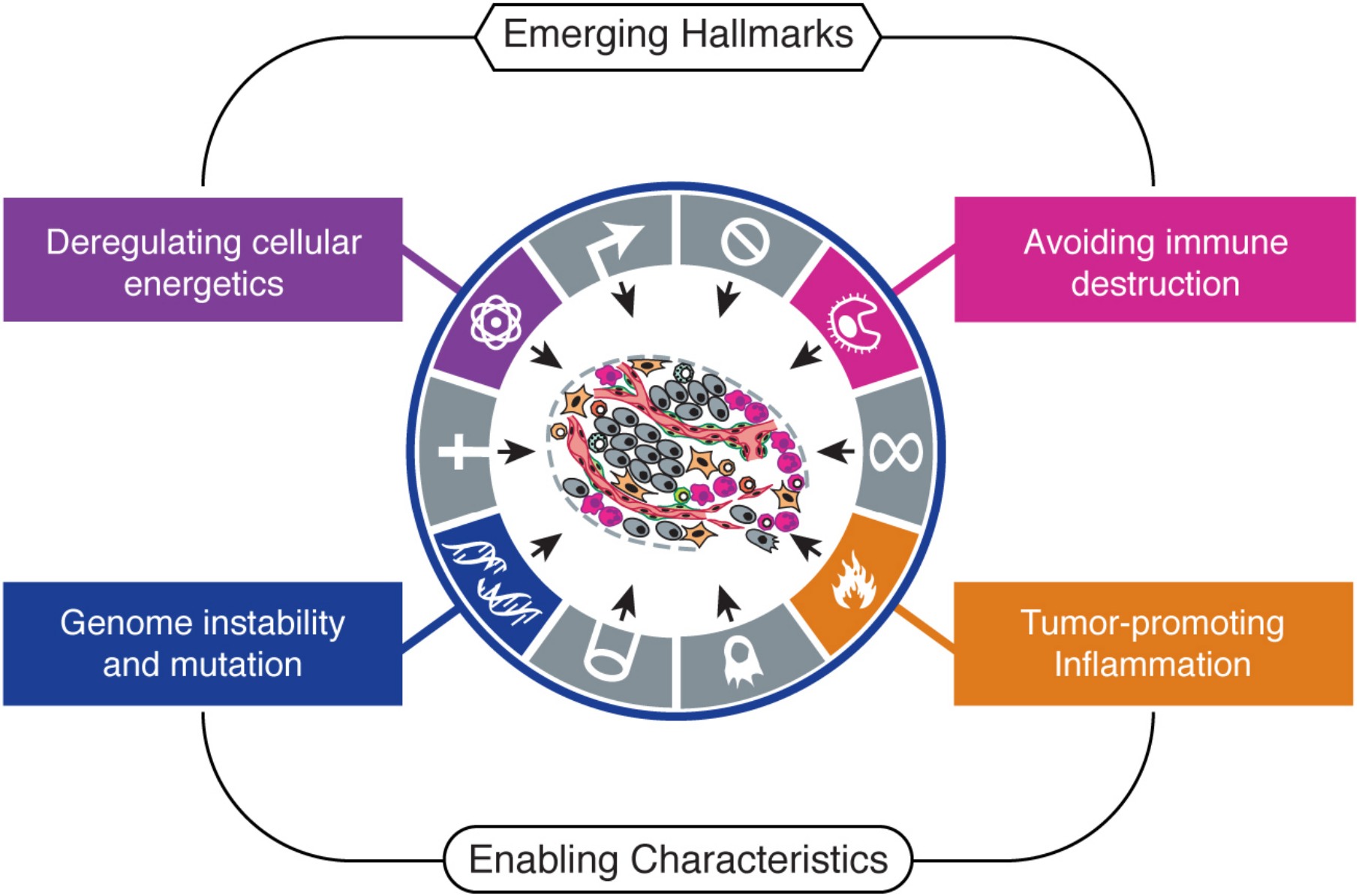
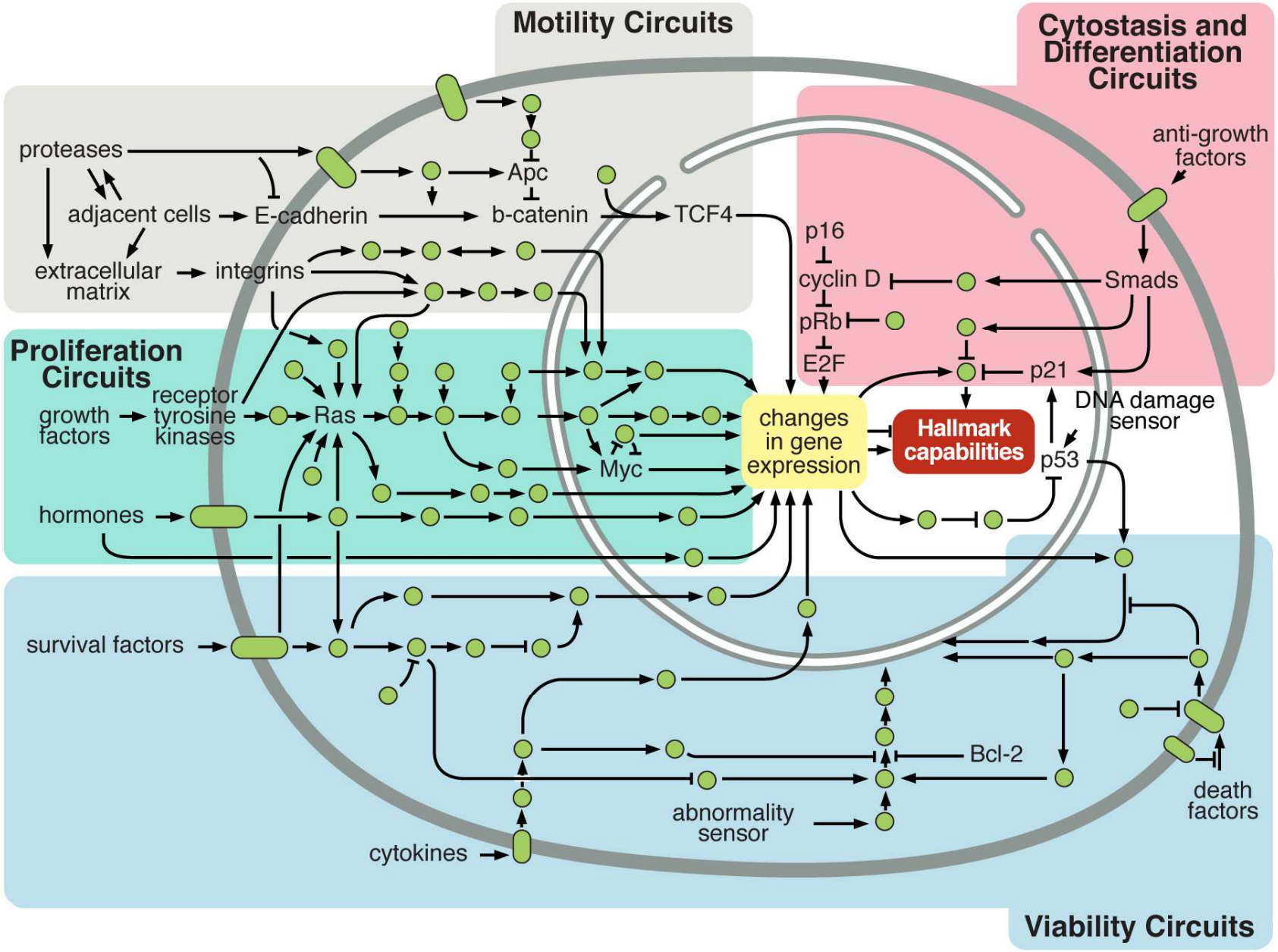


Hanahan and Weinberg, 2011

Cell PRESS

CIRCUITOS INTEGRADOS EN CANCER



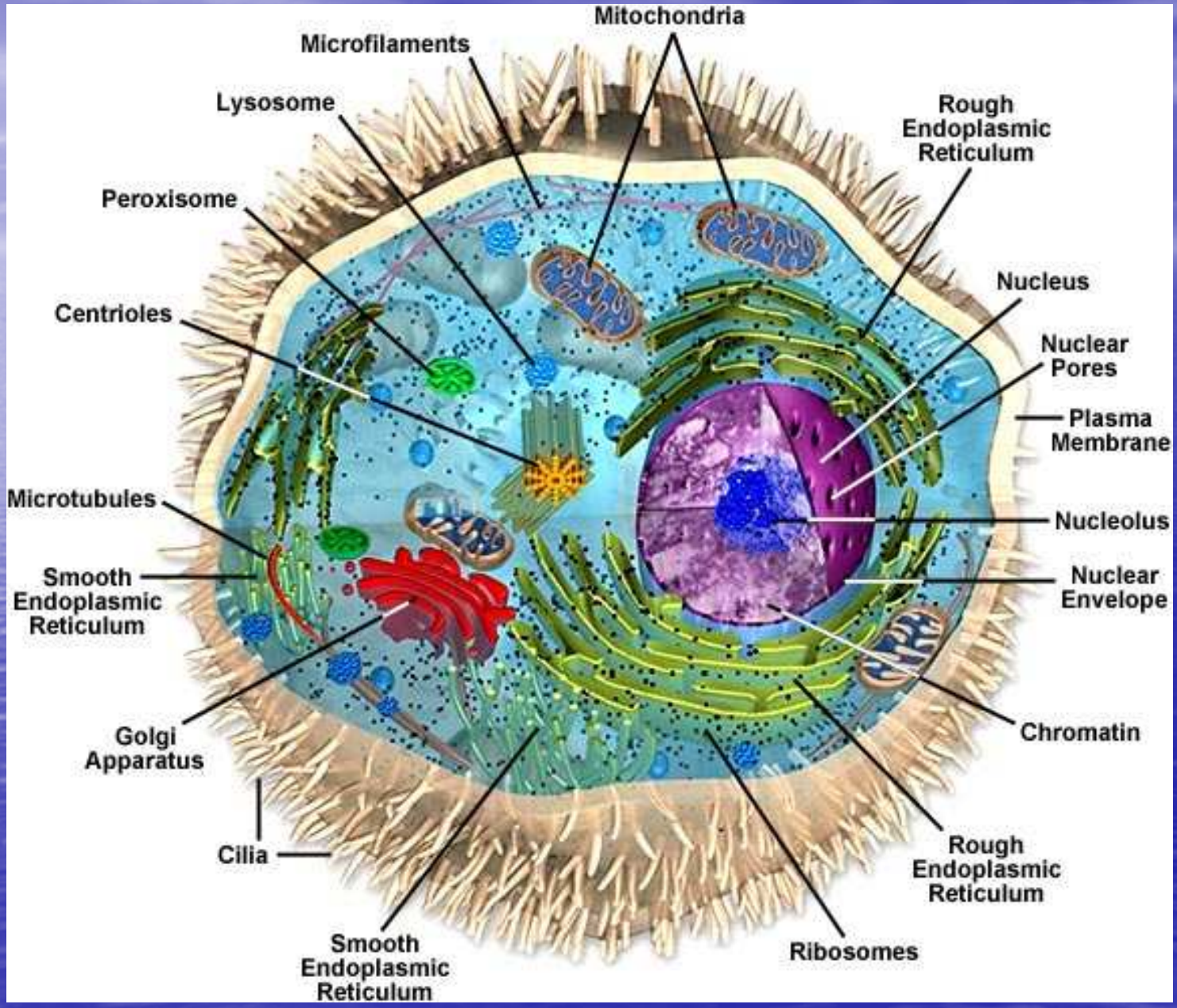
Hanahan and Weinberg, 2011

Cell PRESS

METABOLISMO Y CÁNCER

METABOLISMO ENERGETICO DEREGULADO

Glucosa, insulina, metabolismo y cáncer

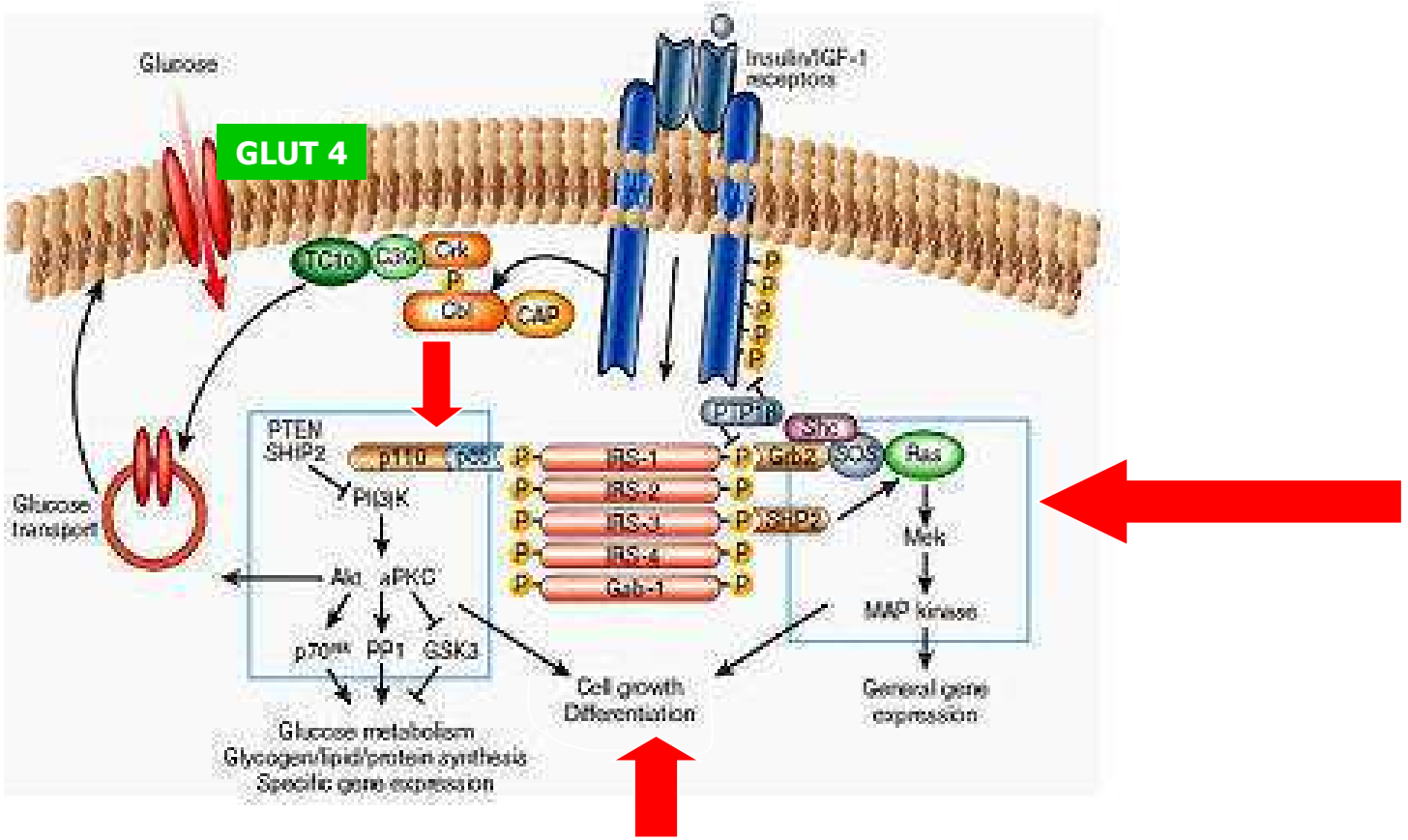

Mitochondria
Microfilaments
Lysosome
Rough Endoplasmic Reticulum
Peroxisome
Nucleus
Centrioles
Nuclear Pores
Plasma Membrane
Microtubules
Nucleolus
Smooth Endoplasmic Reticulum
Nuclear Envelope
Chromatin
Golgi Apparatus
Cilia
Rough Endoplasmic Reticulum
Smooth Endoplasmic Reticulum
Ribosomes

La insulina es un factor de crecimiento

BANTING Y BEST (TORONTO, 1921)

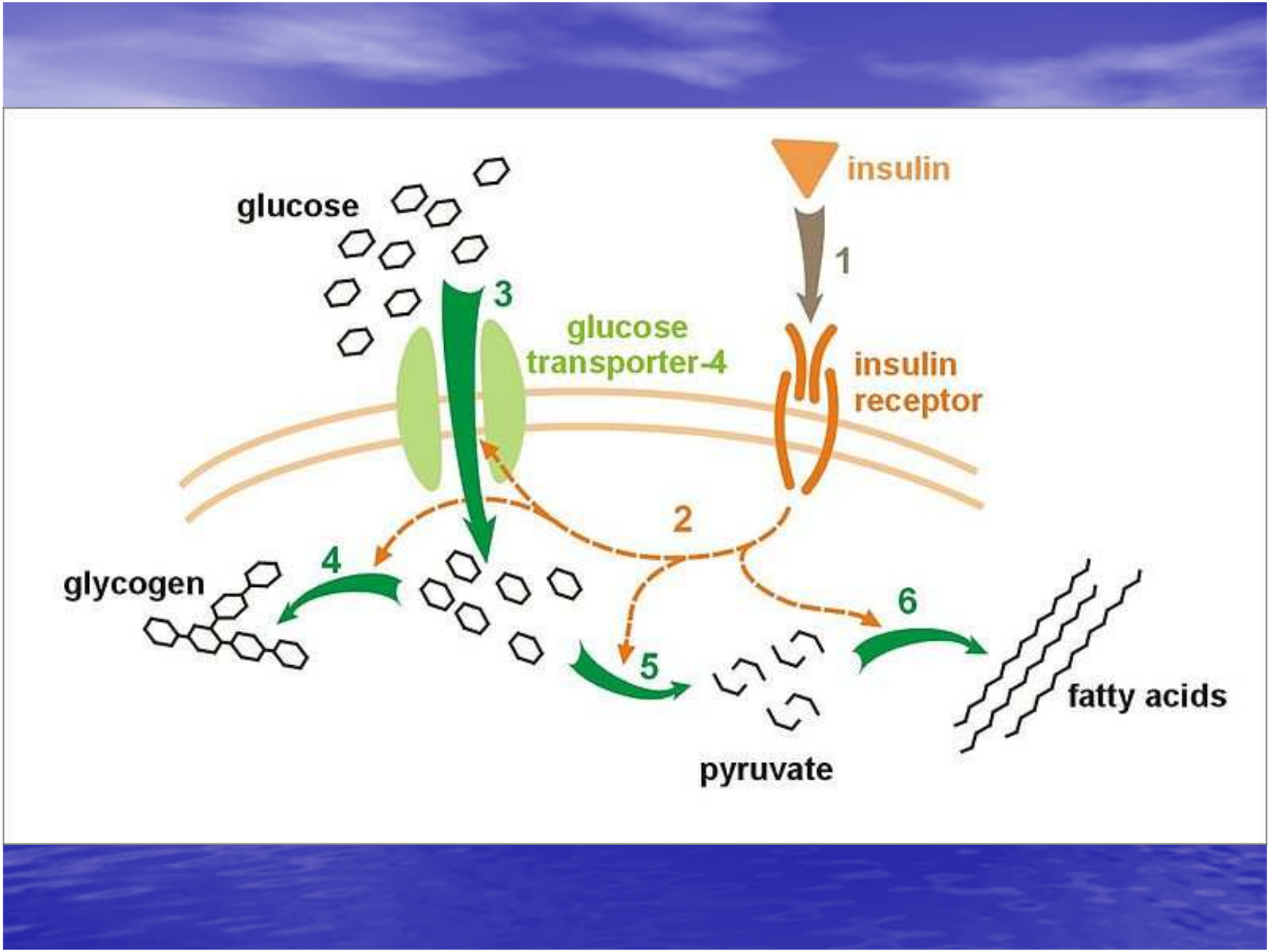
BANTING Y MACLEOD, PREMIO NOBEL DE MEDICINA, 1923

Mechanisms of Insulin Action



Tyrosine kinase receptors, including the **insulin receptor**, mediate their activity by causing the addition of a phosphate group to particular tyrosine residues on certain proteins within a cell. The "substrate" proteins that are phosphorylated by the Insulin receptor include a protein called "IRS-1" for "insulin receptor substrate 1".

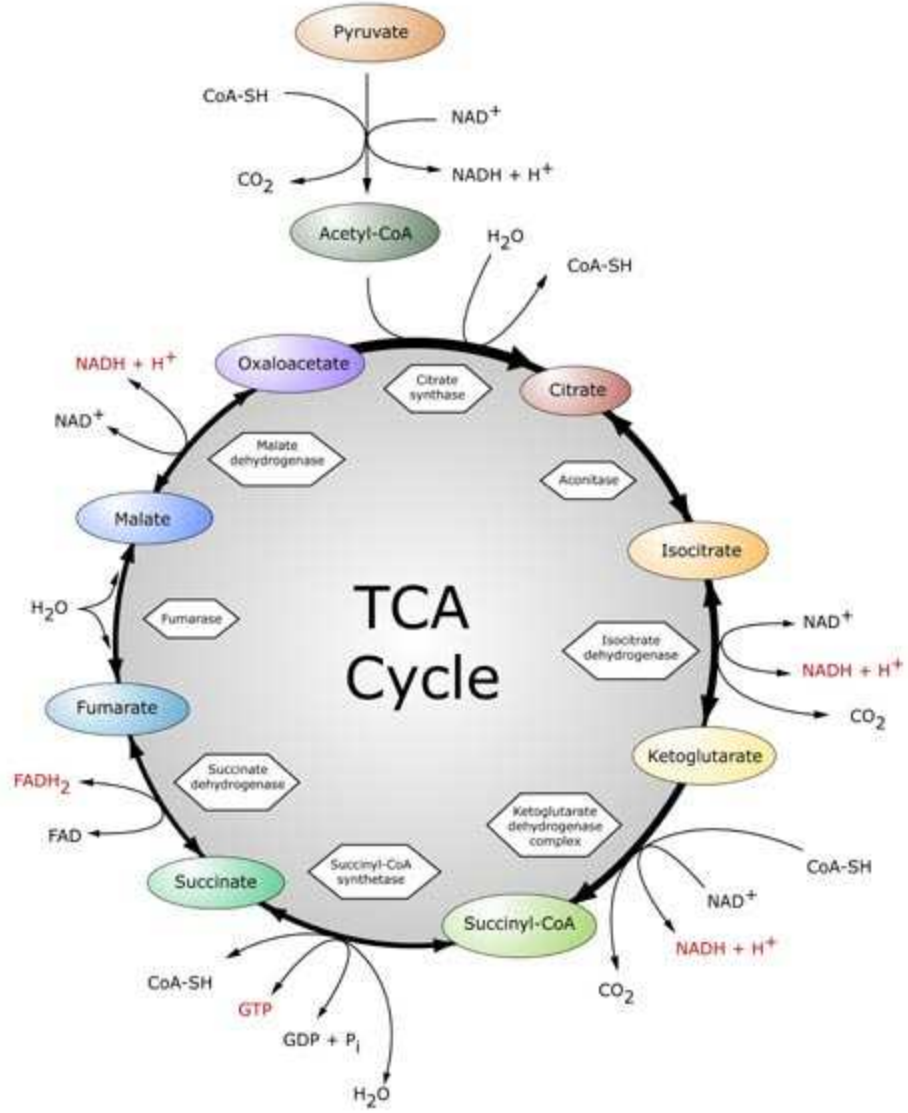
IRS 1 binding and phosphorylation eventually leads to an increase in the high affinity GLUT4 (Glucose transporter 4) molecules on the outer membrane of insulin-responsive tissues, including Myocytes and Adipocytes. Thus there is an increase in the uptake of Glucose molecules from blood into these cells. The glucose transporter GLUT4 is transported from cellular vesicles to the cell surface, where it then can mediate the transport of glucose into the cell.


insulin
glucose
1
3
glucose
transporter-4
insulin
receptor
2
4
glycogen
6
5
fatty acids
pyruvate

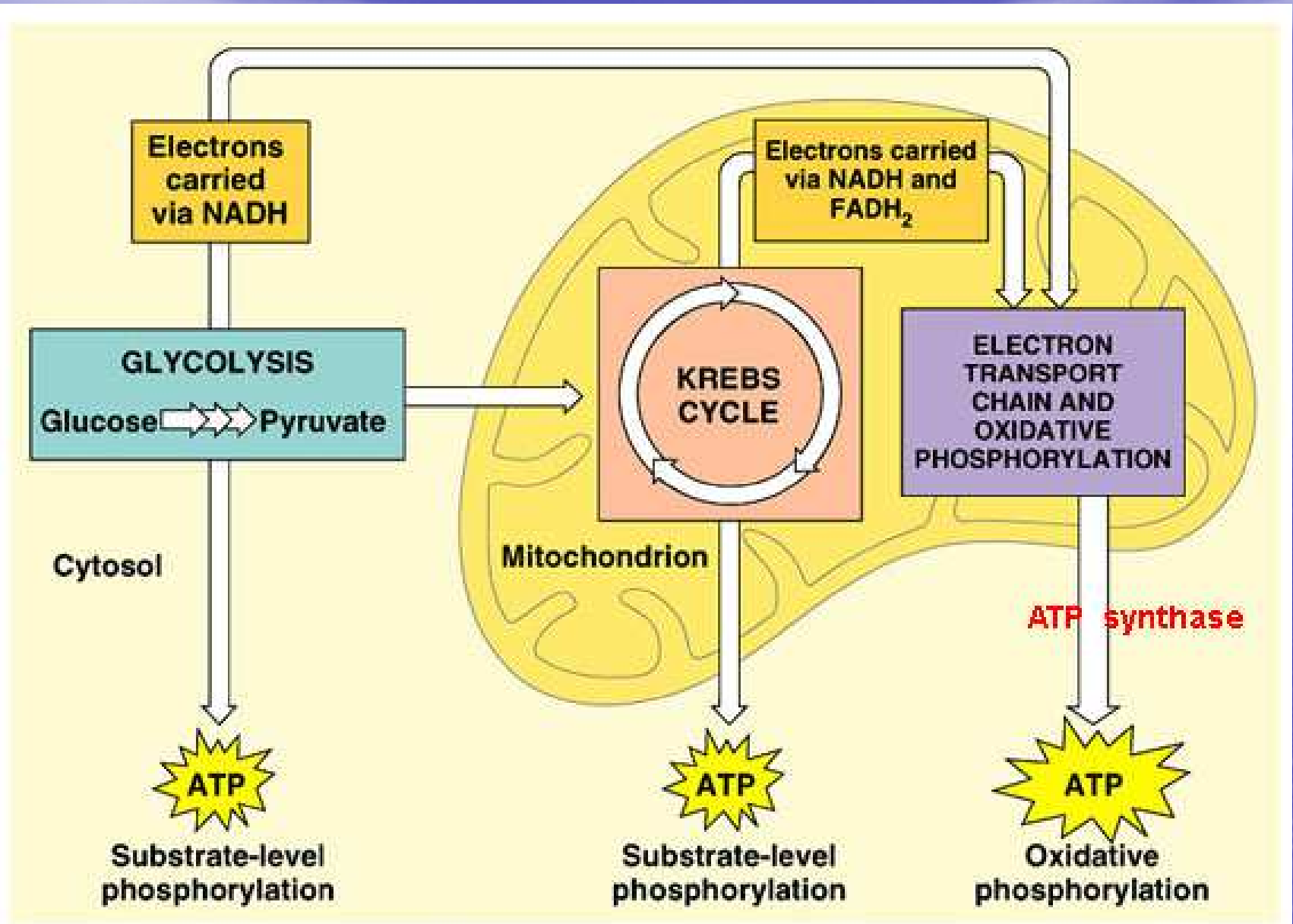
GLUCOSA

ACIDO PIRUVICO

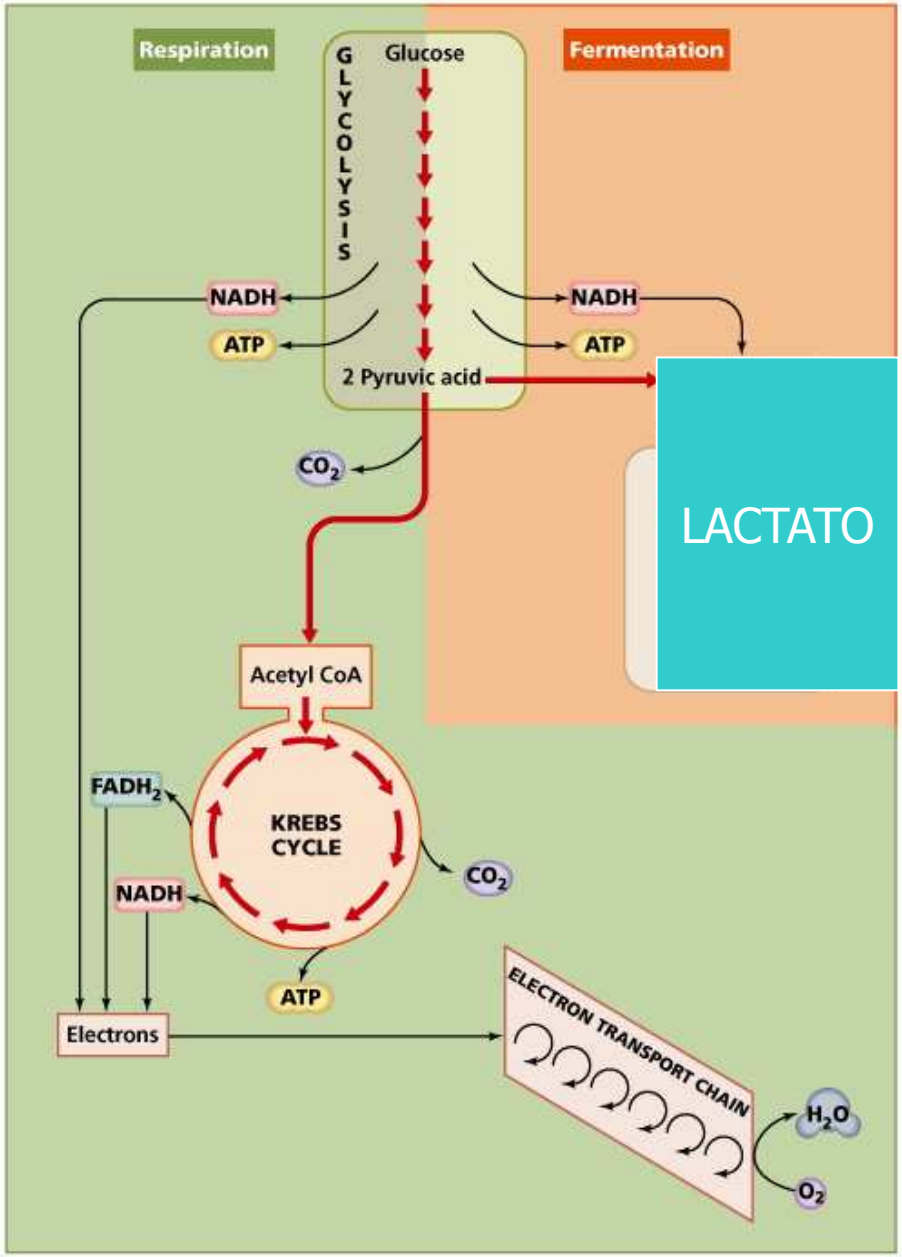
ACIDO LACTICO



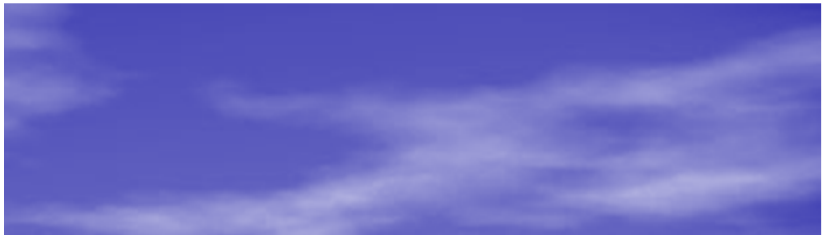
VISTA GENERAL Y GLOBAL DE LA PRODUCCION DE ENERGIA

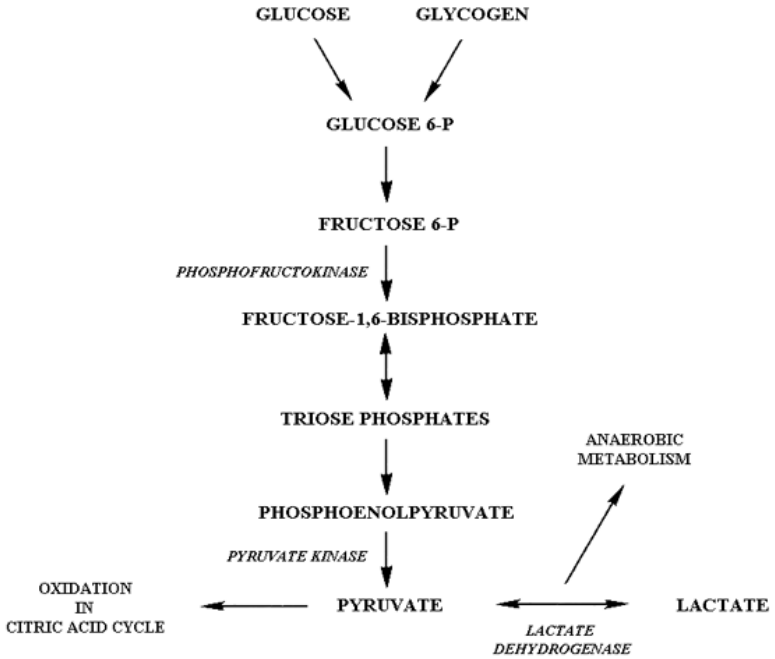


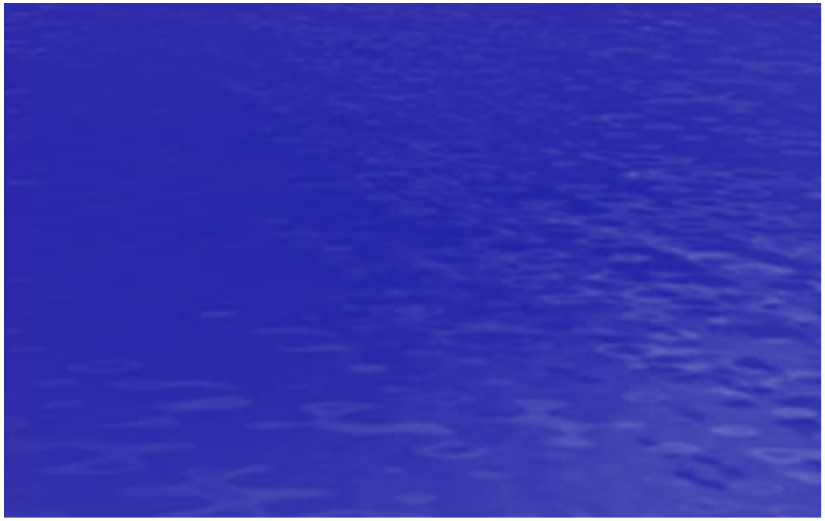
Copyright © Pearson Education, Inc., publishing as Benjamin Cummings

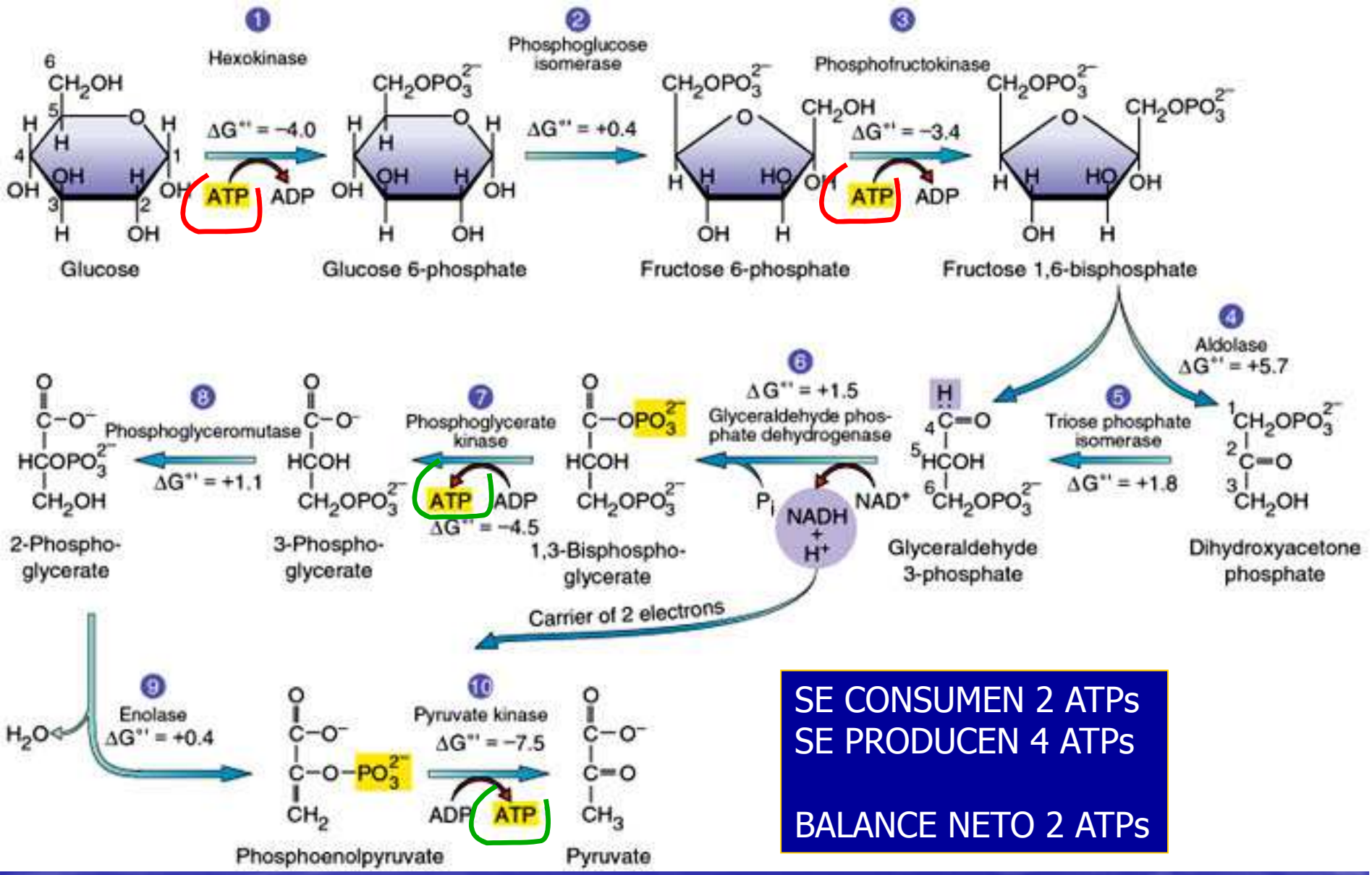


Copyright © 2006 Pearson Education, Inc., publishing as Benjamin Cummings.



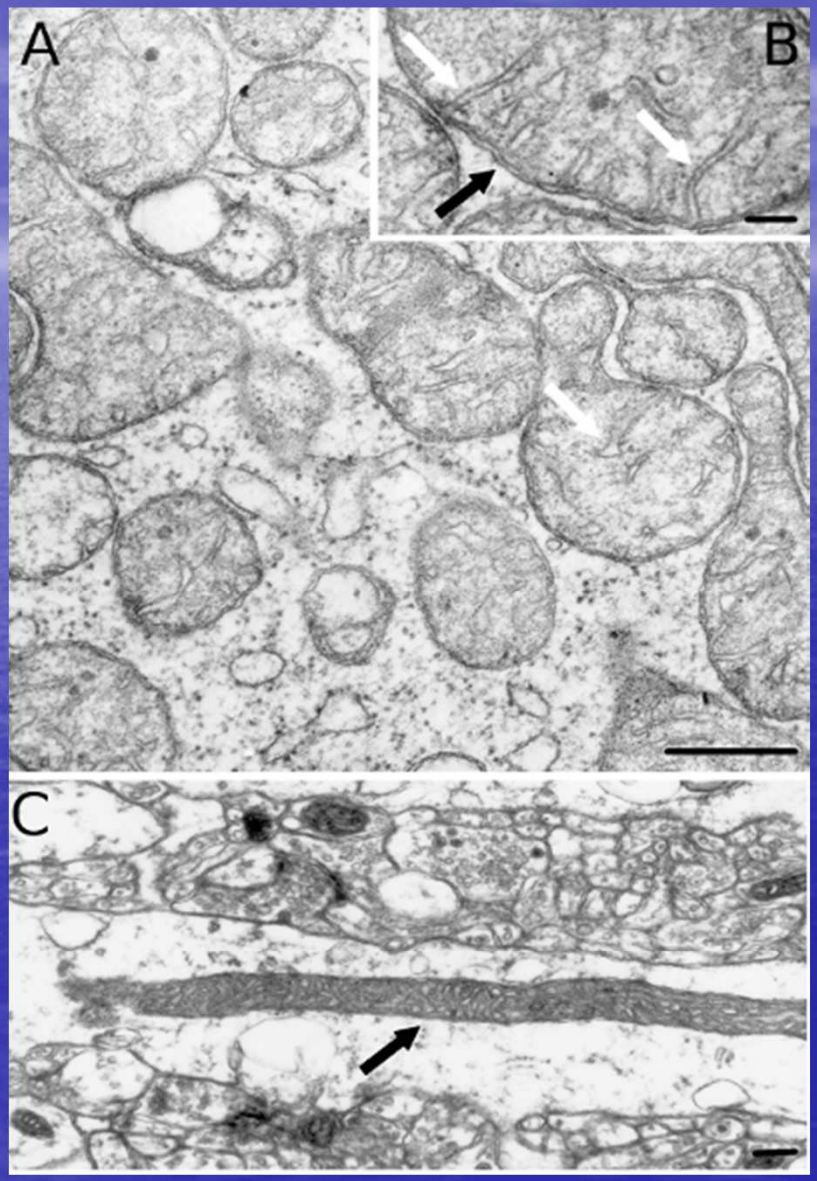




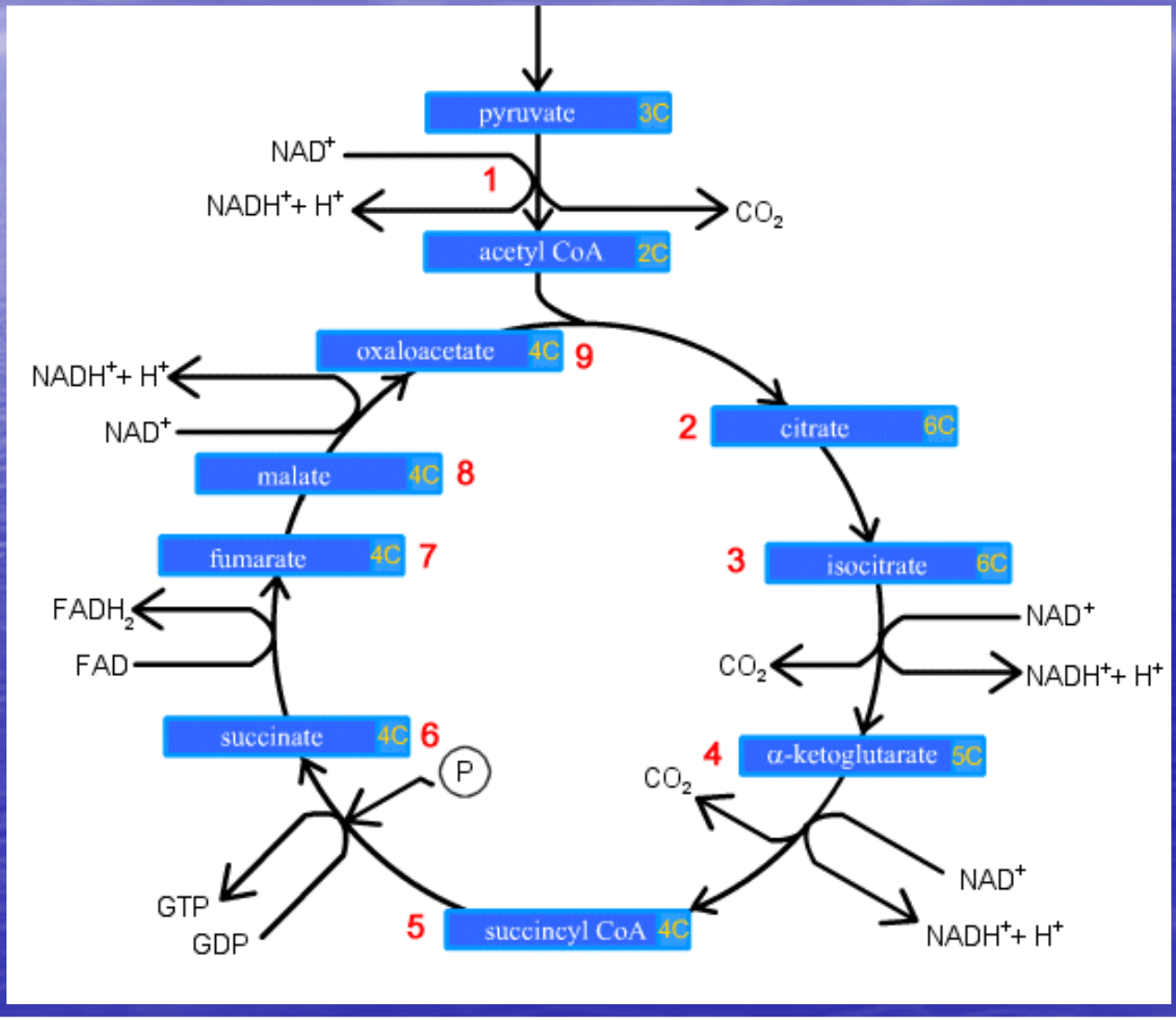


SE CONSUMEN 2 ATPs
SE PRODUCEN 4 ATPs

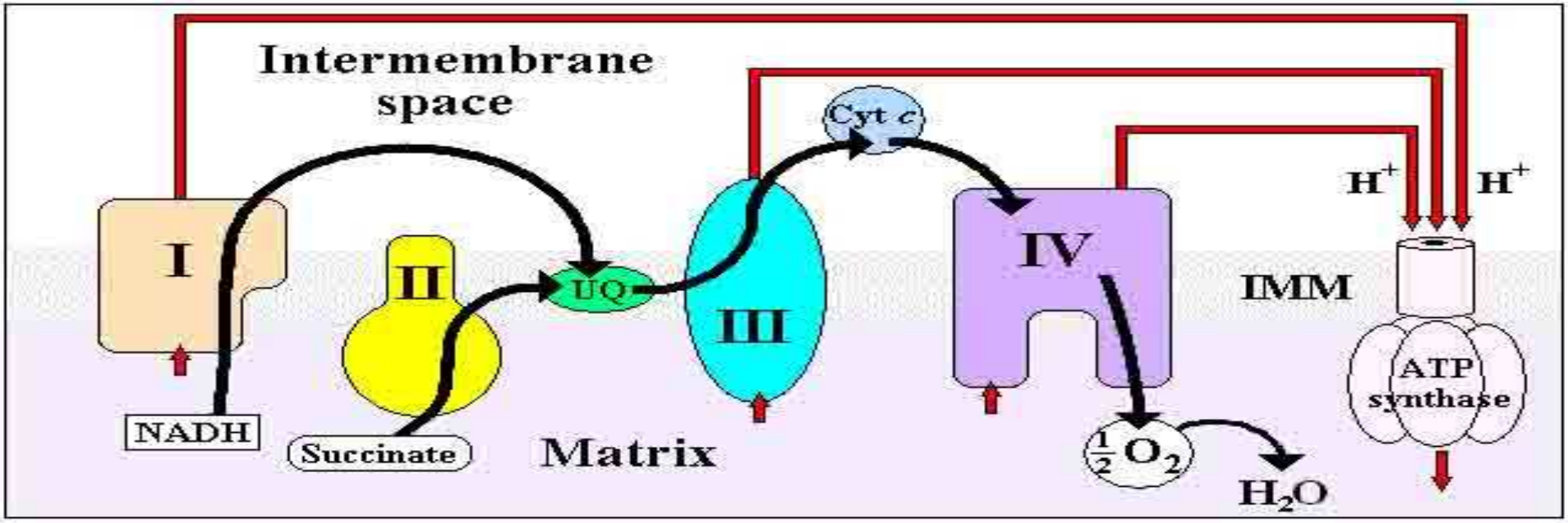
BALANCE NETO 2 ATPs


A
B
C

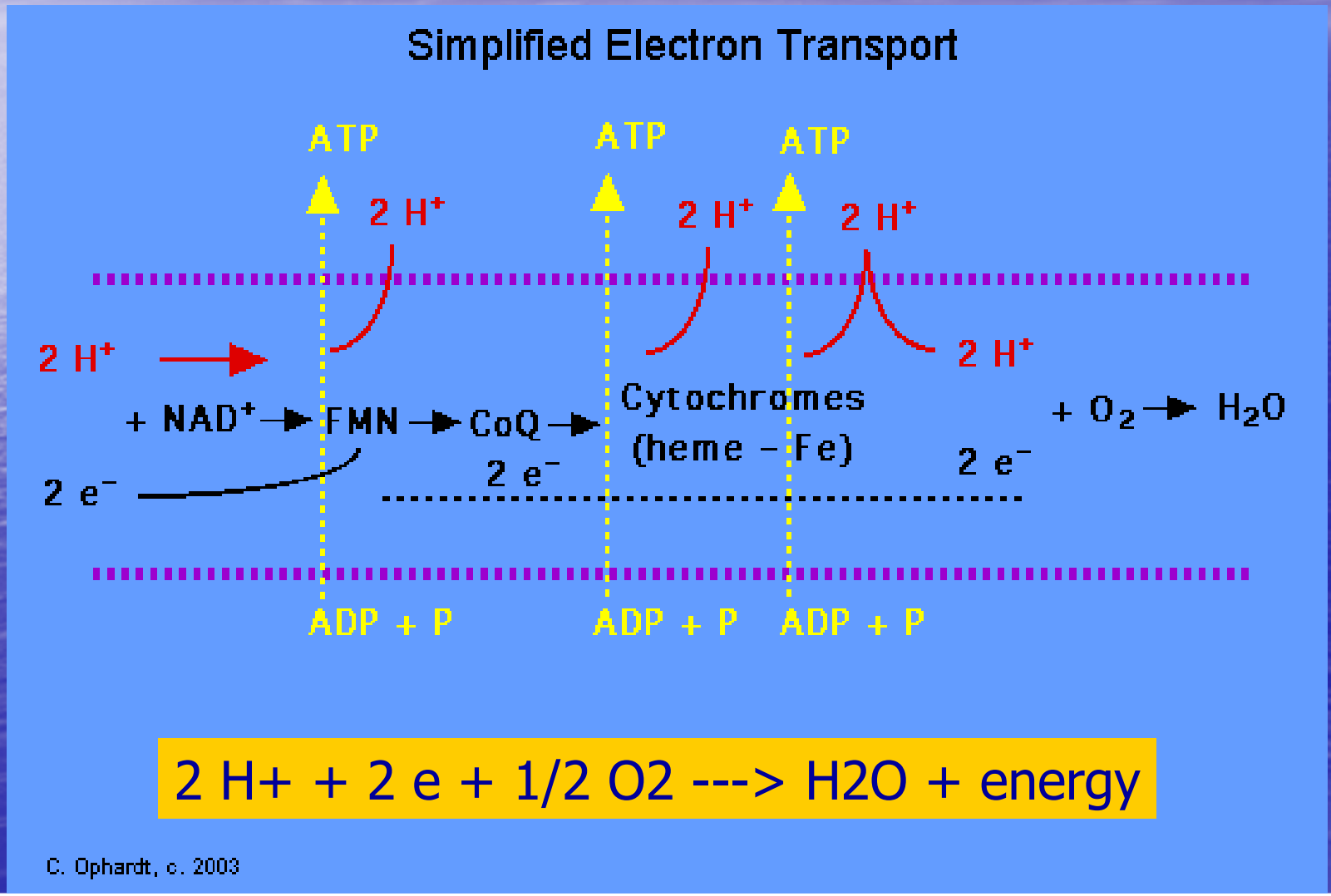
El ciclo de Krebs y la cadena respiratoria producen 36 ATPs



La cadena de transporte de electrones

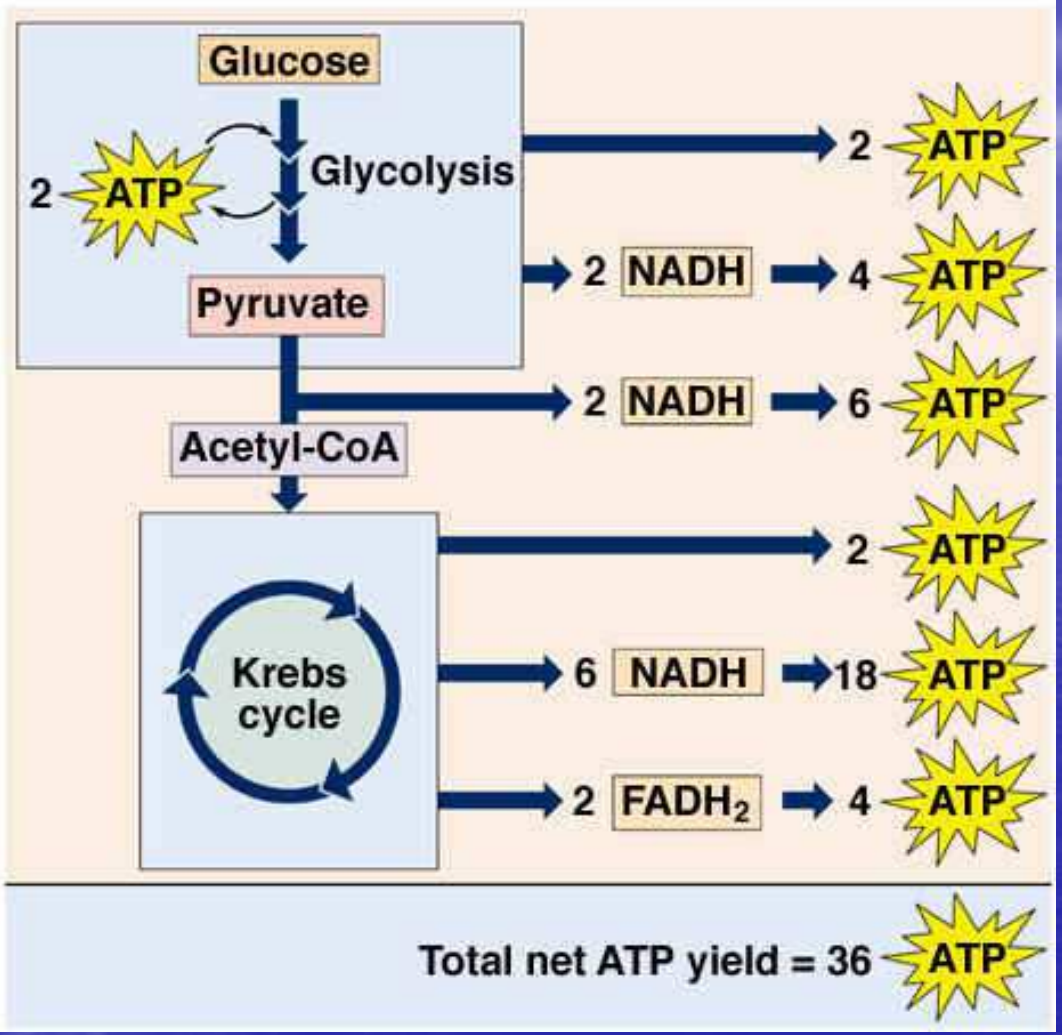


La cadena de transporte de electrones



Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.

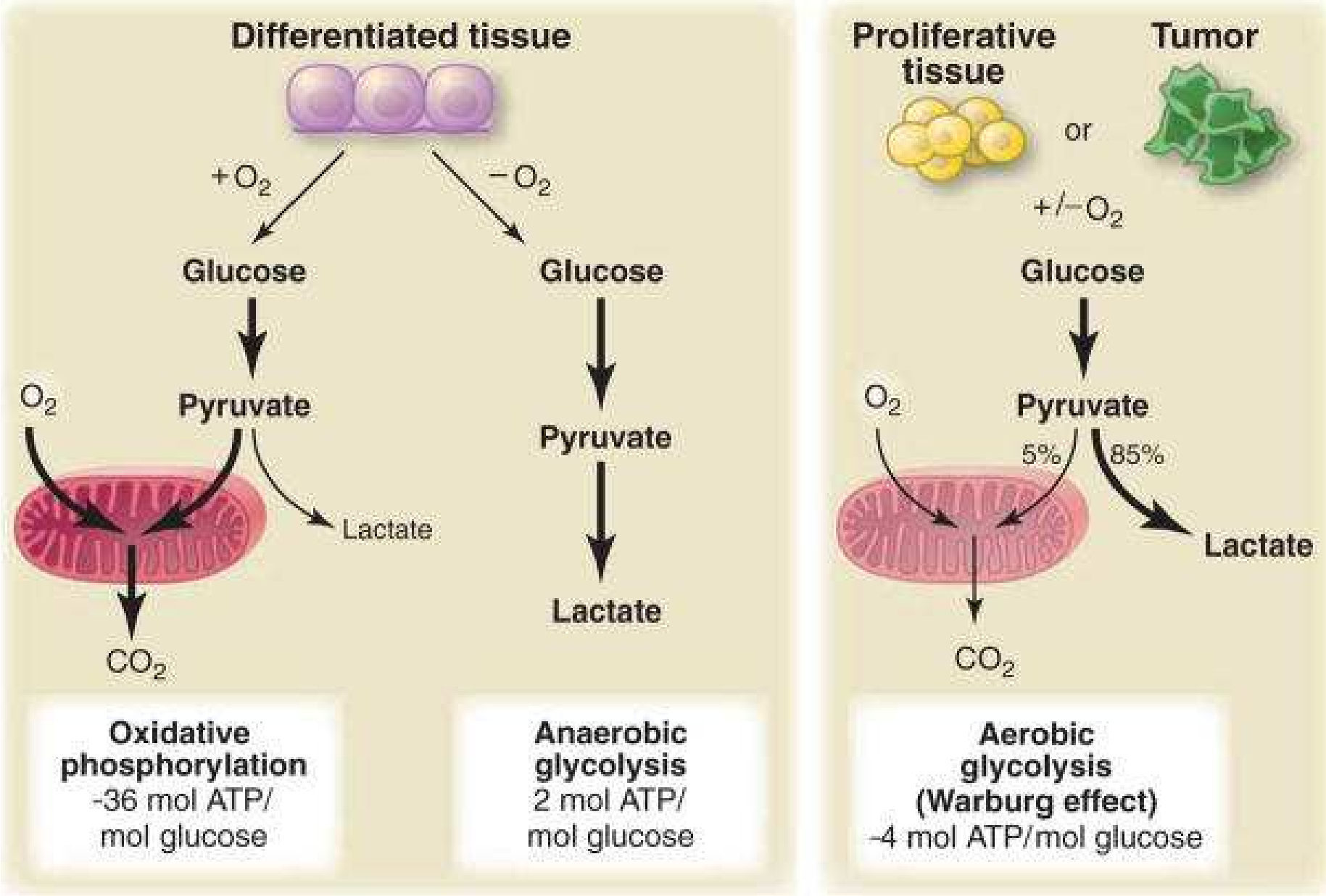
ATP Theoretical Yield

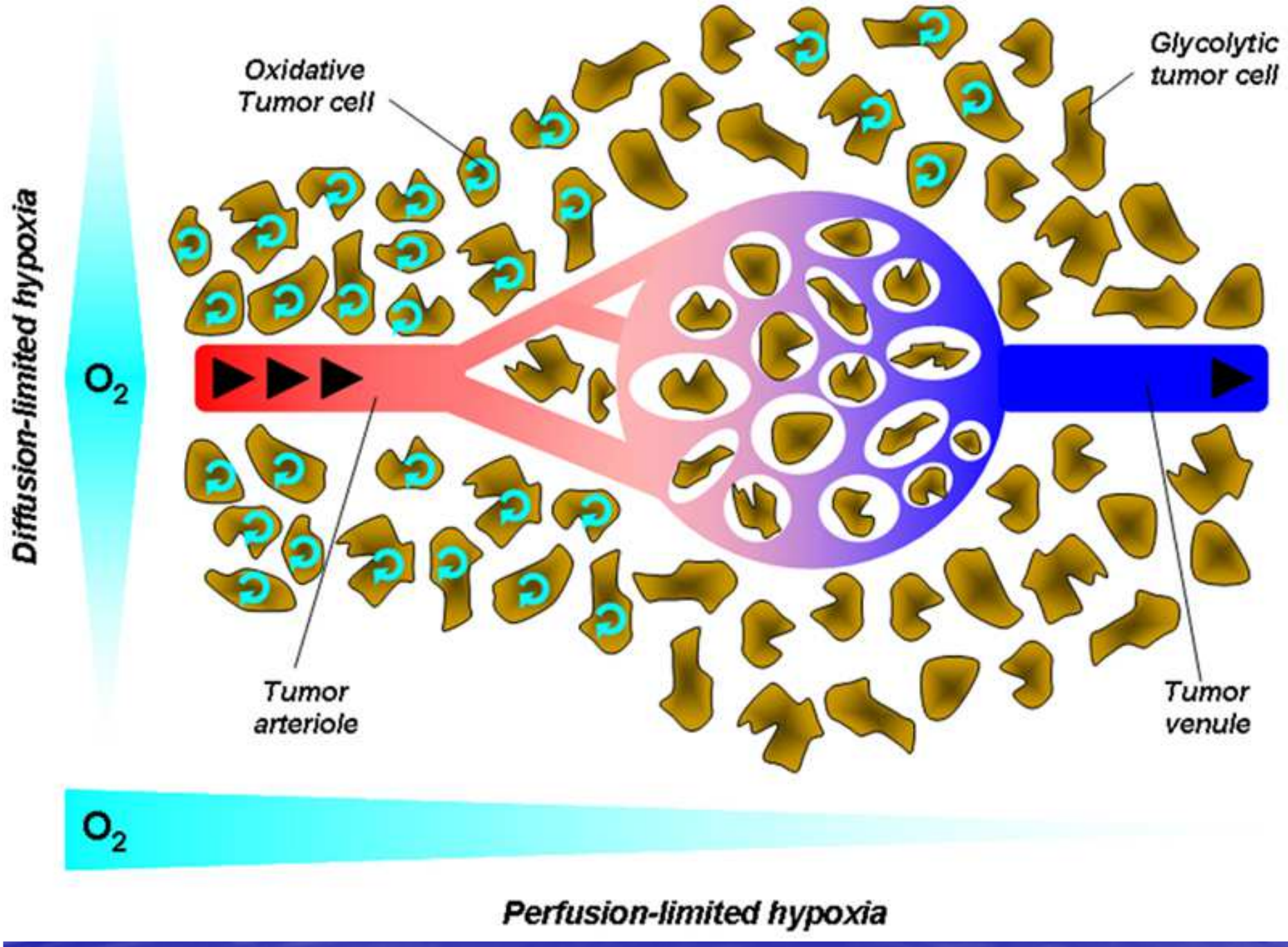


BALANCE ENERGETICO

El efecto Warburg

Otto Warburg. Premio Nobel de Fisiología 1931


Differentiated tissue
+O2
−O2
Glucose
Glucose
O2
Pyruvate
Pyruvate
Lactate
Lactate
CO2
Oxidative phosphorylation
-36 mol ATP/ mol glucose
Anaerobic glycolysis
2 mol ATP/ mol glucose
Proliferative tissue
or
Tumor
+/−O2
Glucose
O2
Pyruvate
5%
85%
Lactate
CO2
Aerobic glycolysis (Warburg effect)
-4 mol ATP/mol glucose


Oxidative
Tumor cell
Glycolytic
tumor cell
Diffusion-limited hypoxia
O2
Tumor
arteriole
Tumor
venule
O2
Perfusion-limited hypoxia

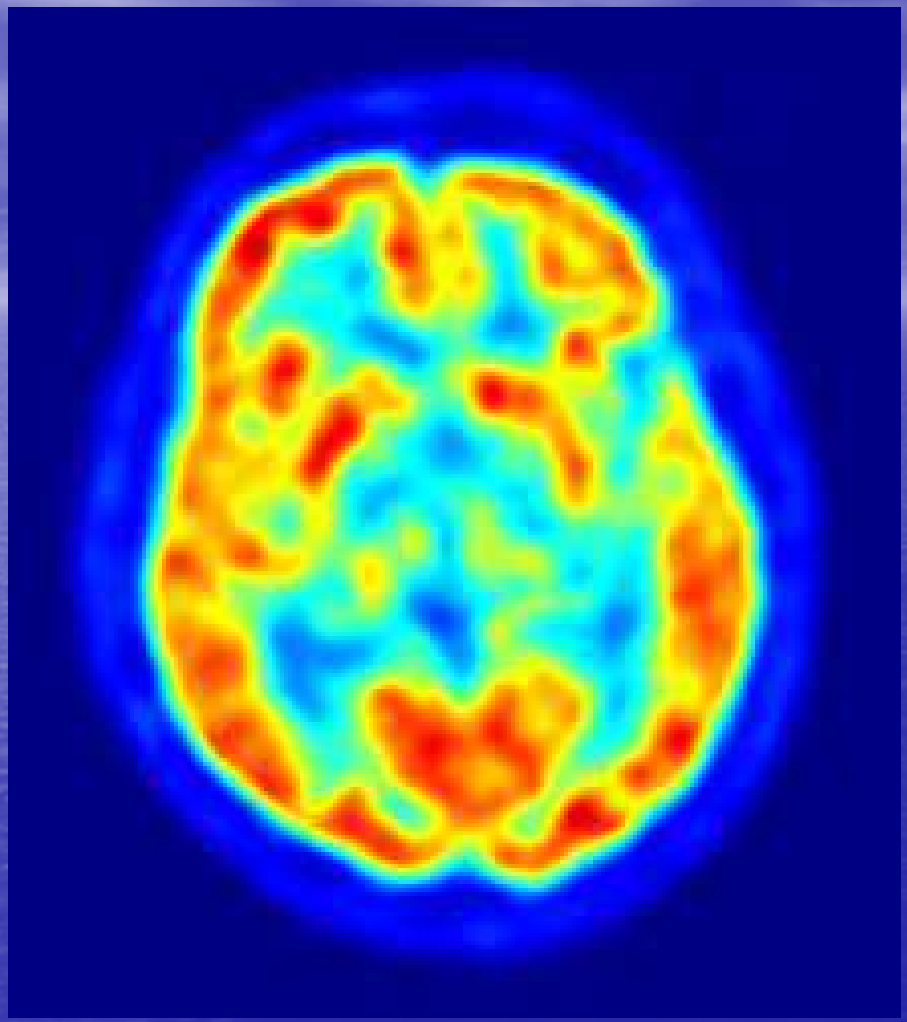
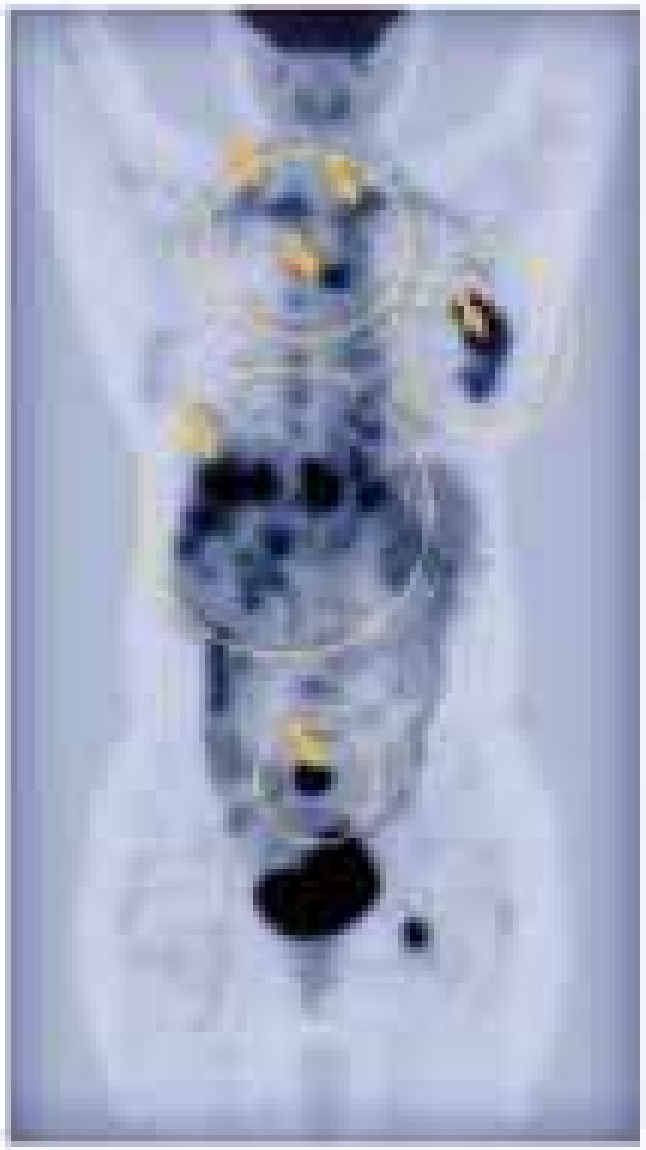


IMAGEN DE CEREBRO EN PET SCAN



PET SCAN DE LINFOMA ANTES Y DESPUES TRATAMIENTO (FDG)

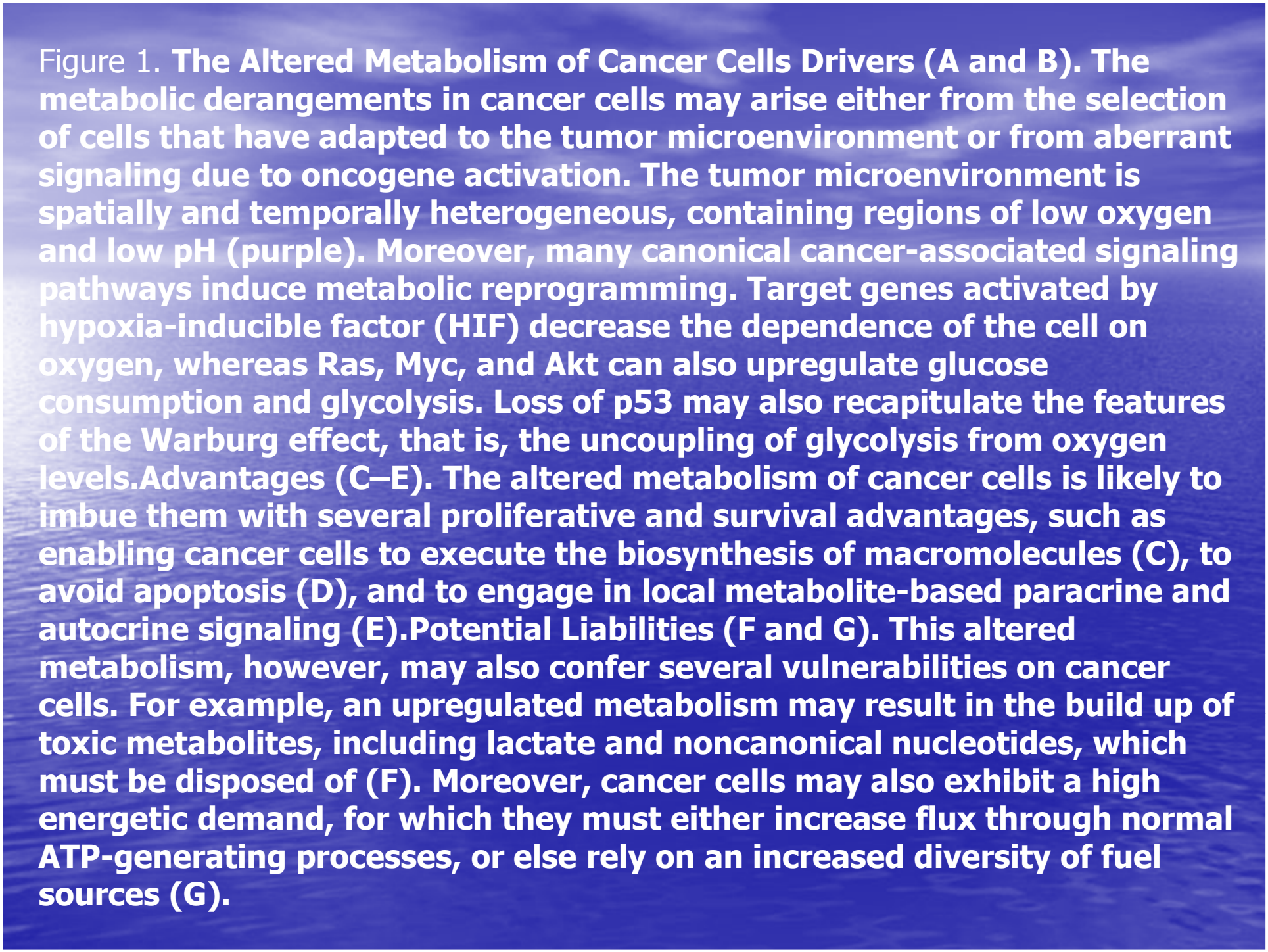
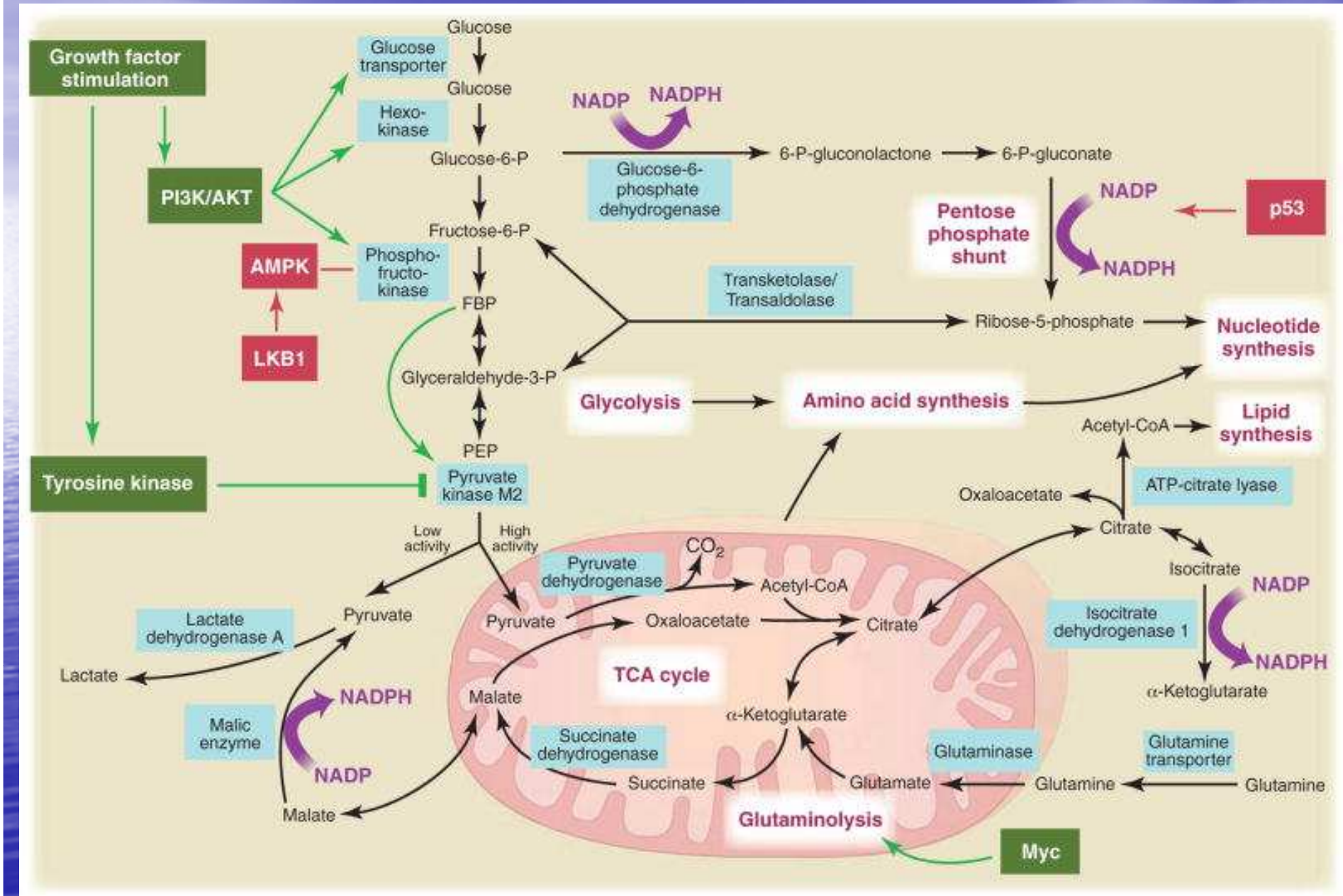


Figure 1. **The Altered Metabolism of Cancer Cells Drivers (A and B). The metabolic derangements in cancer cells may arise either from the selection of cells that have adapted to the tumor microenvironment or from aberrant signaling due to oncogene activation. The tumor microenvironment is spatially and temporally heterogeneous, containing regions of low oxygen and low pH (purple). Moreover, many canonical cancer-associated signaling pathways induce metabolic reprogramming. Target genes activated by hypoxia-inducible factor (HIF) decrease the dependence of the cell on oxygen, whereas Ras, Myc, and Akt can also upregulate glucose consumption and glycolysis. Loss of p53 may also recapitulate the features of the Warburg effect, that is, the uncoupling of glycolysis from oxygen levels.Advantages (C–E). The altered metabolism of cancer cells is likely to imbue them with several proliferative and survival advantages, such as enabling cancer cells to execute the biosynthesis of macromolecules (C), to avoid apoptosis (D), and to engage in local metabolite-based paracrine and autocrine signaling (E).Potential Liabilities (F and G). This altered metabolism, however, may also confer several vulnerabilities on cancer cells. For example, an upregulated metabolism may result in the build up of toxic metabolites, including lactate and noncanonical nucleotides, which must be disposed of (F). Moreover, cancer cells may also exhibit a high energetic demand, for which they must either increase flux through normal ATP-generating processes, or else rely on an increased diversity of fuel sources (G).**

Glucose metabolism in cancer



¿El cáncer es tonto?

- ¿Porqué una célula tumoral, que tiene grandes requerimientos de energía prioriza la vía de la glucólisis aerobia que solo produce 2 ATPs, en lugar de la vía de la fosforilación oxidativa que produce 36 ATPs?

Ensayaremos una respuesta

- El cáncer no es tonto.
- Además de energía, la célula tumoral requiere también muchas otras sustancias para elaborar ácidos grasos, proteínas y ribosa fosforilada.
- Estas sustancias se elaboran a partir del ácido láctico, excepto la ribosa.
- Por otro lado, no se produce déficit energético porque la célula tumoral metaboliza 10 veces más moléculas de glucosa en la unidad de tiempo que la célula no tumoral.

El Efecto Warburg es mal entendido

M. G. Vander Heiden *et al.* addressed the question of why a cell would "choose" glycolysis over oxidative phosphorylation, whereby only 2 instead of 36 adenosine 5'-triphosphate (ATP) are obtained per glucose molecule ("Understanding the Warburg Effect: The metabolic requirements of cell proliferation," Reviews, 22 May 2009, p. 1029). However, the question, as well as the proffered explanations, misses the point of Warburg's work. In 1923 and 1924, Warburg and co-workers reported that the rate of respiration in cancer cells is, within the error, identical to that of normal cells, and that the glucose uptake is approximately 10 times higher. Furthermore, for every 13 glucose molecules taken up, 1 is oxidized via respiration, while the remaining 12 are split to form lactic acid (*1, 2*). Thus, in the time that one glucose molecule produces 36 ATP via respiration, 24 additional ATP are generated via aerobic glycolysis. The question posed by Vander Heiden *et al.*, "why do proliferating cells switch to a less efficient metabolism" is wrong on two counts: (i) cancer cells do not switch, but carry out both oxidative phosphorylation and aerobic glycolysis simultaneously, and (ii) glycolysis is not inefficient; even in the absence of oxygen, cancer cells survive because lactic acid production via anaerobic glycolysis yields 2/3 of the ATP that a normal cell produces by respiration. Indeed, it is precisely this enormous uptake of glucose that allows cancerous tissue to be visualized by FDG-PET/CT.

The question of whether or not cancer cells respire normally has dogged the literature since the late 1920s. Experimental results of Warburg and co-workers and of Chance and co-workers (*3, 4*) clearly show that respiration is normal. Why then did Warburg himself in 1956 write that "...the respiration of all cancer cells is damaged..." (*5*)? Warburg later provided clarification that has largely gone unnoticed, writing that the respiration of cancer cells is small relative to the consumption of glucose, but not small relative to the respiration of normal cells (*6*). The confusion may have been prevented had Warburg formulated his definition of respiratory impairment 30 years earlier.

Willem H. Koppenol and Patricia L. Bounds Institute of Inorganic Chemistry, Department of Chemistry and Applied Biosciences, ETH, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland.

¿Qué o quien genera el efecto Warburg (fenotipo de glucólisis aerobia)?

- 1) Alteraciones en la señalización de p53, myc, ras, akt y HIF-I
- 2) Papel de la piruvato kinasa
- 3) Hipoxia del medio ambiente tumoral
- 4) Mutaciones del gen de von Hippel Lindau
- 5) Mutaciones del gen de la succinato dehidrogenasa y/o gen de la fumarasa.
- 6) Alteración del equilibrio VDAC-HK-II (potencial de membrana del poro mitocondrial y hexosakinasa-II)

All cancer cells but not nontransformed cells express a specific splice variant of pyruvate kinase, termed M2-PK, that is less active, leading to the build up of phosphoenolpyruvate. Recent work has revealed that reduced activity of M2-PK promotes a unique glycolytic pathway in which phosphoenolpyruvate is converted to pyruvate by a histidine-dependent phosphorylation of phosphoglycerate mutase, promoting assimilation of glycolytic products into biomass

Bibliografia

- **Vamecq J, Colet JM et all**

PPARs: Interference with Warburg effect and clinical anticancer trials.
PPAR Research Vol 2012 doi 10.1155/2012/304760

- **Vander Heiden MG, Cantley LC,* and Thompson CB**

Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation
Science 22 May 2009: **Vol. 324 no. 5930** pp. 1029-1033 **DOI: 10.1126/science.1160809**

- **Bensinger SJ, Christofk HR**

New aspects of the Warburg effect in cancer cell biology.
Semin Cell Dev Biol. 2012 Jun;23(4):352-61

- **Najafov A, Alessi DR**

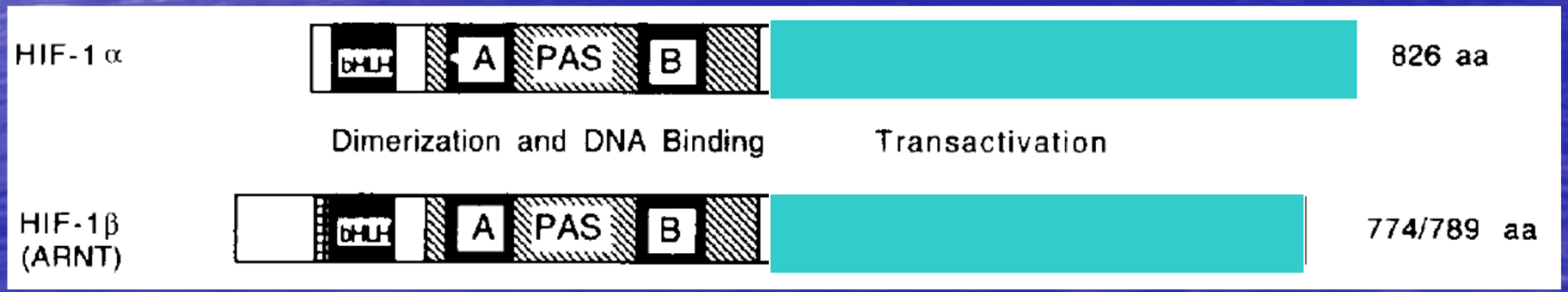
Uncoupling the Warburg effect from Cancer
PNAS (2010) 107:19135-19136

History of HIF research

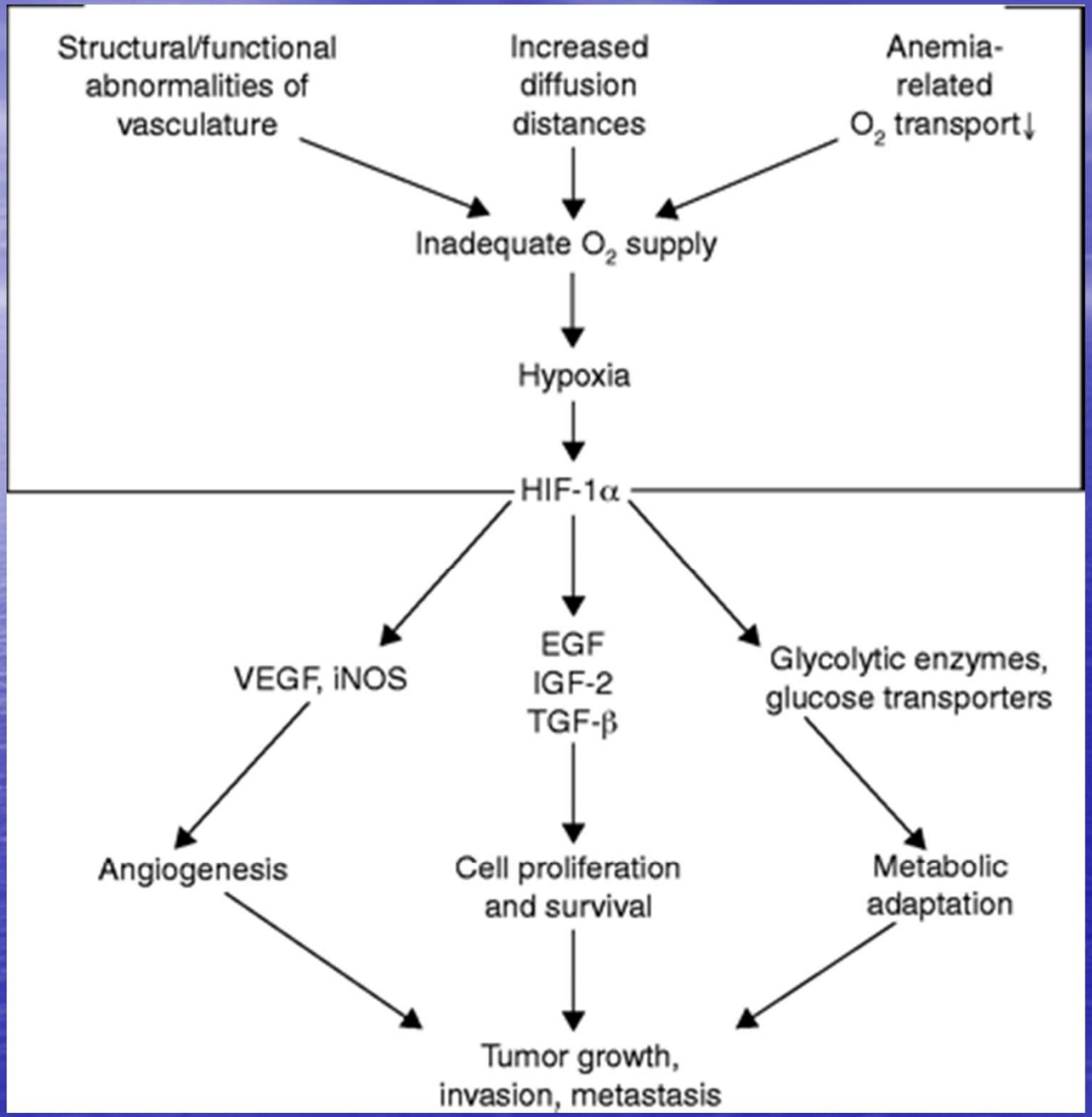
- Clone the Erythropoietin gene(1985)
- Erythropoietin induced by hypoxia(1987)
- Discovery of hypoxic inducible nuclear factor binding to enhancer of EPO gene → named as HIF-1(Semenza GL 1992)
- HIF-1 activity in cell not expressing EPO during hypoxia (1993)
- HIF-1 is upstream to VEGF-A…etc.
- VHL bind to HIF-1 (1999)
- Growth factor and AKT upstream HIF-1(1999)

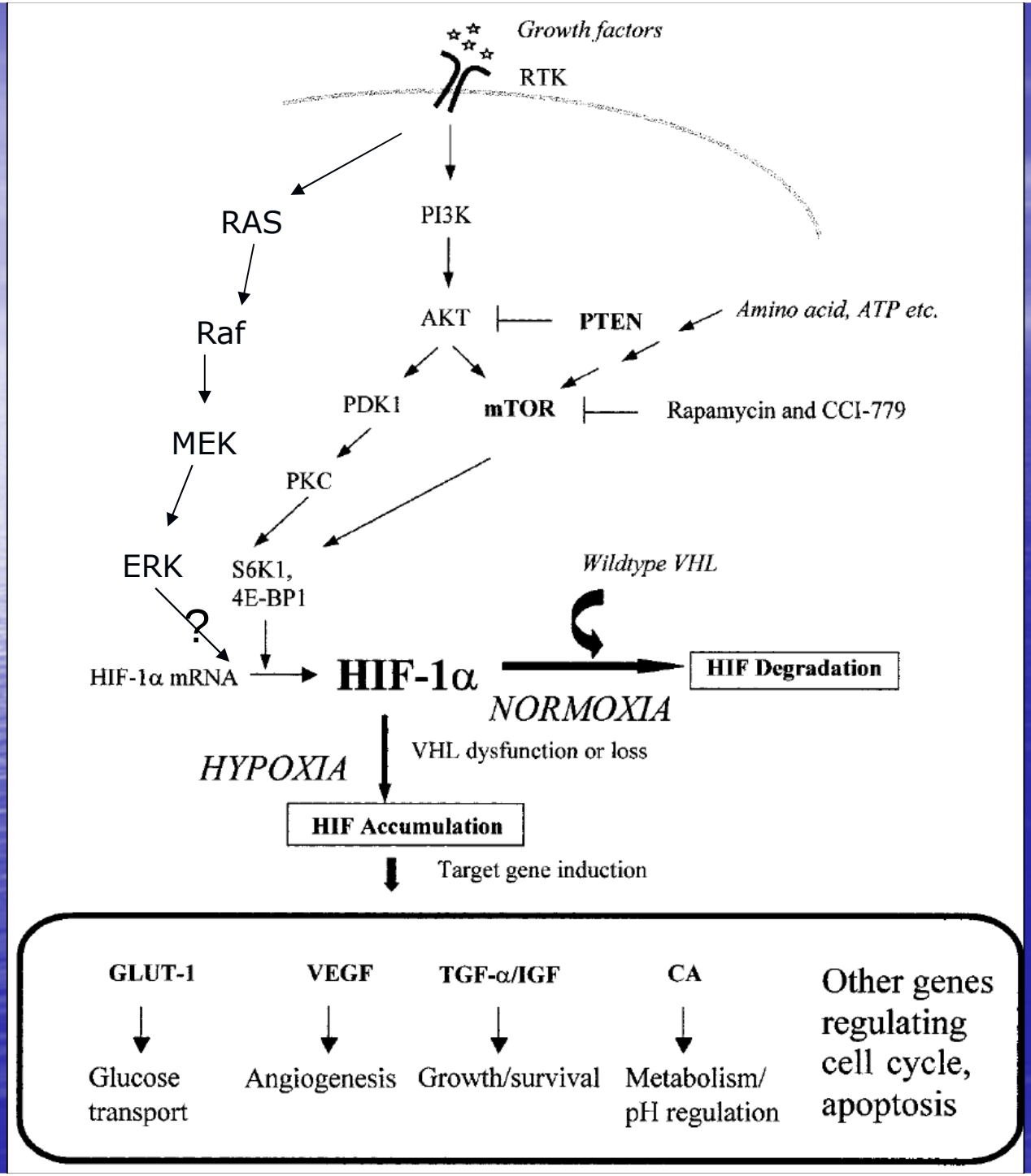
HIF-1

- A heterodimeric member of basic helix-loop-helix (bHLH) family, containing PAS domain
- Compose HIF-1 α and HIF-1β
- Persistent expression of HIF-1 β, identical to aryl hydrocarbon receptor(AHR) nuclear translocator (ARNT)
- Binding to DNA sequence 5'-(A/G)CGTG-3'(HRE)



Trends Cardiovasc med 1996;6:151-7

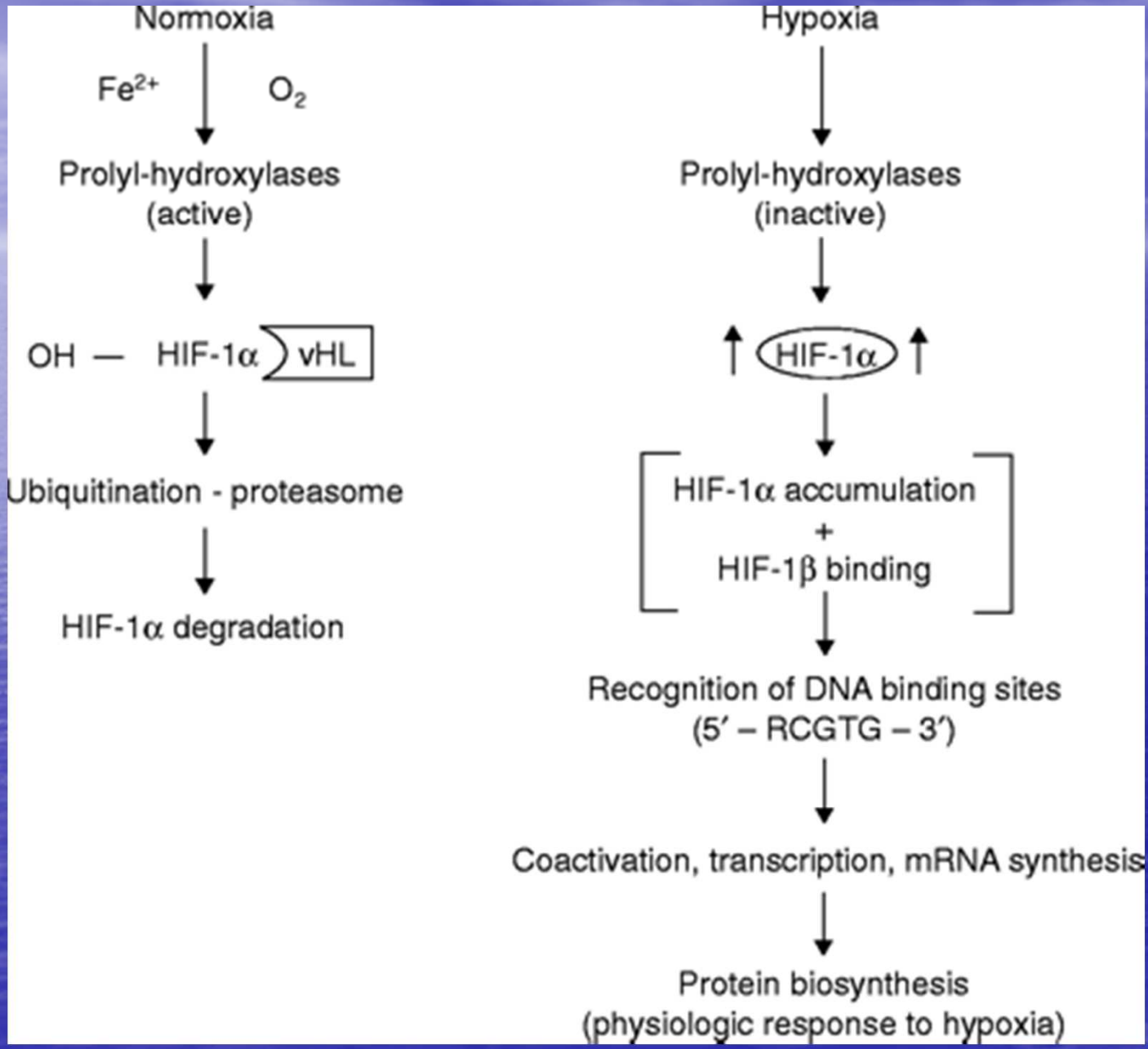

Structural/functional abnormalities of vasculature
Increased diffusion distances
Anemia-related O_2 transport↓
Inadequate O_2 supply
Hypoxia
HIF-1α
VEGF, iNOS
EGF
IGF-2
TGF-β
Glycolytic enzymes, glucose transporters
Angiogenesis
Cell proliferation and survival
Metabolic adaptation
Tumor growth, invasion, metastasis

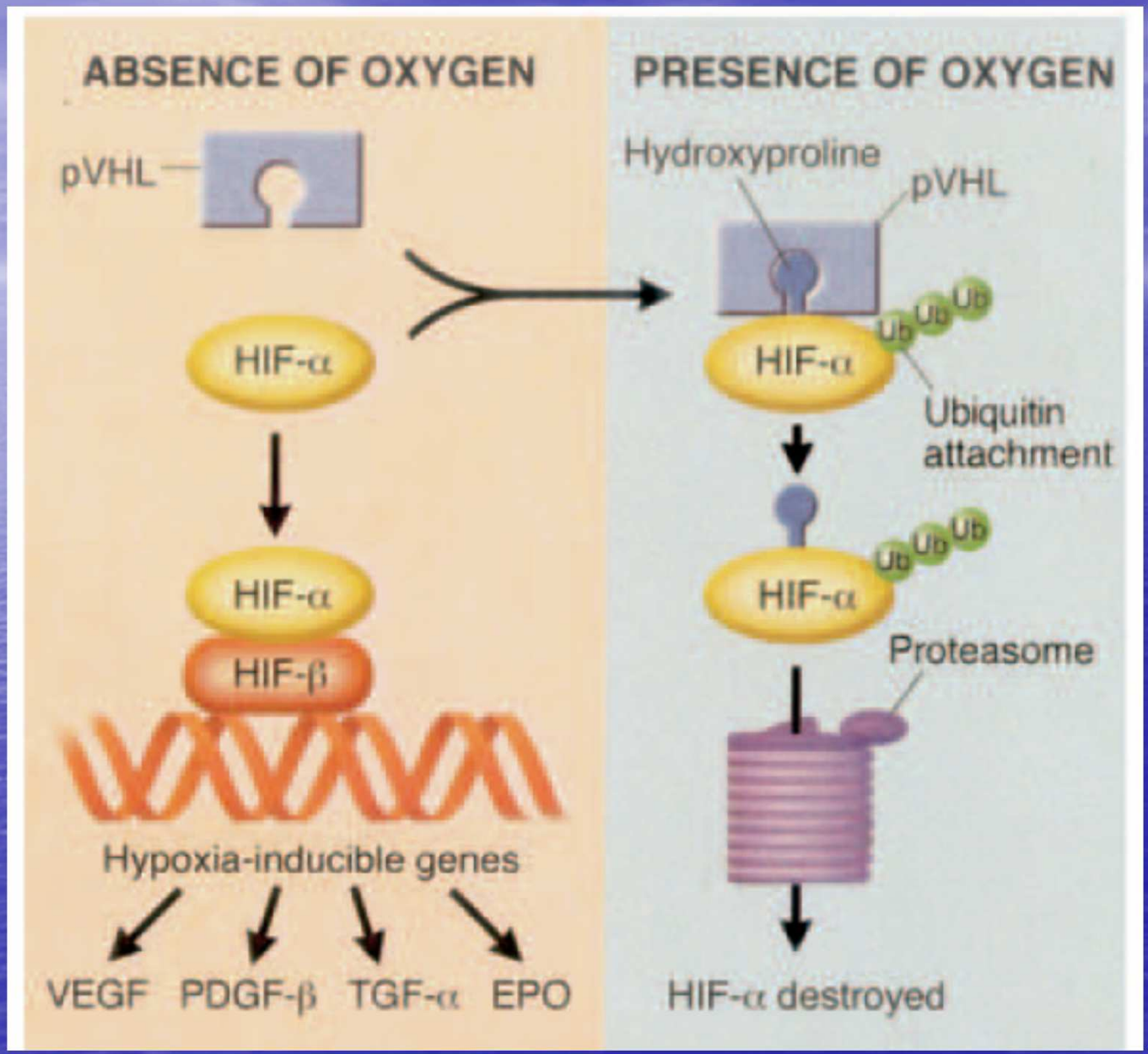


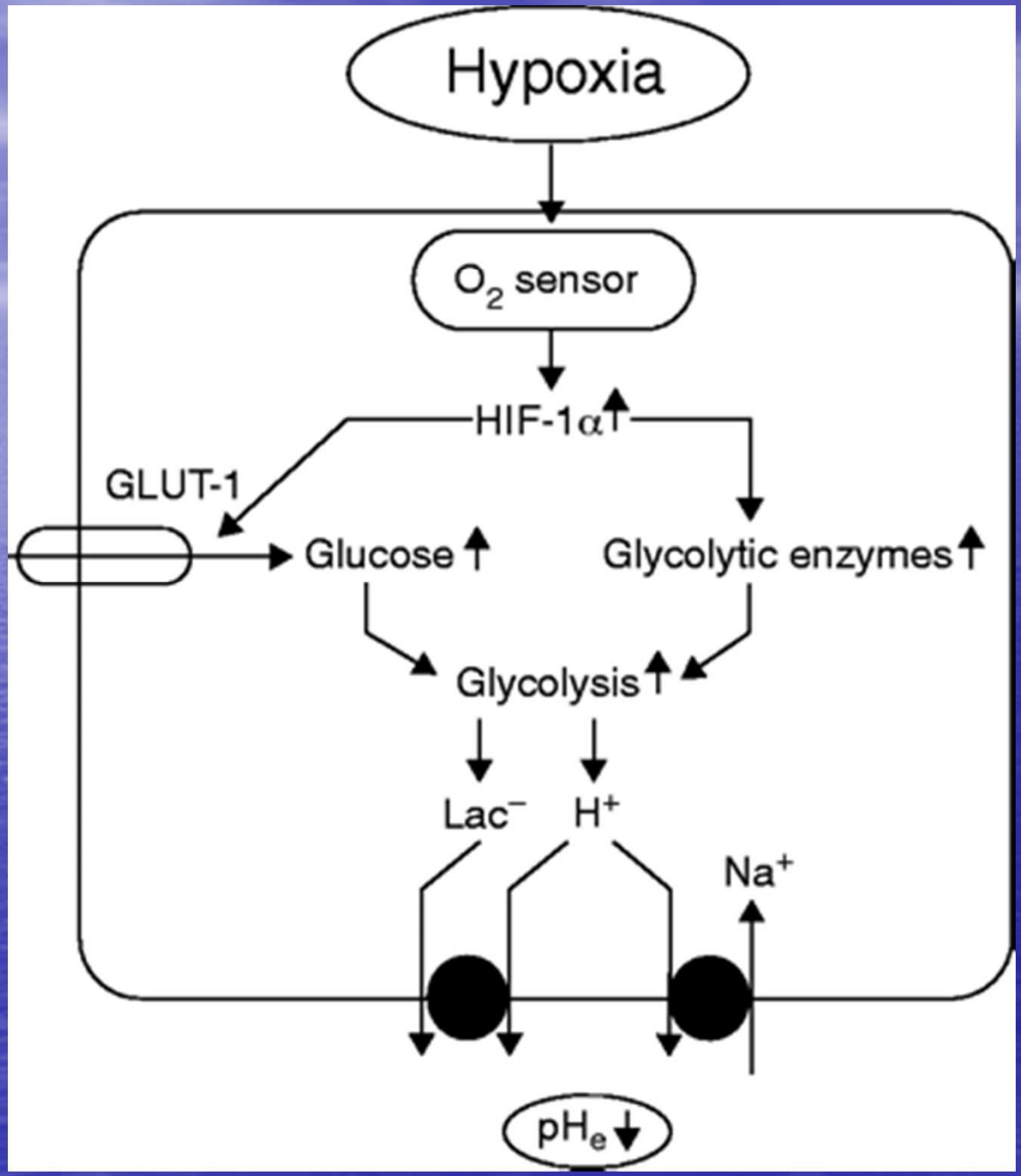
Overview HIF-1 signal pathway

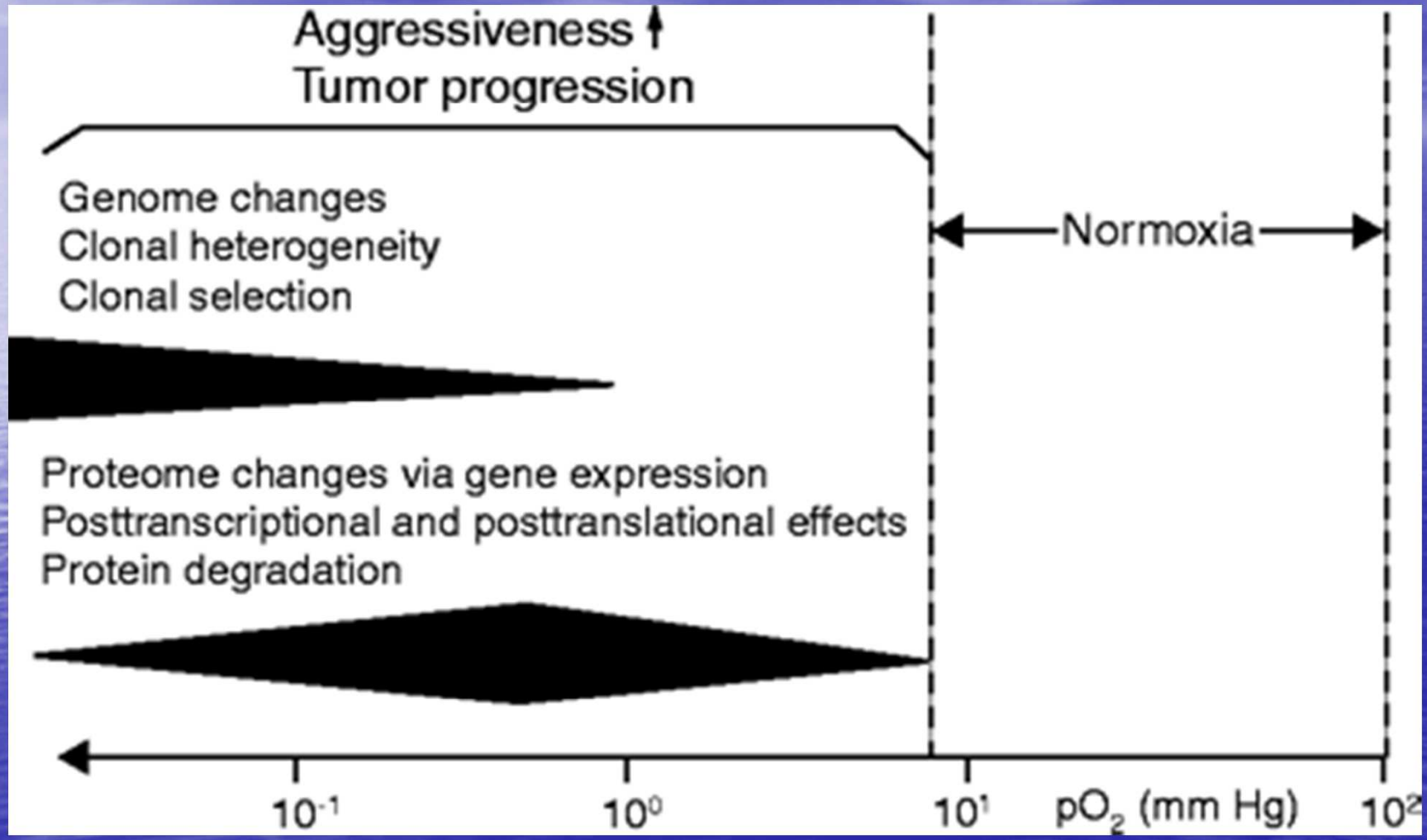
CCR 2003;9:4641-52

modified

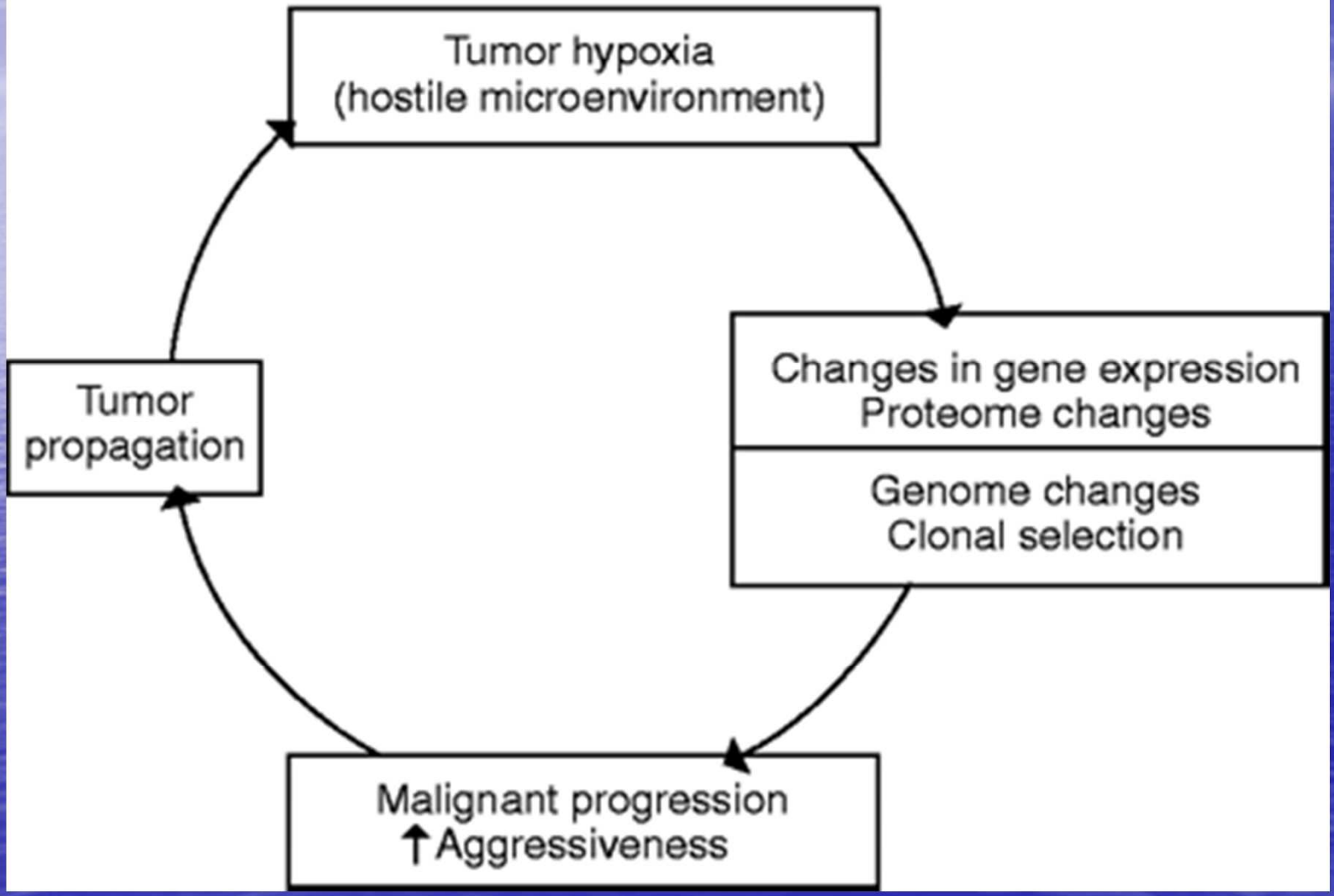

Normoxia
Fe2+
O2
Prolyl-hydroxylases
(active)
OH — HIF-1α vHL
Ubiquitination - proteasome
HIF-1α degradation
Hypoxia
Prolyl-hydroxylases
(inactive)
HIF-1α
HIF-1α accumulation
+
HIF-1β binding
Recognition of DNA binding sites
(5′ – RCGTG – 3′)
Coactivation, transcription, mRNA synthesis
Protein biosynthesis
(physiologic response to hypoxia)


ABSENCE OF OXYGEN
PRESENCE OF OXYGEN
pVHL
HIF-α
HIF-α
HIF-β
Hypoxia-inducible genes
VEGF
PDGF-β
TGF-α
EPO
Hydroxyproline
pVHL
Ub
Ub
Ub
HIF-α
Ubiquitin attachment
Ub
Ub
Ub
HIF-α
Proteasome
HIF-α destroyed


Hypoxia
O_2 sensor
HIF-1α↑
GLUT-1
Glucose↑
Glycolytic enzymes↑
Glycolysis↑
Lac^-
H^+
Na^+
pH_e↓


Aggressiveness
Tumor progression
Genome changes
Clonal heterogeneity
Clonal selection
Normoxia
Proteome changes via gene expression
Posttranscriptional and posttranslational effects
Protein degradation
10^{-1}
10^{0}
10^{1}
pO_2 (mm Hg)
10^{2}

The vicious circle of tumor hypoxia



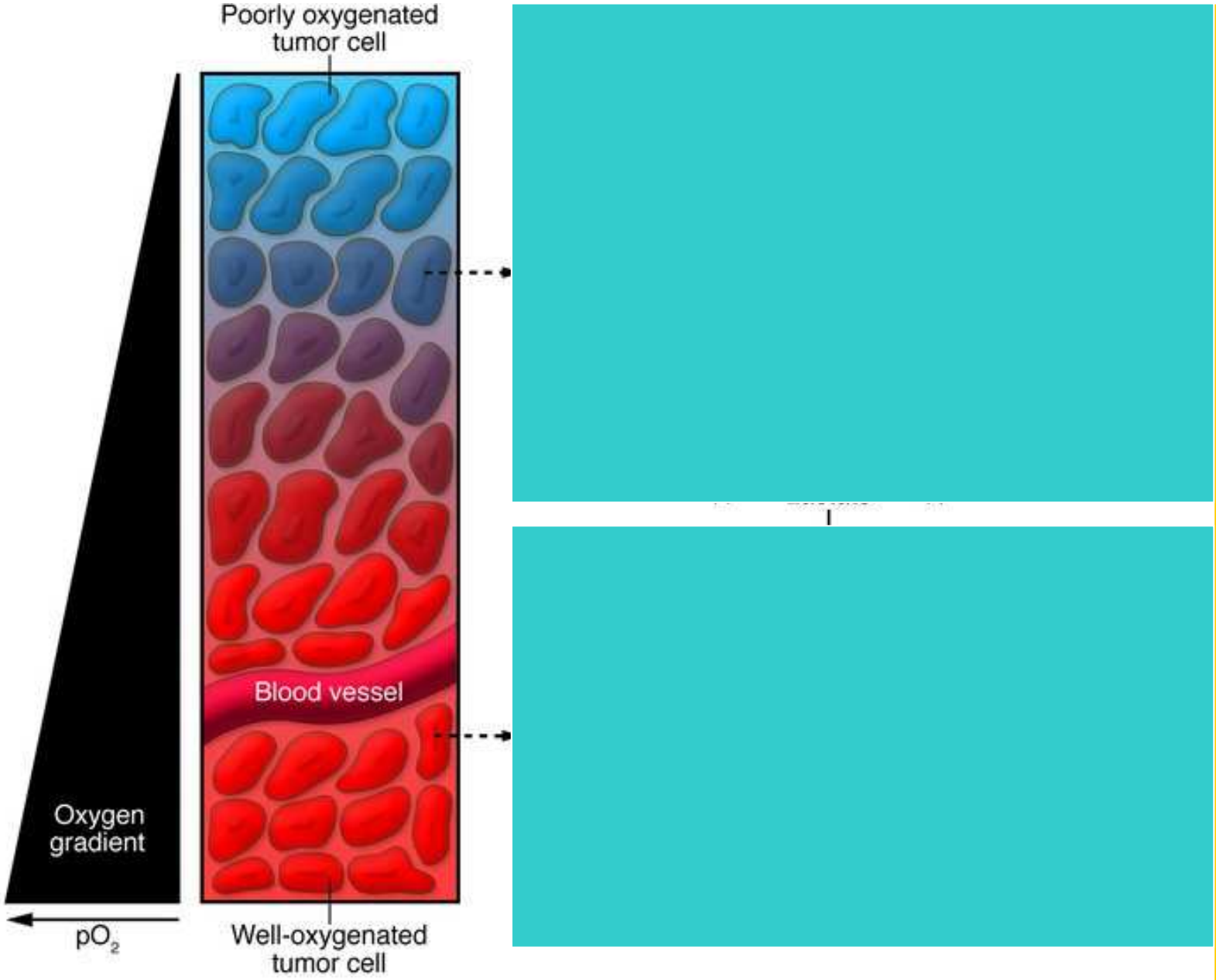
La sorpresa: simbiosis metabólica

- Los tumores se componen de dos tipos celulares:
- A) Células normóxicas que metabolizan glucosa y ácido lactico
- B) Células hipóxicas que producen ácido láctico a partir de glucosa

El ácido láctico producido por las células hipóxicas es incorporado por las células normóxicas y utilizado para elaborar energía y otros productos

La enzima clave para este proceso es MCT1 (monocarboxilate transporter1)

Sonveaux et al. The Journal of Clinical Investigation 2008 Vol 118(12): 3930-3941



Symbiotic Metabolic Process

The Journal of Clinical Investigation