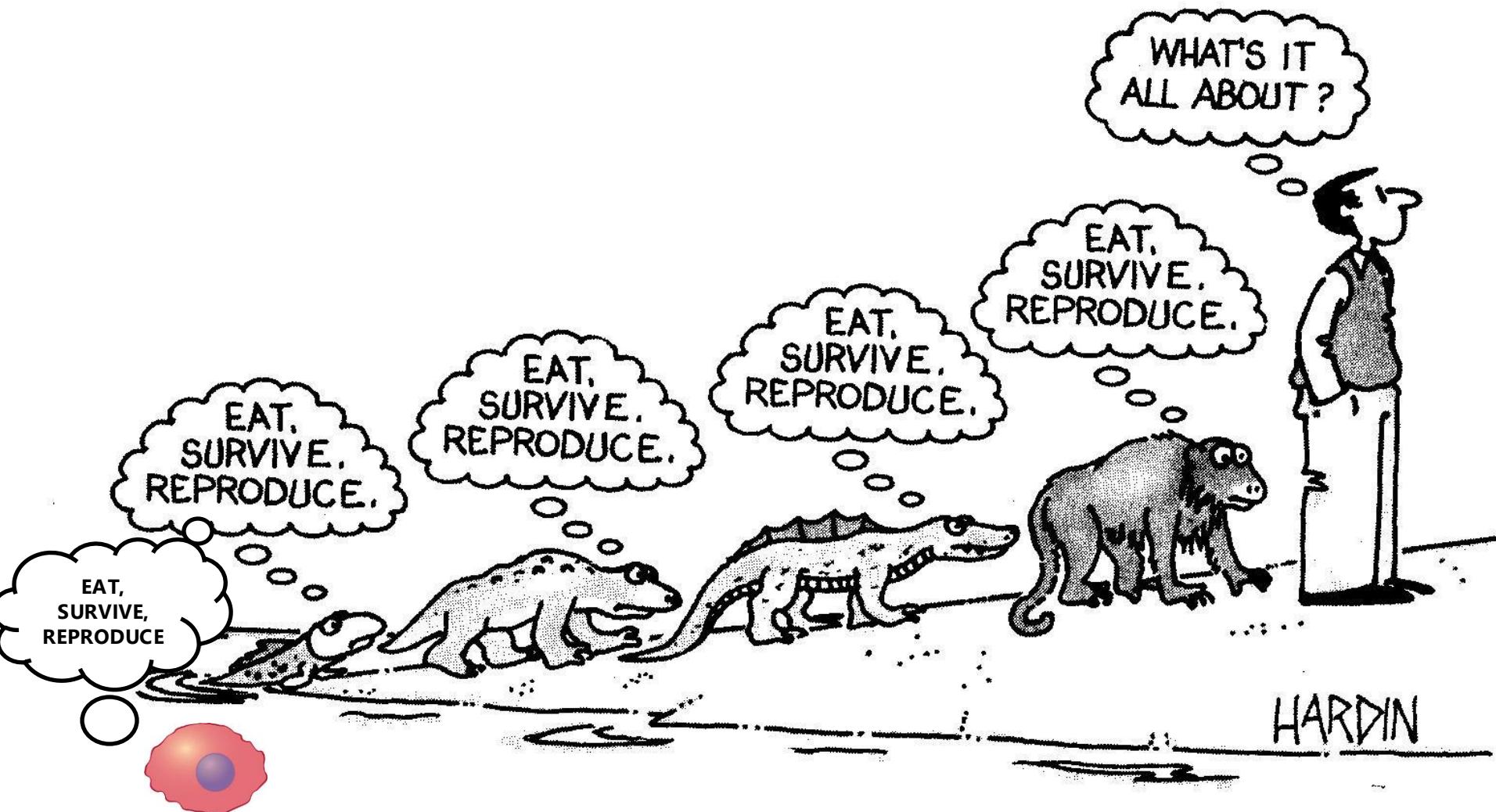


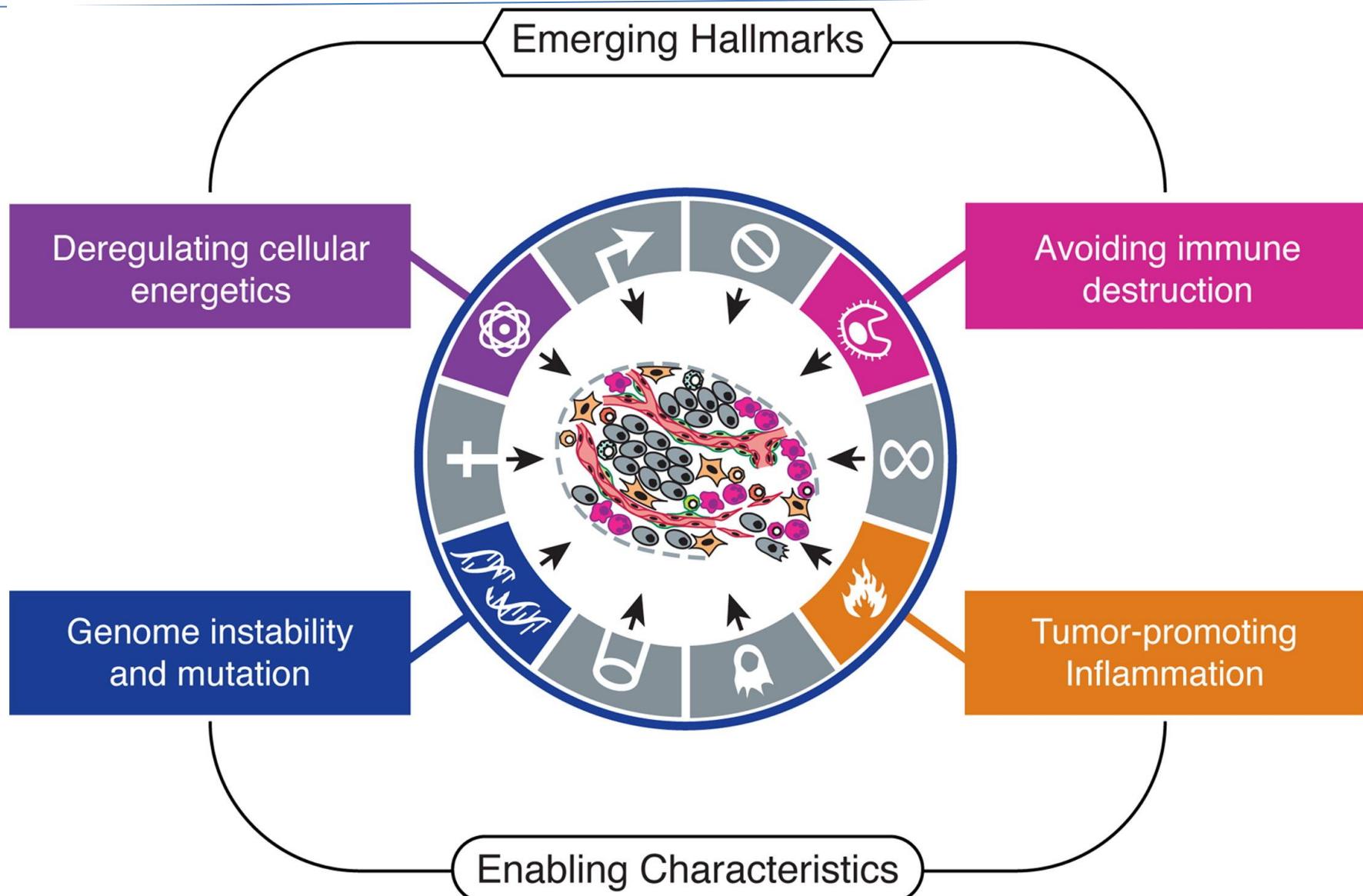
# **CANCER METABOLISM**

# Cancer cells need energy to proliferate



Nat. Hist., 1994, 103(6)

# Dysregulated metabolism is a hallmark of cancer



# Cancer and metabolism: when it all started

Muller observed aberrant metabolism in urine of cancer patients

Warburg observed the increased glycolysis in cancer cell

1887      1890

Freund proposed that blood cancer cells can be killed by reducing glucose

Wassermann hypothesised a role of deregulated respiration in cancer cell

1912

Dr. upon in sin that i amou be de Howe occur The c fact, viz., albur cinon case mala serve leuka incre conci cases and i clusio of te verti malig whic devel ited, a no affec or fe tumo the c vidua

JULY

## Tissue Metabolism in Cancer.

### SUGAR AND CANCER.

The theories of Dr. Freund, Vienna, concerning the cause of the cancer in the German Crown Prince's throat are generally discredited by New-York medical men. According to recent dispatches Dr. Freund's theory is that the blood of patients suffering from cancer contains an abnormal quantity of sugar, and that cancerous growths may be destroyed by a reduction of the amount of sugar.

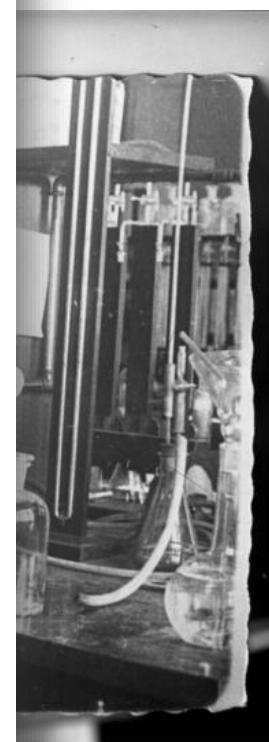
Dr. George F. Shrady, editor of the *Medical Record*, was inclined to be conservative on this subject yesterday. He did not care to speak against a new theory just because it was new, for new theories had frequently developed into something practical. In this case, however, it was different. Dr. Freund, who is unknown as an authority, has advanced a theory wholly inconsistent with the results of years of scientific research. In the first place sugar is present normally in the blood in small quantities. Various diseased conditions of the system occasionally produce an excessive quantity of sugar in the blood, the direct cause of diabetes mellitus, which is most difficult to cure. There is no relation whatever between cancer and sugar in the blood as cause and effect, either active or retroactive. A patient may have diabetes and cancer both at the same time, and the treatment of one would have no effect upon the other. Dr. Shrady did not think that Dr. Mackenzie and the other eminent physicians associated with him would experiment upon the Crown Prince with a new theory. They have always been accustomed to using their own opinions, and independent of outside influence.

The New York Times

Published: December 24, 1887

Copyright © The New York Times

mice succumb under the treatment.  
From *Nature* 18 January 1912



# The timeline of cancer research

Warburg observed the increased glycolysis in cancer cell

Kovacevic observed increased glutaminolysis in cancer cell

1924

1956

1972

1979

Warburg published "On the origin of cancer cell"

cMyc was discovered

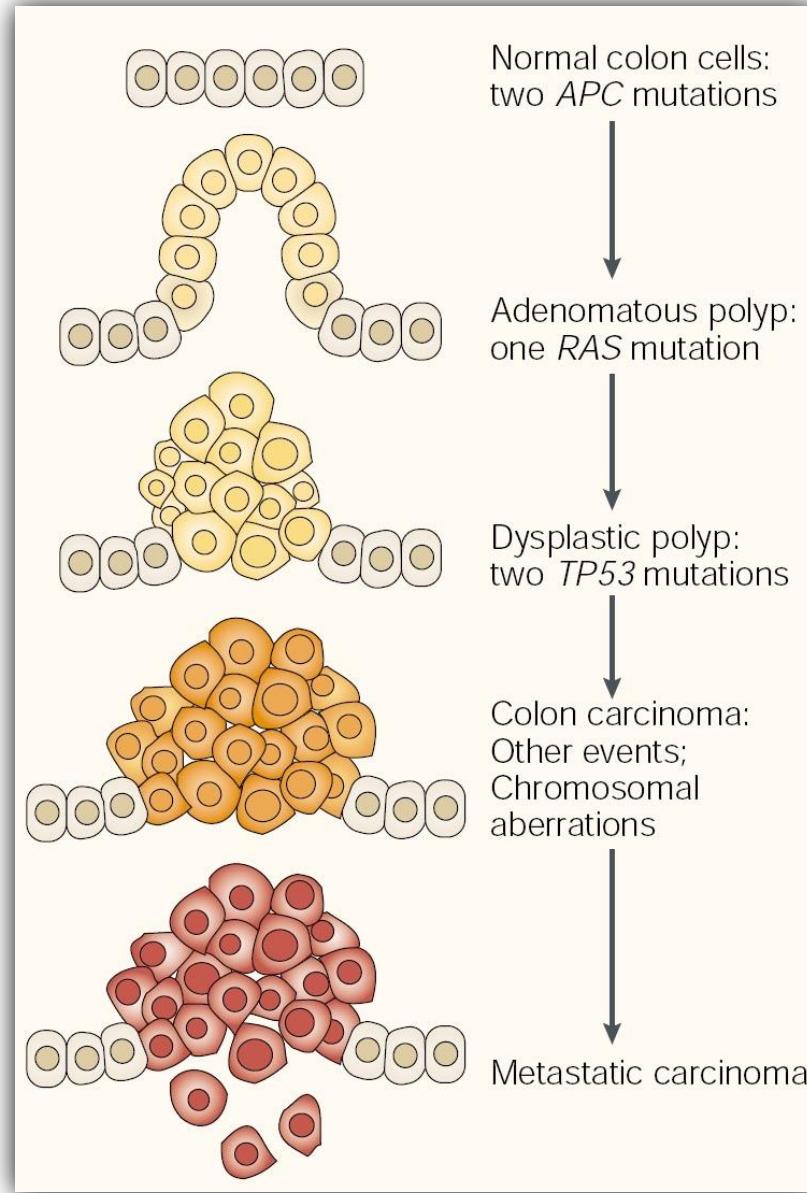
p53 was identified

Biochemistry era

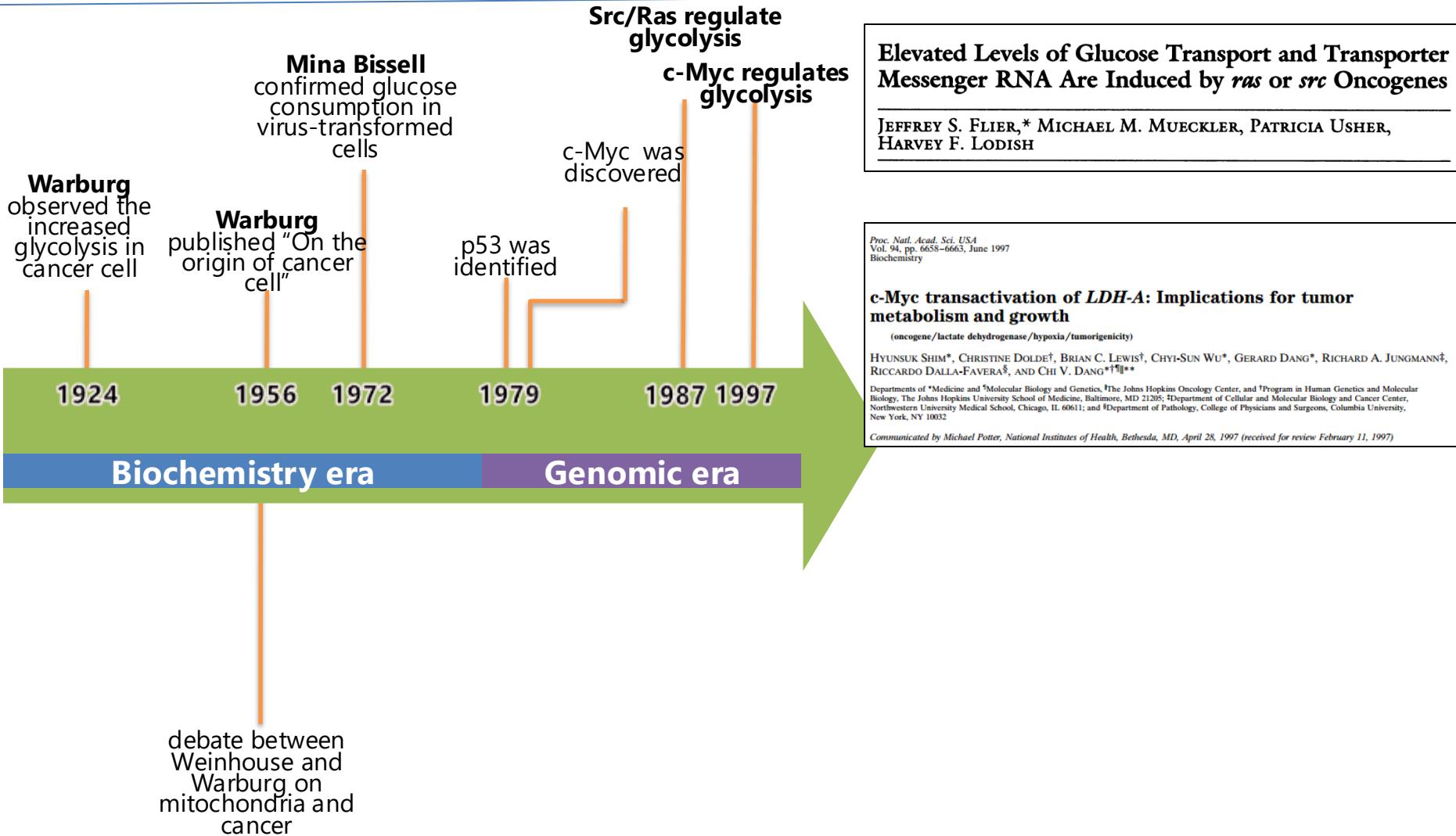
Genomic era

debate between Weinhouse and Warburg on mitochondria and cancer

# Cancer: a genetic disease



# The timeline of cancer research



# Cancer and Metabolism come together

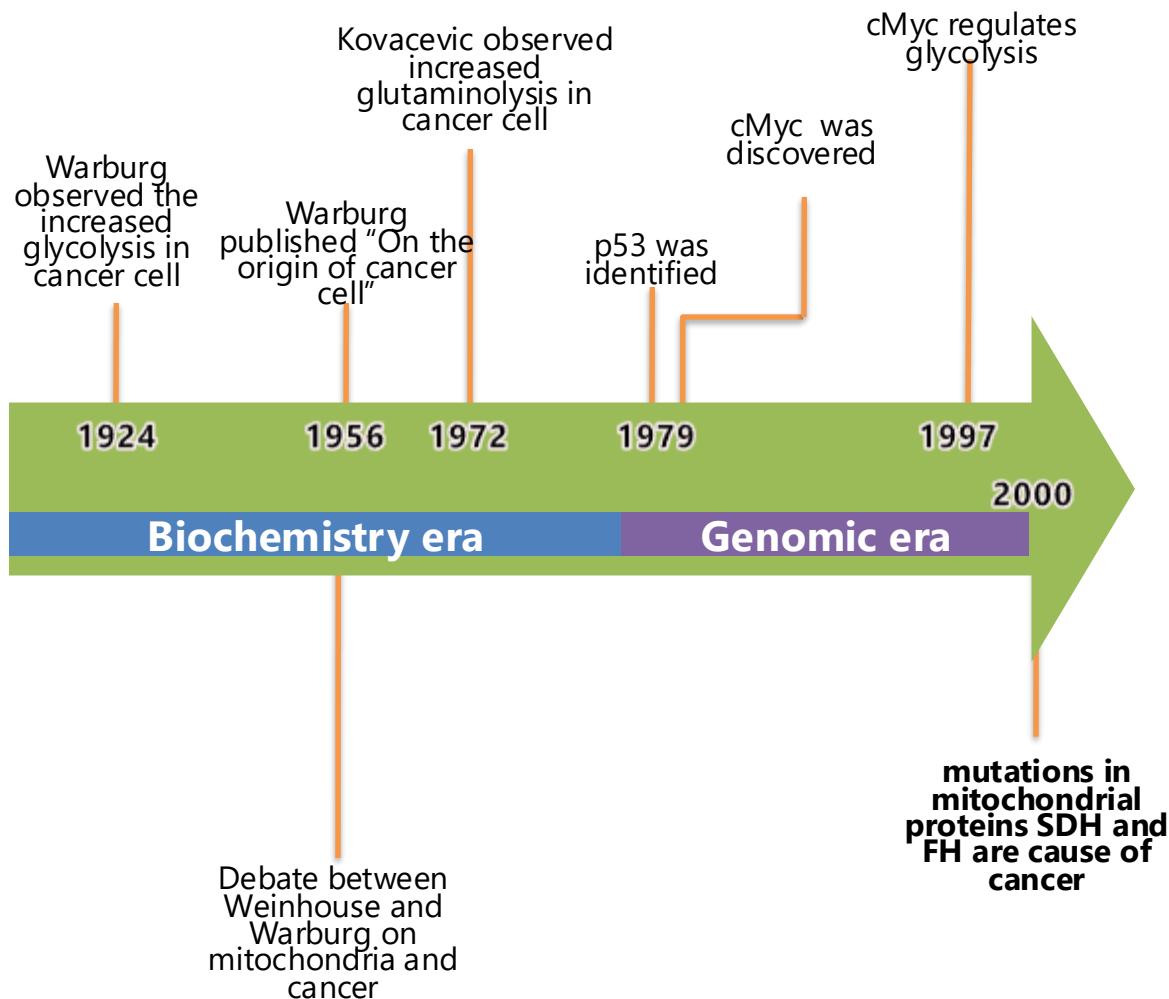
Metabolism

REVIEW

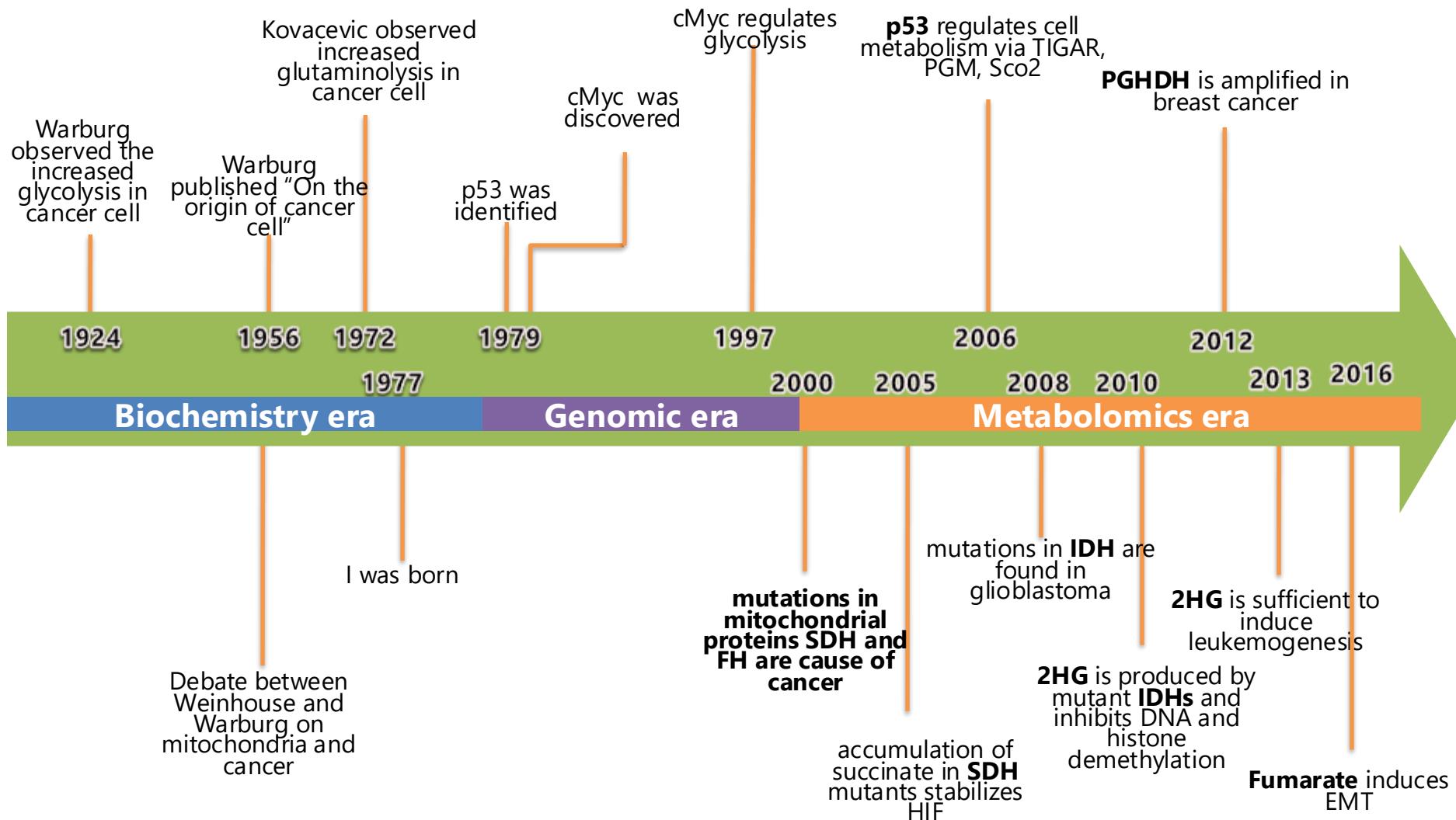
## The Control of the Metabolic Switch in Cancers by Oncogenes and Tumor Suppressor Genes

Arnold J. Levine<sup>1,2\*</sup> and Anna M. Puzio-Kuter<sup>2</sup>

# The timeline of cancer research



# The timeline of cancer research



# Cancer: a metabolic disease?

A groundbreaking new approach to understanding, preventing, and treating cancer

Supported by evidence from more than 1,000 scientific and clinical studies, this groundbreaking book demonstrates that cancer is a metabolic disease and, more importantly, that it can be more effectively managed and prevented when it is recognized as such. Moreover, the book provides detailed evidence that the traditional view of cancer as a genetic disease has been largely responsible for the failure to develop effective therapies and preventive strategies.

*Cancer as a Metabolic Disease* reevaluates the origins of cancer based on the latest research findings as well as several decades of studies exploring the defects in tumor cell energy metabolism. Author Thomas Seyfried is a biochemical geneticist who has been investigating the lipid biochemistry of cancer for thirty years. In this book, he carefully establishes why approaching cancer as a metabolic disease leads to better understanding and management of all aspects of the disease, including inflammation, vascularization, cell death, drug resistance, and genomic instability. In addition, the book explores:

- Origin of metastasis
- New treatment strategies that target tumor cell energy metabolism, including the ketogenic diet
- More effective prevention strategies in light of the metabolic origin of cancer
- Case studies and perspectives from the point of view of physicians, patients, and caregivers

Throughout the book, tables, figures, and graphs summarize key information and clarify complex concepts. In addition, the renowned cancer biochemist Peter Pedersen from Johns Hopkins Medical School also provides a historical perspective on the importance of the information presented in his foreword to the book.

*Cancer as a Metabolic Disease* is essential reading for all cancer researchers and clinicians as well as public health professionals. By treating cancer as a metabolic disease, the book sets readers on a new, more promising path to understanding the origins of cancer and developing new, more effective strategies to treat and prevent it.

THOMAS N. SEYFRIED, PhD, has taught and conducted research in the fields of neurogenetics, neurochemistry, and cancer for more than twenty-five years at Yale University and Boston College. He has published more than 150 scientific articles and book chapters and is on the editorial boards of *Nutrition & Metabolism*, *Journal of Lipid Research*, *Neurochemical Research*, and *ASN Neuro*.

The book cover image, entitled *Progress*, is taken from Robert Pope's book *Illness & Healing: Images of Cancer*. It took Pope an entire autumn to complete the acrylic on canvas painting (182.9 x 121.8 cm), which depicts a multi-generational family visiting their cancer-stricken grandfather in hospital. The image is rich with symbols that spiral and fold into one another. Some symbols convey the negative aspects of life: blindness, sickness, and pollution. Yet, the spiral of figures also suggests that hope and health can be realized through human solidarity and a positive vision of the future. This book conveys similar themes in describing cancer as a metabolic disease that can be managed with non-toxic metabolic solutions. (Reprinted with permission from the Robert Pope Foundation, Dalhousie Medical School, Halifax, Nova Scotia, Canada. Cover art image processing by Daniel A. Kirschner.)

Subscribe to our free Chemistry eNewsletter at  
[wiley.com/newsletters](http://wiley.com/newsletters)

Visit [wiley.com/chemistry](http://wiley.com/chemistry)

 **WILEY**  
wiley.com

 Also available  
as an e-book



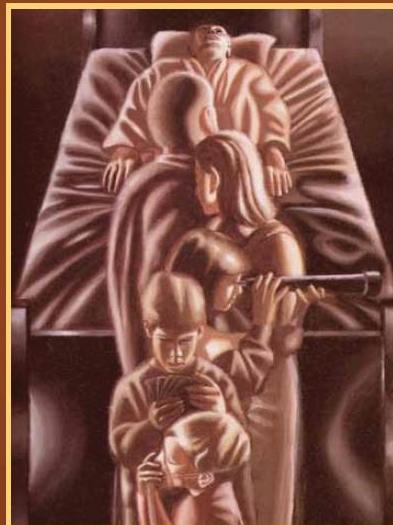
Seyfried

## Cancer as a Metabolic Disease

On the Origin, Management,  
and Prevention of Cancer

# Cancer as a Metabolic Disease

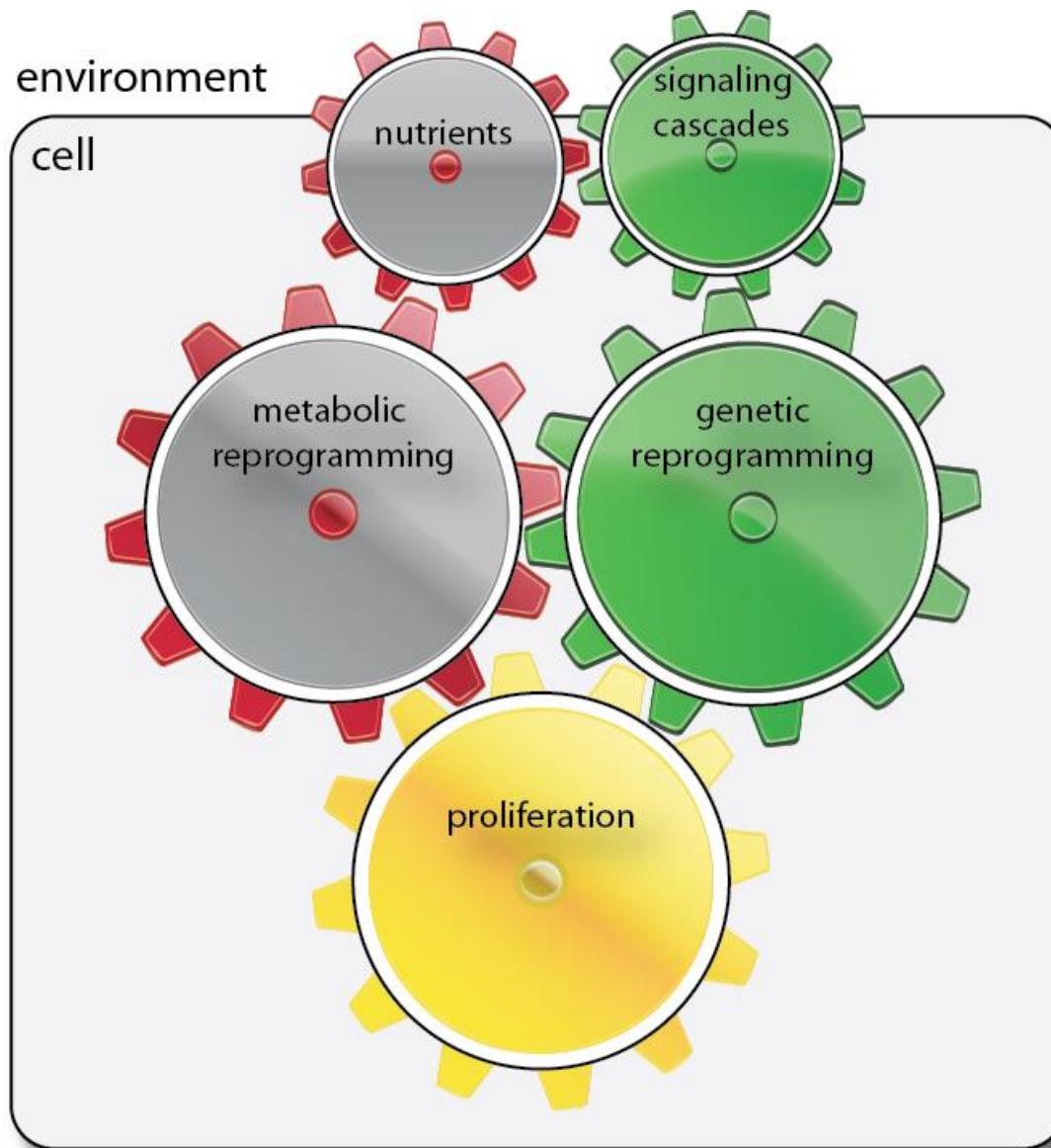
On the Origin, Management,  
and Prevention of Cancer



Thomas N. Seyfried

 WILEY

# A system view of cancer

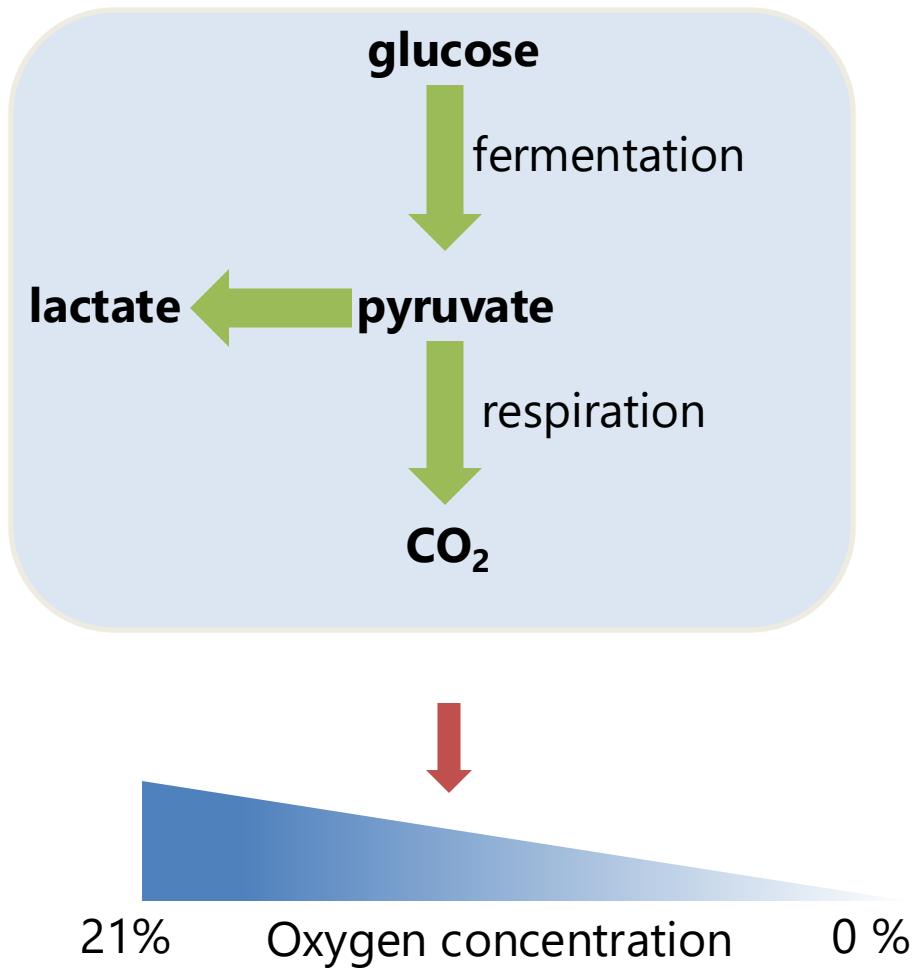


An historical perspective on

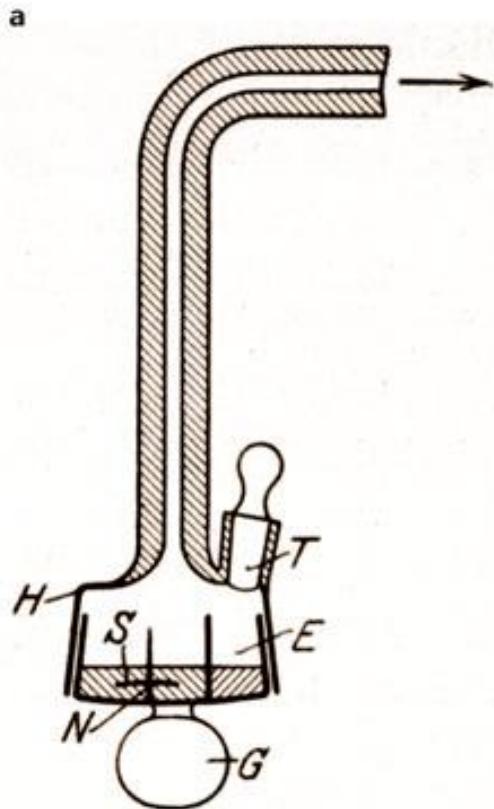
# **CANCER METABOLISM**

# Metabolism in the 19<sup>th</sup> century

Pasteur effect



# Warburg experiments



**b**

*Tabelle I.*  
FLEXNER-JOBLINGESches Rattencarcinom.  
37,5°. Ringerlösung.  $C_{NaHCO_3} = 2,5 \cdot 10^{-2}$ . 0,2 proz. Glucose. 5 proz.  $CO_2$ .  
 $p_H = 7,66$ .

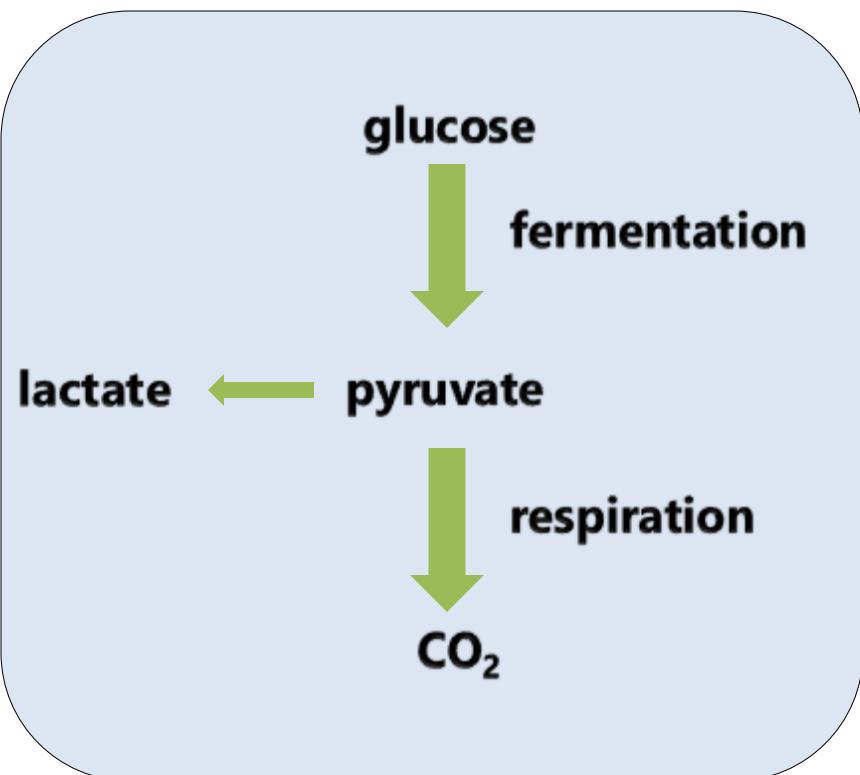
Nr.	I	II	III	IV	V	VI
	$Q_{O_2}$ (Atmung)	$Q_{CO_2}^{O_2}$ (Glykolyse in Sauerstoff)	$Q_{CO_2}^{N_2}$ (Glykolyse in Stickstoff)	Hemmung d. Glykolyse durch Sauerstoff $\left( \frac{III - II}{III} \right) \%$	MEYERHOF- Quotient $\left( \frac{III - II}{I} \right)$	Aerobe Glykolyse Atmung $\left( \frac{II}{I} \right)$
1	— 4,5	+ 21	—	—	—	4,7
2	— 7,8	+ 28	—	—	—	3,6
3	— 11,5	+ 30	—	—	—	2,6
4	— 5,1	+ 18	—	—	—	3,6
5	— 7,5	+ 30,5	—	—	—	4,1
6	— 2,4	+ 17,7	—	—	—	7,4
7	— 4,1	+ 25,6	+ 30,8	18	1,3	5,1
8	— 3,5	+ 19	+ 26,8	29	2,2	5,4
9	— 7,5	+ 22,5	+ 34,6	35	1,6	3,0
10	— 12,8	+ 27	+ 34,5	22	0,6	2,1
11	— 11,8	+ 26	+ 34	24	0,7	2,2
12	— 10,4	+ 22,3	+ 25,3	12	0,3	2,1
13	— 2,5	+ 18,6	+ 28,3	34	3,9	7,6
14	— 9,0	+ 24	+ 30,8	21	0,73	2,7
15	— 11,5	+ 25,5	+ 33,8	25	0,72	2,2
16	— 6,7	+ 27,7	+ 37,0	25	1,4	4,2
17	— 5,5	+ 18	+ 25,6	30	1,4	3,3
18	— 8,9	+ 23,7	+ 27,3	13	0,4	2,7
19	— 4,1	+ 25,7	+ 33,8	24	2,0	6,4
Mittel:	— 7,2	+ 25	+ 31	23	1,3	3,9

Nature Reviews | Cancer

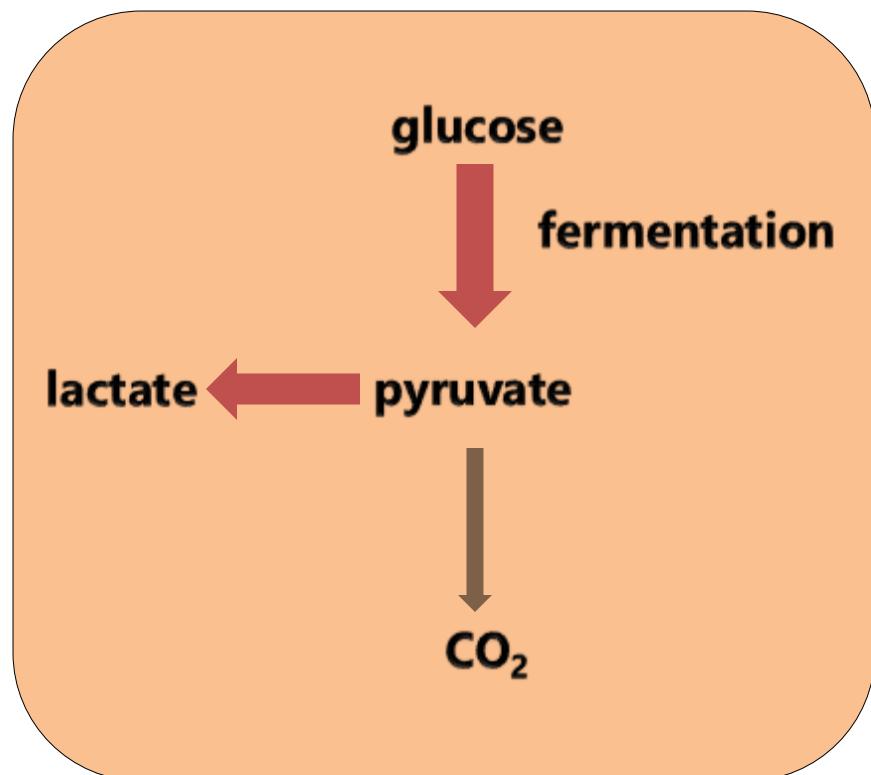
Otto Warburg's contributions to current concepts of cancer metabolism

# Aerobic glycolysis in cancer cells

Normal cell



Cancer cell



# The Warburg hypothesis

24 February 1956, Volume 123, Number 3191

# SCIENCE

The prime cause of cancer is the replacement of the respiration of oxygen...by a fermentation of sugar..."

Injuring of Respiration  
Since the respiration of all cancer cells is damaged, our first question is, How can the respiration of body cells be injured? Of this damage to respiration, it can be said at the outset that it must be *irreversible*, since the respiration of cancer cells never returns to normal.

Normal cell

On the Origin of  
Injury of respiration

Phase I

Our principal experimental object for the measurement of the metabolism of cancer cells is today no longer the tumor but the ascites cancer cells (*I*) living free in the abdominal cavity, which are almost pure cultures of cancer cells with which one can work quantitatively as in chemical analysis. Formerly, it could be said of tumors, with their varying cancer cell content, that they ferment more strongly the more cancer cells they contain, but today we can determine the absolute fermentation values of the cancer cells and find such high values that we come very close to the fermentation values of wildly proliferating *Torula* yeasts.

What was formerly only qualitative has now become quantitative. What was formerly only probable has now become certain. The era in which the fermentation of the cancer cells or its importance could be disputed is over, and no one today can doubt that we understand the origin of cancer cells if we know how their large fermentation originates, or, to express it more fully, if we know how the damaged respiration and the excessive fermentation of the cancer cells

C-11

Aerobic glycolysis

Phase II

De-differentiation

Phase III

Cancer cell

through which the energy, of respiration and fermentation is then made available for life. Since it is known how much adenosine triphosphate can be synthesized by respiration and how much by fermentation, we can write immediately the potential, biologically utilizable energy production of any cells if we have measured their respiration and fermentation. With the ascites cancer cells of the mouse, for example, we find an average respiration of 7 cubic millimeters of oxygen consumed per milligram, per hour, and fermentation of 60 cubic millimeters of lactic acid produced per milligram, per hour. This, converted to energy equivalents, means that the cancer cells can obtain approximately the same amount of energy from fermentation as from respiration, whereas the normal body cells obtain much more energy from respiration than from fermentation. For example, the liver and kidney of an adult animal obtain about 100 times as much energy from respiration as from fermentation.

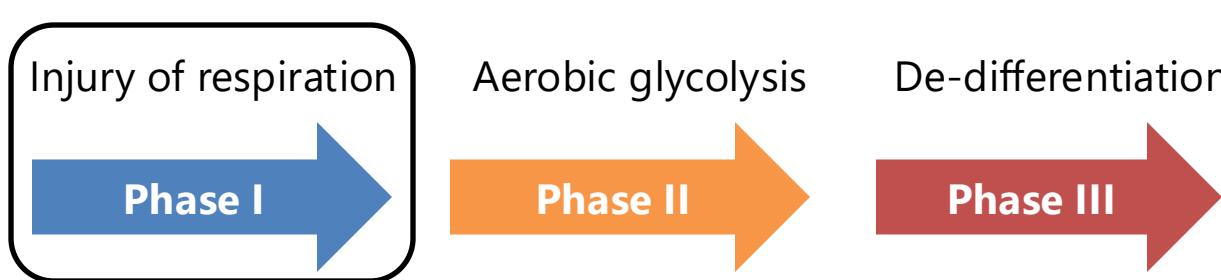
I shall not consider aerobic fermenta-

One method for the destruction of the respiration of body cells is removal of oxygen. If, for example, embryonal tissue is exposed to an oxygen deficiency for some hours and then is placed in oxygen again, 50 percent or more of the respiration is usually destroyed. The cause of this destruction of respiration is lack of energy. As a matter of fact, the cells need their respiratory energy to preserve their structure, and if respiration is inhibited, both structure and respiration disappear.

Another method for destroying respiration is to use respiratory poisons. From the standpoint of energy, this method comes to the same result as the first method. No matter whether oxygen is withdrawn from the cell or whether the oxygen is prevented from reacting by a poison, the result is the same in both cases—namely, impairment of respiration from lack of energy.

I may mention a few respiratory poisons. A strong, specific respiratory poison is arsenious acid, which, as every clinician knows, may produce cancer.

# Dissecting the Warburg hypothesis



Cancer cells originate from normal body cells in *two* phases. The first phase is the irreversible injuring of respiration. Just as there are many remote causes of plague—heat, insects, rats—but only one common cause, the plague bacillus, there are a great many remote causes of cancer—tar, rays, arsenic, pressure, urethane—but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration.

# **Is respiration in cancer cells injured?**

**"...there is no evidence...that the respiration in cancer cell is either quantitatively lowered or fails to lower glycolysis..." Weinhouse, Z. Krebsforsch, 1976**

**Sidney Weinhouse**



# Is hypoxia the cause of mitochondrial dysfunction?



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



Biochemical and Biophysical Research Communications 313 (2004) 459–465

BBRC

[www.elsevier.com/locate/ybbrc](http://www.elsevier.com/locate/ybbrc)

Breakthroughs and Views

## Cancer metabolism: facts, fantasy, and fiction<sup>☆</sup>

Xin Lin Zu\* and Michael Guppy

*Biochemistry and Molecular Biology, School of Biochemical and Chemical Science, University of Western Australia,  
35 Stirling Highway, Crawley, WA 6009, Australia*

Received 19 November 2003

of a hypoxic core in tumours [57–59] and have led to the search for treatment strategies that exploit the hypoxic nature of tumours [60,61]. So perhaps tumours are glycolytic, but not inherently so, and not aerobically glycolytic, but anaerobically glycolytic as a result of a hypoxia-driven Pasteur effect. This would explain the

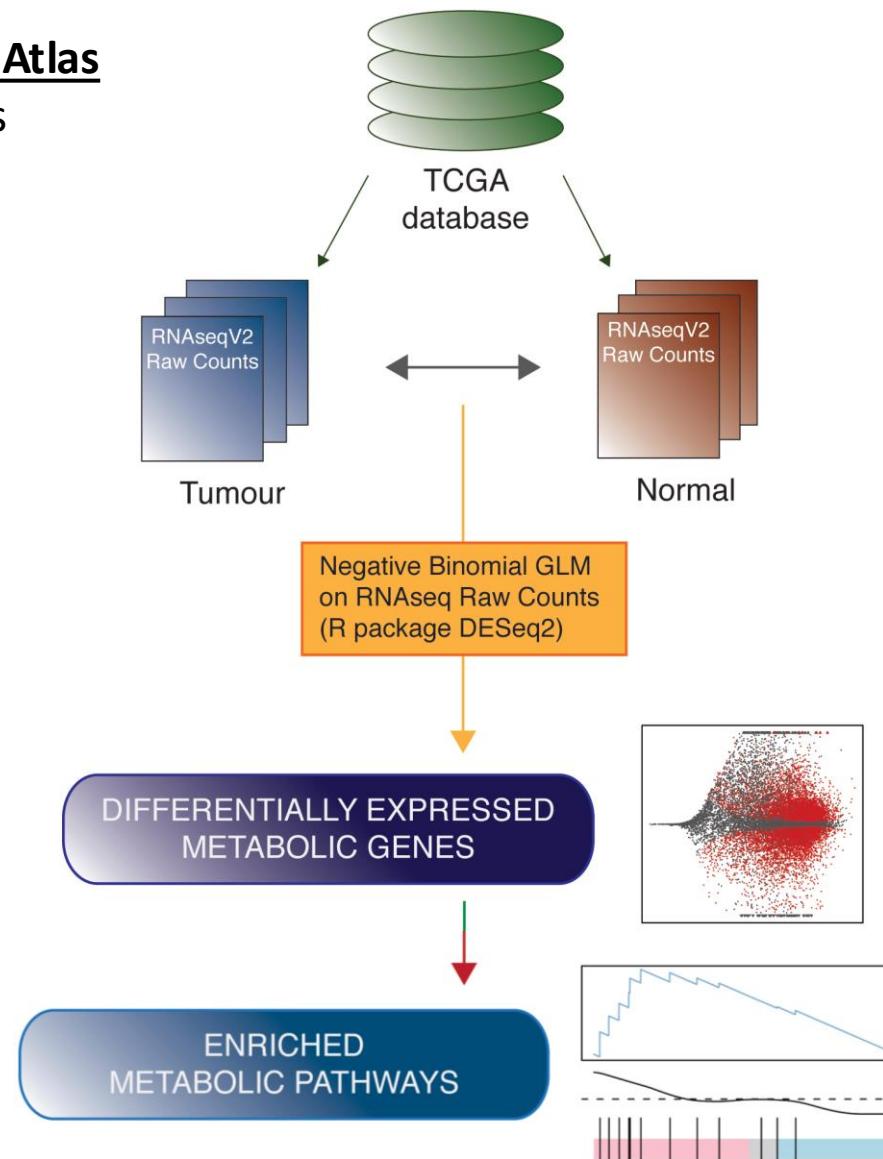
...all Warburg's experiment were performed using well oxygenated tissues

# Metabolic landscape of cancer

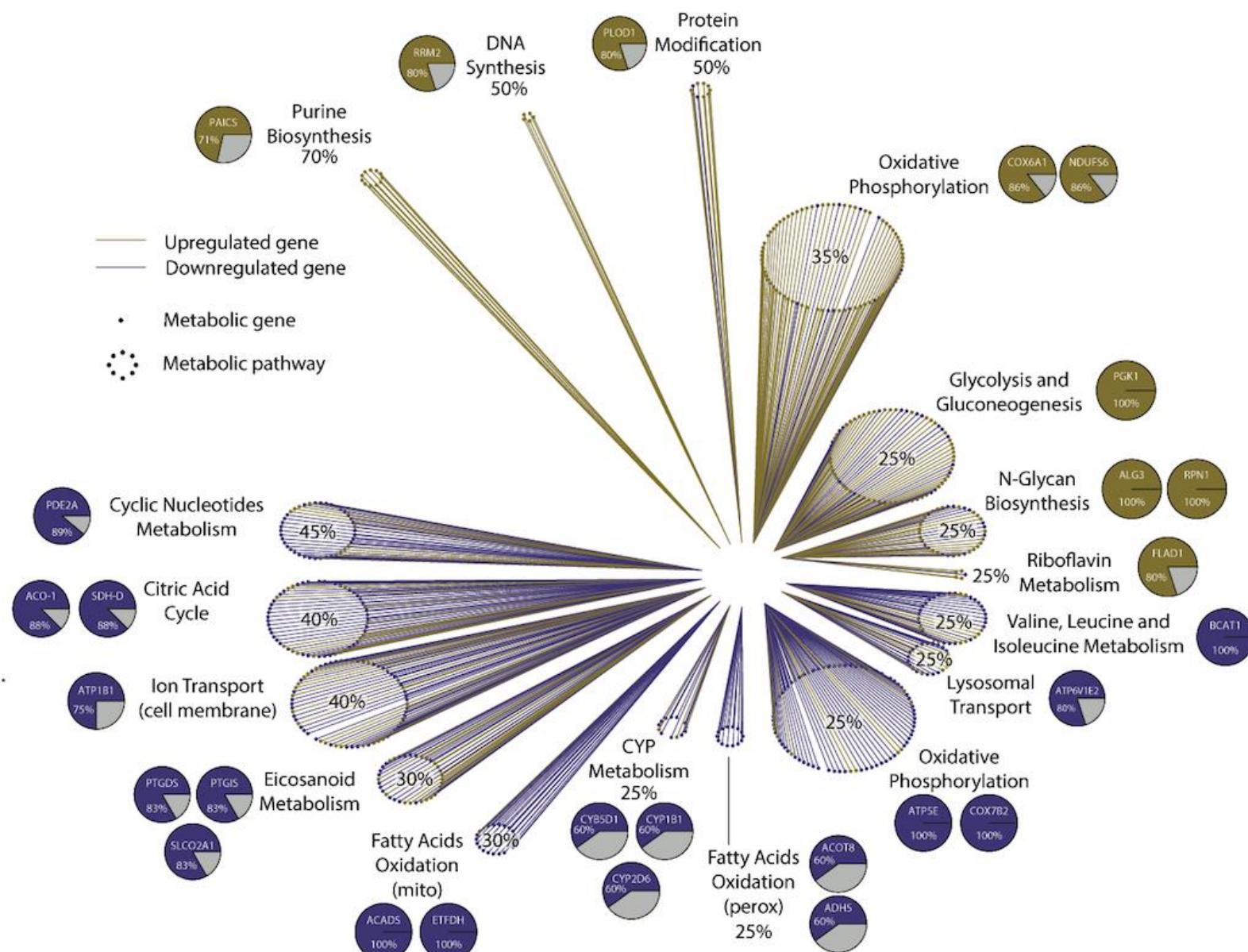
## The Cancer Genome Atlas

22 tumour types

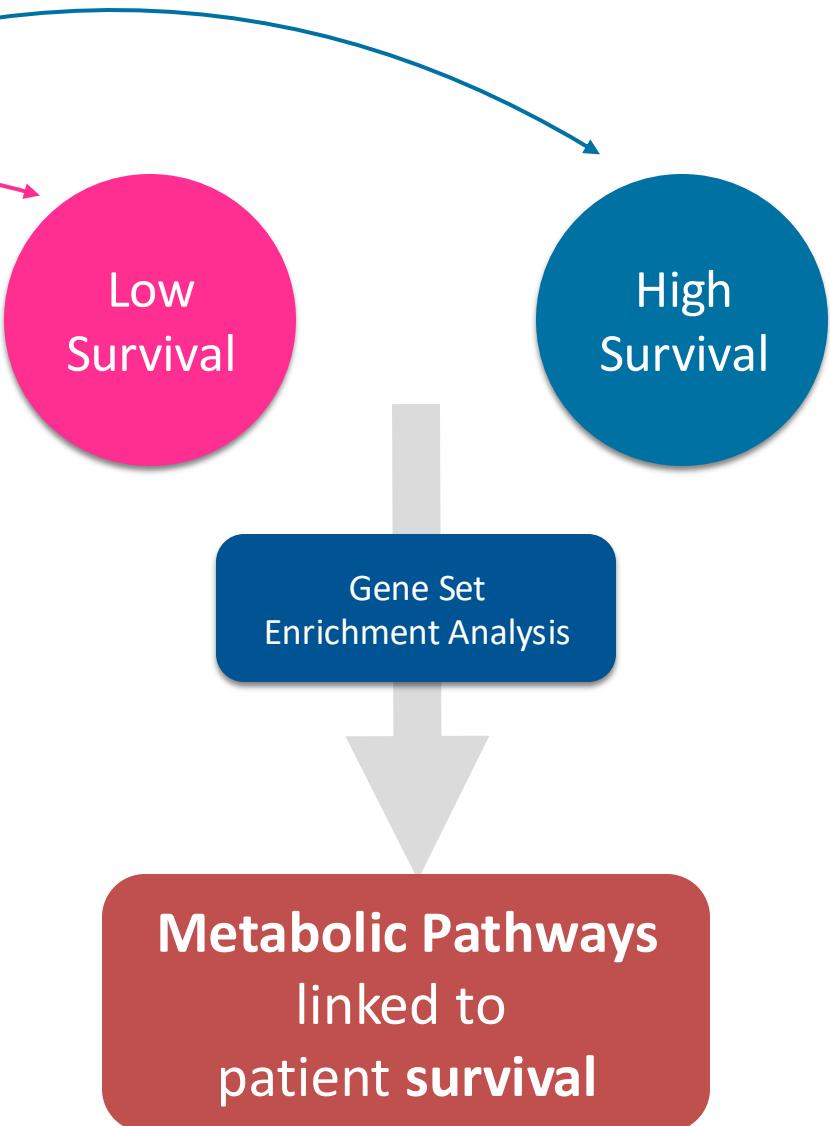
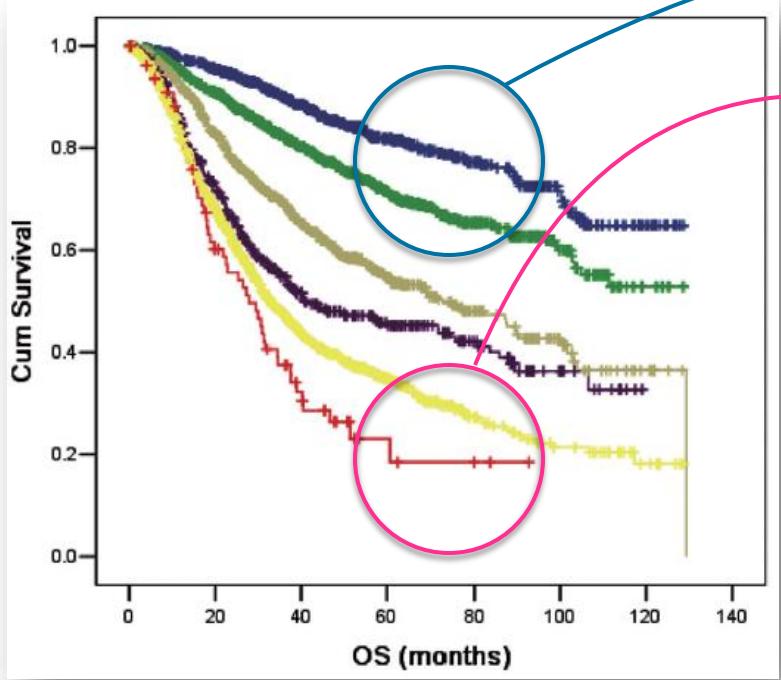
>8000 patients



# The metabolic landscape of cancer

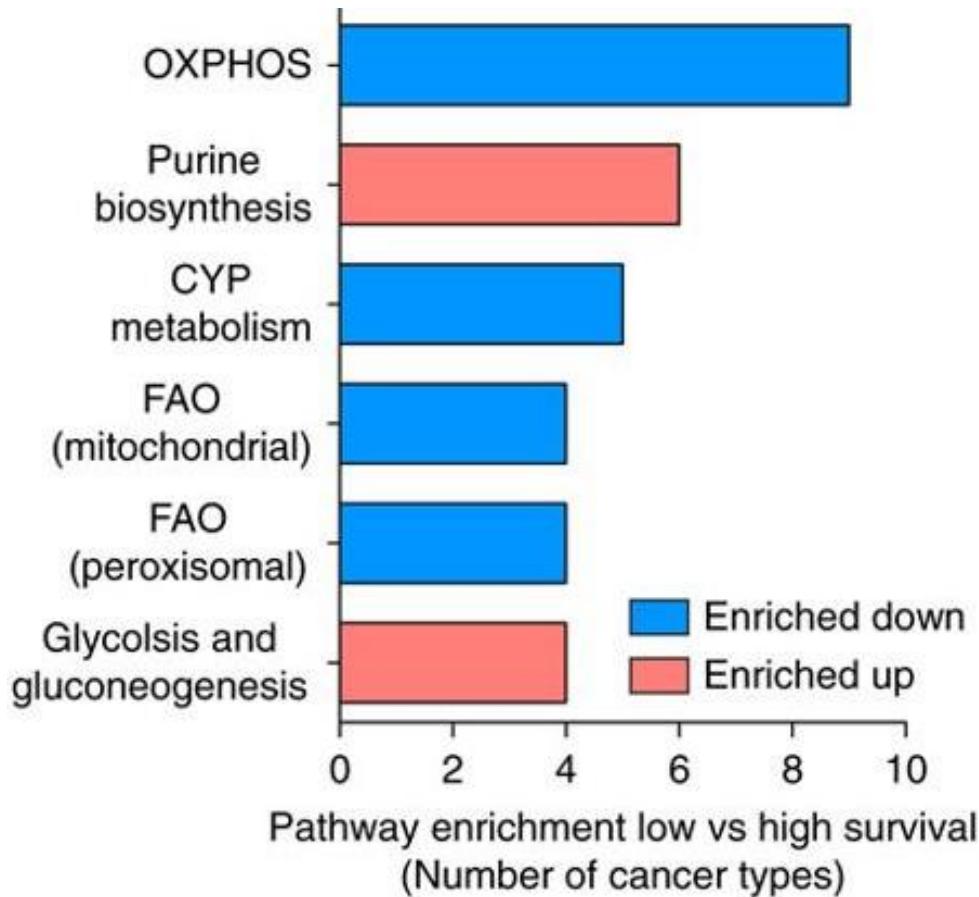


# Metabolism and patient outcome

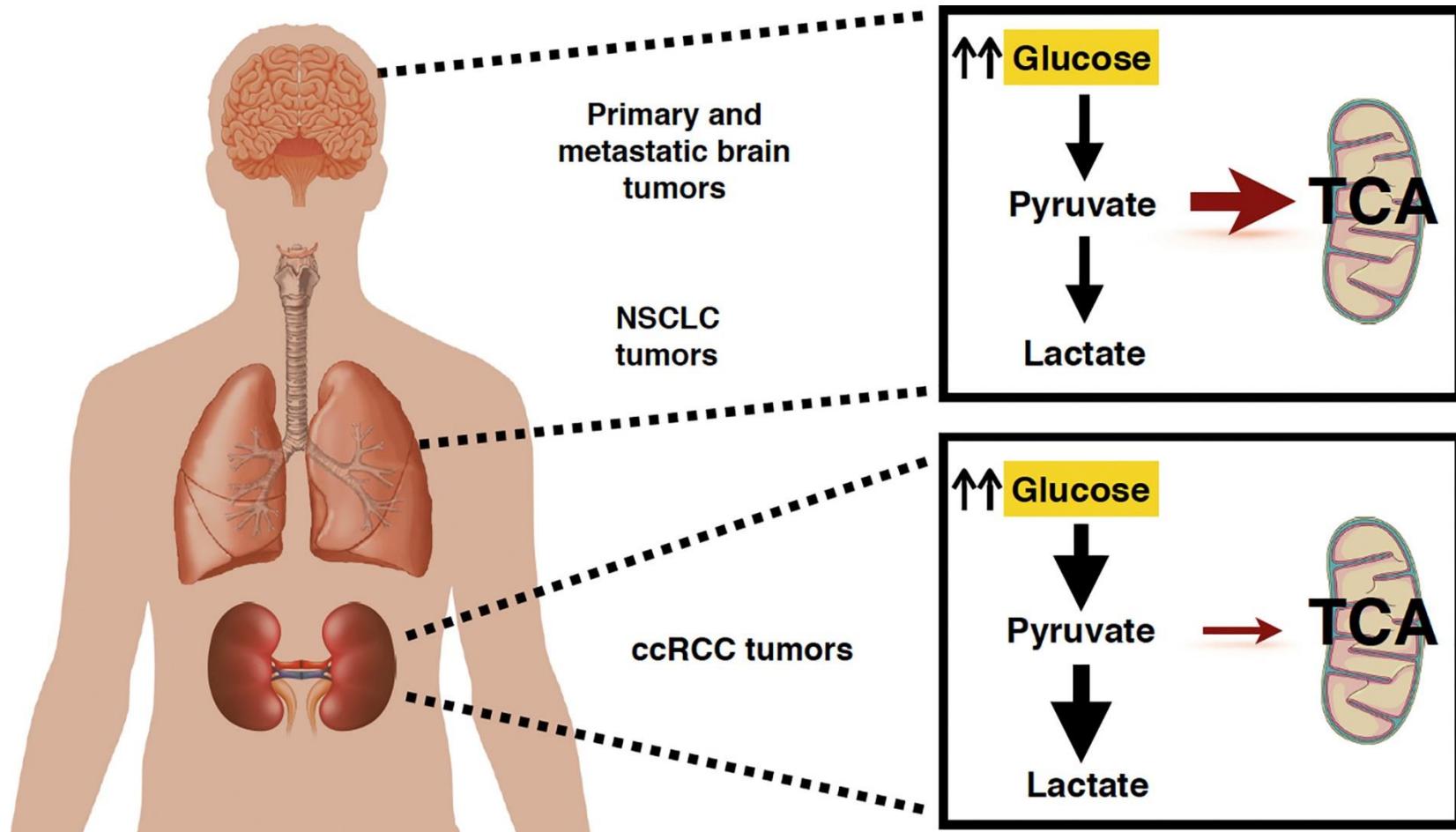


# Metabolism and patient outcome

OXPHOS is suppressed  
in low survival patients

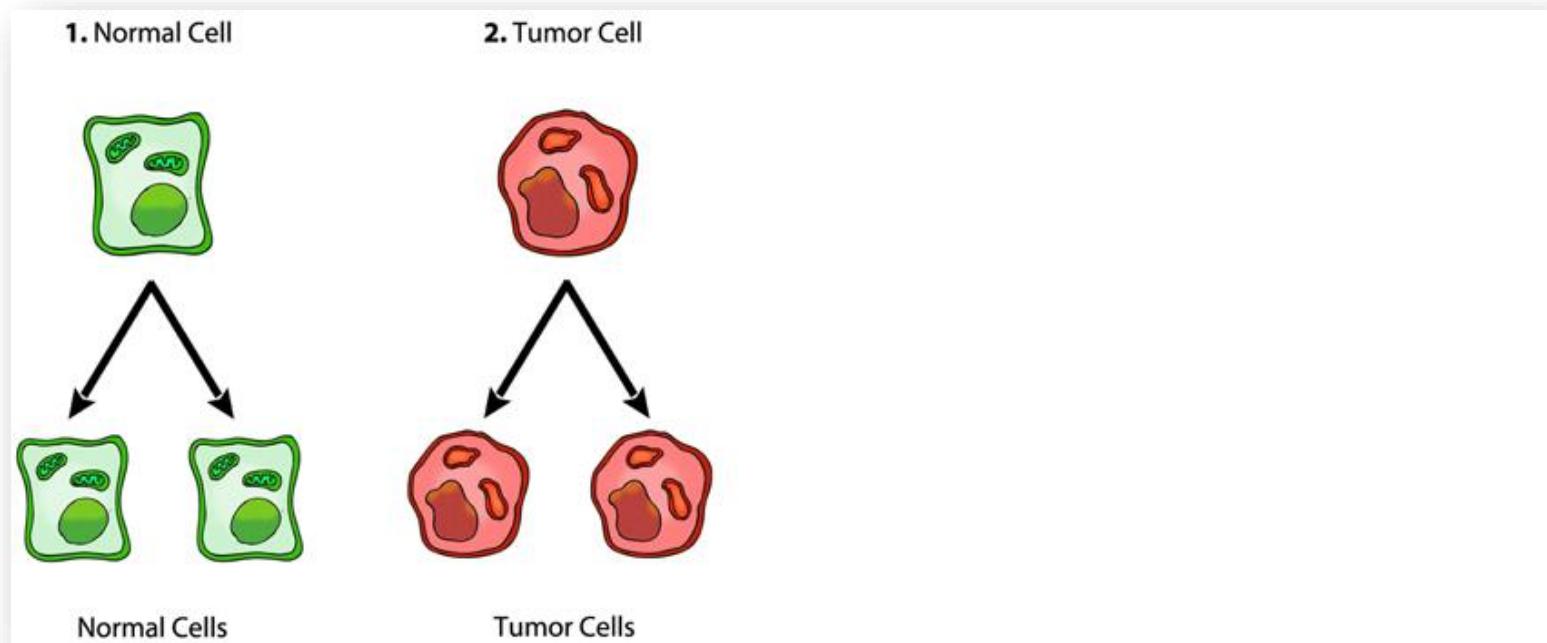


# Evidence from *in vivo* experiments



# **CONSEQUENCES OF MITOCHONDRIAL DYSFUNCTION**

# Oncogenic roles of dysfunctional mitochondria



# Mitochondrial dysfunction can be oncogenic

## Inhibition of oxidative metabolism leads to p53 genetic inactivation and transformation in neural stem cells

Stefano Bartesaghi<sup>a</sup>, Vincenzo Graziano<sup>a,b,1</sup>, Sara Galavotti<sup>a,1</sup>, Nick V. Henriquez<sup>c,1</sup>, Joanne Betts<sup>a</sup>, Jayeta Saxena<sup>a</sup>, Valentina Minieri<sup>a</sup>, Deli A<sup>a</sup>, Anna Karlsson<sup>d</sup>, L. Miguel Martins<sup>e</sup>, Melania Capasso<sup>f</sup>, Pierluigi Nicotera<sup>g</sup>, Sebastian Brandner<sup>c</sup>, Vincenzo De Laurenzi<sup>b</sup>, and Paolo Salomoni<sup>a,2</sup>

<sup>a</sup>Samantha Dickson Brain Cancer Unit, University College London Cancer Institute, London WC1E 6BT, United Kingdom; <sup>b</sup>Department of Experimental and Clinical Sciences, Aging Research Center (Centro Scienze dell'Invecchiamento), University G. d'Annunzio, 66013 Chieti-Pescara, Italy; <sup>c</sup>Institute of Neurology, University College London, London WC1N 3BG, United Kingdom; <sup>d</sup>Karolinska Institute, SE-171 77 Stockholm, Sweden; <sup>e</sup>Medical Research Council Toxicology Unit, Leicester LE1 7HB, United Kingdom; <sup>f</sup>Barts Cancer Institute, Queen Mary University, London E1 2AD, United Kingdom; and <sup>g</sup>Deutsches Zentrum für Neurodegenerative Erkrankungen, 53175 Bonn, Germany

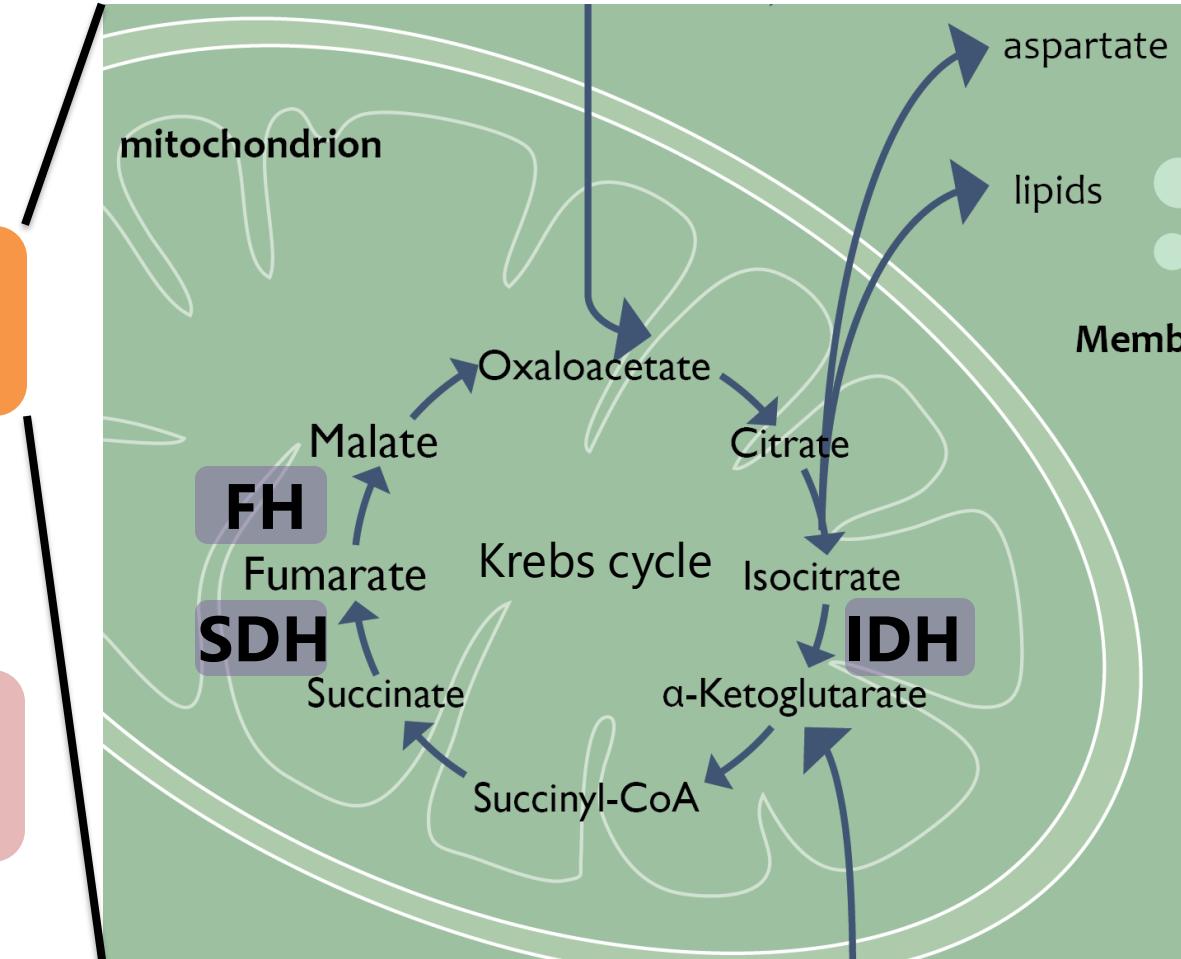
Edited by Douglas R. Green, St. Jude Children's Research Hospital, Memphis, TN, and accepted by the Editorial Board December 10, 2014 (received for review July 11, 2014)

# Mitochondrial dysfunction drives cancer

Metabolic dysregulation



Transformation



**FH=Fumarate Hydratase**

**SDH=Succinate Dehydrogenase**

**IDH=Isocitrate Dehydrogenase**

# FH mutations cause HLRCC

## HLRCC

Germline mutations in *FH* predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer

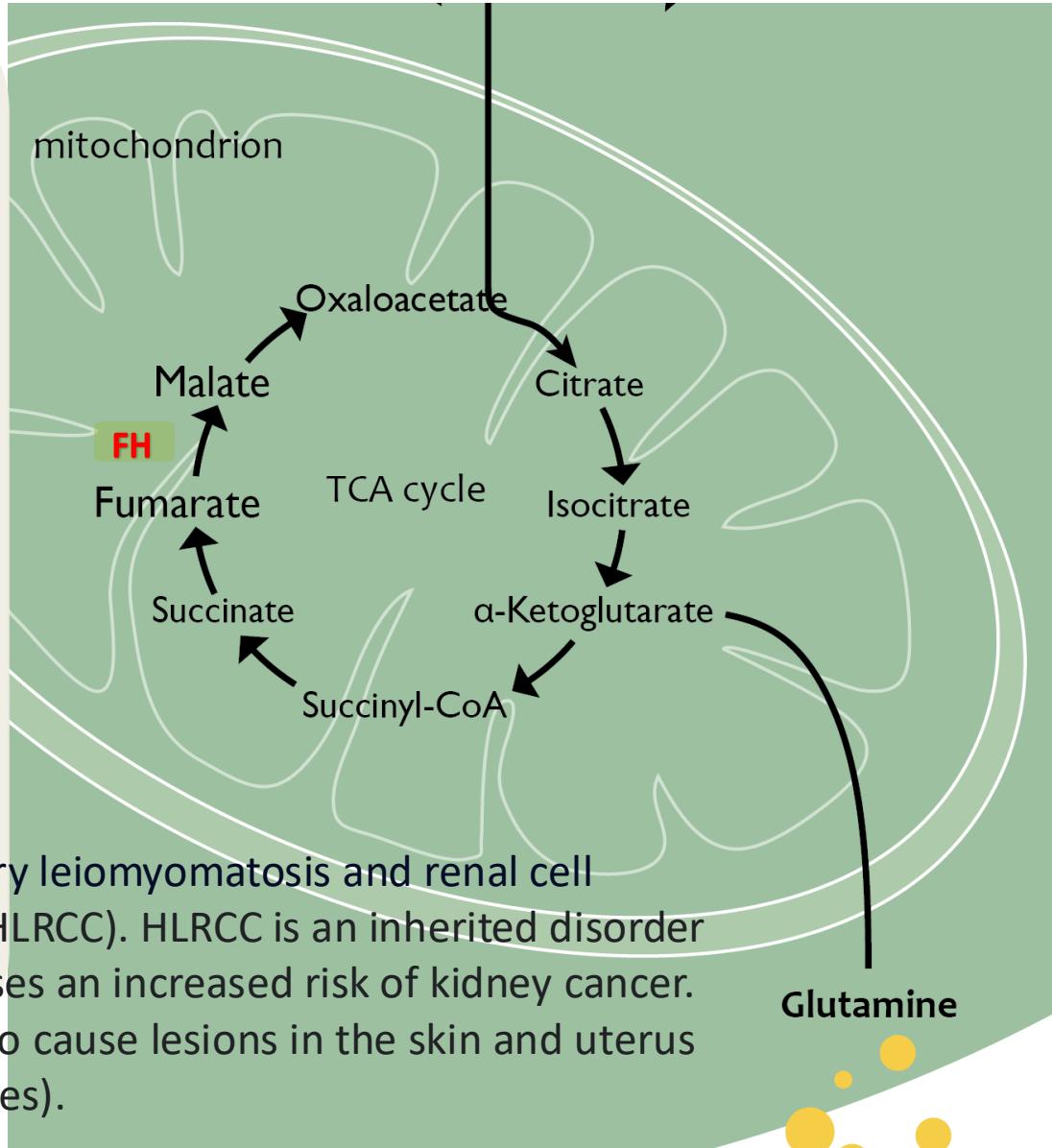
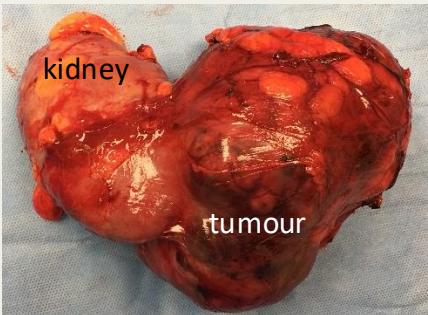
The Multiple Leiomyoma Consortium

Published online: 25 February 2002, DOI: 10.1038/ng849

- Benign tumours of the skin and uterus

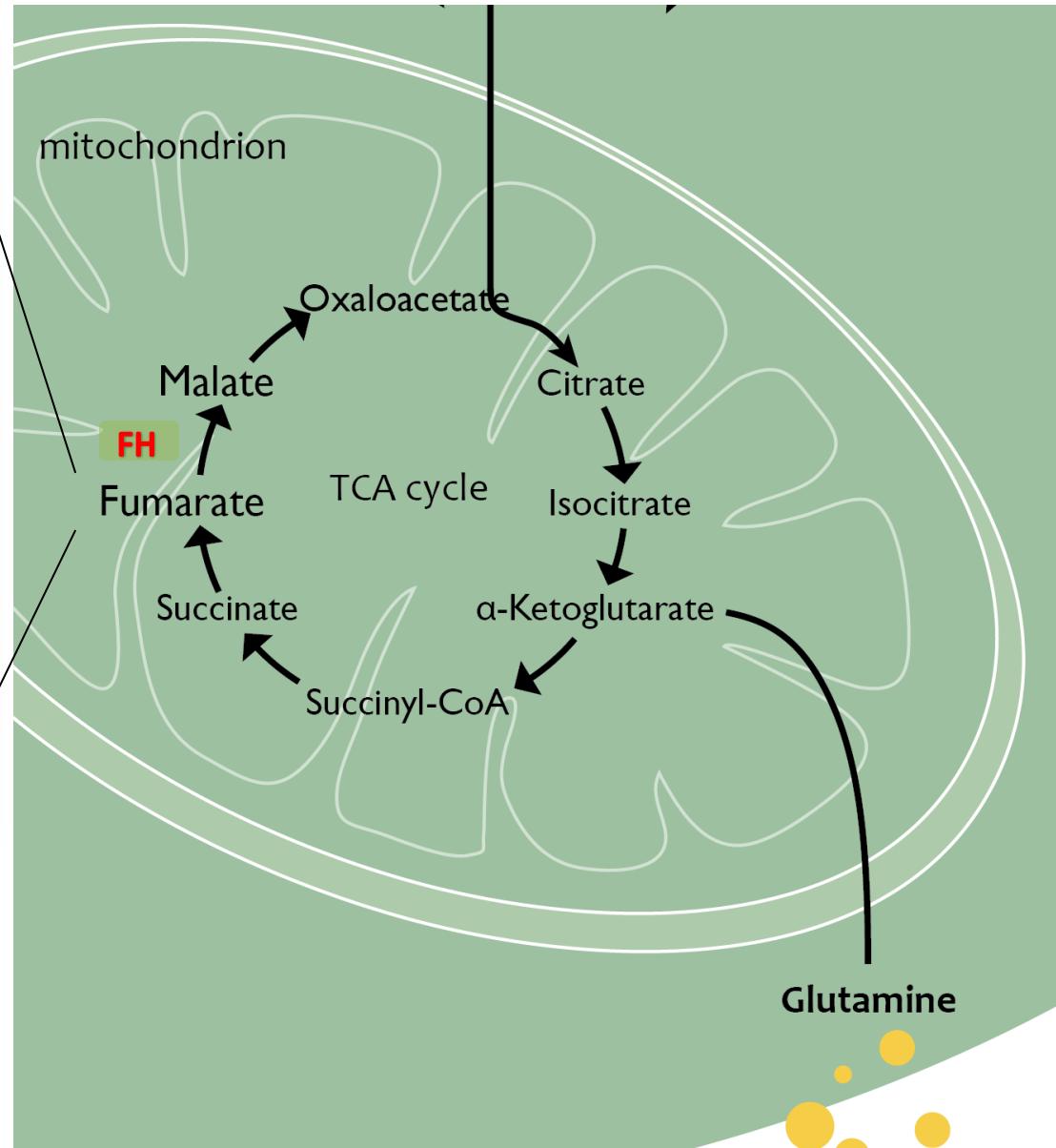
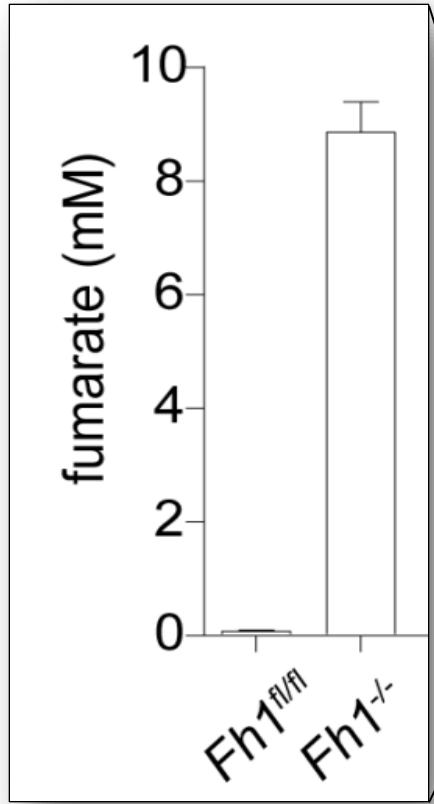


- Papillary type 2 renal cell carcinoma

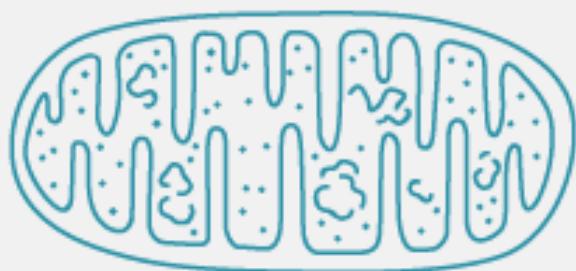


hereditary leiomyomatosis and renal cell cancer (HLRCC). HLRCC is an inherited disorder that causes an increased risk of kidney cancer. It can also cause lesions in the skin and uterus (in females).

# Fumarate accumulates in FH-deficient cells

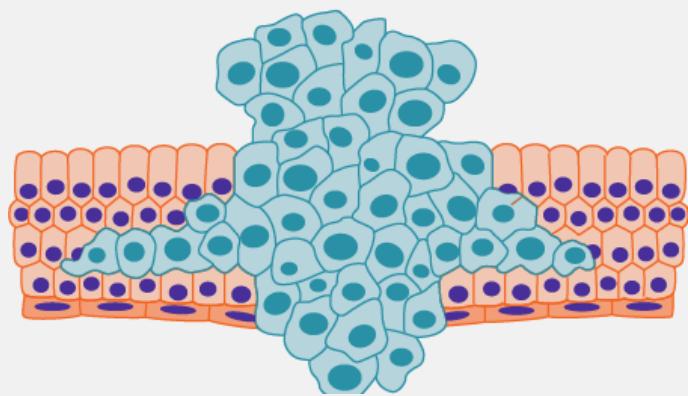


**FH loss**



Fumarate  
EMT  
HIF  
NRF2

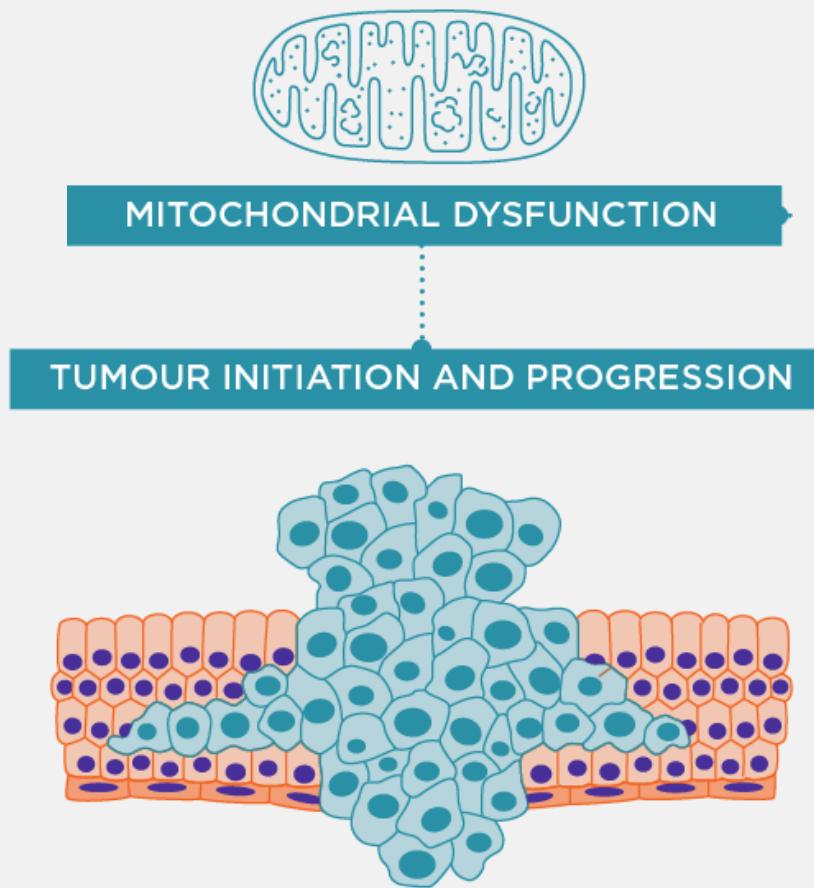
**cancer**



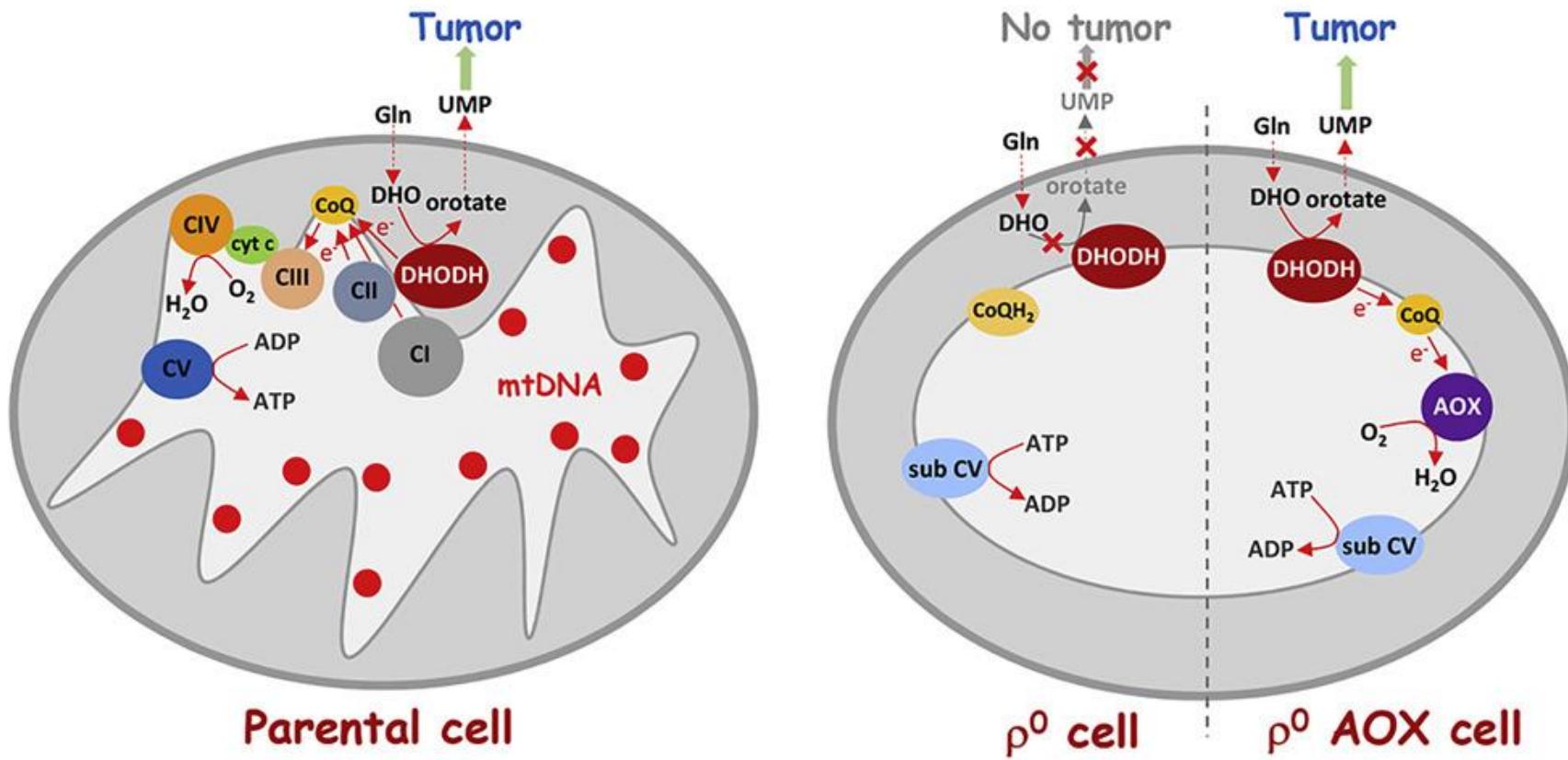
**Metastasis**

# Mitochondrial dysfunction and cancer

“the somatic mutation theory acts like a tranquilizer on those who believe in it” (Rous, 1959).



# ...still, mitochondria are required for cancer cell growth

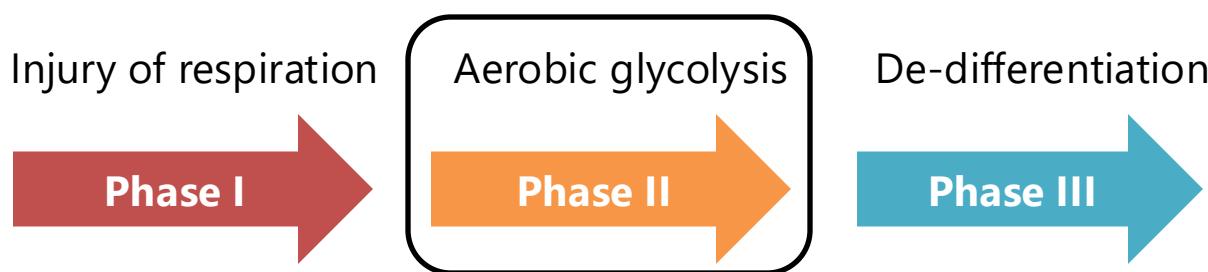


# Mitochondria dysfunction in cancer?

**Mitochondrial function is rewired in cancer cells, but mitochondria are required for cancer cell growth and proliferation**

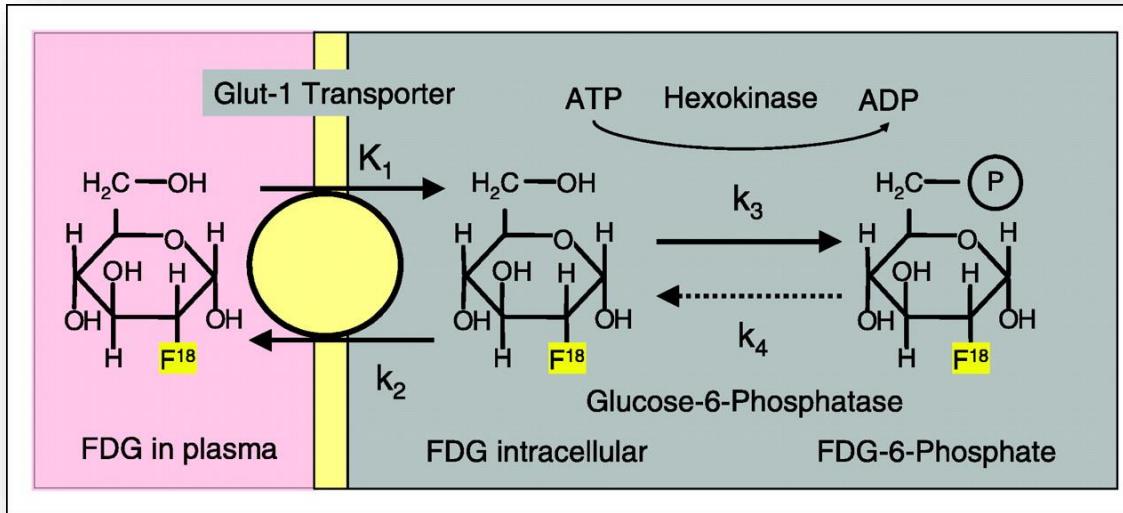
**Mitochondrial dysfunction can activate oncogenic processes**

# The Warburg hypothesis



The irreversible injuring of respiration is followed, as the second phase of cancer formation, by a long struggle for existence by the injured cells to maintain their structure, in which a part of the cells perish from lack of energy, while another part succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy, the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly—the cancer cells.

# Aerobic glycolysis in cancer

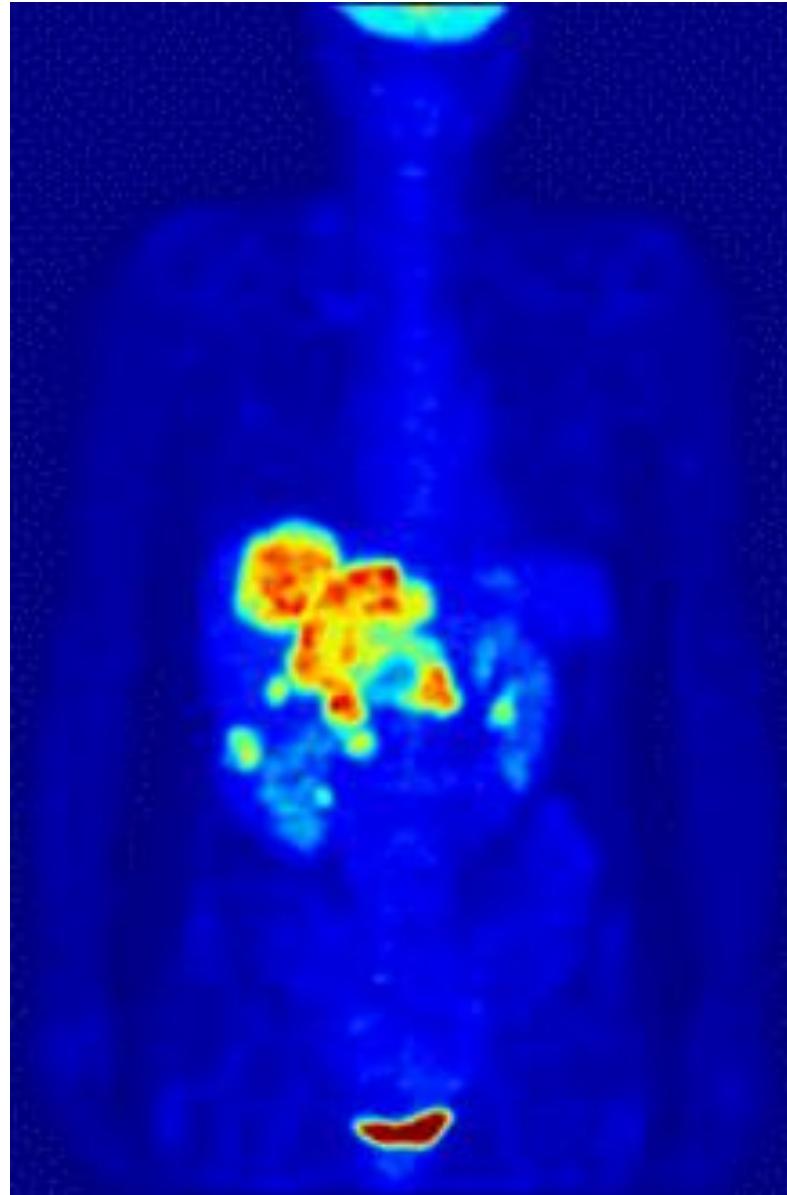


[ $^{18}\text{F}$ ]flouro-2-deoxyglucose (FDG) Positron Emission Tomography (PET)



# FDG-PET shows increase in glucose uptake in cancer

---



[https://en.wikipedia.org/wiki/Positron\\_emission\\_tomography](https://en.wikipedia.org/wiki/Positron_emission_tomography)

# State-of-the-art imaging of cancer metabolism

b

$^1\text{H}$ -MRI

$^{13}\text{C}$ -glucose

$^{13}\text{C}$ -urea

$^{13}\text{C}$ -lactate

100.0%

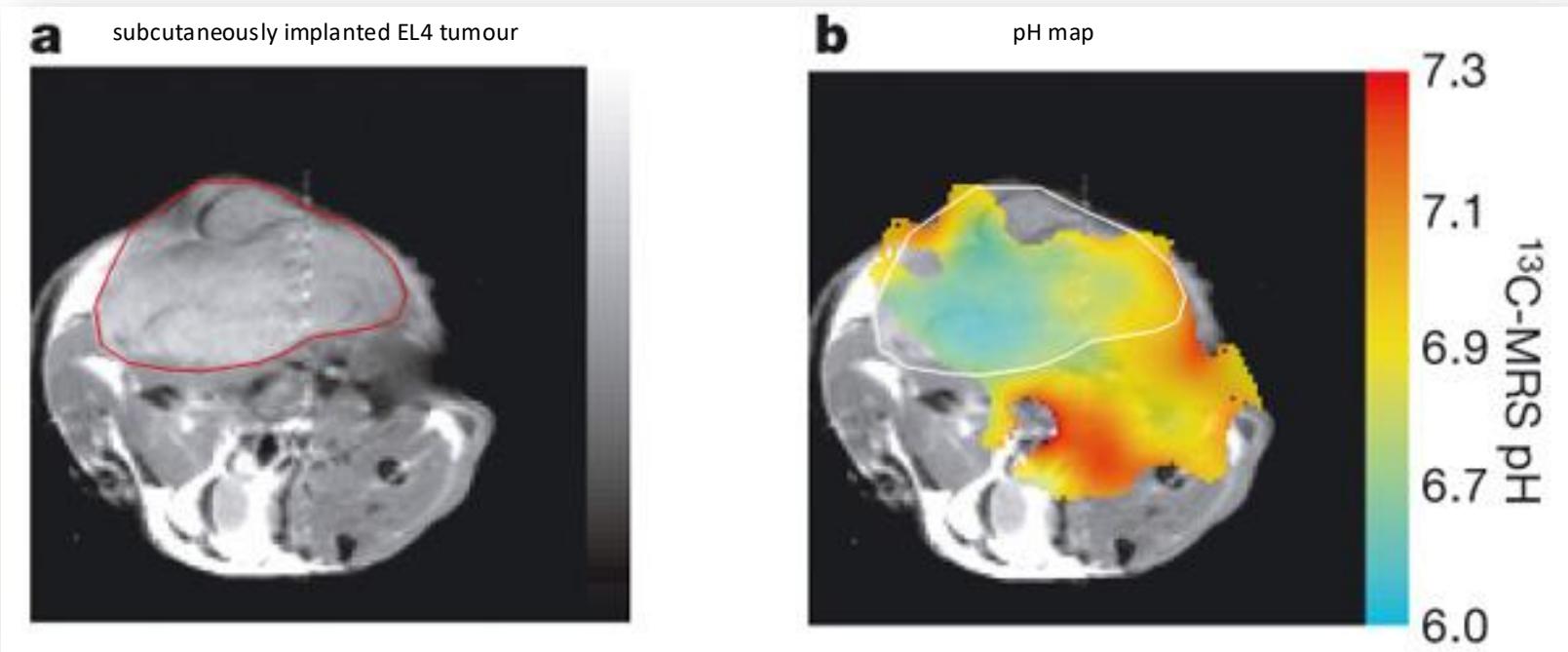
57.5%

15.0%

Magnetic resonance imaging of tumor glycolysis using hyperpolarized  $^{13}\text{C}$ -labeled glucose

Tiago B Rodrigues<sup>1</sup>, Eva M Serrao<sup>1</sup>, Brett W C Kennedy<sup>2</sup>, De-En Hu<sup>2</sup>, Mikko I Kettunen<sup>1-3</sup> & Kevin M Brindle<sup>1-3</sup>

# State-of-the-art imaging of cancer metabolism



## Magnetic resonance imaging of pH *in vivo* using hyperpolarized <sup>13</sup>C-labelled bicarbonate

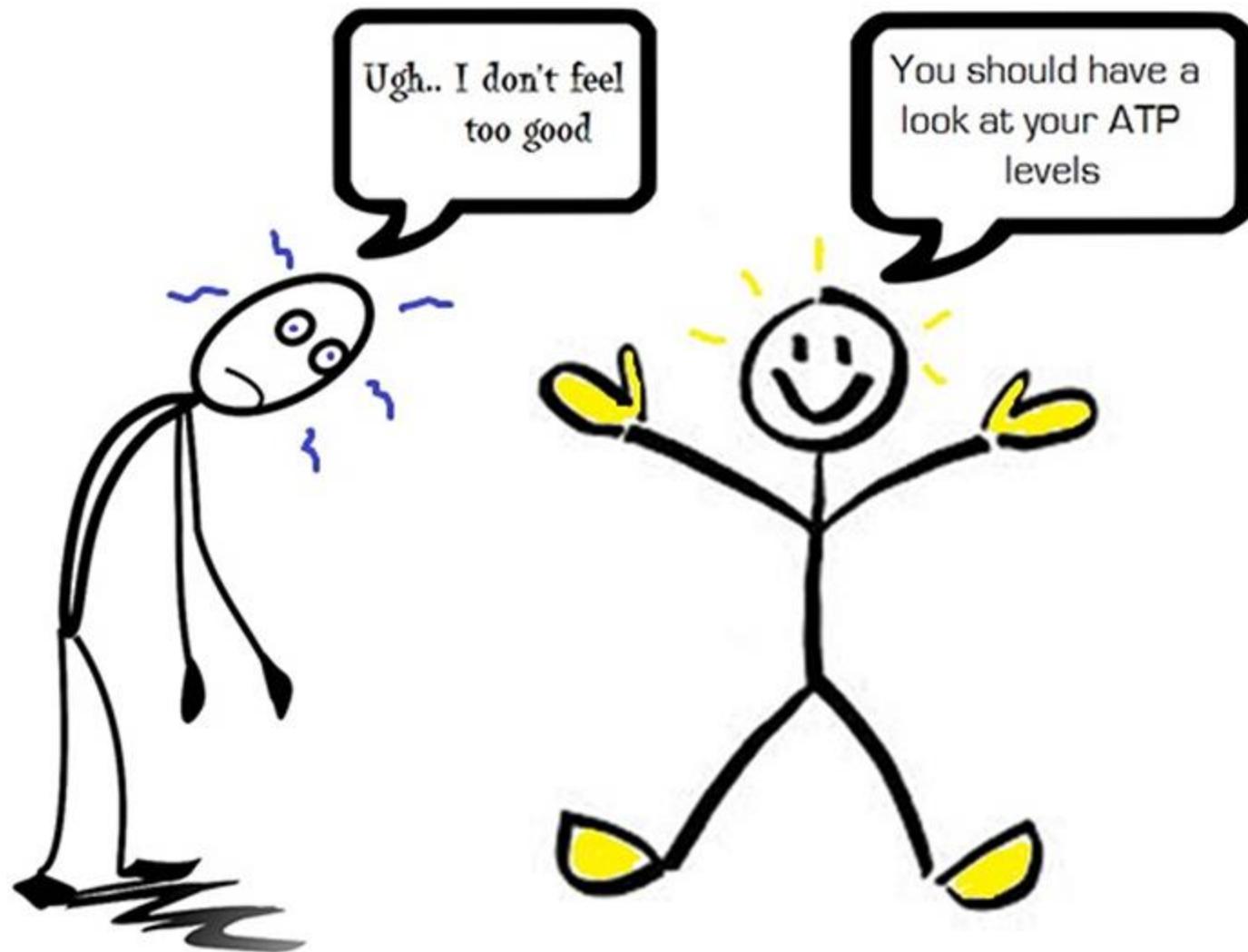
Ferdia A. Gallagher<sup>1,2,3\*</sup>, Mikko I. Kettunen<sup>1,2\*</sup>, Sam E. Day<sup>1,2†</sup>, De-En Hu<sup>1,2</sup>, Jan Henrik Ardenkjær-Larsen<sup>4</sup>, René in 't Zandt<sup>5</sup>, Pernille R. Jensen<sup>5</sup>, Magnus Karlsson<sup>5</sup>, Klaes Golman<sup>5</sup>, Mathilde H. Lerche<sup>5</sup> & Kevin M. Brindle<sup>1,2</sup>

Aerobic glycolysis in cancers is the combined result of oncogenes, tumor suppressors, a hypoxic microenvironment, mtDNA mutations and others.

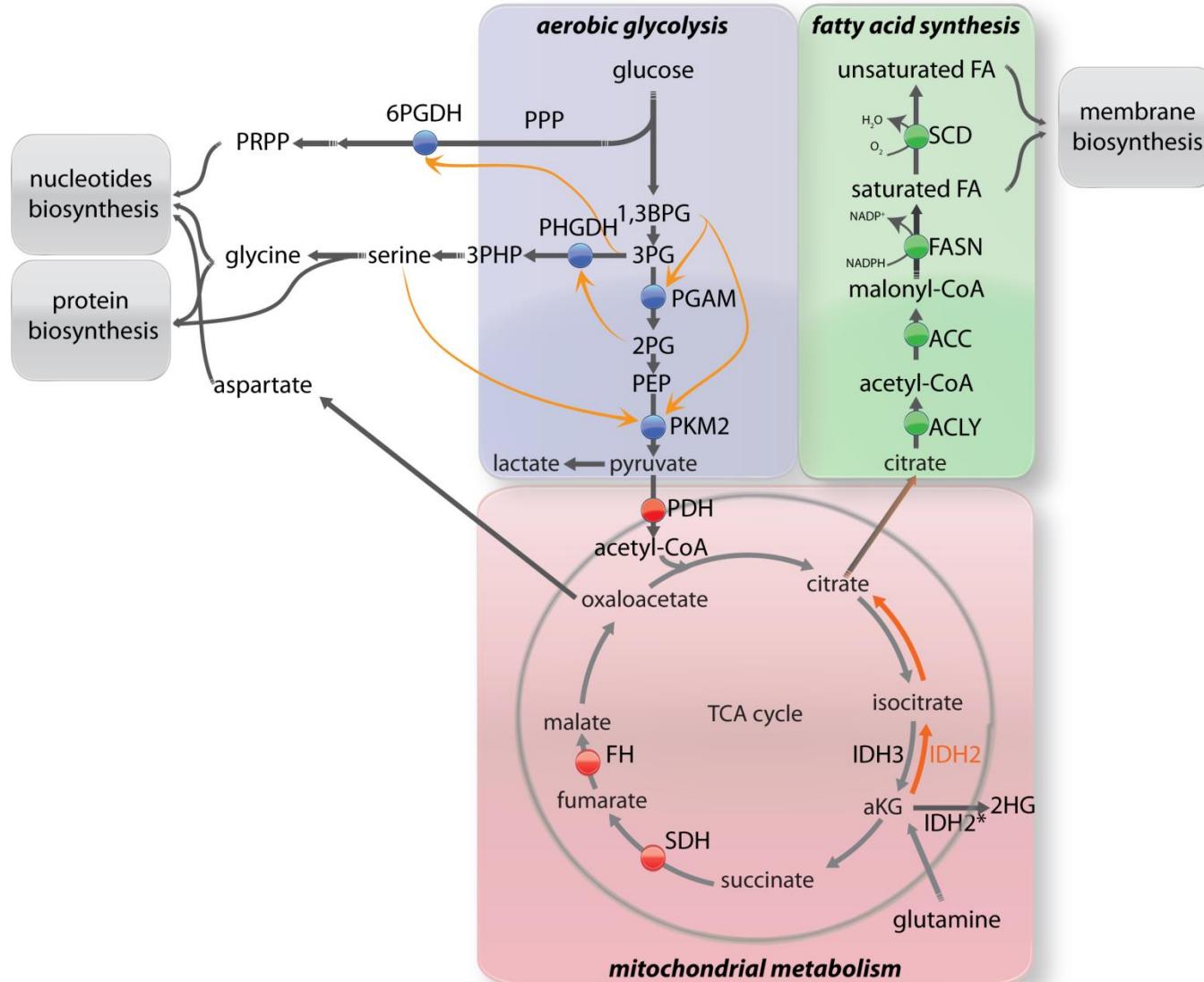
## **CONSEQUENCES OF AEROBIC GLYCOLYSIS**

# Is it all about ATP?

---



# Aerobic glycolysis supports proliferation



# Aerobic glycolysis and migration

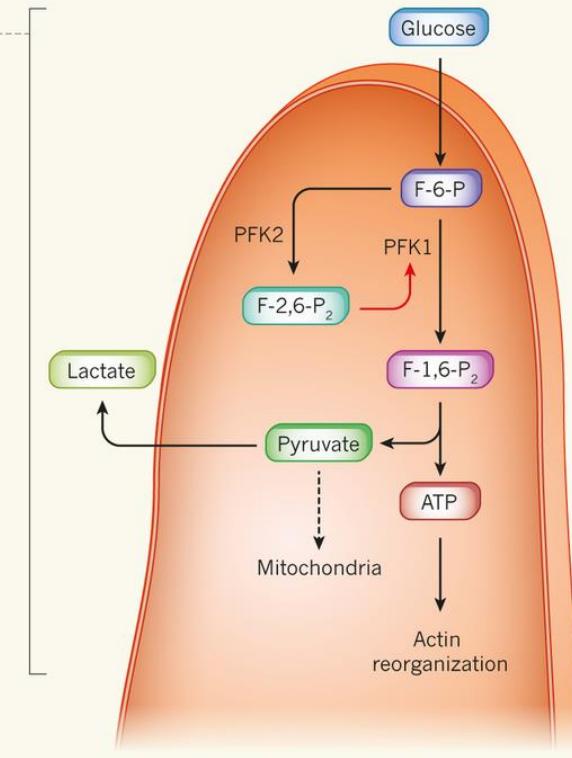
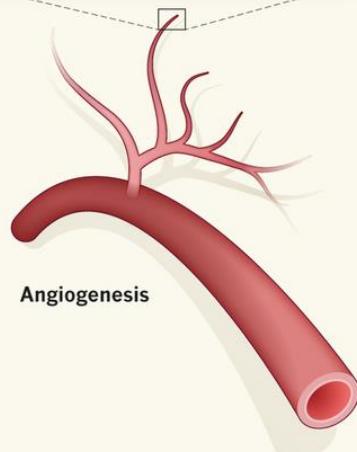
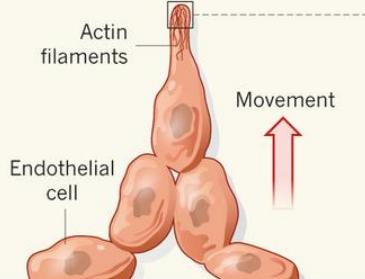
Published online: August 1,

Article

A complex  
identified  
cancer r

Keren Yizhak<sup>1,\*†</sup>

Christian Frezza



ular  
iology

nt C de Boer<sup>4</sup>,

## Current Biology

### Warburg Effect Metabolism Drives Neoplasia in a *Drosophila* Genetic Model of Epithelial Cancer

#### Highlights

- LDH upregulation is required for the transition from hyperplasia to neoplasia
- LDH expression drives tumor formation in the context of EGFR overexpression
- Increased sugar uptake drives tumor formation in the *Drosophila* EGFR model
- Synergy between EGFR and LDHA correlates with poor outcome in human cancer

Eichenlaub et al., 2018, Current Biology 28, 3220–3228  
October 22, 2018 © 2018 The Author(s). Published by Elsevier Ltd.  
<https://doi.org/10.1016/j.cub.2018.08.035>

#### Authors

Teresa Eichenlaub, René Villadsen,  
Flávia C.P. Freitas, ..., Jan Gorodkin,  
Héctor Herranz, Stephen M. Cohen

#### Correspondence

hherranz@sund.ku.dk (H.H.),  
scohen@sund.ku.dk (S.M.C.)

#### In Brief

Eichenlaub et al. examine gene expression changes during the transition from hyperplasia to neoplasia and identify lactate dehydrogenase as a key driver of neoplasia in a *Drosophila* EGFR model. Elevated sugar flux or a high-sugar diet also drive neoplasia. Synergy between EGFR and LDHA correlates with poor clinical outcome in some human cancers.

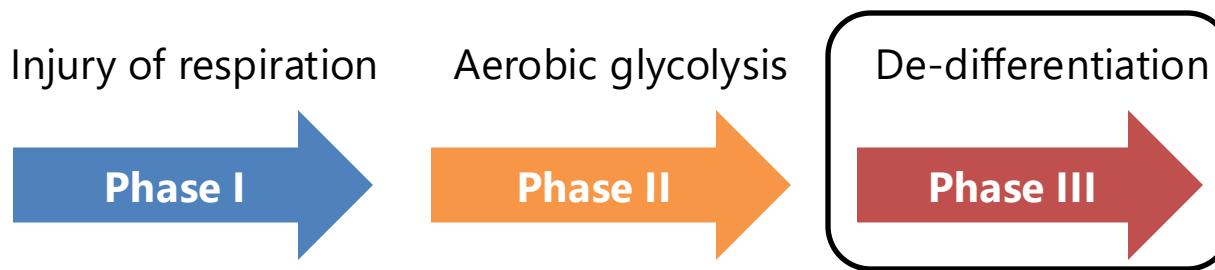
# **Is glycolysis up-regulated in cancer?**

**Aerobic glycolysis is a hallmark of cancer**

**Yet, Aerobic glycolysis is a characteristic of most proliferating cells**

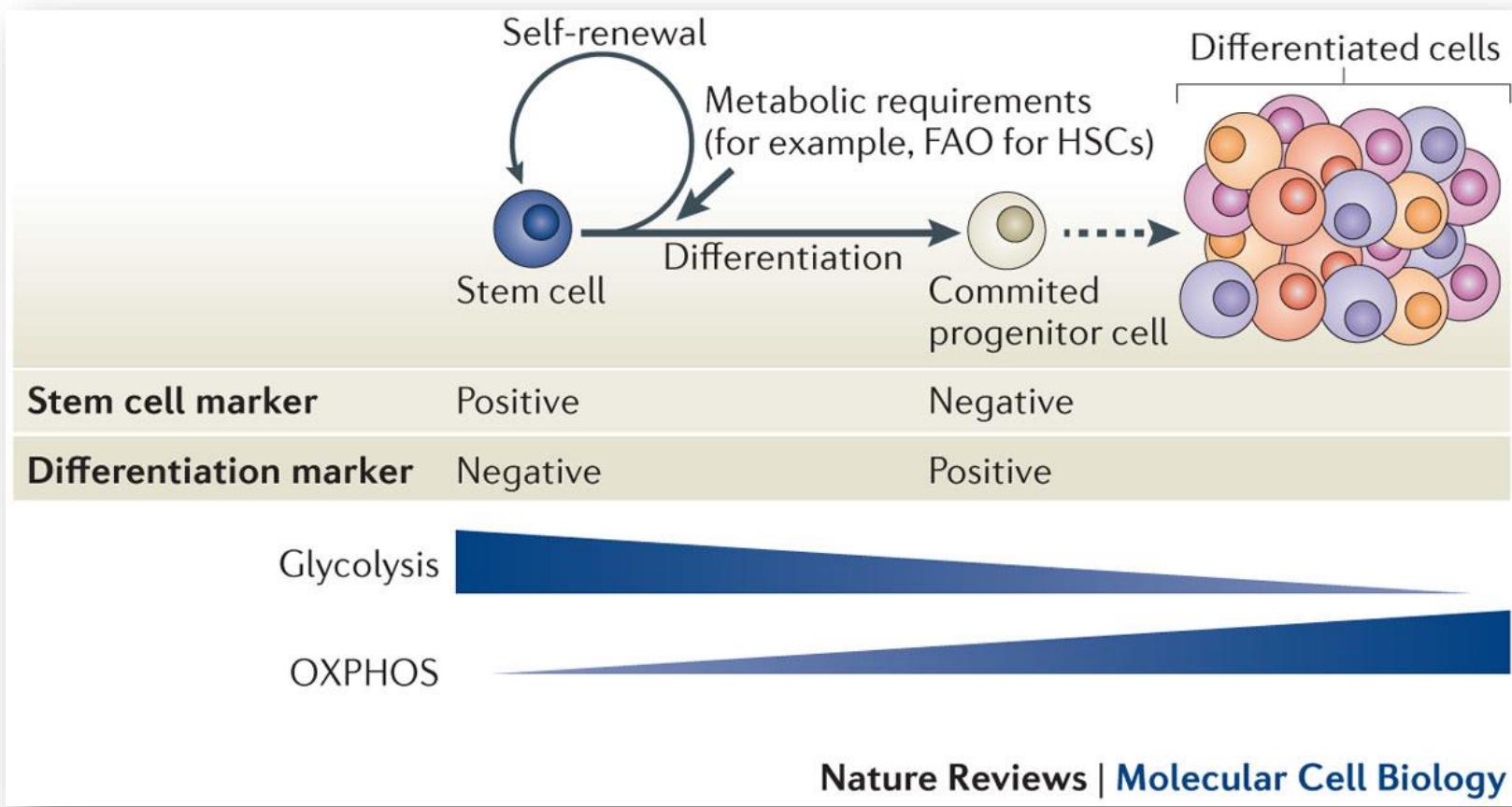
**Aerobic glycolysis provides building blocks for cancer cell growth**

# The Warburg hypothesis



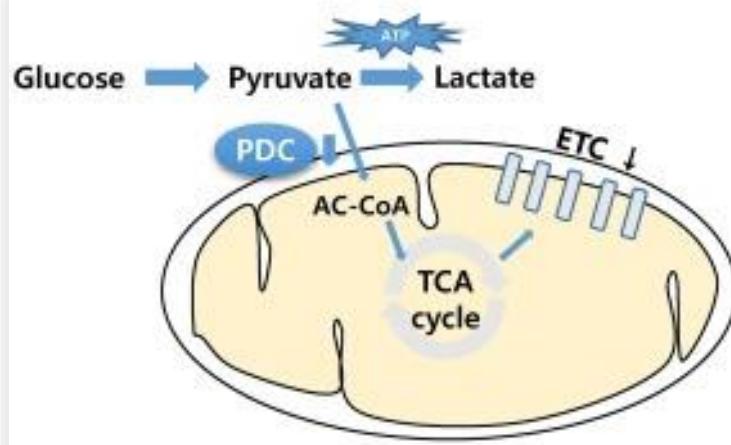
another part succeed in replacing the irretrievably lost respiration energy by fermentation energy. Because of the morphological inferiority of fermentation energy, the highly differentiated body cells are converted by this into undifferentiated cells that grow wildly—the cancer cells.

# Aerobic glycolysis and “stemness”

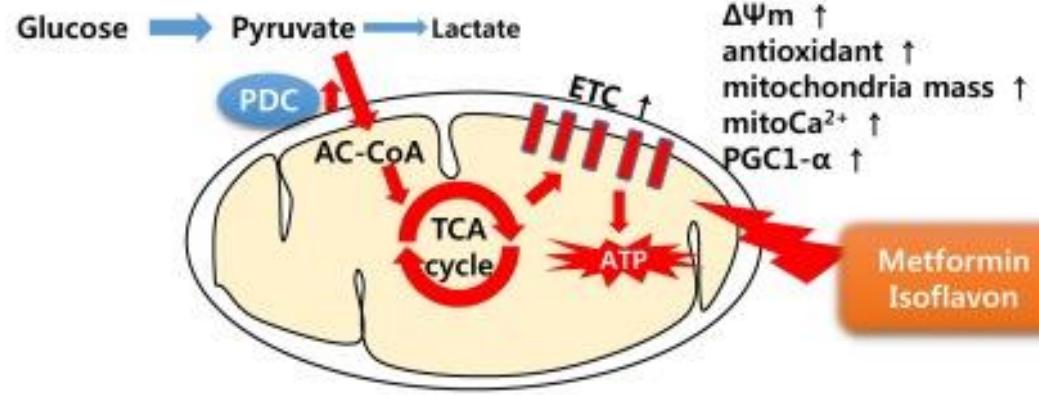


# Cancer stem cells and plasticity

Cancer cells

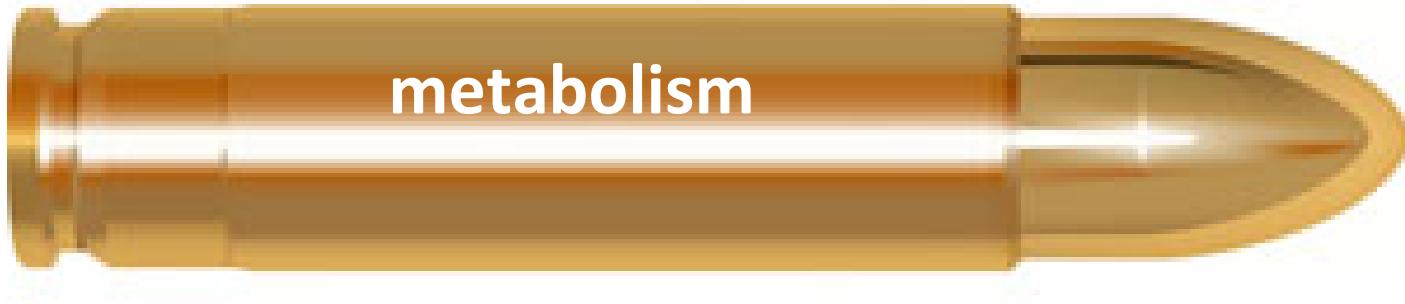


Cancer Stem cells (Breast, Glioma, Ovarian, Colon)



Glycolytic metabolism

OXPHOS metabolism



**CAN WE EXPLOIT ALTERED  
CANCER METABOLISM AS  
THERAPEUTIC STRATEGY?**

# The first example of targeting cancer metabolism?

## The New England Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 238

JUNE 3, 1948

Number 23

### TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)\*

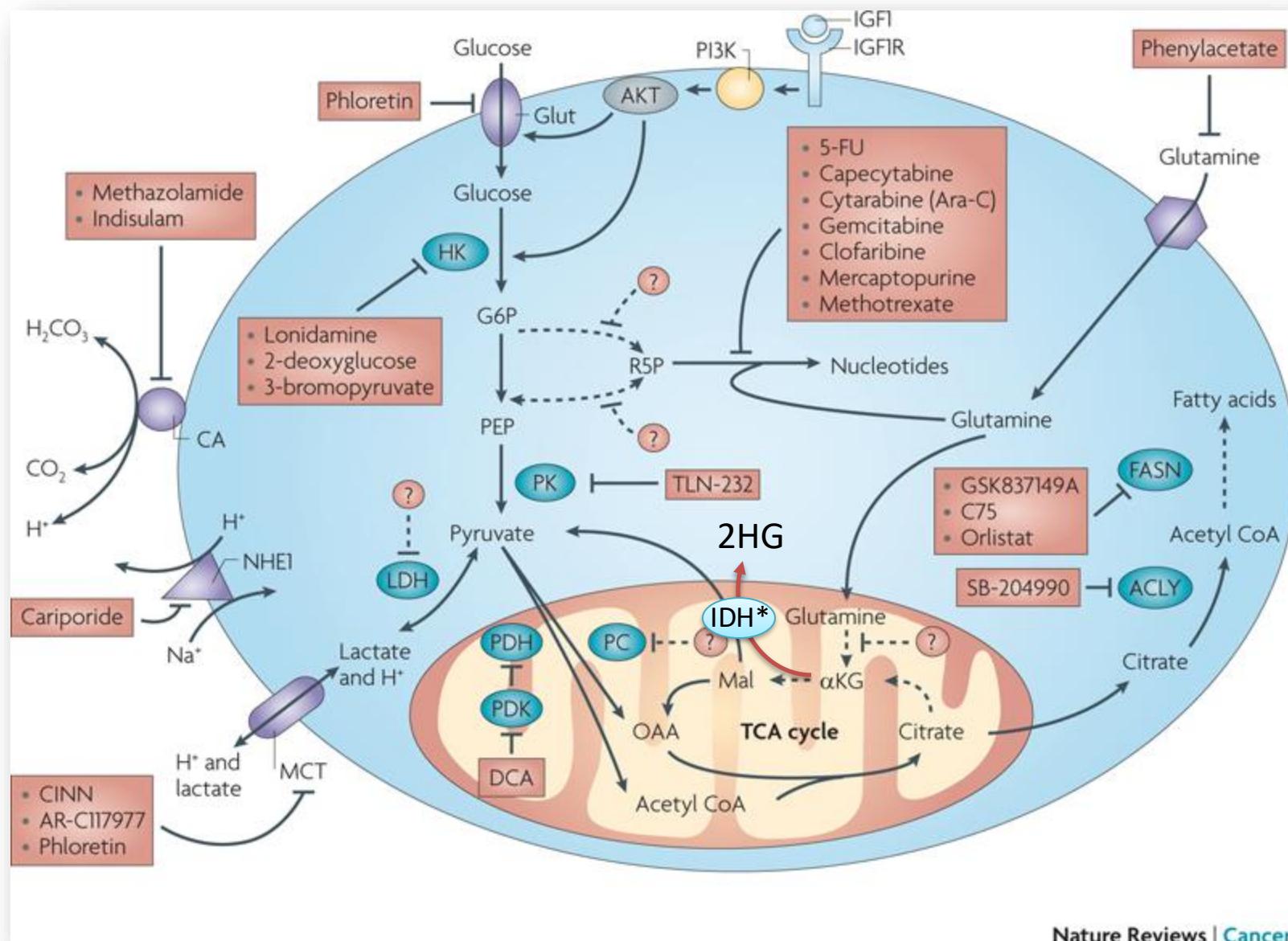
SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§

ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.||

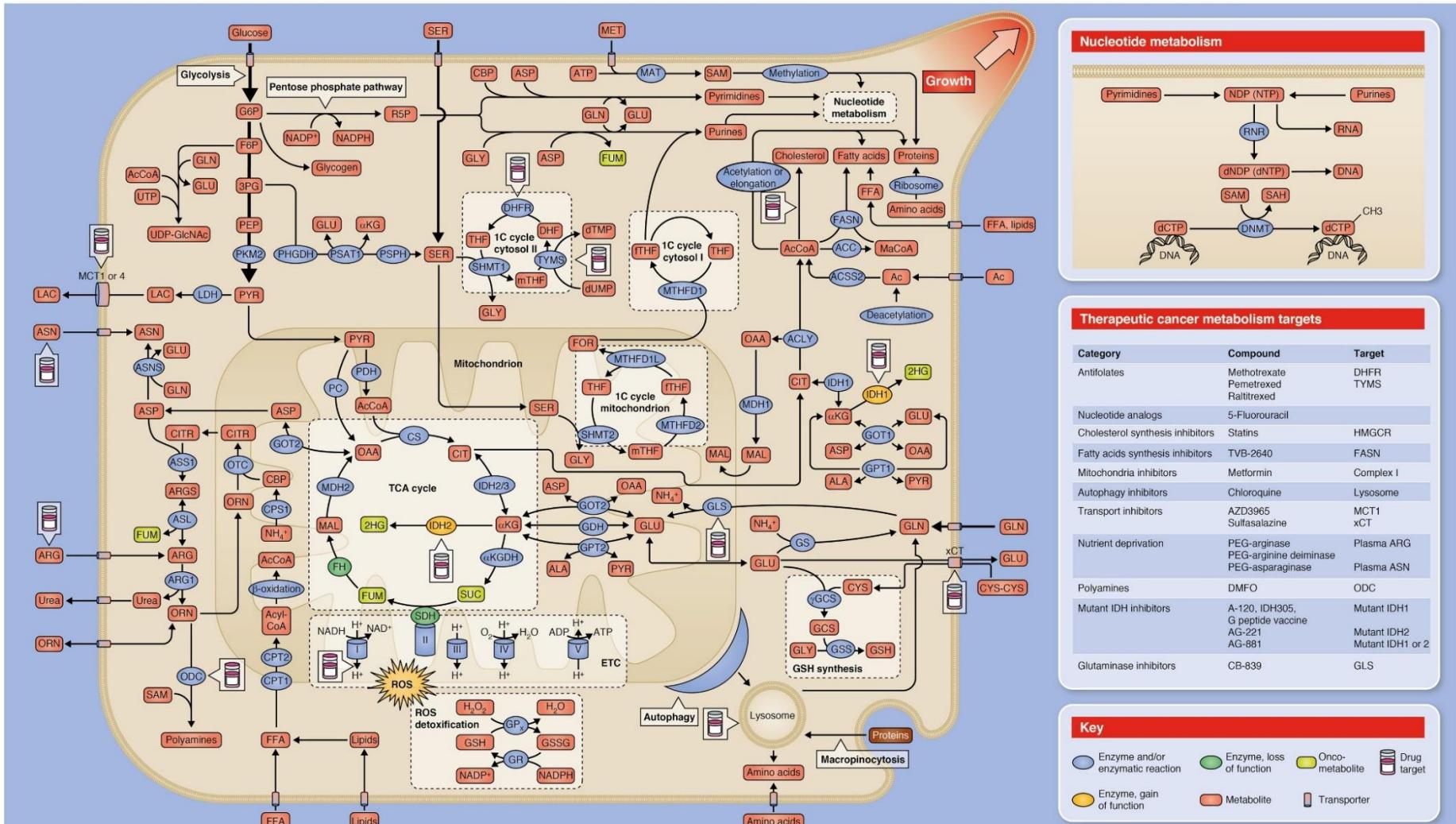
BOSTON



# Targeting cancer metabolism (2010)



# Targeting cancer metabolism (2018)



**Abbreviations:** αKG, α-ketoglutarate; αKGDH, α-ketoglutarate dehydrogenase; 2HG, 2-hydroxyglutarate; 3PG, 3-phosphoglycerate; Ac, acetate; ACC, acetyl-CoA carboxylase; AcCoA, acetyl-CoA; ACLY, ATP citrate lyase; ACSS2, acetyl-CoA synthetase 2; ALA, alanine; ARG, arginine; ARG1, arginase 1; ARGS, arginosuccinate; ASL, argininosuccinate lyase; ASN, asparagine; ASNS, asparagine synthetase; ASP, aspartate; ASS1, argininosuccinate synthase 1; CBP, carbamoyl phosphate; CIT, citrate or isocitrate; CTR, citrulline; CPS1, carbamoyl phosphate synthetase 1; CPT1 or 2, carnitine palmitoyltransferase 1 or 2; GPx, glutathione peroxidase; GR, glutathione reductase; H2O2, hydrogen peroxide; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IDH1, 2 or 3, isocitrate dehydrogenase 1, 2 or 3; LAC, lactate; LDH, lactate dehydrogenase; MaCoA, malonyl-CoA; MAL, malate; MTHFD1, 1L or 2, methenyltetrahydrofolate dehydrogenase 1, 1L or 2; MET, methionine; mTHF, 5,10-methenyl-tetrahydrofolate; MTHFD1, 1L or 2, methenyltetrahydrofolate dehydrogenase 1, 1L or 2; NDP (NTP), nucleotide diphosphate (triphosphate); OAA, oxaloacetate; MDH1 or 2, malate dehydrogenase 1 or 2; ODC, ornithine decarboxylase; ORN, ornithine; OTC, ornithine transcarbamoylase; PEP, phosphoenolpyruvate; PSAT1, phosphoserine aminotransferase; PYR, pyruvate; SAM, S-adenosylmethionine; SHMT1, serine hydroxymethyltransferase 1; SHMT2, serine hydroxymethyltransferase 2; SUO, succinyl-CoA oxidase; TCA, tricarboxylic acid; TYMS, thymidylate synthase; UGP, UDP-glucuronic acid; UGAT, UDP-glucuronyl transferase; UO, uridine monophosphate oxidase; UTP, uridine triphosphate.

GSH, glutathione; GSS, glutathione synthetase; HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; IDH1, 2 or 3, isocitrate dehydrogenase 1, 2 or 3; LAC, lactate; LDH, lactate dehydrogenase; MaCoA, malonyl-CoA; MAL, malate; MTHFD1, 1L or 2, methenyltetrahydrofolate dehydrogenase 1, 1L or 2; MET, methionine; mTHF, 5,10-methenyl-tetrahydrofolate; MTHFD1, 1L or 2, methenyltetrahydrofolate dehydrogenase 1, 1L or 2; NDP (NTP), nucleotide diphosphate (triphosphate); OAA, oxaloacetate; ODC, ornithine decarboxylase; ORN, ornithine; OTC, ornithine transcarbamoylase; PEP, phosphoenolpyruvate; PSAT1, phosphoserine aminotransferase; PYR, pyruvate; SAM, S-adenosylmethionine; SHMT1, serine hydroxymethyltransferase 1; SHMT2, serine hydroxymethyltransferase 2; SUO, succinyl-CoA oxidase; TCA, tricarboxylic acid; TYMS, thymidylate synthase; UGP, UDP-glucuronic acid; UGAT, UDP-glucuronyl transferase; UO, uridine monophosphate oxidase; UTP, uridine triphosphate.

# IDH and GLS inhibitors are in clinic

nature  
biotechnology



Altmetric: 16    Citations: 8

[More detail >>](#)

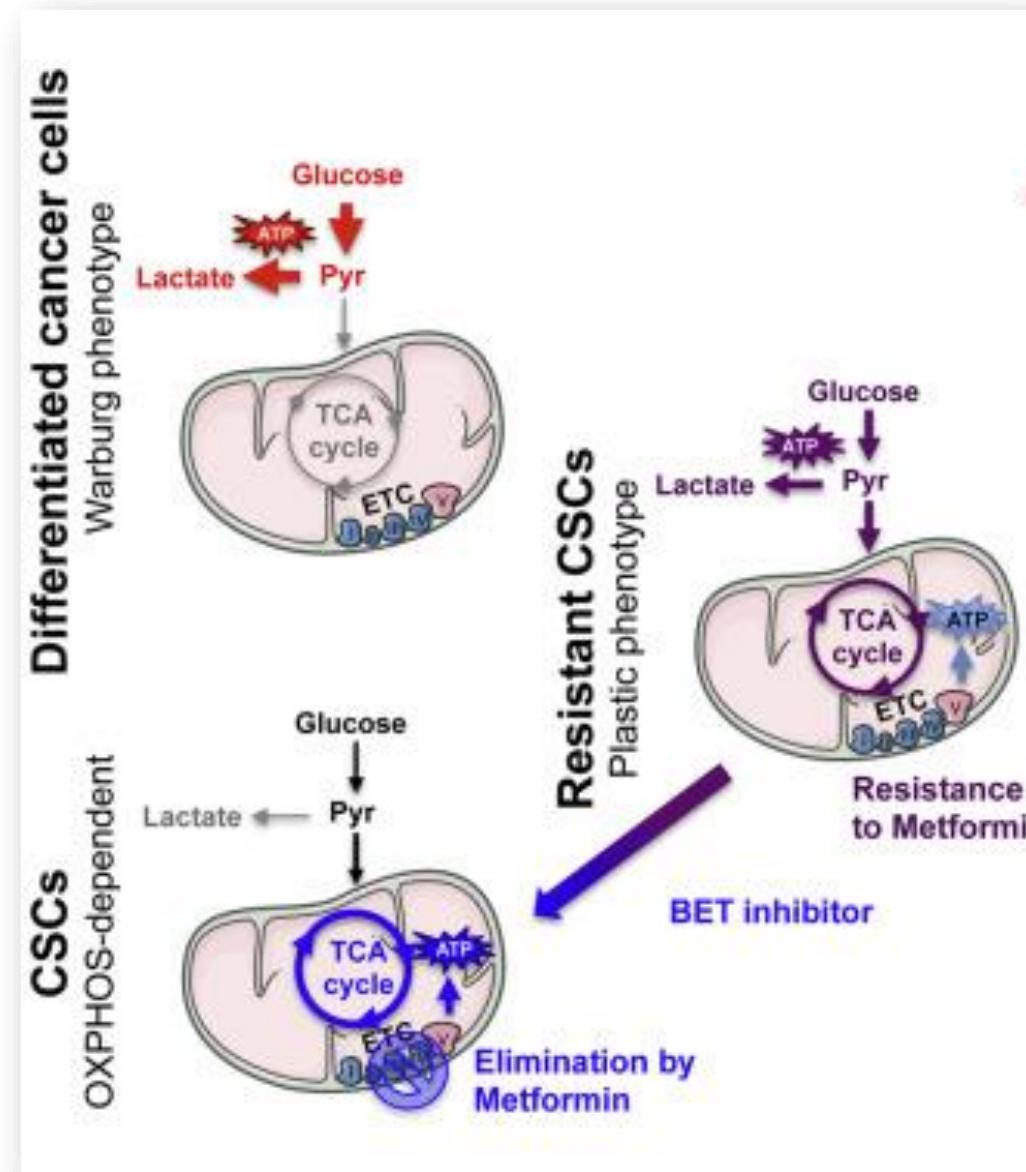
News

## Cancer anabolic metabolism inhibitors move into clinic

Ken Garber

Company/location	Agent	Target	Indications	Status
Agios & Celgene	AG-221, AG-120, AG-881	IDH1 and IDH2	AML, MDS, solid tumors	Phase 3
Polaris Group/San Diego	ADI-PEG 20	Pegylated arginine deiminase	Hepatocellular carcinoma (HCC), others	Phase 3 in HCC missed primary endpoint
Cornerstone Pharmaceuticals/Cranbury, New Jersey	CPI-613	Pyruvate dehydrogenase	AML, MDS, solid tumors	Phase 2
Calithera Biosciences	CB-839	Glutaminase 1	RCC, breast cancer	Phase 1/2
3-V Biosciences	TVB-2640	Fatty acid synthase	Ovarian, breast, lung	Phase 2 pending
Novartis/Basel	IDH305	IDH1	Advanced cancers	Phase 1
Forma Therapeutics/Watertown, Massachusetts	FT-2102	IDH1	AML, MDS	Phase 1
Bayer/Leverkusen, Germany	BAY-1436032	IDH1	Solid tumors	Phase 1
Advanced Cancer Therapeutics/Louisville, Kentucky	PFK-158	PFKFB3	Solid tumors	Phase 1
Aeglea BioTherapeutics/Austin, Texas	AEB-1102	Modified human arginase	AML, MDS, solid tumors	Phase 1

# Resistance through metabolic reprogramming



# Conclusions

**Metabolism of cancer cells is different from that of normal cells**

**Dysregulated metabolism can drive oncogenic processes**

**Altered metabolism offers a therapeutic window to target cancer cells**

# Key references & links

---

- **O. Warburg**, On the origin of cancer cells, *Science*, 1956
- **JS. Flier et al.** Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. *Science*, 1987
- **H. Shim et al.** c-Myc transactivation of *LDH-A*: Implications for tumor metabolism and growth, *PNAS*, 1998
- **D. Hanahan and RA. Weinberg**, Hallmarks of Cancer: next generation, *Cell*, 2011
- **Gaude and Frezza**, Tissue-specific and convergent metabolic transformation of cancer correlates with metastatic potential and patient survival, *Nat Comms*, 2016
- **Pavlova and Thompson**, The emerging hallmarks of cancer metabolism, *Cell Metabolism*, 2016
- **Sanderson et al**, Revisiting the Warburg Effect: Some Tumors Hold Their Breath, *Cell Metabolism* 2018