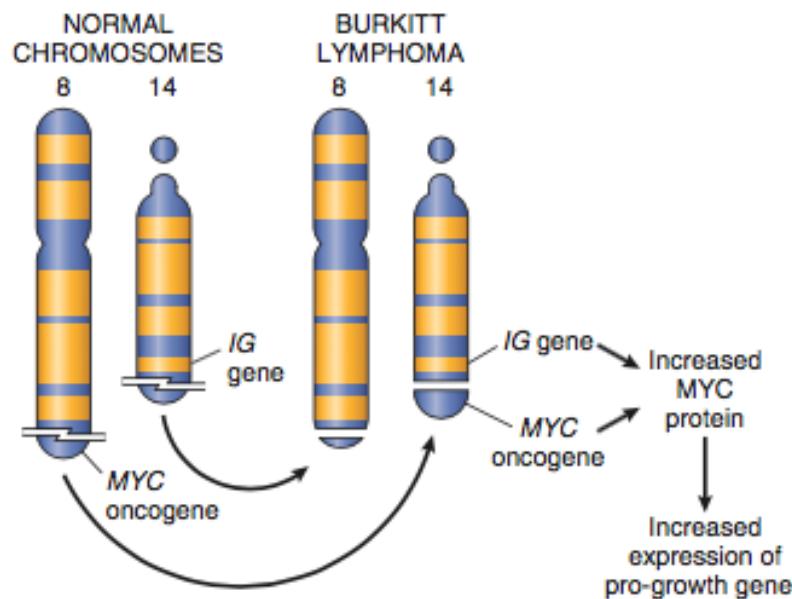
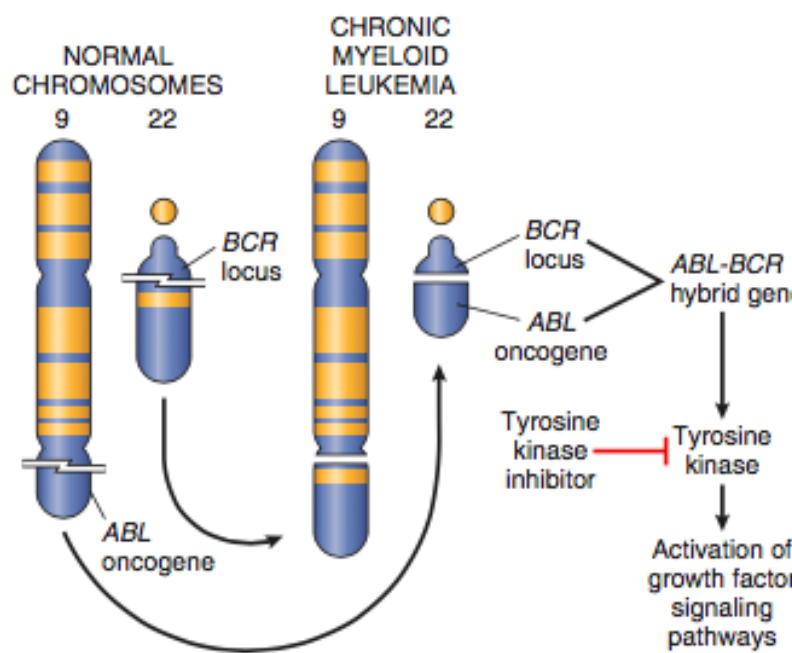
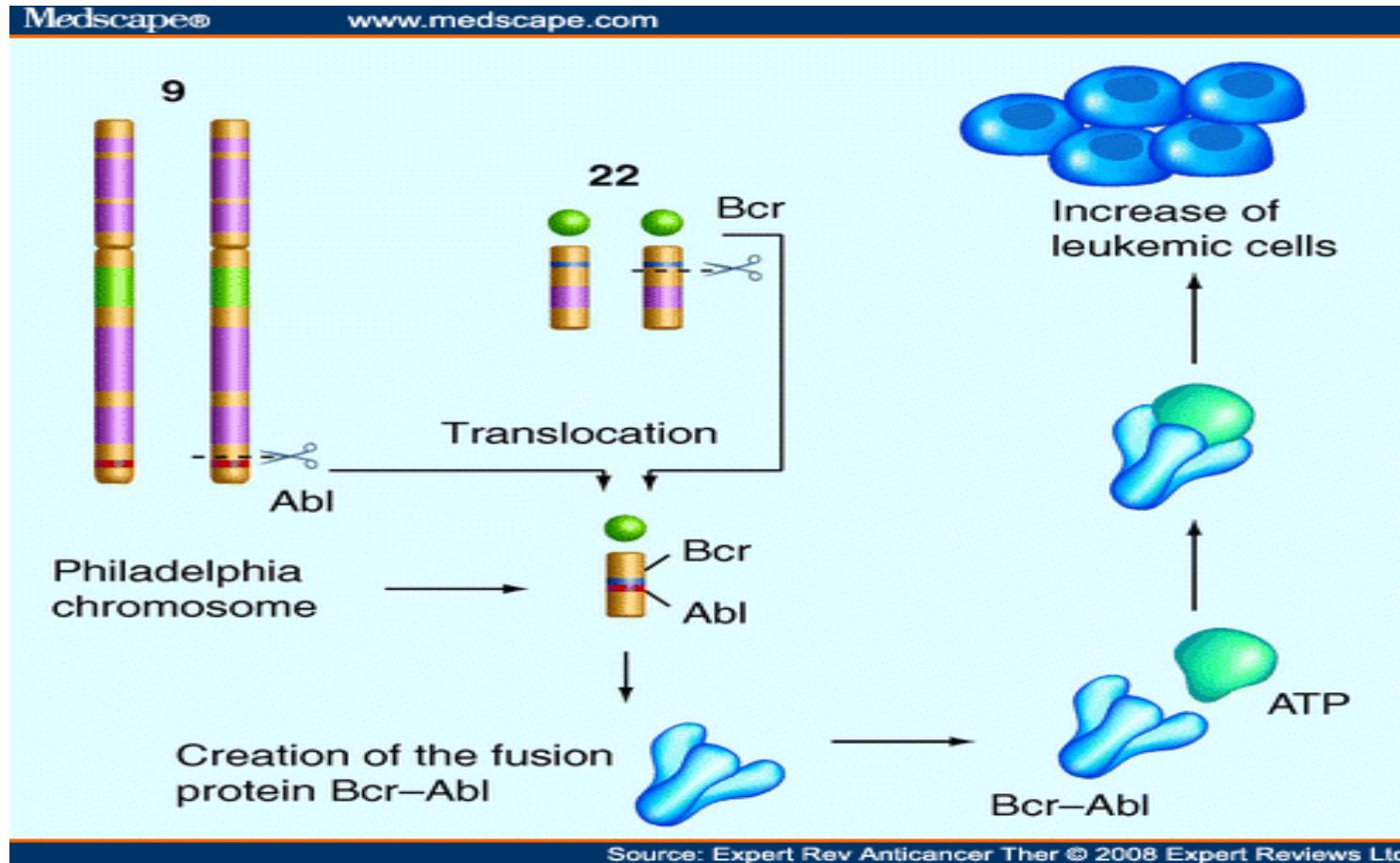


Fig. 6.14 The chromosomal translocations and associated oncogenes in chronic myelogenous leukemia and Burkitt lymphoma.

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 picture, 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

Philadelphia chromosome: an example of a translocation causing a new protein (a kinase) that increases cell proliferation.



Translocations

- Occur mainly in haematogenous 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!

This table shows examples of tumors caused by translocations. Don't memorize it!!

Tumor type	translocation	Oncogene affected	mechanism	notes
BURKITT lymphoma	t(8;14)	MYC	MYC becomes under stimulation of heavy chain gene elements	90% of Burkitt cases have the mutation overexpression
Follicular B cell lymphoma	t(14,18)	BCL2 (antiapoptotic)	Overexpression of BCL2 by immunoglobulin gene elements	overexpression
Chronic myelogenous leukemia (CML)	t(9;22)	BCR-ABL rearrangement	New fusion gene (Philadelphia chromosome)	90% of cases. More details on next slide!
Ewing sarcoma	t(11;22)	EWS – Fli 1 fusion	Fusion gene	EWS is a transcription factor Fusion product
Prostate carcinoma		ETS	Fusion gene	
Lung cancer		ALK	Fusion gene causing activation of ALK kinase	Only 4% of lung tumors have this fusion...these respond to ALK kinase inhibitors

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.

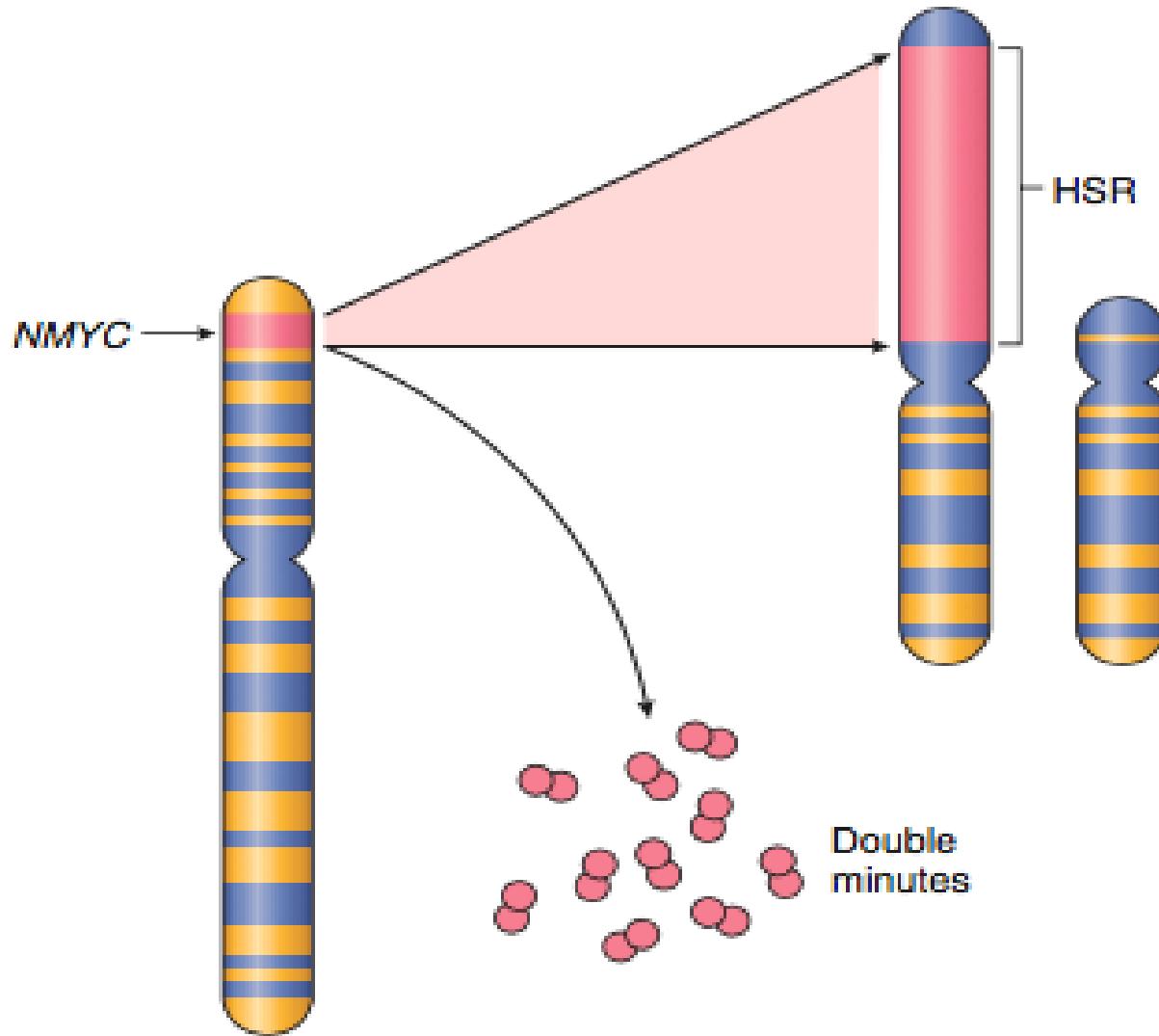


Fig. 6.15 Amplification of the *NMYC* gene in human neuroblastoma. The *NMYC* gene, present normally on chromosome 2p, becomes amplified and is seen either as extrachromosomal double minutes or as a chromosomally integrated homogeneous-staining region (HSR). The integration involves other autosomes, such as 4, 9, or 13. (Modified from Brodeur GM, Seeger RC,

Deletions

- More in non-hematopoietic solid tumors
- 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

- = abnormal number of chromosomes
- Result from errors of the mitotic checkpoint

microRNAs (miRNAs)

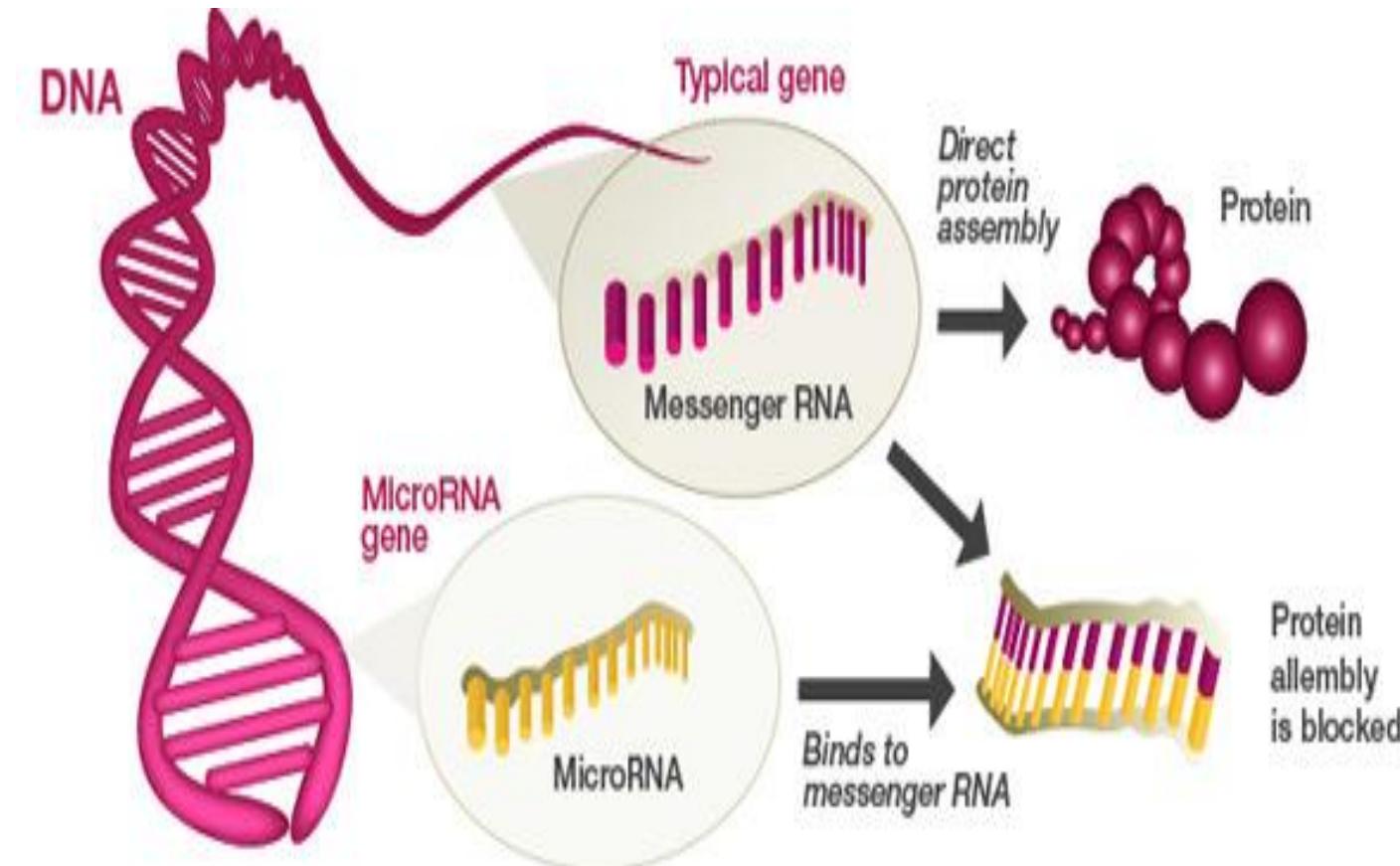
- **Noncoding**, micro RNA segments (22 nucleotides) that are **negative regulators** of the genes.
- They inhibit gene expression **post-transcriptionally** = repress translation or cleave mRNA.
- SO: transcription occurs = messenger RNA formed.. But mRNA is not translated to a protein.
- microRNA can inhibit translation or cleave the messenger (tears the message before it is read)

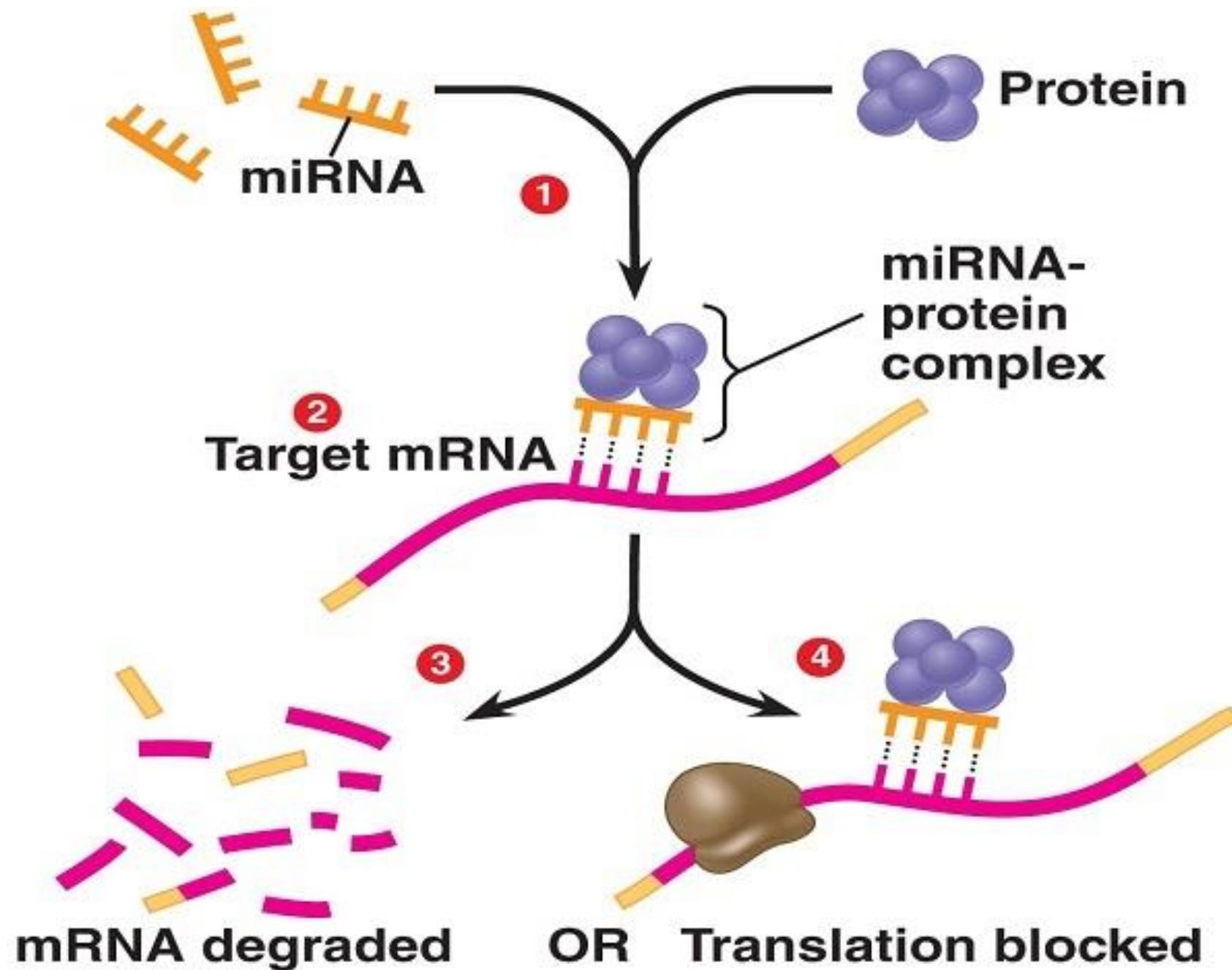
miRNA

- Cause cancer by increasing oncogene expression or decreasing tumor suppressor gene expression.

- miRNAs that target oncogenes.... If reduced, then inhibition caused by microRNA is lost causing overexpression of oncogenes.
- miRNAs that target tumor suppressor genes... if increased they cause downregulation of tumor suppressor genes, resulting in cancer (as if we are functionally reducing the tumor suppressor genes)

miRNAs





epigenetics

- Epigenetics are **reversible** 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. 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*.

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

A photograph of a sunset or sunrise over a body of water. The sky is filled with warm, horizontal bands of orange, yellow, and red. The water in the foreground has subtle, wavy reflections of these colors. The overall atmosphere is peaceful and relaxing.

KEEP
CALM
AND
RELAX