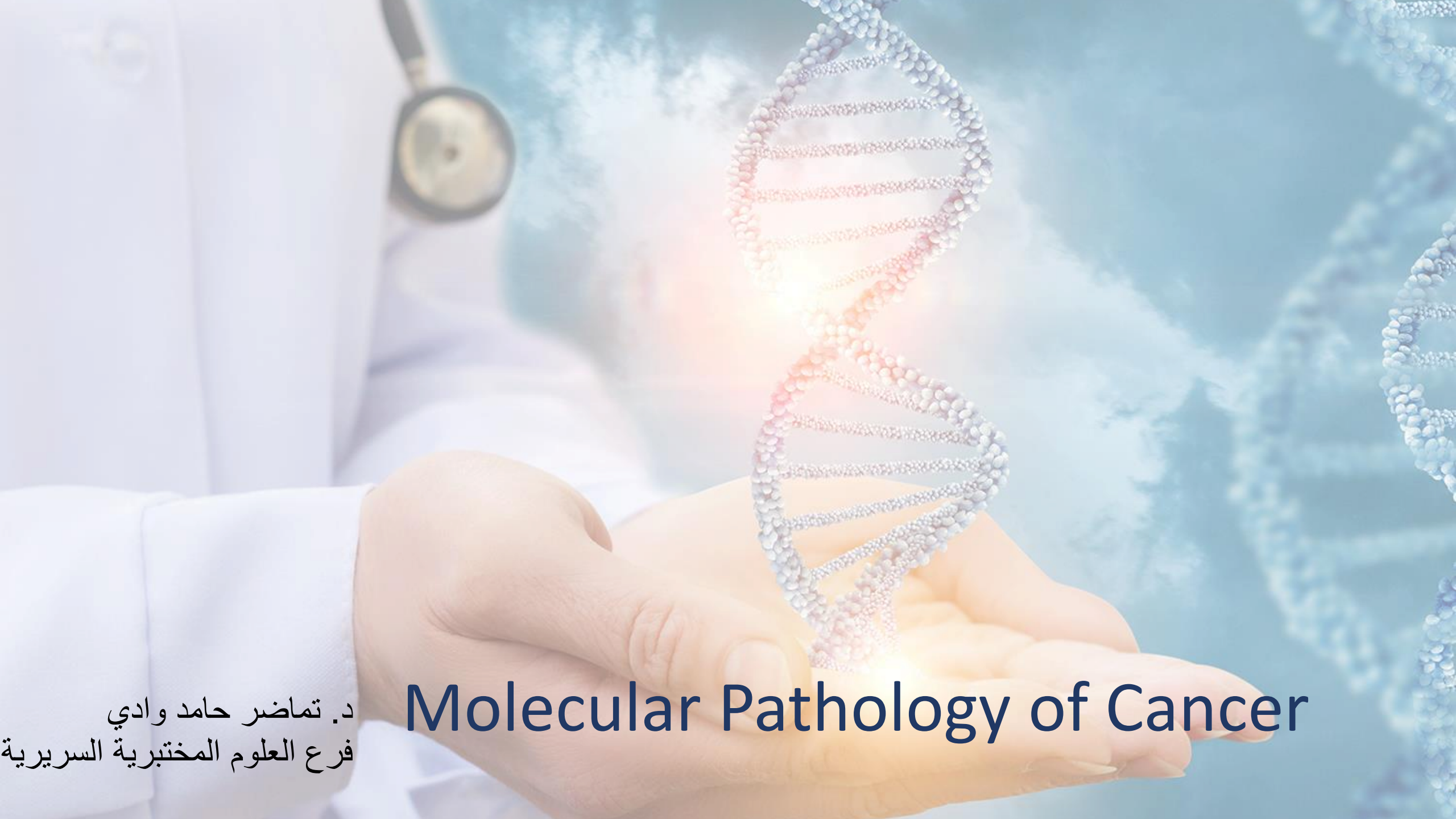

Molecular Pathology of Cancer

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Cancer Definition

- Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer is a disease caused by genetic changes that develop over time.
- Cancer is the result of cumulative mutations that change proteins encoded by cancer-related genes.

- Tumor is not synonymous with cancer. A tumor can be benign, pre-malignant, or malignant, whereas cancer is by definition malignant.

- Only 10% of cancer is inherited, 70% is sporadic, that is, the mutations are not inherited but occur during individual life. Twenty percent of cancer is resulted by infection by pathogens, mainly viruses.

Cancer development

- A wide variety of mutations seems to be involved in the development of cancer. Even mutations in regions of DNA that do not code for proteins can result in under- or over- expression of proteins needed for normal functioning. Other genetic mutations may cause important “checkpoint” proteins to malfunction. Collectively, these mutations can convert a cell’s genome from normal to cancerous.

- If cancer is caused by mutations in critical genes, then people who inherit such mutations would be more susceptible to cancer’s development than people who do not.
- Cancer develops step-by-step, over time, as a result of the accumulation of many molecular changes, each contributing some of the characteristics that eventually produce the malignant state. In addition, the rates of growth of tumors can vary, and it can take years for the tumors to be detectable.

Consequence of the cancer-associated mutations

- Cancer-associated mutations—whether somatic or inherited—alter key cellular functions.
- The specific genetic abnormalities in cancers can be extremely complex, most mutations involve a few general cellular functions:

1. Impairment of the control of cell division (tumor suppressor genes and their proteins)
2. Aberrant activation of pathways that stimulate cell proliferation (oncogenes and their proteins)
3. Inactivation of pathways that lead to cell death (apoptosis).

- Types of mutation varies among tumors. For example, retinoblastoma is caused by loss of activity of the pRB (tumor suppressor protein), chronic myeloid leukemia is caused by activation of the Abelson proto-oncogene, and follicular cell lymphoma is commonly associated with activation of pathways that inhibit apoptosis.

The genes play major roles in tumor formation

- There are two categories of genes play major roles in triggering cancer:

1. **Proto-oncogenes**
2. **Tumor-suppressor genes**

- In their normal forms, proto-oncogenes are involved in normal cellular processes that encourage cell division. Tumor-suppressor genes, on the other hand, play a role in inhibiting cell division, in promoting apoptosis, or both. Most proto-oncogenes and tumor-suppressor genes play key roles in regulating cellular growth and survival during embryonic development. Mutations in these genes account for much of the uncontrolled cell division and evasion of apoptosis that occurs in human cancers.

Examples of proto-oncogenes and tumor-suppressor genes and some of the human cancers associated with mutations in these genes.

Gene Type	Related Cancers
Proto-oncogene *bcl-2*	B-cell lymphoma
Proto-oncogene *HER2/neu* (*erbB-2*)	Breast and ovarian cancers
Proto-oncogene *c-Src*	Colorectal cancers
Proto-oncogene *c-Myc*	Burkitt lymphoma
Tumor-suppressor gene *BRCA1*, *BRCA2*	Breast and ovarian cancers
Tumor-suppressor gene *p53*	Brain tumors; skin, lung, and head and neck cancers
Tumor-suppressor gene *RB*	Retinoblastoma; bone, bladder, and breast cancers
Tumor-suppressor gene *APC*	Colorectal cancers

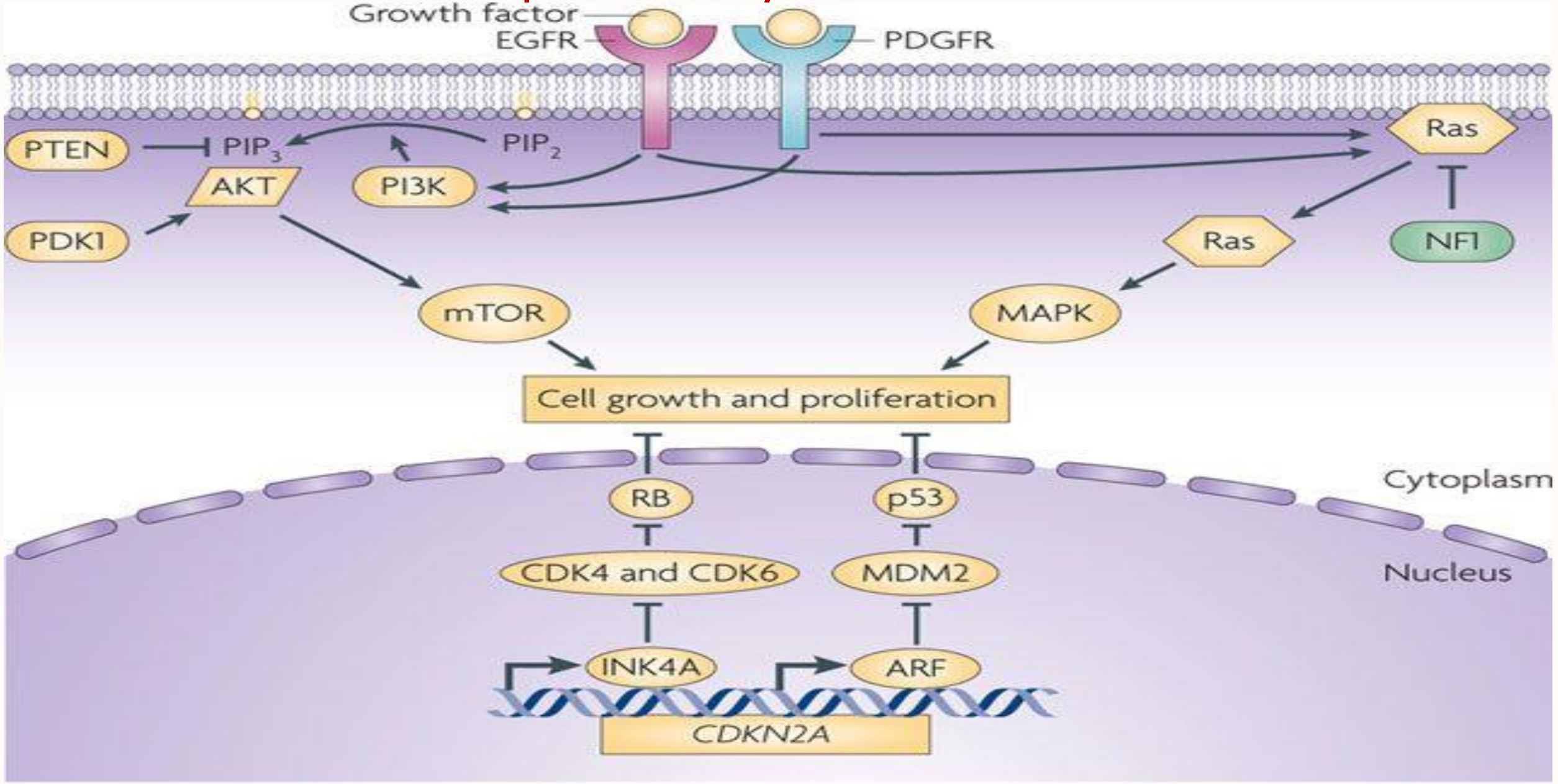
The role of oncogenes in tumor formation

- Oncogenes (tumor-causing genes) represent activated forms of proto-oncogenes that can trigger uncontrolled cell proliferation if their sequence is altered or their expression is incorrectly regulated.

- Several proto-oncogenes are activated by mutations in their sequences. Examples of such proto-oncogenes include *Ras*, *Ret*, and *Myc*. The Ras proteins are membrane receptors that are members of a larger family of proteins known as G proteins.

- The mutations that activate these genes are either **(1)** structural mutations that lead to the constitutive activity of a protein without an incoming signal (e.g., the protein kinases or Ras) or **(2)** regulatory mutations that lead to the expression of the gene at an elevated level or at the wrong place and time (e.g., growth factors or transcription factors).

Molecular pathways involve in cancer



Molecular pathways involve in cancer

- Most proto-oncogenes code for proteins involved in molecular pathways that receive and process growth-stimulating signals from other cells in a tissue. Typically, such signaling begins with the production of a growth factor, a protein that stimulates cell division. Growth factors move through the spaces between cells and attach to specific receptor proteins located on the surfaces of neighboring cells. When a growth-stimulating factor binds to such a receptor, the receptor conveys a stimulatory signal to proteins in the cytoplasm. These proteins transmit stimulatory signals to other proteins in the cell until the division-promoting message reaches the cell's nucleus and activates a set of genes that help move the cell through its growth cycle. Most of the known oncogenes are proto-oncogenes that have been altered or mutated in such a way that they promote cell growth in an abnormal or uncontrolled fashion. The protein products of oncogenes cause growth-promoting pathways to become overactive. As a result, the cell proliferates much faster than it would if the mutation had not occurred. Some oncogenes cause cells to overproduce growth factors. These factors can stimulate the growth of neighboring cells, but they may also drive excessive division of the cells that produced them. Other oncogenes produce aberrant receptor proteins that release stimulatory signals into the cytoplasm even when no growth factors are present in the environment. Still other oncogenes disrupt parts of the signaling cascade that occurs in a cell's cytoplasm causing the cell's nucleus to receive stimulatory messages continuously, even when growth factor receptors are not prompting them.

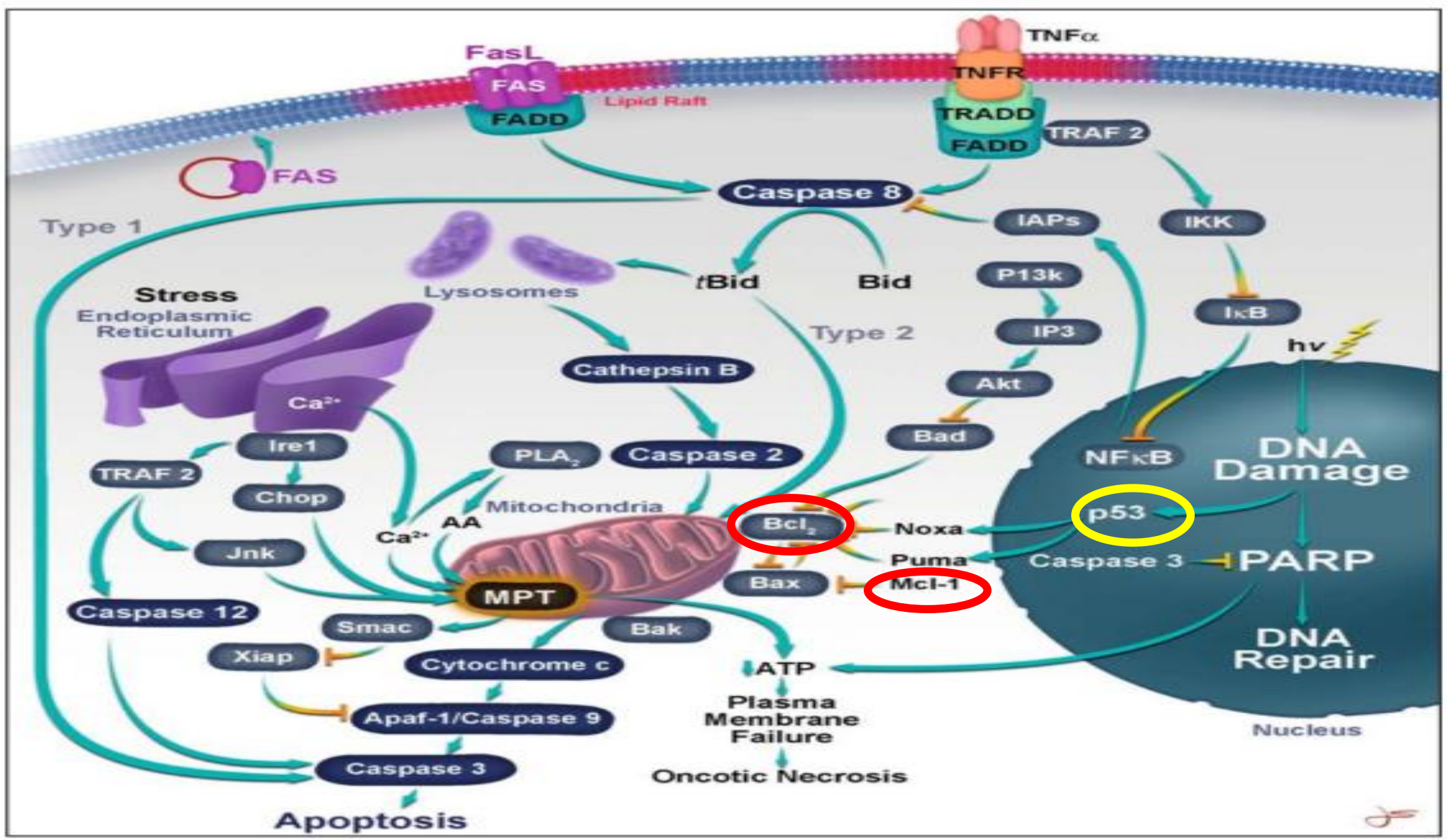
The role of tumor-suppressor genes in tumor formation

- Tumor suppressor genes encode proteins that regulate normal cell proliferation. The products of these genes therefore act like brakes on cell division, and mutations in theses genes are manifested by deregulation of the cell cycle control mechanisms.
- Some tumor-suppressor genes code for proteins that inhibit progression of the cell cycle. When such proteins are inactive or absent, these inhibitory pathways no longer function normally. Other tumor-suppressor genes appear to regulate the flow of signals through growth-stimulating pathways; when these genes do not function properly, such growth-promoting pathways may operate without normal restraint. Mutations in all tumor-suppressor genes, however, apparently inactivate critical tumor-suppressor proteins, depriving cells of this brake on cell division.

Most important tumor-suppressor genes

- Two of tumor-suppressor genes play critical roles in the development of a wide range of tumors. These are the retinoblastoma gene *(RB1)* and the p53 gene *(TP53)*. Mutations in each of these are associated with both familial and sporadic forms of cancer.
- The protein encoded by *RB1* plays a critical role in the regulation of the cell cycle.
- The tumor suppressor and a pro-apoptotic gene, *TP53,* which encodes the protein p53, is induced when DNA is damaged or in the case of other stresses such as hypoxia and cell cycle abnormalities. It binds directly to DNA and leads to the expression of genes that inhibit cell growth or trigger cell death.
- The p53 protein prevents a cell from completing the cell cycle if (**1**) its DNA is damaged or (**2**) the cell has suffered other types of damage. When the damage is minor, p53 halts the cell cycle — hence cell division — until the damage is repaired. When the damage is major and cannot be repaired, p53 triggers the cell to commit suicide by apoptosis (programmed cell death). These functions make *p53* a key player in protecting us against cancer; that is, an important tumor suppressor gene. More than half of all human cancers do, in fact, harbor *p53* mutations and have no functioning p53 protein. Traditional anti-tumor techniques (chemotherapy and radiotherapy) do not directly damage tumor cells, but by causing DNA breaks and thus activating p53 to trigger the apoptosis pathway.

Molecular pathways involve in apoptosis



DNA-repair system

- In addition to the controls on proliferation, cells have the DNA-repair system that can help them avoid runaway cell division. This system operates in virtually every cell in the body, detecting and correcting errors in DNA. Across a lifetime, a person's genes are under constant attack, both by carcinogens in the environment and by chemicals produced in the cell itself. Errors also occur during DNA replication. In most cases, such errors are rapidly corrected by the cell's DNA-repair system.

- Mutations in DNA-repair genes themselves, however, can undermine this repair system in a particularly devastating way. They damage a cell's ability to repair errors in its DNA. For example, the *BRCA1* and *BRCA2* genes play a role in DNA repair, and mutations in them increase the risk of breast and ovarian cancers and possibly other cancers as well.

Molecular targets therapies

- Research on molecular abnormalities in cancer cells has led to the development of a number of drugs that have come onto the market in recent years that specifically target abnormal receptor proteins and proteins within the cytoplasm that transmit stimulatory signals.

- *Interested site :

Introduction to Cancer Biology (Part 1):

Abnormal Signal Transduction

https://www.youtube.com/watch?v=jjfYQMW_nek

Activated tyrosine kinase receptors targeted by vandetanib for Treatment of Medullary Thyroid Cancer