Metabolic Changes in Oncologicial Patients

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BOM DIA

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Metabolic Changes in Cancer Patients

Focus points

- Cancer and Malnutrition
- Long-standing premise of cancer cell metabolism
- Identify the common metabolic changes occurring in cancer patients

CANCER AND NUTRITION

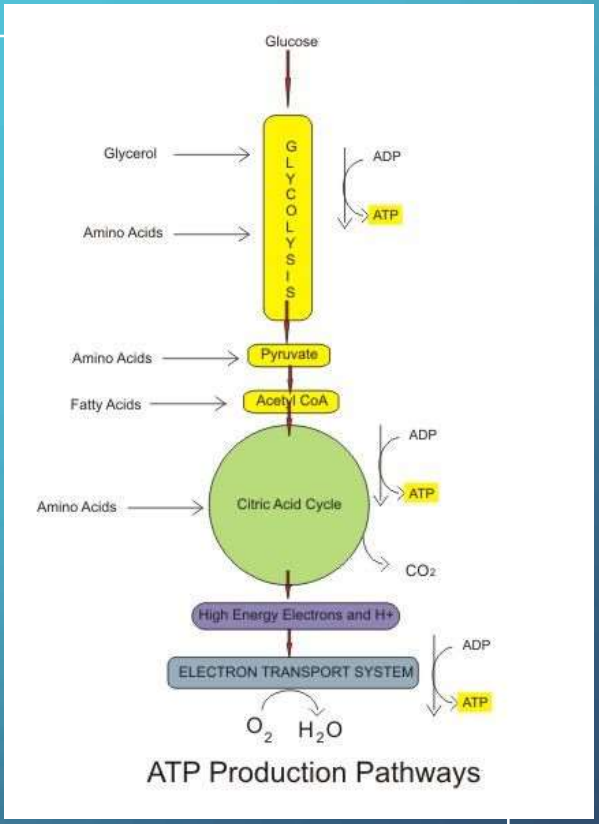
- **MALNUTRITION**
  - Characterized by altered immune response, poor wound healing, fluid & electrolyte imbalances, body weight and body condition changes.
- Malnourished Cancer Patient exhibits:
  - Significantly ↓response to treatment protocols & time to remission
  - Increased morbidity and mortality
  - Diminished quality of life

FACTORS IMPACTING NUTRITIONAL STATUS OF CANCER PATIENT

- Tumor-host competition for energy substrates
- Body's response to anti-neoplastic therapies or treatments
- Patients health status when treatment initiated
- Nutrient intake during and following treatment protocols

COMPETITION FOR ENERGY SUBSTRATES

- Cells require nutrients for growth
- Glucose, via glycolysis
  - ↔ Kreb's Cyle (TCA)
    - → Electron Transport Chain
      - → → → ATP (energy packet)

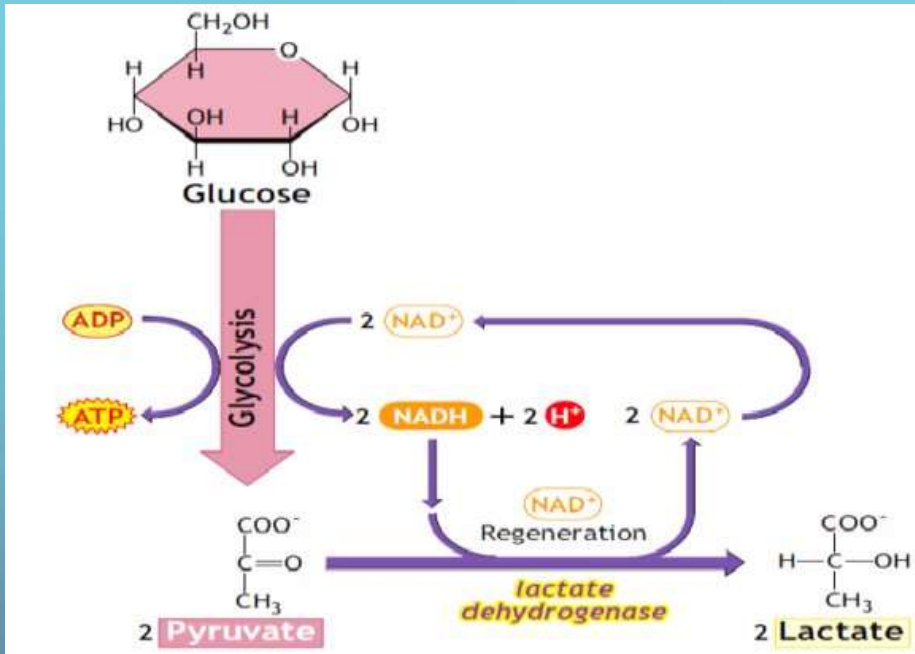


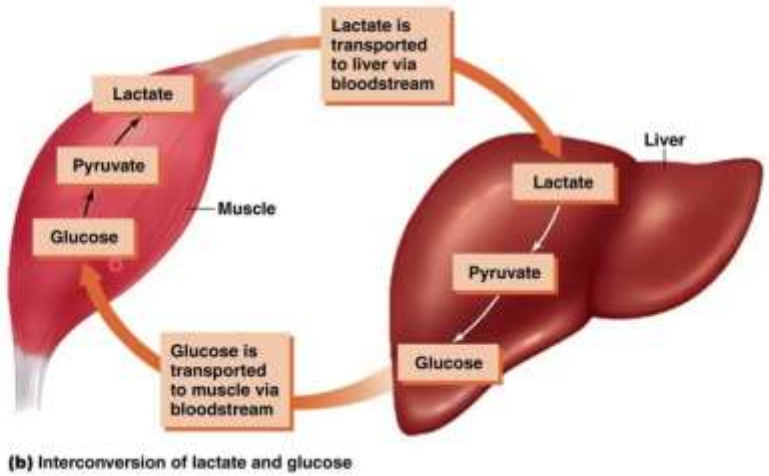
ATP Production Pathways

- Enter … **The Warburg Effect**
  - (1930-1956) Study on tumor metabolism: relationship between glycolysis and cellular bioenergetics

THE WARBURG EFFECT

- Cancer cells exhibit ↑ rates glucose uptake → lactic acid production in an anerobic (low oxygen) environment.





- Lactic acid → Cori Cycle → Glucose available for healthy cell use

WHY DO CANCER CELLS ADAPT ANEROBIC GLUCOSE METABOLISM?

In support of Warburg Effect -

1. To support uncontrollable growth TC's must uptake and incorporate nutrients into their biomass to produce new cells..
   - Amino aids for protein synthesis; nucleic acids for DNA replication; lipids for cell biomembrane synthesis
2. Glycolysis defense mechanism for TC occurs in acidic environment- harmful to normal cells; not harmful to TC's
3. Glycolysis produces less ROS → protects TC genome
4. Glycolysis generates ATP faster vs oxidative phosphorylation when glucose readily available

AEROBIC GLYCOLYSIS ADVANTAGES

- Decrease in apoptosis (cell death)
  - Mitochondria important in regulating apoptosis
- Increase in ROS → decrease in SDH → oxidative stress
- Pseudo-hypoxia
  - Accumulation of fumarate & succinate
  - Activates HIF-1α → cell proliferating and survival
- TC's lose regulation of external signals to uptake nutrients such as glucose (?)

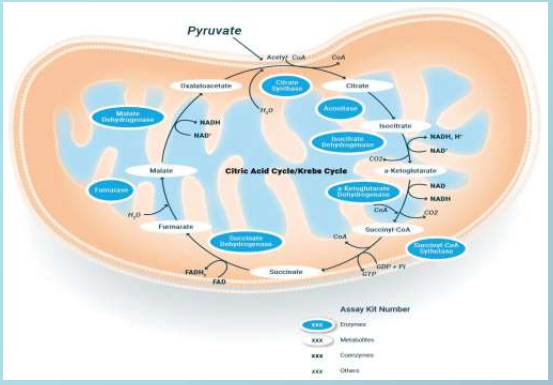
WHAT'S BEHIND THE ALTERED METABOLISM IN CANCER PATIENTS ?

Gene Mutations (mitochondrial dysfunction) influencing metabolism

- **SDH** (succinate dehydrogenase; succinate → fumarate)
- **FH** (fumarate hydrase; fumarate → malate)
- **HIF** (hypoxia-inducible factor)
- **IDH** (isocitrate dehydrogenase,
  - isocitrate → α-ketoglutarate (α-KG) in TCA cycle
- **PK** (pyruvate kinase)
- **P53** (suppressor protein, transcriptional activator)
- **c-myc** (gene serves as a "master regulator" of cellular metabolism and proliferation)

The back story …

Succinate $\xrightarrow{SDH}$ Fumarate .. completion of TCA cycle to support oxidative phosphorylation



But, mutations can occur.

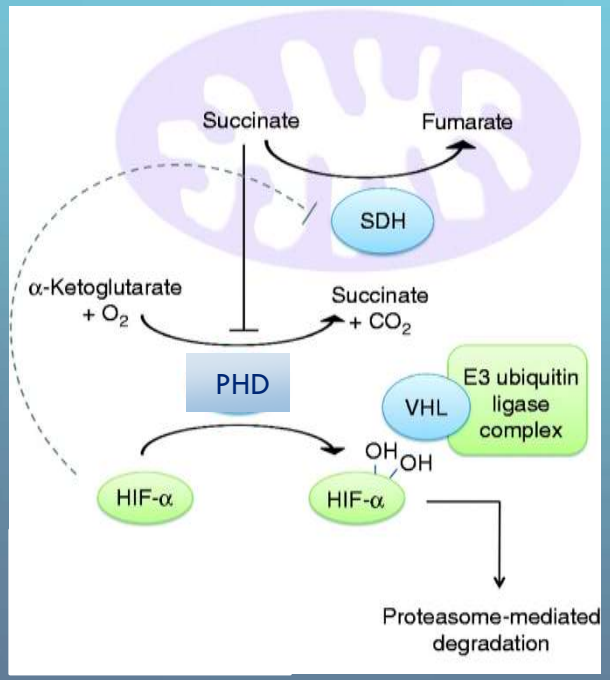
SDH mutations (SDHB, C, D, H5 only) common in paraganglioma, gastric stromal tumors, childhood T-cell acute leukemia

FH mutations common in breast, cerebral and uterine cancers

SDH (FH) mutation oncogenicity influenced by cell hypoxia

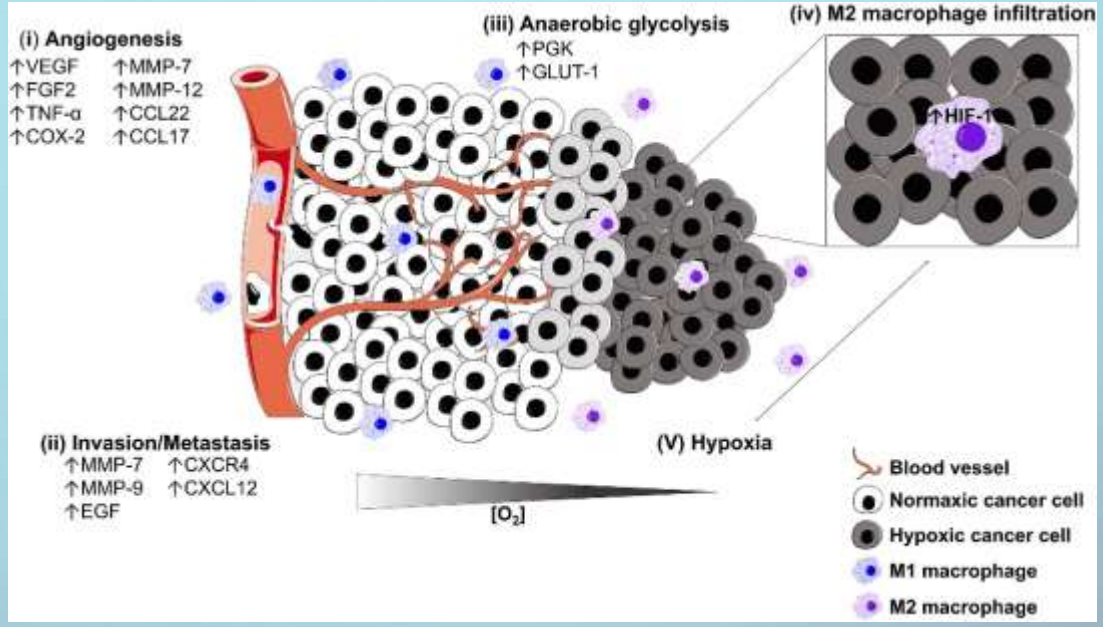
HYPOXIA Considerations-

- Hypoxia stress common in normal cells and tumors, the response is hypoxia-inducible factor **(HIF)**
  - HIF controls migration; differentiation; effector functions on immune cells.
    - Modulates expression of molecular targets (CD137, OX-40, FOXP3, PD-L1)



Normal oxygen environ, HIF-1α is hydroxylated by PHD's, recognized by via VHL-mediated UPP (ubiquitination) pathway for **degradation**

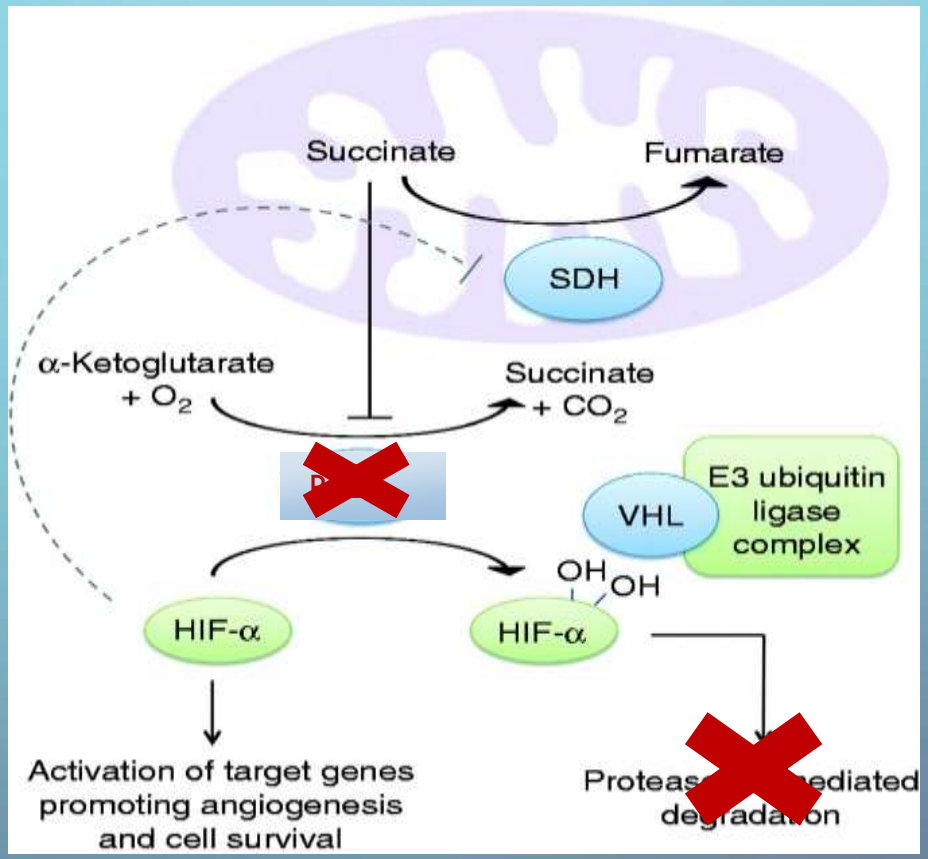
Low O_2 availability (hypoxia), a hallmark of most solid tumors, infiltrating leukocytes experience severe hypoxia once away from nurturing blood vessels. Results in …



Altered cell metabolism and subsequent …

Tumor-promoting stromal environment; Angiogenesis; Continued invasiveness and metabolism Genome instability and mutations; Resistance to therapy; Uncontrolled cell proliferation

SDH (FH) mutation oncogenicity influenced by cell hypoxia



SDH and FH mutations result in accumulated succinate and fumarate (structural analogs of α-ketoglutarate), which inhibit PHDs → activate HIF pathway → HIF into nucleus → up expression HIF target genes including: **GLUTs, PDK, LDH and myc.**

GLUTs allow TCs greater glucose uptake

PDK can inhibit activity of PDH

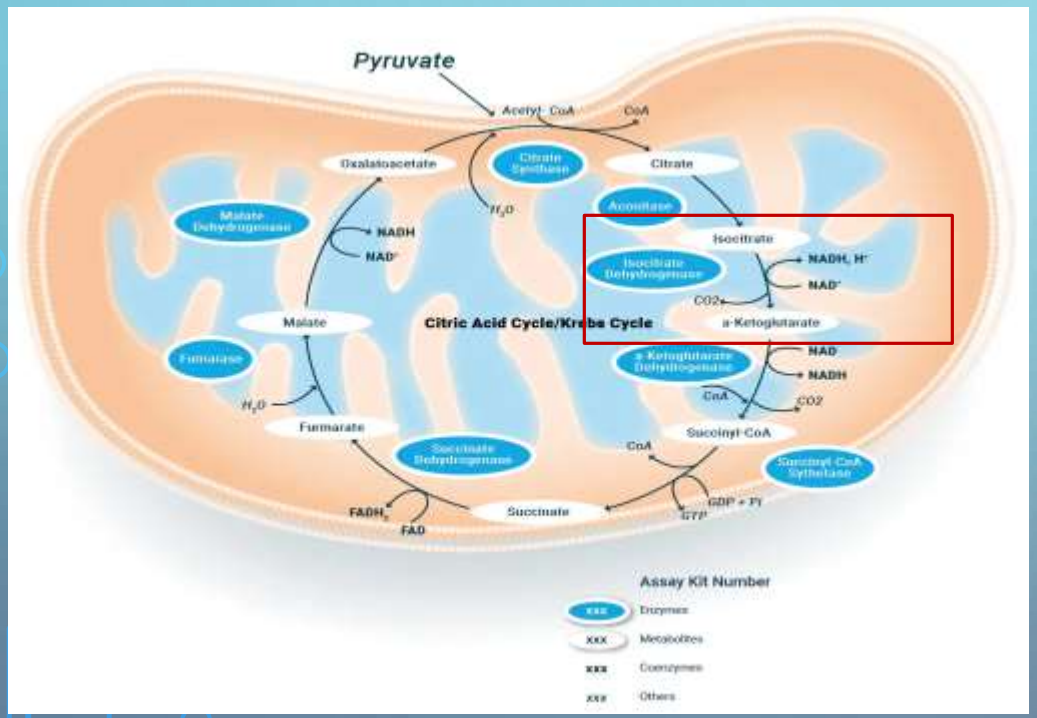
LDH accelerate conversion pyruvate → lactate

Promote Warburg Effect

OTHER GENE MUTATIONS OF INTEREST

IDH (IDH1, IDH2, IDH3) convert isocitrate → α-KG of TCA cycle

- >70% grade II-III gliomas and glioblastomas (IDH1, 2); acute myeloid leukemia, chondrosarcoma
- α-KG $\xrightarrow{\text{IDH mutants}}$ 2-hydrozyglutarate (2-HG) → dioxygenases

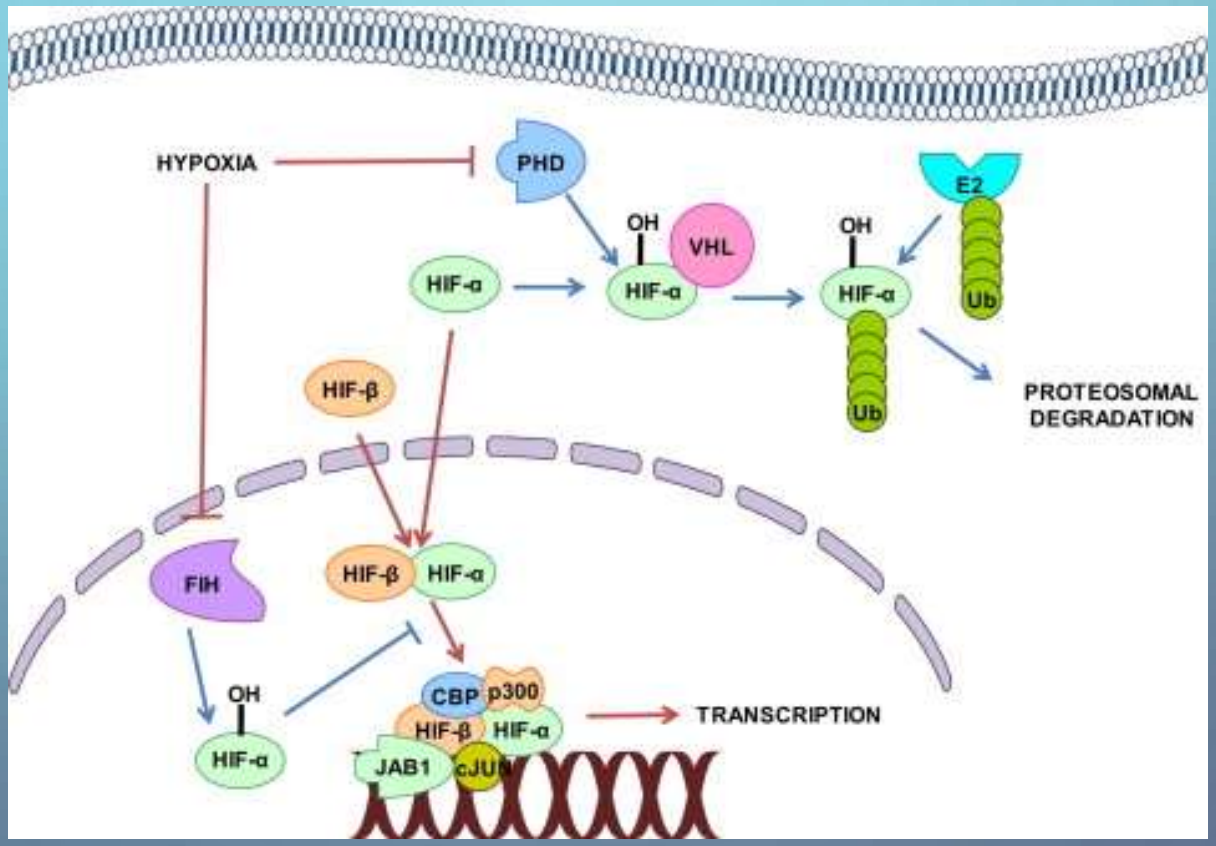


↑2-HG and α-KG ↓inhibits nuclear dioxygenase activity to promote tumor induction

α-KG (ketoglutarate)

OTHER GENE MUTATIONS OF INTEREST

- Downstream targets of IDH mutations include:
  - PHDs
    - Regulation & degradation HIF1α
      - $\uparrow$ HIF-1α promotes aerobic glycolysis & tumorigenesis



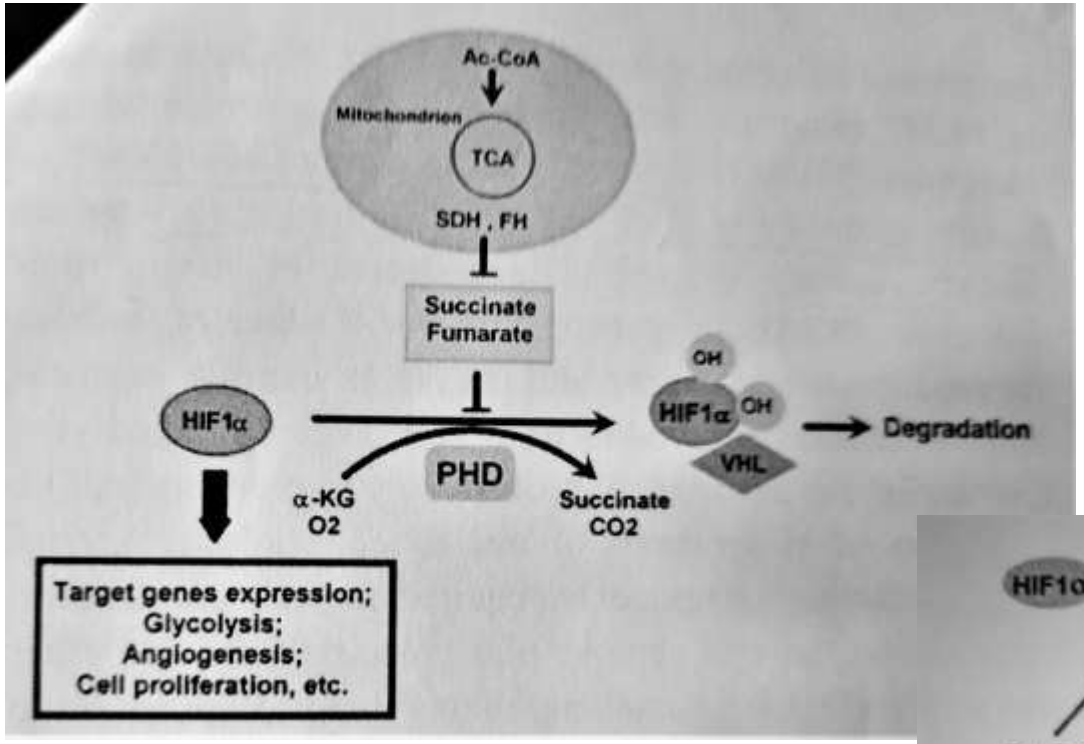
OTHER GENE MUTATIONS OF INTEREST

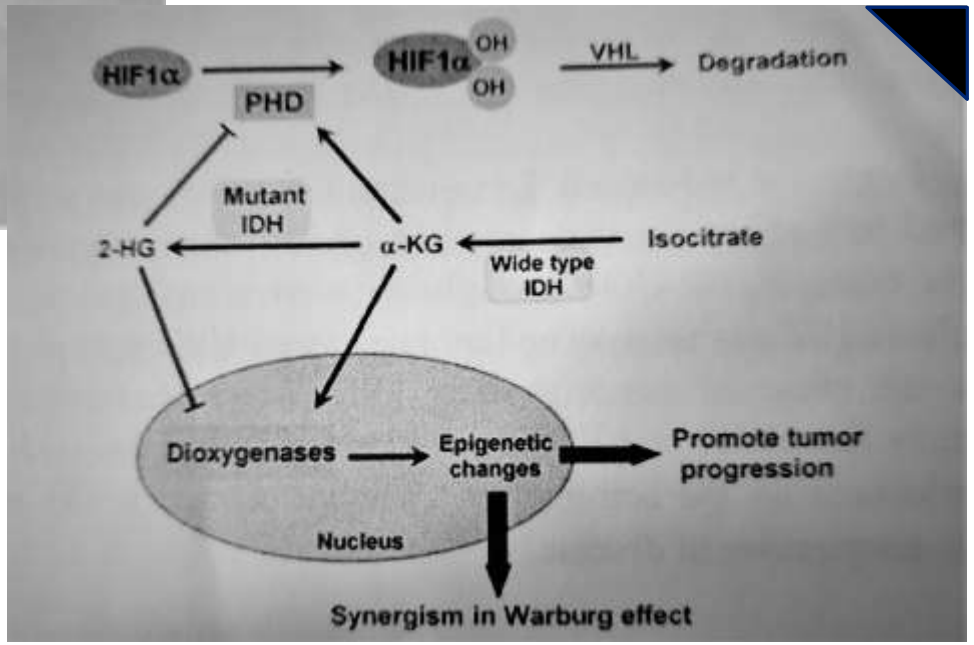
- Downstream targets of IDH mutations include:
  - Histone lysine demethylases (JHDM super family)
    - Catalyzes histone demethylation → altered nucleosome space conformation
  - DNA hydroylases (TET family)
    - Catalyzes hydroxylation 5'-methycytosine → 5-hydroxymethylcytosine → DNA methylation

IDH mutations ⇒ chromatin remodeling & altered DNA demethylation which together induce cell differentiation arrest

JHDM (Jumonji C-terminal domain histone demethylase); TET (ten-eleven-translocation)

SUMMARIZE GENE MUTATIONS



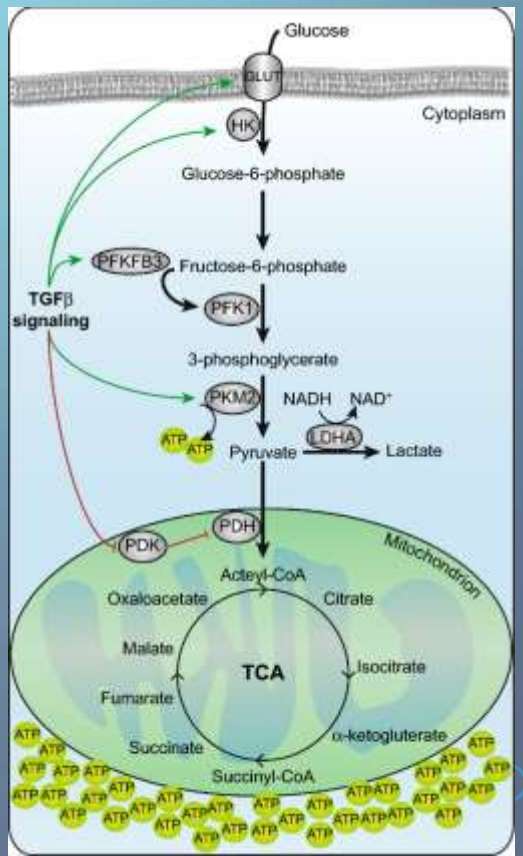


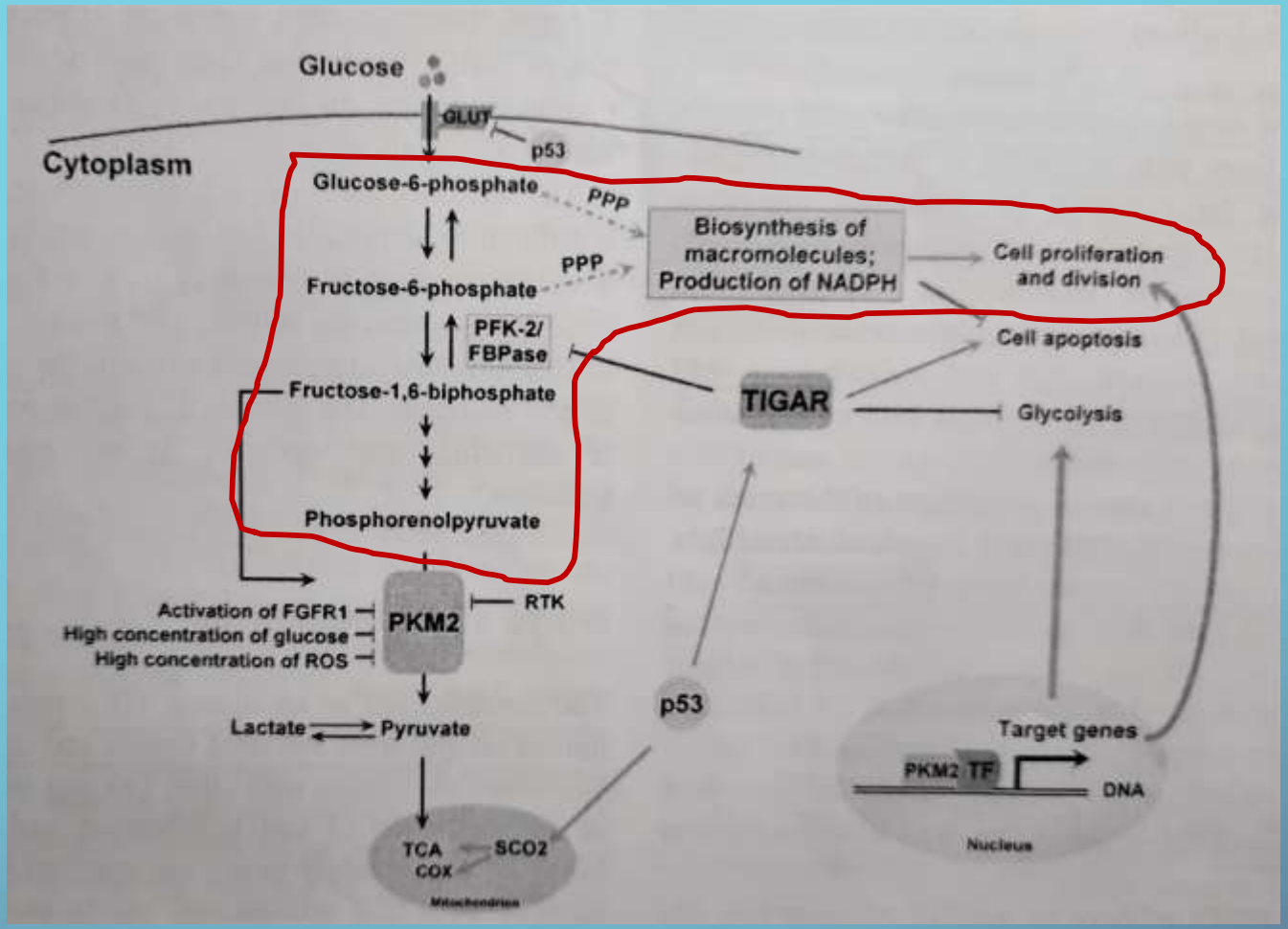
PKM2 SWITCH

- PK, Pyruvate kinase (PKL; PKR; PKM1; PKM2)
- PKM2

Door keeper for glycolytic flux

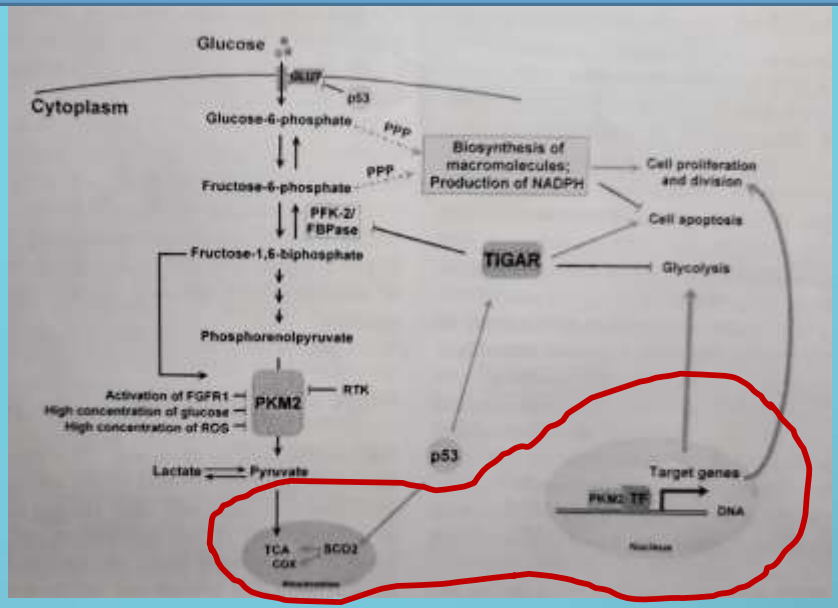
- Development: embryonic cells & rapidly dividing cells
- Phosphoenolpyruvate $\xrightarrow{PKM2}$ Pyruvate
- Rate-limiting enzyme in glycolysis
- 2 forms kept in balance: active as a tetramer and inactive as a dimer
- PKM2 as dimer (inactive) in TC's





PKM2 is in inactive form in TC's → restrain pyruvate → Increase metabolic intermediates up stream (F-1,6-BP; F-6P) into the pentose phosphate pathway (PPP), et al. promoting cell proliferation and division vs apoptosis

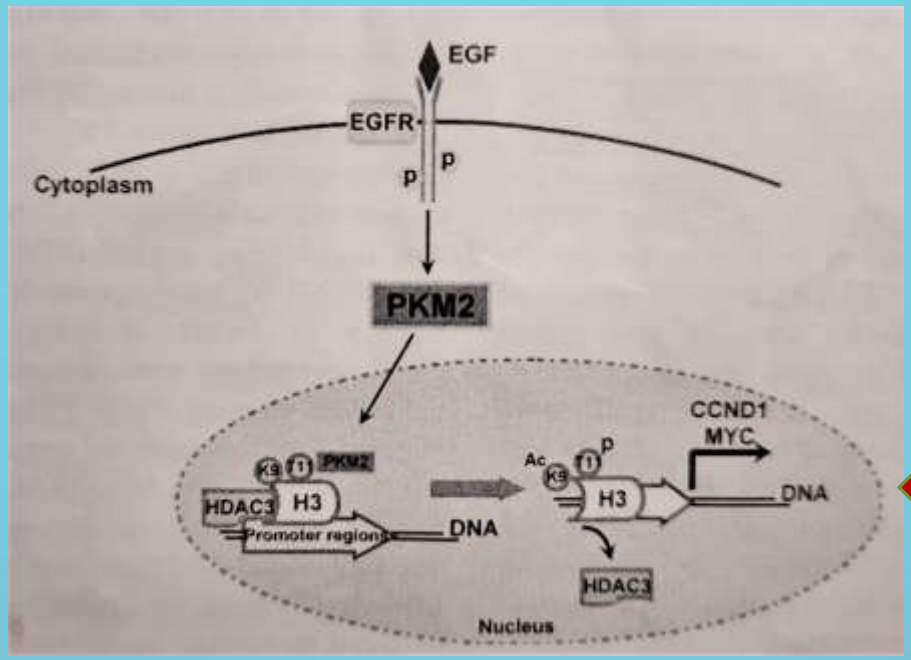
PKM2 as a signaling molecule for tumor progression



PKM2 phosphorylated by fibroblast growth factor type 1 or undergone acetylation → promote chaperone-dependent cell autophagy → allows cells utilize endogenous macromolecules to ensure cell survival

High concentrations of intracellular ROS → decreased PKM2 activity → diverting glucose flux into PPP for cell proliferation

PKM2, in nucleus, acts as transcriptional coactivator to promote HIF target gene expression



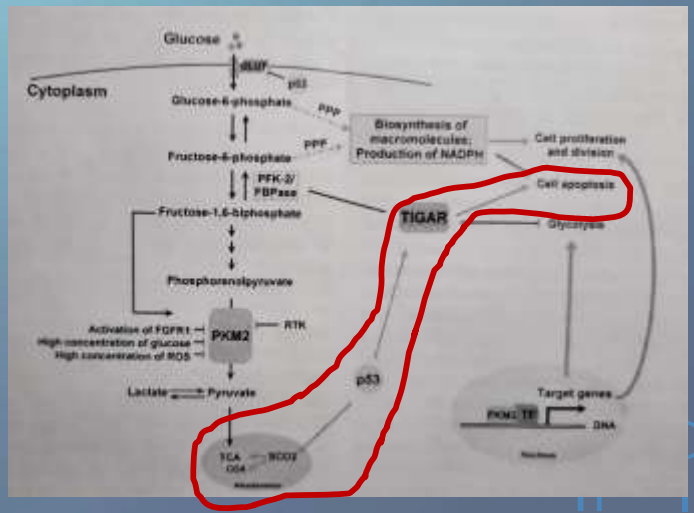
Finally, PKM2 mediated phosphorylation of histone H3 influence EGF-induced expression of cyclin D1 and c-myc,
tumor cell proliferation,cell cycle progression, and tumorigenesis.

This identifies PKM2 as a protein kinase well as serving metabolic functions … influencing TC proliferation from several aspects.

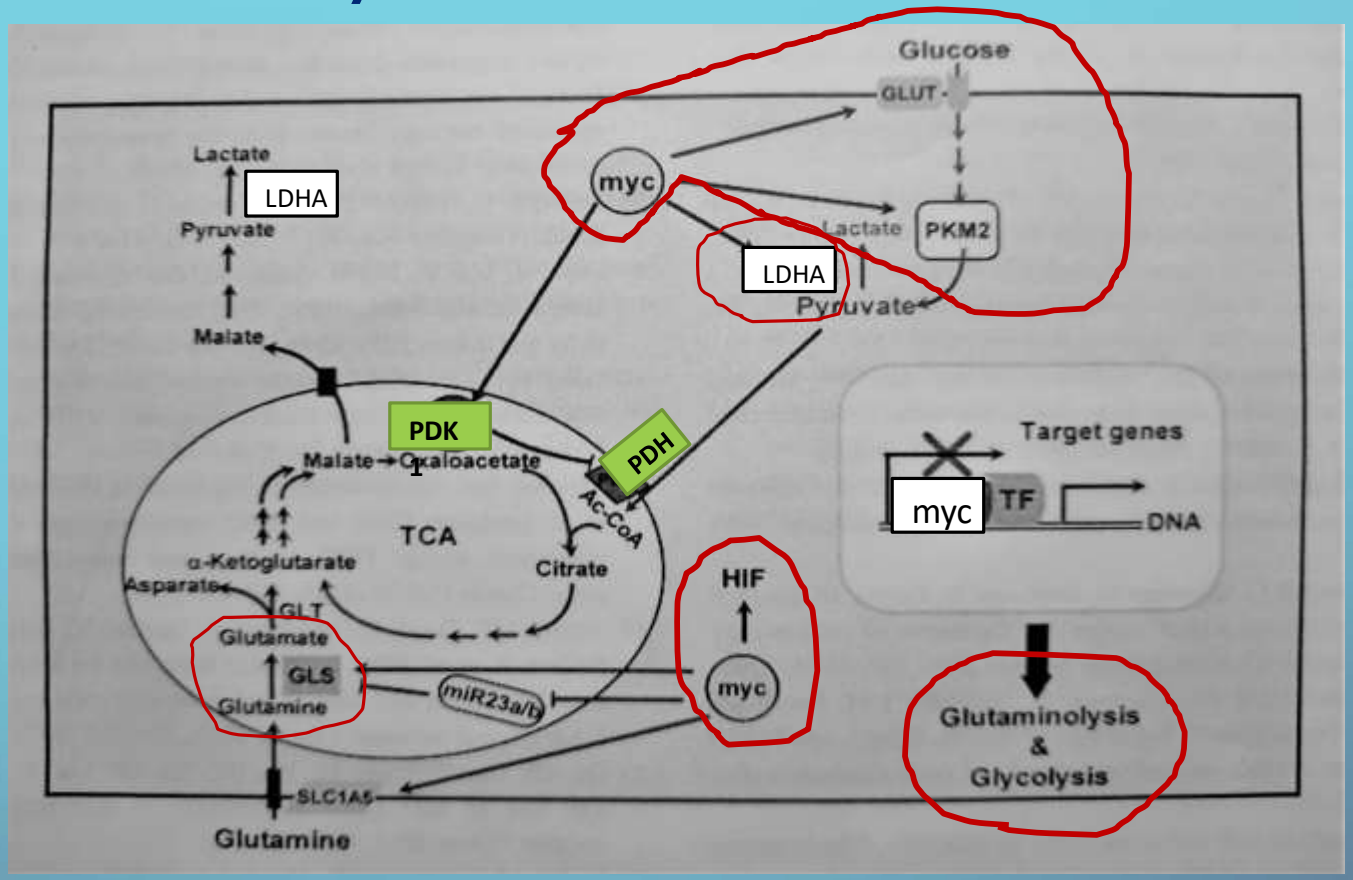
P53 AND METABOLISM

- Important tumor suppressor protein w/ roles in:
  - Normal cell growth, apoptosis, regulation of cell cycle, DNA repair, genome stability
- Central component of stress response as ↑ intracellular ROS, hypoxia, metabolic stress, DNA damage ⇒ activate P53
- Role in regulation glycolysis & ox phos …
  - Alter GLUT 1 & 2 expression, hexokinase genes, TCA cycle enzymes ⇒ slow glucose uptake and slow glycolysis …
  - p53-dependent transcriptional activation of cytochrome-c oxidative 2 synthesis → ↑ mitochondrial respiration

p53 is Warburg Effect regulator!



c-myc AND METABOLISM



C-myc: induces glycolysis and glutaminolysis

increases levels GLUTs and glycolytic enzymes

De-regulated c-myc: increase LDHA expression → lactate

upregulate PDK1 activity → ↓PDH, ox phos

PROTEIN METABOLISM: WHAT TUMORS DO

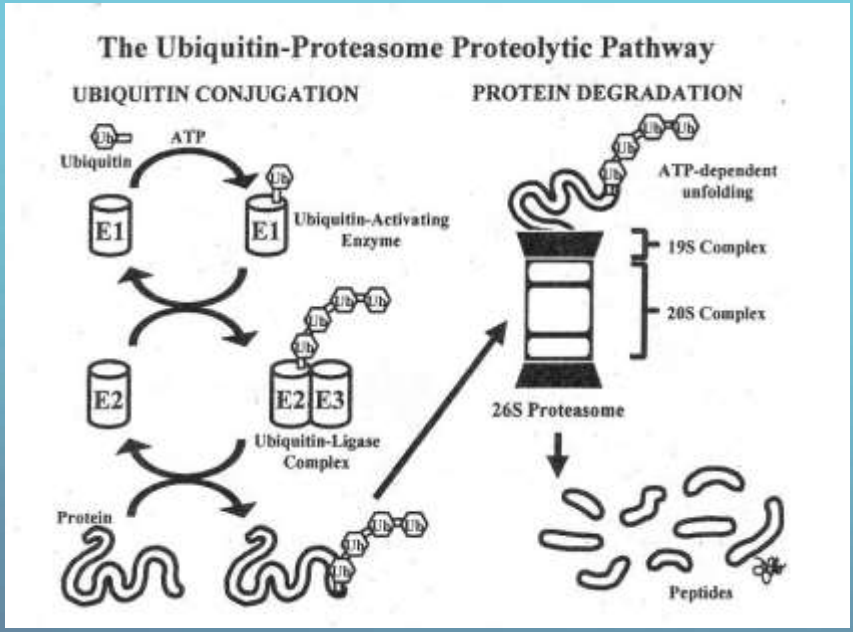
1. Act as N_2 sink, trapping amino acids (protein) to utilize for:
   - oxidation (Energy)
   - protein synthesis
     - Predominately enzymes for synthesis of purines & pyrimidines (building blocks) → cell proliferation

Amino Acid	**Function**
• GLUTAMINE	ATP production; nucleotide synthesis
• Ala, Thre, Ser, Gly	Glucose production
• Arginine	Polyamine & NO synthesis
• Tryptophan	Seratonin synthesis
• Methionine	Methyl gp transfer

2. Modify protein synthesis /degradation of normal cells

→ altered protein status of host

- Up-regulation of ubiquitin-proteosome pathway (UPP)



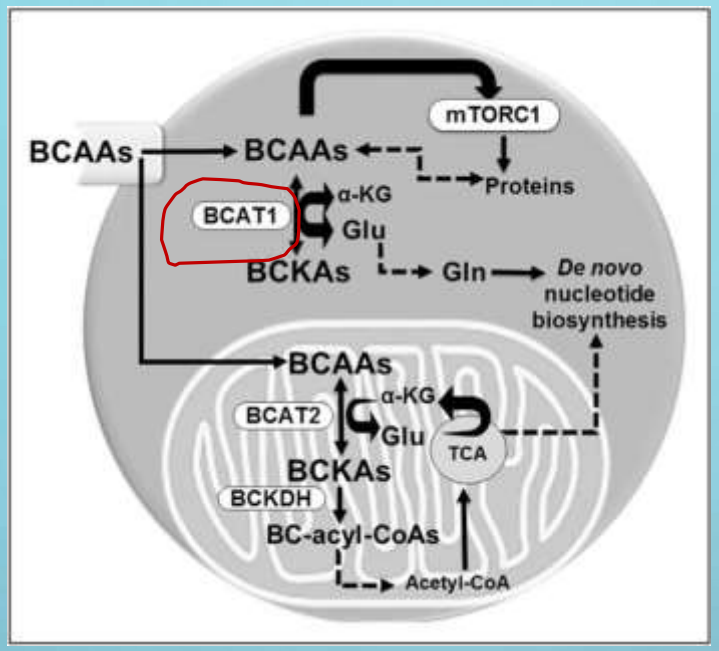
- UPP responsible for > 80% lean tissue wasting in hepatocellular cancer model. (Baracos et al.,1995; Lazarus et al., 1999)
- UPP pathway activated in muscle of gastric cancer patients (Bossola et al., 2003)
- Proteolysis-inducing factor (PIF) found in urine of weight loosing GI cancer patients.
  - PIF →IL-6, IL-8, CRP secretion

Overall (-) N_2 balance

PROTEIN METABOLISM

- The process of oncogenesis is dependent on amino acids, the building blocks for protein synthesis, and a source of energy and metabolites.
- Many cancer types overexpress enzymes that function to degrade amino acids, which not only provide cellular energy and metabolites for anabolic processes but also serve as mechanisms of immune evasion by cancer cells.
  - Example, tumor overexpression of indoleamine-2,3,dioxygenase and arginase depletes the tumor microenvironment of tryptophan and arginine, which is beneficial for tumor growth but also suppresses local cytotoxic T-cell proliferation
    - By using amino acid degrading enzymes as immunosuppressive factors, tumors increase their ability to survive.

- Evidence that the enzymes catalyzing the first step in BCAA degradation are overexpressed in many cancers

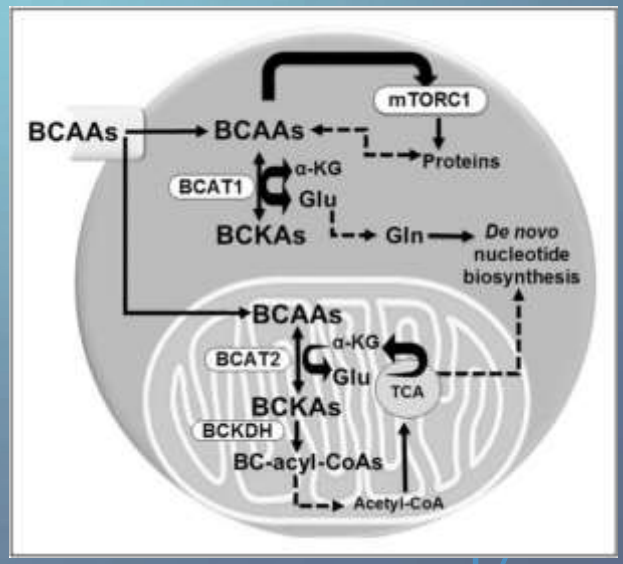


- Cytosolic [branched-chain aminotransferase 1 (BCAT1)] and mitochondrial BCAT2 convert BCAAs into their corresponding branched-chain α-keto acids by transferring the amino group onto α-ketoglutarate and thereby generating glutamate

KEY POINTS

- BCAAs are essential for cancer growth and can act as mammalian target of rapamycin complex 1 agonists, building blocks for protein synthesis, and/or as sources of nitrogen (for nonessential amino acid and nucleotide biosynthesis) and carbon (for the cycle of tricarboxylic acids cycle and energy production).
- Several recent reports have found expression of *BCAT1*, the enzyme involved in the first step of BCAA catabolism, to be a useful diagnostic and prognostic marker in several cancers.
- BCAA metabolism and BCAT1 activity play various functional roles in the progression of different cancer types, which appears to be determined by both the tissue-of-origin and the oncogenic mutations.
- New studies have identified several cancer-specific epigenetic and posttranscriptional mechanisms regulating *BCAT1*, which help to explain its dysregulated gene expression.

- Tumors preferentially uptake the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine.
- BCAAs can be used for protein synthesis or oxidized for energy purposes by tumors.
- BCAAs are essential amino acids; tumors must rely on dietary BCAA intake and their release from protein degradation



Branched-chain amino acid metabolism in cancer.
Ananieva and Wilkinson
Curr Opin Clin Nutr Metab Care. 2018 Jan; 21(1): 64–70.

From there to here … a re-cap

- Reprogramed Metabolism is hallmark of Cancer
- Started with the *Walburg Effect* focusing on accelerated glucose uptake lactic acid production in an anerobic environment. Glucose was identified as predominate energy source while the PPP supported macromolecule synthesis for protein and lipids to further support TC growth and development.

- Later identified several key gene mutations supporting the *Walburg Effect* and revealing additional mechanisms associated with metabolic reprograming in TC's
- Opens the door to appreciating that BOTH cell-signaling disorder, as well as, metabolic alterations pay key roles in Cancer.
- Likewise, understanding the interplay of reprogramed metabolism and TC growth opens up new possibilities for drug and nutritional interventions

THANK YOU

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