

Neoplasia 2023/24

lecture 8

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ILOS

- 1. understand the basic concepts of cell aging.
- 2. realize the importance of avoiding senescence as a hallmark of cancer.
- 3. understand evading apoptosis as a hallmark of cancer.
- 4. listing changes in the apoptotic pathways that can lead to cancer.
- 5. apply this knowledge in clinical scenarios, like follicular lymphoma.
- 6. understand the metabolic changes occurring during tumorigenesis
- 7. understand the basic concepts behind PET scan examination
- 8. understand the effect of autophagy in cancer development
- 9. understand the concept of oncometabolites and their targeted therapy.

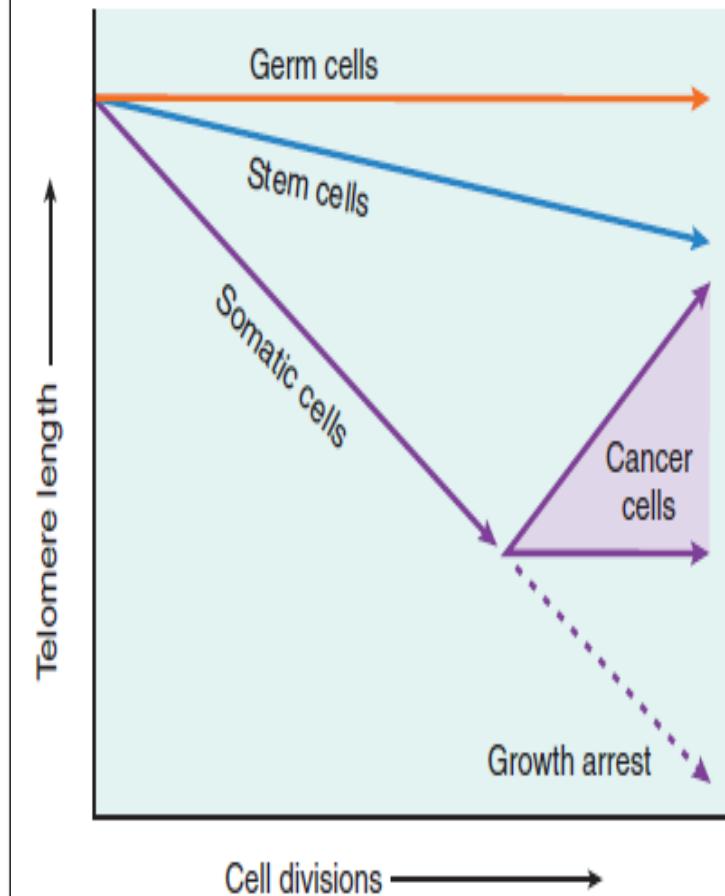
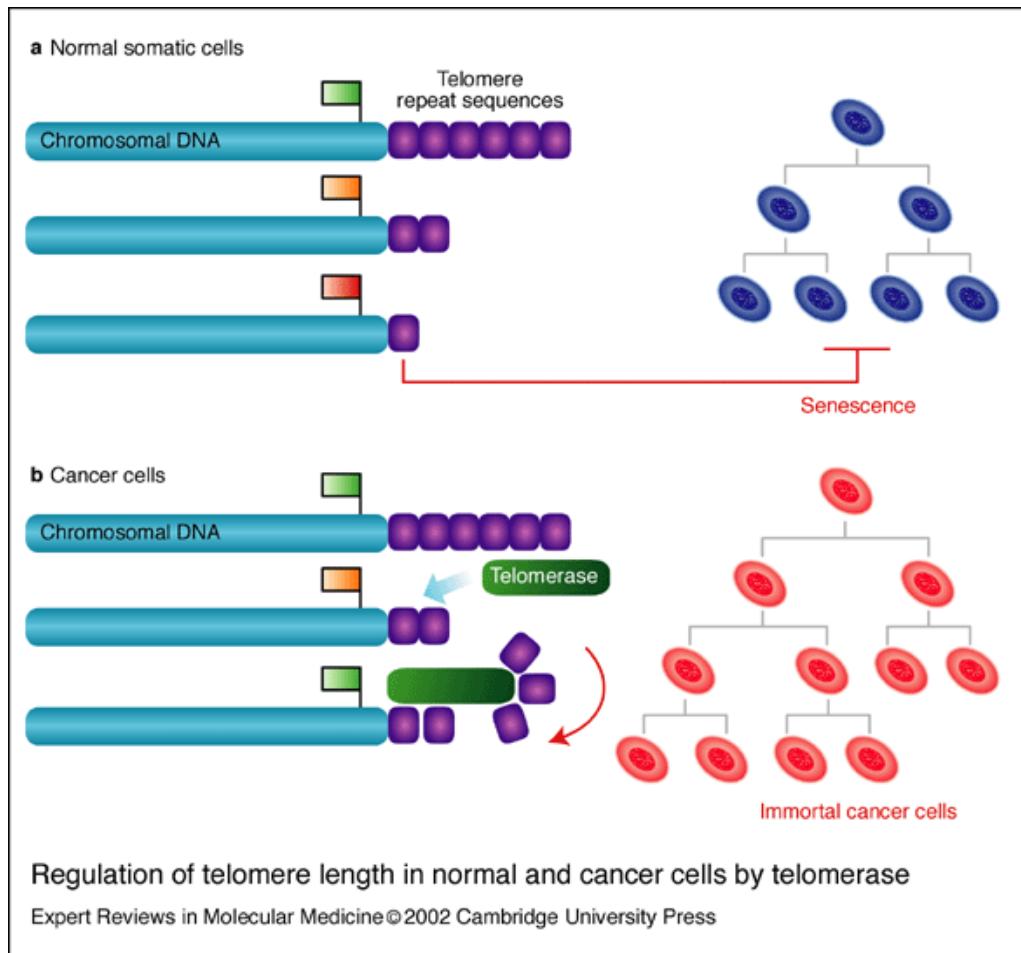
Third hallmark: limitless replicative potential

- Normal cells: limited capacity to duplicate (usually 60 -70 doublings).
- After these doublings cells lose the capacity to replicate and become senescent.
- This is because of progressive shortening of telomeres.

telomeres

- Each cell has a limited replicative potential.
- This is because chromosomes have repeated nucleotide sequences at the ends of each chromosome.
- With each cell replication, telomeres shorten, till they become too short and the chromosomal ends fuse together which causes cell death by apoptosis.
- Stem cells have limitless replicative potential because they have telomerase enzyme which uses its RNA nucleotide sequence to replace the lost telomeres.
- Cancer cells upregulate telomerase transcription and become immortal.

Cell Senescence & Telomeres



- Cells avoid senescence by activating telomerase.
- Telomere length is maintained in all cancer cells.. Mainly by upregulation of telomerase but also by other mechanisms like DNA recombinations

Fourth hallmark

- Evasion of cell death by evading apoptosis.

Apoptosis: a reminder!

- Apoptosis: programmed cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins
- So the cells commit suicide!
- The cells fragment and the fragments are phagocytosed without eliciting inflammatory response

Apoptosis



Extrinsic pathway

- Fas ligand
- Fas receptor
- FADD
- Caspase 8.  FLIP
- Caspase 3
- Decrease any of the above.... Evasion of cell death

extrinsic pathway

- Trigger which starts apoptosis is outside the cells.
- The pathway starts when Fas ligand binds to Fas receptor
- Upon this the receptor is activated; it trimerizes and its cytoplasmic part (death domain) is activated.
- Activation of the receptor attracts a cytoplasmic protein= FADD
- FADD recruits procaspase 8
- Procaspsase cleaved to active caspase 8 (initiation caspase)
- Caspase 8 activates caspase 3 (executioner) which cleaves DNA and cellular protein

Extrinsic pathway

- FLIP is a caspase 8 antagonist
- So if FLIP is increased cells can evade apoptosis
- FLIP-similar proteins are produced by some viruses.. Helping them to keep infected cells alive.

Intrinsic pathway = mitochondrial pathway

- This pathway is stimulated if there is DNA damage secondary to stress, radiation, chemicals or due to withdrawal of survival factors
- This pathway is intrinsic.. So not initiated by membrane receptors... instead it is initiated by increased mitochondrial permeability
- When mitochondrial permeability increases ..cytochrome c leaks out and initiates apoptosis
- Now cytochrome c is in the cytosol.. So it binds APAF 1
- This binding activates caspase 9
- Caspase 9 activates caspase 3

Intrinsic pathway

Internal stresses within cells

Increase mitochondrial permeability

Cytochrome c leaks outside the mitochondria

Cytochrome c binds to APAF1

Caspase 9 activated  IAP

Caspase 3 activated

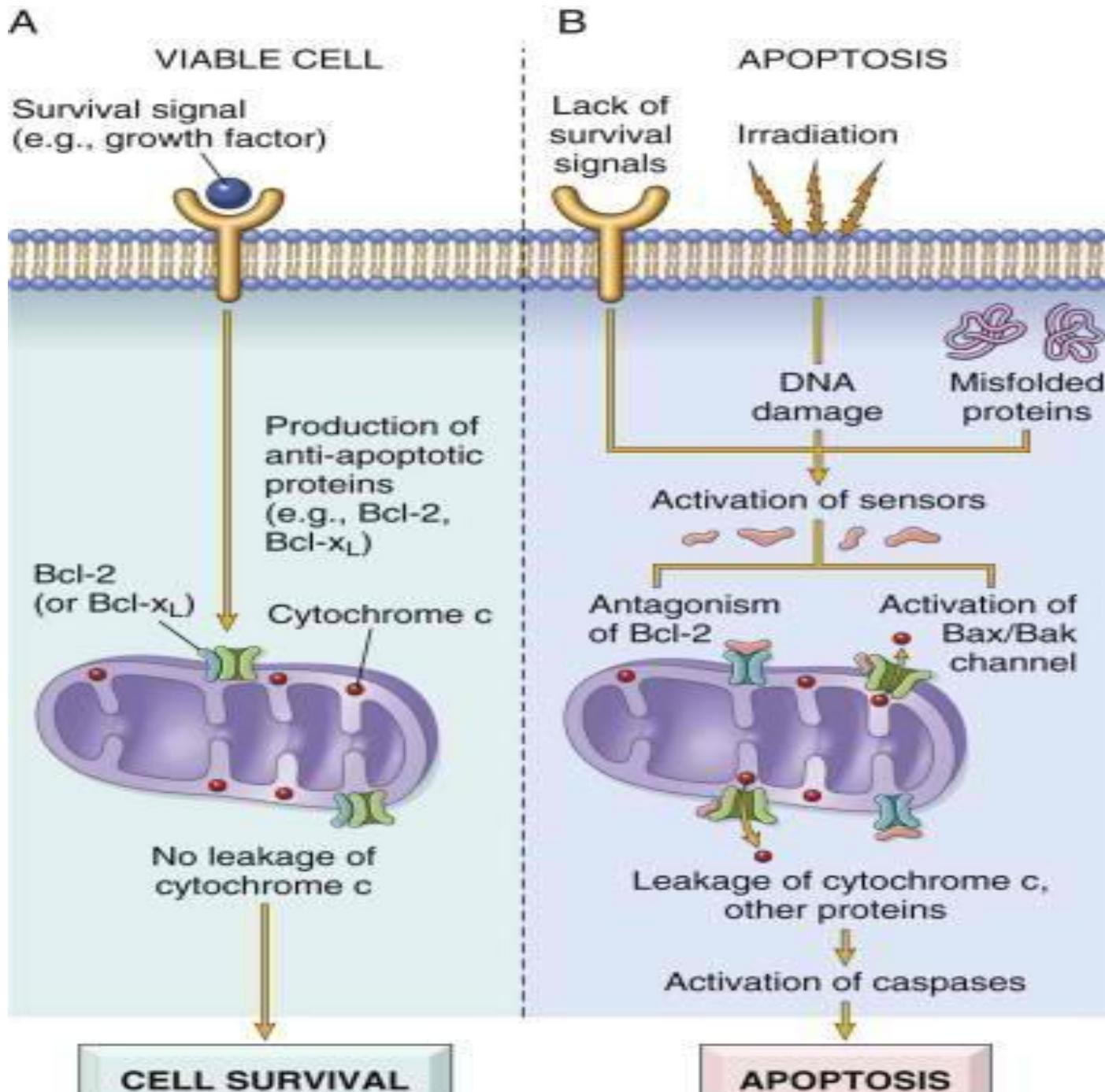
Again: decrease any of these and the cell can avoid apoptosis

Mitochondrial permeability

- Mitochondrial permeability is controlled by BH 3 proteins (BAD, BID, PUMA)
- When BH3 proteins sense internal stress.. Stimulate proapoptotic proteins and inhibit antiapoptotic ones
- Proapoptotic: BAX, BAK
- Antiapoptotic: BCL2, BCL- XI
- So decrease BAD, BID, PUMA, BAX, BAK... NO APOPTOSIS
- Increase BCL2 AND BCL-XI.... No apoptosis

note

- IAP= inhibitor of apoptotic protein , inhibits caspase 9
- So increase IAP and apoptosis can be avoided.



P53 and apoptosis

- DNA damage causes accumulation of **p53** in cells
- It arrests cells in G1 phase of cell cycle to give the cell a chance to repair itself
- If no repair, p53 triggers apoptosis by stimulating bax and bak
- *P53 can be mutated in cancer cells.. If mutated it cannot initiate apoptosis, so the cell survives even if its DNA is damaged.. Longer survival of a cell with damaged DNA increases the chances of accumulating more mutations.. So this cell can become malignant*

IMPORTANT NOTE

- Note that we agreed that ALL the phenotypes (cancer hallmarks) are needed to transform cells.
- But, it should be clear now that we don't need 8 mutations for the 8 hallmarks!
- Example: p53 mutations can cause insensitivity to growth signals, evasion of apoptosis, and reprogramming of energy metabolism: three hallmarks from one mutation!



Fifth hallmark: changes in cell metabolism

- These changes include
- 1. reprogramming of energy metabolism to aerobic glycolysis
- 2. changes in autophagy
- 3. formation of oncometabolites

Reprogramming of energy metabolism

Normal cells obtain energy by:

- Oxidative phosphorylation if oxygen is available. In this process each glucose molecule used produces 36 ATP molecules.
- Anaerobic respiration if oxygen levels are low. In this process glucose is converted to lactic acid and for each glucose molecule used only 2 ATP molecules are produced.

Reprogramming of energy metabolism

- Cancer cells have a third way!
- They convert glucose to lactic acid **even in the presence of adequate oxygen**
- This process is called : aerobic glycolysis or Warburg effect.

Aerobic glycolysis

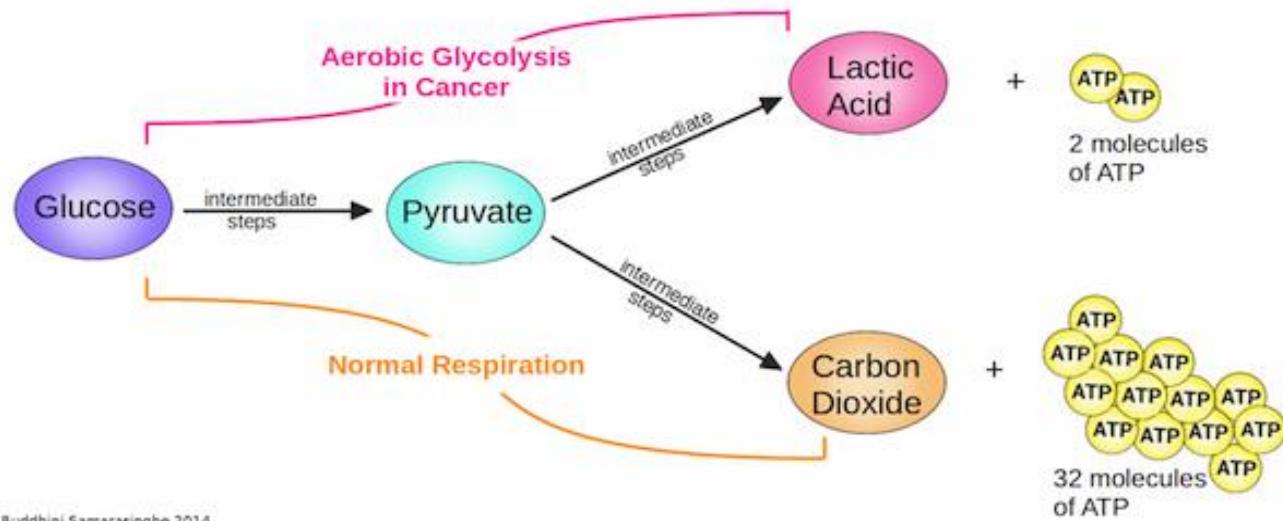
- Cancer cells didn't invent aerobic glycolysis!
- *Actually, rapidly proliferating normal cells, like in embryonic tissues and lymphocytes during immune responses, rely on aerobic fermentation (glycolysis) .*
- So: “Warburg metabolism” is not cancer specific, but instead is a general property of growing cells.

Warburg effect

- Although less ATP is produced... the Warburg effect ensures that **carbon atoms** in glucose (which is converted to Pyruvate) are used **for synthesis of organic compounds** like lipids and proteins which are important in building new cells in the highly proliferative tumor.
- SO: Aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components, whereas mitochondrial oxidative phosphorylation does not.

Note:

- A growing cell must duplicate all of its cellular components—DNA, RNA, proteins, lipid, and organelles—before it can divide and produce two daughter cells.
- While oxidative phosphorylation yields abundant ATP, it fails to produce any carbon atoms that can be used to build the cellular components needed for growth (proteins, lipids, and nucleic acids). Even cells that are not actively growing must shunt some metabolic intermediates away from oxidative phosphorylation in order to synthesize macromolecules that are needed for cellular maintenance.



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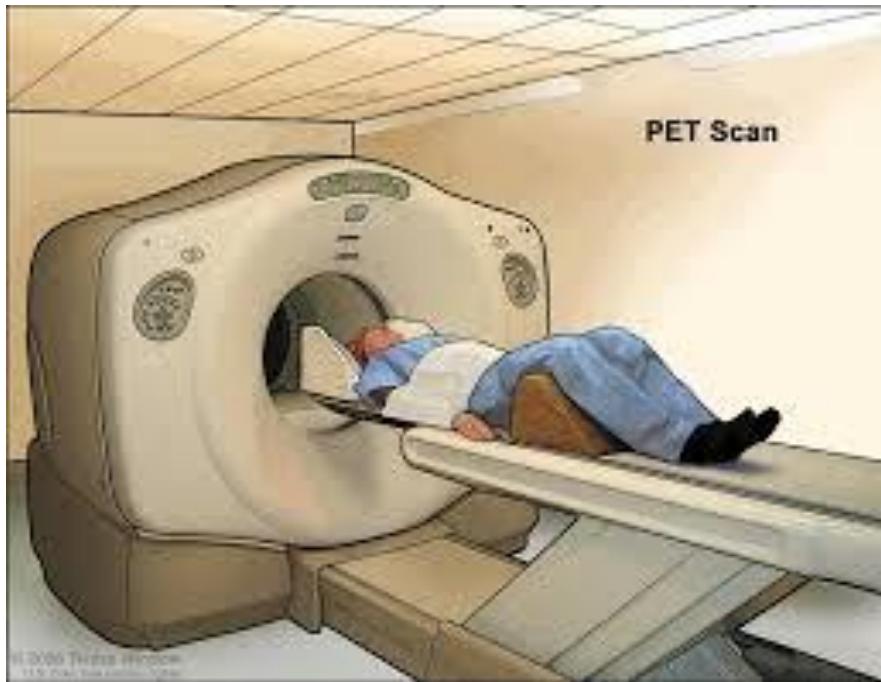
How does cancer cells do this switch of metabolism????

- **Metabolic reprogramming is produced by signalling cascades downstream of growth factor receptors, the very same pathways that are deregulated by mutations in oncogenes and tumors suppressor genes in cancers.**

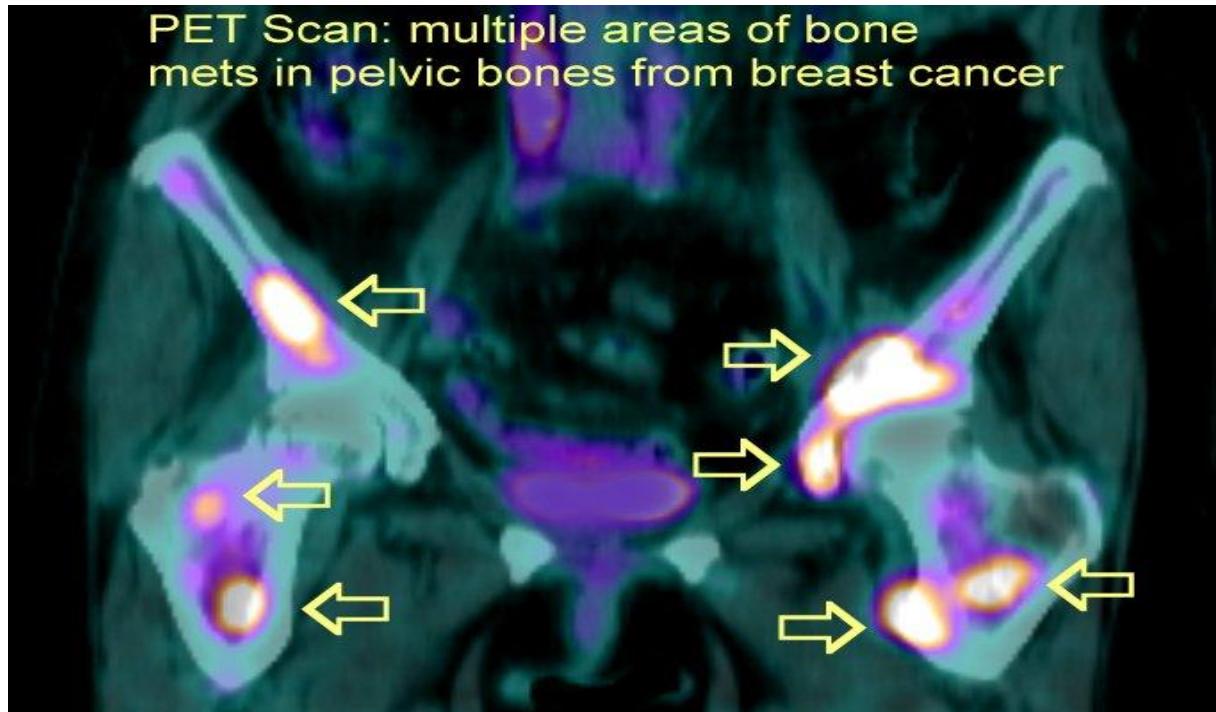
PET scan

- Because of this reprogramming, tumor cells are “glucose hungry”, they take loads of glucose, and this property is used in PET scans
- PET: positron emission tomography
- Patient is injected with a glucose derivative.. Tumor cells take this derivative more than normal cells and as such detected with the scan
- The more proliferative the tumor is... more uptake and more positivity with PET scan

PET scan



PET scan



PET scan



autophagy

- Autophagy is a catabolic process that balances synthesis, degradation and recycling of cellular products
- The recycling of the cell's organelles can produce energy needed for the stressed cells.
- This process can signal cell death if the cell cannot be rescued by the recycling process



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).**
- If this adaptation fails, the cells die.

note

- Although autophagy is an anti-tumor process.... Later on if there is a tumor mass formed, autophagy can help the tumor to survive if it's used to recycle organelles to be used as an energy source .
- Autophagy can help tumor cells to survive during unfriendly climates: for example during chemotherapy treatment.

oncometabolism

- This is a new concept, which was discovered through finding certain mutations in enzymes that participate in the Krebs cycle.
- Of these, mutations in **isocitrate dehydrogenase (IDH)** is the most studied.

How a mutation in IDH causes cancer?

- IDH acquires a mutation involving the active site of the enzyme, so it loses its ability to function as an isocitrate dehydrogenase and instead **acquires a new enzymatic activity that catalyzes the production of 2-hydroxglutarate (2-HG)**.
- 2-HG in turn acts as an **inhibitor of several other enzymes that regulate DNA methylation**,
- DNA methylation is an **epigenetic** modification that controls normal gene expression.
- Abnormal DNA methylation in turn leads to mis-expression of currently unknown cancer genes, which drive cellular transformation and oncogenesis.

Oncometabolite: a metabolic product causing oncogenesis.

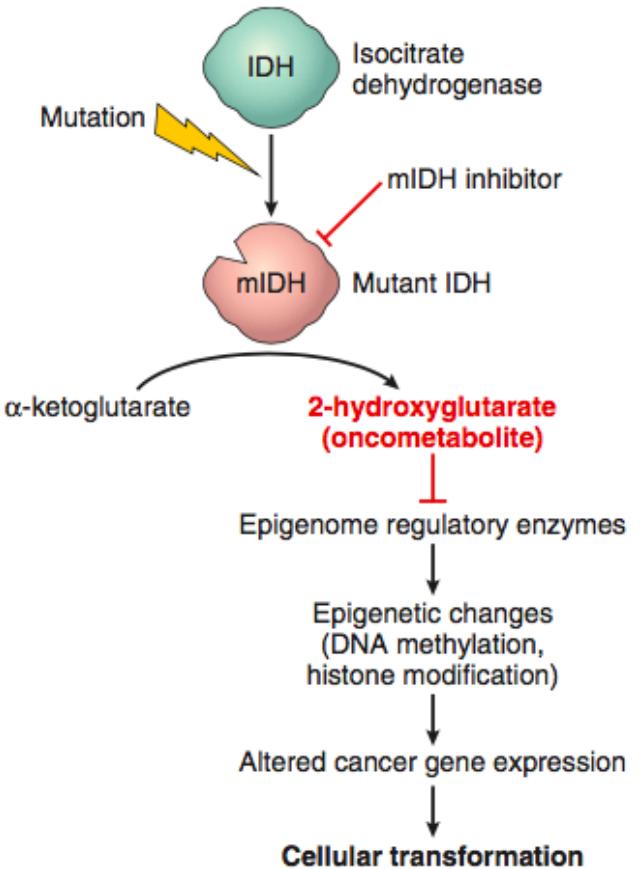


Fig. 6.24 Proposed action of the oncometabolite 2-hydroxyglutarate (2-HG) in cancer cells with mutated isocitrate dehydrogenase (mIDH).

- IDH mutations are found in gliomas, acute myeloid leukaemia, and sarcomas.
- the mutated IDH proteins have an altered structure ,so it has been possible to develop drugs that inhibit mutated IDH and not the normal IDH enzyme.
- These drugs are now being tested in cancer patients and have produced encouraging therapeutic responses.

summary

- The third hallmark of cancer is ability to have limitless replications. This is acquired via upregulating telomerase enzyme.
- Evading apoptosis is an important trait of cancer cells. This occurs via blocking apoptotic or stimulating anti-apoptotic mechanisms.
- Tumor cells have altered metabolism that enhances their survival. These include reprogramming of energy metabolism, autophagy changes and oncometabolite formation.
- Warburg phenomenon= aerobic metabolism= fermentation even with the presence of oxygen. This reduces ATP generated per gram glucose but provides carbon atoms needed for cell division and growth.
- This switch in metabolism is achieved via oncogenes overexpression and tumor suppressor genes inactivation. In both instances there is shift in glucose metabolism.
- Autophagy is evaded in tumors, but is upregulated during stress (chemotherapy or ischemia) to recycle cell components and enhance survival.
- IDH mutations are a prototype for oncometabolites, they act by changing enzyme activity resulting in DNA methylation. New therapies are discovered to target these mutated enzymes.

