METABOLIC ALTERATIONS IN CANCER CELLS

METABOLIC CHARACTERISTICS OF CANCER CELLS

Increased GLYCOLYTIC ACTIVITY (Warburg Effect)

Increased production of LACTATE

Loss of PASTEUR'S EFFECT

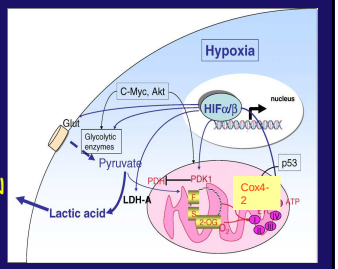
(Oxygen inhibition of glycolysis)

INCREASED CONSUMPTION of GLUTAMINE

INCREASED PROTEIN SYNTHESIS

DECREASED PROTEOLYSIS

DECREASED SYNTHESIS OF FATTY ACIDS (increased lipolysis from host adipose tissue)



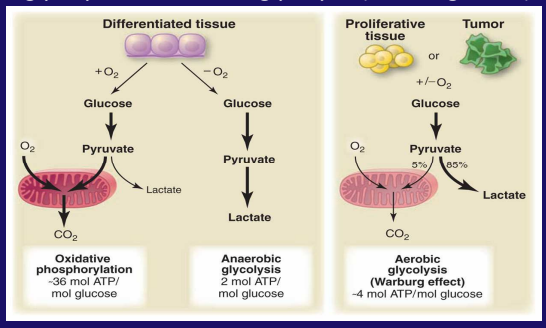
ENERGETIC METABOLISM IN TUMOURS

- WARBURG EFFECT
- In the 1920s, Otto Warburg observed that tumor cells consume a large amount of glucose, much
- more than normal cells, and convert most of it to lactic acid. This phenomenon, now known as the
- 'Warburg effect,' is the foundation of one of the earliest general concepts of cancer: that a
- fundamental disturbance of cellular metabolic activity is at the root of tumor formation and growth.

The Warburg Effect

- Pyruvate is an end-product of glycolysis, and is oxidized within the mitochondria.
- According to Warburg, cancer should be interpreted as a mitochondrial dysfunction.
- As a consequence, most cancer cells predominantly produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria like most normal cells. The latter process is aerobic. Tumour cells typically have glycolytic rates that are up to 200 times higher than those of their normal tissues of origin; this occurs even if oxygen is plentiful
- He postulated that this change in metabolism is the fundamental cause of cancer

Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect)



In proliferating cells, ~10% of the glucose is diverted into biosynthetic pathways upstream of pyruvate production. Cancer cells consume approx 200x glucose with respect to normal quiescent cells.

The Warburg effect describes the enhanced conversion of glucose to lactate by tumor cells, even in the presence of adequate oxygen.

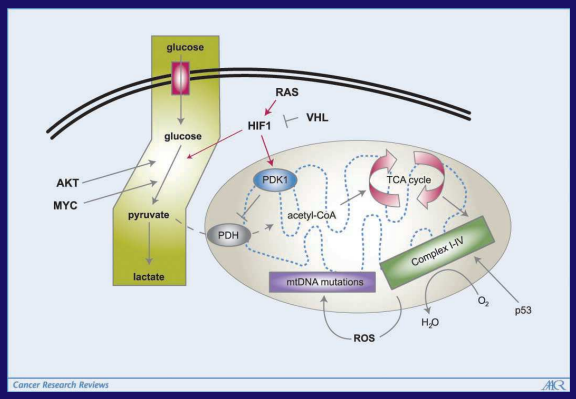
Activation of the AKT oncogene results in increased glucose transportation and stimulation of HK2 activity, which enhances glycolytic rates.

MYC oncogene activates glycolytic genes and mitochondrial biogenesis, which can result in ROS production. ROS could, in turn, cause mtDNA mutations that render mitochondria dysfunctional.

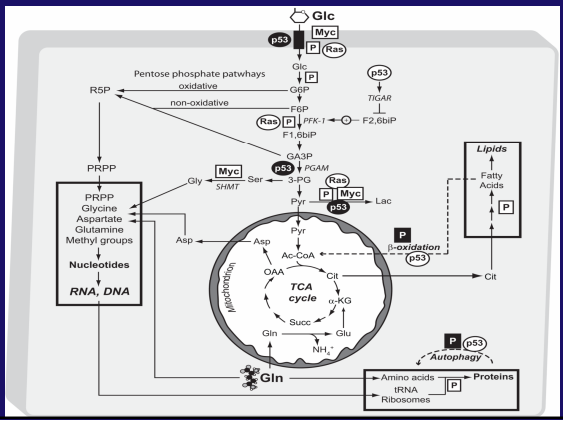
P53 stimulates respiration through activation of a component of the respiratory chain. HIF-1, increased by RAS, transactivates glycolytic genes as well as directly activates the PDK1 gene, which in turn inhibits PyruvateDH. (PDH catalyzes the conversion of pyruvate to acetyl-CoA, which enters the TCAcycle)

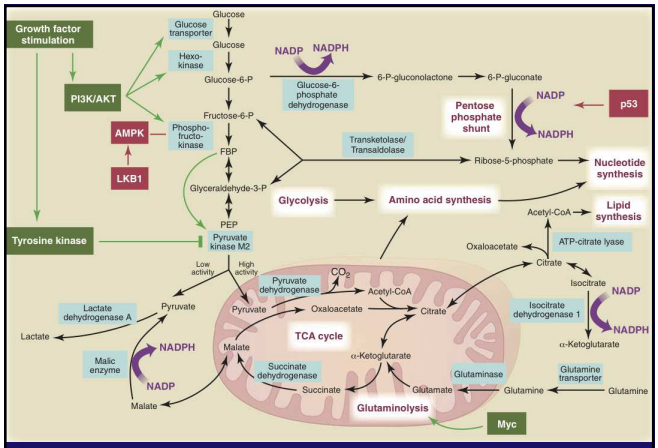
Inhibition of PDH by PDK1 attenuates mitochondrial function, resulting in the shunting of pyruvate to lactate.

CONTRIBUTORS TO THE WARBURG EFFECT



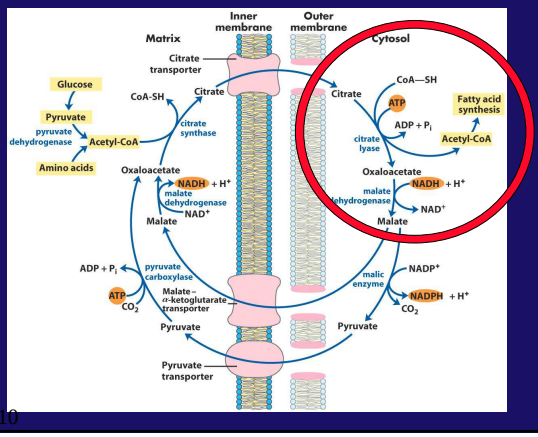
Tumor suppressors and proto-oncogenes regulate the metabolic pathways involved in tumor growth





Cancer cells utilizes GLUTAMINE as energetic source in TCA cycle

remember citrate lyase?



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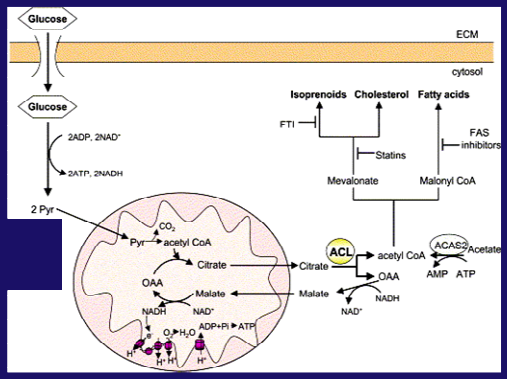
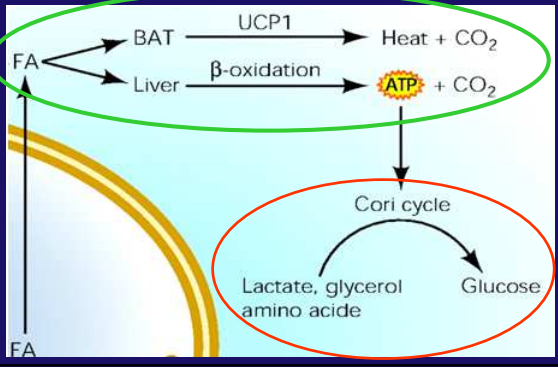
FA synthesis is reduced in glycolytic tumor cells



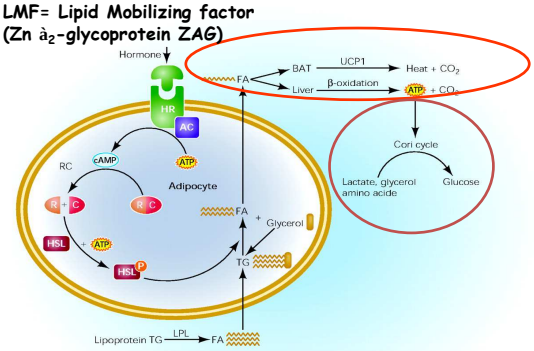
Hatzivassiliou et al. (2005) Cancer Cell 8, 1-11

ALTERED LIPID METABOLISM IN CANCER CELLS:

as a consequence lipolysis in adipose tissue of host is increased

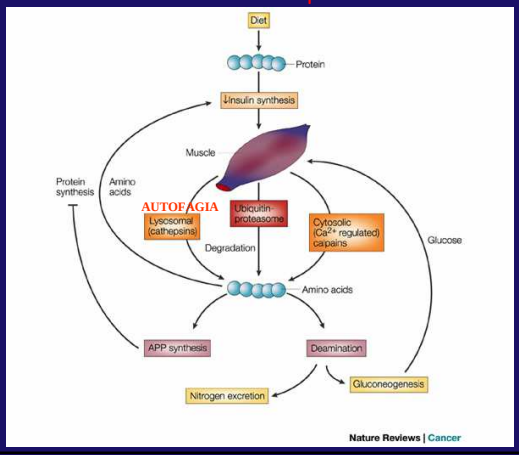


LMF= Lipid Mobilizing factor (Zn à$_2$-glycoprotein ZAG)

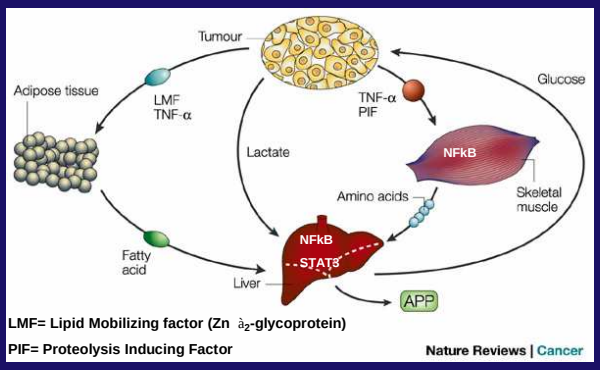


HR, Hormone receptor; AC, adenylate cyclase; FA, fatty acid; BAT, brown adipose tissue; RC, regulatory and catalytic subunits of cAMP-dependent protein kinase; HSL, hormone-sensitive lipase; P, phosphorylation; TG, triglycerides; LPL, lipoprotein lipase; UCP1, Uncoupling Protein1)

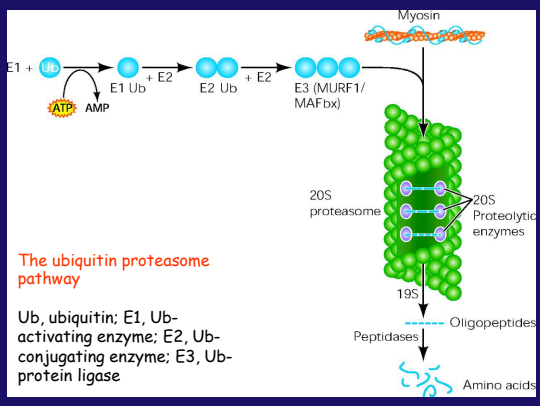
Alterazioni del metabolismo proteico nei tumori



Fattore PIF e proteolisi nei pazienti neoplastici



Pif è una glicoproteina di 24 KD che agisce a livello muscolare promuovendo la proteolisi dipendente dal attività del proteasoma, mentre a livello epatico stimola la sintesi di proteine di fase acuta e di IL-6 ed IL-8



The ubiquitin proteasome pathway

Ub, ubiquitin; E1, Ub-activating enzyme; E2, Ub-conjugating enzyme; E3, Ub-protein ligase