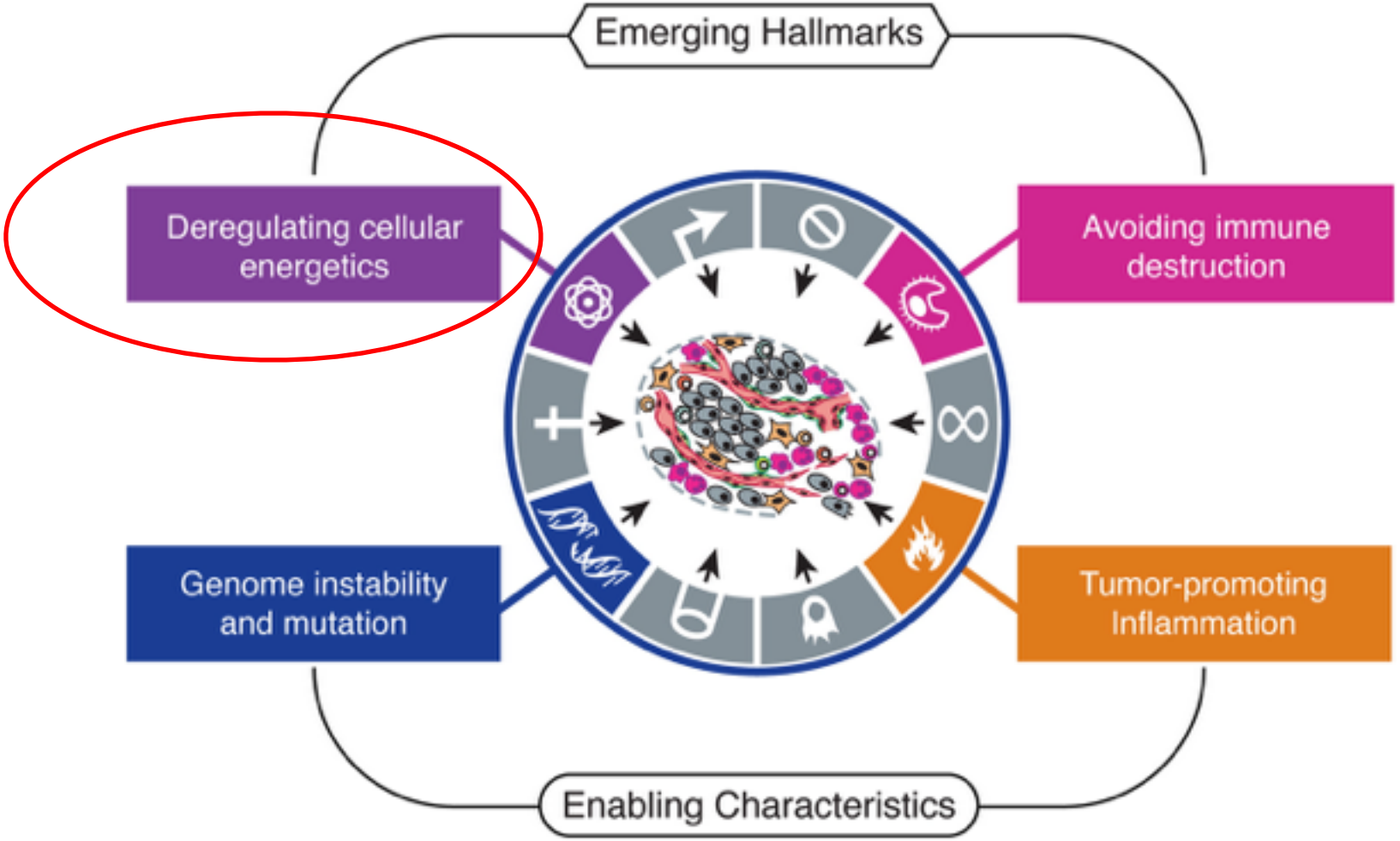
Oncology for Scientists
RPN 530
Fall 2016

Cancer Cell Metabolism

Gokul Das, Ph.D.
Department of Pharmacology & Therapeutics
Center for Genetics & Pharmacology (CGP)
Room 4-304
Tel: 845-8542
Email: gokul.das@roswellpark.org

An Emerging Hallmark: Reprogramming Energy Metabolism

Acquired Abilities for Cancer Progression: Cancer Hallmarks 2000 vs 2011



Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011, 144:646

Metabolism (Overview)

Metabolism:

- Collection of controlled intracellular biochemical reactions that convert nutrients and endogenous molecules to energy and matter (proteins, nucleic acids, and lipids) that sustain life

- A sequence of chemical reactions, where the product of one reaction serves as a substrate for the next, is called a metabolic pathway or biochemical pathway

  The set of reactions occurring within the cell are called intermediary metabolism or intermediate metabolism

- Most metabolic pathways take place in specific regions of the cell

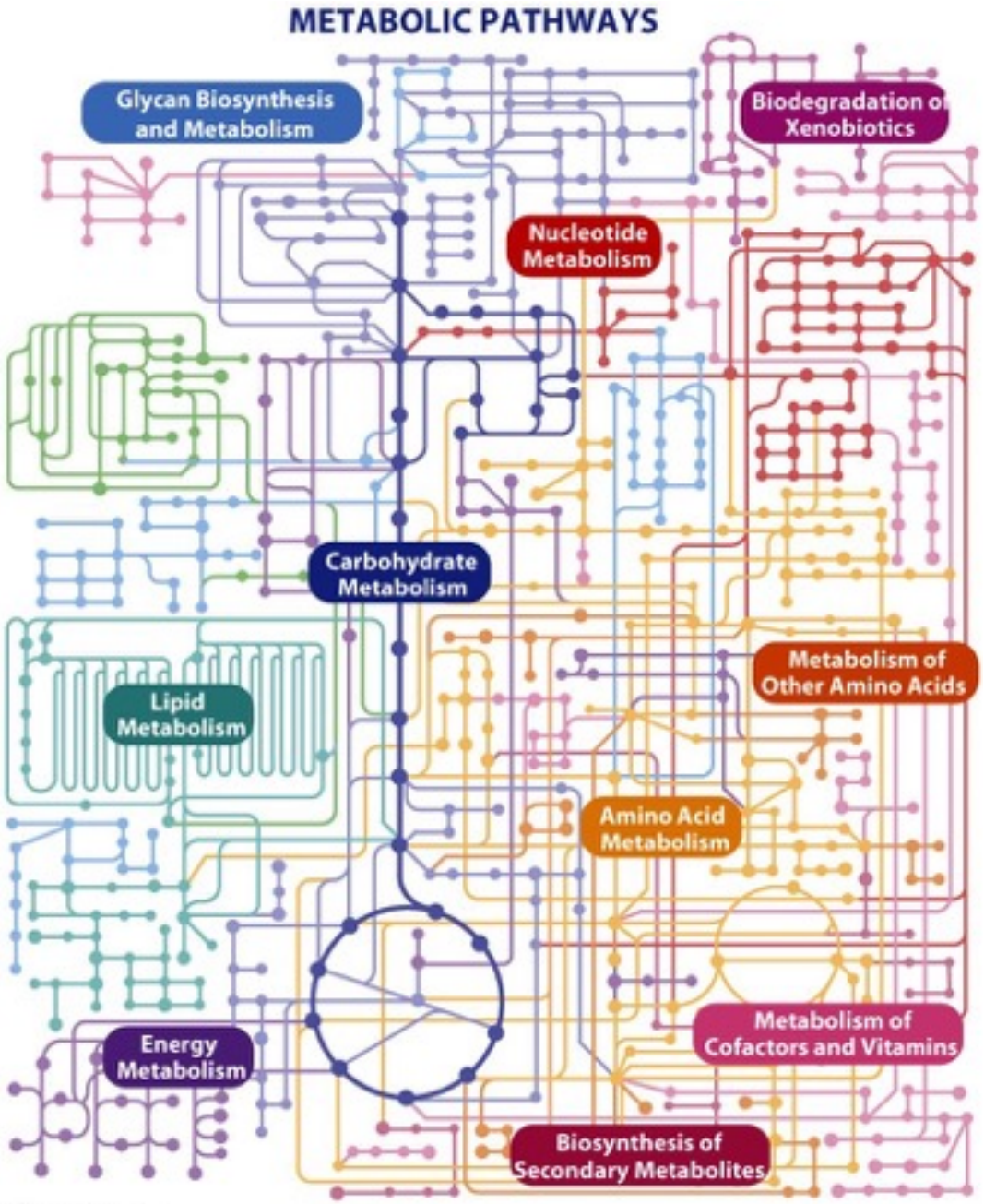


Figure 15-1
Lehninger Principles of Biochemistry, Fifth Edition

Map of Metabolic Pathways

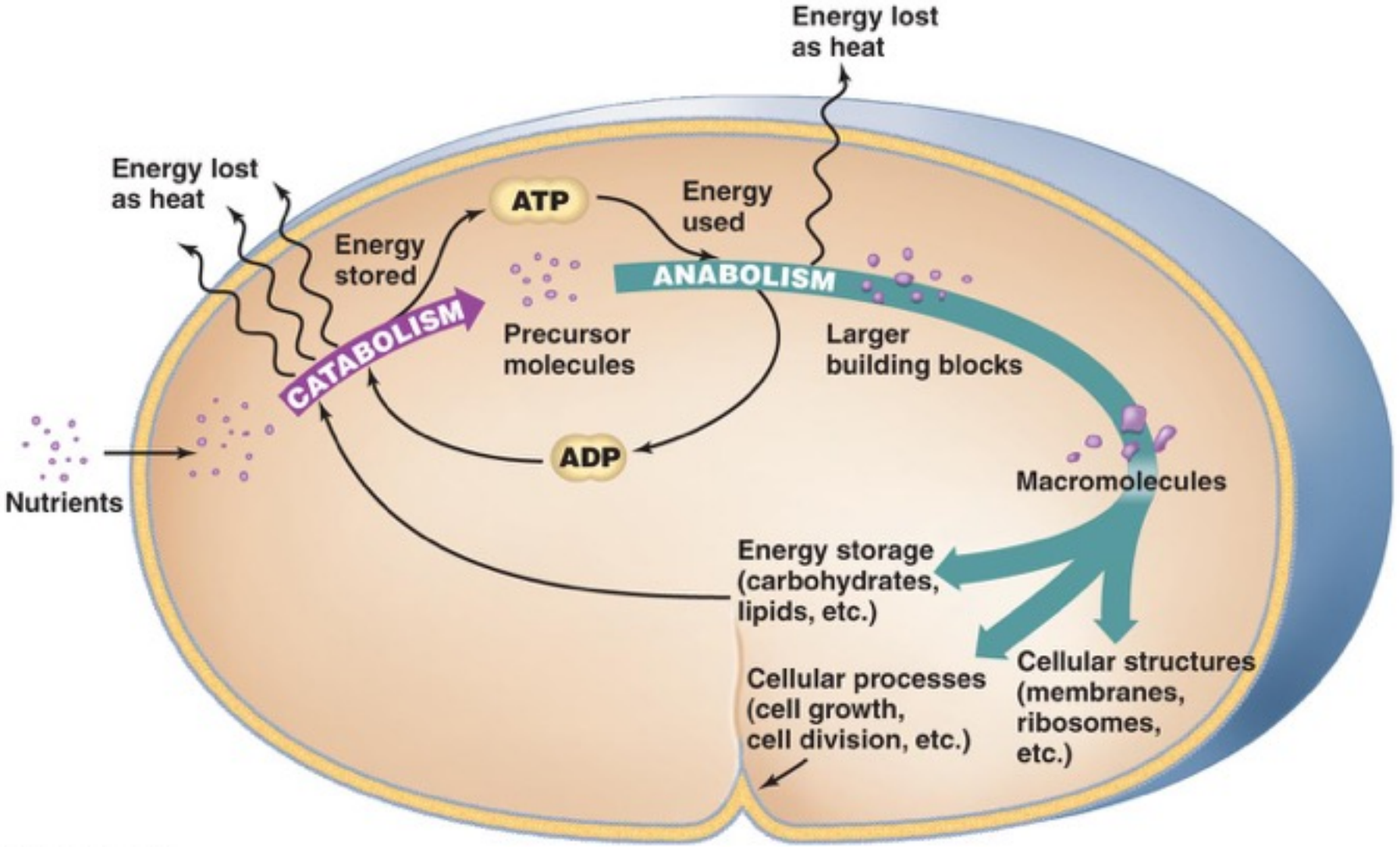
Basic Chemical Reactions Underlying Metabolism

Catabolism and Anabolism

- Two major classes of metabolic reactions

- Catabolic pathways
  - Break larger molecules into smaller products
  - Exergonic (release energy)
- Anabolic pathways
  - Synthesize large molecules from the smaller products of catabolism
  - Endergonic (require more energy than they release)

Metabolism Composed of Catabolic and Anabolic Reactions



Bioenergetics

Cell Energy

ATP is the main energy currency of cells

Formation of ATP

Degradation of glucose and glycogen

-Glycolysis

Oxidative formation of ATP

- Oxidative phosphorylation

Anaerobic pathways

- Do not involve O_2

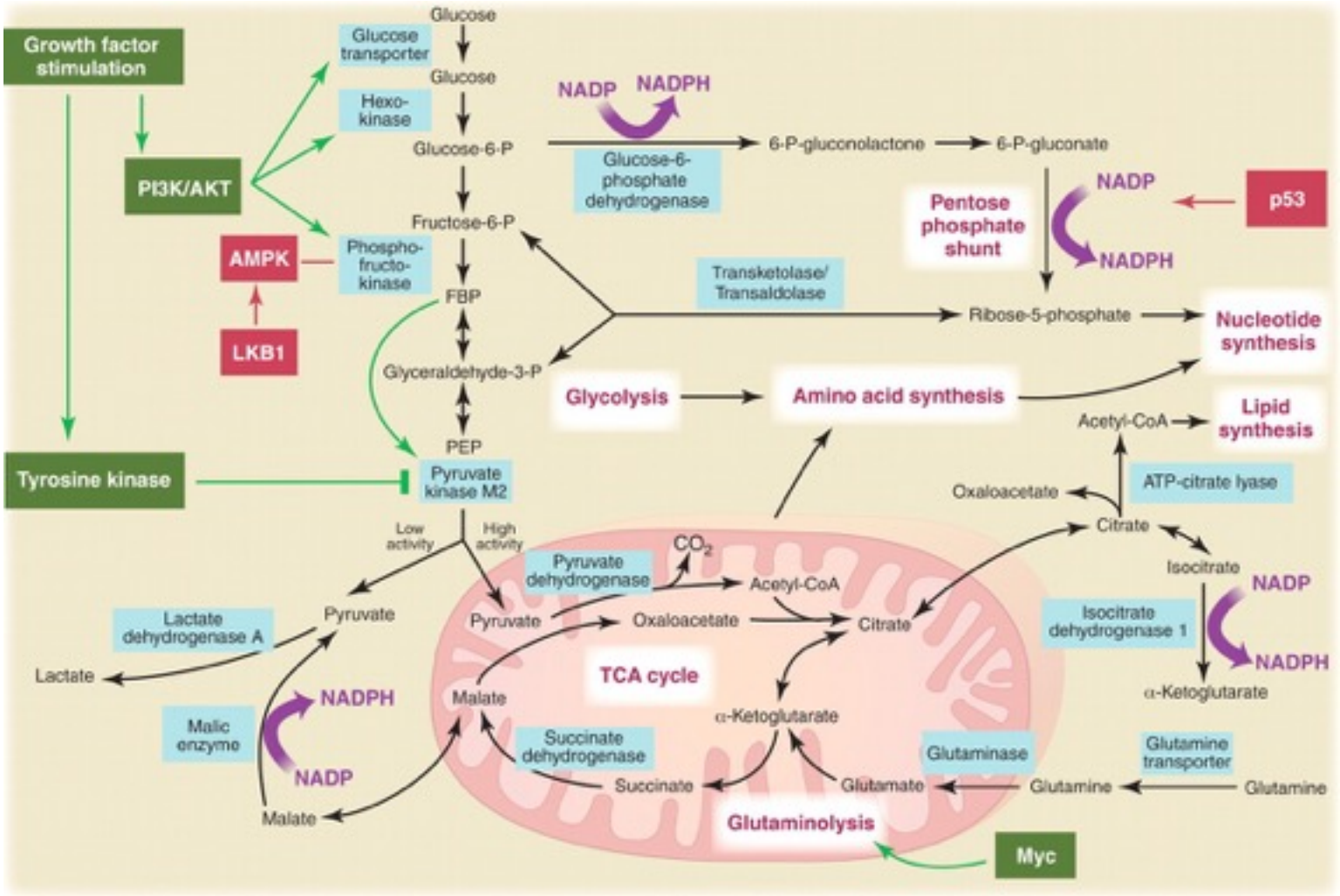
- Glycolysis

Aerobic pathways

- Require O_2

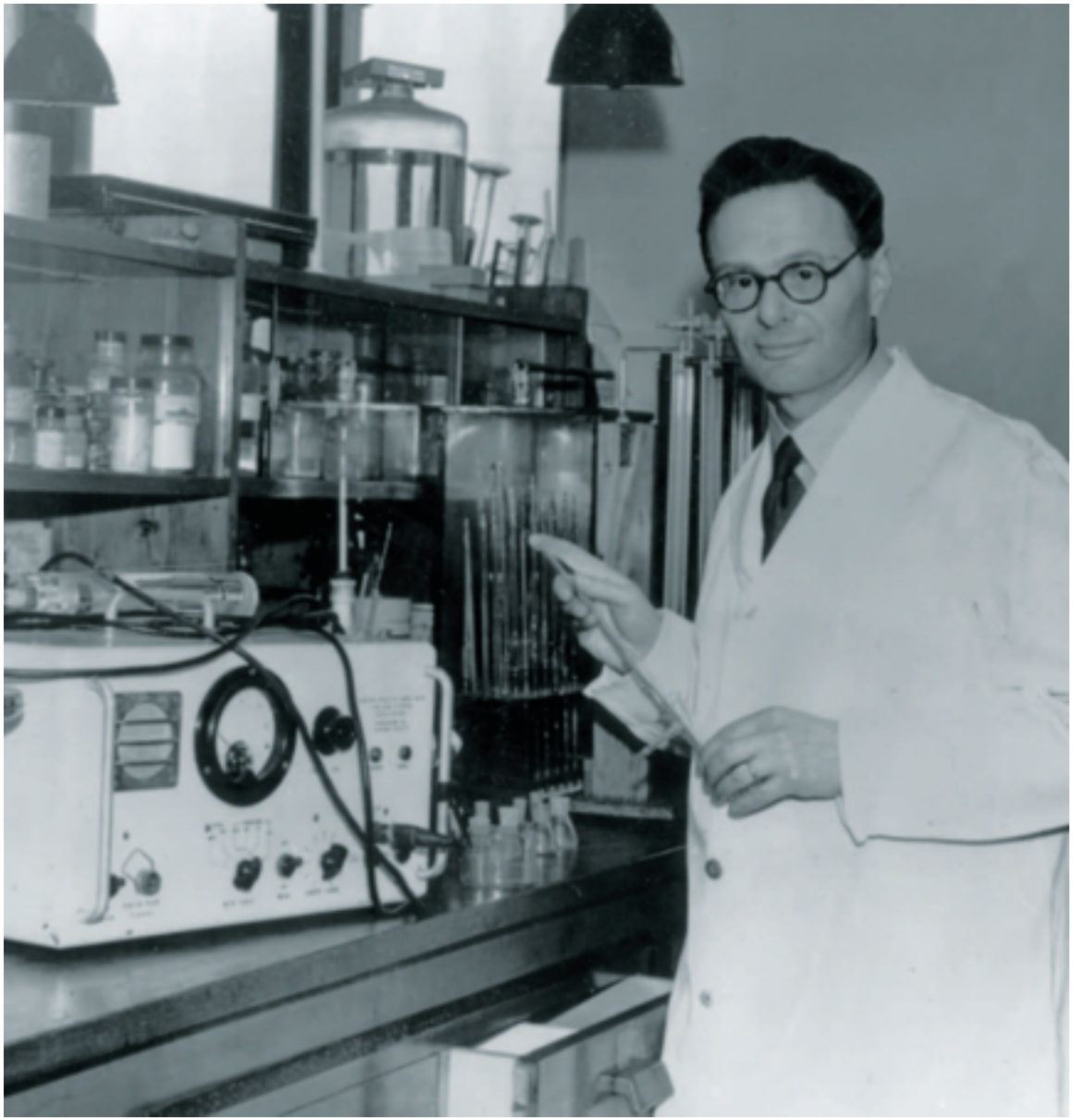
- Oxidative phosphorylation

Fig. 3 Metabolic pathways active in proliferating cells are directly controlled by signaling pathways involving known oncogenes and tumor suppressor genes.



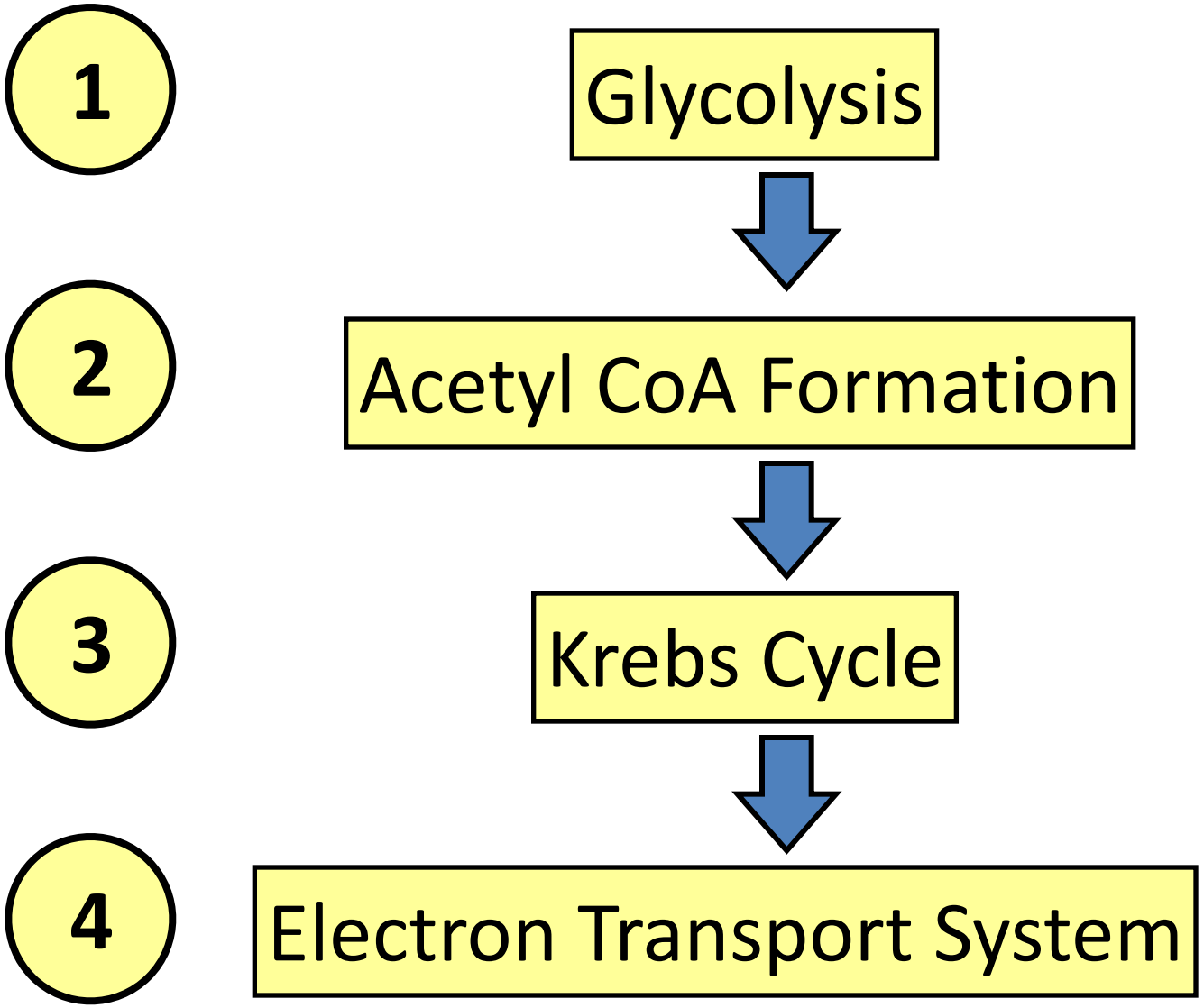
Matthew G. Vander Heiden et al. Science 2009;324:1029-1033

Kreb's Cycle/TCA Cycle

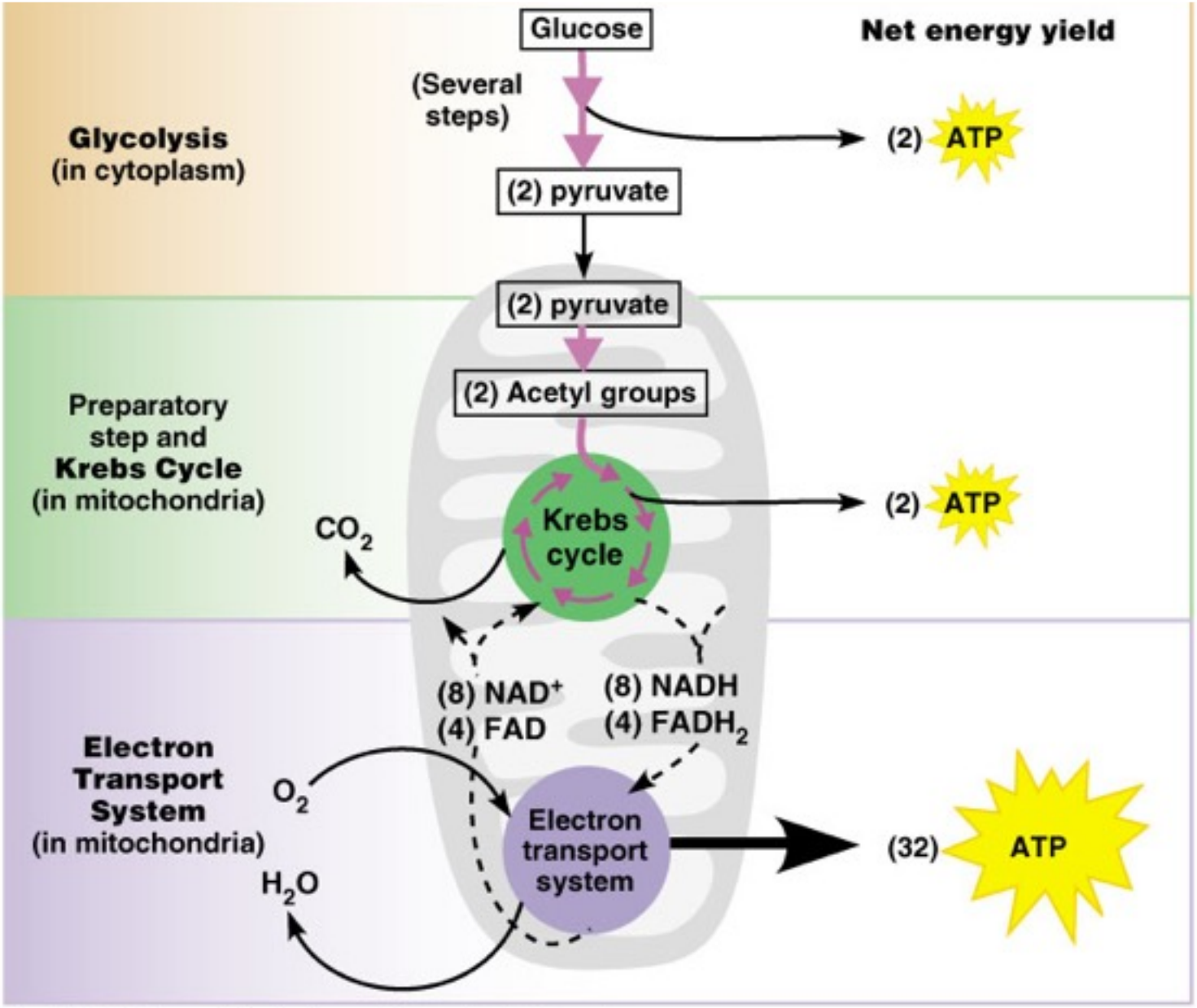


Hans Krebs, Nobel Prize in 1953; *Science* 2010, 330:1338

Basic Steps Involved

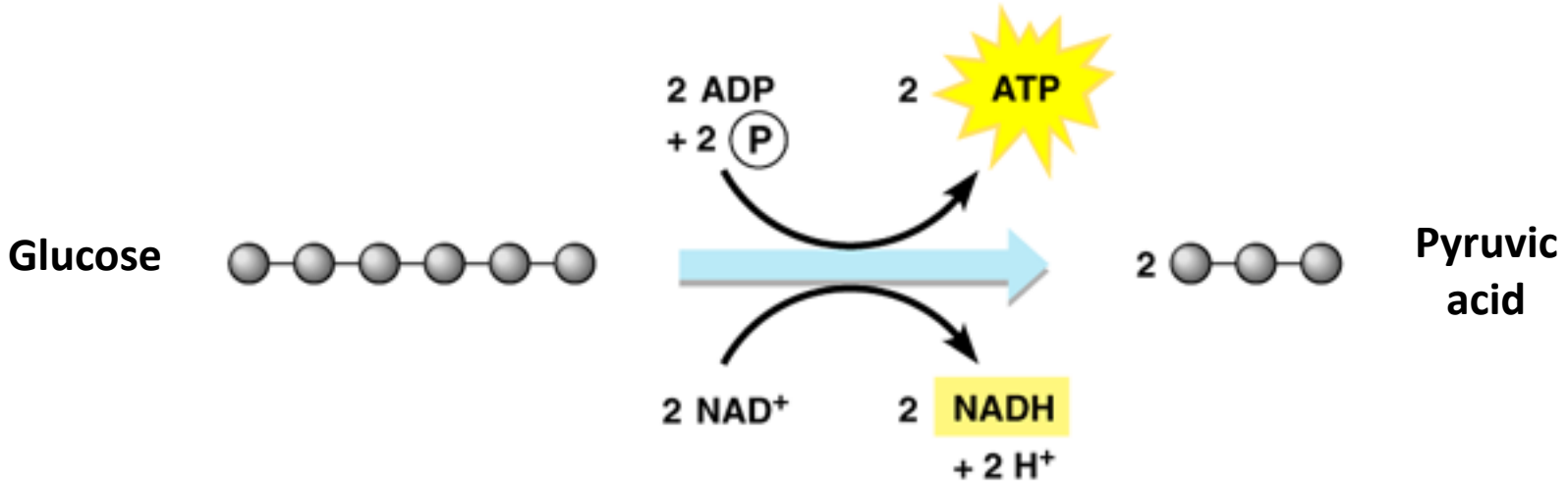


ATP Generating Metabolic Pathways



Glycolysis

- Glycolysis ("splitting of sugar") breaks down glucose into two molecules of pyruvate
- Occurs in the cytoplasm and has two major phases
  - Energy investment phase
  - Energy payoff phase
- Occurs whether or not O_2 is present
- Glycolysis harvests chemical energy by oxidizing glucose to pyruvic acid
- The oxidation of glucose to pyruvic acid produces ATP and NADH



Energy yield: 2 ATP and 2 NADH

Balance Sheet for Glycolysis

Input

1 Glucose

2 ADP + P_i

2 NAD^+

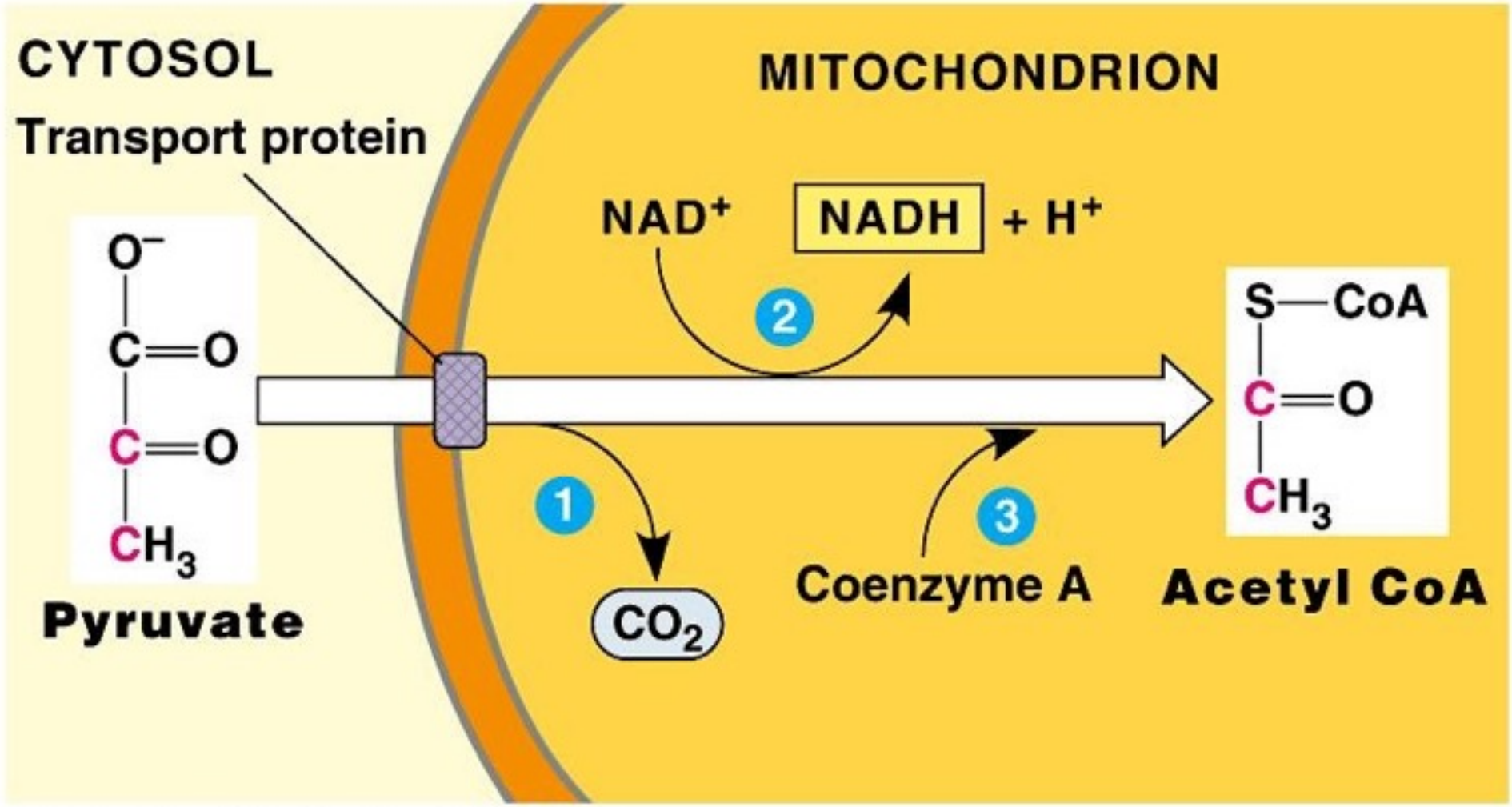
Output

2 Pyruvate

2 ATP

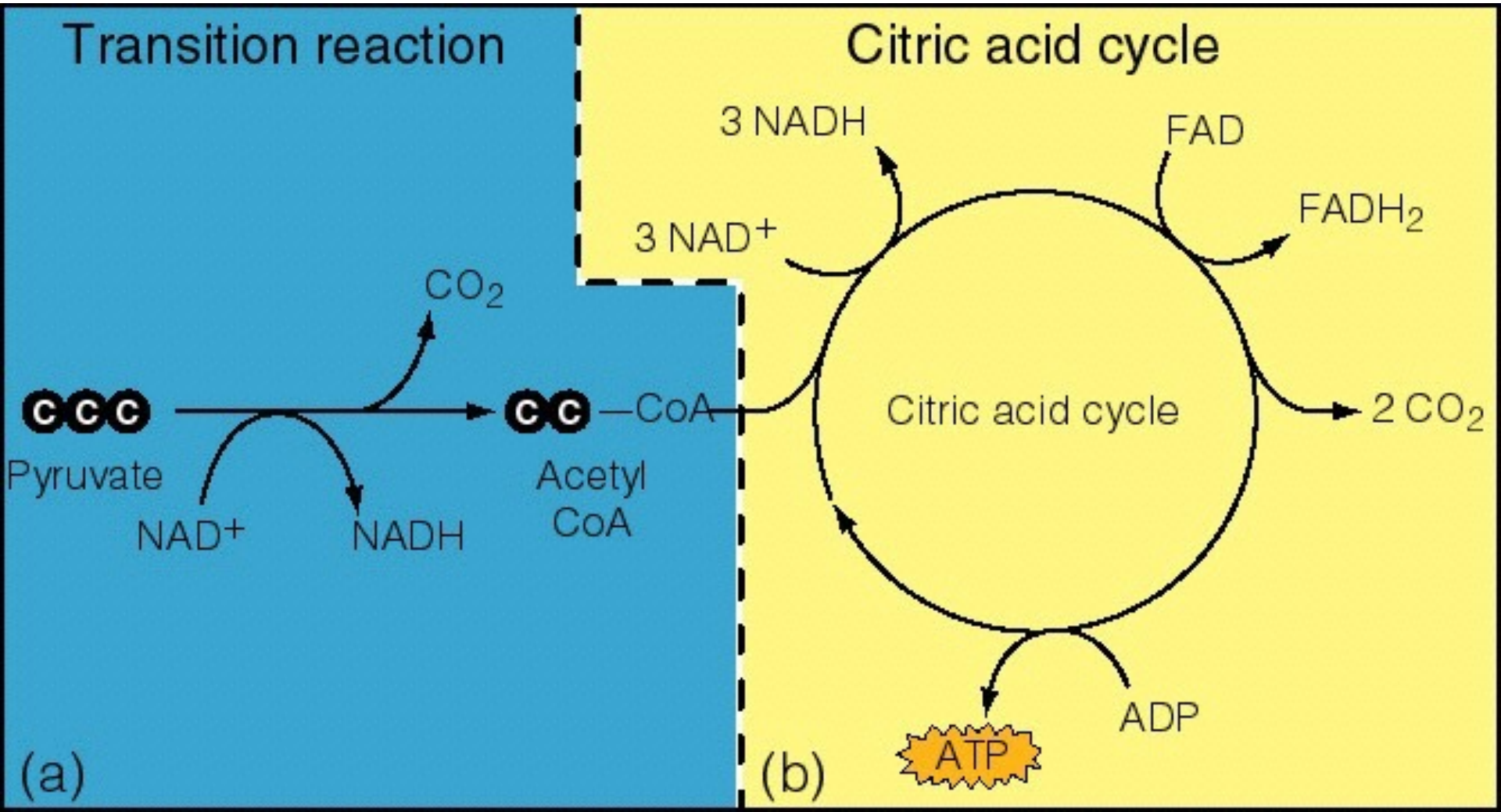
2 NADH

Transition Reaction

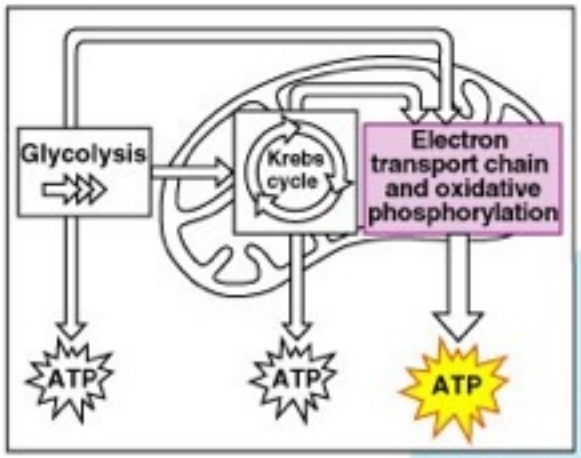


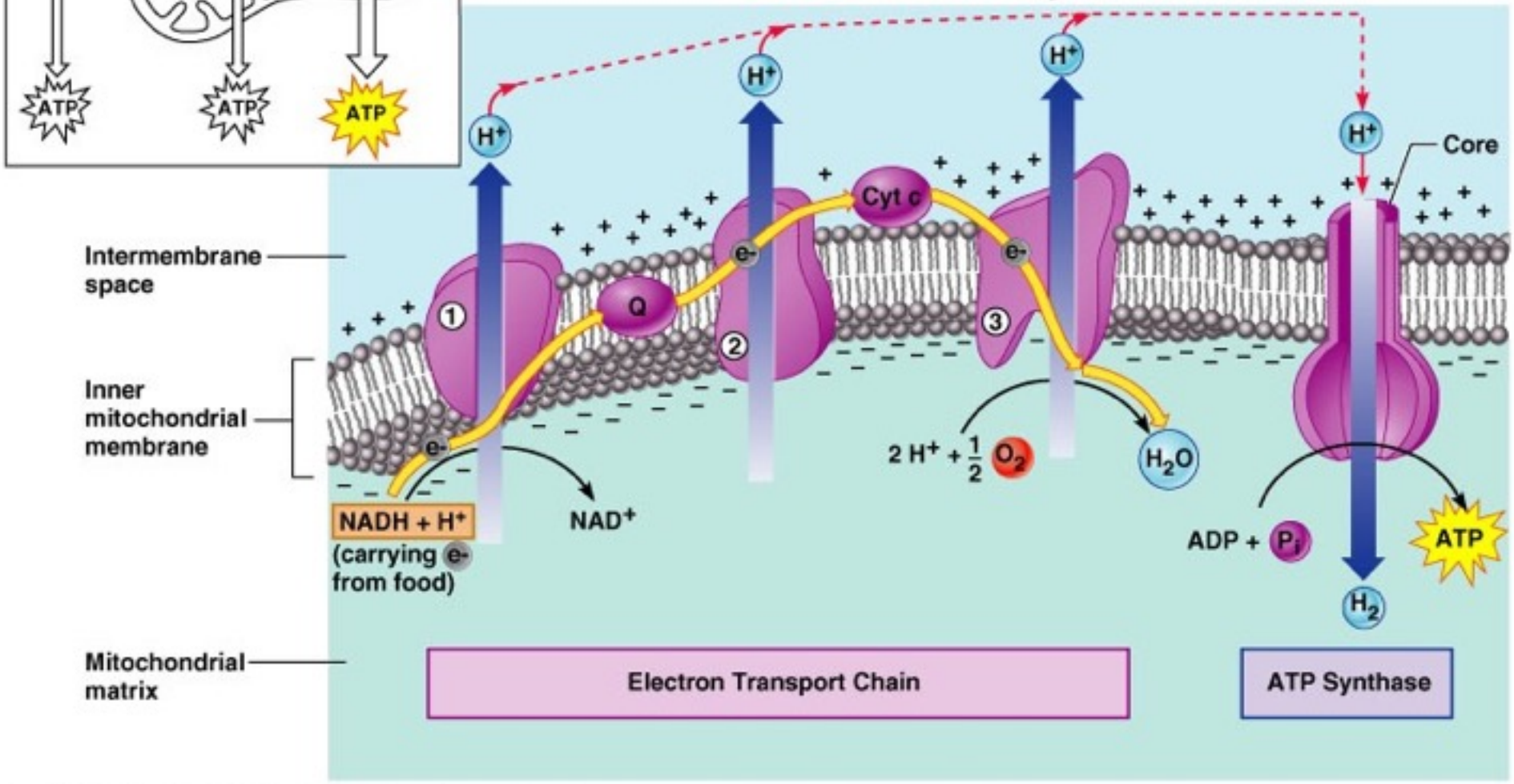
Transition Reaction

Krebs Cycle (Citric Acid Cycle)



Oxidative Phosphorylation





Overall ATP Production

Electron Transport System	34	
Citric Acid Cycle	2	
Glycolysis	2	
SUBTOTAL	38	
NADH Transport into Mitochondrion*		-2
TOTAL	36	

(-2) some ATP is used to pump NADH across membrane so ~ **36 ATP**

The high-energy ATP molecules store 7.3 kcal of energy per mole

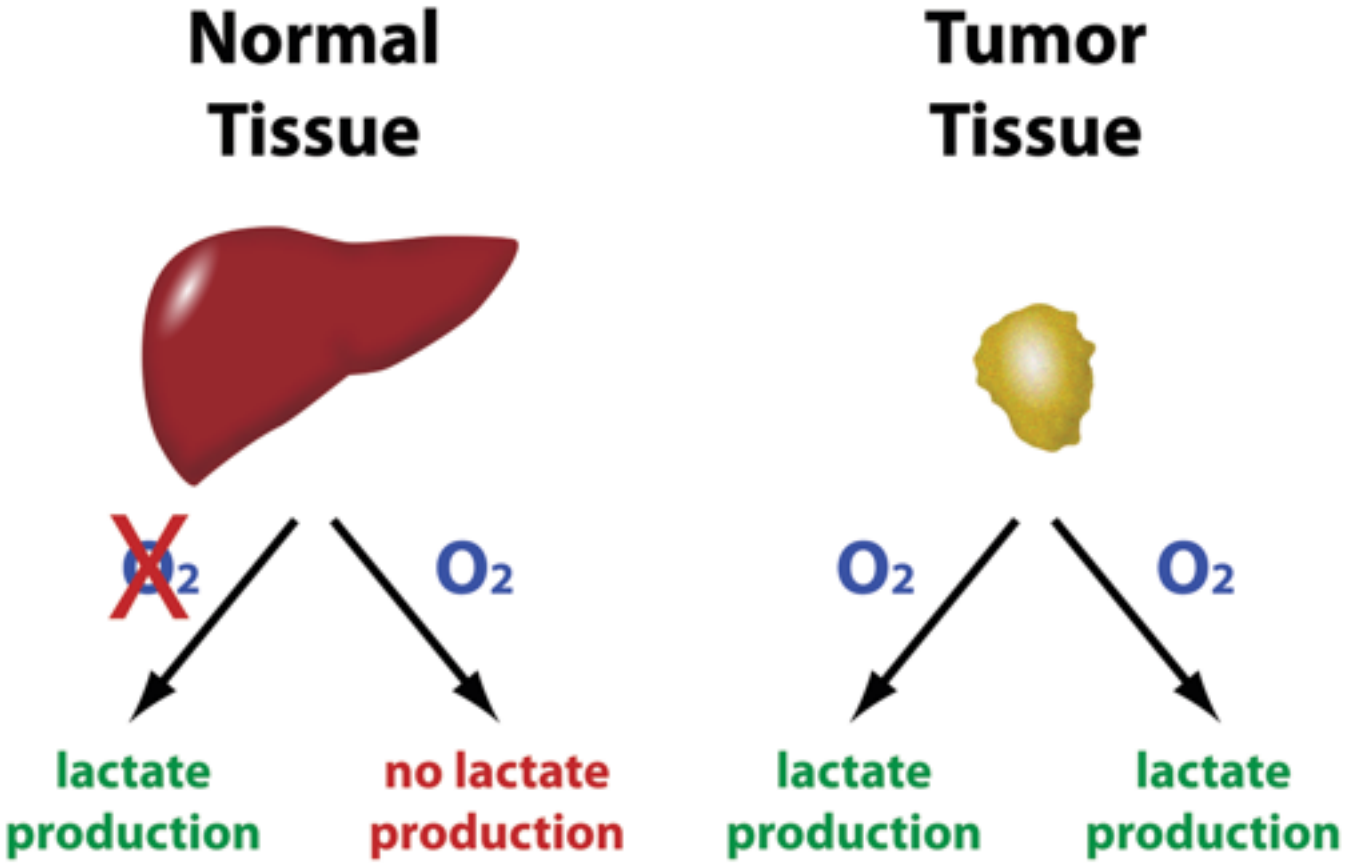
Net ATP Yield

34 to 36 molecules ATP for every glucose molecule

about 40% efficiency

The high-energy ATP molecules store 7.3 kcal of energy per mole

How is Cancer Cell Metabolism different ?



Matthew G. Vander Heiden, Science Webinar.

The Warburg Theory of Cancer or "Warburg hypothesis"

Warburg hypothesis 1924

"Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar… " -- Dr. Otto H. Warburg in Lecture

Dr. Otto H. Warburg
(1883 – 1970)

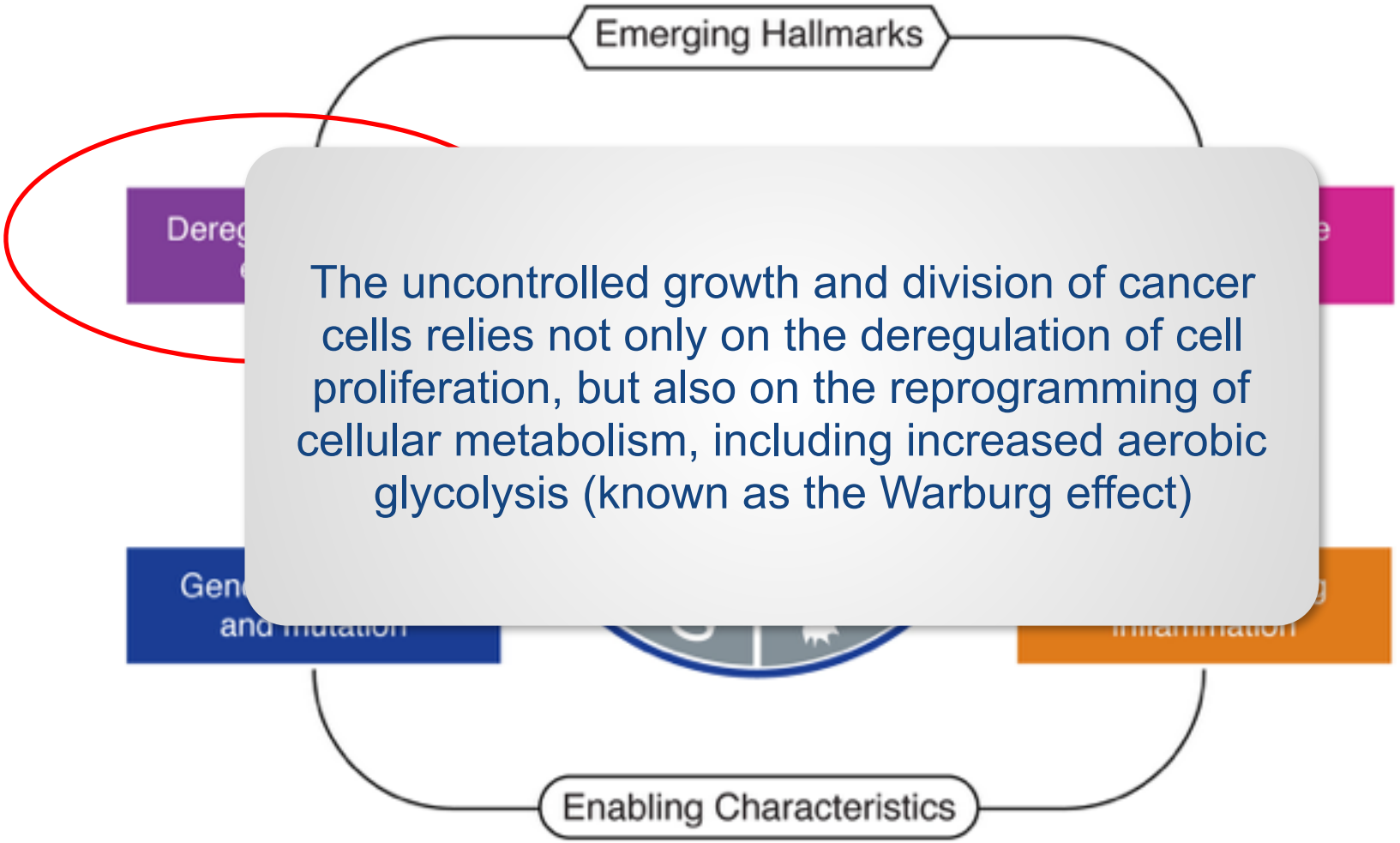
On the Origin of Cancer Cells. Otto Warburg
Science 24 February 1956: 309-314.

What is the Warburg Effect?

Observation that most cancer cells predominantly produce energy through a high rate of glycolysis followed by lactic acid fermentation, rather than through oxidative phosphorylation in the mitochondria

An Emerging Hallmark: Reprogramming Energy Metabolism

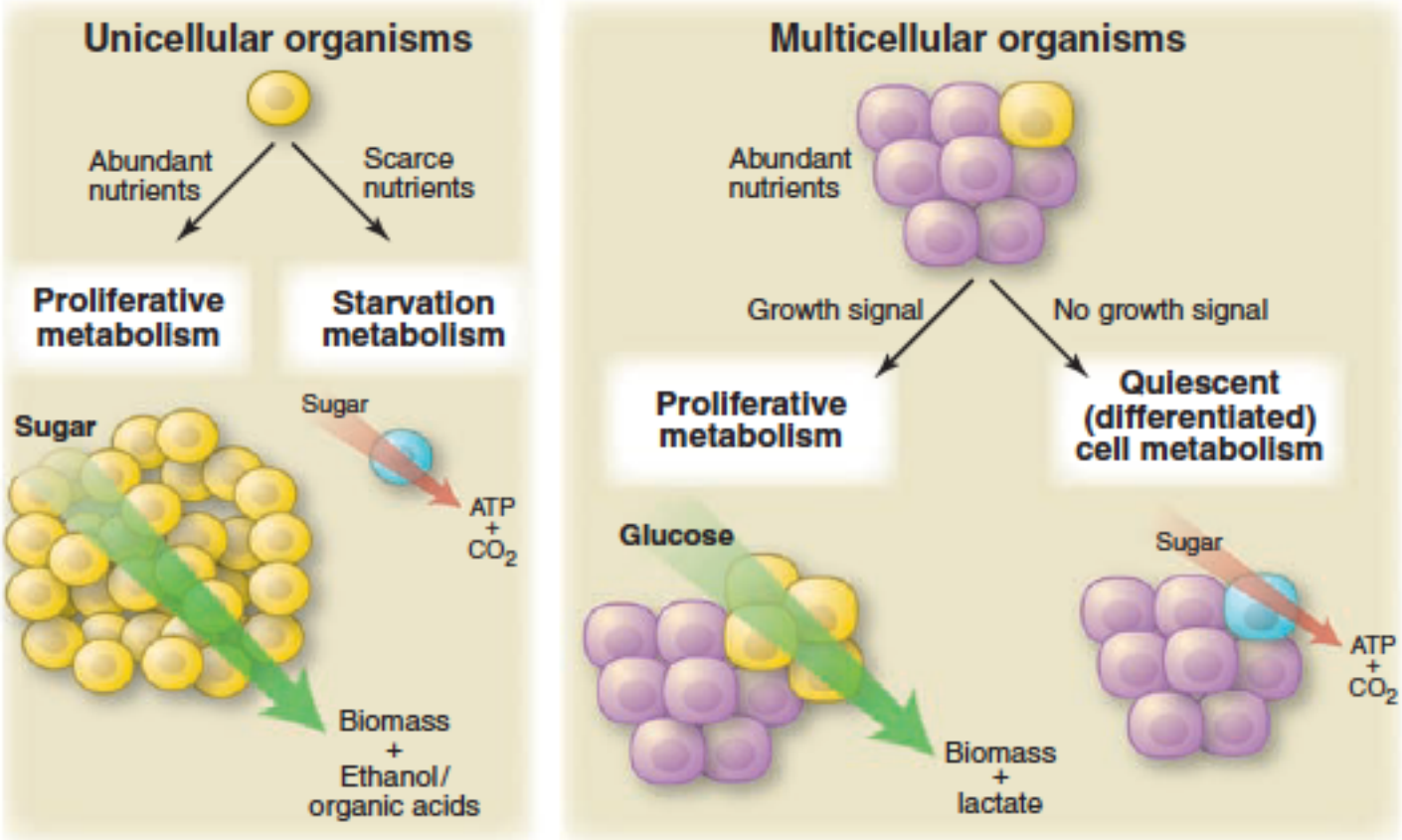
Acquired Abilities for Cancer Progression: Cancer Hallmarks 2000 vs 2011



The uncontrolled growth and division of cancer cells relies not only on the deregulation of cell proliferation, but also on the reprogramming of cellular metabolism, including increased aerobic glycolysis (known as the Warburg effect)

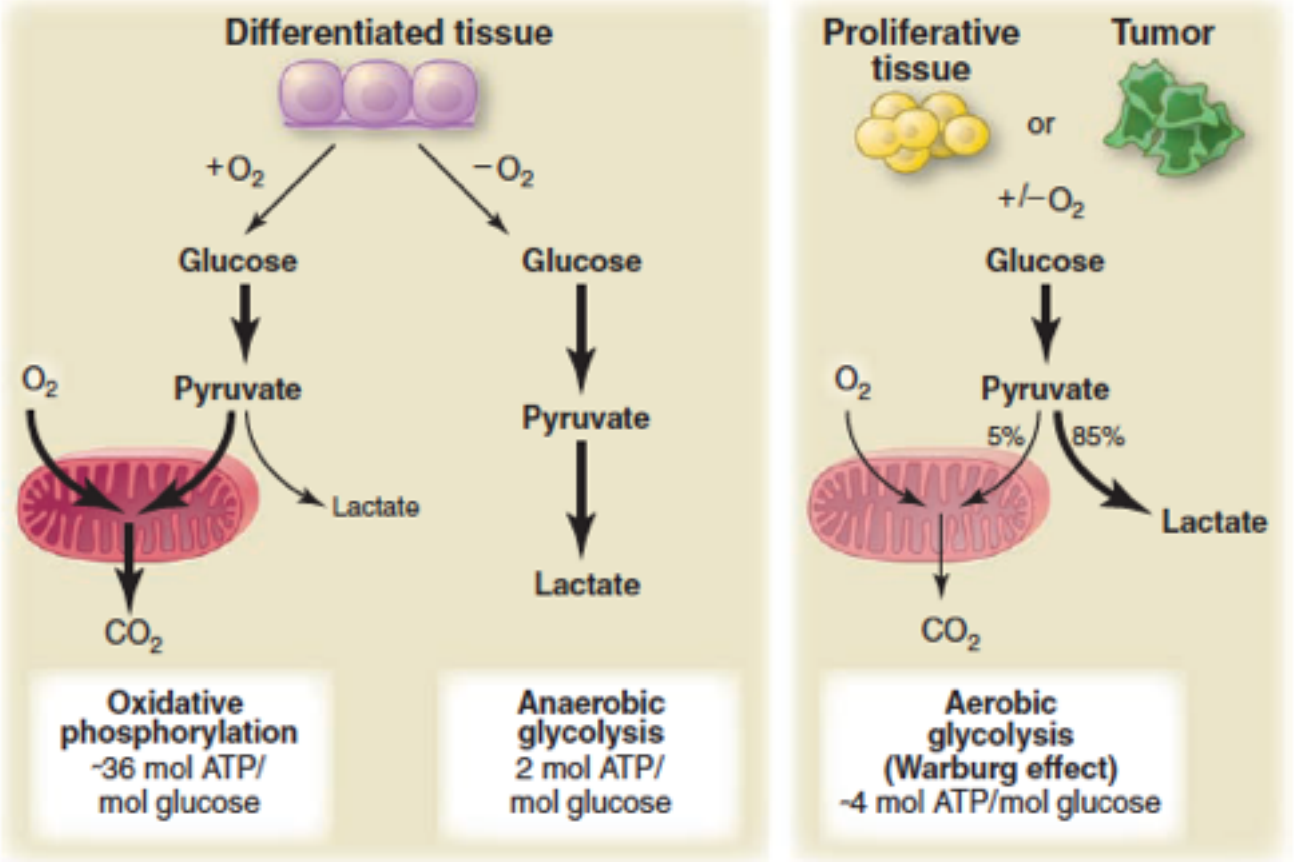
Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011, 144:646

Glycolysis and Oxidative Phosphorylation



. Microbes and cells from multicellular organisms have similar metabolic phenotypes under similar environmental conditions. Unicellular organisms undergoing exponential growth often grow by fermentation of glucose into a small organic molecule such as ethanol. These organisms, and proliferating cells in a multicellular organism, both metabolize glucose primarily through glycolysis, excreting large amounts of carbon in the form of ethanol, lactate, or another organic acid such as acetate or butyrate. Unicellular organisms starved of nutrients rely primarily on oxidative metabolism, as do cells in a multicellular organism that are not stimulated to proliferate. This evolutionary conservation suggests that there is an advantage to oxidative metabolism during nutrient limitation and nonoxidative metabolism during cell proliferation.

Matthew G. Vander Heiden et al, 2009. *Science*, 324:1029-1033



Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect). In the presence of oxygen, nonproliferating (differentiated) tissues first metabolize glucose to pyruvate via glycolysis and then completely oxidize most of that pyruvate in the mitochondria to CO_2 during the process of oxidative phosphorylation. Because oxygen is required as the final electron acceptor to completely oxidize the glucose, oxygen is essential for this process. When oxygen is limiting, cells can redirect the pyruvate generated by glycolysis away from mitochondrial oxidative phosphorylation by generating lactate (anaerobic glycolysis). This generation of lactate during anaerobic glycolysis allows glycolysis to continue (by cycling NADH back to NAD^+), but results in minimal ATP production when compared with oxidative phosphorylation. Warburg observed that cancer cells tend to convert most glucose to lactate regardless of whether oxygen is present (aerobic glycolysis). This property is shared by normal proliferative tissues. Mitochondria remain functional and some oxidative phosphorylation continues in both cancer cells and normal proliferating cells. Nevertheless, aerobic glycolysis is less efficient than oxidative phosphorylation for generating ATP. In proliferating cells, ~10% of the glucose is diverted into biosynthetic pathways upstream of pyruvate production.

Warburg Effect

Cells	Q_{O2}	$Q_M^{O_2}$	$Q_M^{N_2}$
Ascites cancer cells	-7	30	70
Earle's cancer cells (high malignancy)	-7	30	70
Earle's cancer cells (low malignancy)	-13	10	25
Chorion of young embryos	-17	0	35

The higher the malignancy, the greater the fermentation and the smaller the respiration

QO_2: oxygen consumed/ml

Q_M^{O2}: lactic acid produced aerobically /ml

Q_M^{N2}: lactic acid produced anaerobically /ml

Science 1956;124: (3215) 269-70

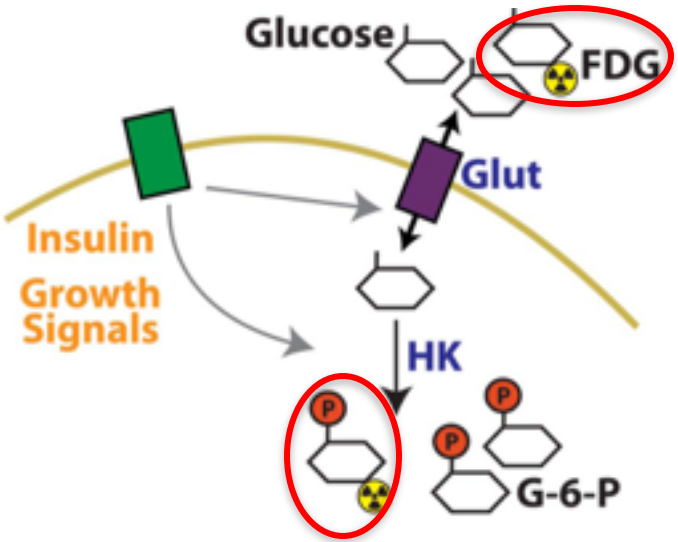
Clinical FDG-PET Scanning Exploits Cancer Metabolism

- **^{18}F-FDG: [18]F-flourodeoxyglucose (FDG) Imaging**
- **^{18}F -FDG is a glucose analog with replacement of the oxygen in C-2 position with 18-fluorine. Though it behaves as glucose in many situations, there are some important differences that should be understood.**

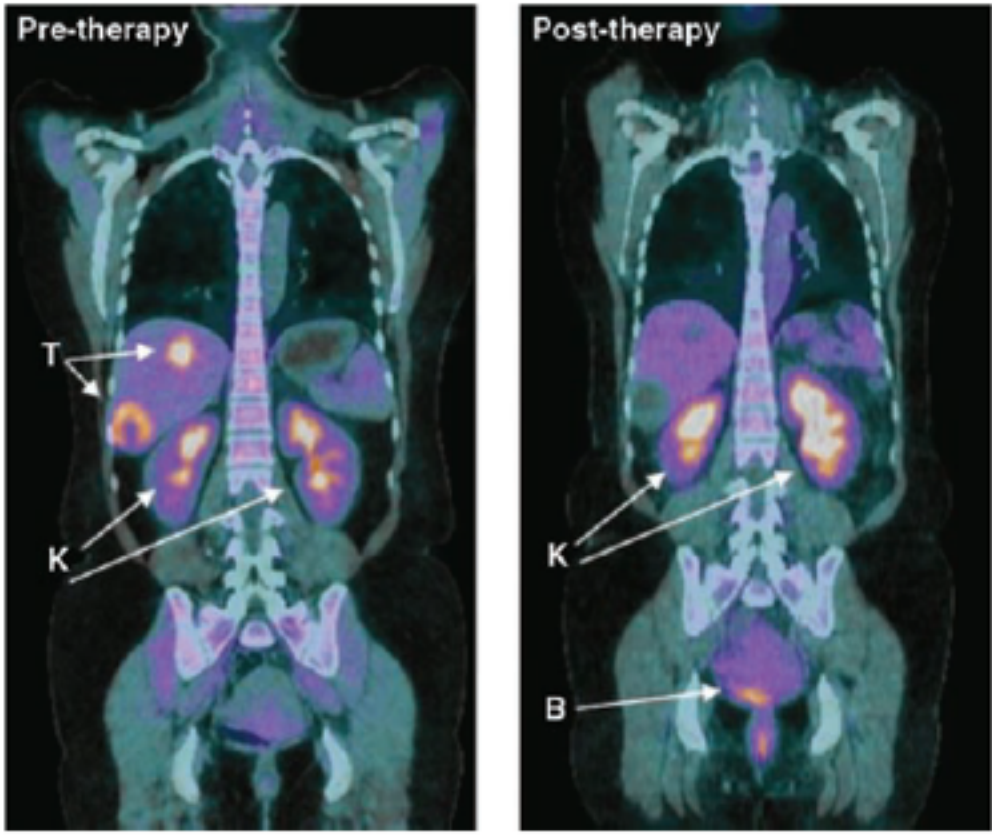
- **Uptake: Just as glucose, FDG is actively transported into the cell mediated by a group of structurally related glucose transport proteins (GLUT). Once intracellular, glucose and FDG are phosphorylated by hexokinase as the first step toward glycolysis. Normally, once phosphorylated glucose continues along the glycolytic pathway for energy production. FDG however cannot enter glycolysis and becomes effectively trapped intracellularly as FDG-6-Phosphate. Tumor cells display increased number of glucose transporters, particularly GLUT-1 and GLUT-3, as well as higher levels of hexokinase, isoforms type I and II. Tumor cells are highly metabolically active (high mitotic rates) ,and favor the more inefficient anaerobic pathway adding to the already increased glucose demands. These combined mechanisms allow for tumor cells to uptake and retain higher levels of FDG when compared to normal tissues.**

- **FDG is not cancer specific and will accumulate in areas with high levels of metabolism and glycolysis. Therefore increased uptake can be expected in sites of hyperactivity (muscular, nervous); active inflammation (infection, sarcoid, arthritis, etc.); tissue repair, etc.**

Clinical FDG-PET Scanning Exploits Cancer Metabolism



Cancer: Principles & Practice of Oncology 9th Edition



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]

Matthew G. Vander Heiden et al, 2009. *Science,* 324:1029-1033

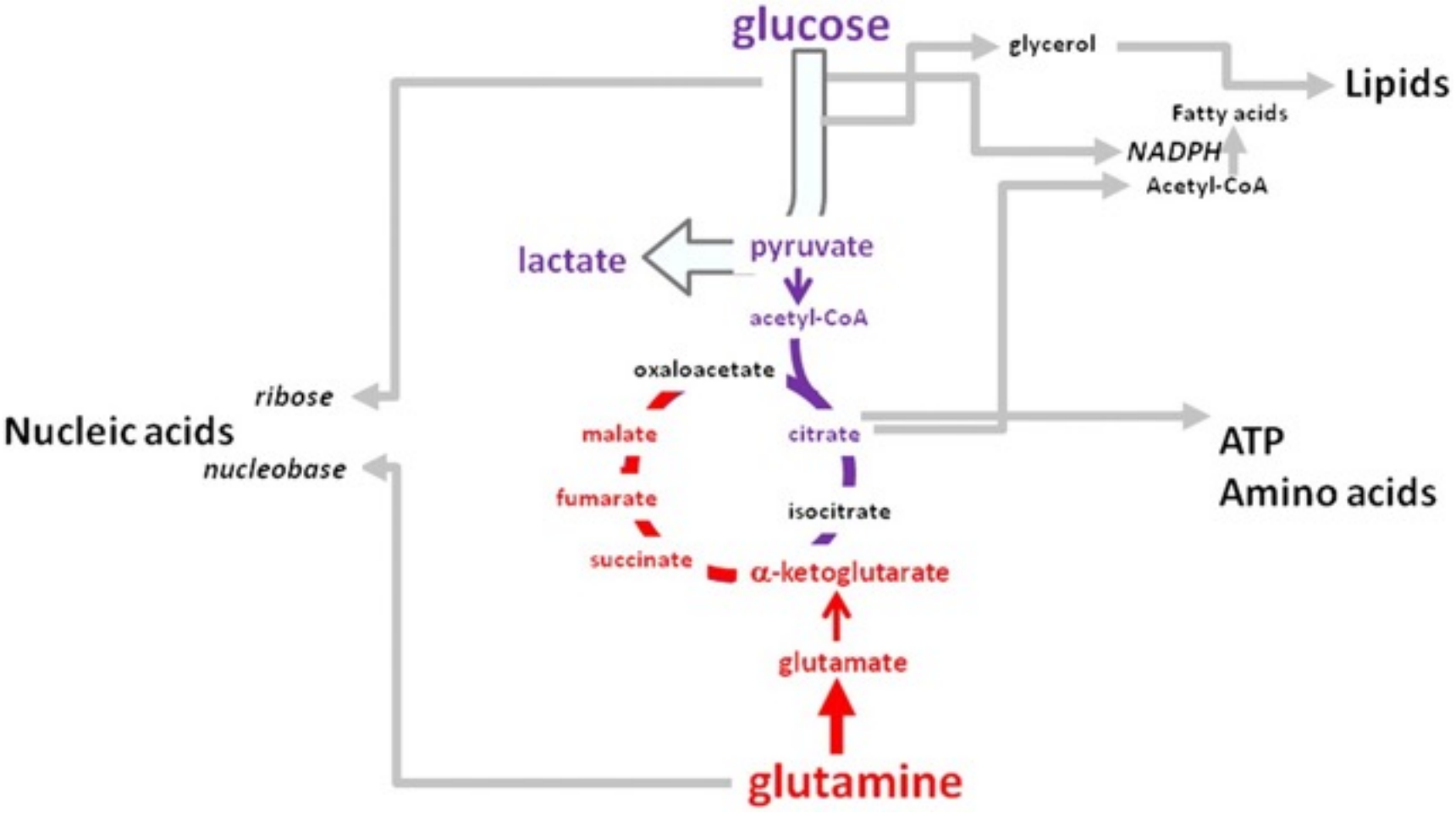
Cancer Cell Metabolism: Warburg and Beyond

The Possible Advantages of the Altered Metabolism of Cancer Cells

Altered Metabolism Provides Substrates for Biosynthetic Pathways

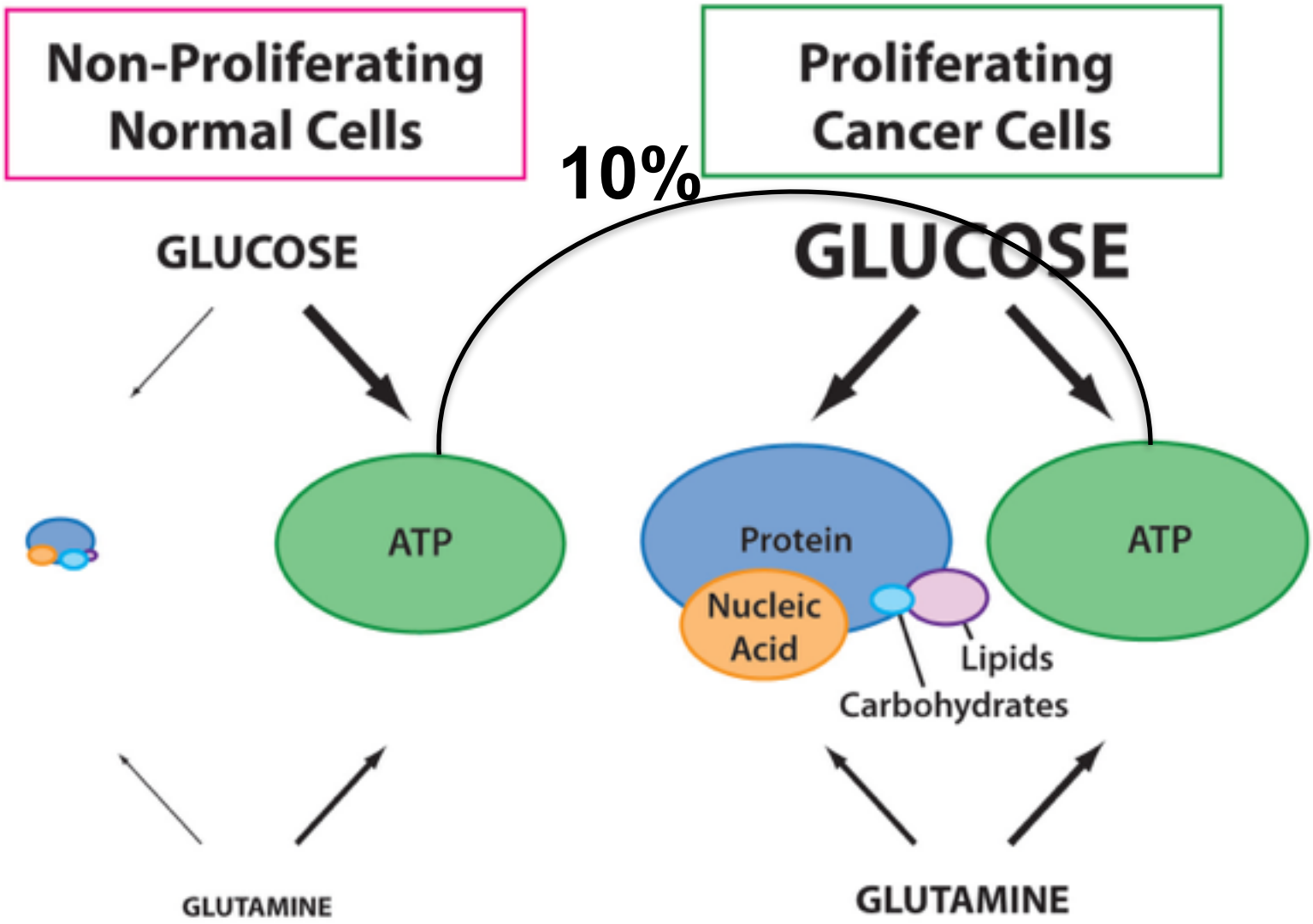
- Aerobic glycolysis is about 100 times faster than oxidative-phosphorylation in the mitochondria
- Increased glycolysis allows the diversion of glycolytic intermediates into various biosynthetic pathways
- Facilitates the biosynthesis of the macromolecules and organelles required for assembling new cells
- Ensures that cancer cells have a ready supply of building blocks needed for macromolecule synthesis

Glucose and Glutamine Feed Cell Growth and Proliferation



Dang C V Genes Dev. 2012;26:877-890

Most of the Increased Nutrient Uptake in Cancer is Used to Support Biosynthesis



Matthew G. Vander Heiden. Nat Rev Drug Discov. 2011

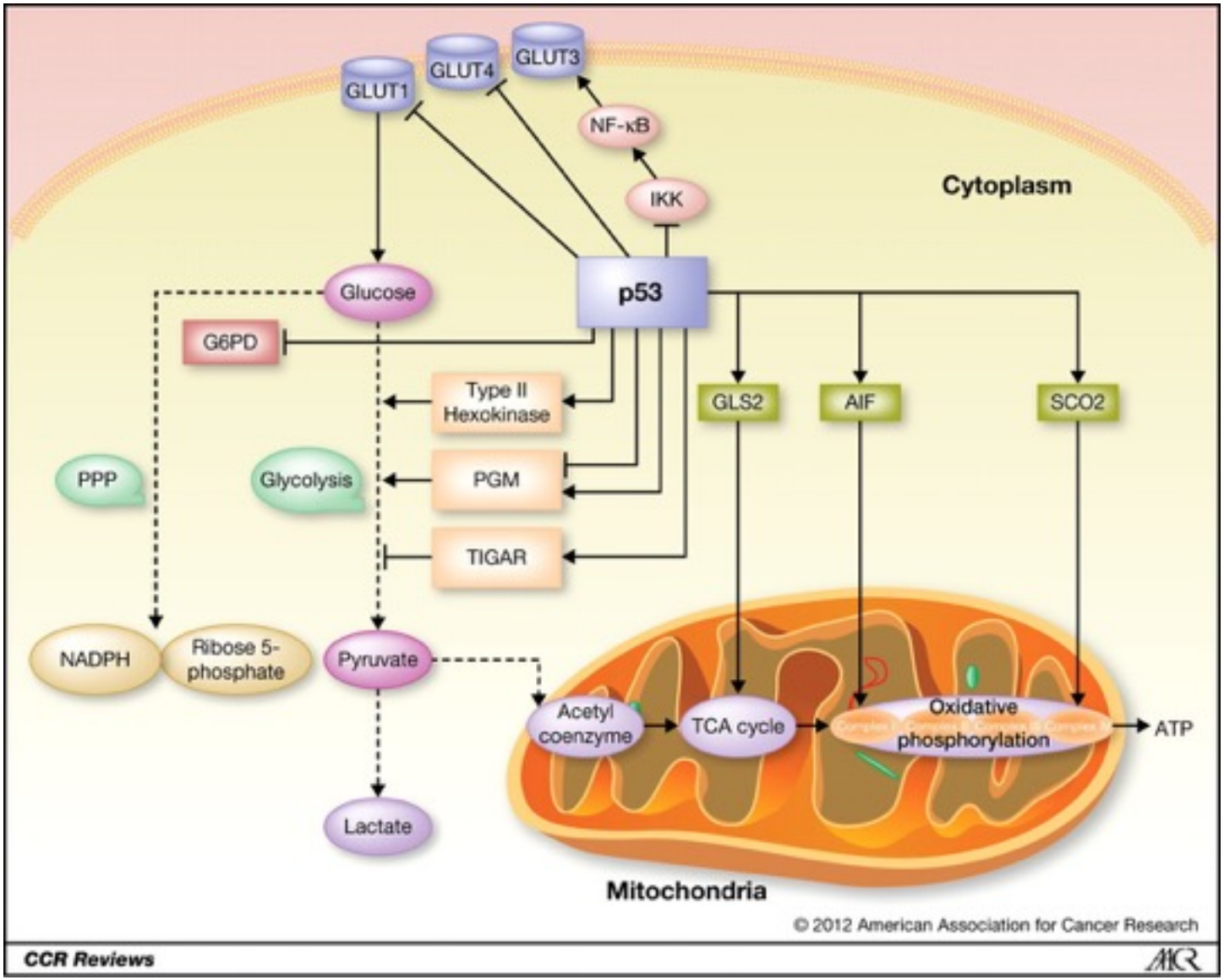
The Possible Drivers of the Altered Metabolism of Cancer Cells

- **The tumor microenvironment selects for altered metabolism**

  Hypotheses: Hypoxic conditions (A decrease in ambient O_2 availability and levels)

  - Persistent metabolism of glucose to lactate even in aerobic conditions is an adaptation to intermittent hypoxia in pre-malignant lesions
  - Upregulation of glycolysis leads to microenvironmental acidosis requiring evolution to phenotypes resistant to acid-induced cell toxicity
  - Subsequent cell populations with upregulated glycolysis and acid resistance have a powerful growth advantage, which promotes unconstrained proliferation and invasion

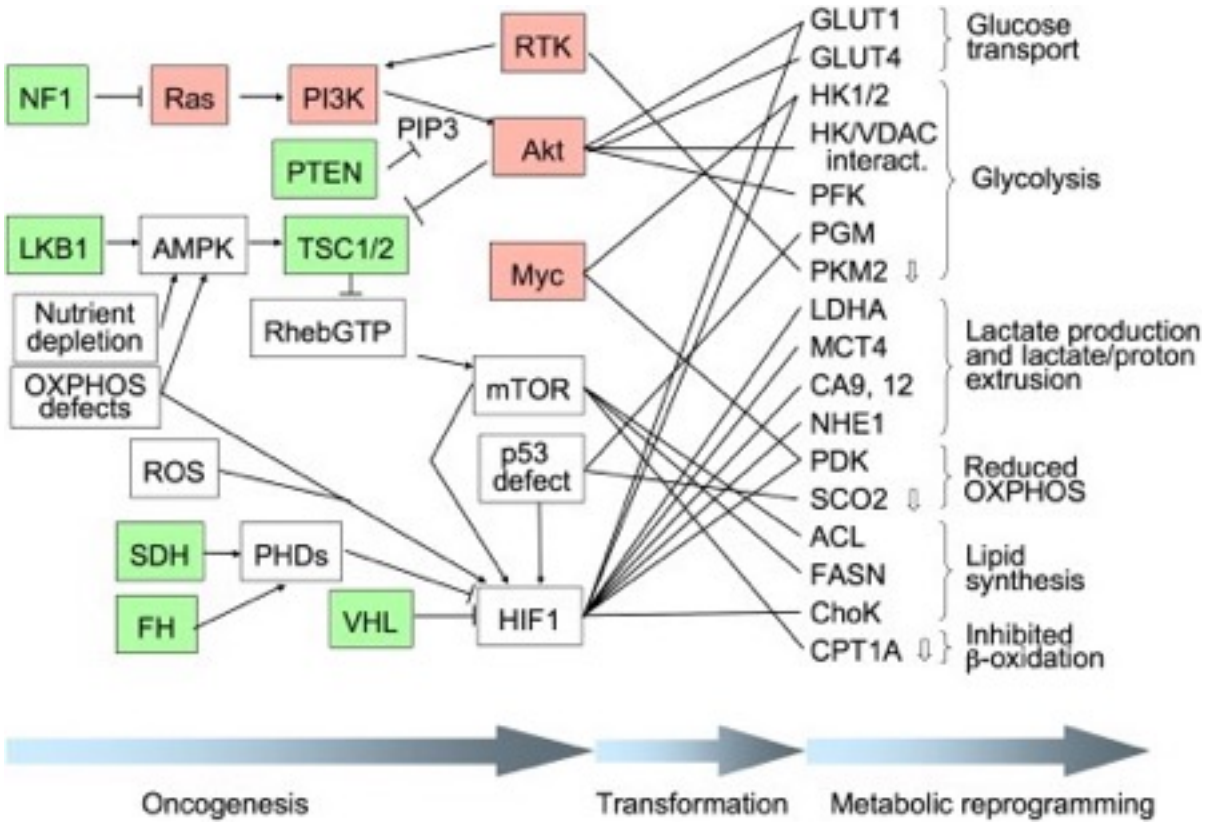
P53 Regulates Cellular Metabolism



Shen L et al. Clin Cancer Res 2012;18:1561-1567

Clinical Cancer Research

Molecular Mechanisms of Cancer-Specific Metabolic Reprogramming



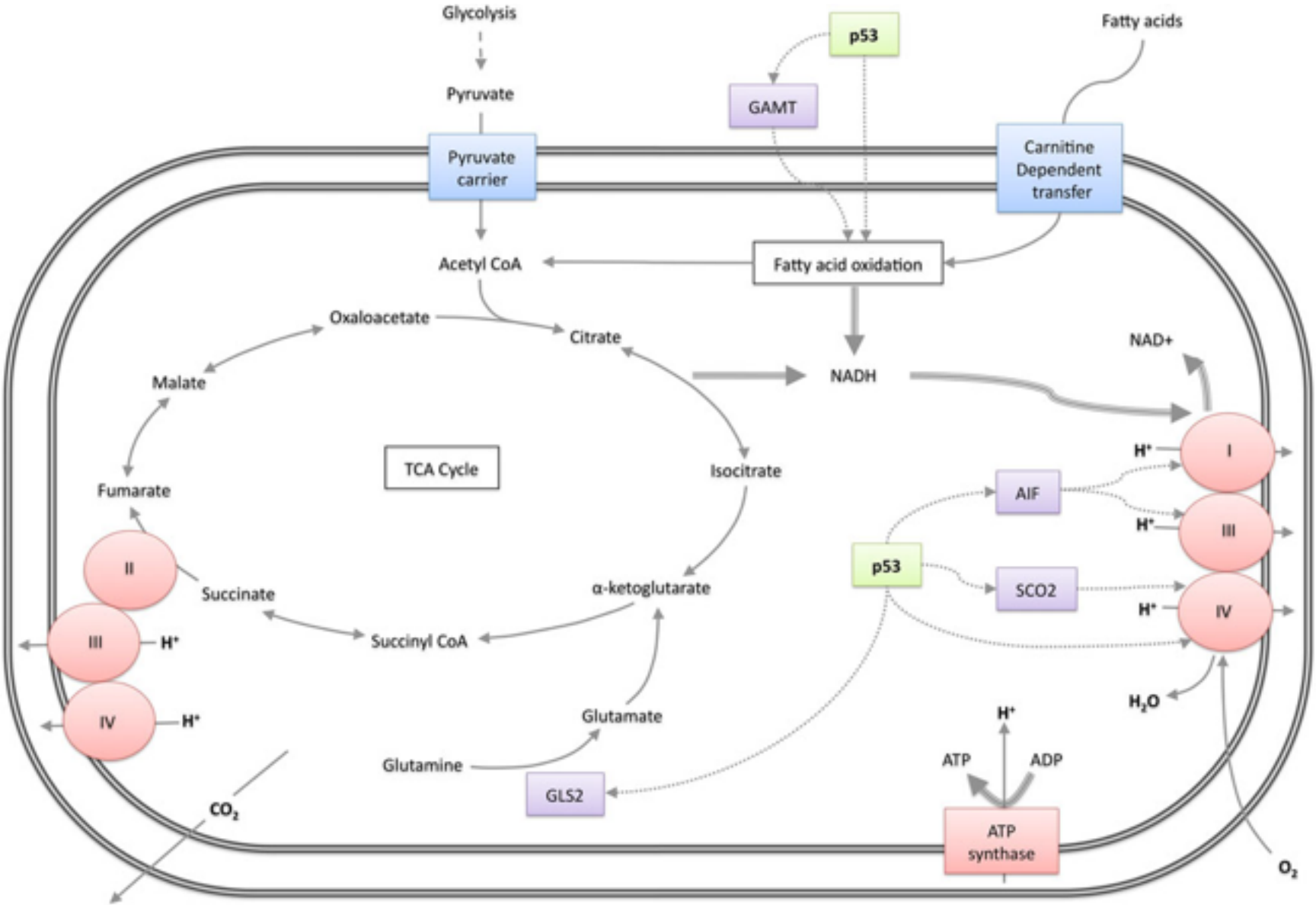
As a result of oncogenic gain-of-function events (pink) or the loss of tumor suppressors (green) affecting the PI3K/Akt/mTOR/HIF axis and/or inactivation of the p53 system, a stereotyped pattern of metabolic changes is induced, leading to cancer-associated alterations in metabolism. Note that arrows connecting different proteins do not necessarily indicate direct interactions. ACL, ATP citrate lyase; AMPK, AMP-activated kinase; CA9 and CA12, carbonic anhydrases 9 and 12; ChoK, choline kinase; CPT, carnitine palmitoyltransferase; FH, fumarate hydratase; GLUT, glucose transporter; HIF, hypoxia-inducible factor; HK, hexokinase; OXPHOS, oxidative phosphorylation; LAT1, L-type amino acid transporter 1; LDHA, lactate dehydrogenase isoform A; MCT, monocarboxylate transporter; mTOR, mammalian target of rapamycin; NF, neurofibromin; PDK, pyruvate dehydrogenase kinase; PFK, phosphofructokinase; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol triphosphate; PGM, phosphoglycerate mutase; PHD, prolyl hydroxylase; PKM2, pyruvate kinase isoform M2; SCO2, synthesis of cytochrome *c* oxidase 2; SDH, succinate dehydrogenase; TSC, tuberous sclerosis complex; VDAC, voltage-dependent anion channel; VHL, von Hippel-Lindau ubiquitin ligase.

Guido Kroemer, & Jacques Pouyssegur, 2008. Cancer Cell, 13: 472-482.

Table 1. Metabolic Effects of Selected Oncogenes and Tumor Suppressor Genes

Gene	Effects	Disease	Reference
Oncogenes			
PI3K	Activates Akt via PIP3; reduces (via Akt) expression of the β-oxidation enzyme carnitine palmitoyltransferase 1A (CPT1A)	Ovarian and gastrointestinal cancer	Deberardinis et al. (2006)
Akt	Upregulates fatty acid synthase (FASN); activates mTOR complex 1	Breast and ovarian cancer	Wang et al. (2005)
Her2	Increases, through activation of PI3K, Akt, and mTOR, expression of FASN and acetyl-CoA carboxylase α (ACCα) at the translational level	Mammary carcinoma	Yoon et al. (2007)
Tyrosine kinases	Generate phosphotyrosines that can bind to pyruvate kinase isoform PKM2, converting it from a tetramer to a less active dimer	Multiple cancers	Christofk et al. (2008b)
E7 from HPV16	Binds PKM2, converting it from a tetramer to a less active dimer	Cervical carcinoma	Mazurek et al. (2005)
Tumor Suppressors			
p53	Required for expression of SCO2 and hence optimal OXPHOS; enhances the expression of TIGAR, a glycolysis inhibitor; reduces the expression of the glycolytic enzyme phosphoglyceromutase	Multiple cancers	Matoba et al. (2006); Bensaad et al. (2006); Kondoh et al. (2005)
VHL	Ubiquitin ligase required for degradation of HIF-1α	Clear cell renal carcinoma	Shaw and Cantley (2006)
TSC1 (hamartin) and TSC2 (tuberin)	Negative regulators of Rheb (which inhibits mTOR)	Tuberous sclerosis complex and lymphangioleiomyomatosis	Shaw and Cantley (2006)
PTEN	Negative regulator of class I PI3K	Cowden syndrome and prostate cancer	Shaw and Cantley (2006)
LKB1	Required for activation of AMPK	Peutz-Jeghers syndrome and sporadic lung adenocarcinoma	Shaw and Cantley (2006)
NF1	Negative regulator of RAS and PI3K-Akt pathway	Neurofibromatosis	Shaw and Cantley (2006)
PML	Negative regulator of mTOR complex 1	Promyelocytic leukemia and lung cancer	Shaw and Cantley (2006)
Succinate dehydrogenase subunits SDHB, C, and D	Accumulated succinate competitively inhibits HIF-1α prolyl hydroxylases (PHDs)	Paraganglioma (SDHB, C, and D) and pheochromocytoma (SDHB and D)	Gottlieb and Tomlinson (2005)
Fumarate hydratase (fumarase)	Accumulated fumarate inhibits PHDs	Leiomyomatosis and papillary renal carcinoma	Gottlieb and Tomlinson (2005)

Cancer Cell. 2008 Jun; 13(6):472-82



p53 and mitochondrial respiration. Basal p53 levels transcriptionally activate synthesis of cytochrome oxidase 2 (SCO2) and apoptosis-inducing factor (AIF), which support the function of mitochondrial respiratory chain complexes I, III & IVand acts directly on complex IV subunit 1. p53 transcriptionally activates glutaminase 2 (GLS2), which catalyses the conversion of glutamine to glutamate. p53 regulates FAO via transcriptional activation of guanidinoacetate aminotransferase (GAMT), and possibly by other mechanisms.

Maddox O.D.K. and Vousden, K.H. 2011, *J Mol Med*, 89:237-245

CANCER

p53 turns on the energy switch

"...p53, one of the most frequently mutated genes in human cancers, regulates ... glycolytic pathways through its direct transcriptional targets."

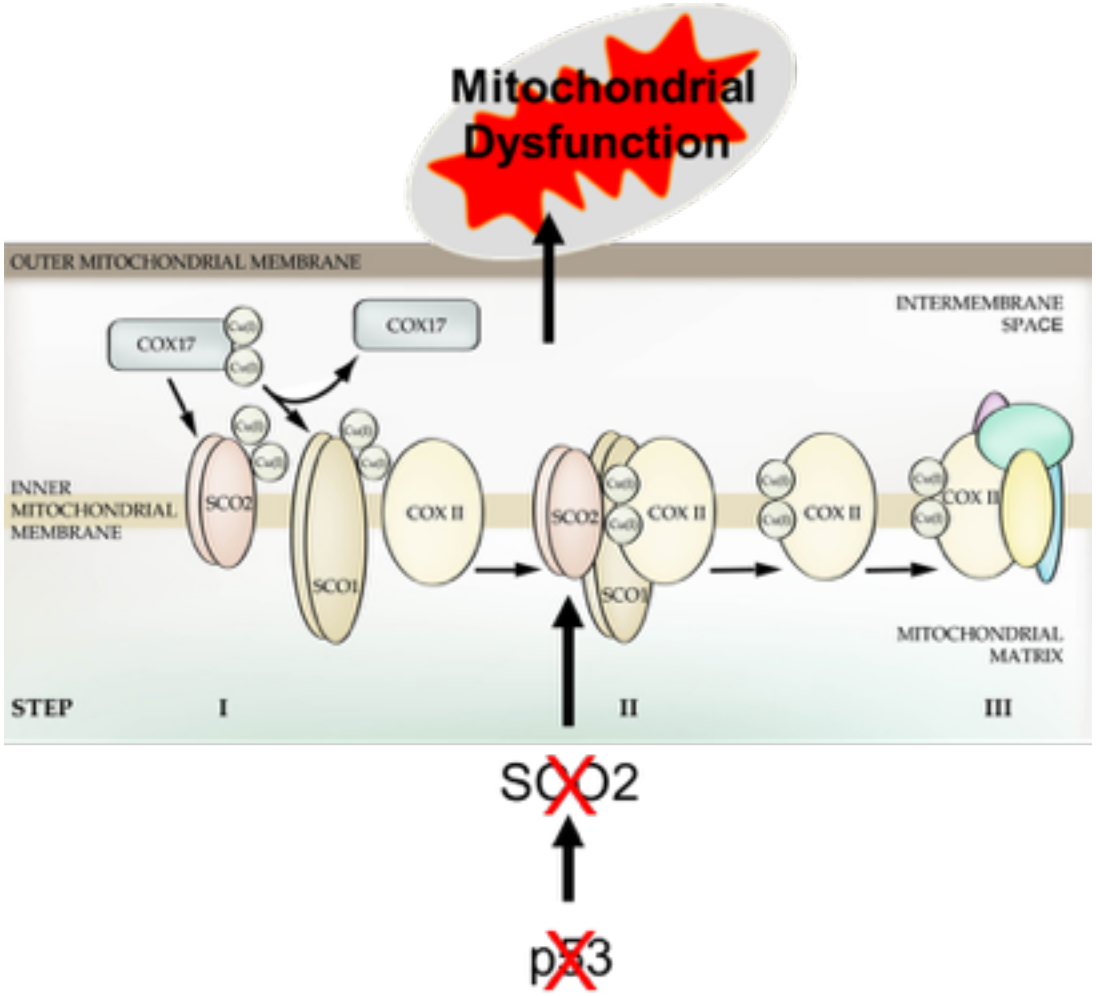
NATURE REVIEWS | MOLECULAR CELL BIOLOGY

p53 Regulates Mitochondrial Respiration

Satoaki Matoba,[1] Ju-Gyeong Kang,[1] Willmar D. Patino,[1] Andrew Wragg,[1] Manfred Boehm,[1] Oksana Gavrilova,[2] Paula J. Hurley,[3] Fred Bunz,[3] Paul M. Hwang[1*]

16 JUNE 2006 VOL 312 **SCIENCE**

p53 and Mitochondrial Respiration



Science 2006;312:1650-4

Reciprocity between Regulatory State and Metabolic State

- **“If regulatory state (transcription factors, signaling pathways, etc.) is accepted to control metabolic state, is it not also unconditionally certain that metabolic state will reciprocally control the regulatory state itself? Understanding this reciprocity, and digging to the bottom of it, is where the future lies”.**

Steve McKnight, *Science* 2010, 330:1138-39

Mutation of Metabolic Genes in Cancer

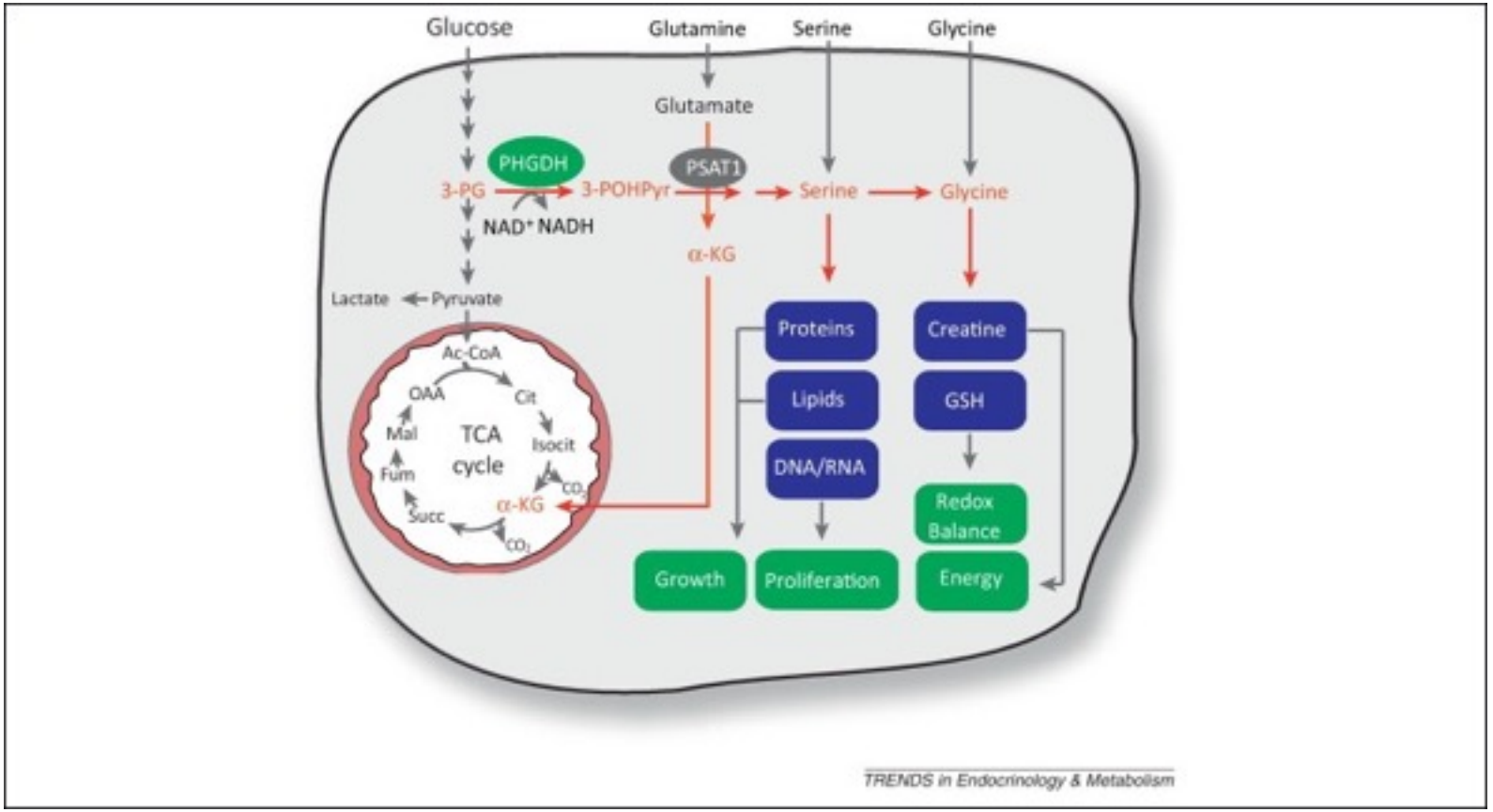
Mutation of 8 metabolic genes in cancer

Enzyme and subcellular location	Gene (chromosomal location)	Reaction catalyzed	Somatic tumor types or tumor syndromes[a]	Mutation frequency[b]
IDH1	*IDH1* (2q33.3)	Isocitrate + $NADP^+$ → α-KG + NADPH + CO_2	Glioma[c]	Somatic, ~75%
Isocitrate			Cartilaginous tumors[d]	Somatic, ~75%
Dehydrogenase 1			AML[e]	Somatic, ~20%
Cytoplasm			Thyroid carcinoma[f]	Somatic, 16%
Peroxisome			Melanoma	Somatic, 4/39
			Prostate carcinoma	Somatic, 2/75
IDH2	*IDH2* (15q26.1)	Isocitrate + $NADP^+$ → α-KG + NADPH + CO_2	Paraganglioma	Somatic, 1/131
Isocitrate			Cholangiocarcinoma[g]	Somatic, 23%
Dehydrogenase 2			Colorectal carcinoma	Somatic, 2/180
Mitochondria			T-cell lymphoma[i]	Somatic, 45%
FH	*FH* (1q42.1)	Fumarate + H_2O → s-Malate	HLRCC[g]	Germline: autosomal dominant
Fumarate			MCUL[h]	Germline: autosomal dominant
Hydratase			Renal cell carcinoma	Somatic, 1/3
Mitochondria			Melanoma	Somatic, 1/14
Cytoplasm			Leydig cell tumor	Germline mutation + somatic LOH, 2/29
			Ovarian cystadenoma[i]	Germline, 2/33
			Leiomyoma	LOH + somatic mutation, 1.3%
			Lung adenocarcinoma	Somatic, 1.1%
SDH	*SDHA* (5p15.33)	Succinate + ubiquinone → fumarate + ubiquinol	Familial paraganglioma	Germline: autosomal dominant
Succinate	*SDHB* (1p36.1)		Merkel cell carcinoma	Somatic, 2/7
Dehydrogenase	*SDHC* (1q23.3)		Paraganglioma	LOH + germline, 6/36
Mitochondria	*SDHD* (11q23.1)		Midgut carcinoid	LOH + somatic, 2/18
	SDHAF2 (11q12.2)			

a. IDH1 and IDH2 mutations are grouped together due to their mechanistic similarity and exclusive occurrence in the tumors.
b. For studies with sample number less than 100, the actual numbers, instead of percentages of mutation are given.
c. Glioma includes all WHOI-IV glioma.
d.Includes central enchondromas and chondrosarcomas, periosteal chondromas, and cartilaginous tumors associated with Maffuci and Ollier syndrome.
e. AML, acute myelogenous leukemia.
f. All histological subtypes.
g. HLRCC, hereditary leiomyoma with renal cell carcinoma.
HLRCC, hereditary leiomyoma with renal cell caa.
h. MCUL, multiple cutaneous and uterine leiomyoma.
i. Mucinous histological subtype.
j. GIST, gastrointestinal stromal tumor.
k. Intrahepatic cholangiocarcinoma only, no mutations were found in extrahepatic cholangiocarcinoma.
l. Angioimmunoblastic T-cell lymphoma confirmed by molecular signature (w/o confirmation rate was 20%). no mutations were found in other peripheral T-cell lymphomas.

Oerman etal., 2012. *Seinars Cell Dev Biol*., 23:370-380

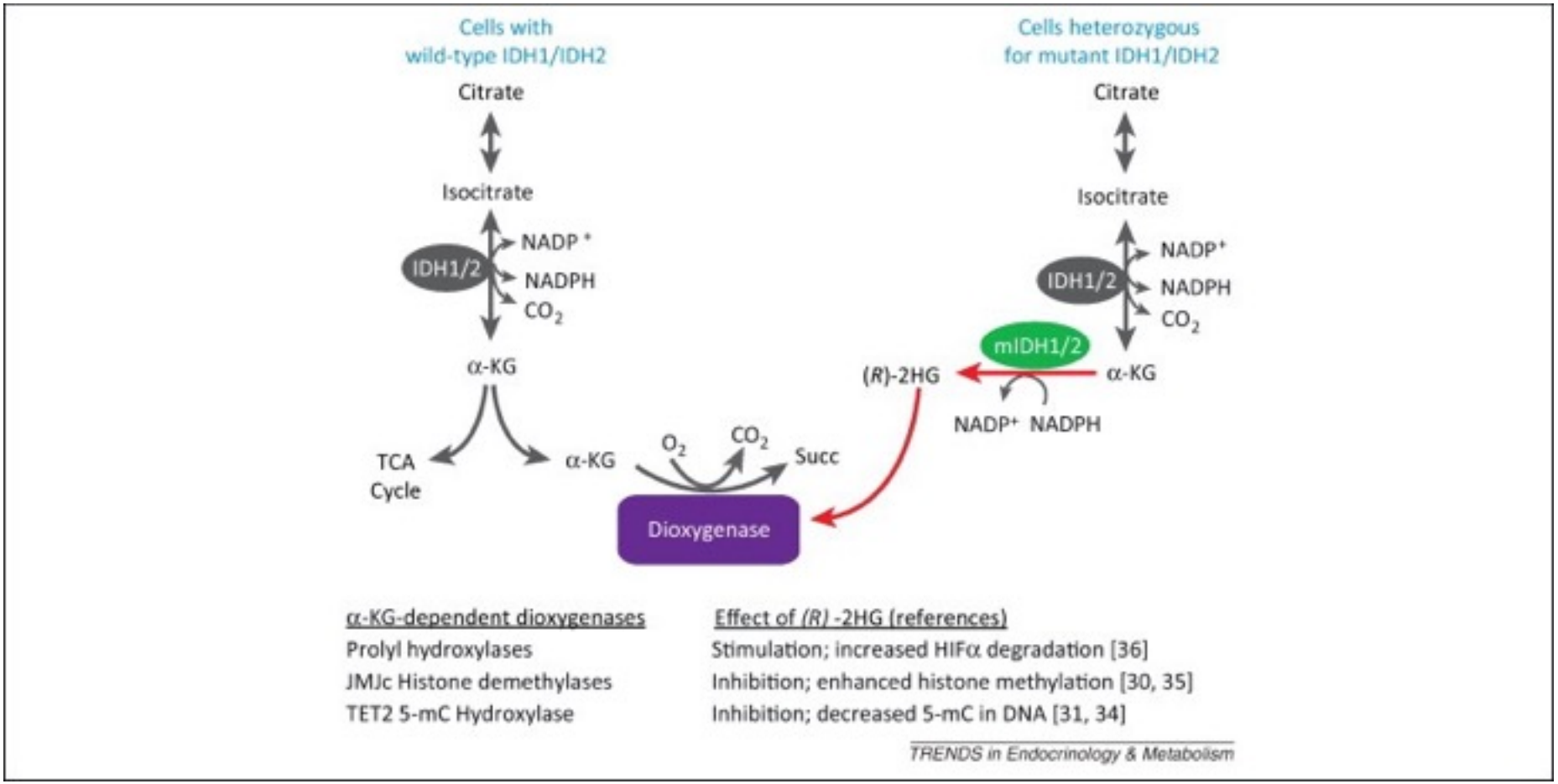
Phosphoglycerate dehydrogenase (PHGDH): a TCA Cycle Enzyme Overexpressed in some Human Tumors



Phosphoglycerate dehydrogenase is overexpressed in some cancers and catalyzes a growth-promoting metabolic pathway. Glycolytic cancer cells convert glucose into pyruvate, which can then be oxidized in the mitochondria or converted into lactate. Cells containing enhanced expression of the enzyme phosphoglycerate dehydrogenase (PHGDH), either as the result of genomic amplification of its gene on chromosome 1p12 or through other mechanisms, divert 3-phosphoglycerate (3-PG) away from glycolysis into the serine/glycine biosynthetic pathway (red arrows), which generates several important metabolic intermediates. Along this pathway, transamination of 3-phospho-hydroxypyruvate (3-POHpyr) by the enzyme phosphoserine aminotransferase-1 (PSAT1) generates α-ketoglutarate (α-KG), which can then be oxidized in the tricarboxylic acid (TCA) cycle. Serine and glycine are used to produce glutathione, proteins, nucleic acids, phospholipids, and sphingolipids, and other molecules required for cell growth and proliferation. Abbreviations: Ac-CoA, acetyl coenzyme A; Cit, citrate; Fum, fumarate; GSH, glutathione, Isocit, isocitrate; Mal, malate; OAA, oxaloacetate; Succ, succinate

Andrew R. Mullen, Ralph J. DeBerardinis, 2012. *Trends in Endocrinology & Metabolism*, 23:552-559

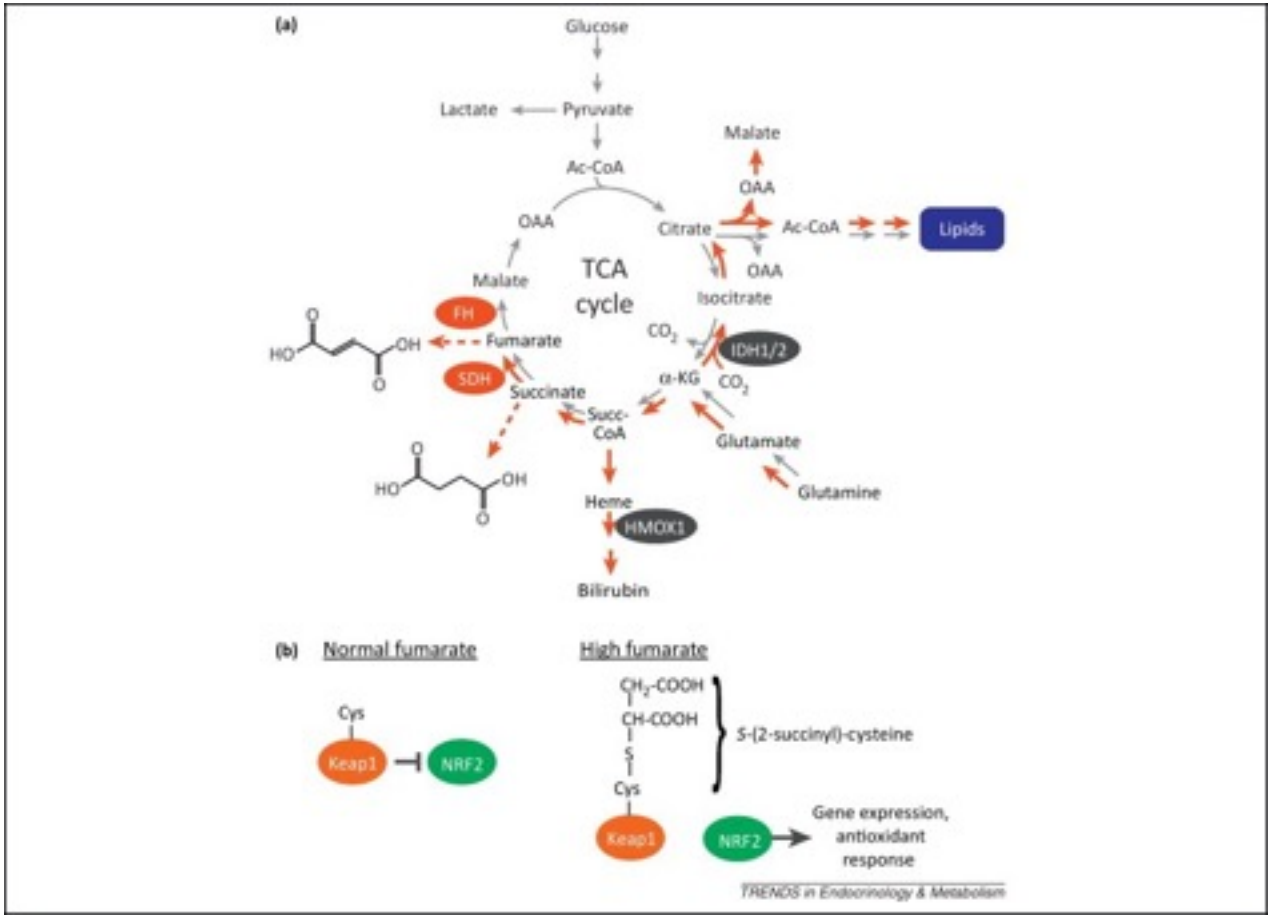
Mutation in a TCA Cycle Enzyme Produces an "Oncometabolite"



Mutant IDH1/2 enzymes produce an oncometabolite with pleiotropic effects on cell signaling and epigenetics. Normal cells contain wild-type isocitrate dehydrogenases *IDH1* and *IDH2* (gray). These enzymes catalyze the reversible conversion of isocitrate to α-ketoglutarate (α-KG), generating NADPH and CO_2. α-KG can be oxidized in the TCA cycle or used as a cofactor by α-KG-dependent dioxygenase enzymes. Tumor cells with somatically-acquired, heterozygous active site mutations in *IDH1* or *IDH2* (mIDH1/2, green) display a neomorphic enzyme activity that reduces α-KG to *R*(–)-2-hydroxyglutarate [(*R*)-2HG], using NADPH as a cofactor. Owing to its structural similarity to α-KG, (*R*)-2HG modulates the function of α-KG-dependent dioxygenases, stimulating prolyl hydroxylase activity, and inhibiting several enzymes that regulate histone and DNA modifications. Together, these processes exert complex effects on gene expression that probably contribute to the malignancy of *IDH1/2*-mutant cells. Abbreviation: Succ, succinate.

Andrew R. Mullen, Ralph J. DeBerardinis, 2012. *Trends in Endocrinology & Metabolism*, 23:552-559

Effects of mutation of TCA cycle enzymes on metabolism and gene expression



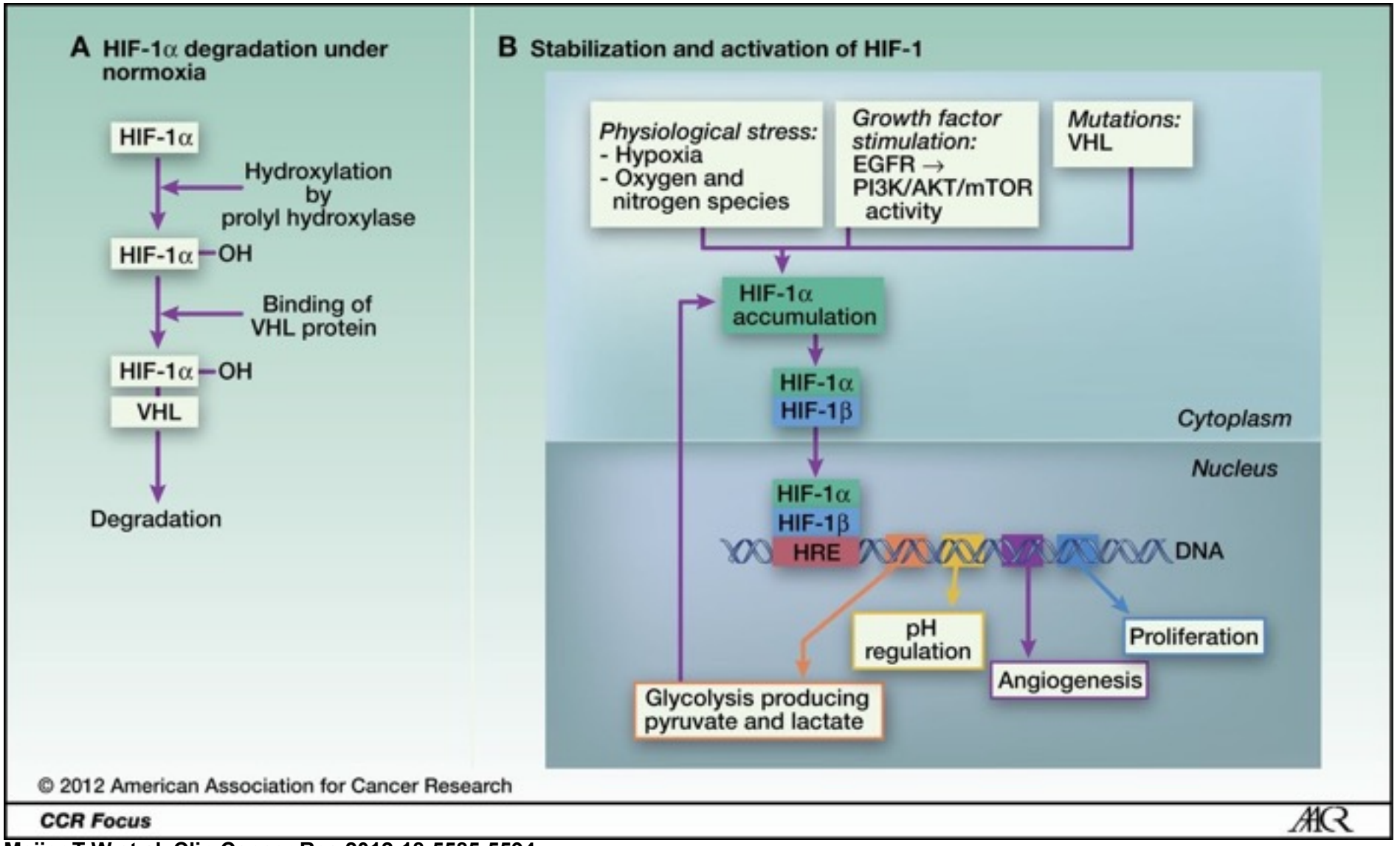
(a) Succinate dehydrogenase (SDH) and fumarate hydratase (FH) are TCA cycle enzymes and tumor suppressors. In normal cells, succinate and fumarate are generated through oxidative metabolism of glutamine-derived α-ketoglutarate (α-KG) (gray arrows). Subsequent metabolism around the TCA cycle generates citrate for lipid synthesis. SDH and FH deficiency interrupt this pathway, with accumulation of succinate and fumarate, respectively. FH-deficient cells redirect TCA cycle metabolism in two ways (red arrows). First, the cells shunt succinyl-CoA into a pathway of heme biosynthesis and degradation, culminating in the secretion of bilirubin. Inhibiting heme oxygenase-1 (HMOX1) in this pathway selectively kills cells with FH deficiency. Second, to produce citrate, the cells use reductive carboxylation of glutamine-derived α-KG. IDH1 and/or IDH2 participate in this reaction, and subsequent metabolism of citrate produces acetyl-CoA for fatty acid/lipid synthesis, and other TCA cycle intermediates such as oxaloacetate and malate, which are normally produced downstream of FH. **(b)** Keap1 is an electrophile sensor. In the absence of fumarate and other electrophiles, Keap1 negatively regulates the transcription factor Nrf2, targeting it for degradation. In FH-deficient cells, cysteine residues on Keap1 are modified by fumarate-dependent succination, in which cysteine is converted to *S*-(2-succinyl)-cysteine. Nrf2, now active, can activate the transcription of genes involved in the antioxidant response. Abbreviations: Ac-CoA, acetyl coenzyme A; Cys, cysteine; HMOX1, heme oxygenase-1; IDH1/2, isocitrate dehydrogenase isoforms 1 and 2; OAA, oxaloacetate; Succ-CoA, succinyl coenzyme A.

Andrew R. Mullen, Ralph J. DeBerardinis, 2012. *Trends in Endocrinology & Metabolism*, 23:552-559

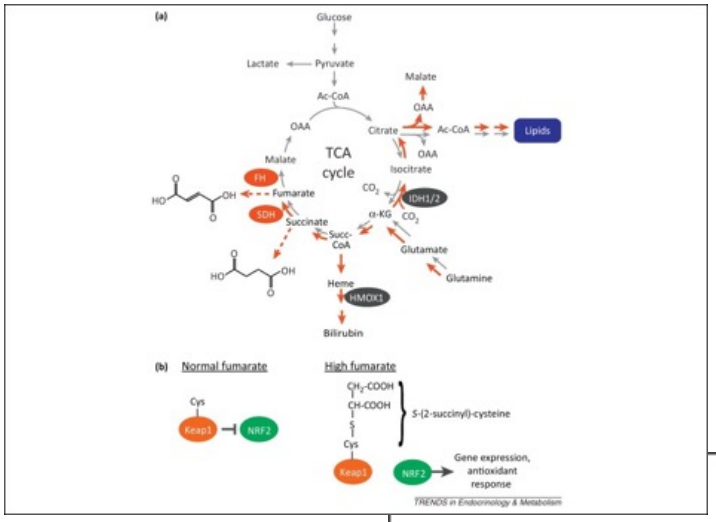
HIF Regulation: An Example for Bidirectional Nuclear-Mitochondrial Communication

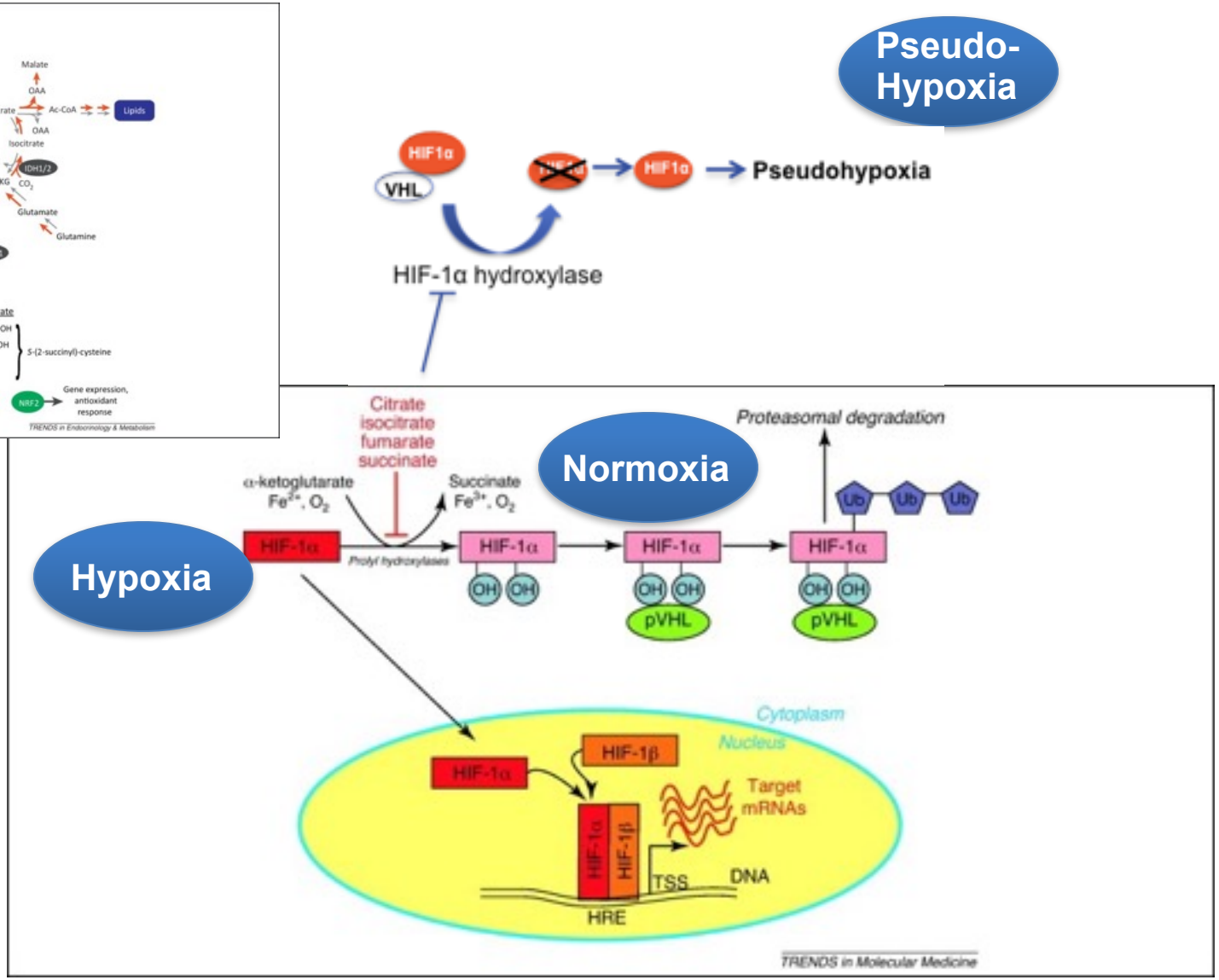
HIF: Hypoxia Inducible Factor

HIF-1 Pathway



Meijer T W et al. Clin Cancer Res 2012;18:5585-5594



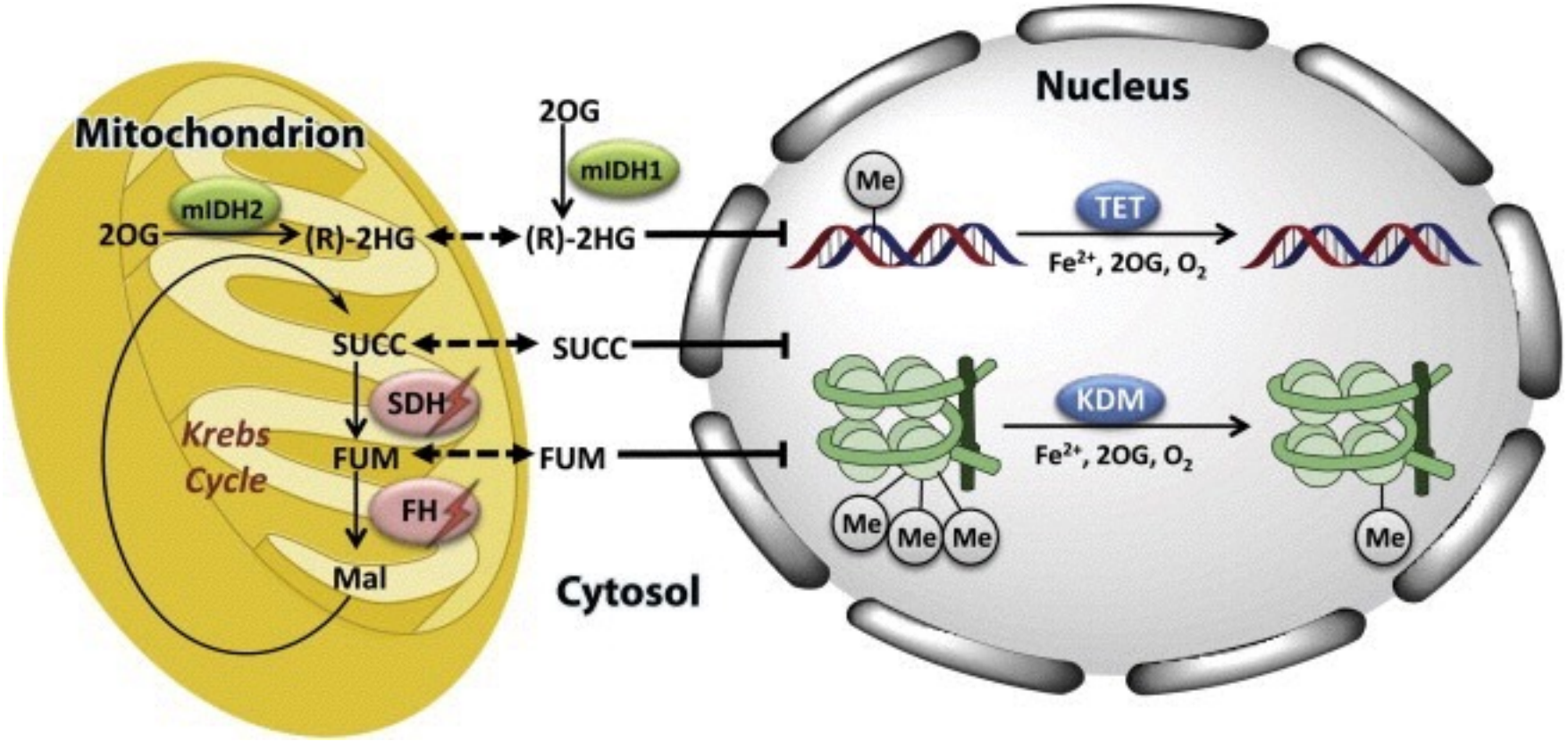


Role of TCA cycle metabolites in the regulation of hypoxia inducible factor (HIF) α subunits in hypoxic, pseudohypoxic and nonhypoxic conditions.

Nuno Raimundo, Bora E. Baysal, Gerald S. Shadel, *Trend in Molecular Medicine*, 2011. 17: 641-649.

Epigenetic Reprogramming by Oncometabolites

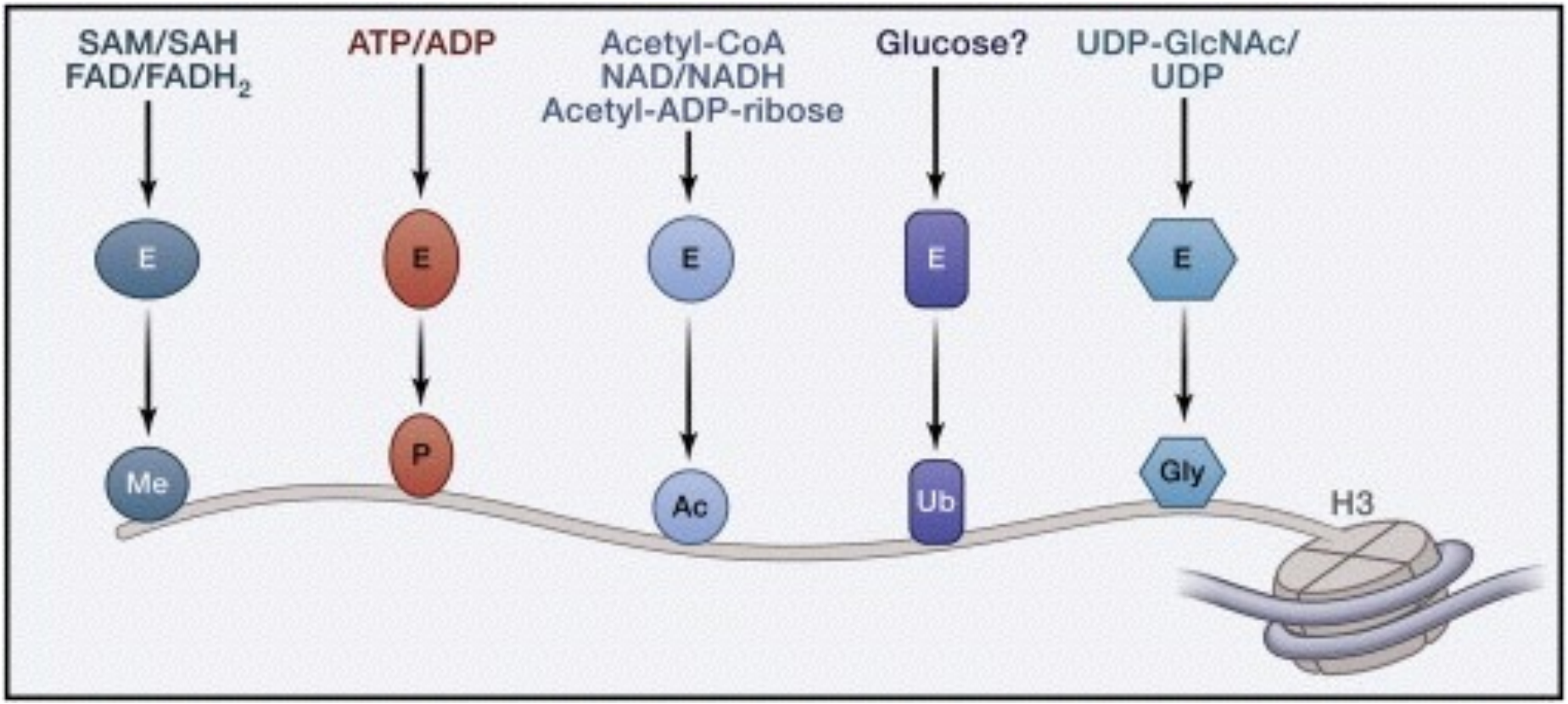
Epigenetic Reprogramming by Oncometabolites



Mutations in the metabolic enzymes isocitrate dehydrogenase (IDH)-1 and -2, succinate dehydrogenase (SDH), and fumarate hydratase (FH) lead to abnormal accumulation of (R)-2-hydroxyglutarate [(R)-2HG], succinate, and fumarate, respectively. Their accumulation inhibits the activities of 2-oxoglutarate (2OG)-dependent dioxygenases, including the TET family of DNA modifying enzymes and the JmjC domain-containing histone lysine demethylases (KDMs). Subsequent epigenetic alterations result in cell differentiation arrest and promote malignant transformation. Thus, epigenetic modification, through the action of oncometabolites, is a shared feature among IDH-, SDH-, and FH-associated cancers. SUCC, succinate; FUM, fumarate; Mal, malate; mIDH1/2, mutant IDH1/2; Me, methyl group.

Ming Yang, Patrick J. Pollard. *Cancer Cell*, 2013, 23: 709–711

Chromatin-Remodeling Enzymes “Sense” Cellular Metabolism



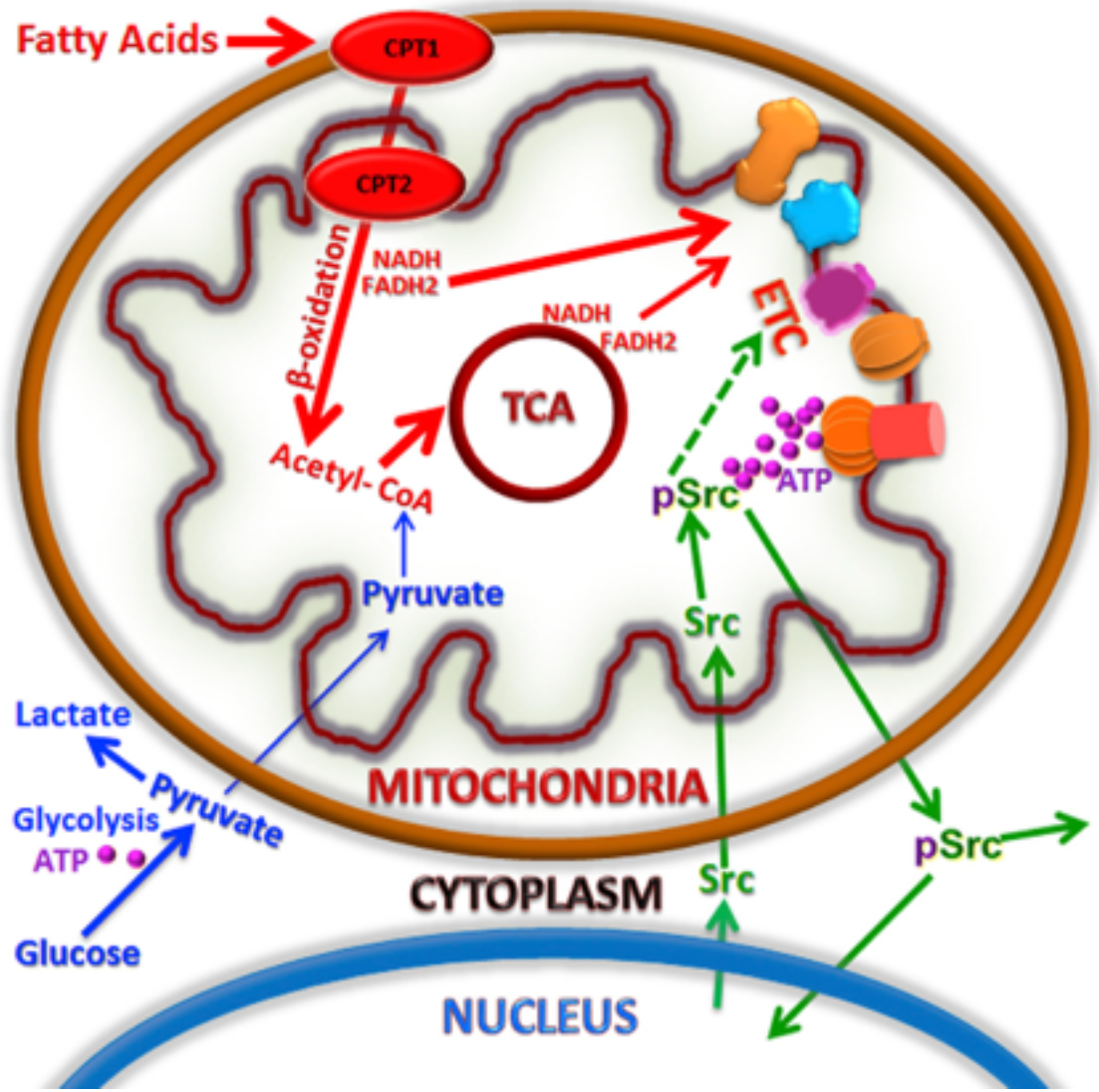
Schematic representation of the histone H3 tail with residues that can be modified by various enzymes (E), leading to phosphorylation (P), acetylation (Ac), methylation (Me), ubiquitination (Ub), and glycosylation (Gly). These modifications have been associated with changes in chromatin organization, gene activation, silencing, and several other nuclear functions. Each enzyme utilizes cellular metabolites, whose availability would dictate the efficacy of the enzymatic reaction.

Sayako Katada, Axel Imhof, Paolo Sassone-Corsi, 2012. *Cell,* 148:-24-28

Mitochondria as a Driver of Cancer

Fatty Acid Oxidation-Driven Src Links Mitochondrial Energy Reprogramming and Oncogenic Properties in Triple-Negative Breast Cancer

Etoxomir



Park et al (Benny Abraham Kaipparettu Lab, BCM), 2016, ***Cell Reports***, 14: 1-12

Fatty acid oxidation drives Myc-overexpressing triple negative breast cancer.

Camarda r et al., 2016. *Nature Medicine*, 22: 427-432.

Metabolism Contributes to Cancer

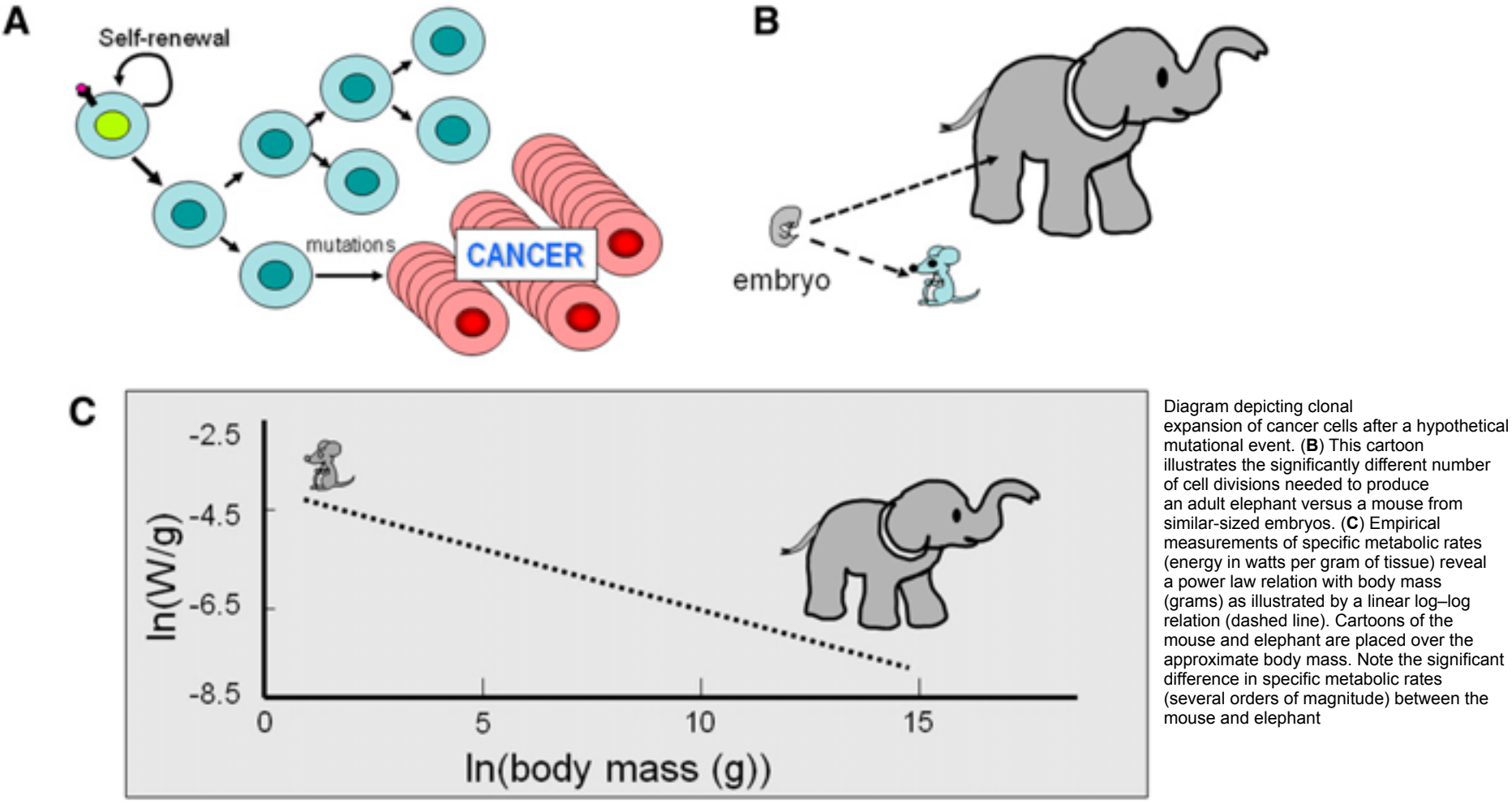
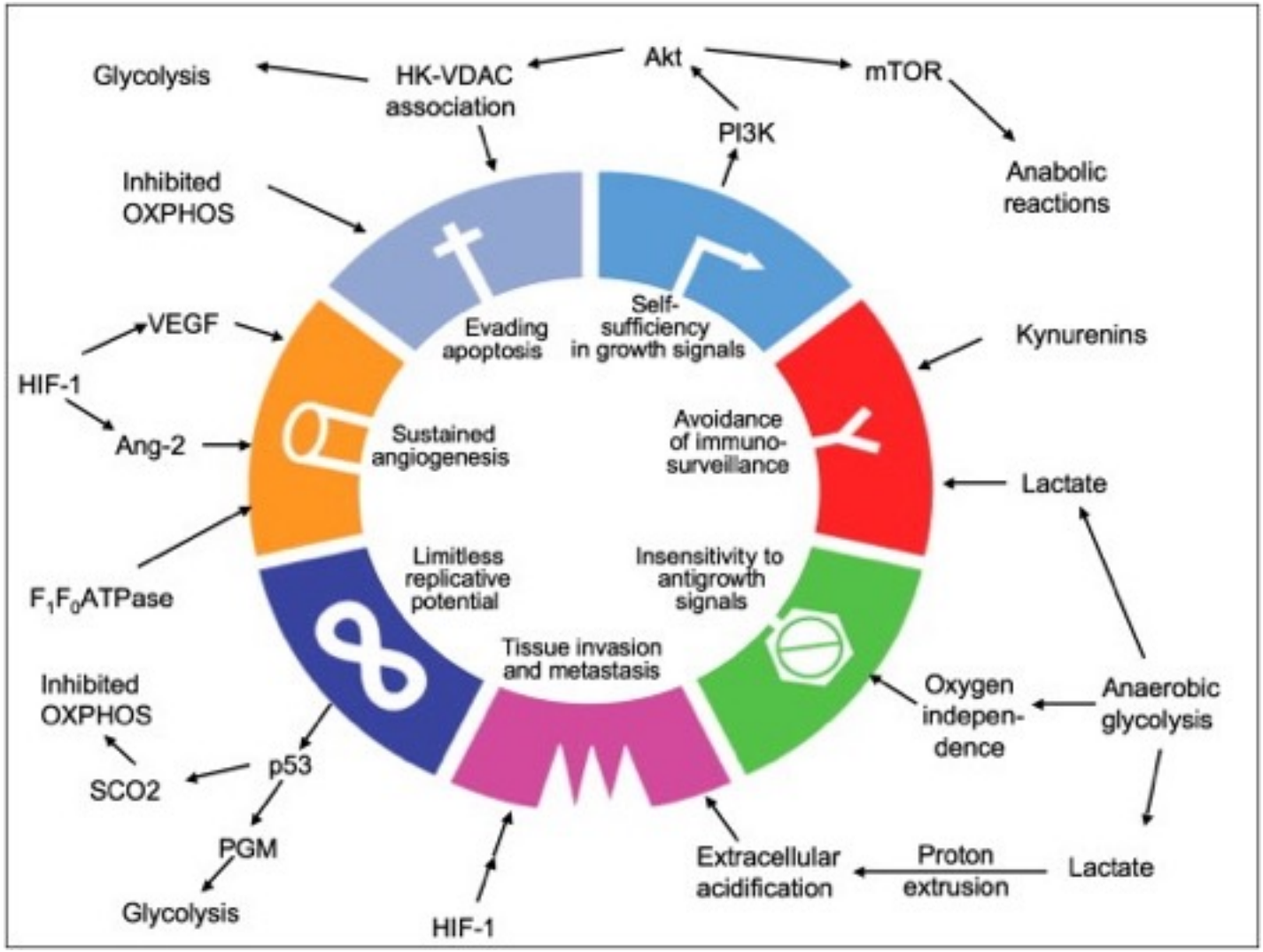


Diagram depicting clonal expansion of cancer cells after a hypothetical mutational event. (**B**) This cartoon illustrates the significantly different number of cell divisions needed to produce an adult elephant versus a mouse from similar-sized embryos. (**C**) Empirical measurements of specific metabolic rates (energy in watts per gram of tissue) reveal a power law relation with body mass (grams) as illustrated by a linear log–log relation (dashed line). Cartoons of the mouse and elephant are placed over the approximate body mass. Note the significant difference in specific metabolic rates (several orders of magnitude) between the mouse and elephant

C.V. Dang, 2012. *Genes & Development*, 26: 877-890

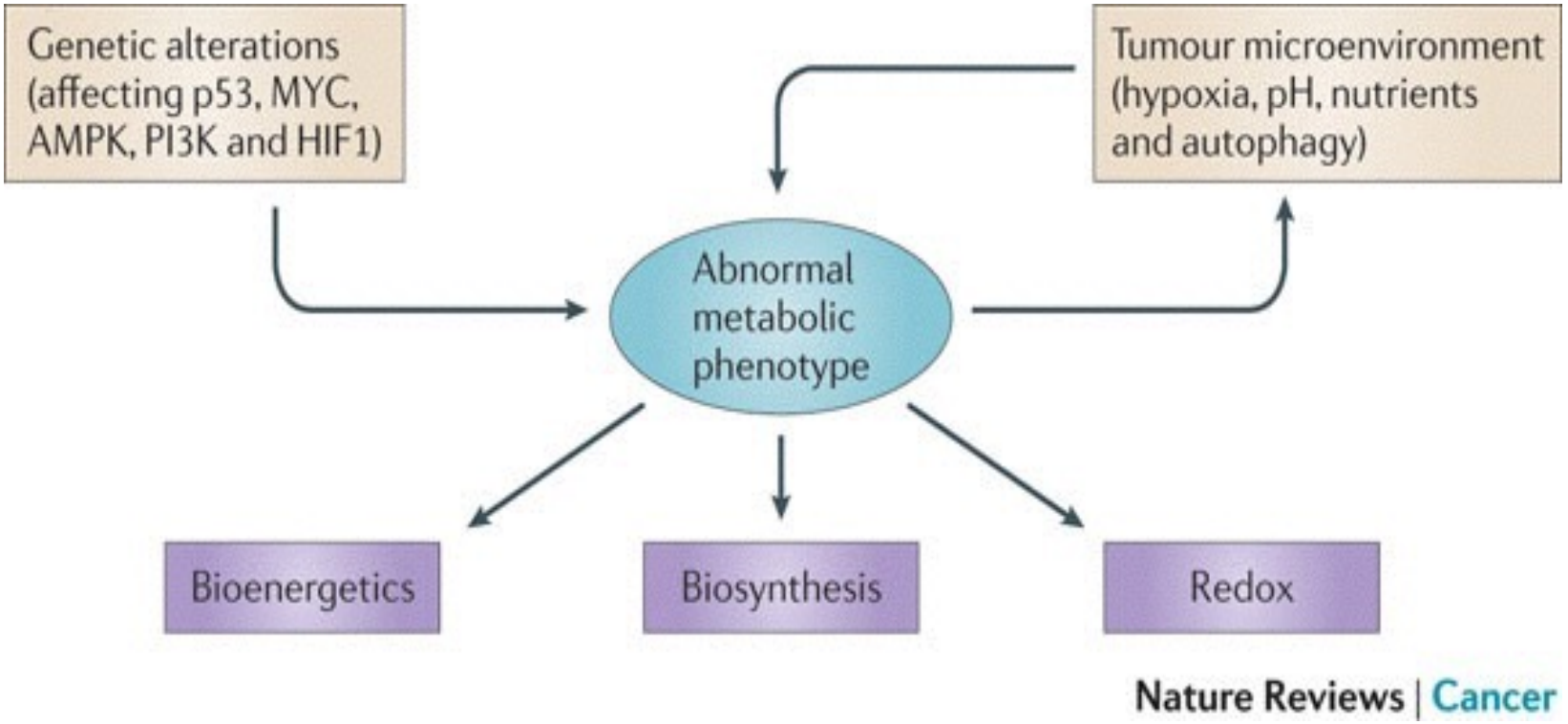
Therapeutic Strategies



The Seven Hallmarks of Cancer and Their Links to Tumor Metabolism
The hypothetical links between different metabolic alterations and the seven nonmetabolic characteristics of neoplasia (circle) are depicted. Centripetal arrows (pointing from the inside outwards) indicate how the seven hallmarks of cancer can impinge on metabolism. Centrifugal arrows (pointing from the outside inwards) illustrate how neoplasia-associated metabolic reprogramming can contribute to the acquisition of the seven hallmarks. Ang-2, angiopoietin-2; GLUT, glucose transporter; HIF, hypoxia-inducible factor; HK, hexokinase; OXPHOS, oxidative phosphorylation; PGM, phosphoglycerate mutase; PI3K, phosphatidylinositol 3-kinase; SCO2, synthesis of cytochrome *c* oxidase 2; VDAC, voltage-dependent anion channel; VEGF, vascular endothelial growth factor.

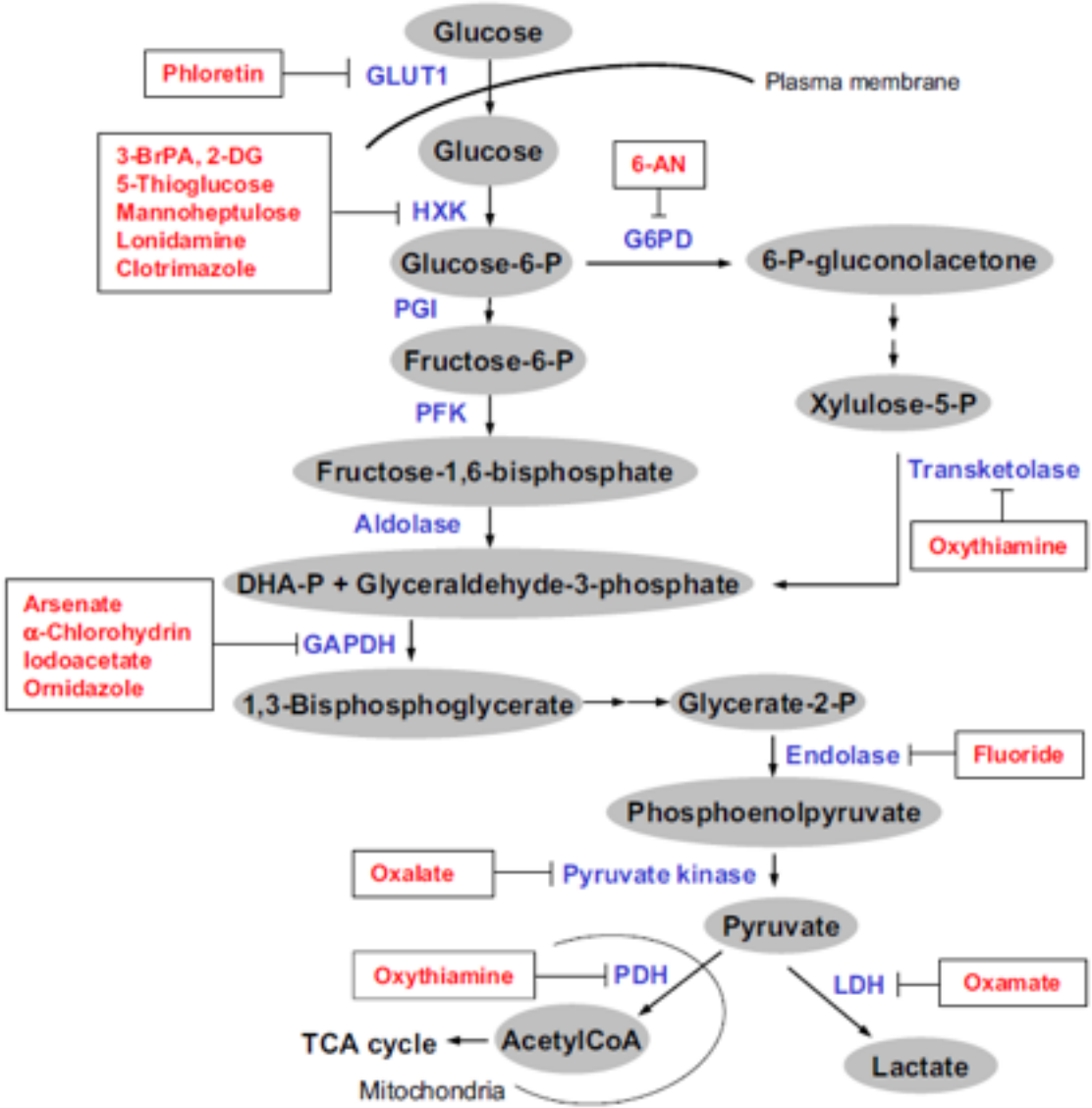
Kroemer and Pouyssegur, 2008. *Cancer Cell*, 13:472-482

Summary: Factors Affecting Cancer Metabolism



TW Mak et al., Nat Rev Cancer, 2011

Glycolytic Inhibitors With Anticancer Activity



Oncoene 2006; 25:4633-46 , J Bioegnerg Biomembr 2007; 39:267-74

Glycolytic Inhibitors With Anticancer Activity

Table 1 Chemicals targeting glycolysis-related enzymes

Compound	Target	Tumor Type	Response	Concentration	Trial	N° Trial or Reference
2-DG	HK	Prostate Cancer	–	30 mg/kg daily	Phase I/II	NCT00633087 (suspended)
		Advanced solid tumors	–		Phase I	NCT0009677 (completed)
		Ovarian carcinoma Mesothelioma	Apoptosis	5 mM	Pre-clinical	(Zhang et al. 2006)
		Alveolar Rhabdomyosarcoma	Apoptosis	2-10 mM	Pre-clinical	(Ramirez-Peinado et al. 2011)
Lonidamine	HK	Glioblastoma multiforme	Partial stabilization	450 mg daily (+15 mg daily diazepan)	Phase II	(Oudard et al. 2003)
		Benign Prostatic hyperplasia	Tumor volume Reduction	150 mg daily	Phase II	(Ditonno et al. 2005)
Imatinib (Gleevec)	Bcr-Abl	Chronic myeloid leukemia	–	400 mg daily	Approved agent	(Druker et al. 2006)
	KIT	Gastrointestinal stromal tumor	–	400 mg daily	Approved agent	(Demetri et al. 2002)
Oxythiamine	TKTL-1	Lewis lung carcinoma	Anti-metastatic effect	500 mg/kg daily	Pre-clinical	(Yang et al. 2010)
		Ehrlich's ascites tumor cells	Tumor growth inhibition	400 mg/kg daily	Pre-clinical	(Boros et al. 1997)
FX11	LDH-A	Human lymphoma Human pancreatic cancer	Tumor growth inhibition	42 μg daily	Pre-clinical	(Le et al. 2010)
CHC	MCT1	Colon and lung carcinoma	Necrosis Radiosensitization	125 mM	Pre-clinical	(Sonveaux et al. 2008)

Oncogene (2006) 25, 4633–4646, J Bioenerg Biomembr. 2012 Feb;44(1):17-29

Potential Metabolic Targets for the Treatment of Cancer

Target	Desired Effects	Examples of Compounds	Reference
Glycolysis			
Glucose uptake	Inhibition of glucose transport or of the initial steps of glycolysis	2-deoxyglucose has radiosensitizing and chemosensitizing effects	Simons et al. (2007)
Hexokinase (HK1 and HK2)	Inhibition of enzymatic activity and dissociation from mitochondria	3-bromopyruvate has potent antitumor effects in vitro and in vivo	Kim et al., 2007b and Pedersen, 2007
Pyruvate dehydrogenase kinase 1 (PDK1)	Inhibition of PDK1 for deinhibition of pyruvate dehydrogenase	Dichloroacetate (DCA)	Bonnet et al. (2007)
Lactate dehydrogenase A (LDHA)	Inhibition	siRNA	Fantin et al. (2006)
Pyruvate kinase (PK) isoenzyme PKM2	Translocation of PKM2 to the nucleus for induction of apoptosis	Somatostatin and its derivative TT-232 (in vitro)	Stetak et al. (2007)
Fatty Acid Synthesis			
ATP citrate lyase (ACL)	Inhibition	SB-2049990 inhibits pancreatic cancer growth in nude mice	Hatzivassiliou et al. (2005)
Acetyl-CoA carboxylase (ACC)	Inhibition	Soraphen A induces apoptosis or autophagy in vitro	Beckers et al. (2007)
Fatty acid synthase (FASN)	Inhibition	Cerulenin and its derivative C57 inhibit human ovarian cancer cell growth in SCID mice	Wang et al. (2005)
Choline kinase (ChoK)	Inhibition	MN58b reduces phosphomonoesters in human cancer xenografts	Al-Saffar et al. (2006)
HIF			
HIF-1α prolyl hydroxylases (PHDs)	Activation of PHDs for inhibition of HIF, achieved by reversal of fumarate- or succinate-mediated inhibition of PHDs	Cell-permeating α-ketoglutarate derivatives reverse HIV activation in SDH- or FH-deficient cells in vitro	MacKenzie et al. (2007)
Hypoxia-inducible factor 1 (HIF-1)	Inhibition of DNA binding	Echinomycin	(Kong et al. (2005)
Reactive	Antioxidants	N-acetylcysteine (NAC); vitamin C	Gao et al. (2007)

Kroemer and Pouyssegur, 2008. *Cancer Cell*, 13:472-482

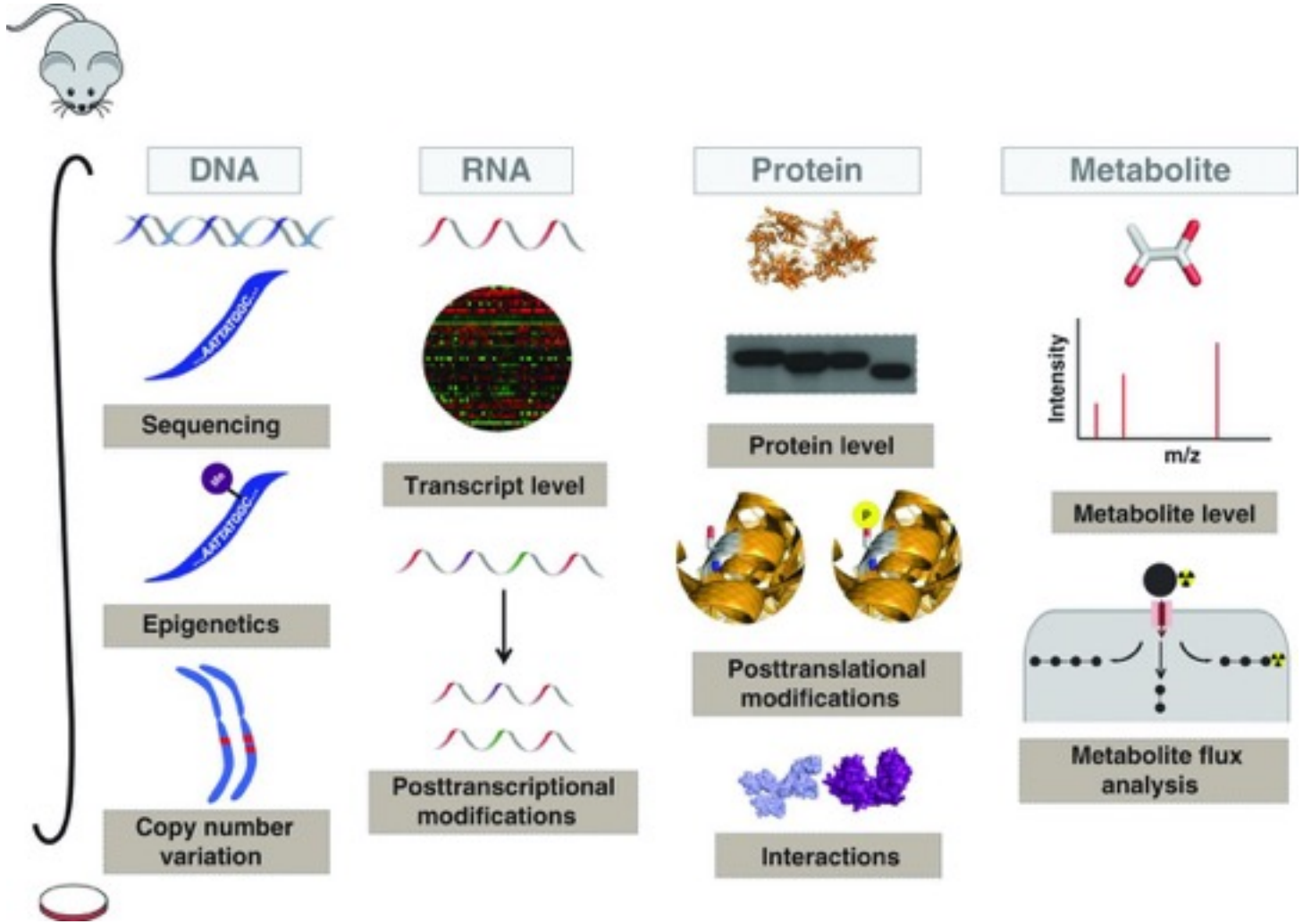
Table 2 Strategies to target anabolic pathways for cancer treatment

Table 2 | **Strategies to target anabolic pathways for cancer treatment**

Target pathway and protein	Agent	Development stage	Observations	Refs
Nucleic acid synthesis				
Dihydrofolate reductase	Methotrexate, pemetrexed, and pralatrexate (antifolates)	Approved as anticancer agents	• Methotrexate used mainly in oncology clinical practice to treat lymphomas and leukaemias, bladder cancer, and gestational trophoblastic tumours, although also used extensively in the treatment of autoimmune diseases • Pemetrexed used mainly in non-small-cell lung cancer and pralatrexate in T-cell lymphomas	201
Thymidylate synthase	5-fluorouracil, capecitabine, and S-1 (pyrimidine analogues)	Approved as anticancer agents	Used mainly in clinical practice to treat gastrointestinal malignancies	88
Adenine/adenosine deaminase	Pentostatin, 6-mercaptopurine, and cladribine (purine analogues)	Approved as anticancer agents	Used mainly to treat haematological malignancies	NA
DNA polymerase/ ribonucleotide reductase	Gemcitabine, cytarabine, and fludarabine (purine and pyrimidine analogues); hydroxyurea	Approved as anticancer agents	• Gemcitabine is a widely used agent in clinical oncology practice • Cytarabine, fludarabine, and hydroxyurea are used mainly in patients with haematological malignancies	NA
Lipid synthesis				
Fatty acid synthase (FASN)	TVB-2640	Preclinical studies	Anticancer effects in vitro	105
ATP citrate lyase (ACL)	Hydroxycitrate	Preclinical studies	Anticancer effects in vitro	102
Acetyl-CoA carboxylase (ACC)	ND-010976	Preclinical studies and clinical studies	• Anticancer effects in vitro • Phase I clinical trials in hepatocellular carcinoma are ongoing	103
Choline kinase	TCD-717, CK37, MN58b, RSM932A, and RNAi	TCD-717 is in clinical development	• Anticancer effects in vitro and in vivo • Phase I clinical trial has been completed, but no data on anticancer activity is available	104,108
Mevalonate pathway				
HMG-CoA reductase (HMGCR)	Statins, such as simvastatin and atorvastatin	Approved for the treatment of hypercholesterolaemia	Anticancer effects currently under investigation in >20 clinical trials	109,110
Pentose phosphate pathway				
Phosphoglycerate mutase (PGAM1)	PGMI-004A and RNAi	Preclinical studies	Anticancer effects in vitro and in vivo	219
Amino acid metabolism				
Phosphoglycerate dehydrogenase (PHGDH)	RNAi	Preclinical studies	Inhibition of tricarboxylic acid cycle anaplerosis	93,94
Asparagine availability	L-asparaginase	Approved as anticancer agent	Used in clinical practice to treat acute lymphoblastic leukaemia	NA
Arginine availability	Pegylated arginine deiminase (ADI-PEG20)	Clinical development: phase II clinical trials	• Randomized phase II trial in patients with mesothelioma showed prolonged progression-free survival compared with best supportive care • Multiple phase II trials are ongoing	220
Indoleamine-2,3-dioxygenase (IDO)	Epacadostat and indoximod	Clinical development: phase III trials are ongoing	• IDO is a rate-limiting enzyme in tryptophan catabolism, which generates kynurenine (inhibition limits tryptophan availability) • Clinical responses have been observed in phase II clinical trials	46,92

Martinez-Outschoorn, U. E. *et al.* (2016) Cancer metabolism: a therapeutic perspective
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.60

Application and Integration of Tools to Study Tumor Metabolism



Cantor J R , and Sabatini D M Cancer Discovery 2012;2:881-898

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