Corso di Biologia Cellulare del Cancro AA 2018-2019

LA RIPROGRAMMAZIONE DEL METABOLISMO NEL CANCRO

La riprogrammazione del metabolismo è un hallmark del cancro

Indipendenza dai segnali di crescita

Resistenza ai segnali inibitori della crescita

Riprogrammazione del metabolismo cellulare

Evasione dal sitema immunitario

Evasione dai meccanismi oncosoppressivi intrinseci

Potenziale replicativo illimitato

Mutazione e instabilità genomica

Infiammazione pro-tumorale (cell nonautonomous)

Angiogenesi (cell nonautonomous)

Invasione e metastasi (CSCs)

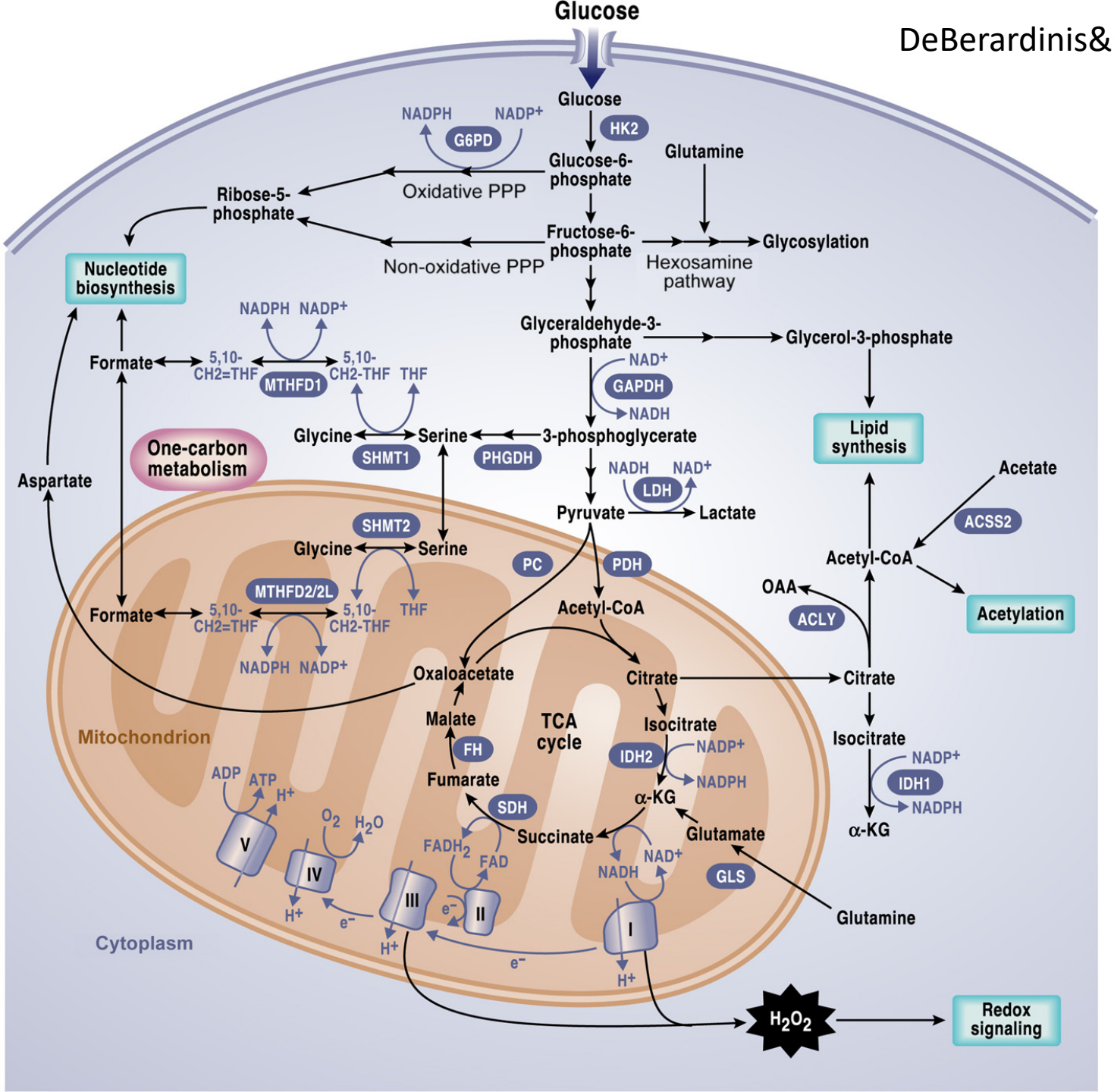
Il metabolismo cellulare

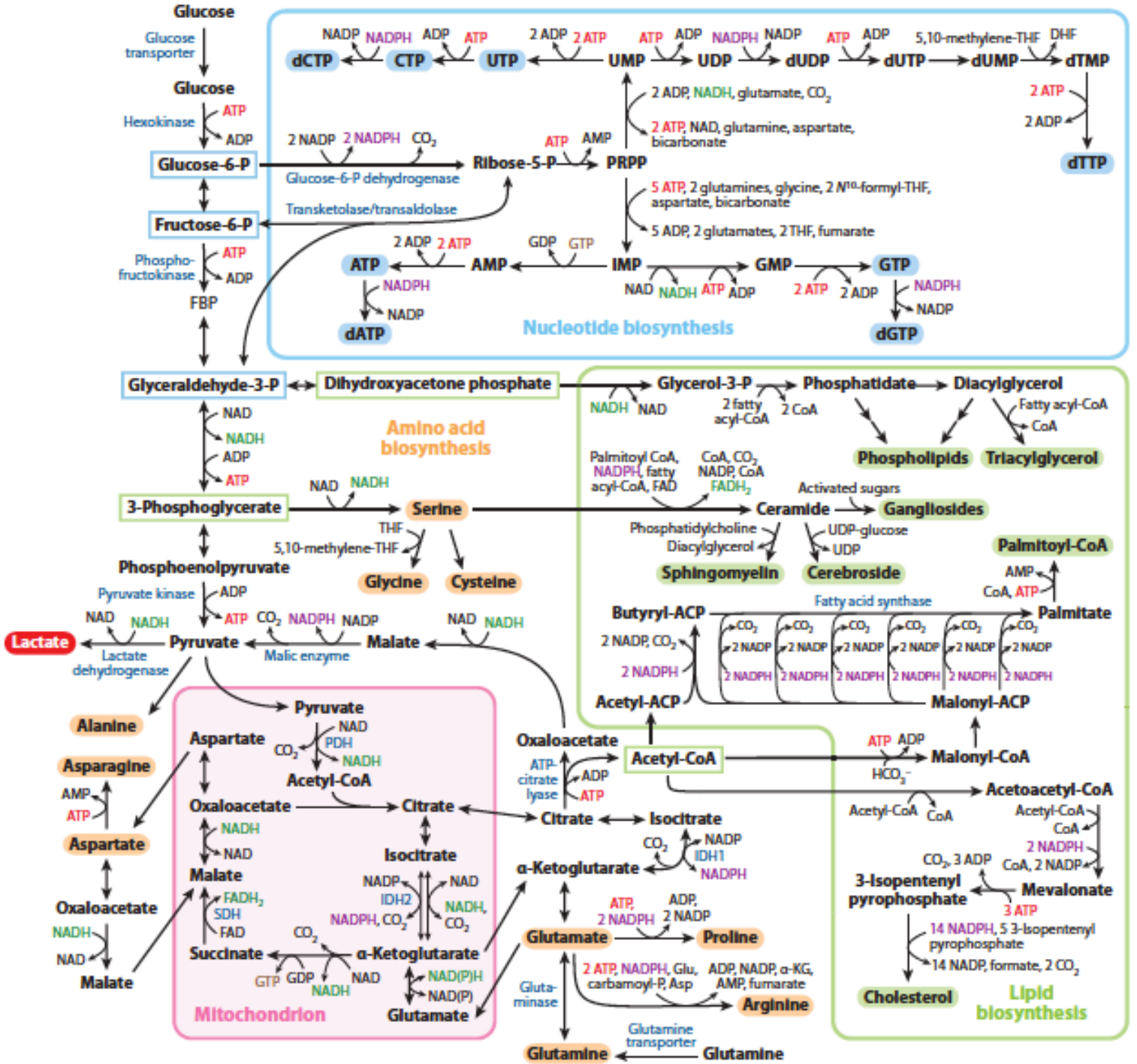
L'insieme delle reazioni chimiche intracellulari
che convertono i nutrienti in energia (ATP)
e biomolecole (proteine, acidi nucleici e lipidi)

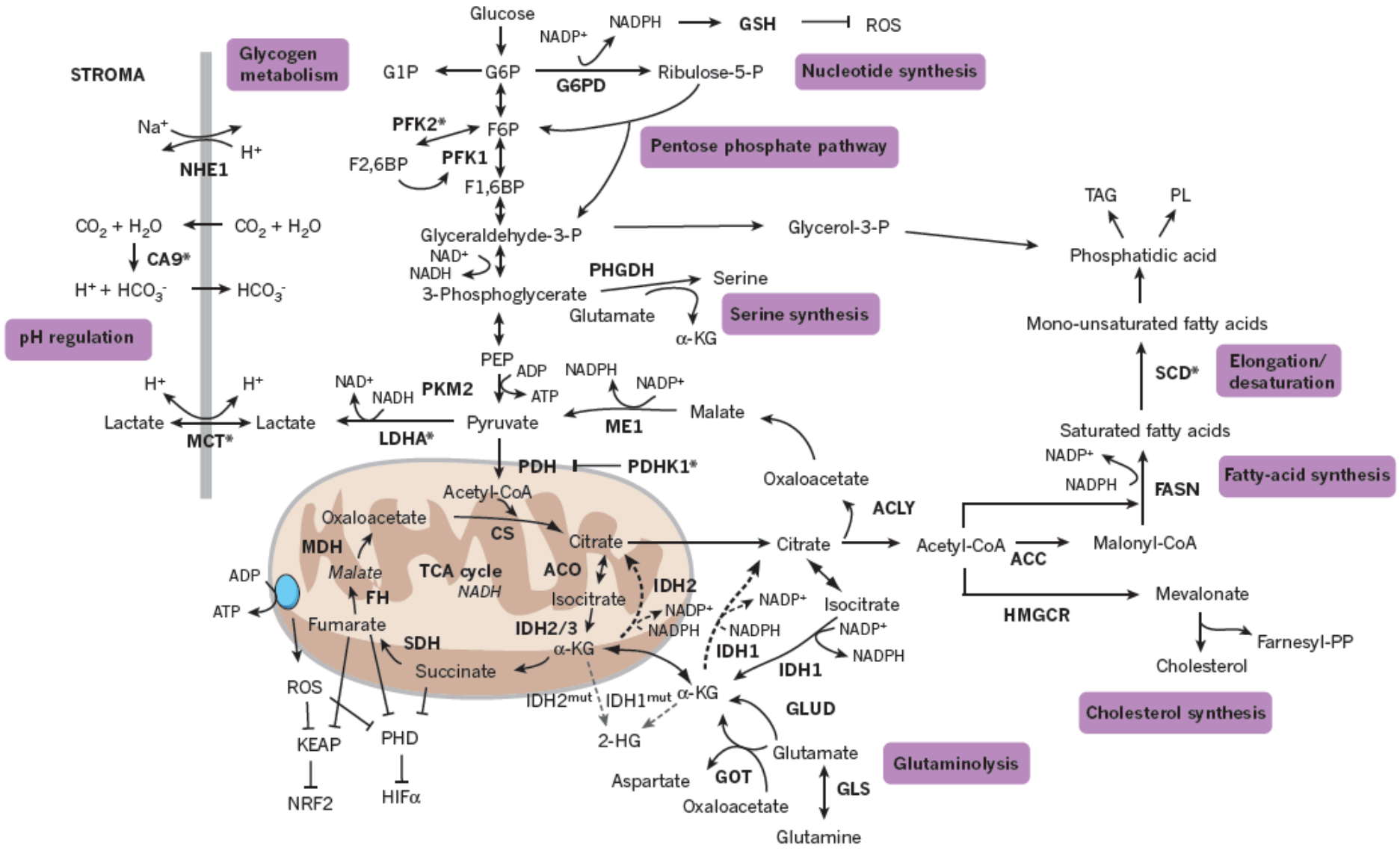
Attività bioenergetiche = generazione di ATP dai nutrienti

Attività anaboliche = generazione di biomassa dai nutrienti

DeBerardinis&Chandel Science 2016




Glucose
Glucose transporter
Glucose
Hexokinase
ATP
ADP
Glucose-6-P
Fructose-6-P
Phospho-fructokinase
FBP
Glyceraldehyde-3-P
Dihydroxyacetone phosphate
NAD
NADH
ADP
ATP
3-Phosphoglycerate
Phosphoenolpyruvate
Pyruvate kinase
Lactate
Pyruvate
Lactate dehydrogenase
Malic enzyme
Malate
Alanine
Asparagine
Aspartate
Oxaloacetate
Citrate
Isocitrate
α-Ketoglutarate
Succinate
Fumarate
SDH
FADH2
FAD
PDH
CO2
Acetyl-CoA
Mitochondrion
2 NADP
2 NADPH
CO2
Glucose-6-P dehydrogenase
Transketolase/transaldolase
Ribose-5-P
PRPP
AMP
GDP
GTP
IMP
GMP
dGTP
dATP
dTTP
dCTP
CTP
UTP
UMP
UDP
dUDP
dUTP
dUMP
dTMP
DHF
5,10-methylene-THF
2 ADP, NADH, glutamate, CO2
2 ATP, NAD, glutamine, aspartate, bicarbonate
5 ATP, 2 glutamines, glycine, 2 N10-formyl-THF, aspartate, bicarbonate
5 ADP, 2 glutamates, 2 THF, fumarate
Nucleotide biosynthesis
Amino acid biosynthesis
Serine
Glycine
Cysteine
THF
5,10-methylene-THF
Glycerol-3-P
Phosphatidate
Diacylglycerol
2 fatty acyl-CoA
2 CoA
Fatty acyl-CoA
CoA
Phospholipids
Triacylglycerol
Palmitoyl CoA, NADPH, fatty acyl-CoA, FAD
CoA, CO2, NADP, CoA
FADH2
Ceramide
Activated sugars
Gangliosides
Phosphatidylcholine
Diacylglycerol
Sphingomyelin
UDP-glucose
UDP
Cerebroside
Palmitoyl-CoA
AMP
CoA, ATP
Fatty acid synthase
Butyryl-ACP
Palmitate
2 NADP, CO2
2 NADPH
Acetyl-ACP
Malonyl-ACP
Oxaloacetate
ATP-citrate lyase
Acetyl-CoA
Malonyl-CoA
HCO3−
Acetoacetyl-CoA
Acetyl-CoA
CoA
2 NADPH
CO2, 3 ADP
3-Isopentenyl pyrophosphate
Mevalonate
3 ATP
14 NADPH, 5 3-Isopentenyl pyrophosphate
14 NADP, formate, 2 CO2
Cholesterol
Lipid biosynthesis
IDH1
IDH2
NADPH, CO2
NADP(H)
NAD(P)
ATP, 2 NADPH
ADP, 2 NADP
Glutamate
Proline
2 ATP, NADPH, Glu, carbamoyl-P, Asp
ADP, NADP, α-KG, AMP, fumarate
Arginine
Glutaminase
Glutamine
Glutamine transporter


Glucose
NADPH
GSH
ROS
NADP+
Glycogen metabolism
STROMA
G1P
G6P
G6PD
Ribulose-5-P
Nucleotide synthesis
Na+
H+
NHE1
PFK2*
F6P
Pentose phosphate pathway
F2,6BP
PFK1
F1,6BP
TAG
PL
CO2 + H2O
CO2 + H2O
CA9*
Glyceraldehyde-3-P
Glycerol-3-P
Phosphatidic acid
NAD+
NADH
PHGDH
Serine
H+ + HCO3-
HCO3-
3-Phosphoglycerate
Glutamate
α-KG
Serine synthesis
pH regulation
Mono-unsaturated fatty acids
PEP
ADP
ATP
NADPH
NADP+
SCD*
Elongation/ desaturation
H+
H+
NAD+
NADH
PKM2
Malate
Lactate
Lactate
Pyruvate
ME1
MCT*
LDHA*
Saturated fatty acids
NADP+
NADPH
FASN
Fatty-acid synthesis
PDH
PDHK1*
Oxaloacetate
Acetyl-CoA
ACLY
Oxaloacetate
CS
Citrate
Citrate
Acetyl-CoA
ACC
Malonyl-CoA
MDH
Malate
TCA cycle
NADH
ACO
IDH2
Isocitrate
NADP+
NADPH
NADP+
NADPH
Isocitrate
ADP
ATP
FH
Fumarate
IDH2/3
α-KG
IDH1
NADP+
NADPH
NADP+
NADPH
HMGCR
Mevalonate
SDH
Succinate
Farnesyl-PP
Cholesterol
ROS
IDH2mut
IDH1mut
α-KG
GLUD
Cholesterol synthesis
KEAP
PHD
2-HG
Glutamate
Glutaminolysis
Aspartate
GOT
GLS
NRF2
HIFα
Oxaloacetate
Glutamine

Il metabolismo del cancro è un "vecchio" ambito di ricerca

Otto Heinrich Warburg

Nobel prize 1931

che ha conosciuto una notevole espansione nell'ultimo decennio

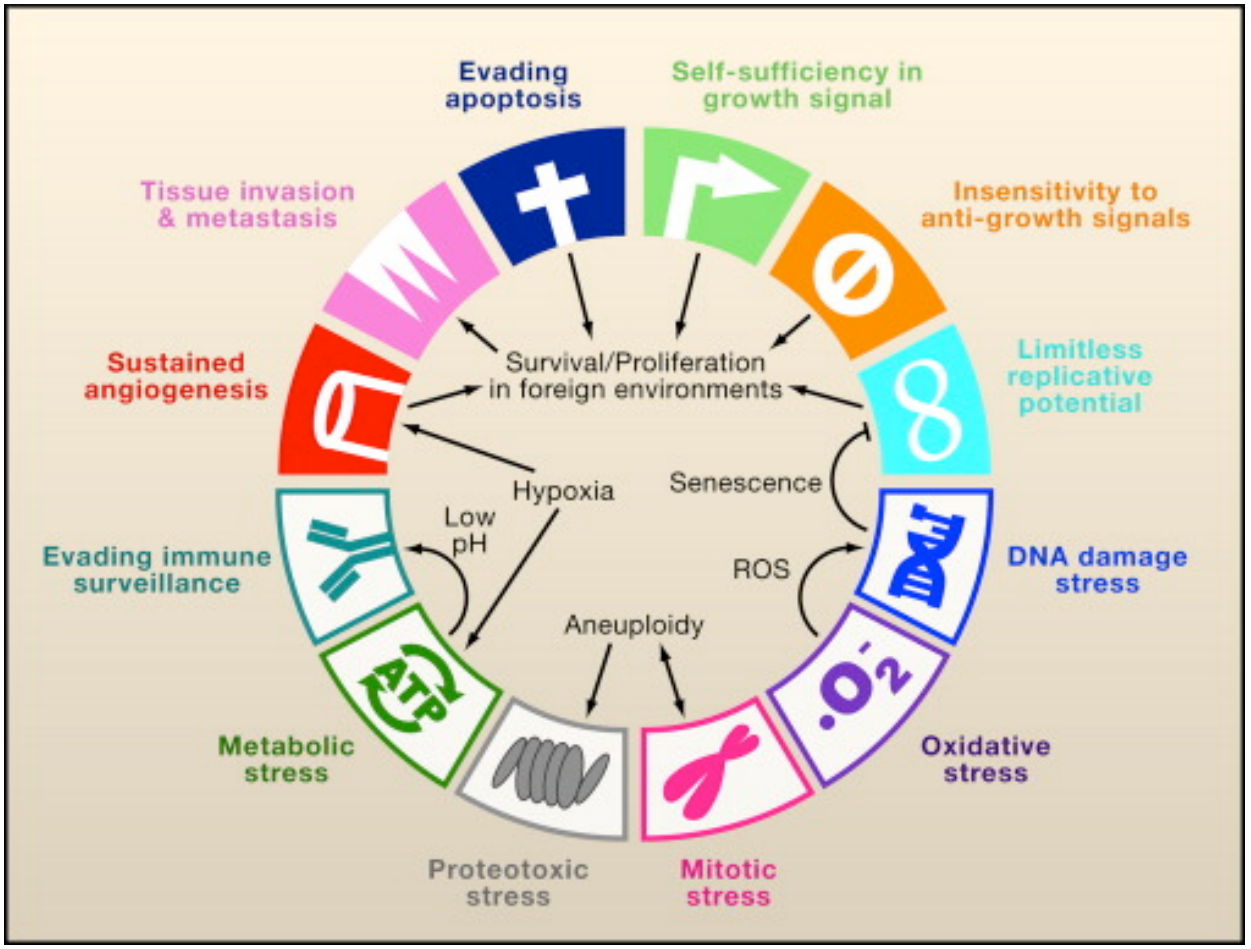
Domande:

1. In cosa consiste la riprogrammazione del metabolismo nel cancro?

2. Quali vantaggi selettivi conferisce alle cellule tumorali?

3. Come possono essere sfruttate queste conoscenze ai fini diagnostici e terapeutici?

La riprogrammazione del metabolismo è un hallmark del cancro



Le cellule tumorali necessitano di riprogrammare il metabolismo per far fronte alle richieste energetiche e biosintetiche associate al loro elevato tasso di proliferazione e per adattarsi al microambiente.

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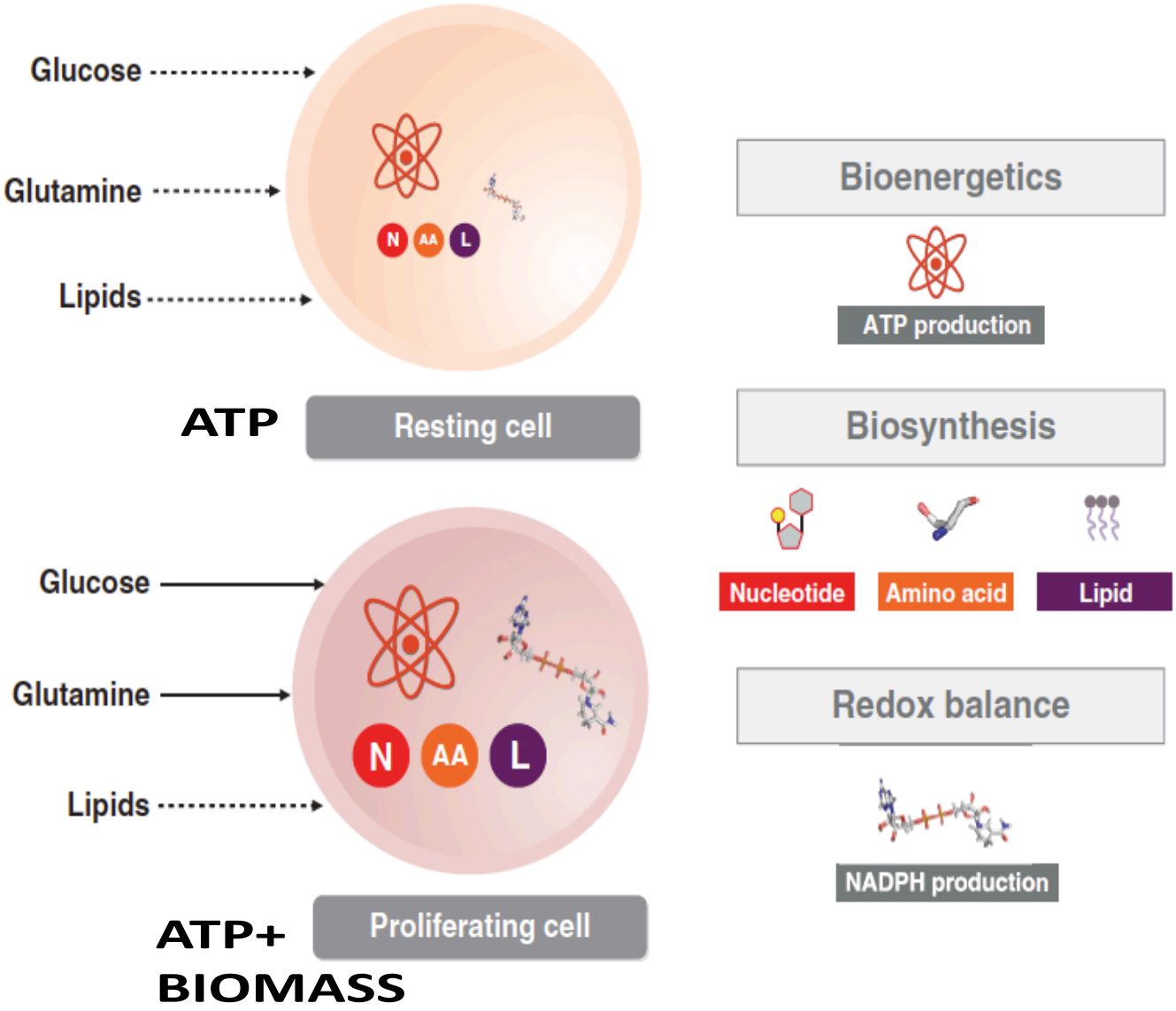
Attività metaboliche di cellule quiescenti e proliferanti



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a. Alterazioni dei processi bioenergetici (glicolisi, glutaminolisi, beta-ossidazione)
b. Aumento della biosintesi (nucleotidi, proteine, lipidi)
c. Alterazione del bilancio redox
d. Mutazioni di geni metabolici e oncometaboliti

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Supporta crescita e proliferazione aberrante

= meccanismi importanti fin dalle prime fasi in cui il tumore sopporta limitazioni di nutrienti

Supporta la sopravvivenza tumorale in condizioni di stress.

= meccanismi che possono assumere importanza durante evoluzione/cascata metastatica

Il programma bioenergetico delle cellule tumorali in 3 punti

Ilaria Persico - Finale Locale di Trieste - FameLab Italia 2017
https://www.youtube.com/watch?v=7aDu7zrbHmw

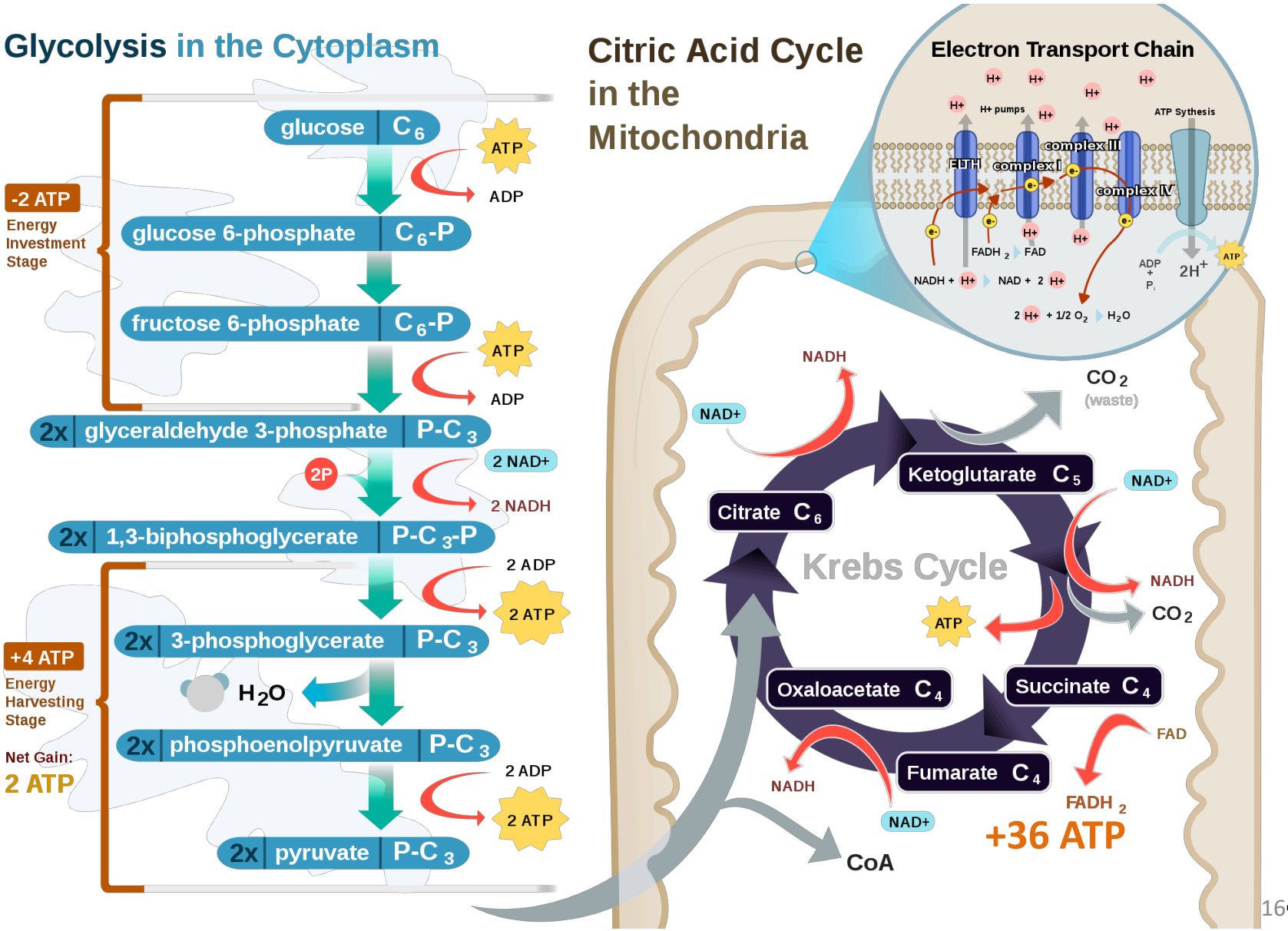
L'effetto Warburg

Warburg osservò che cellule tumorali consumano grandi quantità di glucosio e producono lattato anche in condizioni normossiche

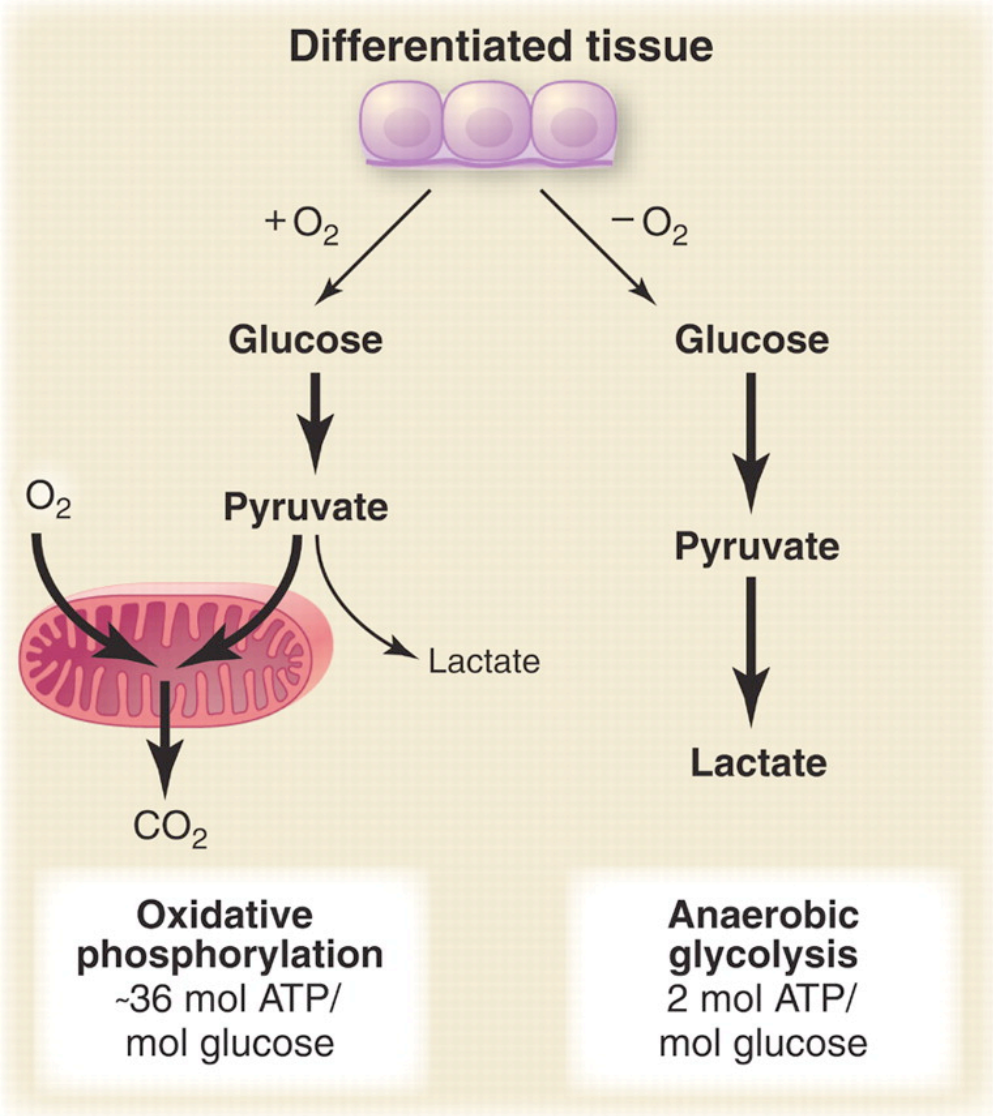
Otto Heinrich Warburg

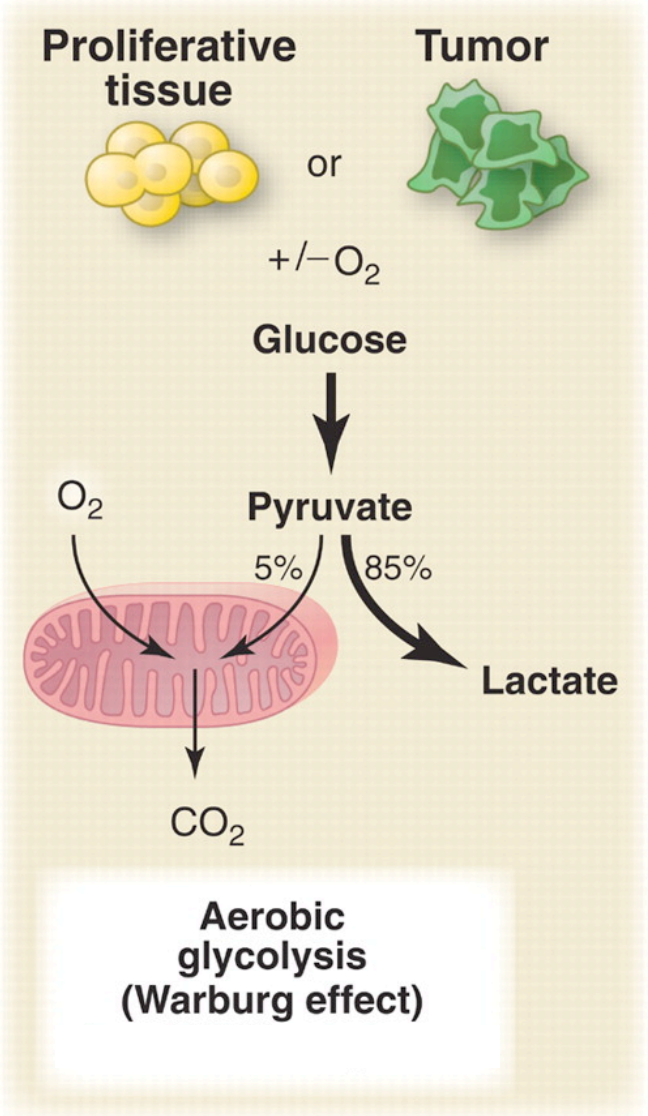
Nobel prize 1931

Generazione di ATP dal glucosio: glicolisi, TCA e OxPhos



L'effetto Warburg e la glicolisi aerobica



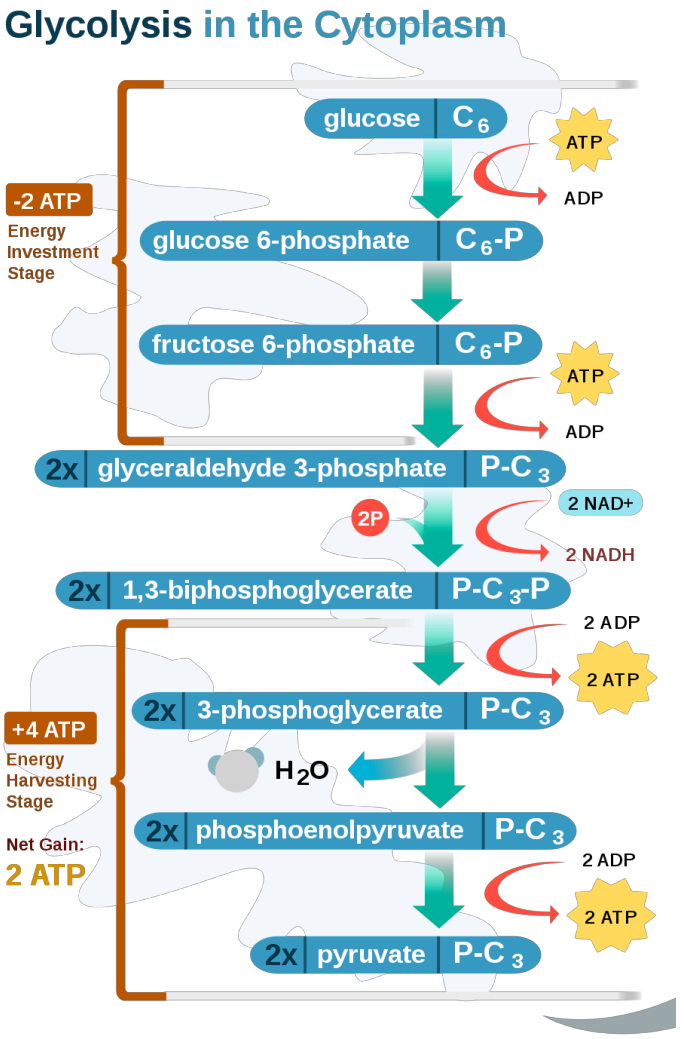


Organismi unicellulari hanno un metabolismo basato sulla fermentazione

By definition, **cancer** involves the inappropriate proliferation of cells, and the metabolic phenotype of cancer cells must represent a solution that regulates metabolic pathways to achieve a balance between **ATP production** and **biomass production.**

A major source of cellular energy and new cell mass is **glucose**. Glucose is metabolized via **glycolysis** to pyruvate, which can be oxidatively metabolized to CO2 in the tricarboxylic acid (TCA) cycle to generate large amounts of ATP through the process of oxidative phosphorylation. Pyruvate also can be reductively metabolized to organic acids or alcohols (e.g., lactate, acetate, or ethanol), a process known as fermentation.

Glucose fermentation does not require oxygen, but it is far less efficient than the TCA cycle coupled to oxidative phosphorylation in generating ATP. **Despite decreased efficiency in ATP production, many fast-growing unicellular organisms rely primarily on glucose fermentation during proliferation regardless of oxygen availability.**



Thus, cancer cells revert to a metabolic phenotype that is characteristic of rapidly dividing cells, which suggests that aerobic glycolysis **must provide advantages** during proliferation

La glicolisi è meno efficiente del TCA/Oxphos in termini energetici, ma può generare ATP più velocemente

Glycolysis is inefficient in terms of ATP production, as it generates only two ATPmolecules per molecule of glucose, whereas complete oxidation of one glucose molecule by oxidative phosphorylation can generate up to 36 ATP molecules. Despite its low efficiency in ATP yield per molecule of glucose, aerobic glycolysis can generate more ATP than oxidative phosphorylation by producing ATP at a **faster rate**. Cancer cells thus maintain ATP levels by simply “burning” more glucose.

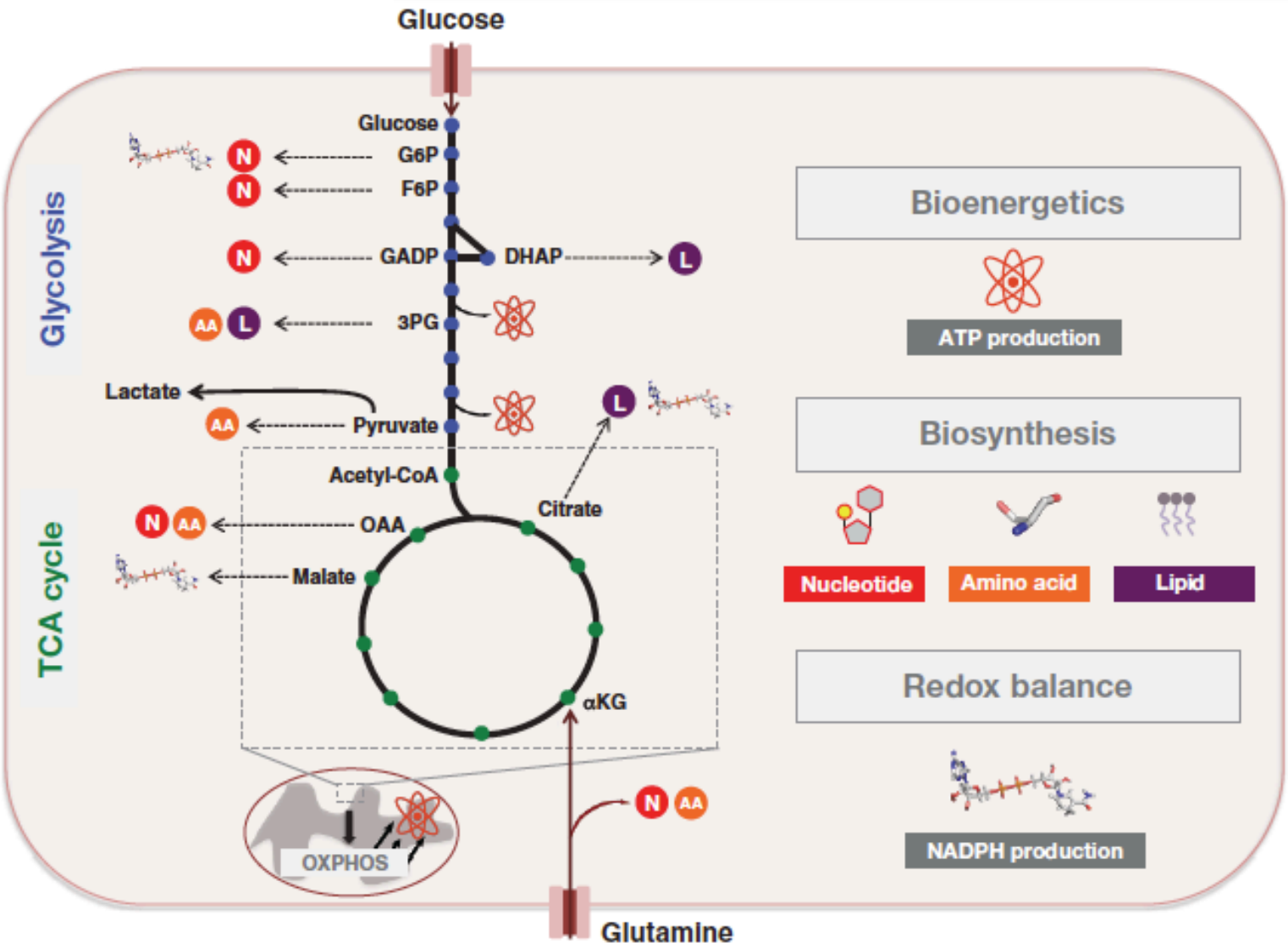
Le cellule tumorali utilizzano i mitocondri e l'OxPhos per produrre ATP, tuttavia la maggiorparte del glucosio è utilizzata nella glicolisi aerobia

The great majority of tumor cells have the capacity to produce energy through glucose oxidation (that is, the process by which glucose-derived carbons enter the TCA cycle and are oxidized to CO2, producing ATP through oxidative phosphorylation).

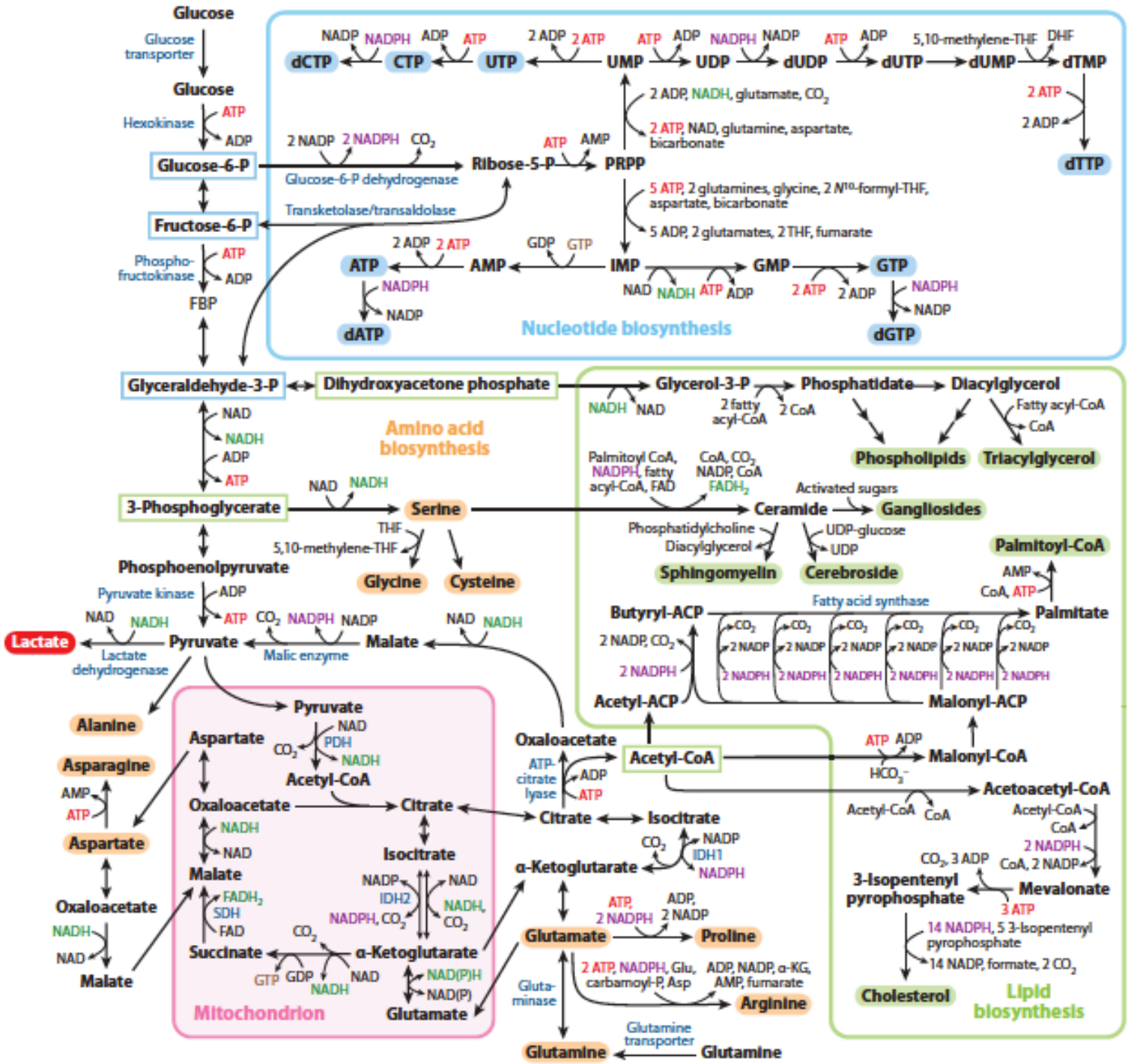
Furthermore, **limiting glycolytic ATP production by inhibiting the activity of pyruvate kinase fails to prevent tumorigenesis, suggesting that the major role of glycolysis is not to supply ATP**.

Moreover, **mitochondrial metabolism is necessary for cancer cell proliferation and tumorigenesis. Thus, despite their high glycolytic rates, most cancer cells generate the majority of ATP through mitochondrial function.**

Vantaggi della glicolisi aerobia



Permette l'assimilazione del glucosio in precursori biosintetici per la generazione di biomassa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2 NADPH
CO2
Fructose-6-P
Transketolase/transaldolase
Phospho-fructokinase
FBP
Ribose-5-P
PRPP
ATP
AMP
5 ATP, 2 glutamines, glycine, 2 N10-formyl-THF, aspartate, bicarbonate
5 ADP, 2 glutamates, 2 THF, fumarate
2 ADP, NADH, glutamate, CO2
2 ATP, NAD, glutamine, aspartate, bicarbonate
UMP
UDP
dUDP
dUTP
dUMP
dTMP
dTTP
5,10-methylene-THF
DHF
CTP
UTP
dCTP
ATP
AMP
GDP
GTP
IMP
GMP
GTP
dATP
dGTP
NADPH
NADP
NAD
NADH
Nucleotide biosynthesis
Glyceraldehyde-3-P
Dihydroxyacetone phosphate
Amino acid biosynthesis
3-Phosphoglycerate
Serine
Glycine
Cysteine
THF
5,10-methylene-THF
Phosphoenolpyruvate
Pyruvate kinase
Lactate
Pyruvate
Lactate dehydrogenase
Malic enzyme
Malate
Glycerol-3-P
Phosphatidate
Diacylglycerol
2 fatty acyl-CoA
2 CoA
Fatty acyl-CoA
CoA
Phospholipids
Triacylglycerol
Palmitoyl CoA, NADPH, fatty acyl-CoA, FAD
CoA, CO2 NADP, CoA FADH2
Ceramide
Activated sugars
Gangliosides
Phosphatidylcholine
Diacylglycerol
Sphingomyelin
UDP-glucose
UDP
Cerebroside
Palmitoyl-CoA
AMP
CoA, ATP
Fatty acid synthase
Butyryl-ACP
Palmitate
2 NADP, CO2
2 NADPH
Acetyl-ACP
Malonyl-ACP
Alanine
Asparagine
Aspartate
Oxaloacetate
Malate
Pyruvate
PDH
Acetyl-CoA
Citrate
Isocitrate
α-Ketoglutarate
Succinate
IDH2
IDH1
SDH
FADH2
FAD
Mitochondrion
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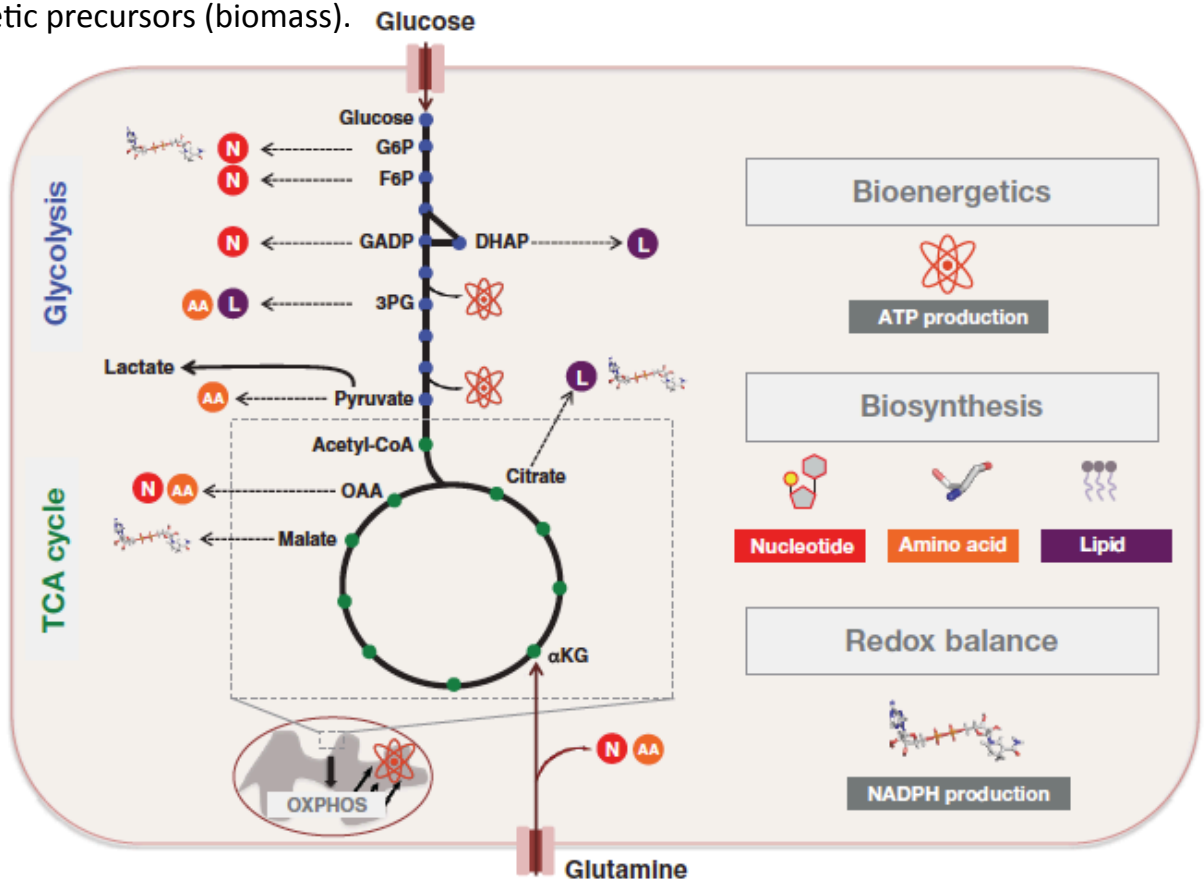
3 ATP
3-Isopentenyl pyrophosphate
CO2, 3 ADP
14 NADPH, 5 3-Isopentenyl pyrophosphate
14 NADP, formate, 2 CO2
Cholesterol
Lipid biosynthesis
Glutamate
Proline
Arginine
2 ATP, NADPH, Glu, carbamoyl-P, Asp
ADP, NADP, α-KG, AMP, fumarate
Glutaminase
Glutamine
Glutamine transporter

Vantaggi della glicolisi aerobia

ATP is necessary to maintain homeostasis and cell survival; loss of intracellular ATP results in cell necrosis or apoptosis. Additional ATP is necessary for cell proliferation: macromolecular synthesis of DNA, RNA, proteins and many biosynthetic precursors (biomass).



ATP generated from aerobic glycolysis is undoubtedly important for cellular function and plays an important role in biosynthesis for at least some proliferating cells. However, the importance of aerobic glycolysis for proliferating cells likely extends beyond rapid ATP production **to allow nutrient assimilation into biosynthetic precursors and facilitate biomass accumulation**.

A MAJOR FUNCTION OF AEROBIC GLYCOLYSIS IS TO SUPPORT MACROMOLECULAR SYNTHESIS

Generating new daughter cells requires the replication of all cellular contents, including DNA, RNA, proteins, and lipids. **Glucose** can provide the precursors for the chemical constituents (e.g., nucleotides, amino acids, and lipids) that are used to build macromolecules essential for cell division. Therefore, a main function of upregulated glycolysis in proliferating cells may be to maintain the levels of glycolytic intermediates needed to support biosynthesis. Understanding the role of glycolysis during proliferation requires a thorough analysis of central carbon metabolism and its myriad connections to macromolecular biosynthesis:

- Through glycolysis, glucose is a significant carbon source for purine and pyrimidine nucleotides via production of **RIBOSE-5-P** (Pentose Phosphate Pathway).

- In addition to supporting nucleotide biosynthesis, glycolysis is also a source of carbon for lipid precursors for membranes. A large proportion of the cell membrane carbon is derived from **acetyl-CoA** or from glycolysis intermediates.

- The high requirement of protein content needed for proliferation imposes a large amino acid requirement on proliferating cells. Amino acid availability provides the dominant input for the cell growth signal transduction machinery. The majority of AA derive from **glycolysis** and **glutaminolysis**.

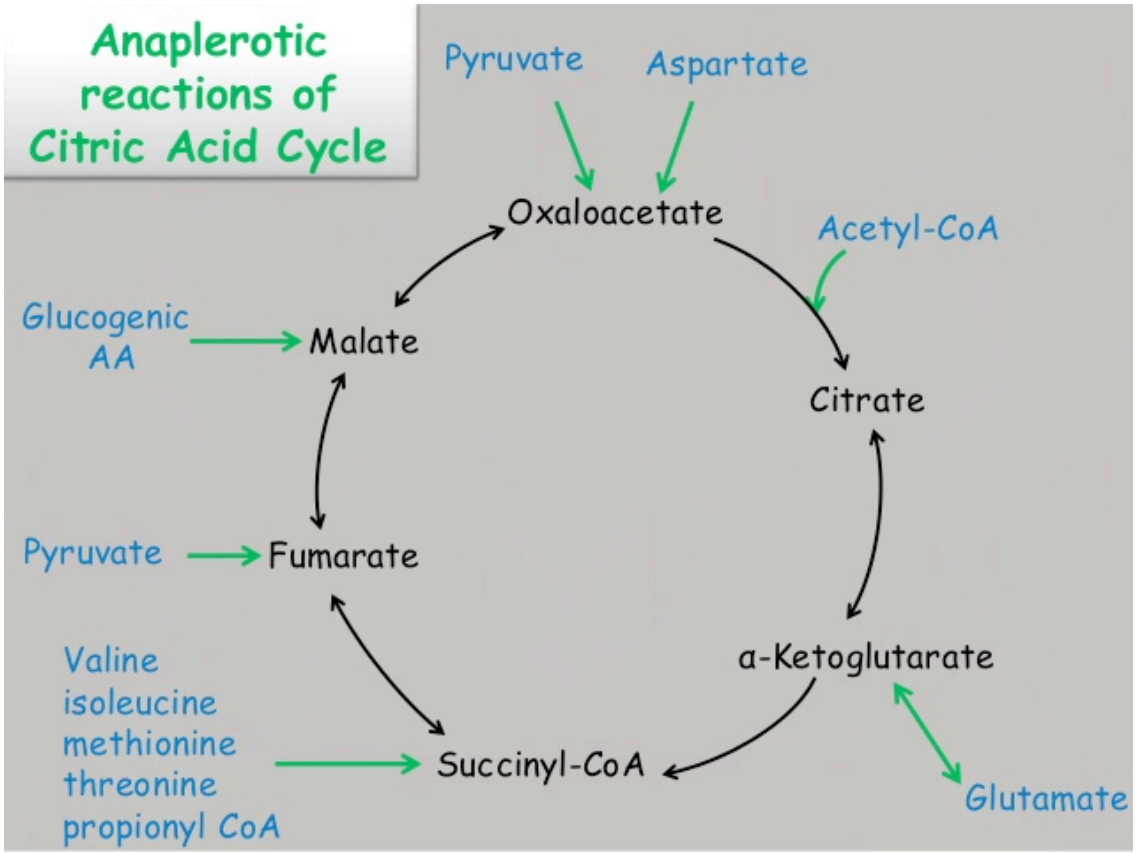
For instance, synthesis of palmitate, a major constituent of cellular membranes, requires 7 molecules of ATP, 16 carbons from 8 molecules of acetyl-CoA (coenzyme A), and 28 electrons from 14 molecules of NADPH [nicotinamide adenine dinucleotide phosphate (NADP+), reduced].
Likewise, synthesis of amino acids and nucleotides also consumes more equivalents of carbon and NADPH than of ATP.

A glucose molecule can generate up to 36 ATPs, or 30 ATPs and 2 NADPHs [if diverted into the pentose phosphate shunt], or provide 6 carbons for macromolecular synthesis (Vander Heiden et al. Science 2009).

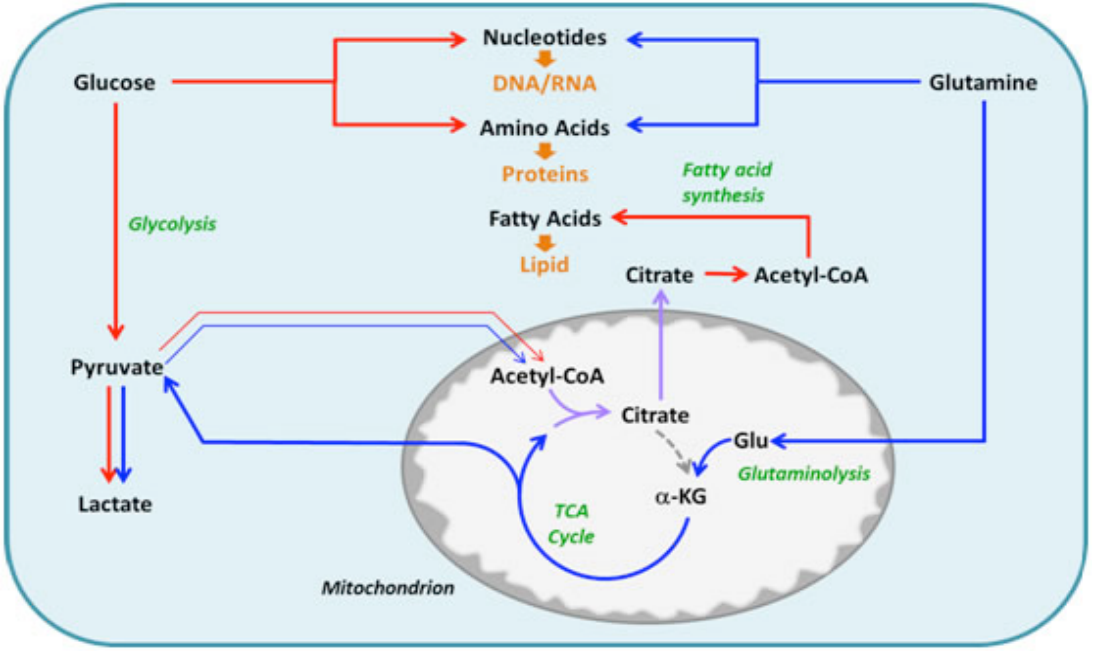
Vie anaplerotiche

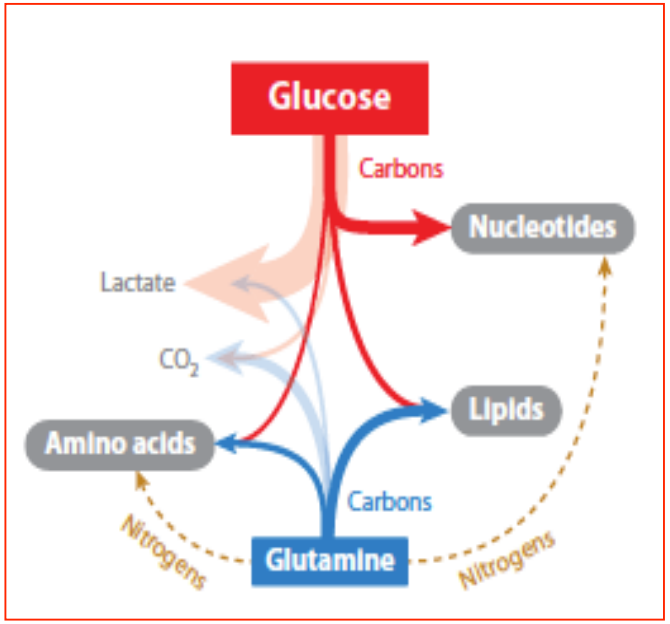
Reazioni che generano intermedi del TCA

1. GLUTAMINOLISI (produce a-ketoglutarato)
2. Carbossilazione del piruvato (produce ossalacetato)
3. Ossidazione degli AA isoleucina e valina



Glutamine addiction

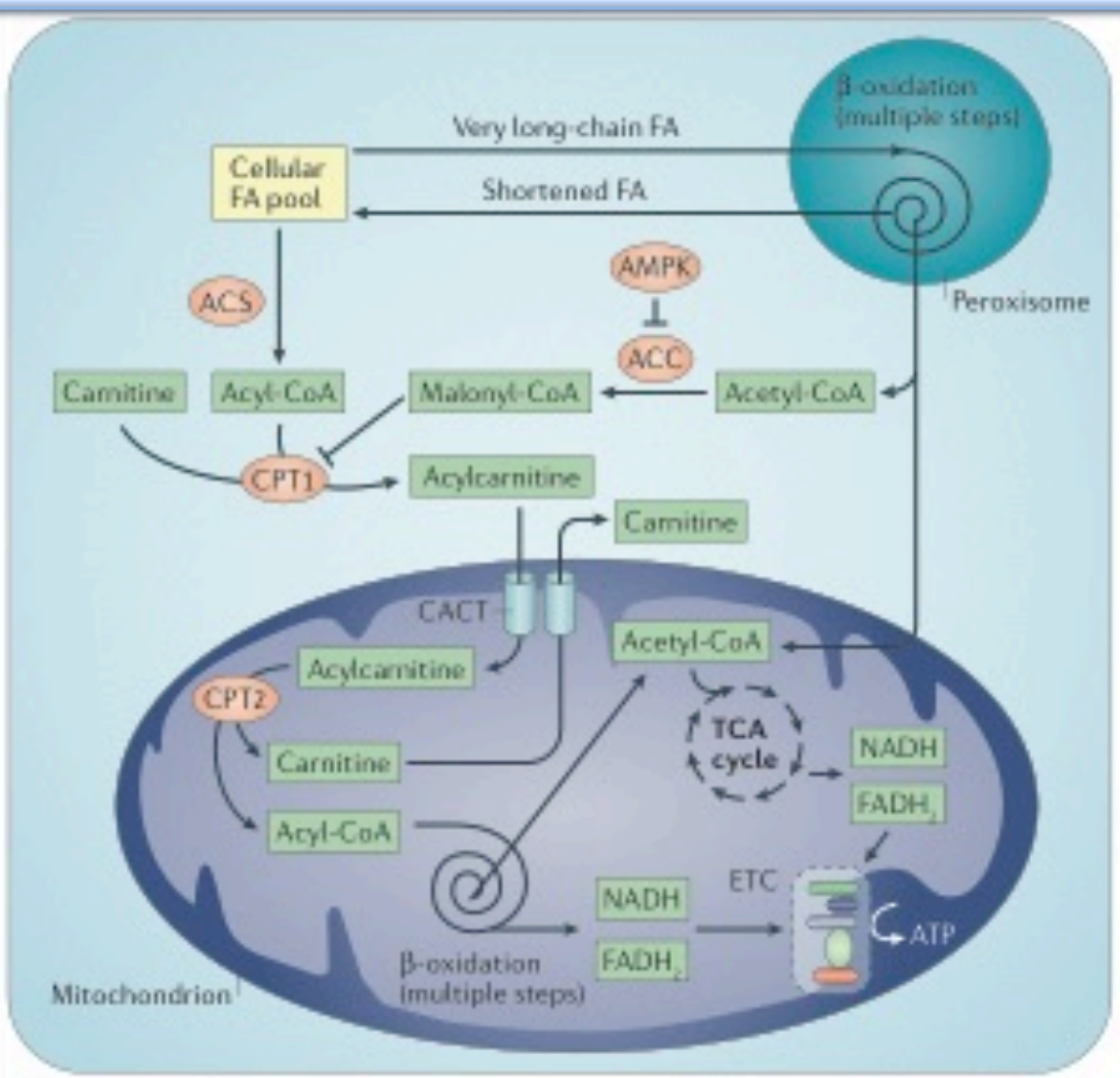




It has long been known that cell culture medium must be supplemented with high concentrations of glutamine to support robust cell proliferation. However, it has recently been shown that transformation stimulates glutaminolysis and that many tumour cells are critically dependent on this amino acid.
In proliferating cells, glutamine carbons are converted to **amino acids, TCA cycle intermediates, lipids, lactate, and CO2.**
Glutamine is the most abundant AA in human serum. After glutamine enters the cell, glutaminase enzymes convert it to glutamate, which has several fates. Glutamate can be converted directly into GSH by the enzyme glutathione cysteine ligase (GCl). reduced GSH is one of the most abundant **antioxidants** found in mammalian cells and is vital to controlling the redox state of all subcellular compartments. Glutamate can also be converted to αKG and **enter the TCA cycle**. This process of anapleurosis supplies the carbon input required for the TCA cycle to function as a biosynthetic 'hub' and permits the production of other amino acids and fatty acids.

La beta-ossidazione degli acidi grassi produce

Acetil-CoA, NADH e FADH2



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   a. Valutazione diagnostica mediante imaging non invasivo dei tumori

   b. Valutazione prognostica: prevedere l'evoluzione tumorale (metabolic signatures)

   c. Bloccare la crescita e la progressione tumorale interferendo con processi biochimici essenziali (non-oncogene addiction)

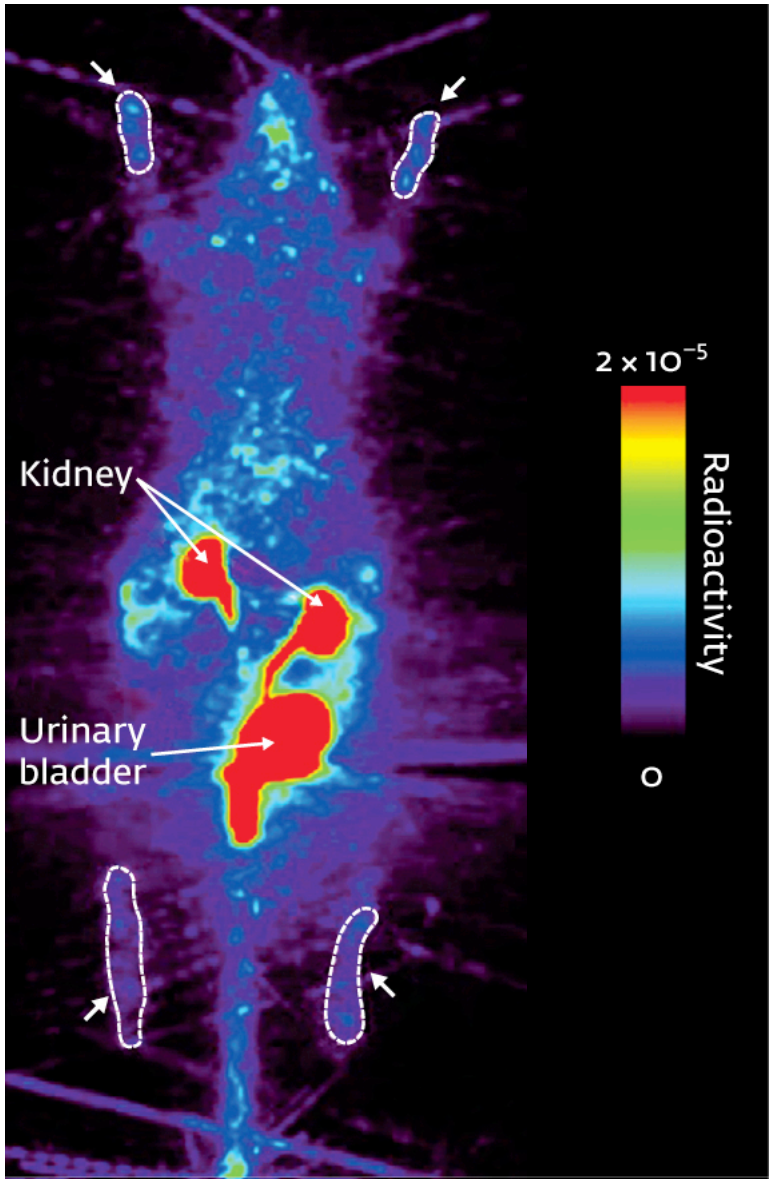
L'effetto Warburg

Warburg osservò che cellule tumorali consumano grandi quantità di glucosio e producono lattato anche in condizioni normossiche

Otto Heinrich Warburg

Nobel prize 1931

Applicazione diagnostica: PET fluorodeoxyglucose positron emission tomography



Diminuzione dell'uptake di glucosio in risposta a terapia

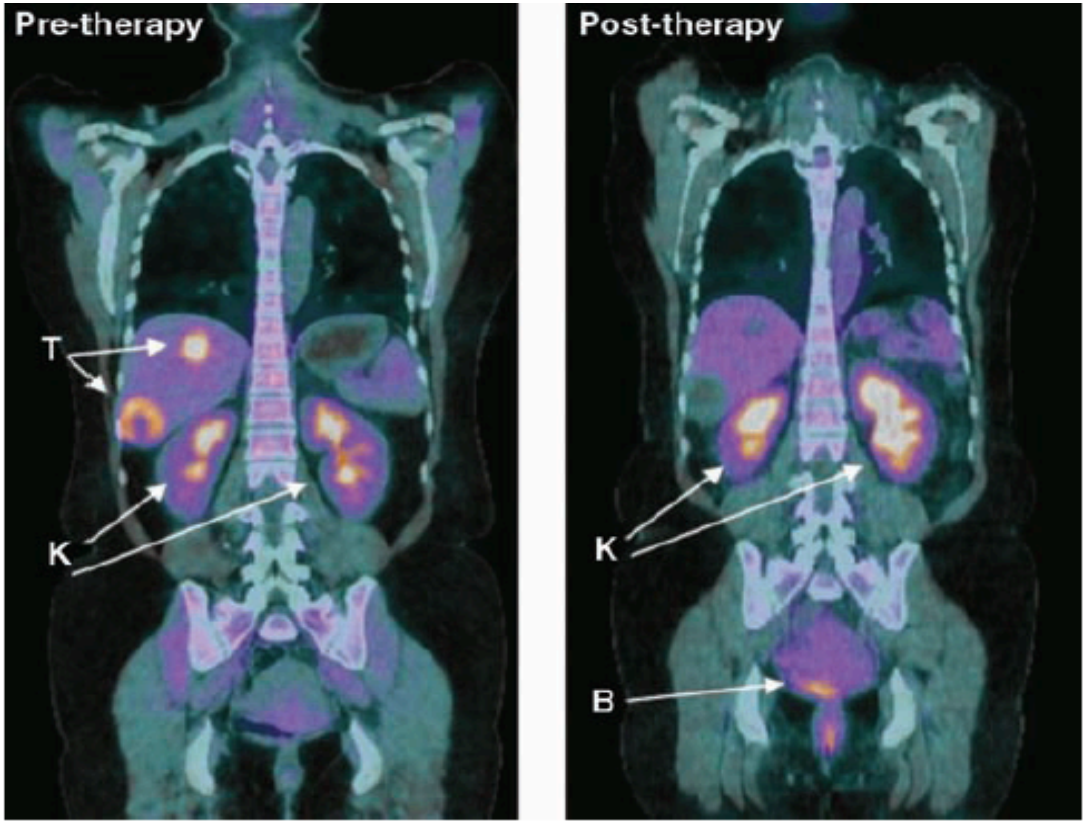
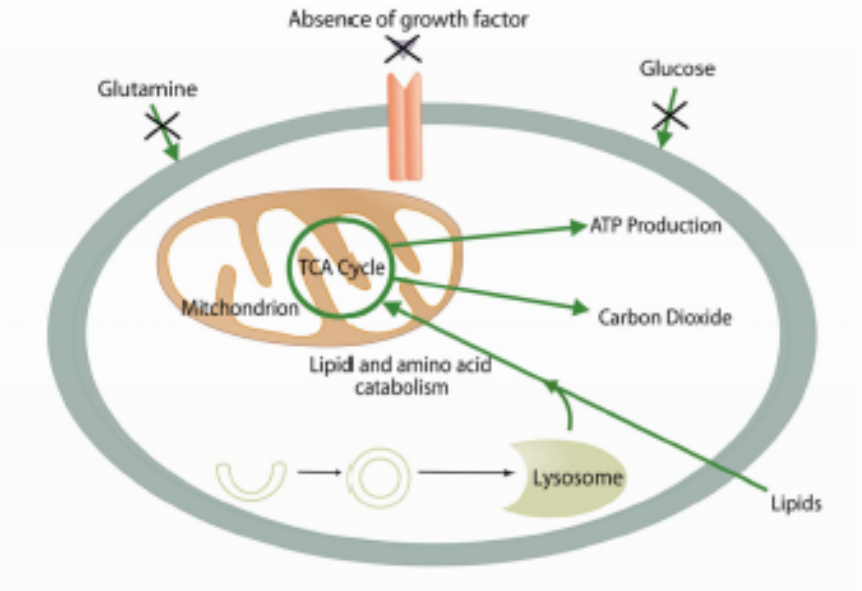
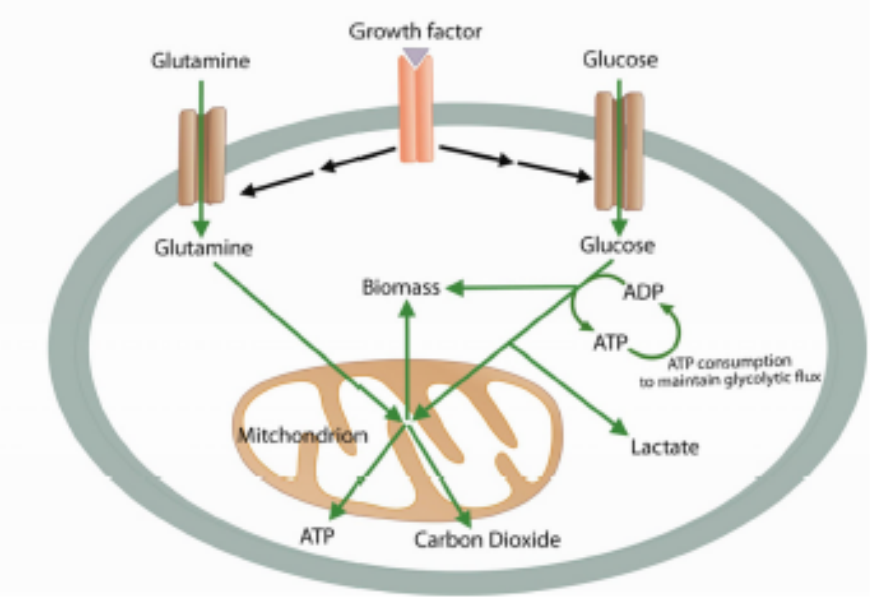


Fig. 4. Decreased metabolism of glucose by tumors, visualized by PET with the glucose analog FDG, predicts response to anticancer therapy. Shown are fused coronal images of FDG-PET and computerized tomography (CT) obtained on a hybrid PET/CT scanner after the infusion of FDG in a patient with a form of malignant sarcoma (gastrointestinal stromal tumor) before and after therapy with a tyrosine kinase inhibitor (sunitinib). The tumor (T) is readily visualized by FDG-PET/CT before therapy (**left**). After 4 weeks of therapy (**right**), the tumor shows no uptake of FDG despite persistent abnormalities on CT. Excess FDG is excreted in the urine, and therefore the kidneys (K) and bladder (B) are also visualized as labeled. [Image courtesy of A. D. Van den Abbeele, Dana-Farber Cancer Institute, Boston]

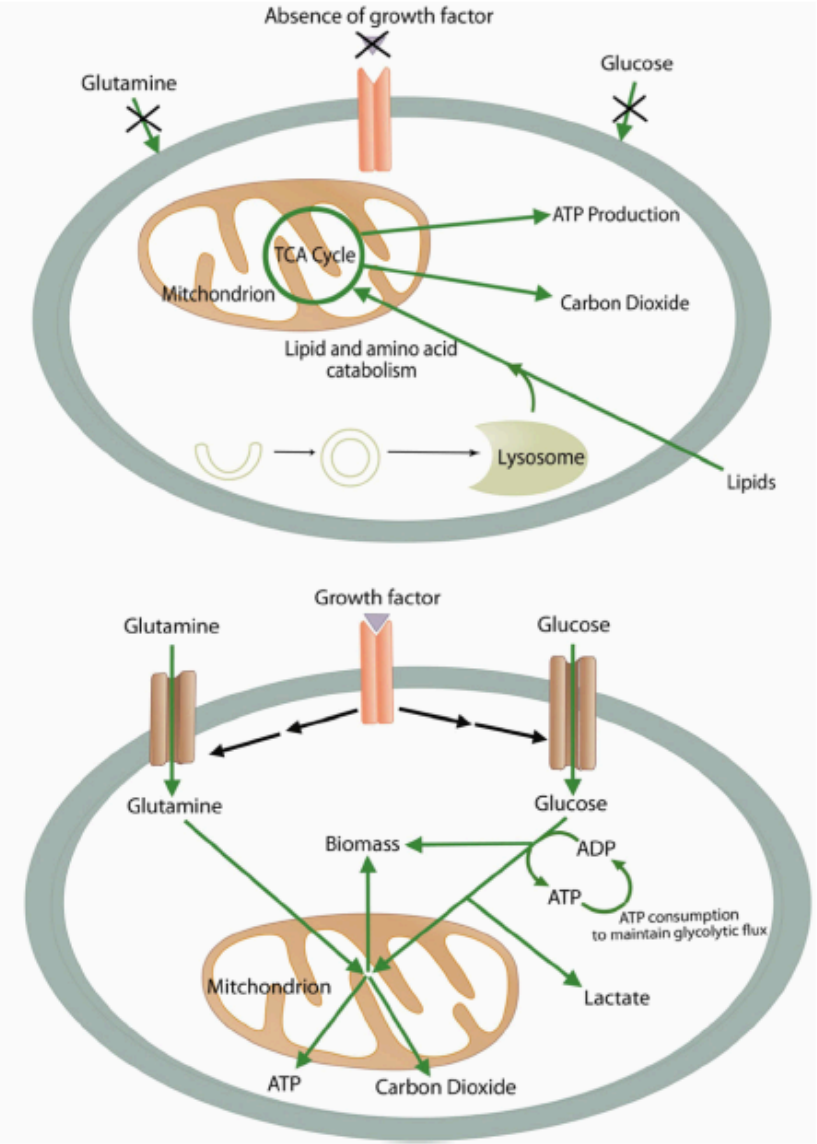
Coordinazione tra growth signaling e uptake di nutrienti





In multicellular organisms, most cells are exposed to a constant supply of nutrients. Survival of the organism requires control systems that prevent aberrant individual cell proliferation when nutrient availability exceeds the levels needed to support cell division. Uncontrolled proliferation is prevented because **mammalian cells do not normally take up nutrients from their environment unless stimulated to do so by growth factors**. Cancer cells overcome this growth factor dependence by acquiring genetic mutations that functionally alter receptor-initiated signaling pathways. In cancer some of these pathways (PI3K, EGFR, Ras…) are constitutively activate

Coordinazione tra growth signaling e metabolismo



Metabolism in Quiescent versus Proliferating Cells: Both Use Mitochondria

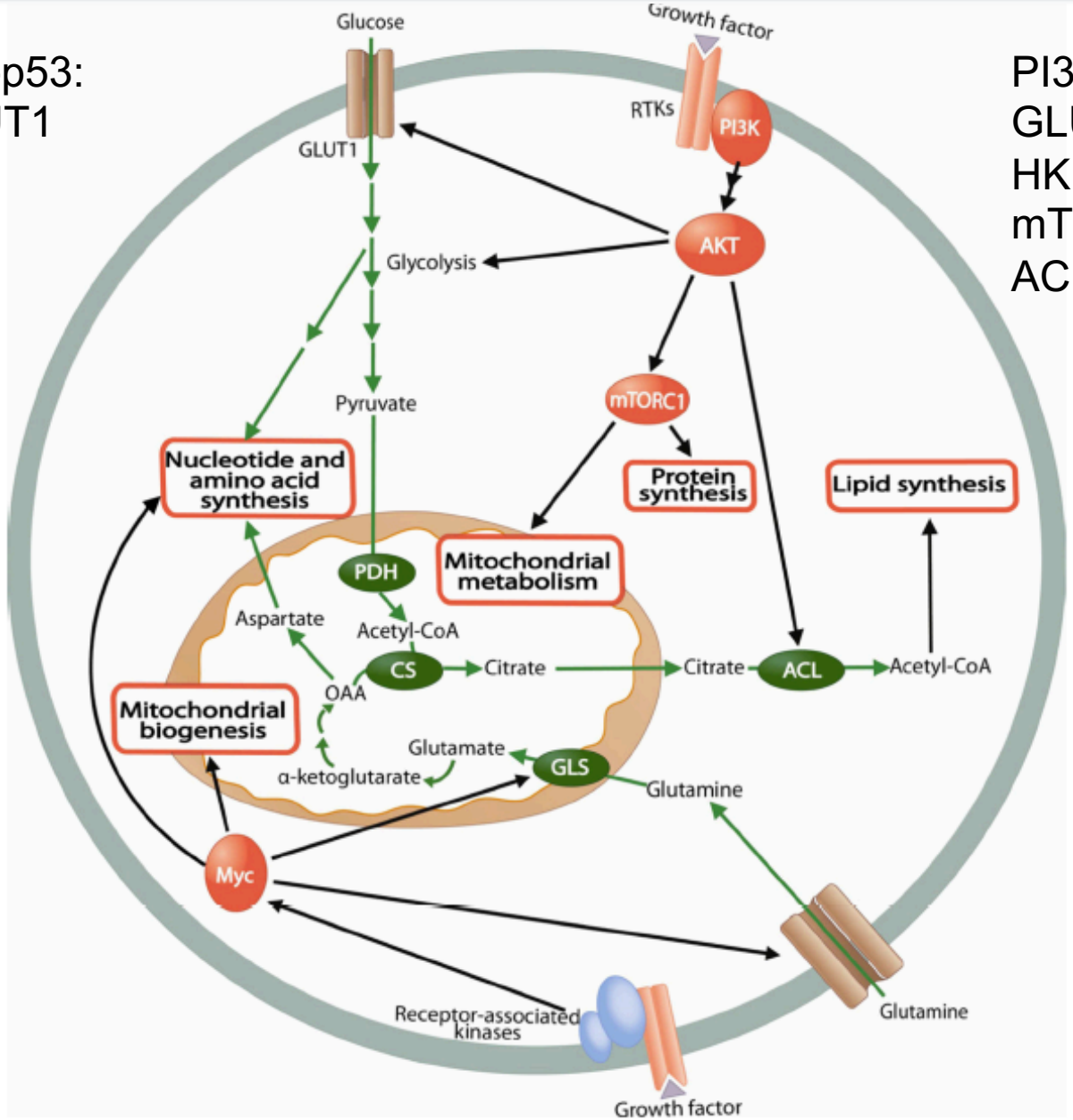
(A) In the absence of instructional growth factor signaling, cells in multicellular organisms lack the ability to take up sufficient nutrients to maintain themselves. Neglected cells will undergo autophagy and catabolize amino acids and lipids through the TCA cycle, assuming sufficient oxygen is available. This oxidative metabolism maximizes ATP production.

(B) Cells that receive instructional growth factor signaling are directed to increase their uptake of nutrients, most notably glucose and glutamine. The increased nutrient uptake can then support the anabolic requirements of cell growth: mainly lipid, protein, and nucleotide synthesis (biomass). Excess carbon is secreted as lactate. Proliferating cells may also use strategies to decrease their ATP production while increasing their ATP consumption. These strategies maintain the ADP:ATP ratio necessary to sustain glycolytic flux. Green arrows represent metabolic pathways, while black arrows represent signaling.

GF signaling induce direttaemnte alterazioni del metabolismo

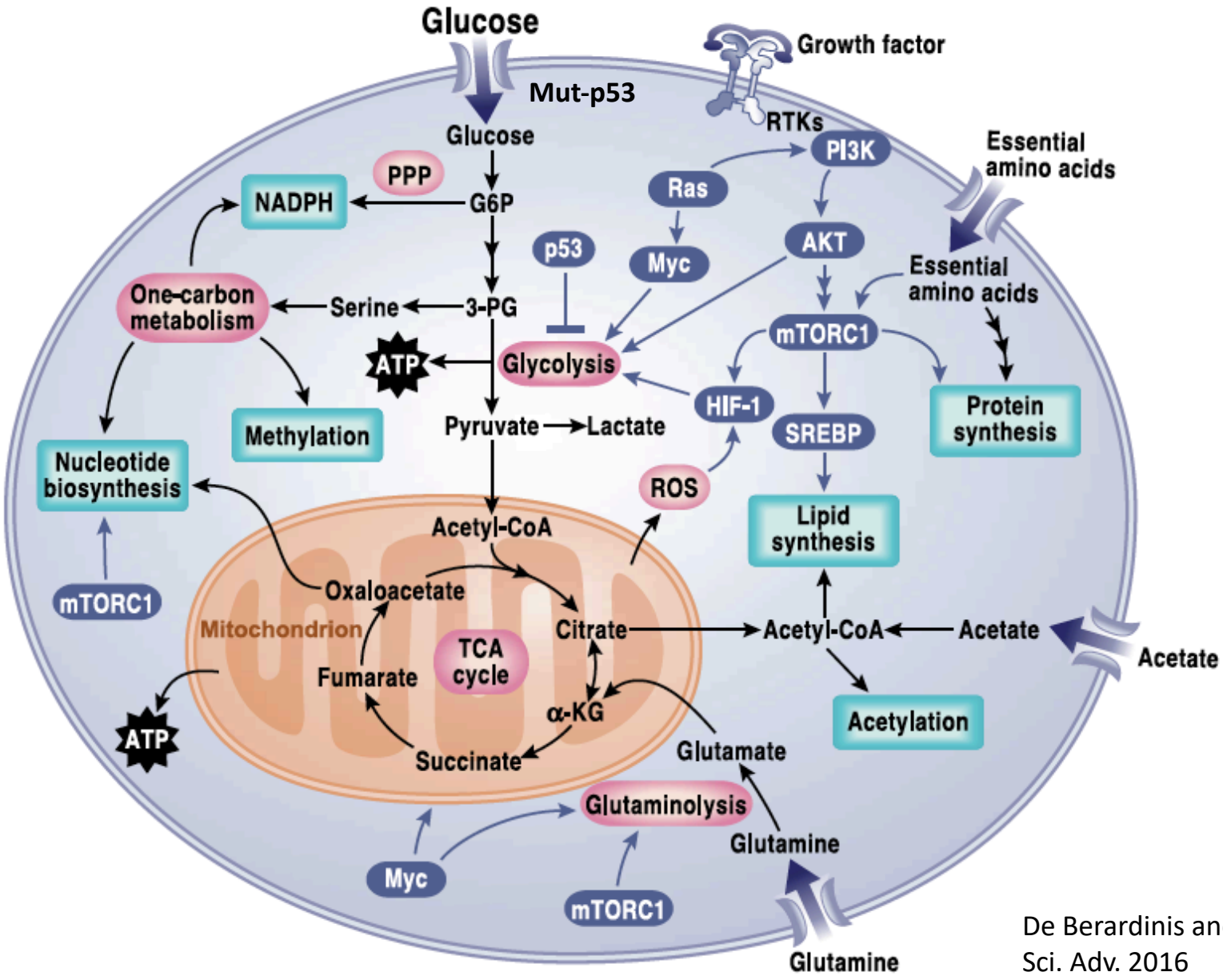
Mut-p53:
GLUT1

PI3K/AKT:
GLUT1
HK and PFK
mTOR
ACLY



Myc:
- Glutamine

Oncogeni e oncosoppressori controllano il metabolismo



De Berardinis and Chandel
Sci. Adv. 2016

Oncogeni e oncosoppressori controllano il metabolismo

Alterations in Classic Oncogenes Directly Reprogram Cell Metabolism to Increase Nutrient Uptake and Biosynthesis

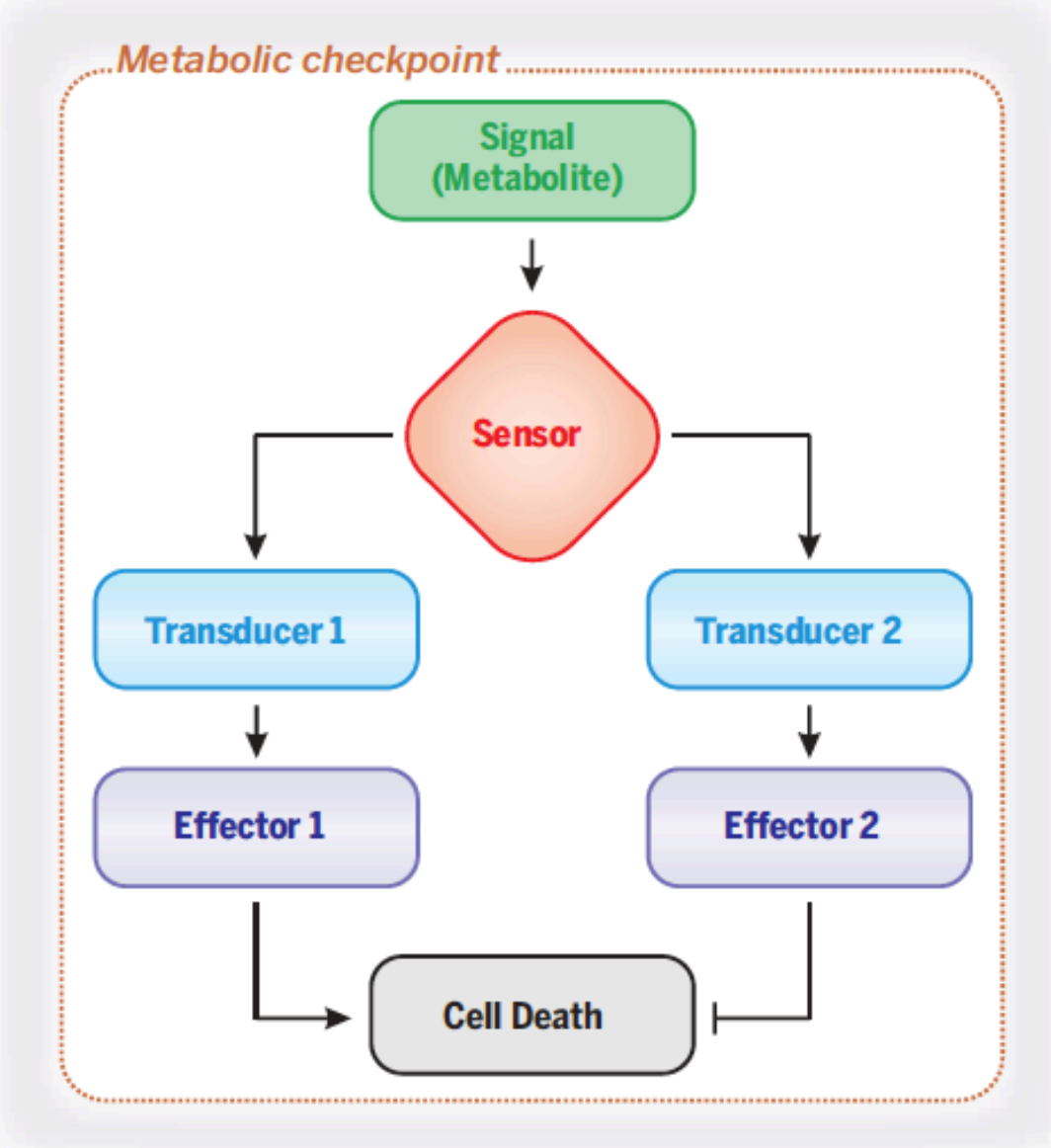
PI3K/Akt signaling downstream of receptor tyrosine kinase (RTK) activation increases glucose uptake through the transporter **GLUT1**, and increases flux through **glycolysis**. Branches of glycolytic metabolism contribute to nucleotide and amino acid synthesis.
Akt also activates ATP-citrate lyase (**ACL**), promoting the conversion of mitochondria-derived citrate to acetyl-CoA for lipid synthesis.
Mitochondrial citrate can be synthesized when glucose- derived acetyl-CoA, generated by pyruvate dehydrogenase (PDH), condenses with glutamine-derived oxaloacetate (OAA) via the activity of citrate synthase (CS).

mTORC1 promotes **protein synthesis and mitochondrial metabolism**.

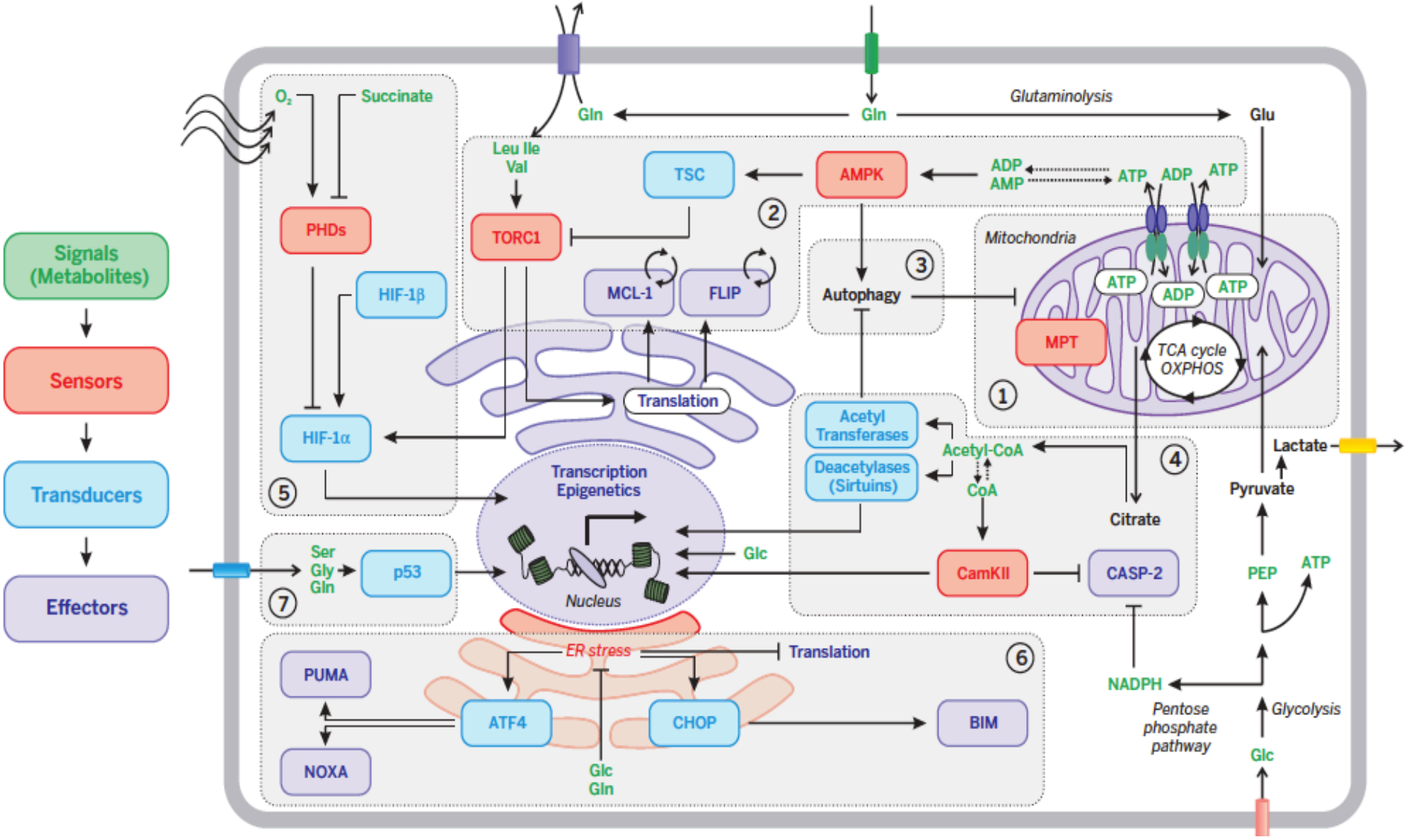
Myc increases **glutamine uptake** and the conversion of glutamine into a mitochondrial carbon source by promoting the expression of the enzyme **glutaminase** (GLS). Myc also promotes **mitochondrial biogenesis**. In addition, Myc promotes **nucleotide and amino acid synthesis**, both through direct transcriptional regulation and through increasing the synthesis of mitochondrial metabolite precursors.

I checkpoint del metabolismo

convertono perturbazioni nei livelli di metaboliti in stimoli di sopravvivenza o morte



I checkpoint del metabolismo



Nutrient and oxygen supplies, activation (reflecting extracellular signals or intracellular events, such as oncogenic mutations), as well as the differentiation state of a cell influence the metabolic pathways engaged for the production of energy and biomaterials. In response to changes in these conditions, cells either adapt or die. Extending a classical convention referring to the cell cycle and DNA damage response, it has been proposed the existence of metabolic checkpoints that dictate the consequences of such alterations on cell fate. Metabolic checkpoints can be defined as molecular mechanisms that regulate cellular functions in response to metabolic fluctuations and comprise four components: signals, sensors, transducers, and effectors.

Major metabolic signals that arise as a consequence of changes in nutrient availability or intracellular metabolic pathways include the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio, the acetyl-coenzyme A (acetyl-CoA)/CoA) ratio, the ratios of oxidized and reduced nicotinamide adenine dinucleotide (NAD+/NADH), as well as the amounts of lipid products, glycosylated proteins, and reactive oxygen species (ROS).
Specific sensors directly interact with these metabolic cues to initiate downstream events, thereby affecting signal transducers, including those involved in cell death regulation. The sensors of a metabolic checkpoint are proteins that physically interact with and respond to metabolic signals by changes in their biological status and consequently initiate downstream signaling events.

Metabolic checkpoints in cell death regulation.

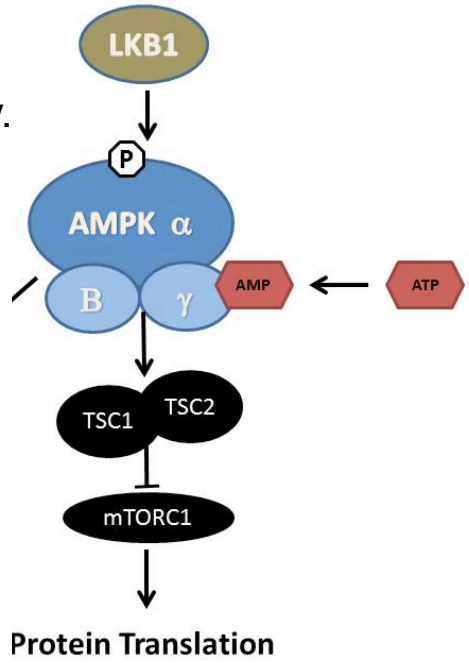
Several metabolic checkpoints are in place to convert **metabolic perturbations (signals)**, which are detected by specific **systems (sensors)**, into vital or lethal stimuli that are dispatched to components of the cell death–regulatory machinery (effectors) through one or more signaling nodes (transducers).
These include (but are not limited to)

the **mitochondrial checkpoint**, in part impinging on the so-called MPT (1);
the **AMPK-TORC1 checkpoint**, which is based on the very short half- life of antiapoptotic proteins such as FLIPL and MCL-1 (2);
the **autophagy** checkpoint, which is extensively interconnected with other checkpoints (3);
the acetyl-CoA/CoA checkpoint, which controls cell death through both transcriptional and posttranslational mechanisms (4);
the **HIF-1 checkpoint**, integrating signals about oxygen availability and TCA cycle proficiency (5);
the **ER stress checkpoint**, which operates by altering the abundance of multiple BH3-only proteins (6);
as well as the **p53 checkpoint**, detecting the availability of non- essential amino acids and converting it into an adaptive or lethal response (7).
Glc, glucose; OXPHOS, oxidative phosphorylation; PEP, phosphoenolpyruvate.

ATP checkpoint: AMPK e TORC

Two evolutionary conserved signaling molecules, AMPK and mTOR, are central players in the coordinated sensing of cellular metabolic state and dictation of cell fate. AMPK is a kinase whose activation requires both the binding of AMP-ADP and phosphorylation by the upstream signaling kinases LKB1. Whereas AMP serves as a potent **allosteric activator of AMPK**, both AMP and ADP promote and stabilize the activating phosphorylation of AMPK. Given its relatively high affinity for AMP-ADP, AMPK is generally considered a sensor of the intracellular concentration of AMP and ADP, which is indicative of bioenergetic status.

Extracellular growth factors and nutrients converge on the regulation of mTOR, a component of two functional multicomponent protein complexes, TORC1 and TORC2 involved in inducing protein translation. Activation of the protein-kinase activity of TORC1 requires the derepression of TSC1-TSC2, a inhibitory component of the complex. When ATP is limiting (and in the presence of high concentrations of AMP and ADP), AMPK directly phosphorylates essential components of TORC1, such as TSC2. This generally leads to inhibition of TORC1 activity. as a central signal transducer that functions in metabolic checkpoints by ATP-sensing pathways to determine cell fate.



p53 risponde alla deprivazione di nutrienti

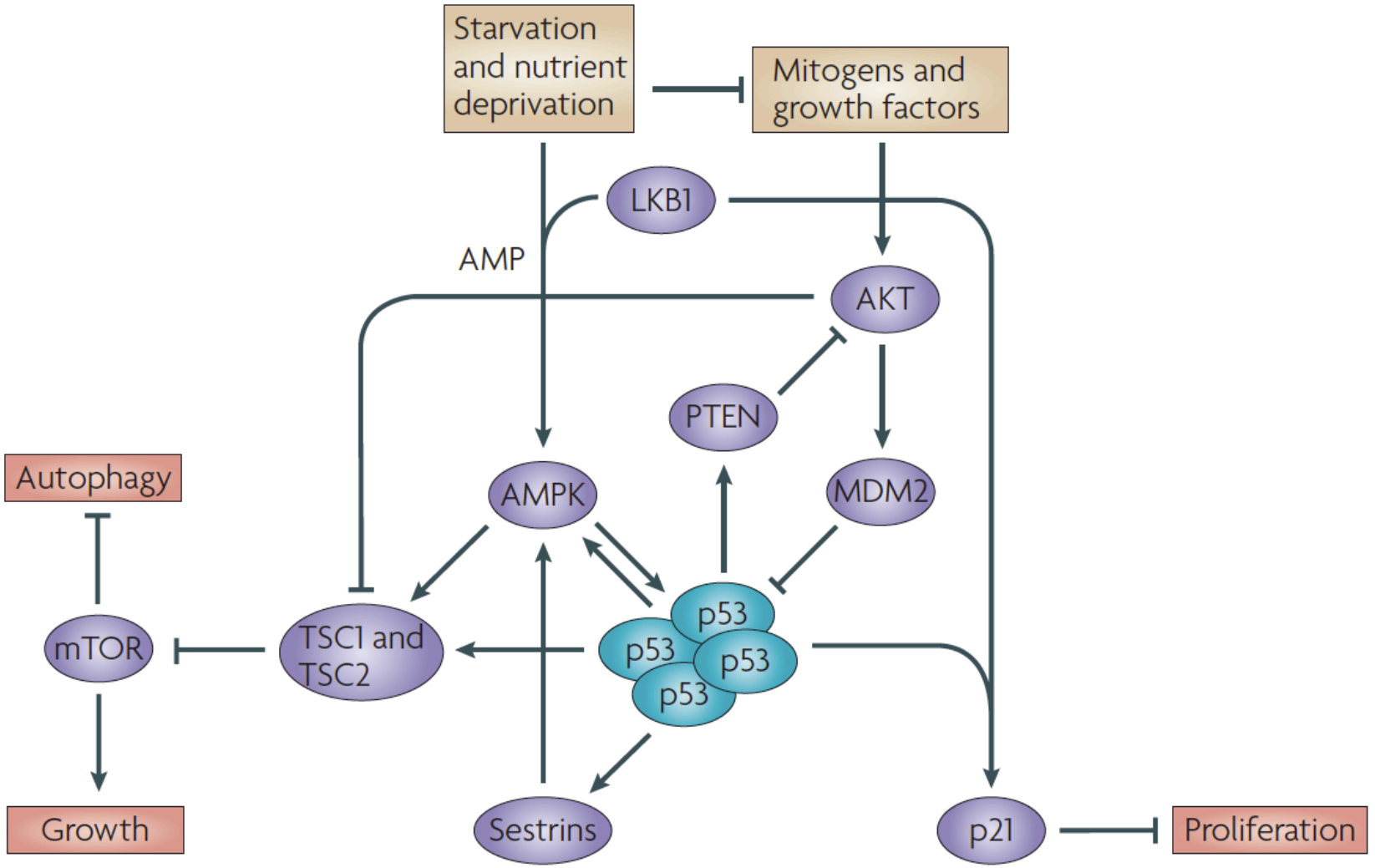
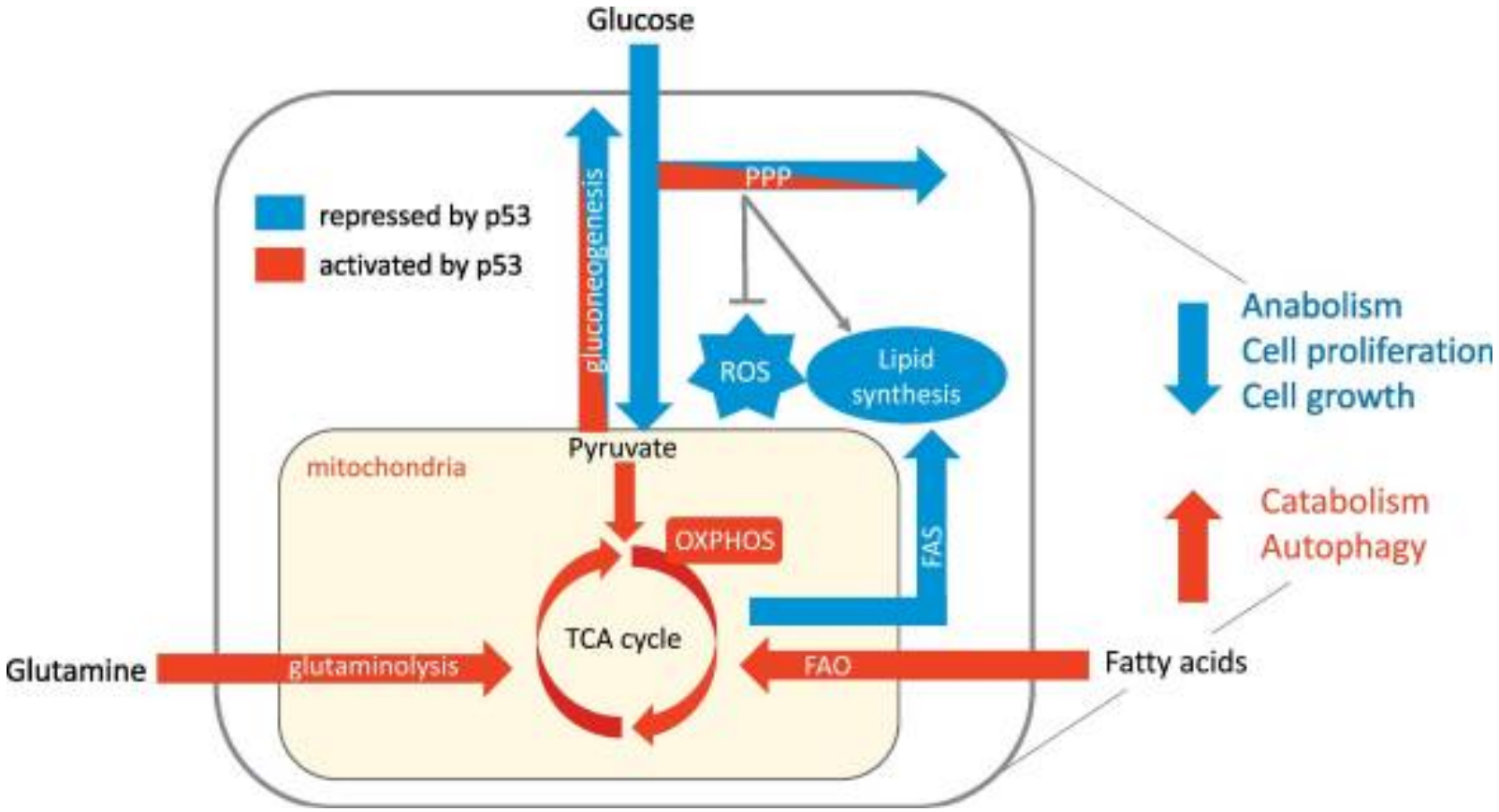


Figure 1 | **Nutrient deprivation signals to p53.** The activation of p53 in response to a

Regolazione del metabolismo da p53



Under conditions of metabolic stress, p53 induces catabolic pathways and autophagy to maintain energy production and cell survival while inhibiting anabolic pathways, cell growth and proliferation. p53 inhibits glycolysis and promotes mitochondrial respiration, while also limiting lipid biosynthesis and promoting lipolysis. Note that while oxidative phosphorylation is a major source of mitochondrial ROS, maintenance of mi- tochondrial health by p53 is likely to limit oxidative stress through this source. In addition to PPP activation, p53 controls ROS through numerous other mechanisms .