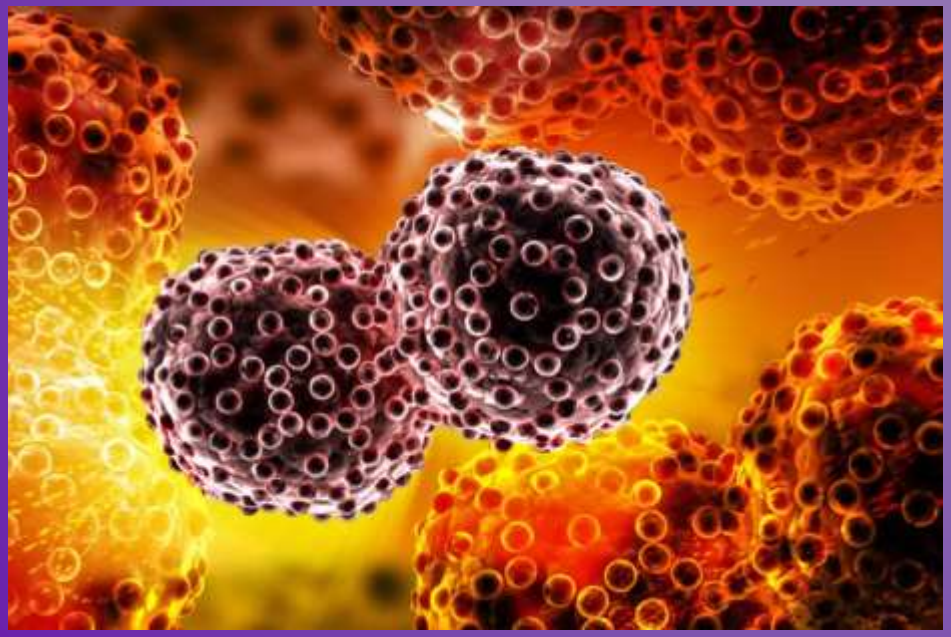
Neoplasia 4



Dr. Eman Kreishan, M.D.

29-12-2021

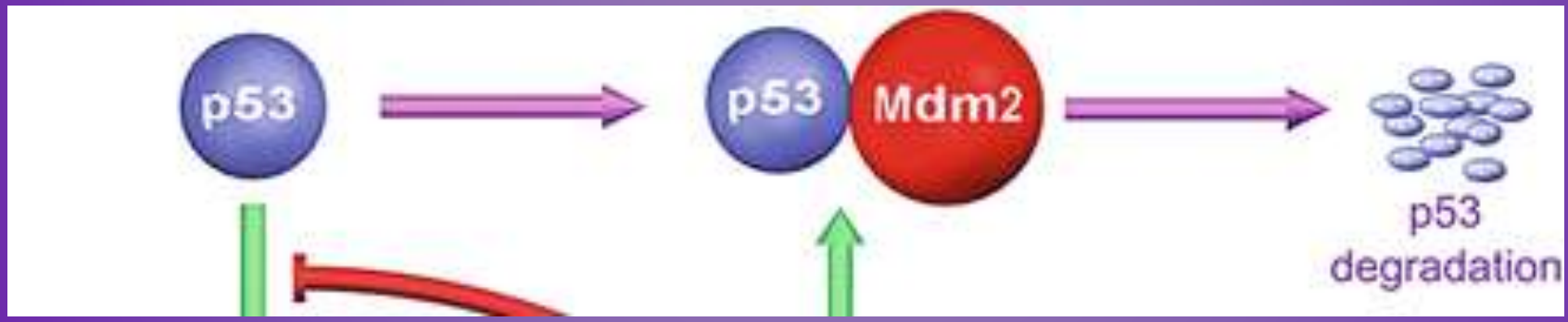
2.TP53: Guardian of the Genome

- The p53 protein is a transcription factor that thwarts neoplastic transformation by three interlocking mechanisms:

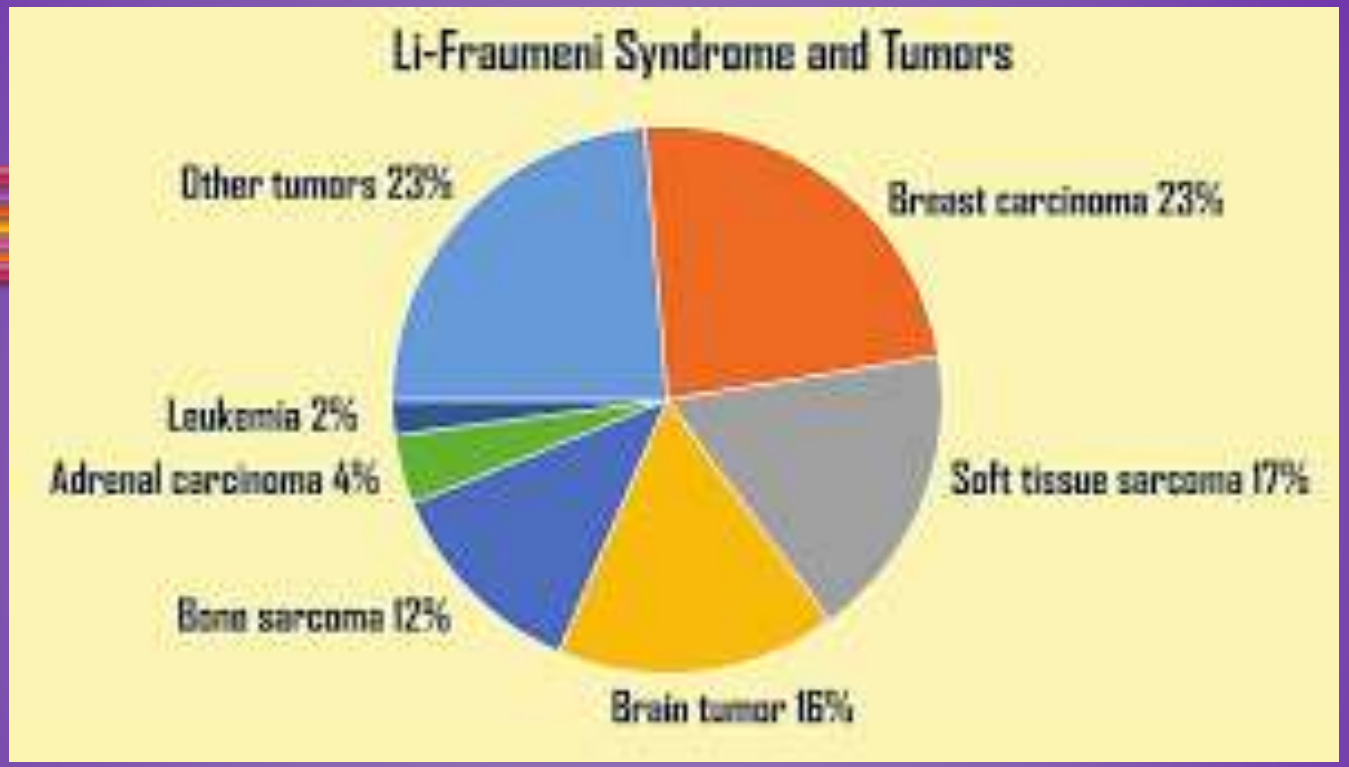
  - activation of temporary cell cycle arrest (termed quiescence).
  - induction of permanent cell cycle arrest (termed senescence).
  - triggering of programmed cell death (termed apoptosis)

- p53 plays a central role in maintaining the integrity of the genome.

In nonstressed, healthy cells, p53 has a short half-life (20 minutes) because of its association with MDM2, a protein that targets p53 for destruction

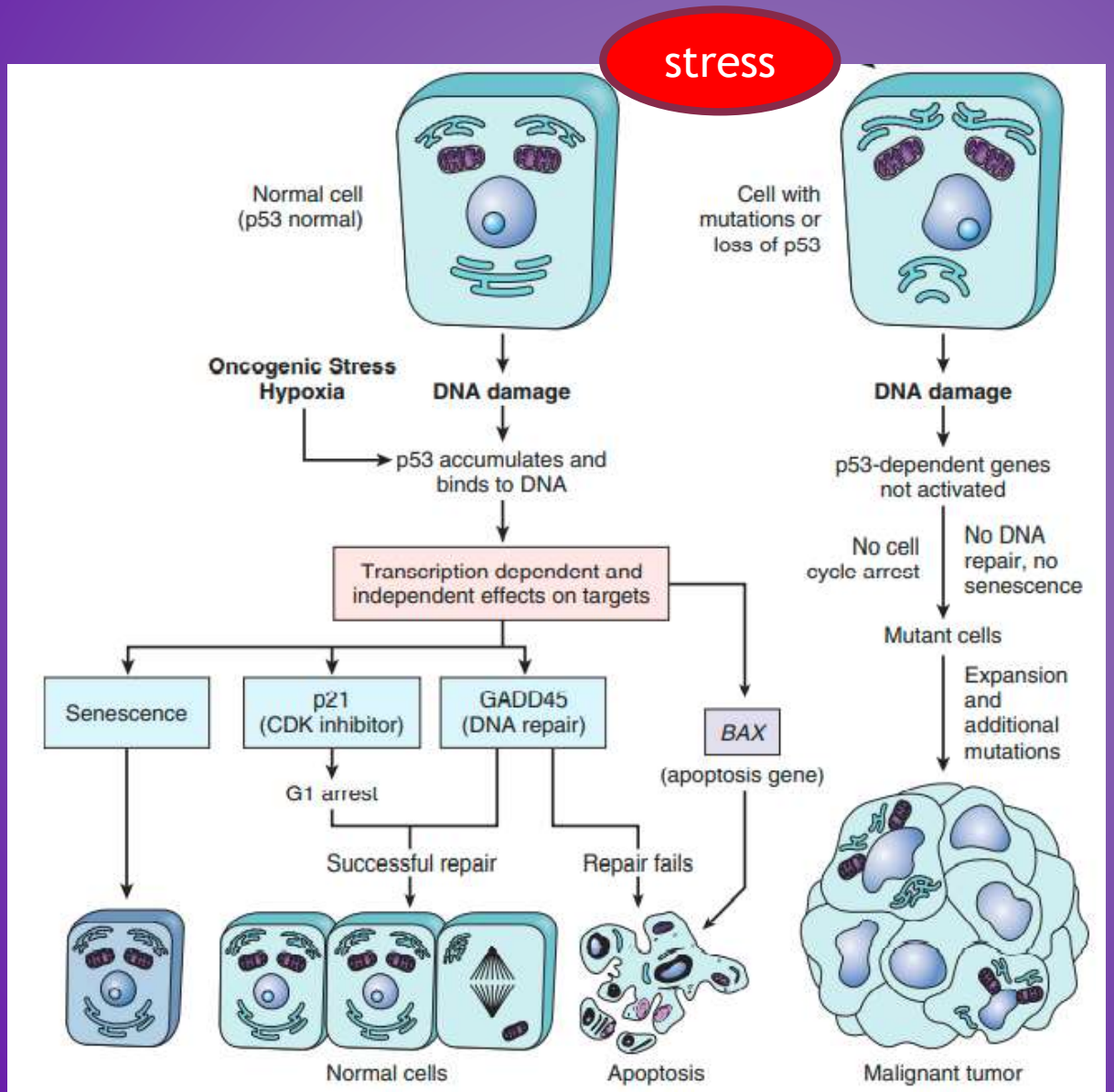


Li-Fraumeni syndrome (LFS) is an inherited condition caused by mutation in TP53



Patients with the Li-Fraumeni syndrome have a 25-fold greater chance of developing a malignant tumor by 50 years of age compared with the general population

➢p53 can be viewed as a central monitor of internal stress, directing the stressed cells toward one of the previous pathways.



stress

✓Ionizing radiation
✓ Carcinogens
✓ Mutagens

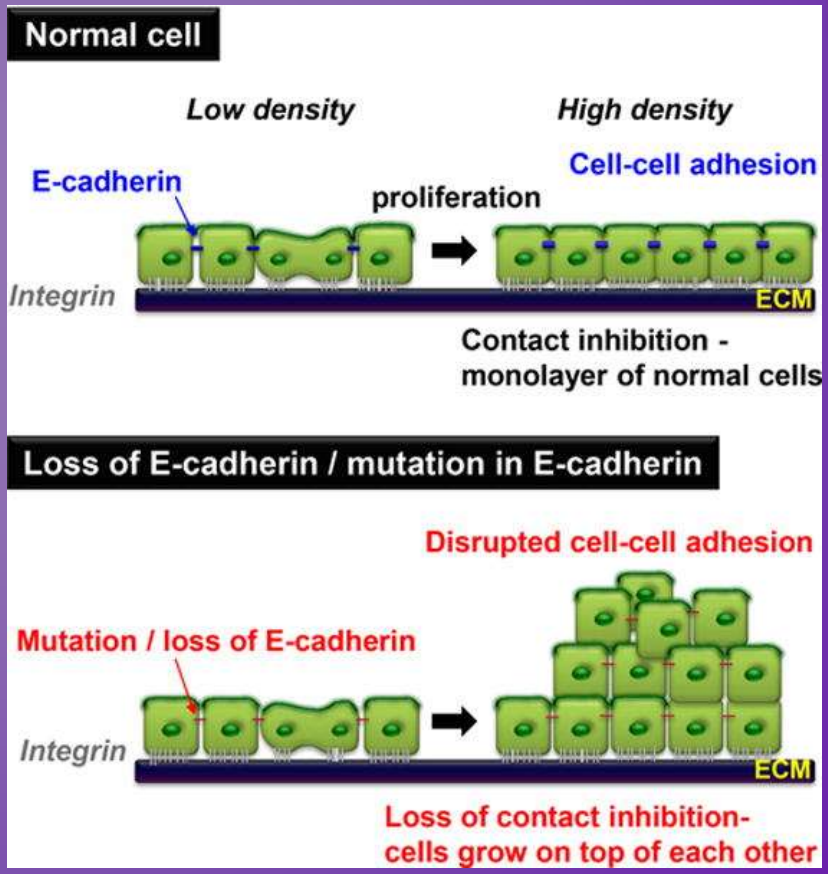
3. Transforming Growth Factor-β Pathway

- TGF-β is a potent inhibitor of proliferation.
- Seen in most normal epithelial, endothelial, and hematopoietic cells.
- In many forms of cancer, the growth-inhibiting effects of the TGF-β pathways are impaired by mutations affecting TGF-β signaling.
- Mutations affecting the TGF-β receptor are seen in cancers of the colon, pancreas, stomach, and endometrium

4. Contact Inhibition.

- Normally, nontransformed cells stop proliferating once they form confluent monolayers.
- But
- When cancer cells are grown in the laboratory, their proliferation fails to be inhibited when they come in contact with each other

- E-cadherin binding between cells is important in mediating contact inhibition of proliferation when cells reach confluence.
- Loss of E-cadherin expression results in loss of contact inhibition and is associated with increased cell motility and advanced stages of cancer

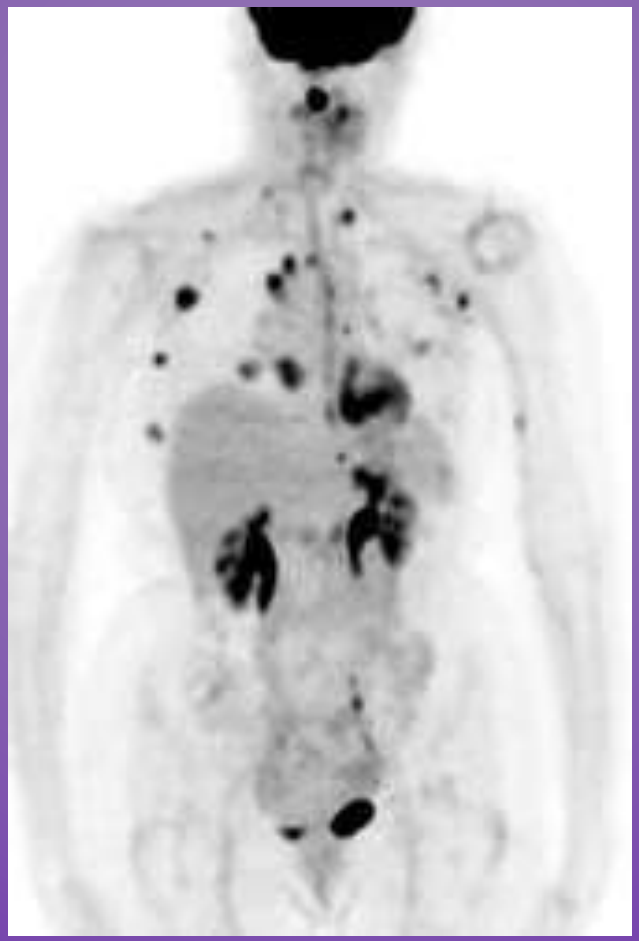


III Altered Cellular Metabolism

- Even in the presence of ample oxygen, cancer cells demonstrate a distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactose (fermentation) via the glycolytic pathway

- This phenomenon, called the Warburg effect and also known as aerobic glycolysis

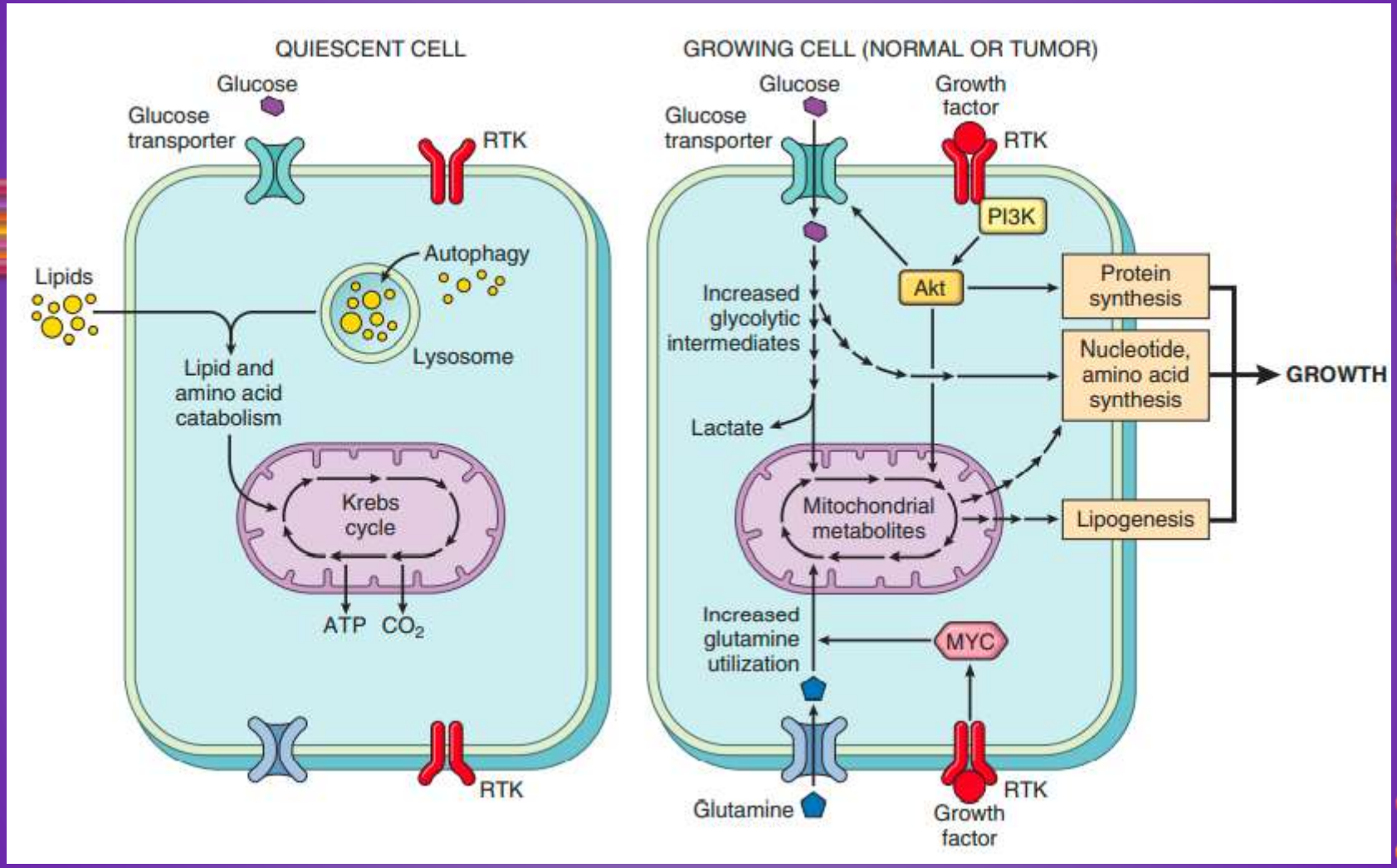
- Clinically, the “glucose-hunger” of tumors is used to visualize tumors via positron emission tomography (PET) scanning, in which patients are injected with a glucose derivative that is preferentially taken up into tumor cells



- aerobic glycolysis generates two molecules of ATP per molecule of glucose.
- While
- oxidative phosphorylation generates up to 36 molecules of ATP per molecule of glucose.

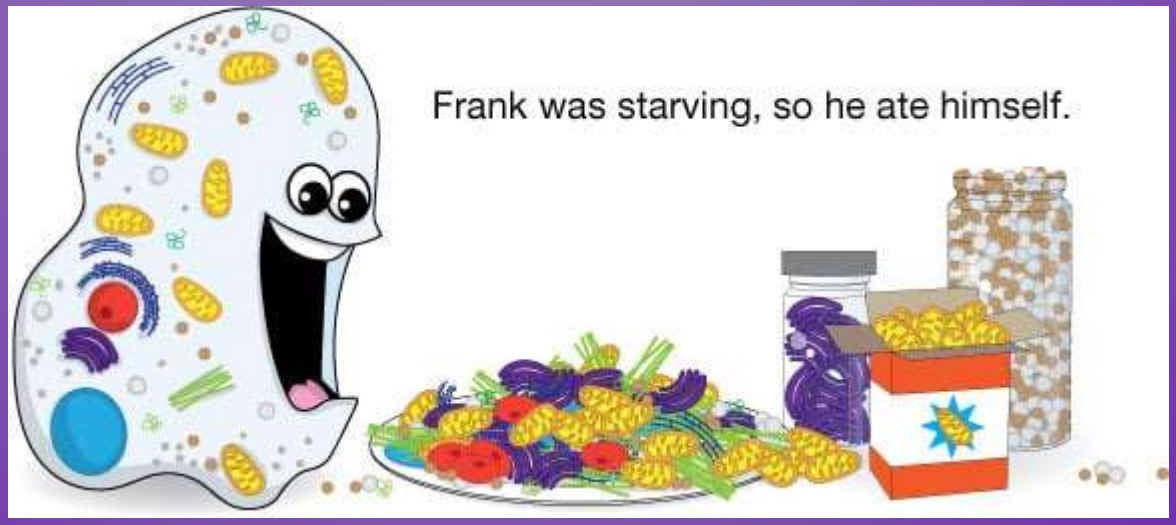
- So why cancer cell rely on seemingly inefficient glycolysis ?

- The answer to this question: Aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components


QUIESCENT CELL
Glucose
Glucose transporter
RTK
Lipids
Autophagy
Lysosome
Lipid and amino acid catabolism
Krebs cycle
ATP
CO_2
RTK
GROWING CELL (NORMAL OR TUMOR)
Glucose
Glucose transporter
Growth factor
RTK
PI3K
Akt
Protein synthesis
Increased glycolytic intermediates
Nucleotide, amino acid synthesis
GROWTH
Lactate
Mitochondrial metabolites
Lipogenesis
Increased glutamine utilization
MYC
Glutamine
RTK
Growth factor

Beyond the Warburg effect, there are two other links between metabolism and cancer

- 1. Autophagy
- 2. oncometabolism.



1. Autophagy

- Autophagy is a state of severe nutrient deficiency in which cells not only arrest their growth, but also cannibalize their own organelles, proteins, and membranes as carbon sources for energy production.

- Tumor cells often seem to be able to grow under marginal environmental conditions without triggering autophagy, suggesting that the pathways that induce autophagy are deranged .

- under conditions of severe nutrient deprivation, tumor cells may use autophagy to become “dormant,” a state of metabolic hibernation that allows cells to survive hard times for long periods

2. Oncometabolism

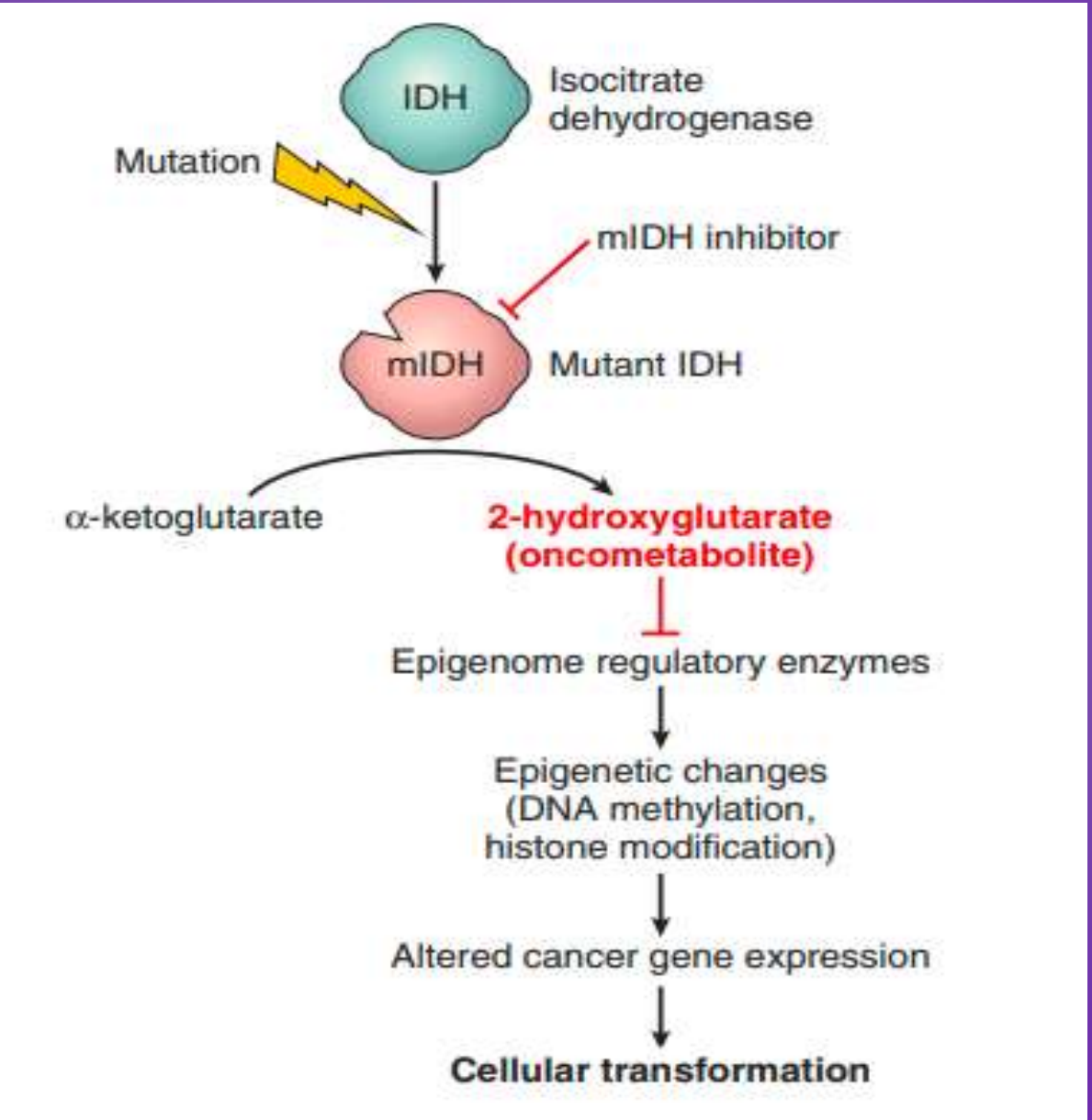
- They are mutations in enzymes that participate in the Krebs cycle.

- Of these, mutations in isocitrate dehydrogenase (IDH) have garnered the most interest, as they have revealed a new mechanism of oncogenesis termed oncometabolism.

- Oncogenic IDH mutations have been described in :

❖ Cholangiocarcinomas.
❖ gliomas.
❖ acute myeloid leukemias.
❖ sarcomas.

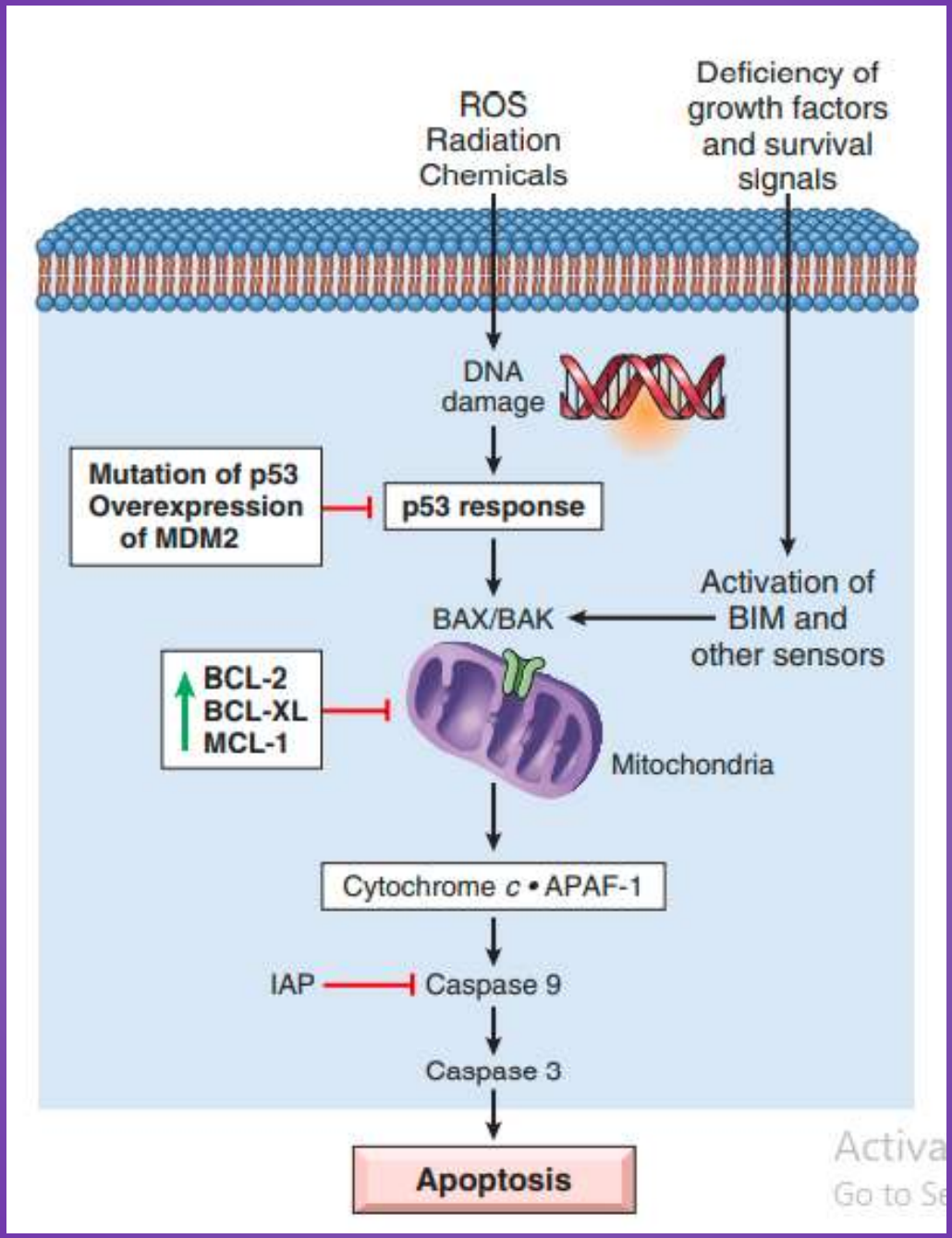
mutated IDH acts as an oncoprotein by producing 2-HG, which is considered a prototypical oncometabolite.



IV Evasion of Cell Death

- Tumor cells frequently contain mutations in genes that regulate apoptosis, making the cells resistant to cell death.

- evasion of apoptosis by cancer cells occurs mainly by way of acquired mutations and changes in gene expression that disable key components of the intrinsic pathway.

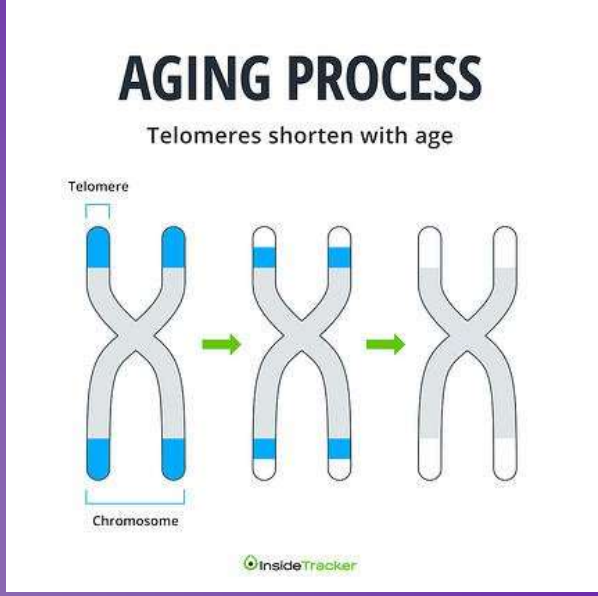

ROS
Radiation
Chemicals
Deficiency of
growth factors
and survival
signals
DNA
damage
Mutation of p53
Overexpression
of MDM2
p53 response
Activation of
BIM and
other sensors
BAX/BAK
BCL-2
BCL-XL
MCL-1
Mitochondria
Cytochrome c • APAF-1
IAP
Caspase 9
Caspase 3
Apoptosis

Major mechanisms by which apoptosis is evaded by cancer cells

- 1. Loss of TP53 function:
- prevents the upregulation of PUMA, a pro-apoptotic BH3-only that is a direct target of p53.
- As a result, cells survive levels of DNA damage and cell stress that otherwise would result in their death

- 2. Overexpression of anti-apoptotic members of the BCL2 family:
- Overexpression of BCL2 is a common event leading to the protection of tumor cells from apoptosis, e.g follicular lymphoma

V. Limitless Replicative Potential (Immortality)

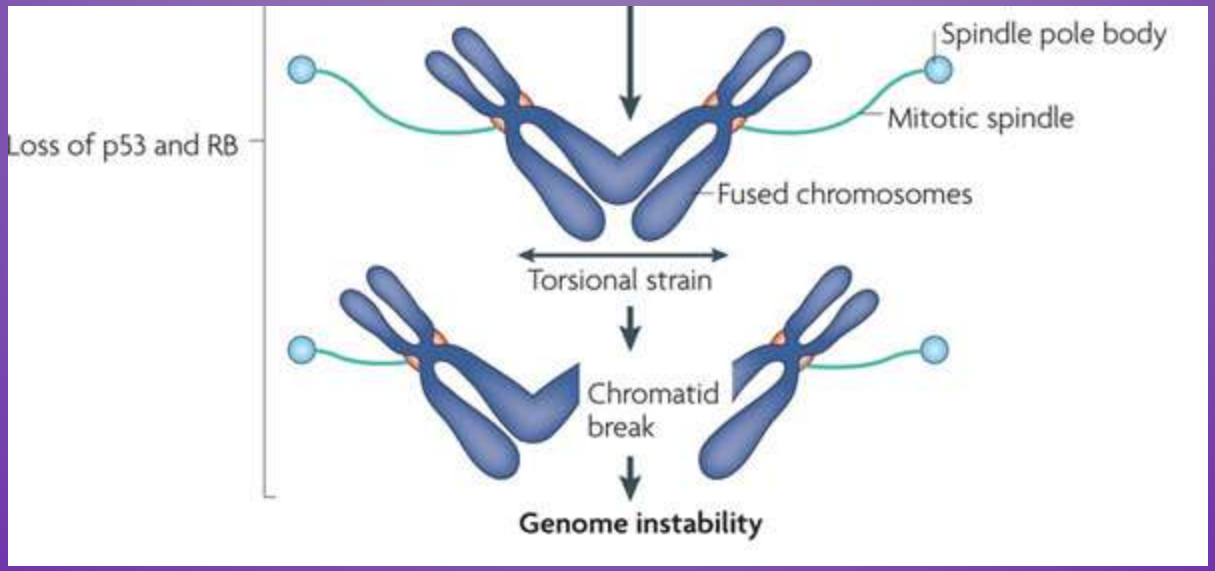


- Tumor cells, unlike normal cells, are capable of limitless replication.
- most normal human cells have a capacity of at most 70 doublings. Thereafter, the cells lose the ability to divide and enter replicative senescence.
- This phenomenon occure due to progressive shortening of telomeres at the ends of chromosomes

- Limitless Replicative Potential (Immortality) of the tumor cells is due to:

  - telomere maintenance
    - By: lengthening of telomeres
    - upregulation of the enzyme telomerase

- Markedly eroded telomeres are recognized by the DNA repair machinery as double-stranded DNA breaks, leading to cell cycle arrest and senescence, mediated by TP53 and RB.
- In cells in which TP53 or RB mutations are disabled by mutations, the nonhomologous end-joining pathway is activated as last effort to save the cell, joining the shortened ends of two chromosomes.



VI. Sustained Angiogenesis

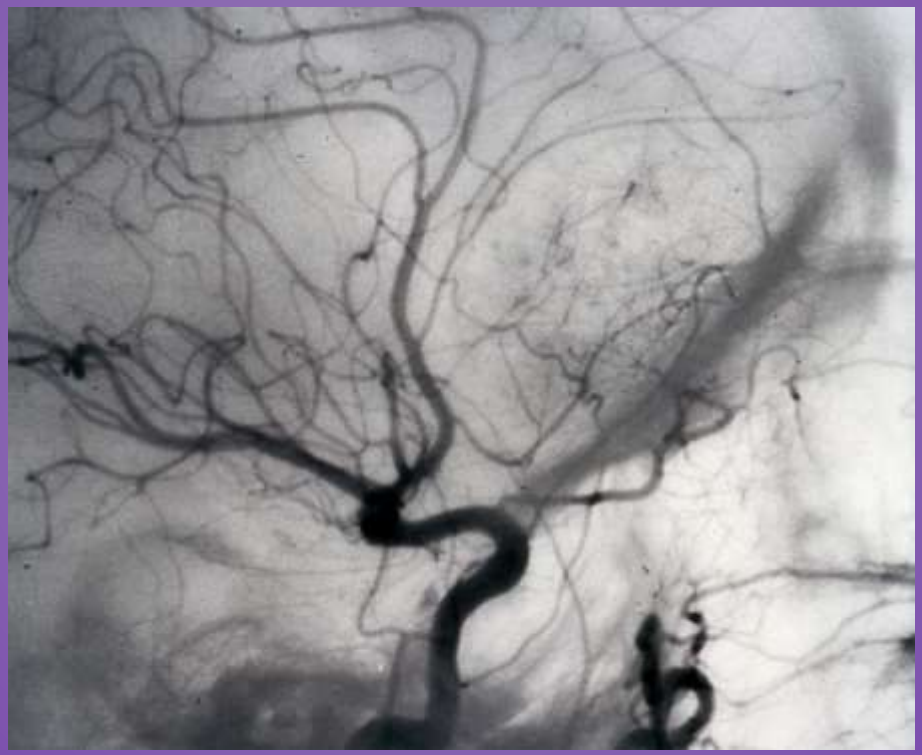
- Even if a solid tumor possesses all of the genetic aberrations that are required for malignant transformation, it cannot enlarge beyond 1 to 2 mm in diameter unless it has the capacity to induce angiogenesis.

- <u>Neovascularization has a dual effect on tumor growth:</u>

  - perfusion supplies needed nutrients and oxygen.

  - angiogenesis contributes to metastasis

- Neovascularization not entirely normal; the vessels are leaky and dilated, and have a haphazard pattern of connection, features that can be appreciated on angiograms



Angiogram of meningioma

How do growing tumors develop a blood supply?

- angiogenesis is controlled by a balance between angiogenesis promoters and inhibitors; in angiogenic tumors this balance is directed toward promoters.

- molecular basis of the angiogenesis involves:

- increased production of angiogenic factors.
- E.g proangiogenic basic fibroblast growth factors (bFGF)

- loss of angiogenic inhibitors;
- E.g angiostatin and endostatin

The local balance of angiogenic and anti-angiogenic factors is influenced by several factors:

- 1. Relative lack of oxygen due to hypoxia stabilizes HIF1α, an oxygen-sensitive transcription factor, which then activates the transcription of proangiogenic cytokines such as VEGF.

- 2. Mutations involving tumor suppressors and oncogenes in cancers also tilt the balance in favor of angiogenesis.
- E.g , p53 stimulates
- ❖ expression of antiangiogenic molecules, such as thrombospondin-1
- ❖ represses expression of proangiogenic molecules, such as VEGF. Thus, loss of p53 in tumor cells provides a more permissive environment for angiogenesis.

Thank you.