Cancer as a metabolic disease

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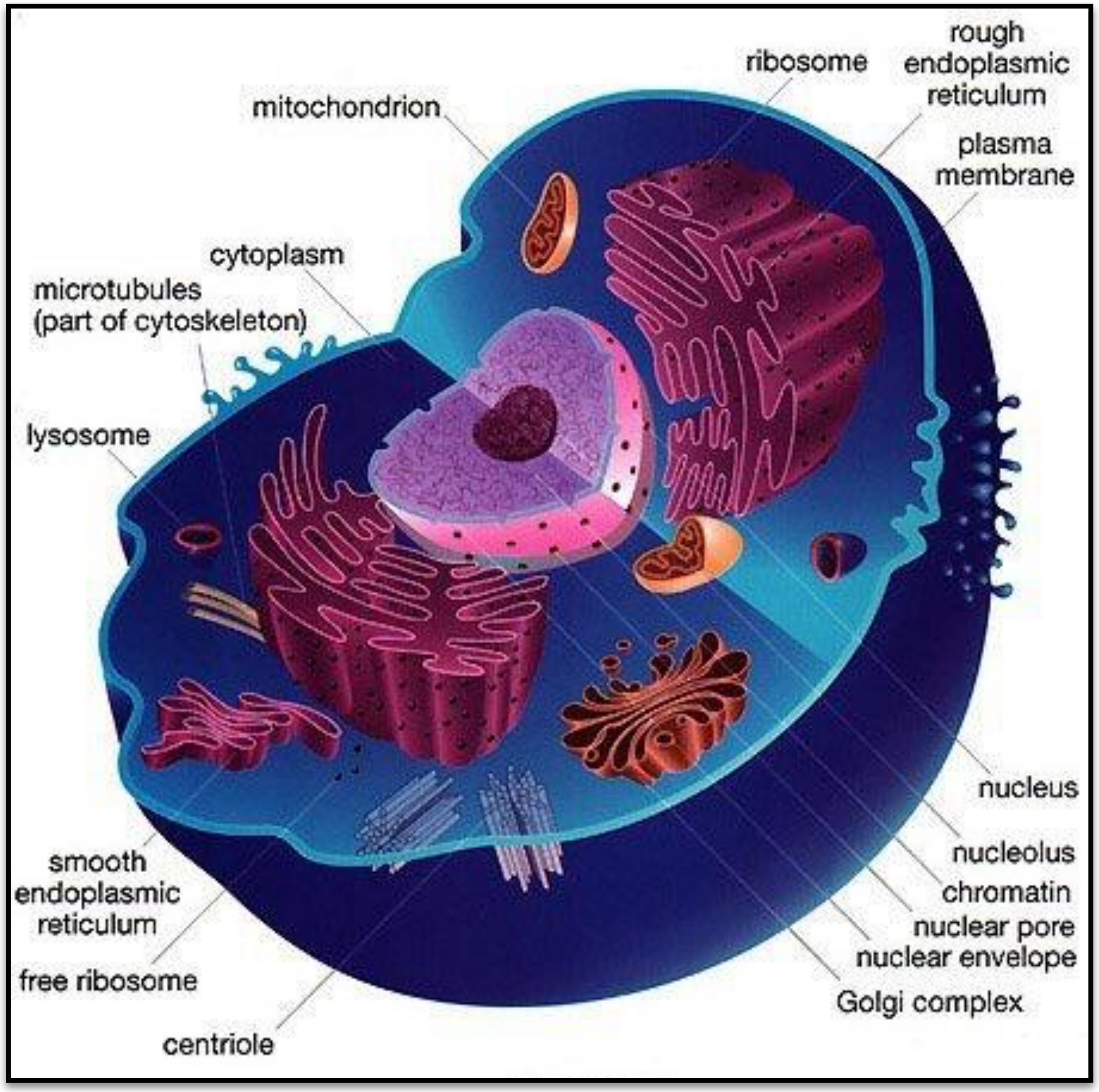
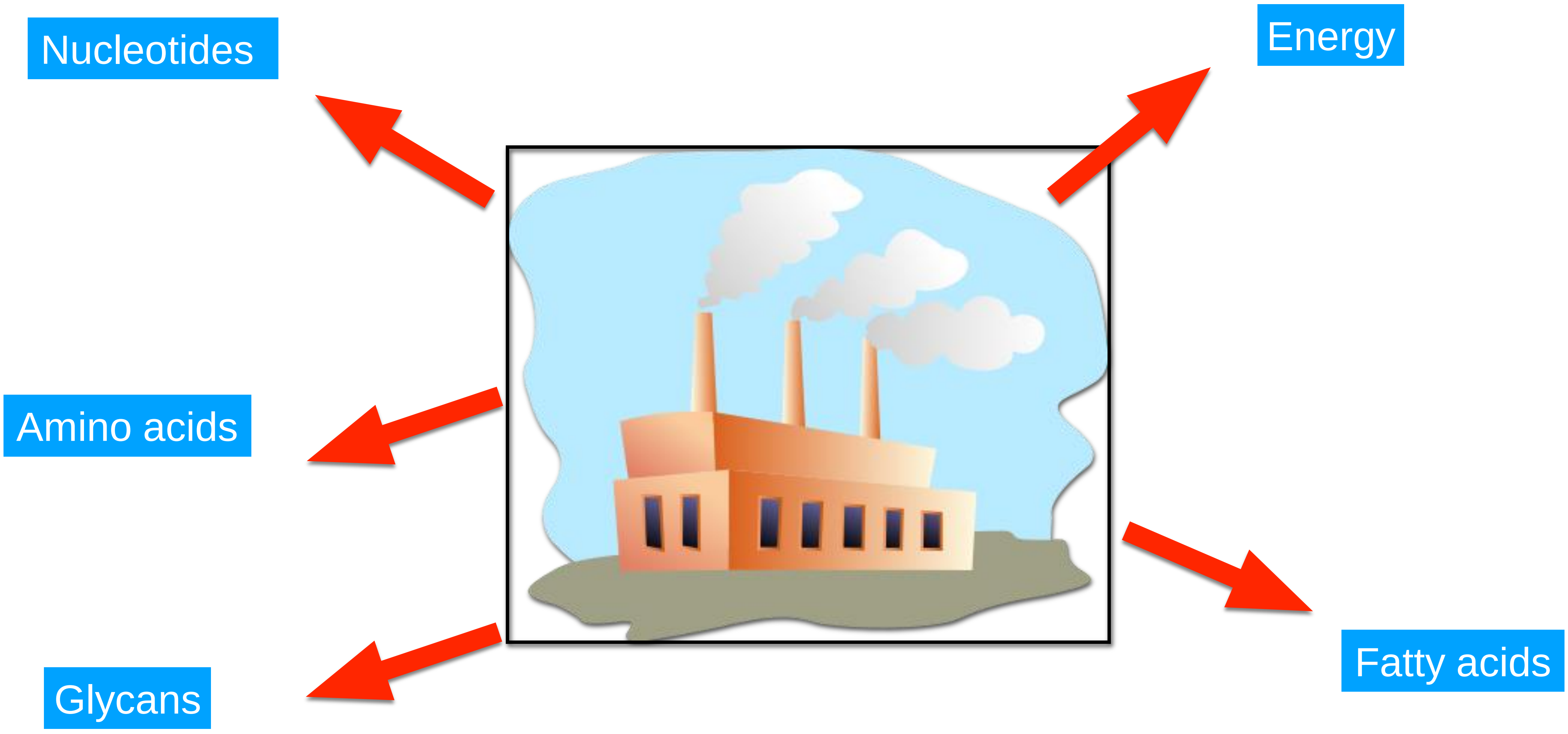
Mammalian cell



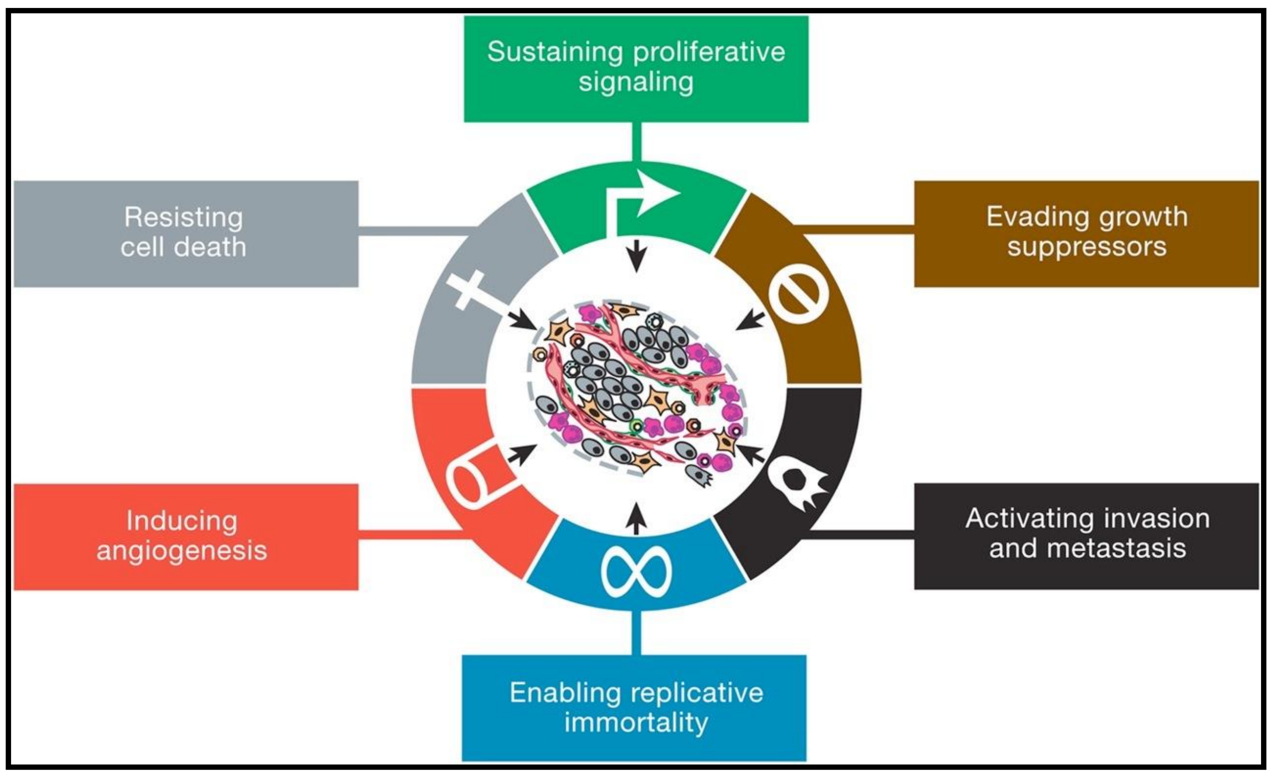
https://amit1b.wordpress.com/the-molecules-of-life/10-the-living-cell-gallery/

Mammalian cell as a factory



Hallmark of cancer

The most fundamental trait of cancer cells involves their ability to sustain chronic proliferation.



Cell, Vol. 100, 57–70, January 7, 2000, Copyright ©2000 by Cell Press

The Hallmarks of Cancer

Douglas Hanahan* and Robert A. Weinberg†
*Department of Biochemistry and Biophysics and Hormone Research Institute
University of California at San Francisco
San Francisco, California 94143
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Massachusetts Institute of Technology
Cambridge, Massachusetts 02142

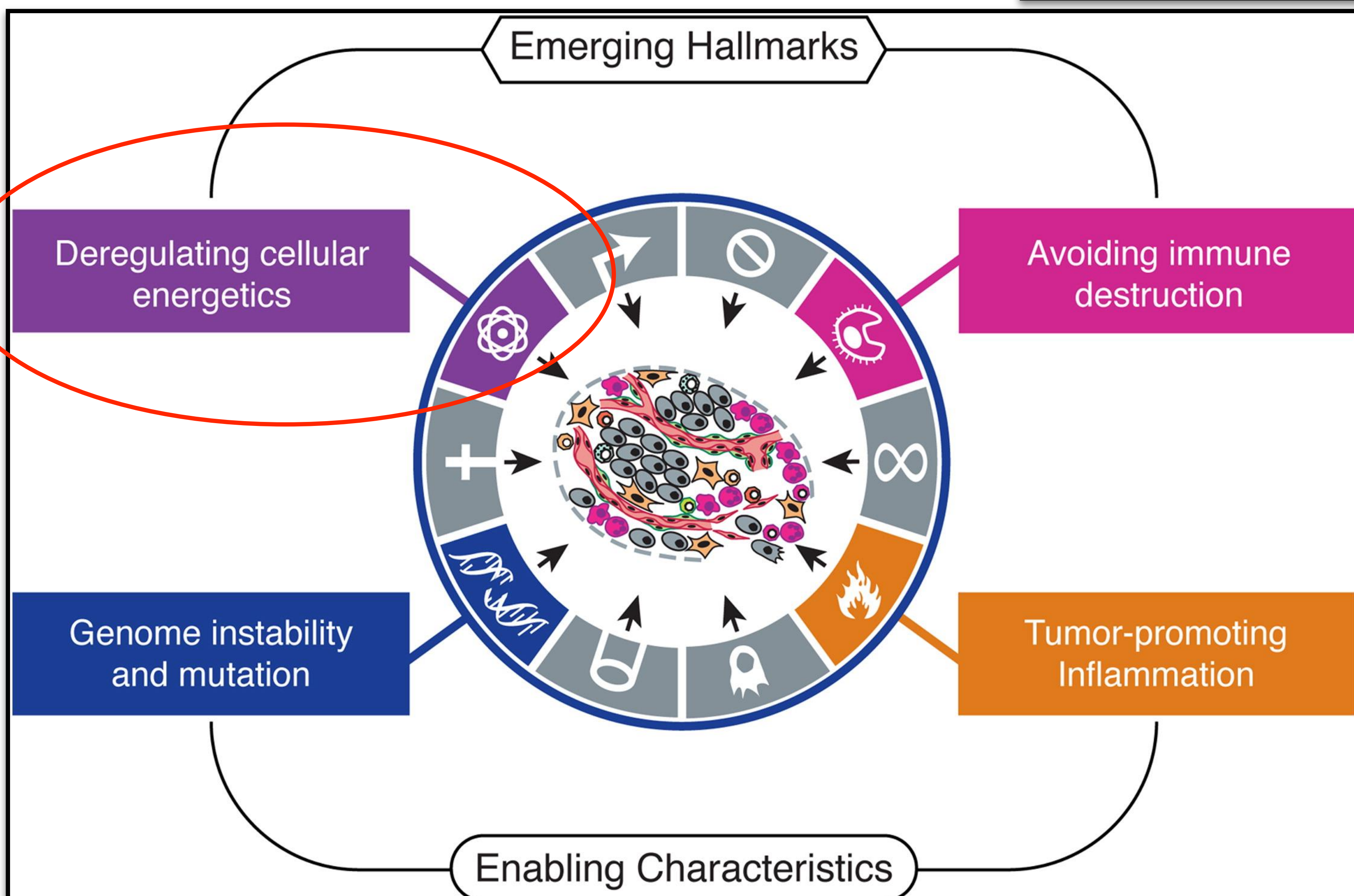
Hanahan, D., and Weinberg, R.A. (2000). The Hallmarks of Cancer. Cell 100, 57–70.

Emerging hallmark of cancer

Cancer metabolism

Hallmarks of Cancer: The Next Generation

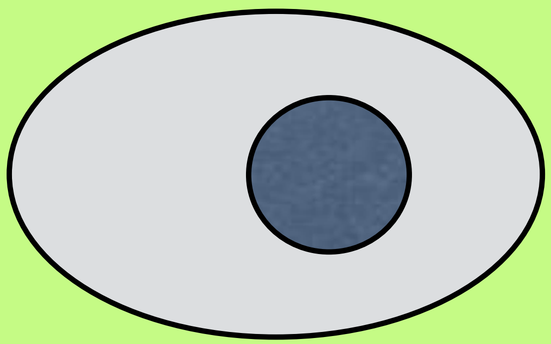
Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013



Hanahan, D., and Weinberg, R. A. (2011) Hallmarks of Cancer: The Next Generation. Cell. 144, 646–674

The metabolism of cell proliferation

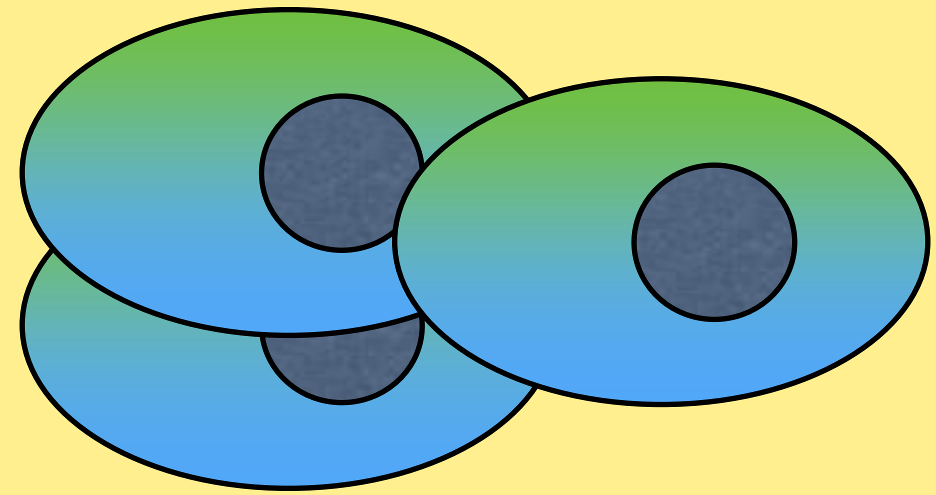
Resting cells



ATP | **Energy**

Maintain homeostatic processes

Proliferating cells



ATP | **Energy**

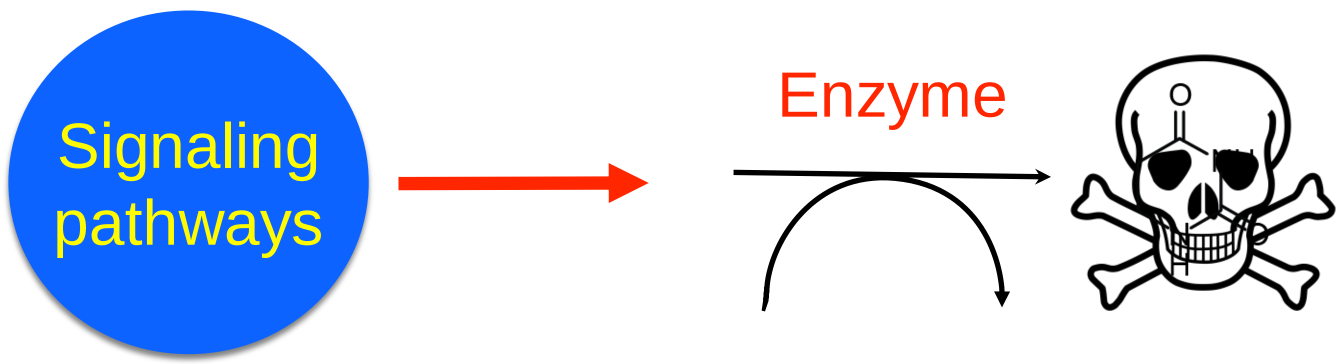
Nucleotides
Amino Acids
Fatty Acids
Redox

Building blocks

Support rapid growth

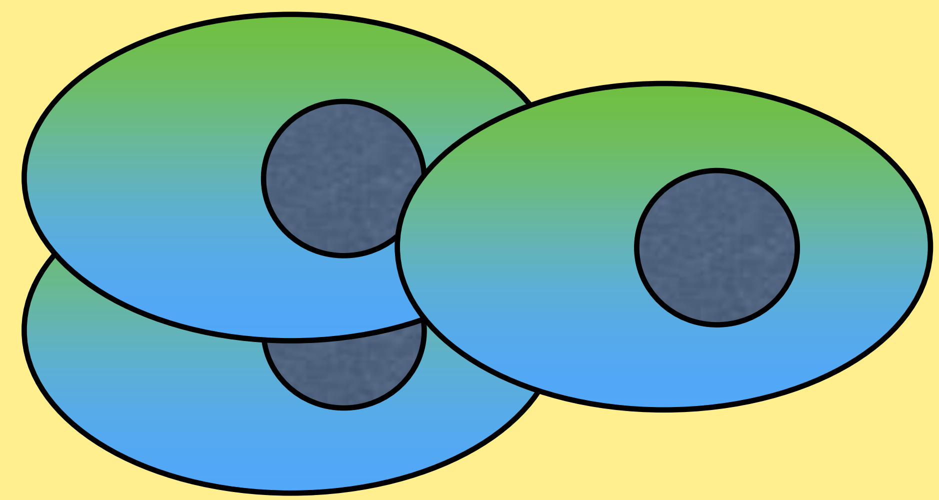
Cancer metabolism: current challenges

Which metabolic pathways are essential for cancer cells?



Metabolic processes that are essential for cancer cells

Proliferating cells



Building blocks

Support rapid growth

Leading Questions

Warburg Effect

- What are the molecular mechanisms that regulate the WA?
- Is WA a byproduct or an integrated part of the cancer

Metabolism and cancer

- Can metabolism be the drivers of cancers?

Amino acid metabolism in cancer

- What is the role of AA metabolism in cancer

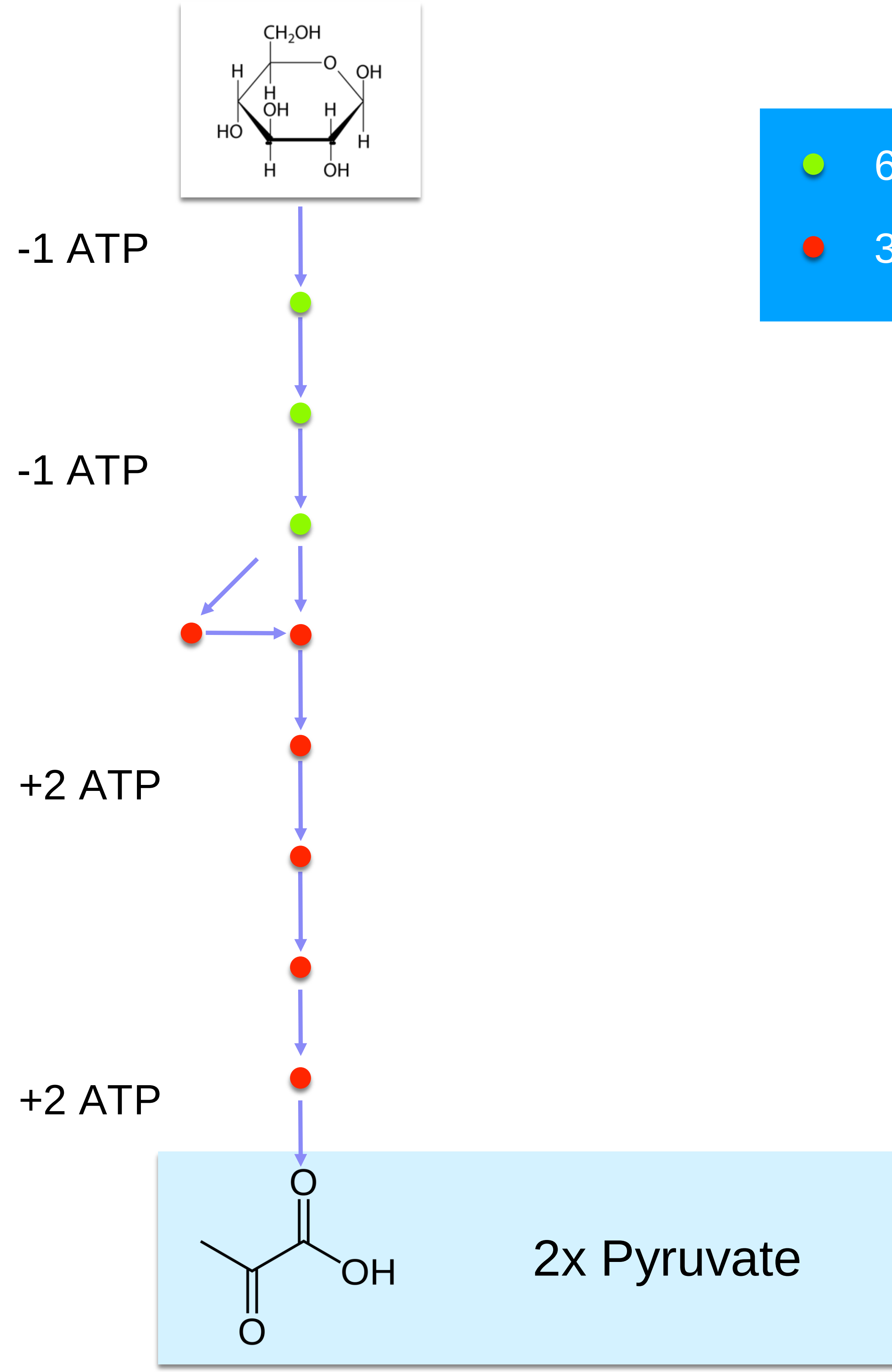
Oncogenic signaling and metabolic pathways in cancer

- mTOR pathway as an example

Antimetabolites

- How can we exploit metabolic dependency for tumor inhibition?

Glycolysis

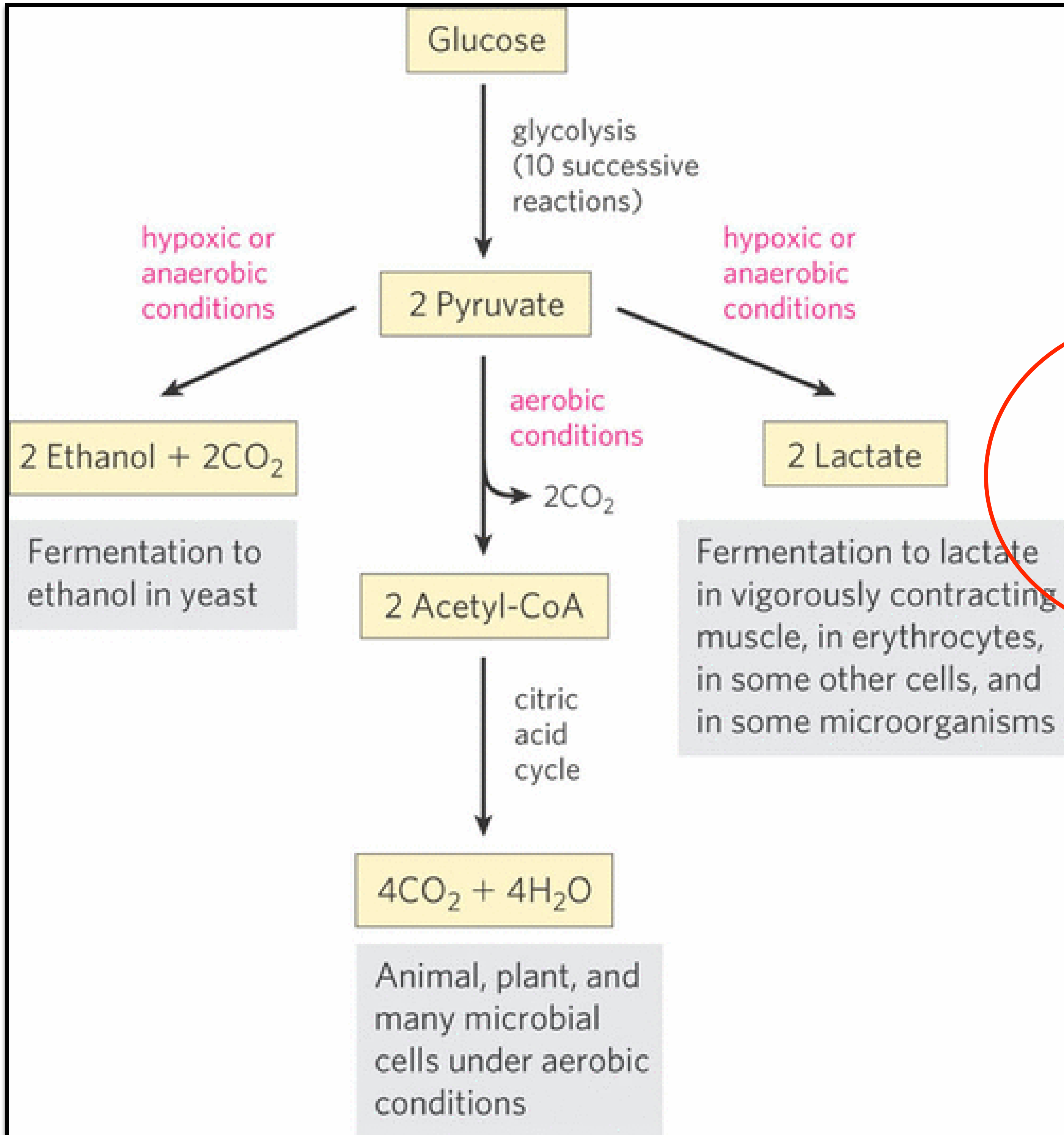


- 6 carbon molecule
- 3 carbon molecule

The glycolysis pathways yields 2mol ATP/mol of glucose

Catabolic fate of pyruvate

Fermentation



Lactate

TCA cycle

Figure 14-4 Lehninger

Lactic acid is produced under aerobic conditions

- **Lactic acid** fermentation—occurs in **muscle cells**

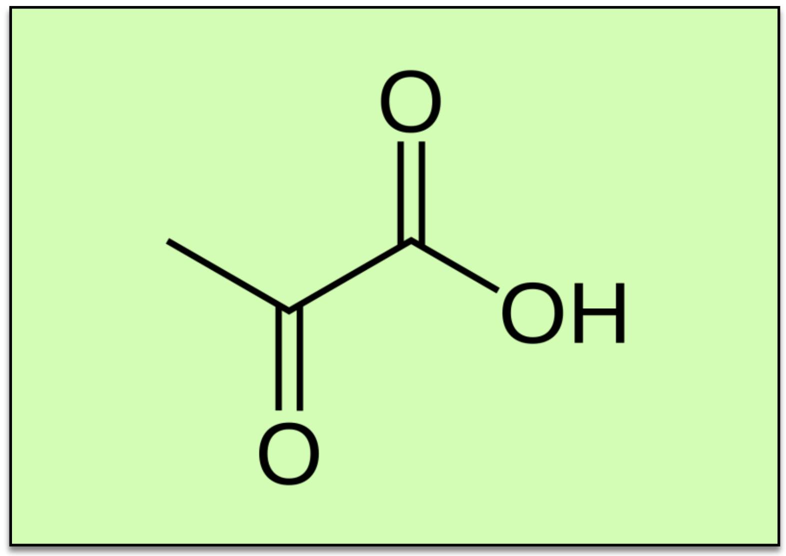
  Lactic acid is produced in the muscles during rapid **exercise** when the body **cannot** supply enough **oxygen** to the tissues—causes **burning sensation** in muscles

glucose ⟶ lactic acid + carbon dioxide + **2 ATP**

The Warburg effect

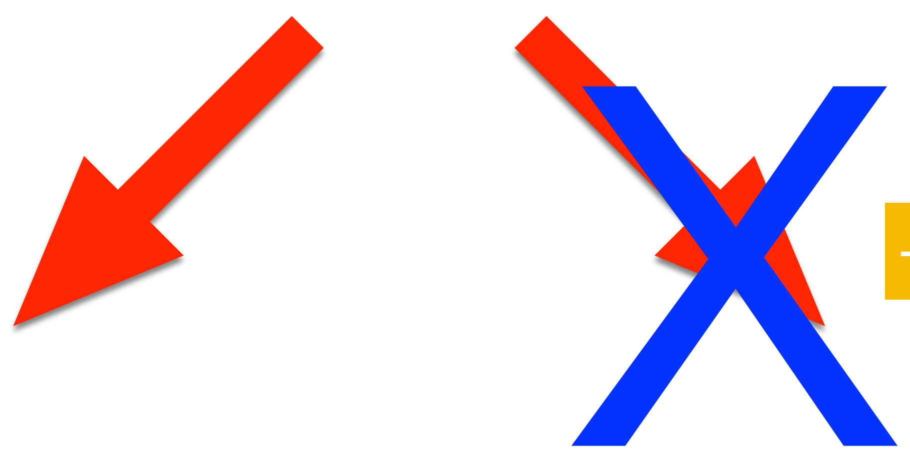
Otto Warburg

Pyruvate



Anaerobic glycolysis

$-O_2$



$+O_2$

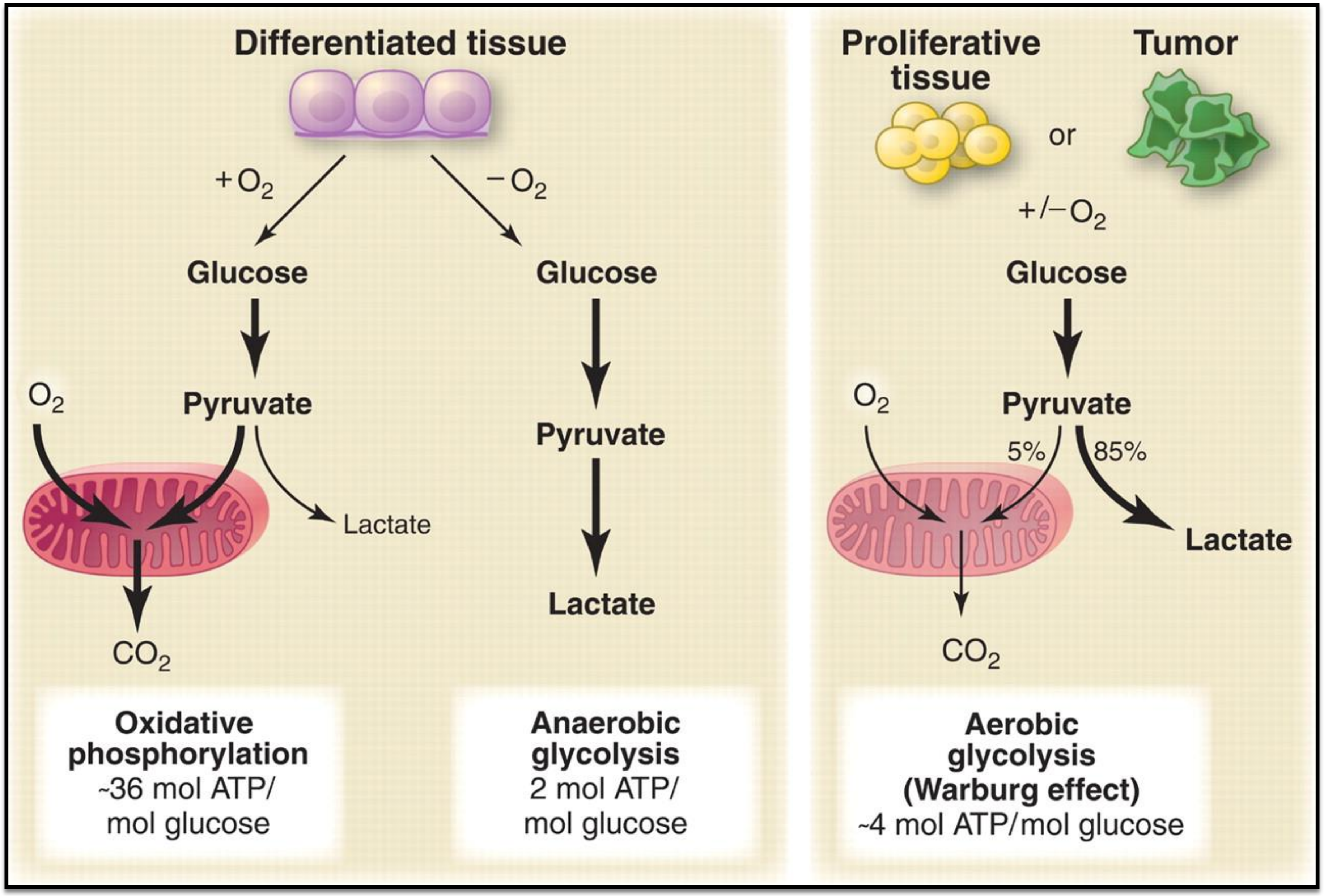
Aerobic glycolysis

2 mol ATP/mol of glucose

31 mol ATP/mol of glucose

First indication of cancer dependent metabolic remodelling

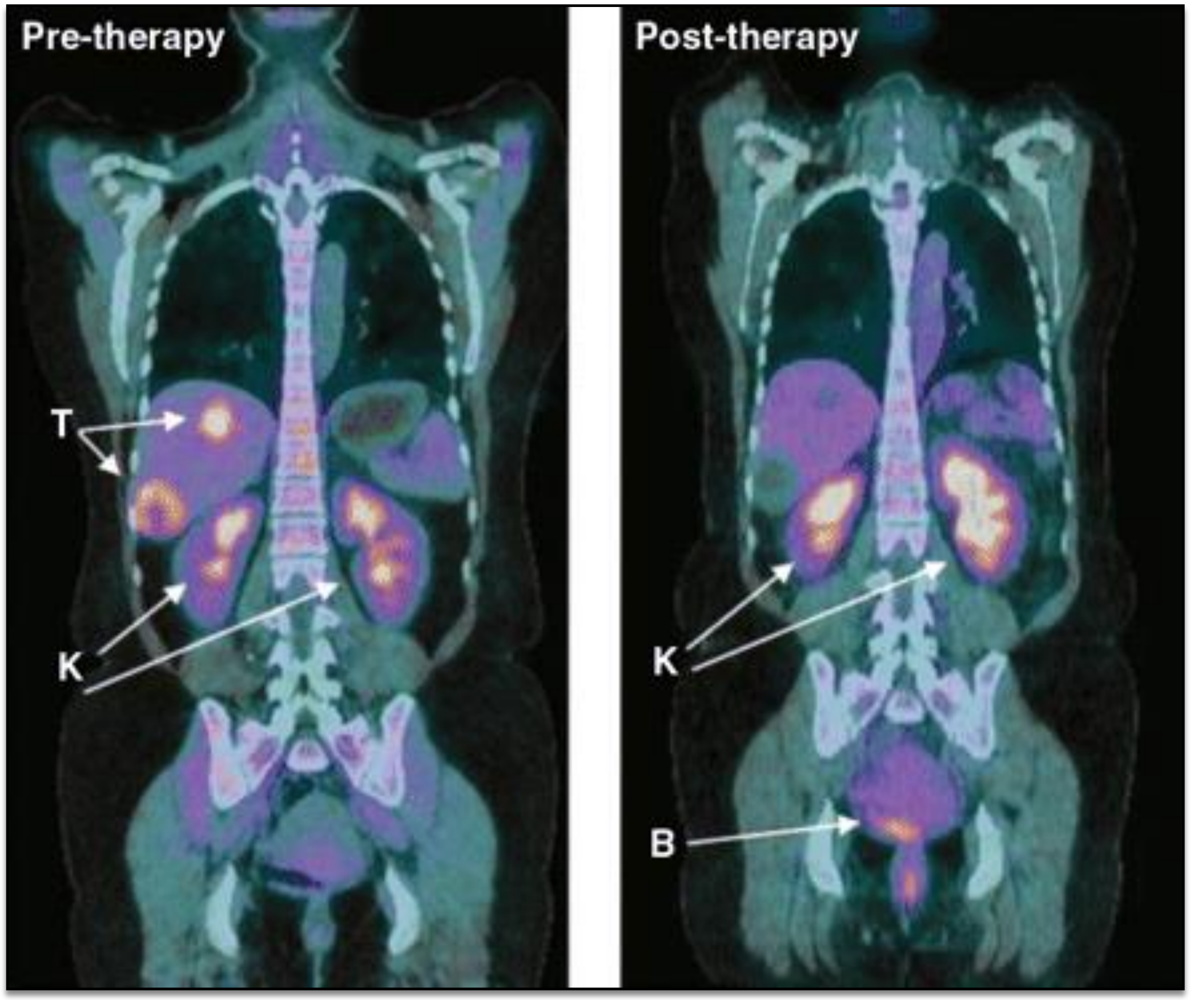
Aerobic glycolysis



Cell produce large amount of lactate regardless of the availability of oxygen

Vander Heiden, M. G., Cantley, L. C., and Thompson, C. B. (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 324, 1029–1033

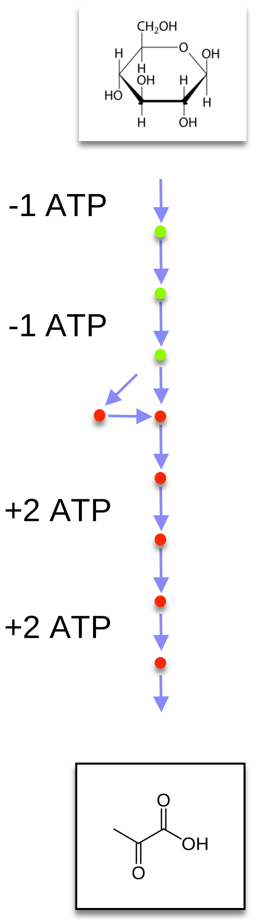
Detection of tumors by glucose analogs



Decreased metabolism of glucose by tumors, visualised by PET with the glucose analog FDG

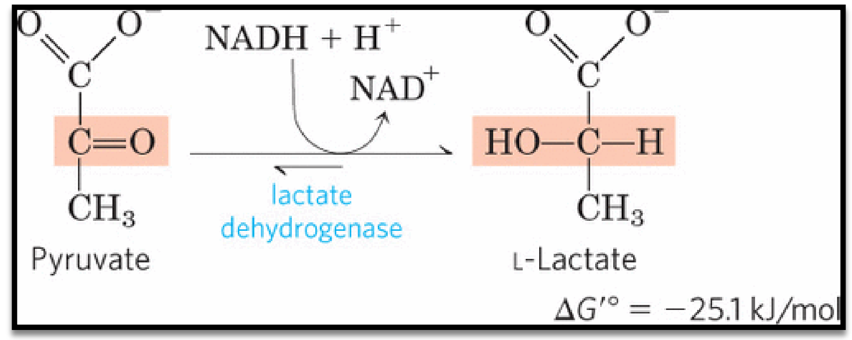
Vander Heiden, M. G., Cantley, L. C., and Thompson, C. B. (2009) Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 324, 1029–1033

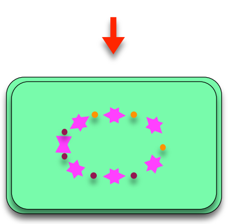
Suggested molecular mechanics for Warburg effect



Lactate

LDH





LDHA (LDH5) functions as a prognosis marker in many tumors including:

lymphoma, prostate cancer, renal cell carcinoma (RCC), and melanoma

Course leading Questions

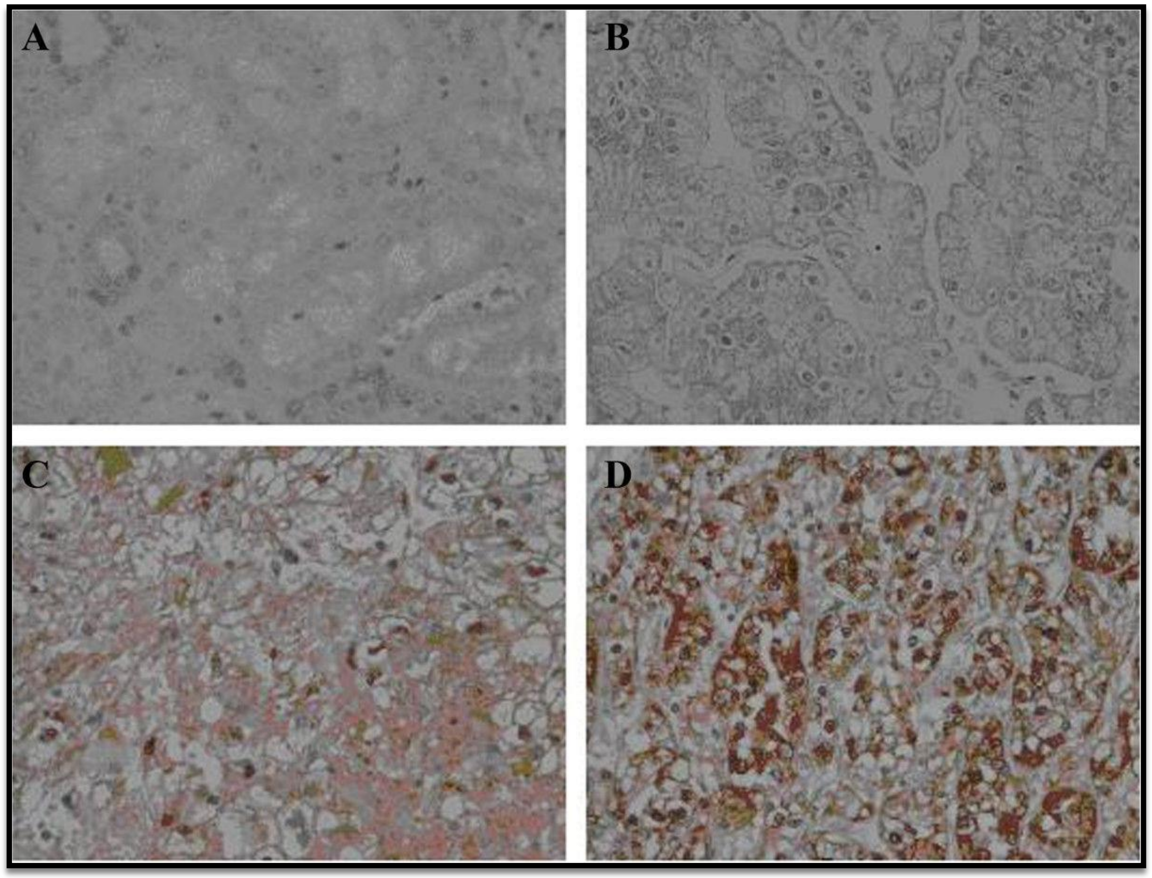
Warburg Effect

What are the molecular mechanisms that regulate the WA?

Is WA a byproduct or an integrated part of the cancer

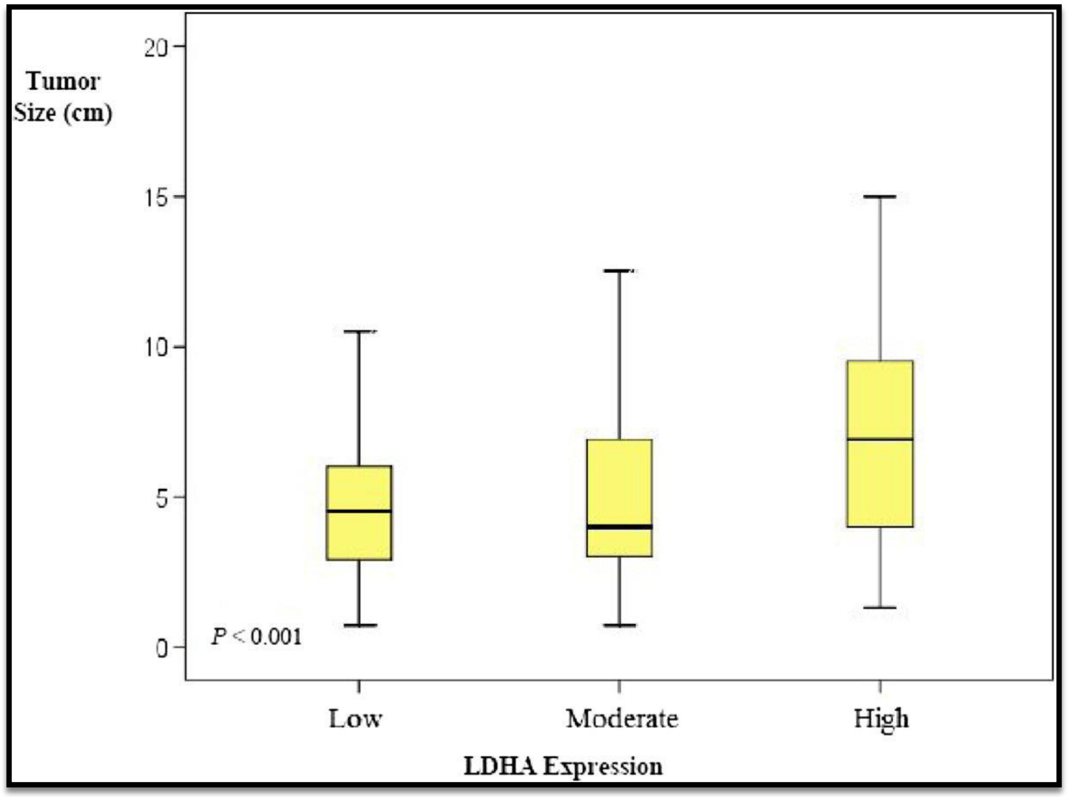
Lactate Dehydrogenase as a tumor marker

LDHA protein expression by immunohistochemistry



(A) Normal kidney proximal tubular epithelium,
(B) weak
(C) moderate
(D) strong staining Clear Cell Renal Cell Carcinoma

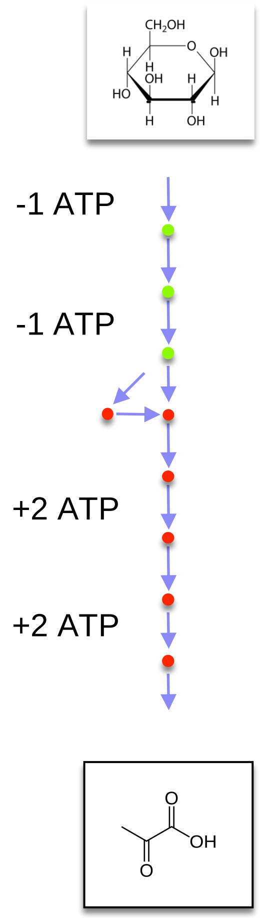
Box plot representing LDHA expression levels in relation to tumor size



Girgis, H., Masui, O., White, N. M., Scorilas, A., Rotondo, F., Seivwright, A., Gabril, M., Filter, E. R., Girgis, A. H., Bjarnason, G. A., Jewett, M. A., Evans, A., Al-Haddad, S., Siu, K. M., and Yousef, G. M. (2014) Lactate Dehydrogenase A is a potential prognostic marker in clear cell renal cell carcinoma. Molecular Cancer. 13, 101

Lactate Dehydrogenase KD

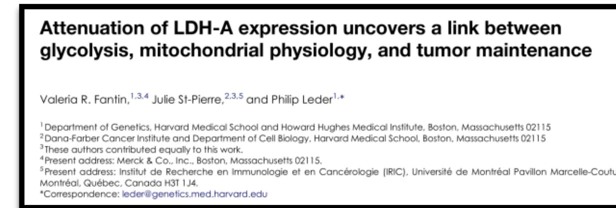
LDH-A suppression interferes with tumorigenicity of malignant cell



Lactate

L2-5/10 LDH-A-KD

L2-5.c 15 LDH-A rescue



Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance

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[1] Department of Genetics, Harvard Medical School and Howard Hughes Medical Institute, Boston, Massachusetts 02115
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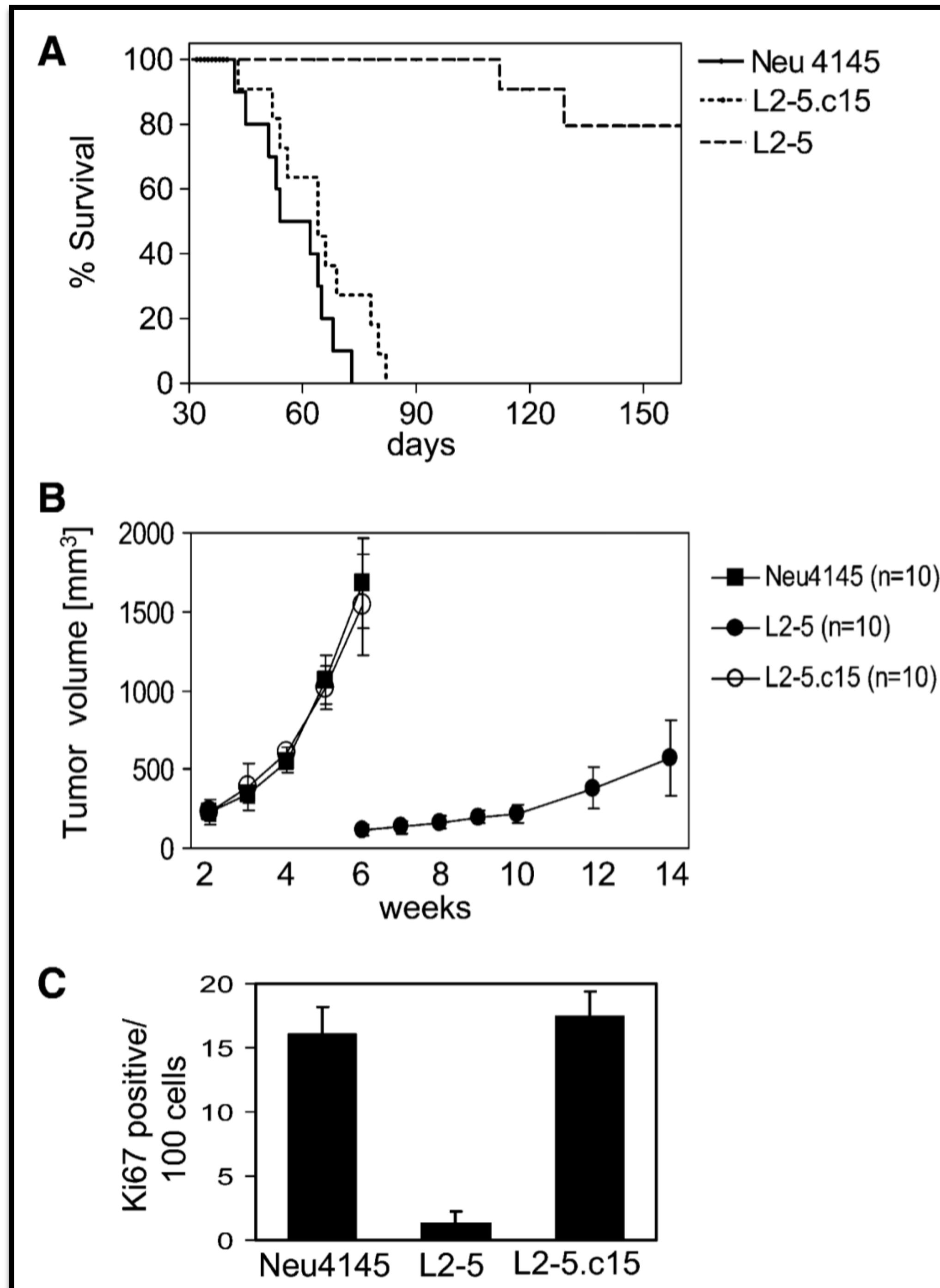
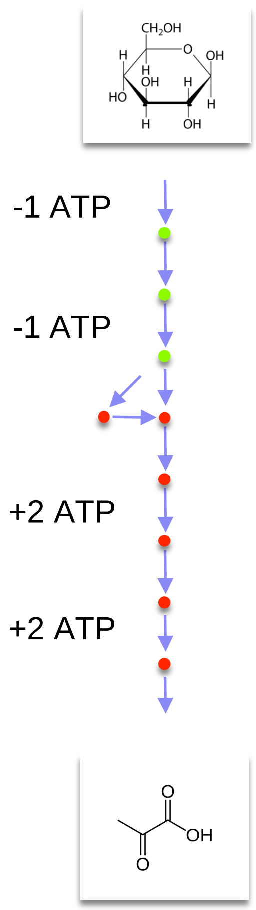
*Correspondence: leder@genetics.med.harvard.edu

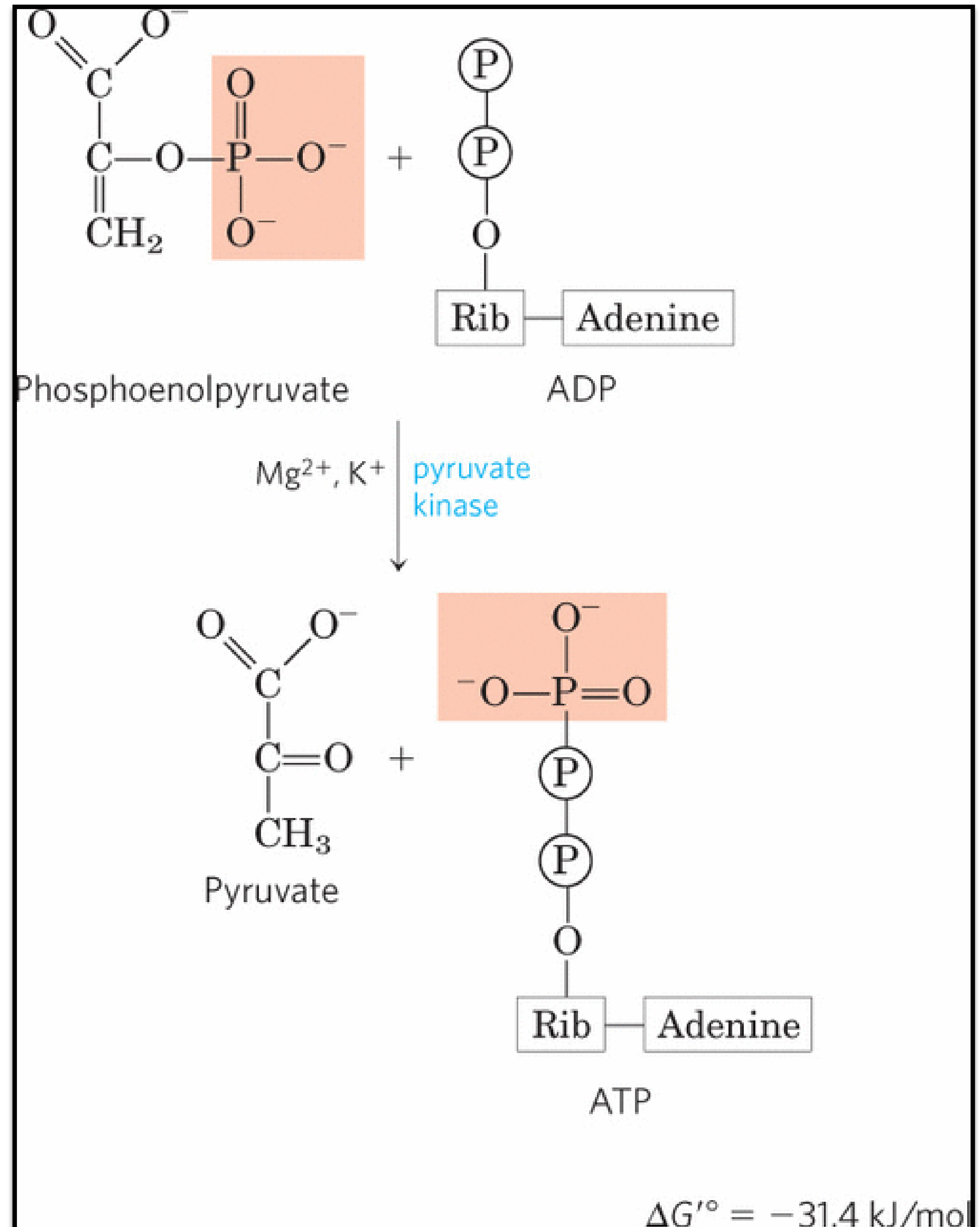


Ki67- mitotic marker

Pyruvate kinase

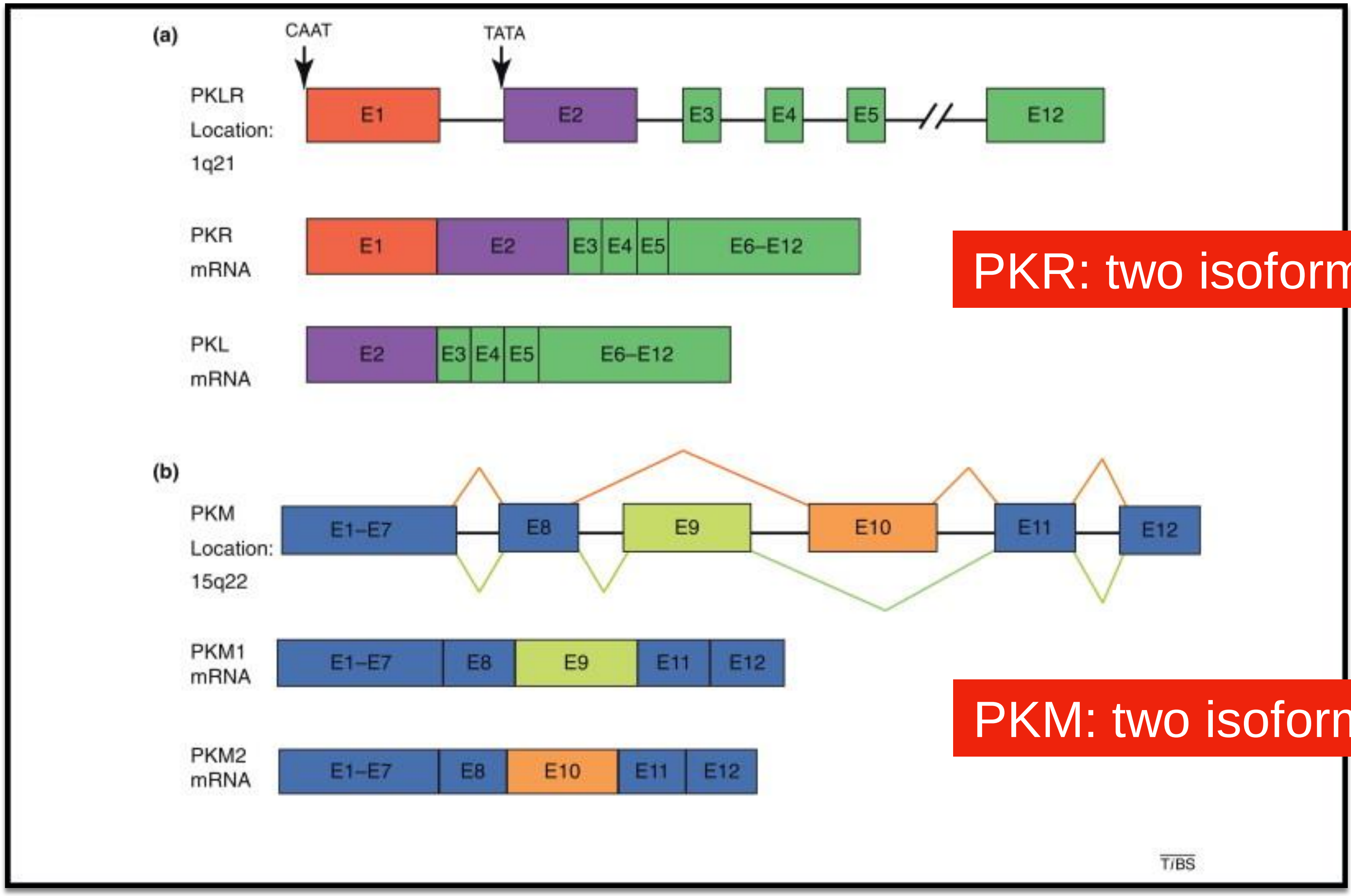


Pyruvate kinase



Different isoforms of PK

There are four isoforms of Pyruvate kinase
Encoded by two genes:



PKR: two isoforms

PKR: red blood cells

PKL: Liver

PKM: two isoform

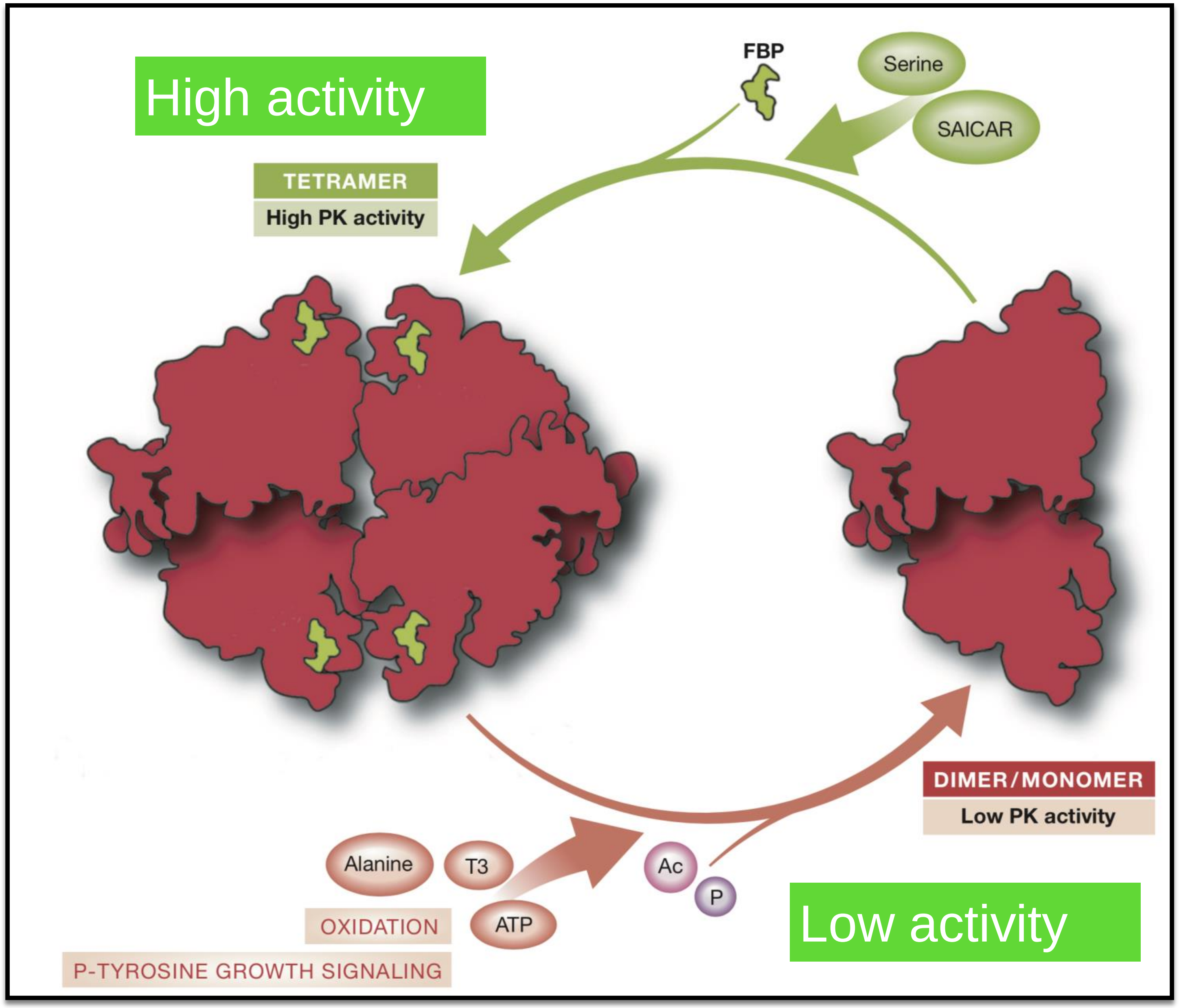
PKM1: Adult

PKM2: Embryo

1. Chaneton, B., and Gottlieb, E. (2012) Rocking cell metabolism: revised functions of the key glycolytic regulator PKM2 in cancer. Trends Biochem Sci. 37, 309–316

PKM2 activity is tightly regulated

PKM2 enzymatic activity can be inhibited by a variety of mechanisms

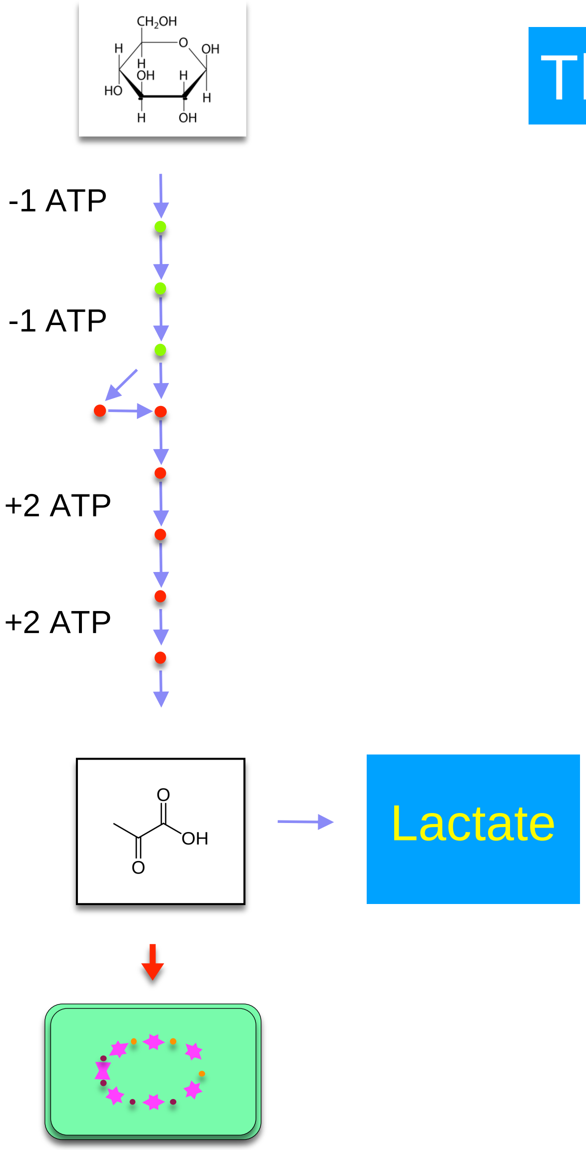


SAICAR, an intermediate of de novo purine biosynthesis

Ability to inhabit PKM2 provides advantage to prolifertating cells

Dayton, T. L., Jacks, T., and Vander Heiden, M. G. (2016) PKM2, cancer metabolism, and the road ahead. EMBO Rep. 17, e201643300–1730

PKM



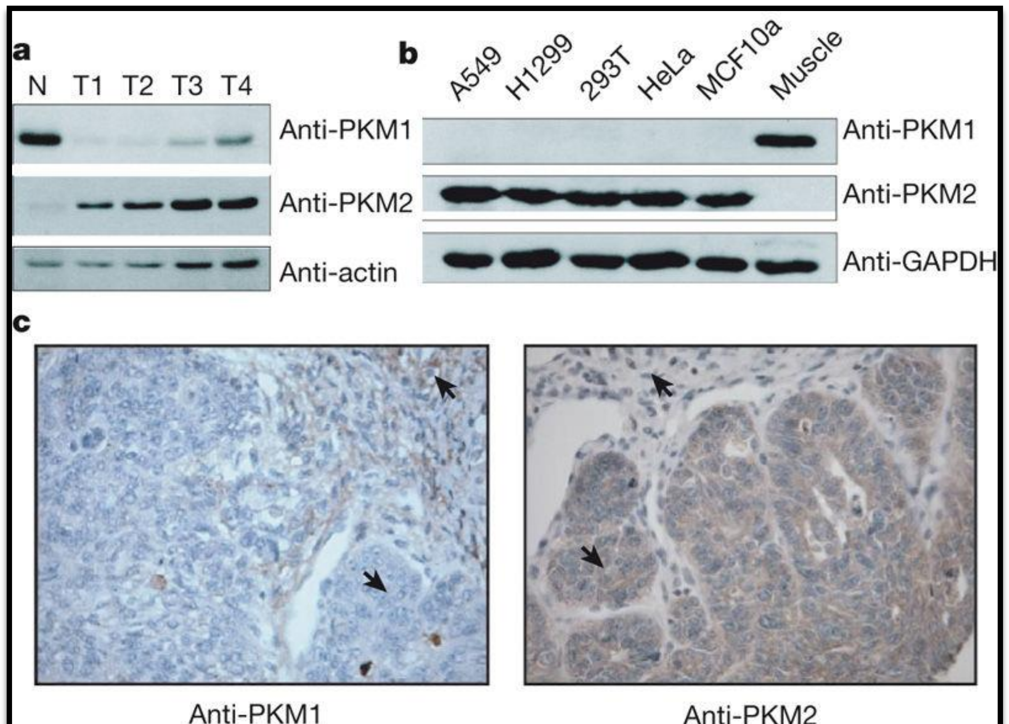
There are two isoforms of PKM2


nature Vol 452|13 March 2008|doi:10.1038/nature06734

LETTERS

The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth

Heather R. Christofk[1], Matthew G. Vander Heiden[1,2], Marian H. Harris[3], Arvind Ramanathan[4], Robert E. Gerszten[4,5,6], Ru Wei[4], Mark D. Fleming[3], Stuart L. Schreiber[4,7] & Lewis C. Cantley[1,8]



PKM1 expressed in normal tissues

PKM2 expressed in cancer

PKM1 is a more active enzyme than PKM2

Christofk, H. R., Vander Heiden, M. G., Harris, M. H., Ramanathan, A., Gerszten, R. E., Wei, R., Fleming, M. D., Schreiber, S. L., and Cantley, L. C. (2008) The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature. 452, 230–233

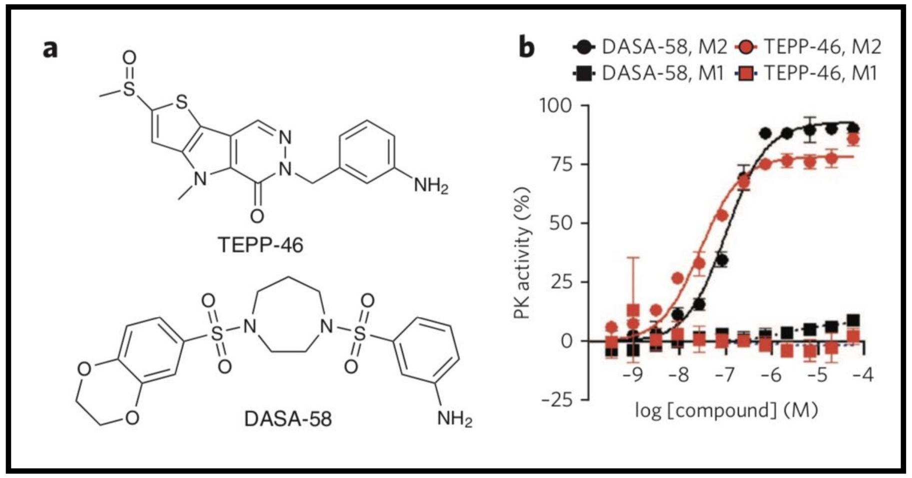
Activating PKM2 suppress tumorgenesis


nature chemical biology
ARTICLE
PUBLISHED ONLINE: 26 AUGUST 2012 | DOI: 10.1038/NCHEMBIO.1060

Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis

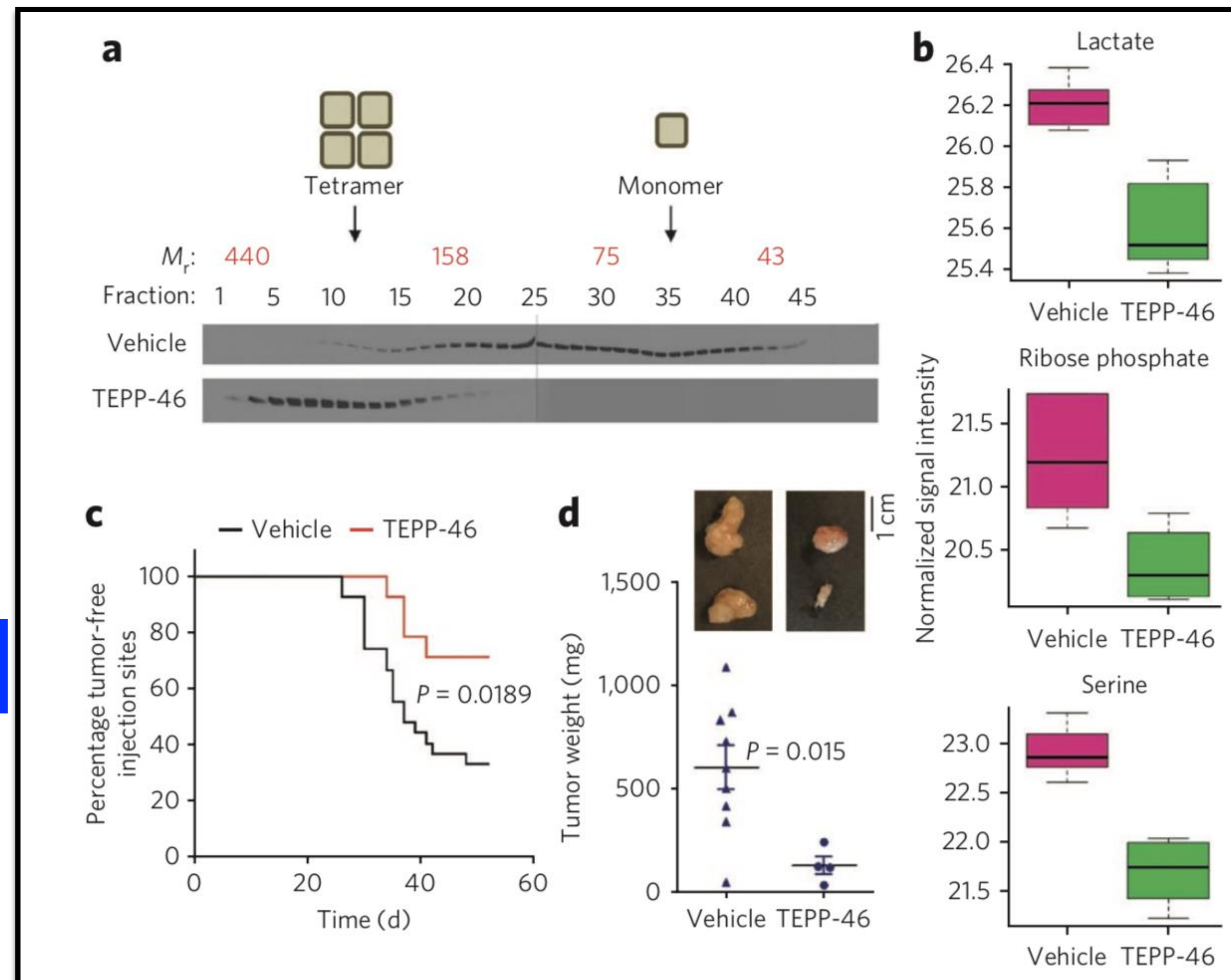
Dimitrios Anastasiou[1,2,13], Yimin Yu[3,13], William J Israelsen[3,13], Jian-Kang Jiang[4], Matthew B Boxer[4], Bum Soo Hong[5], Wolfram Tempel[5], Svetoslav Dimov[5], Min Shen[4], Abhishek Jha[6], Hua Yang[7], Katherine R Mattaini[3], Christian M Metallo[8], Brian P Fiske[3], Kevin D Courtney[1,2,9], Scott Malstrom[3], Tahsin M Khan[3], Charles Kung[7], Amanda P Skoumbourdis[4], Henrike Veith[4], Noel Southall[4], Martin J Walsh[4], Kyle R Brimacombe[4], William Leister[4], Sophia Y Lunt[3], Zachary R Johnson[3], Katharine E Yen[7], Kaiko Kunii[7], Shawn M Davidson[3], Heather R Christofk[1], Christopher P Austin[4], James Inglese[4], Marian H Harris[10], John M Asara[1,11], Gregory Stephanopoulos[6], Francesco G Salituro[7], Shengfang Jin[7], Lenny Dang[7], Douglas S Auld[4], Hee-Won Park[5,12], Lewis C Cantley[1,2], Craig J Thomas[4] & Matthew G Vander Heiden[3,9]*

TEPP-46 activates PKM2



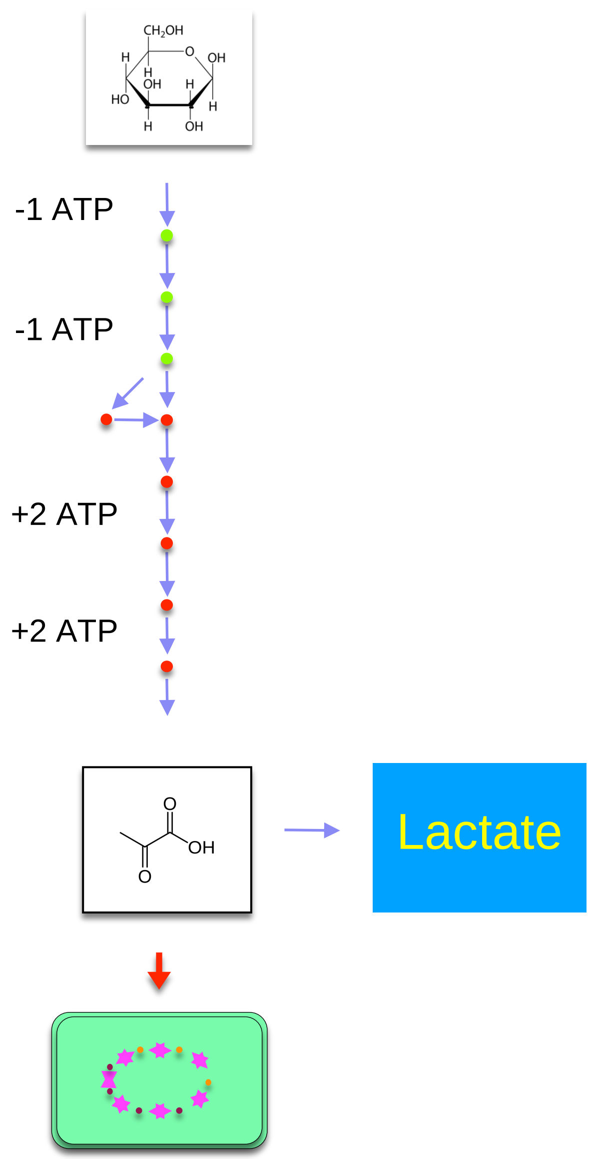
TEPP-46 affects glycolysis intermediates

TEPP-46 decrease tumor growth

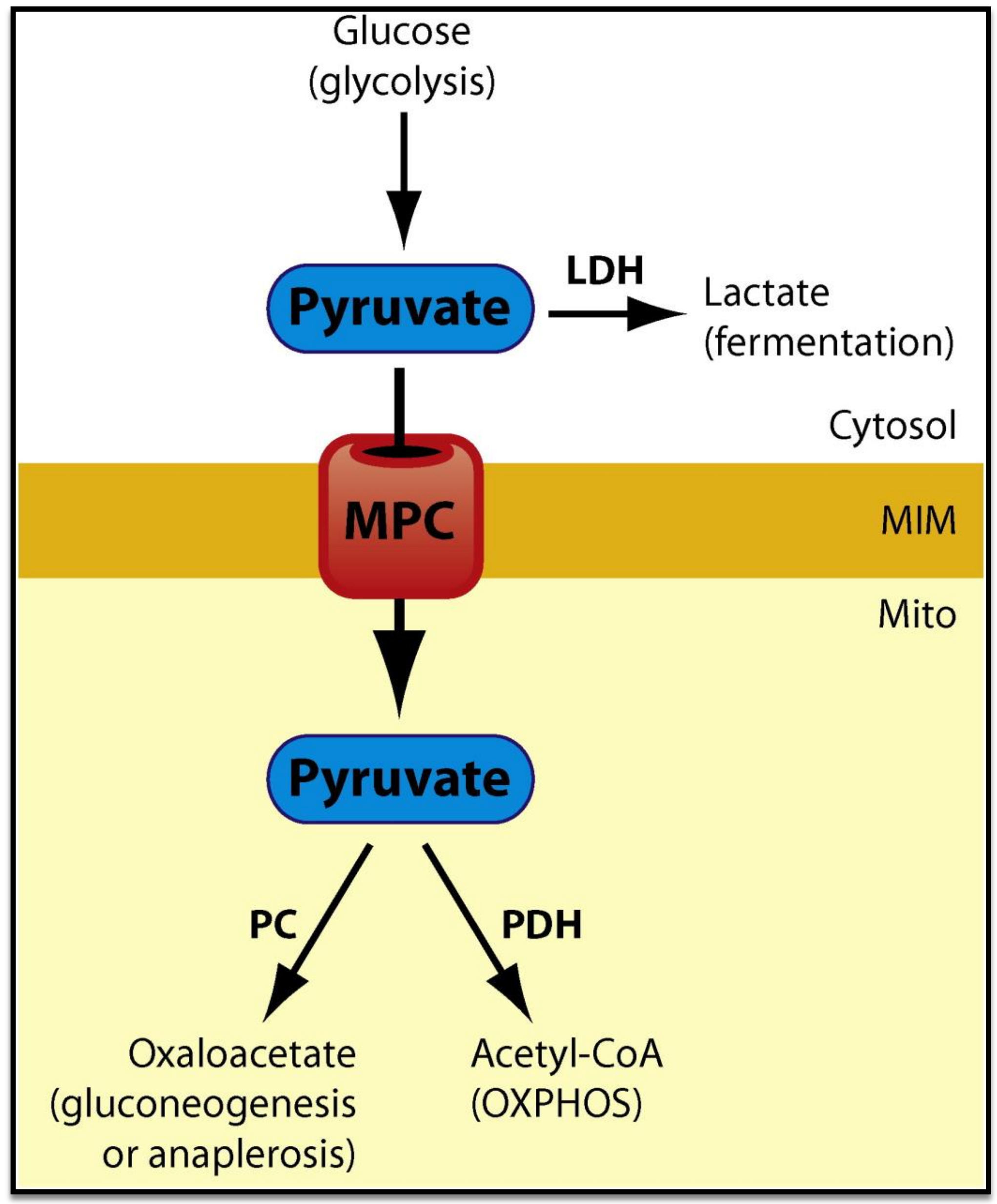


Anastasiou, D., Yu, Y., Israelsen, W. J., Jiang, J.-K., Boxer, M. B., Hong, B. S., Tempel, W., Dimov, S., Shen, M., Jha, A., Yang, H., Mattaini, K. R., Metallo, C. M., Fiske, B. P., Courtney, K. D., Malstrom, S., Khan, T. M., Kung, C., Skoumbourdis, A. P., Veith, H., Southall, N., Walsh, M. J., Brimacombe, K. R., Leister, W., Lunt, S. Y., Johnson, Z. R., Yen, K. E., Kunii, K., Davidson, S. M., Christofk, H. R., Austin, C. P., Inglese, J., Harris, M. H., Asara, J. M., Stephanopoulos, G., Salituro, F. G., Jin, S., Dang, L., Auld, D. S., Park, H.-W., Cantley, L. C., Thomas, C. J., and Vander Heiden, M. G. (2012) Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis. Nat Chem Biol. 8, 839–847

Mitochondrial Pyruvate Carrier (MPC)



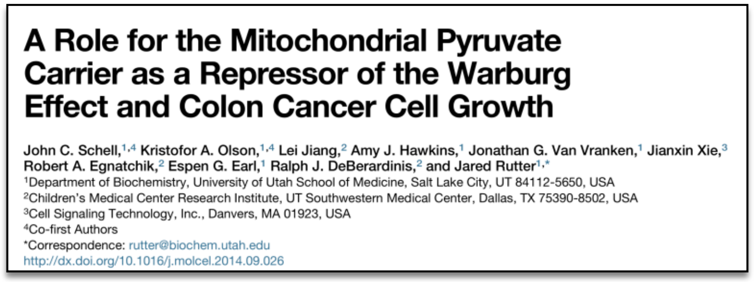
Gatekeeper of pyruvate entry to the mitochondria



Two inform MPC1 and 2

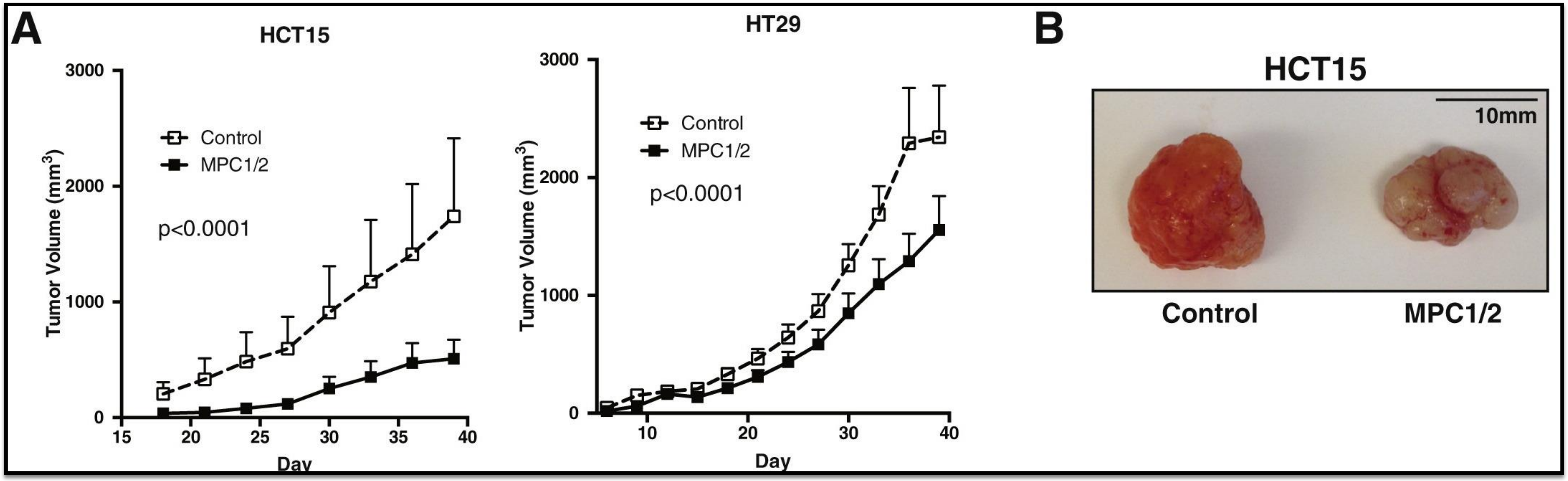
Bender, T., and Martinou, J.-C. (2016) The mitochondrial pyruvate carrier in health and disease: To carry or not to carry? Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 1863, 2436–2442

MPC1/2 re-expression decreases tumor size


A Role for the Mitochondrial Pyruvate Carrier as a Repressor of the Warburg Effect and Colon Cancer Cell Growth

John C. Schell,[1,4] Kristofor A. Olson,[1,4] Lei Jiang,[2] Amy J. Hawkins,[1] Jonathan G. Van Vranken,[1] Jianxin Xie,[3] Robert A. Egnatchik,[2] Espen G. Earl,[1] Ralph J. DeBerardinis,[2] and Jared Rutter[1,*]
[1]Department of Biochemistry, University of Utah School of Medicine, Salt Lake City, UT 84112-5650, USA
[2]Children's Medical Center Research Institute, UT Southwestern Medical Center, Dallas, TX 75390-8502, USA
[3]Cell Signaling Technology, Inc., Danvers, MA 01923, USA
[4]Co-first Authors
*Correspondence: rutter@biochem.utah.edu
http://dx.doi.org/10.1016/j.molcel.2014.09.026

MPC1/2 slowed tumor growth



Schell, J. C., Olson, K. A., Jiang, L., Hawkins, A. J., Van Vranken, J. G., Xie, J., Egnatchik, R. A., Earl, E. G., Deberardinis, R. J., and Rutter, J. (2014) A Role for the Mitochondrial Pyruvate Carrier as a Repressor of the Warburg Effect and Colon Cancer Cell Growth. Mol Cell. 56, 400–413

Leading Questions

Metabolism and cancer

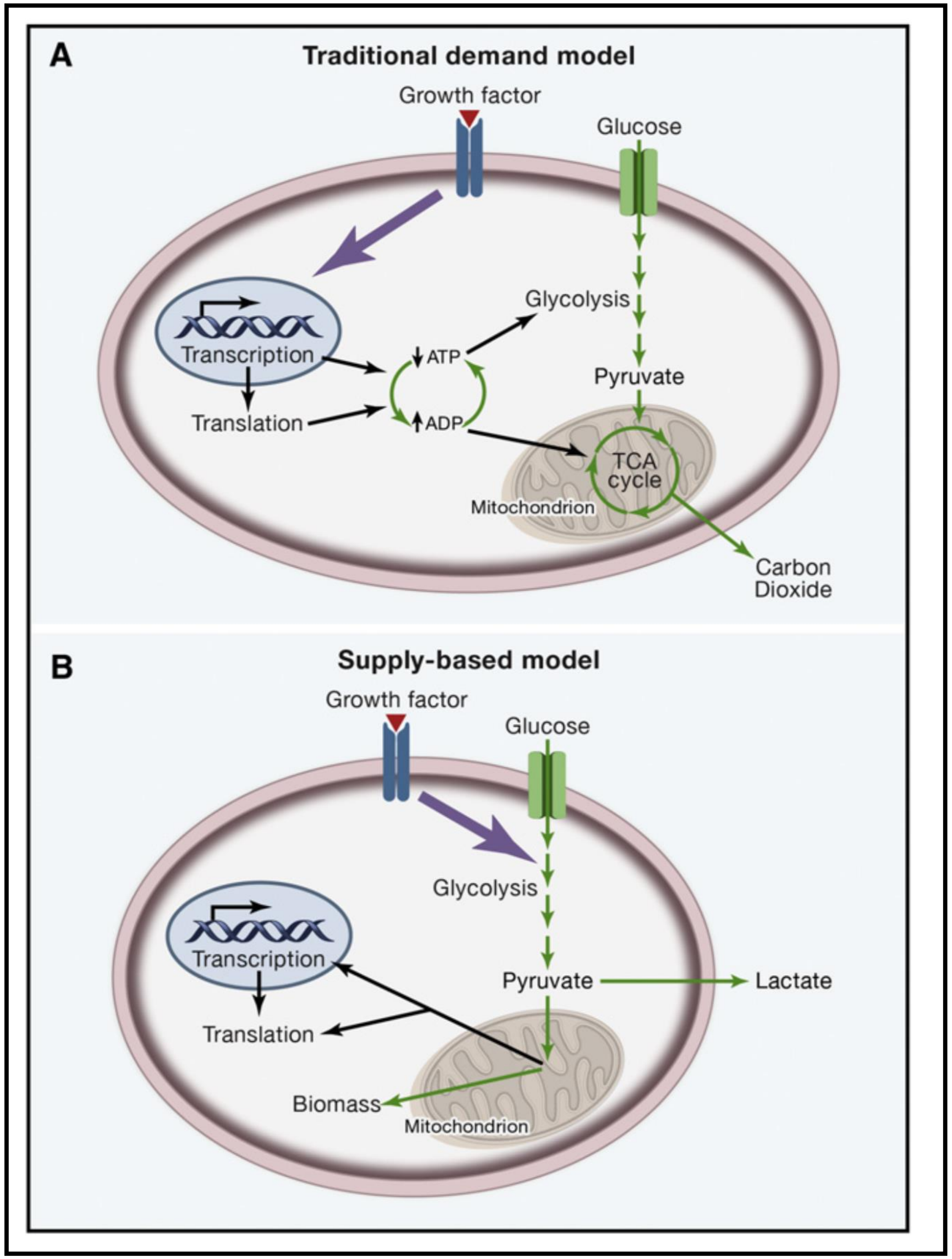
Can metabolism be the drivers of cancers?

Traditional model

Metabolism is altered in response to growth factor

Supply-based model

Growth factor signaling directly reprograms nutrient uptake and metabolism



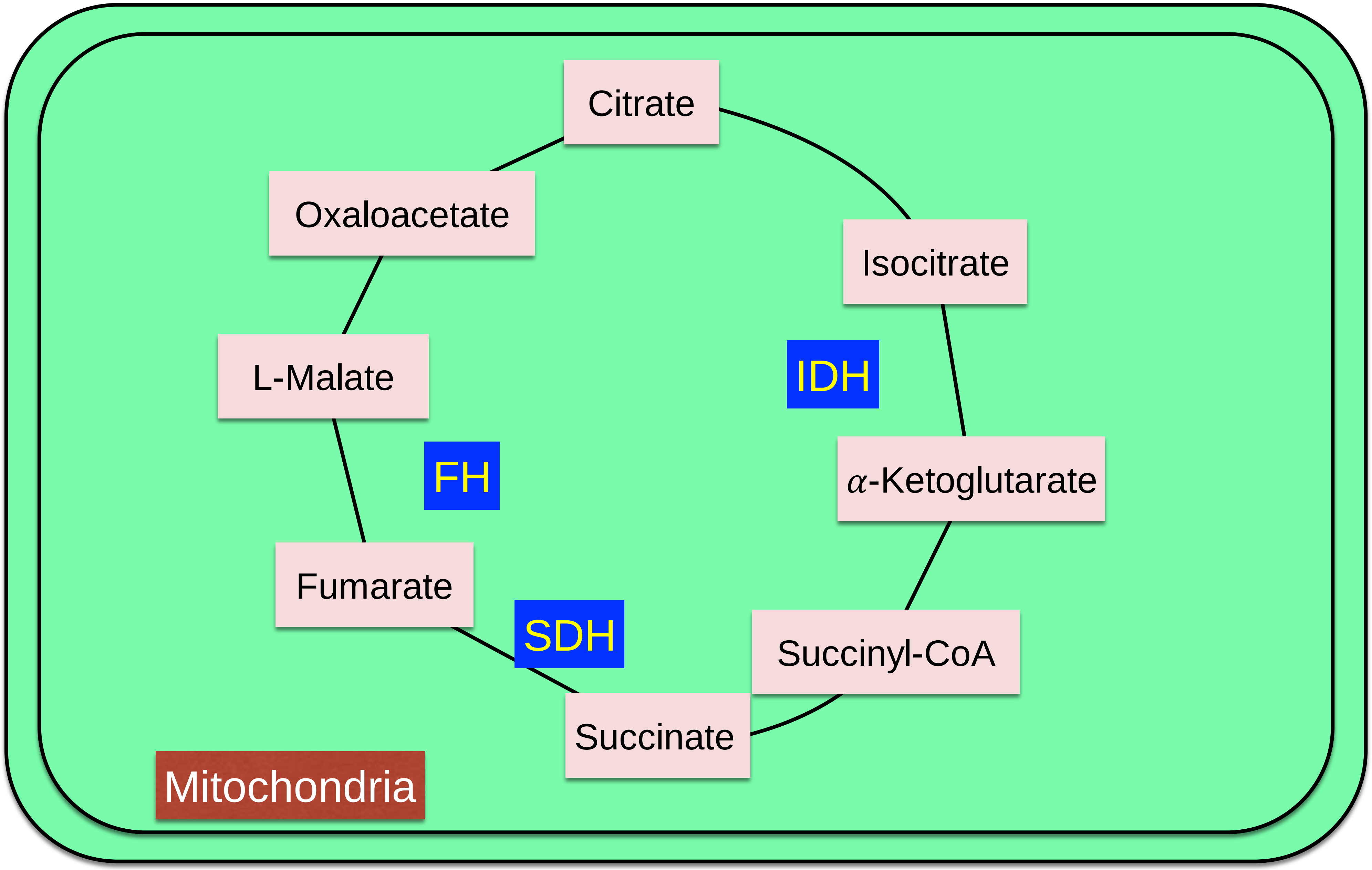
Human tumor suppressor genes that have been cloned

Evading growth suppressors

Metabolic gene

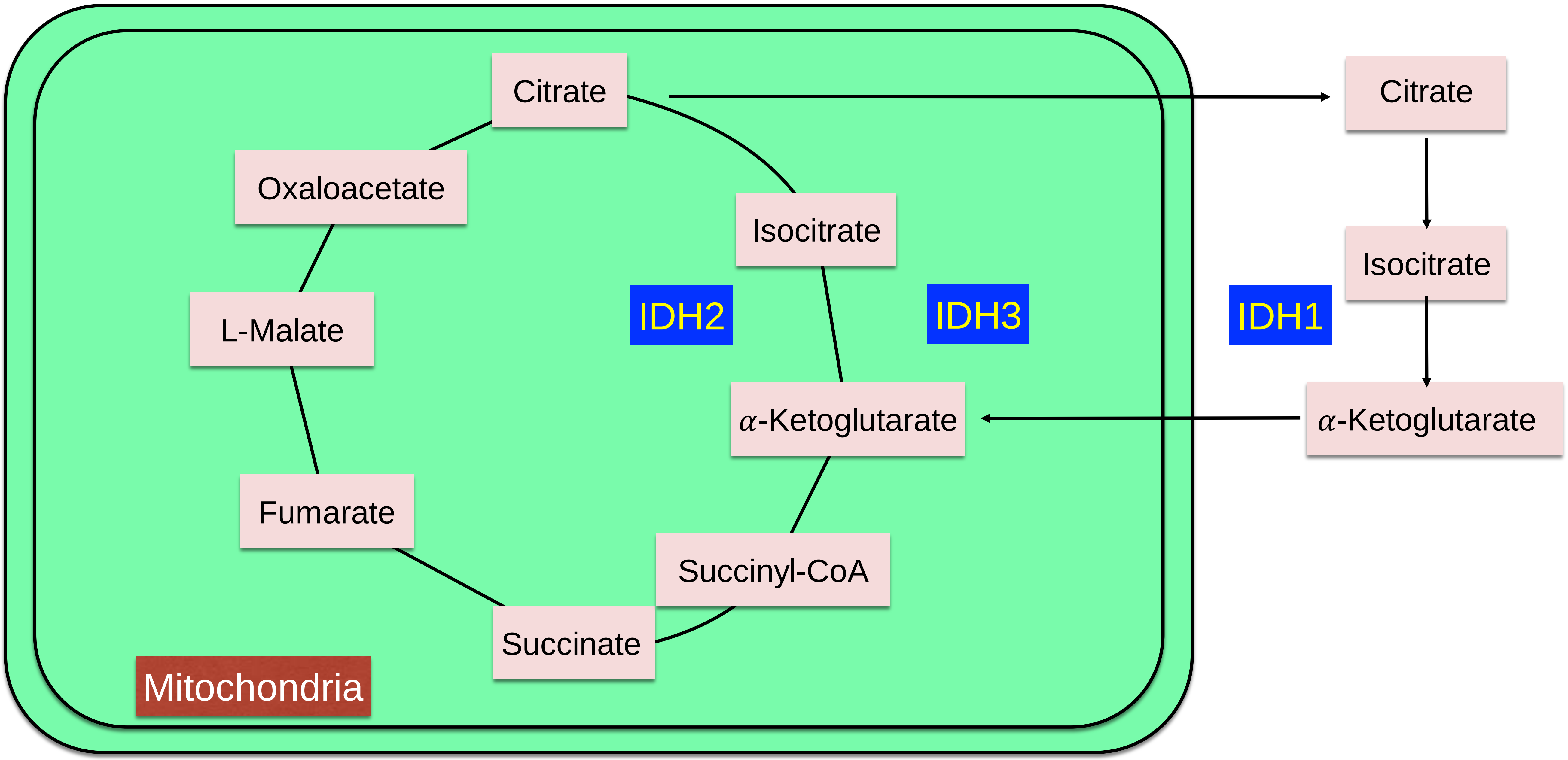
Name of gene	Chromosomal location	Familial cancer syndrome	Sporadic cancer	Function of protein
RUNX3	1p36	—	gastric carcinoma	TF co-factor
HRPT2	1q25–32	parathyroid tumors, jaw fibromas	parathyroid tumors	chromatin protein
FH	1q42.3	familial leiomyomatosis[a]	—	fumarate hydratase
FHIT	3p14.2	—	many types	diadenosine triphosphate hydrolase
RASSF1A	3p21.3	—	many types	multiple functions
TGFBR2	3p2.2	HNPCC	colon, gastric, pancreatic carcinomas	TGF-β receptor
VHL	3p25	von Hippel–Lindau syndrome	renal cell carcinoma	ubiquitylation of HIF
hCDC4	4q32	—	endometrial carcinoma	ubiquitin ligase
APC	5p21	familial adenomatous polyposis coli	colorectal, pancreatic, and stomach carcinomas; prostate carcinoma	β-catenin degradation
NKX3.1	8p21	—	prostate carcinoma	homeobox TF
p16^{INK4A} [b]	9p21	familial melanoma	many types	CDK inhibitor
p14^{ARF} [c]	9p21	—	all types	p53 stabilizer
PTC	9q22.3	nevoid basal cell carcinoma syndrome	medulloblastomas	receptor for hedgehog GF
TSC1	9q34	tuberous sclerosis	—	inhibitor of mTOR[f]
BMPR1	10q21–22	juvenile polyposis	—	BMP receptor
PTEN[d]	10q23.3	Cowden's disease, breast and gastrointestinal carcinomas	glioblastoma; prostate, breast, and thyroid carcinomas	PIP_3 phosphatase
WT1	11p13	Wilms tumor	Wilms tumor	TF
MEN1	11p13	multiple endocrine neoplasia	—	histone modification, transcriptional repressor
BWS/CDKN1C	11p15.5	Beckwith–Wiedemann syndrome	—	p57^{Kip2} CDK inhibitor
SDHD	11q23	familial paraganglioma	pheochromocytoma	mitochondrial protein[e]
RB	13q14	retinoblastoma, osteosarcoma	retinoblastoma; sarcomas; bladder, breast, esophageal, and lung carcinomas	transcriptional repression; control of E2Fs
TSC2	16p13	tuberous sclerosis	—	inhibitor of mTOR[f]
CBP	16p13.3	Rubinstein–Taybi	AML[g]	TF co-activator
CYLD	16q12–13	cylindromatosis	—	deubiquitinating enzyme
CDH1	16q22.1	familial gastric carcinoma	invasive cancers	cell–cell adhesion
BHD	17p11.2	Birt–Hogg–Dube syndrome	kidney carcinomas, hamartomas	unknown
TP53	17p13.1	Li–Fraumeni syndrome	many types	TF
NF1	17q11.2	neurofibromatosis type 1	colon carcinoma, astrocytoma	Ras-GAP
BECN1	17q21.3	—	breast, ovarian, prostate	autophagy
PRKAR1A	17.q22–24	multiple endocrine neoplasia[h]	multiple endocrine tumors	subunit of PKA
DPC4[i]	18q21.1	juvenile polyposis	pancreatic and colon carcinomas	TGF-β TF
LKB1/STK11	19p13.3	Peutz–Jegher syndrome	hamartomatous colonic polyps	serine/threonine kinase
RUNX1	21q22.12	familial platelet disorder	AML	TF
SNF5[j]	22q11.2	rhabdoid predisposition syndrome	malignant rhabdoid tumors	chromosome remodeling
NF2	22q12.2	neurofibroma-position syndrome	schwannoma, meningioma; ependymoma	cytoskeleton–membrane linkage

Mutated metabolic enzymes in cancer



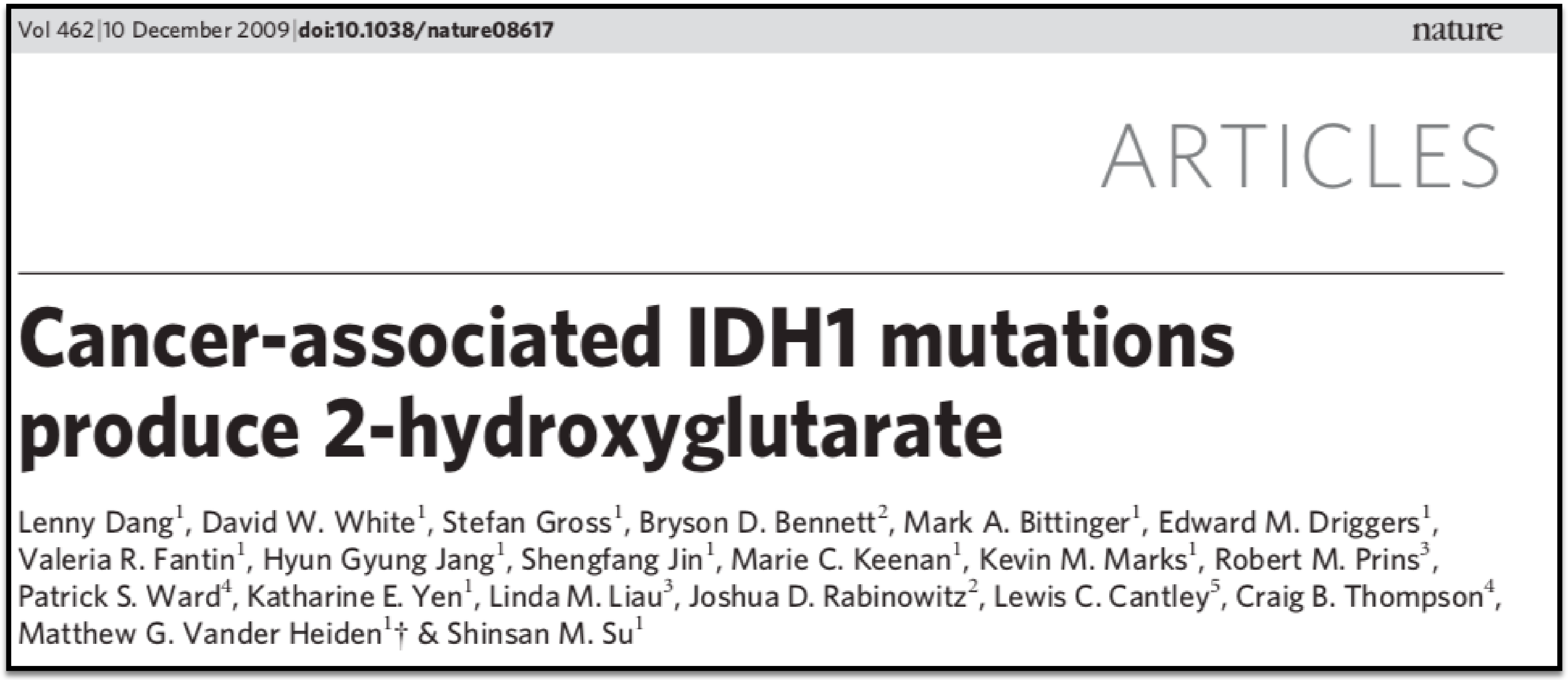
Isocitrate dehydrogenase (IDH)

Exists as three isoform:



IDH mutation in cancer

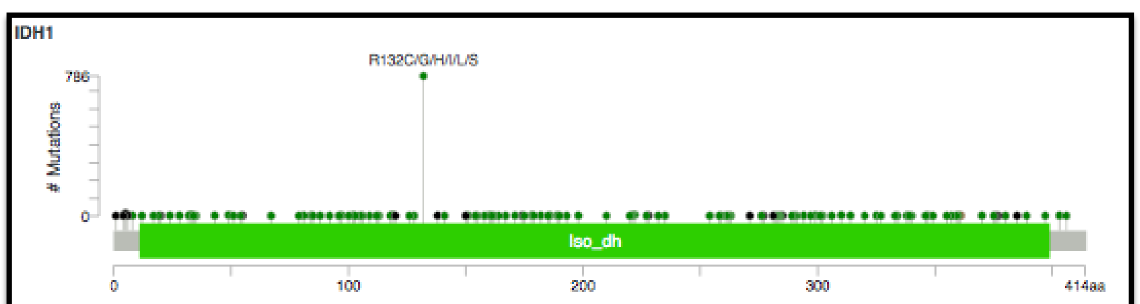
IDH1 is mutated in 80% of grade II–III gliomas


Vol 462 | 10 December 2009 | doi:10.1038/nature08617 nature

ARTICLES

Cancer-associated IDH1 mutations produce 2-hydroxyglutarate

Lenny Dang[1], David W. White[1], Stefan Gross[1], Bryson D. Bennett[2], Mark A. Bittinger[1], Edward M. Driggers[1], Valeria R. Fantin[1], Hyun Gyung Jang[1], Shengfang Jin[1], Marie C. Keenan[1], Kevin M. Marks[1], Robert M. Prins[3], Patrick S. Ward[4], Katharine E. Yen[1], Linda M. Liau[3], Joshua D. Rabinowitz[2], Lewis C. Cantley[5], Craig B. Thompson[4], Matthew G. Vander Heiden[1]† & Shinsan M. Su[1]

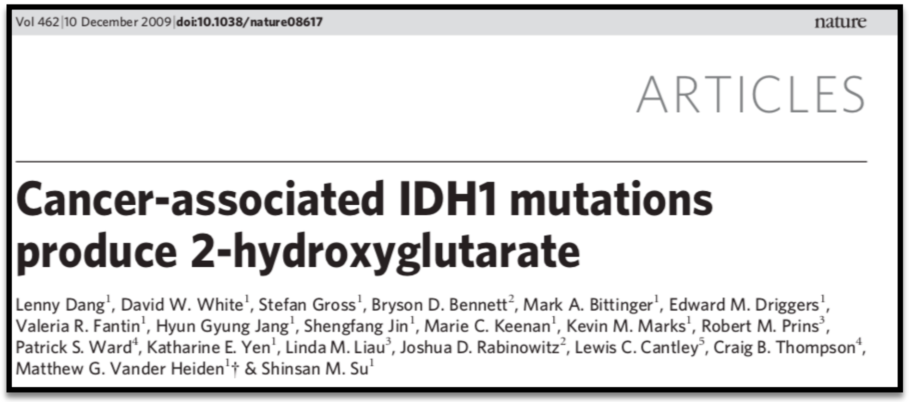


IDH mutation are selected at early stages of tumorigenesis

What does this mutation do to the enzymatic activity?

Dang L, et al. (2009) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 462(7274):739–744.

IDH1 mutations produce 2-hydroxyglutarate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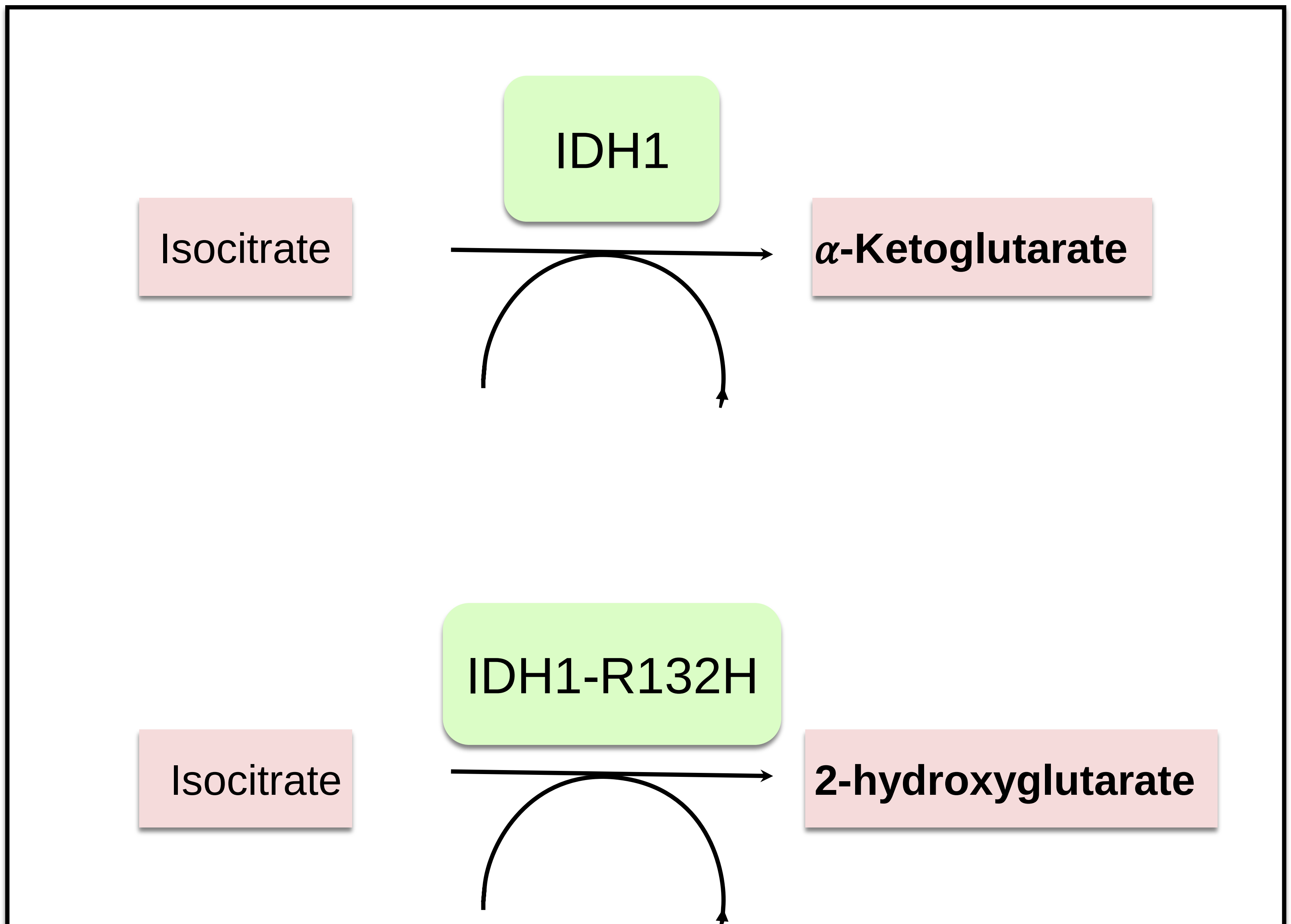
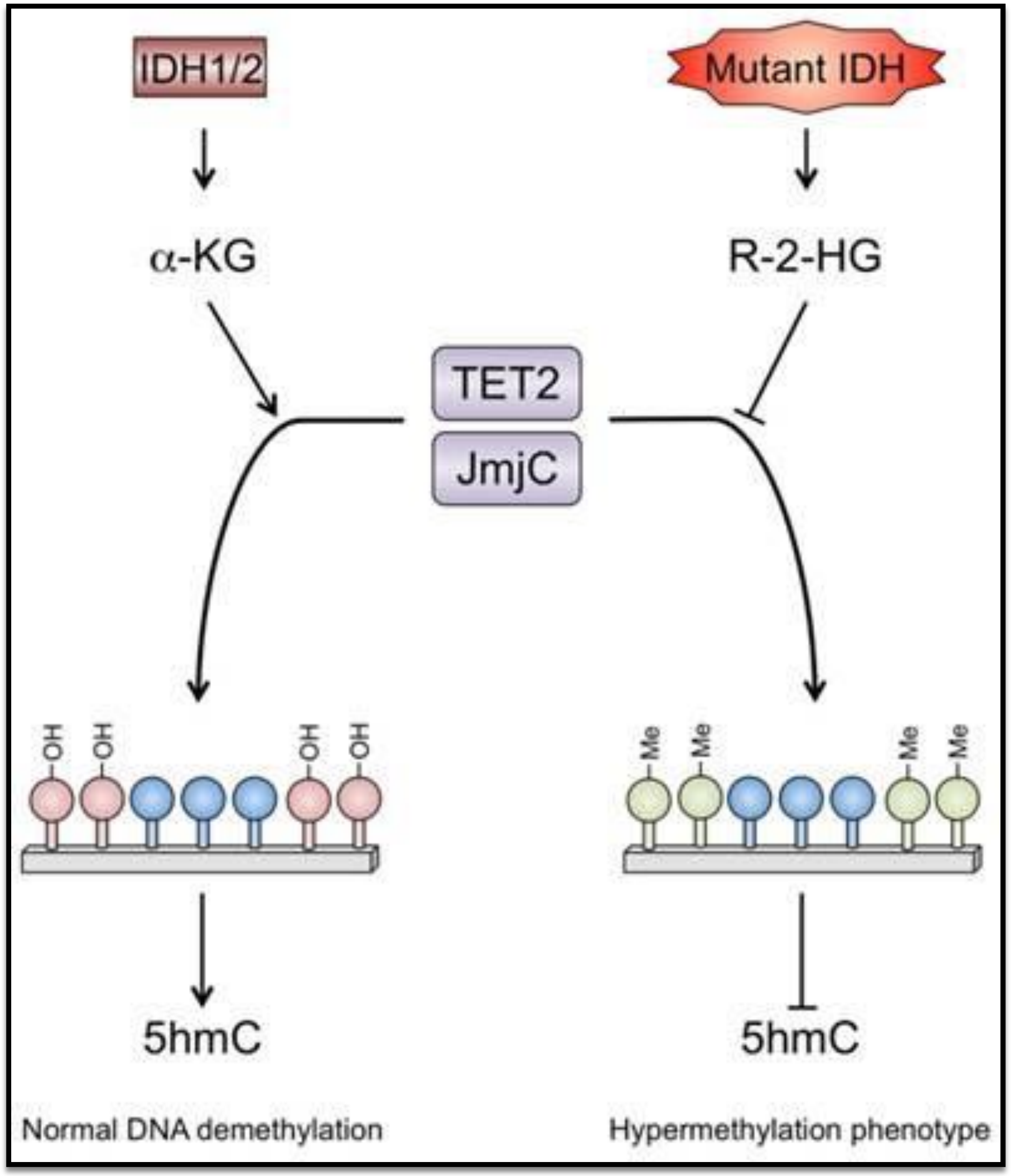


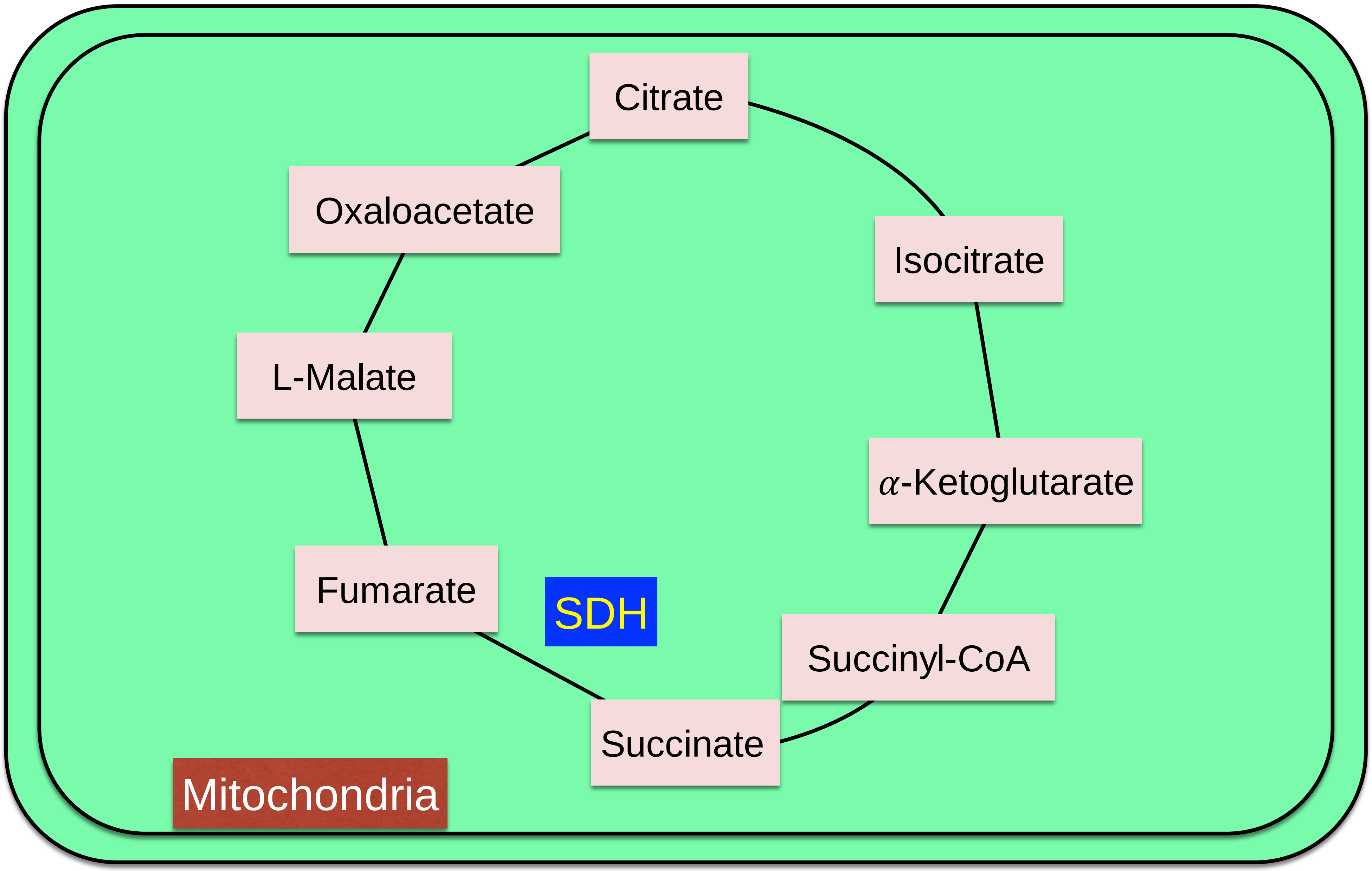
How do 2HG affect the cells?

2-hydroxyglutarate

IDH movie



Succinate Dehydrogenase



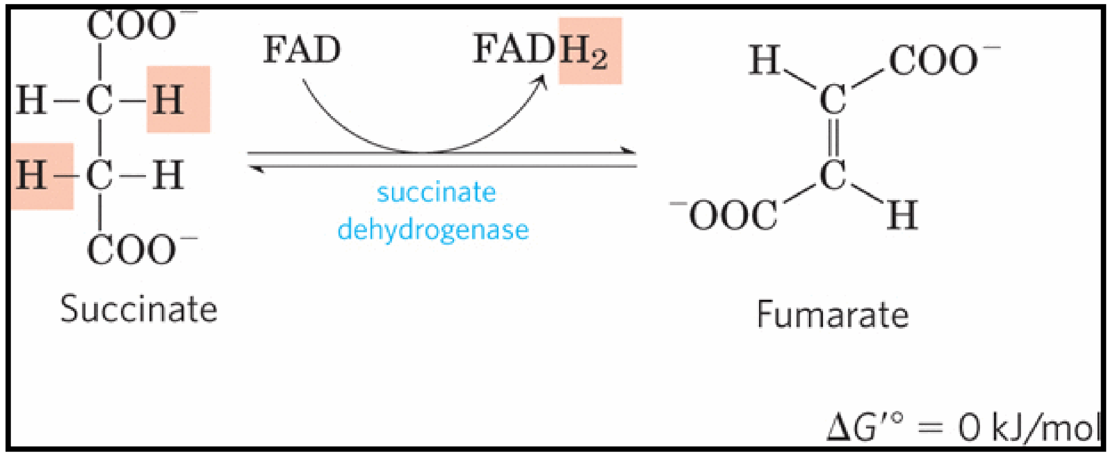


Figure 16 Lehninger

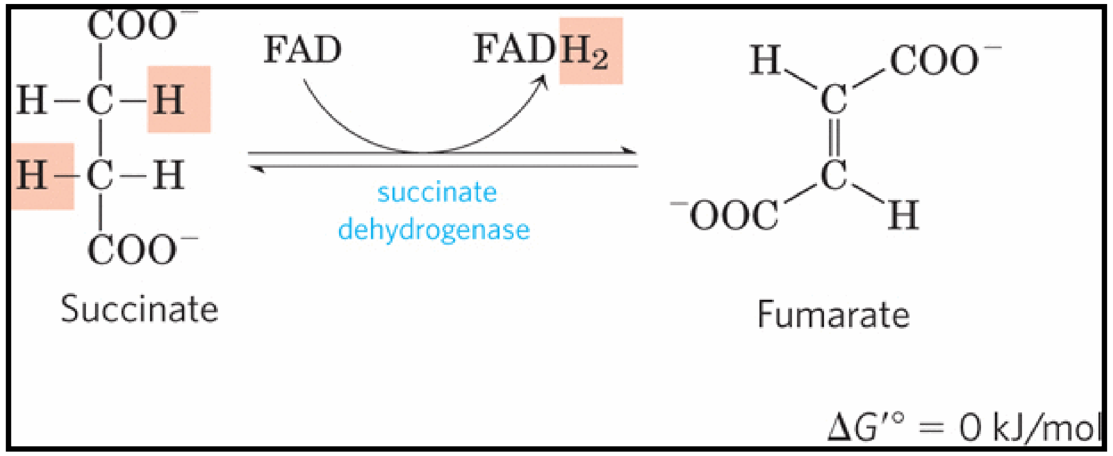
SDH mutation

SDH was the first mitochondrial enzyme found mutated in cancer

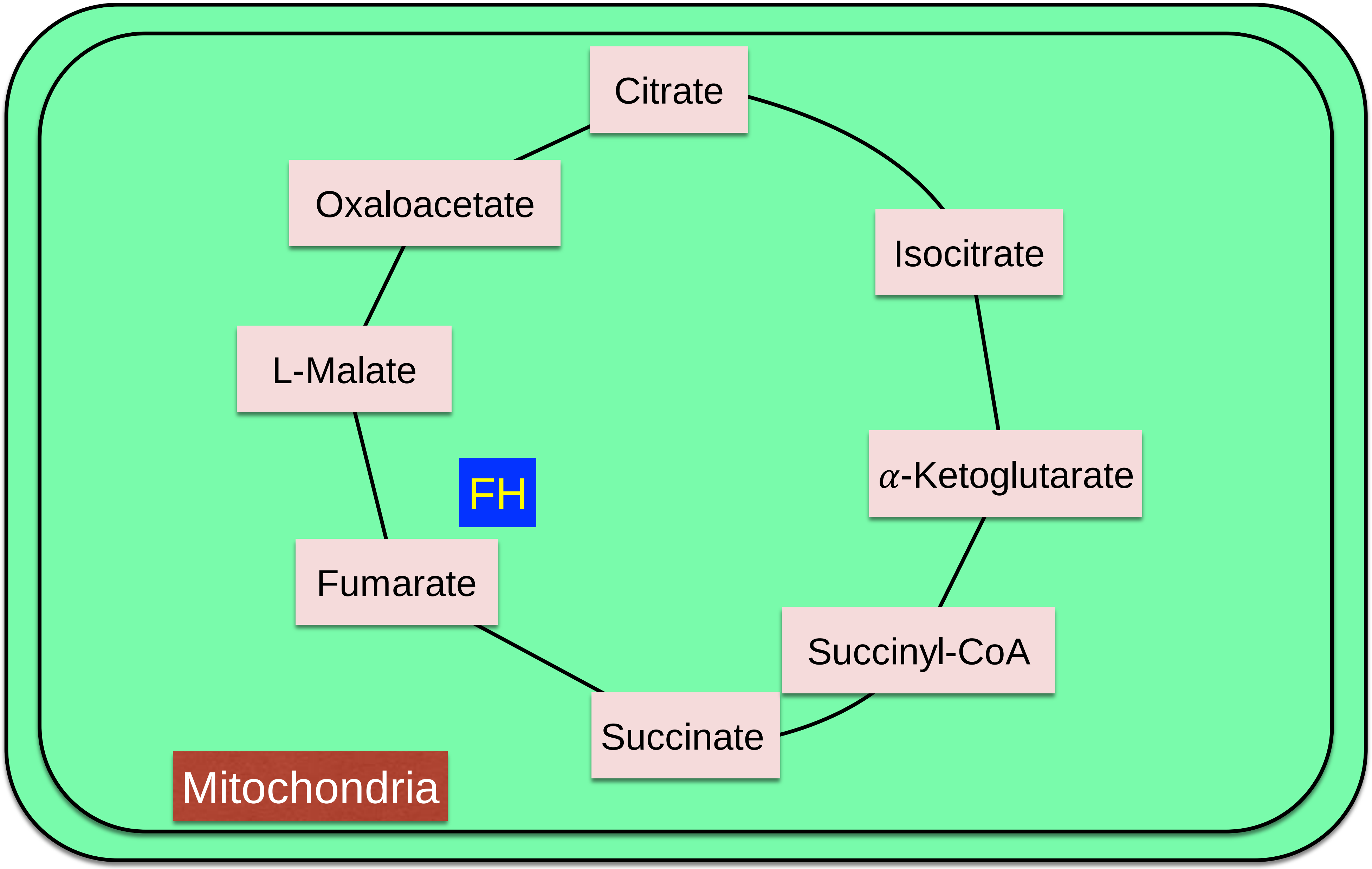
Mutations in SDH are found in familial paraganglioma and pheochromocytoma, renal carcinomas, T-Cell leukaemia, and gastrointestinal stromal tumours

SDH mutants leads to Succinate accumulation

What is the function of succinate in cancer?



Fumarate hydratase



FH converts fumarate to malate

FH mutation

heterozygous FH mutations followed by the loss of heterozygosity of the second allele cause Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC).

FH mutants leads to fumarate accumulation

What is the function of fumarate in cancer?

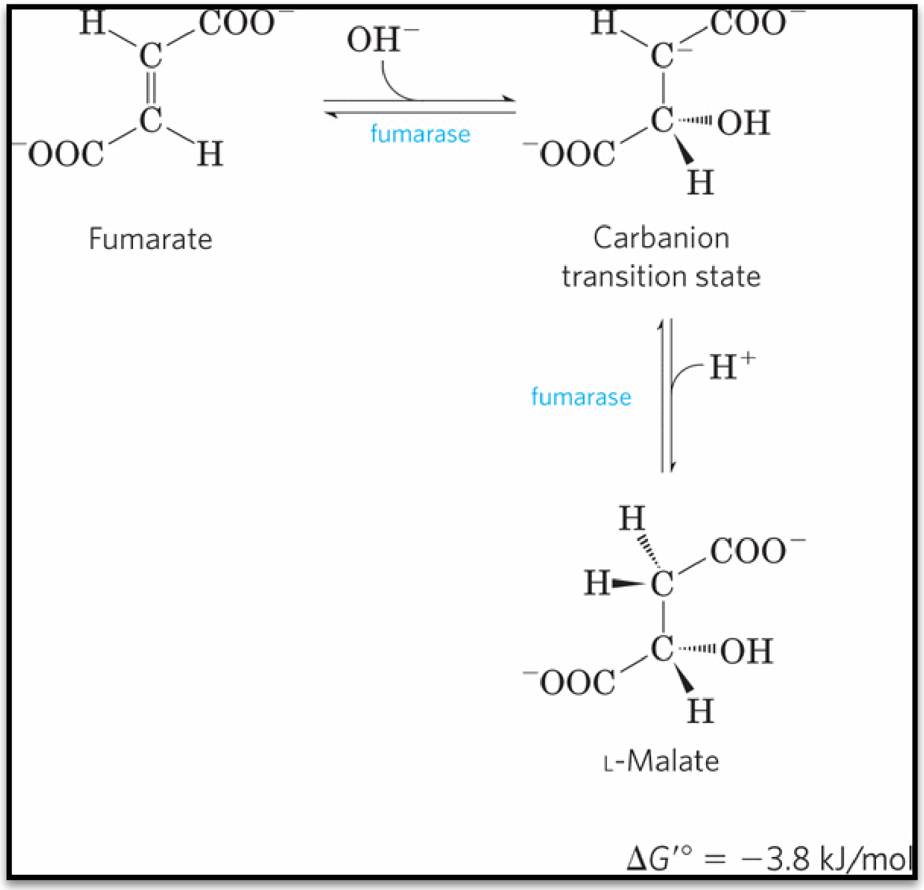
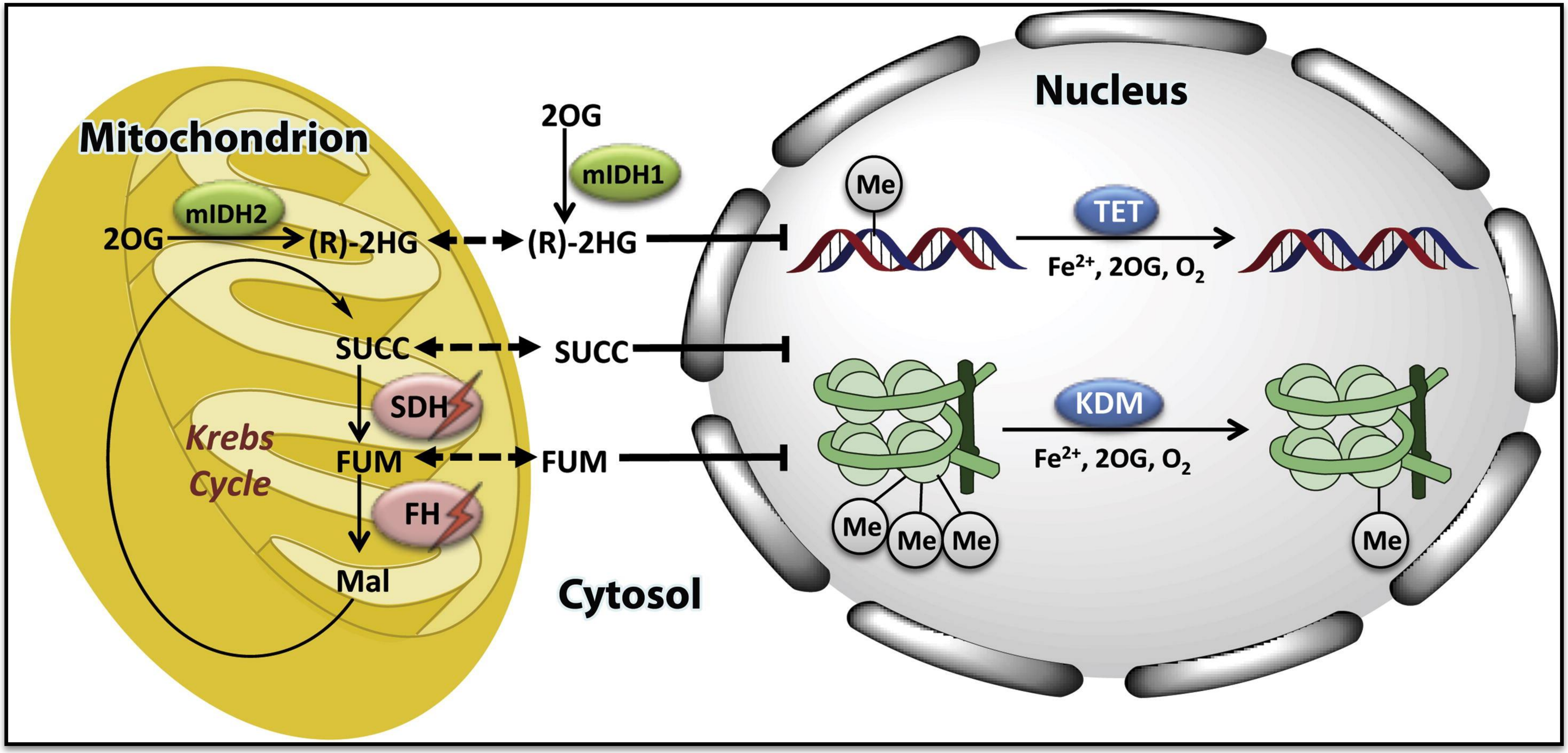


Figure 16 Lehninger

Epigenetic Reprogramming by Oncometabolites

Modification in the function of all three enzymes leads to epigenetic changes



Yang M, Pollard PJ (2013) Succinate: A New Epigenetic Hacker. Cancer Cell 23(6):709–711.

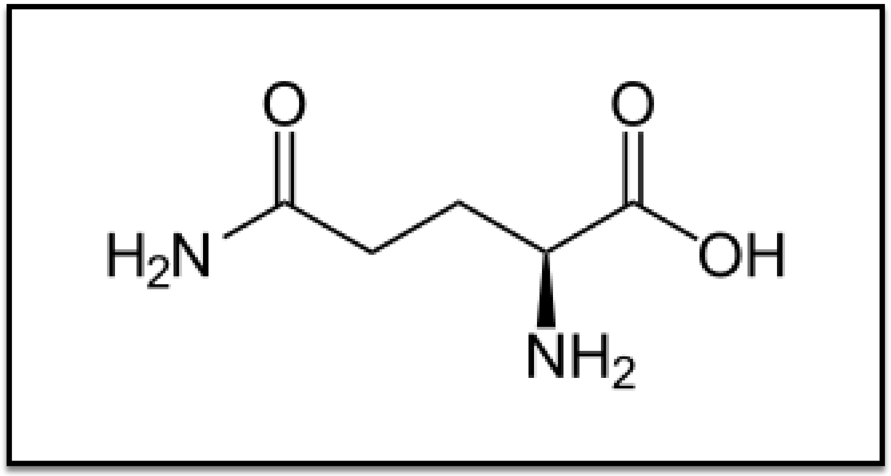
Amino acid and cancer

Glutamine

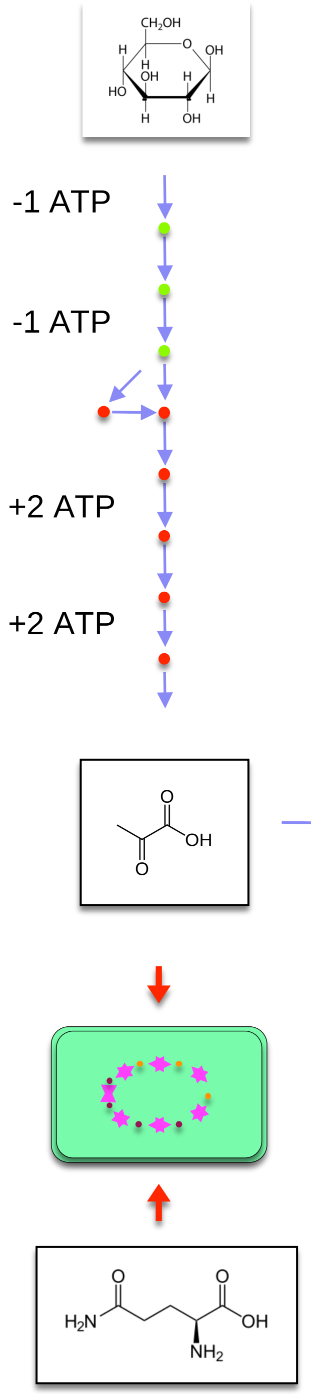
The most abundant amino acid in the plasma

Major carrier of nitrogen between the organs

Proliferating cells use glutamine as the nitrogen donor for biosynthesis of nucleotides, nonessential amino acids, and hexosamines

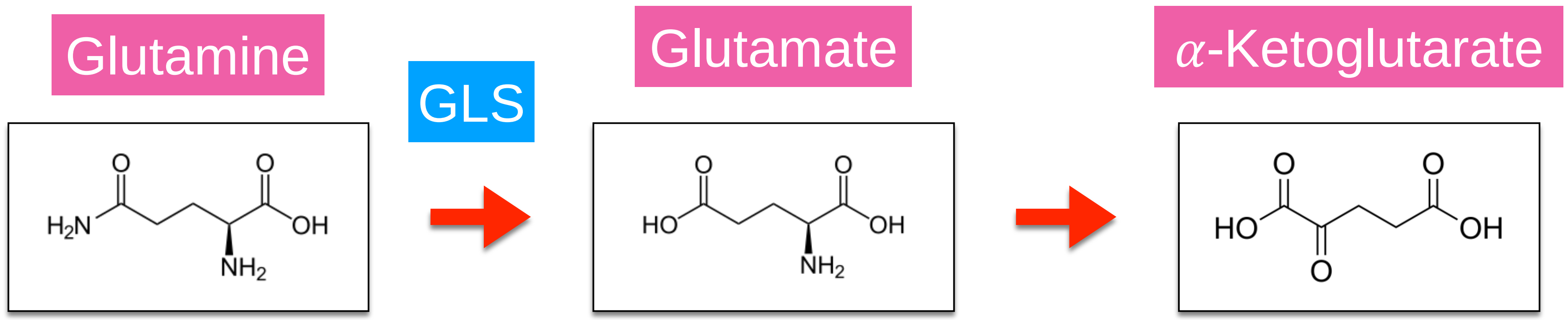


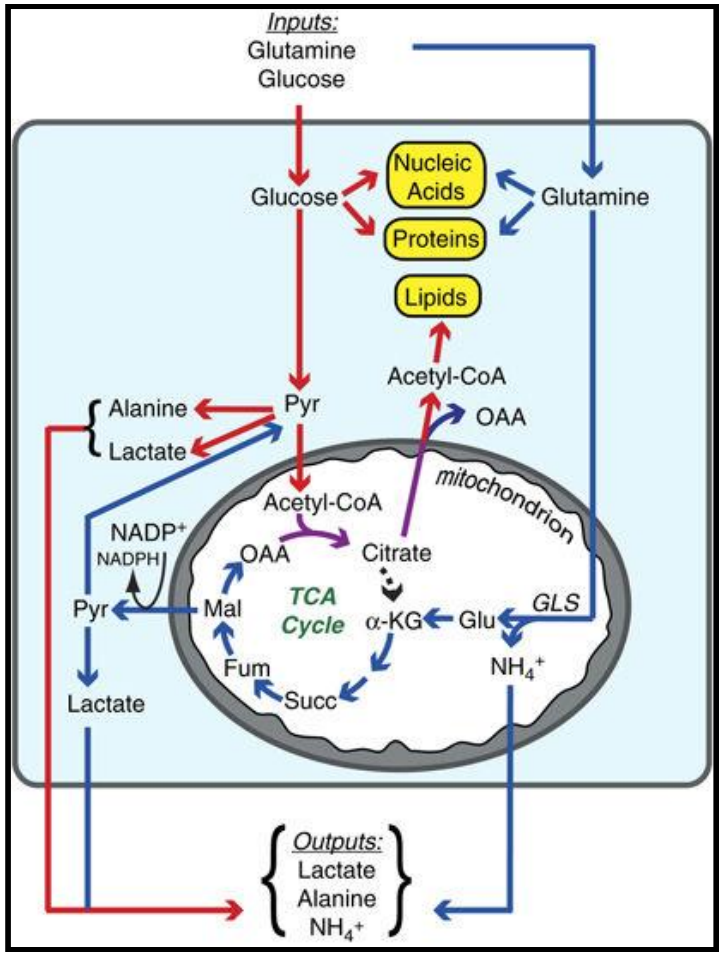
Glutamine can fuel the TCA cycle



Lactate

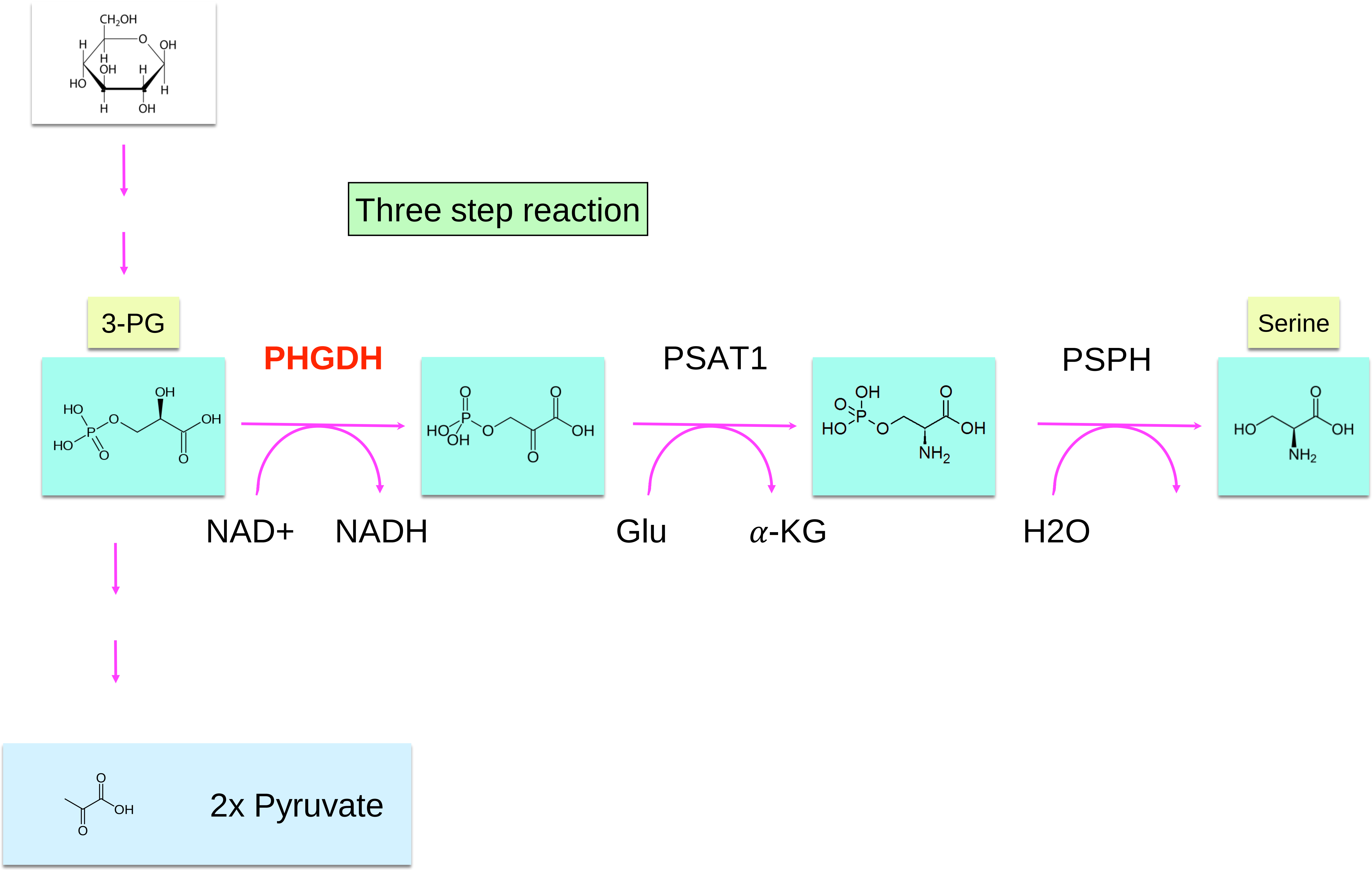
Glutamine





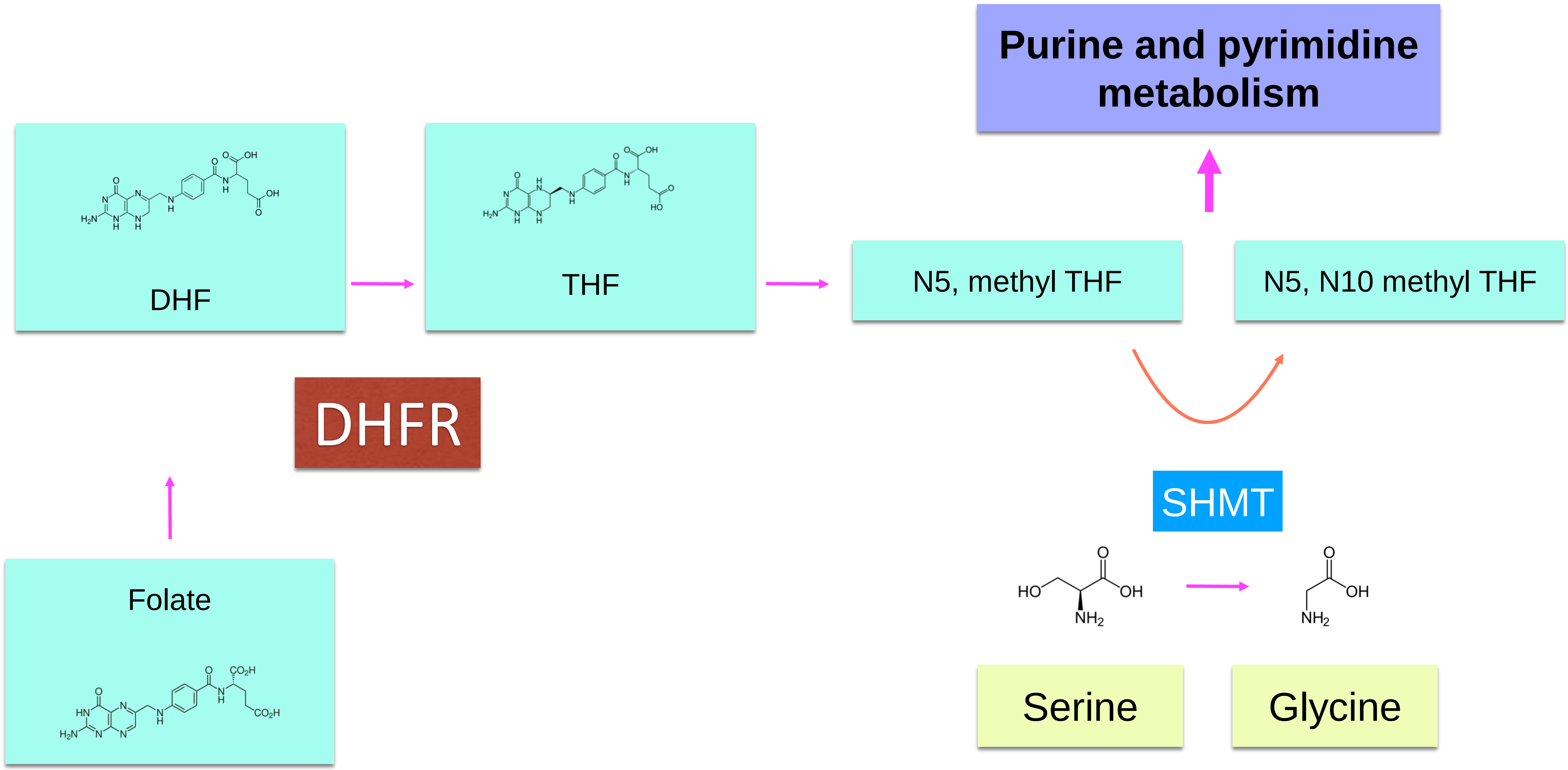
Deberardinis RJ, Cheng T (2009) Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene 29(3):313.

Serine Synthesis Pathway (SSP)



Possemato, R., Marks, K. M., Shaul, Y. D.,et. al. (2011) Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. Nature. 476, 346–350

Serine and one-carbon metabolism



Serine conversion to glycine, transfer of one carbon to N5, methyl-THF

This carbon is essential for nucleotide metabolism

PHGDH amplification in cancer

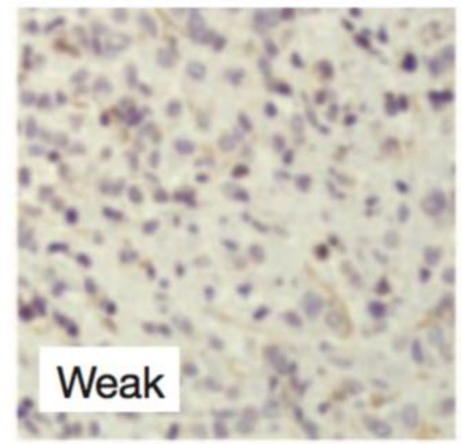
PHGDH expression is associated with aggressive breast cancer markers

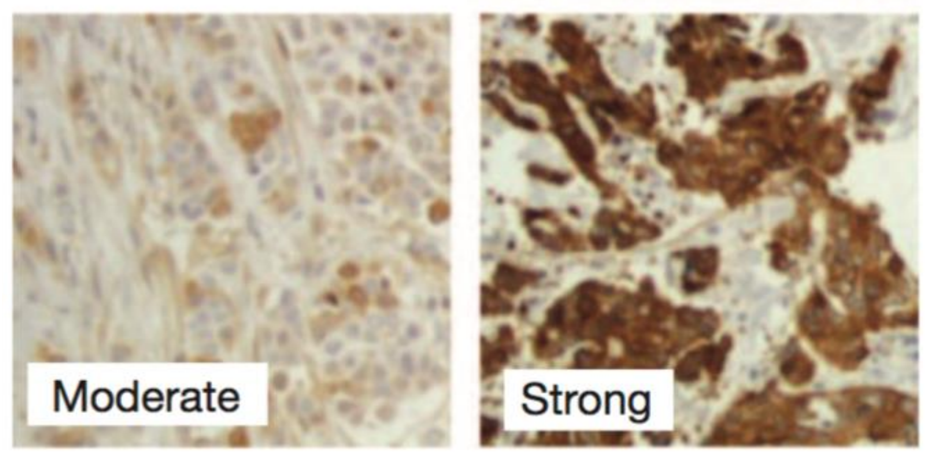
c

Staining intensity

	Weak	Moderate	Strong
ER^-, $Her2^-$	0	4	11
ER^-, $Her2^+$	2	3	12
ER^+, $Her2^-$	13	4	4
ER^+, $Her2^+$	12	11	6

*





Staining of PHGDH in different breast cancer samples

PHGDH is also overexpressed in gliomas

Possemato, R., Marks, K. M., Shaul, Y. D., Pacold, M. E., Kim, D., Birsoy, K., Sethumadhavan, S., Woo, H.-K., Jang, H. G., Jha, A. K., Chen, W. W., Barrett, F. G., Stransky, N., Tsun, Z.-Y., Cowley, G. S., Barretina, J., Kalaany, N. Y., Hsu, P. P., Ottina, K., Chan, A. M., Yuan, B., Garraway, L. A., Root, D. E., Mino-Kenudson, M., Brachtel, E. F., Driggers, E. M., and Sabatini, D. M. (2011) Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. Nature. 476, 346–350

Metabolic enzymes as drug targets

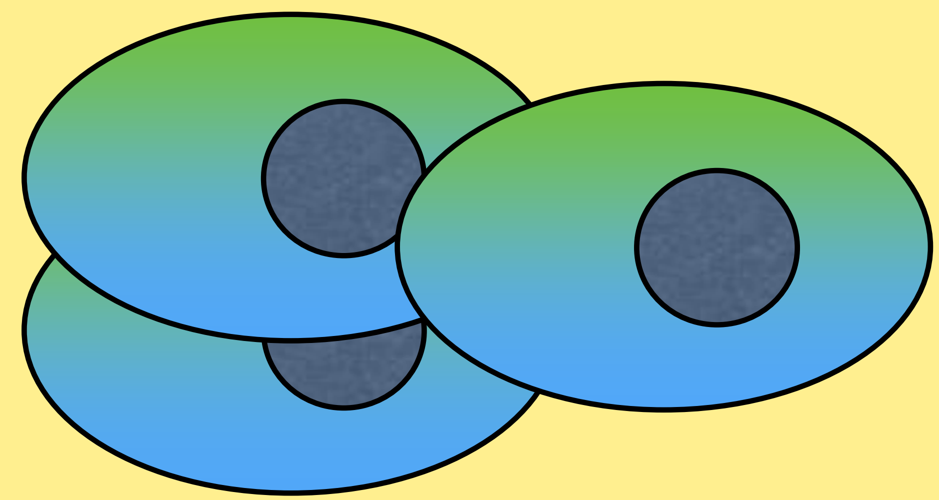
All improve overall survival

However, many of these drugs also target normal proliferating cells

Antimetabolites

5-fluorouracil
Methotrexate
Hydroxyurea

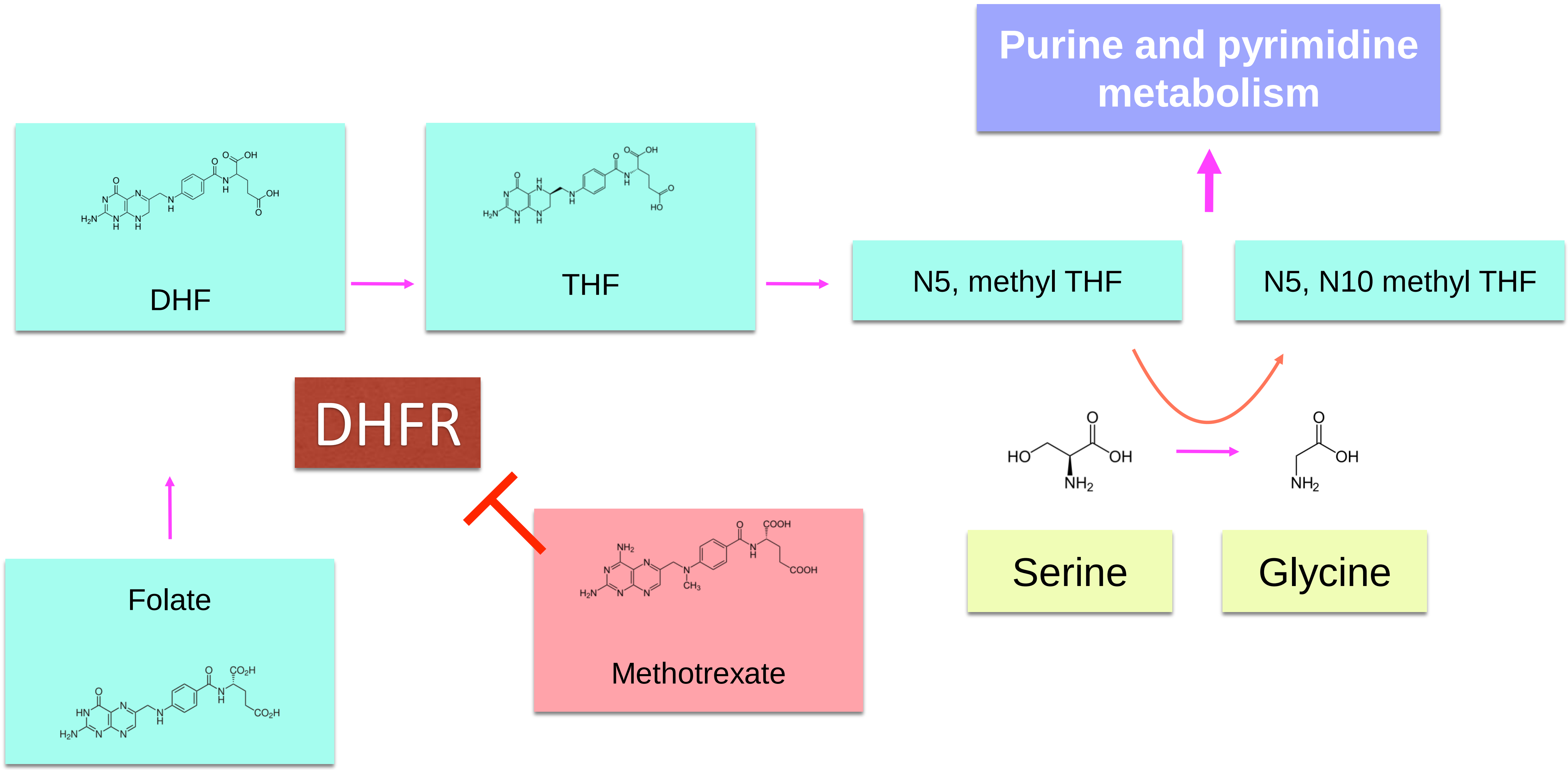
Proliferating cells



Building blocks

Support rapid growth

Methotrexate

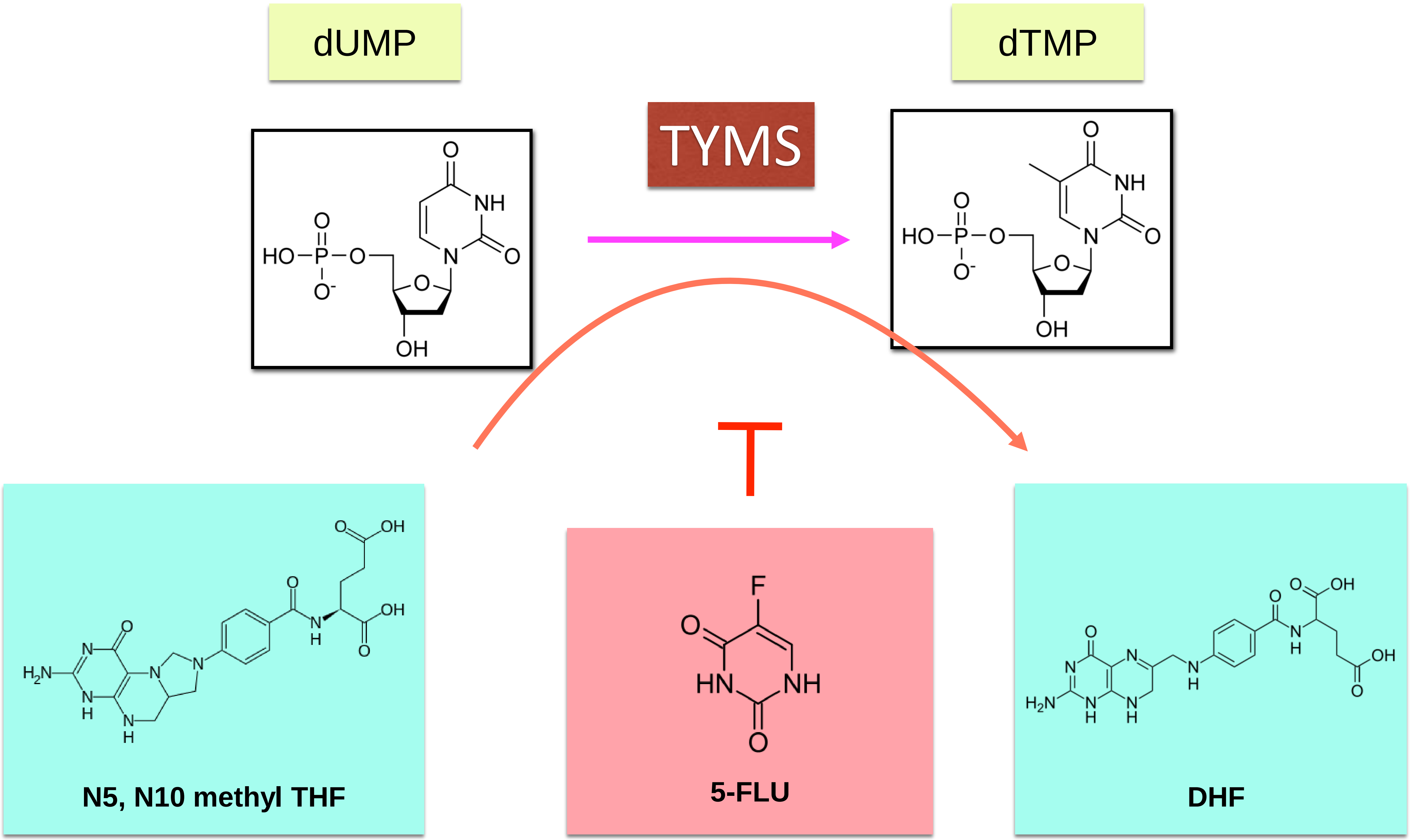


Serine conversion to glycine, transfer of one carbon to N5, methyl-THF

This carbon is essential for nucleotide metabolism

Methotrexate inhibits the ability of cells to synthesise nucleotides

5-fluorouracil



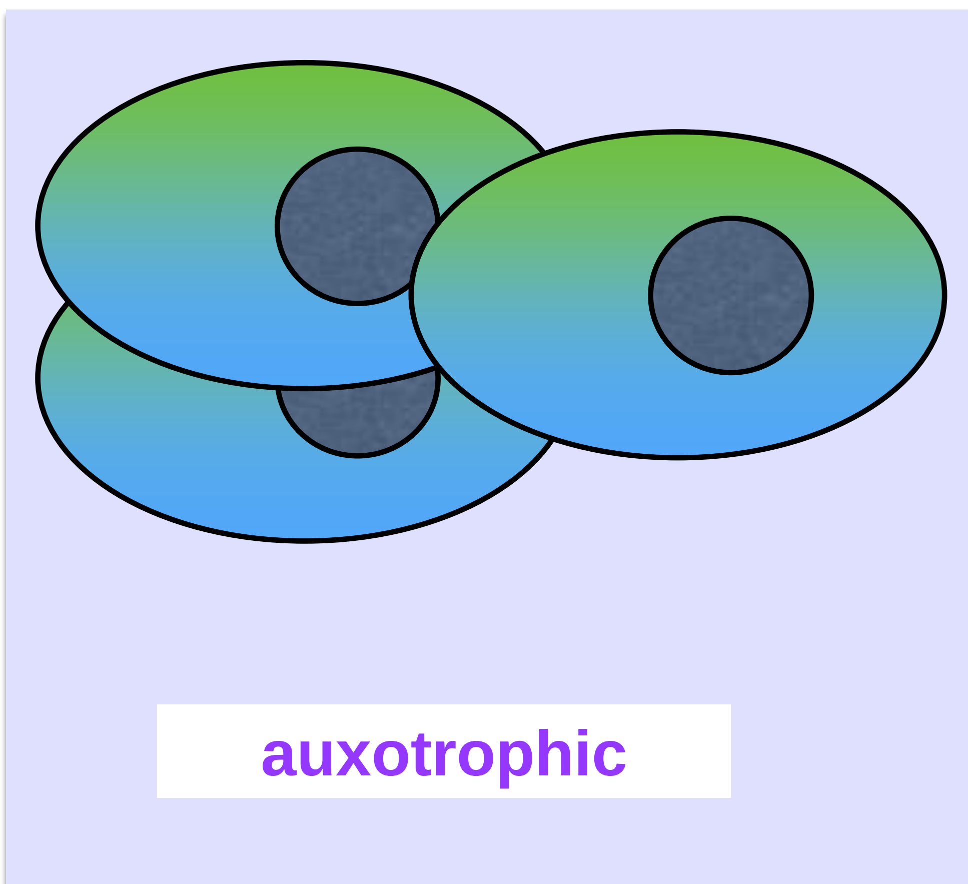
- 5-FLU inhibits TYMS, an important enzyme in pyrimidine synthesis

Metabolic liabilities

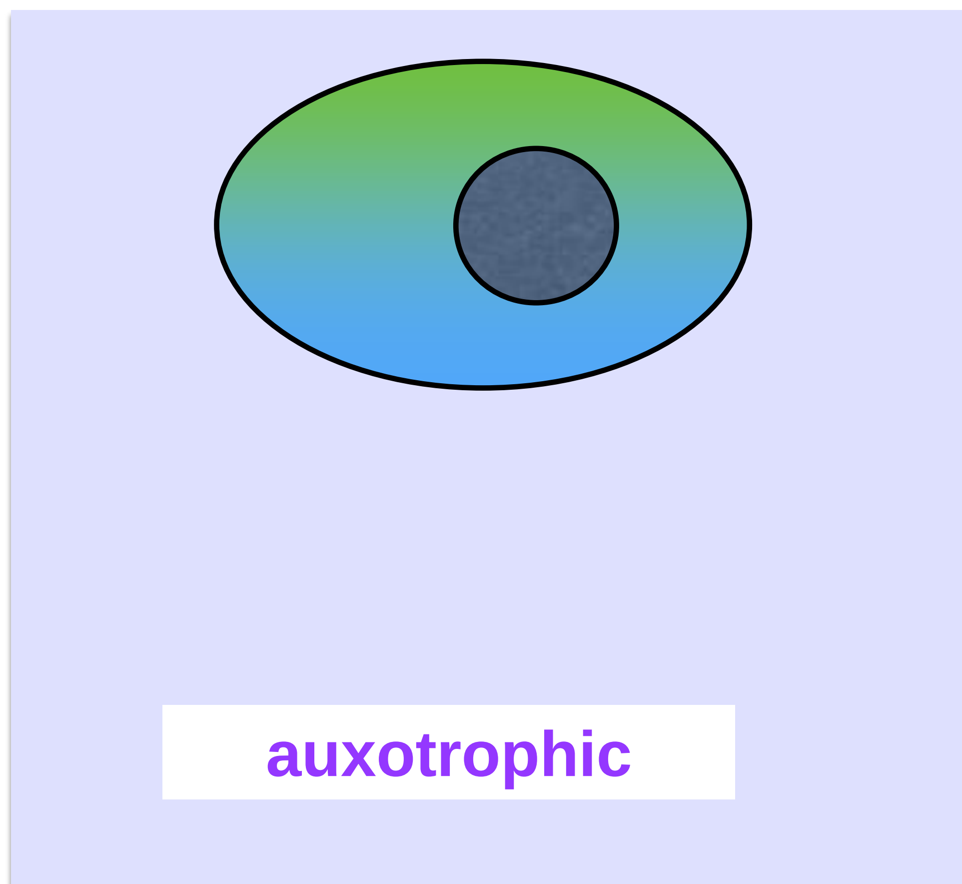
Several tumor types are auxotrophic for 1 or more amino acids owing to deficiencies in a corresponding endogenous biosynthesis or salvage pathway.

Thus,

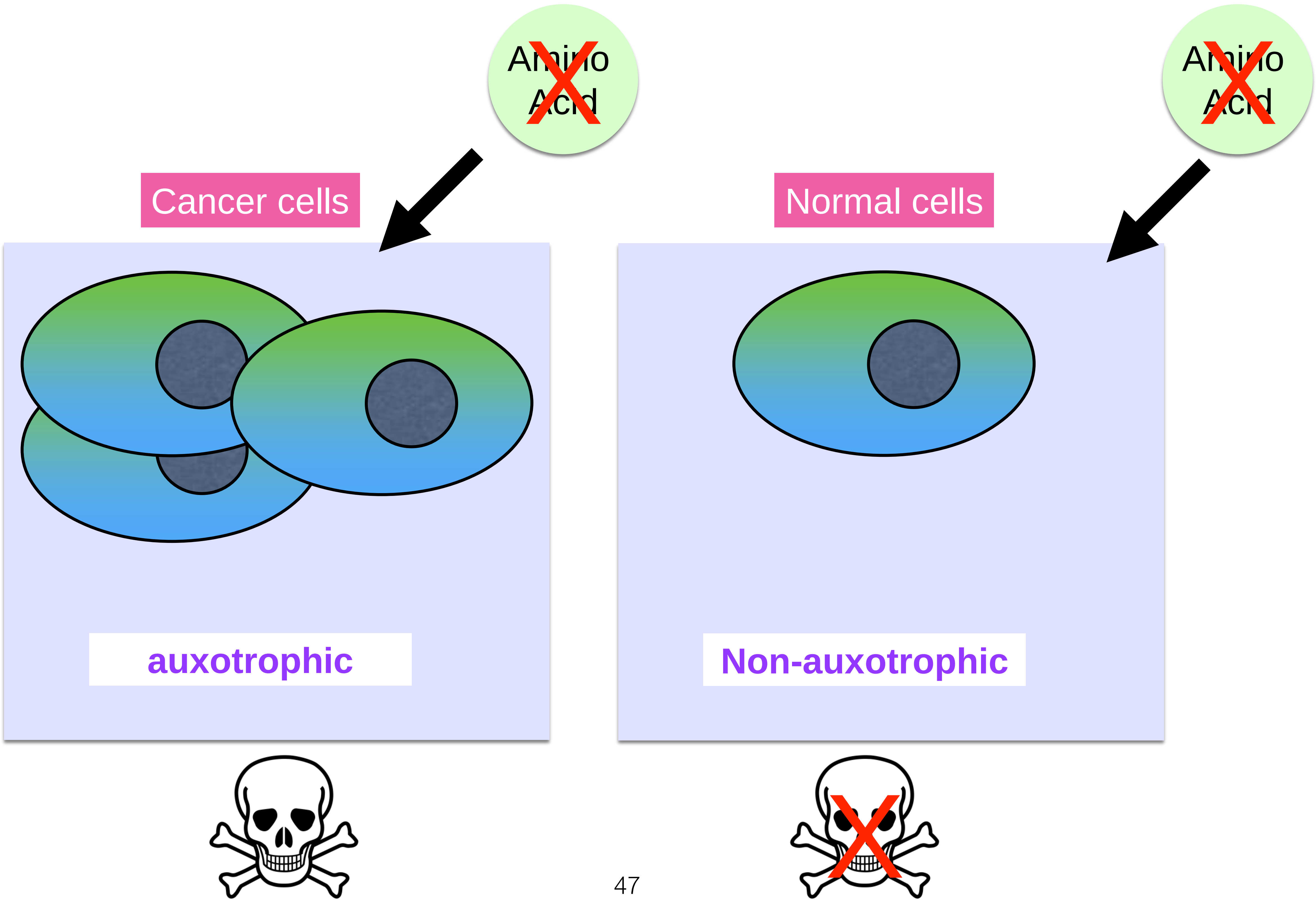
Cancer cells



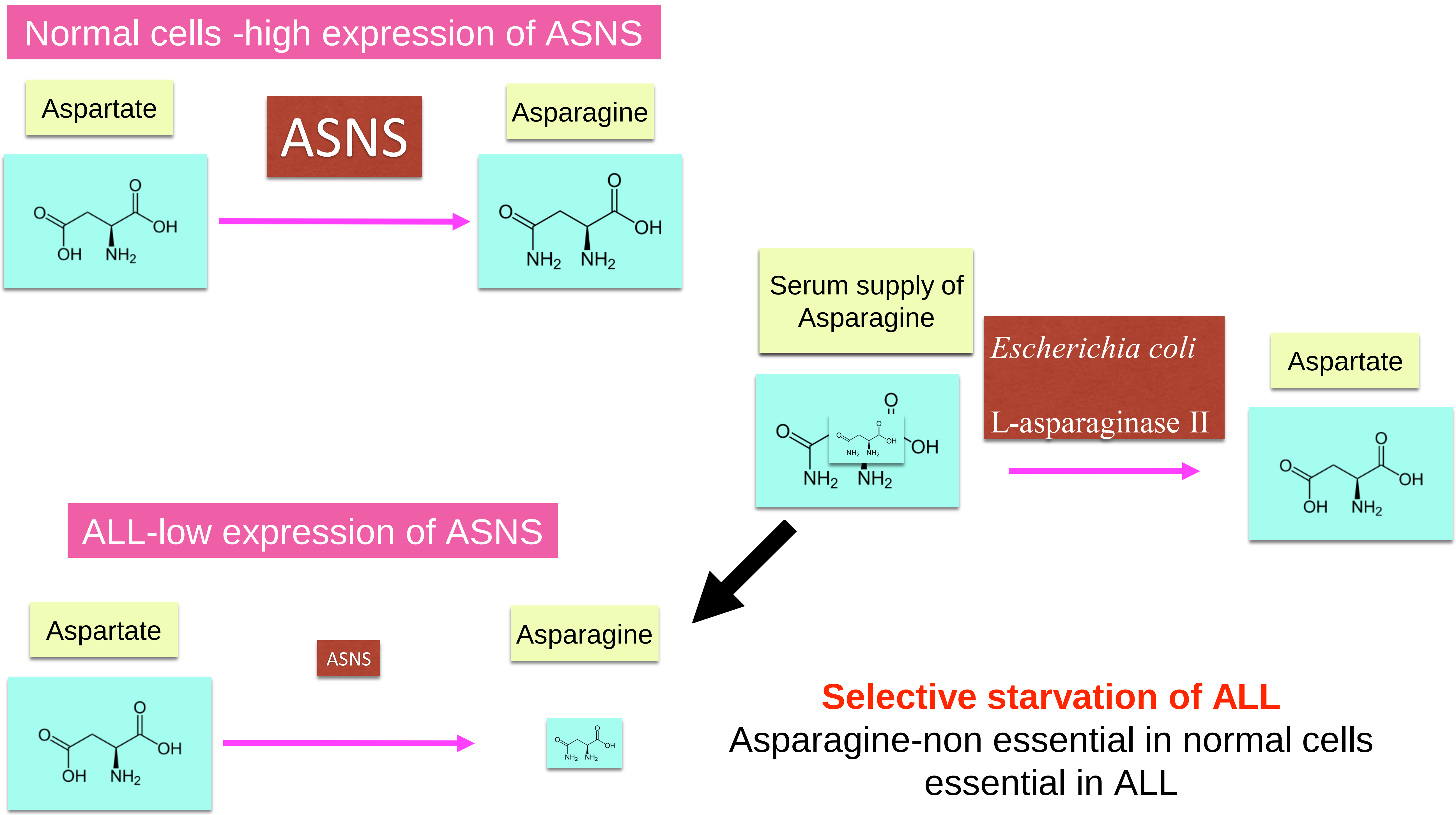
Normal cells



Metabolic liabilities



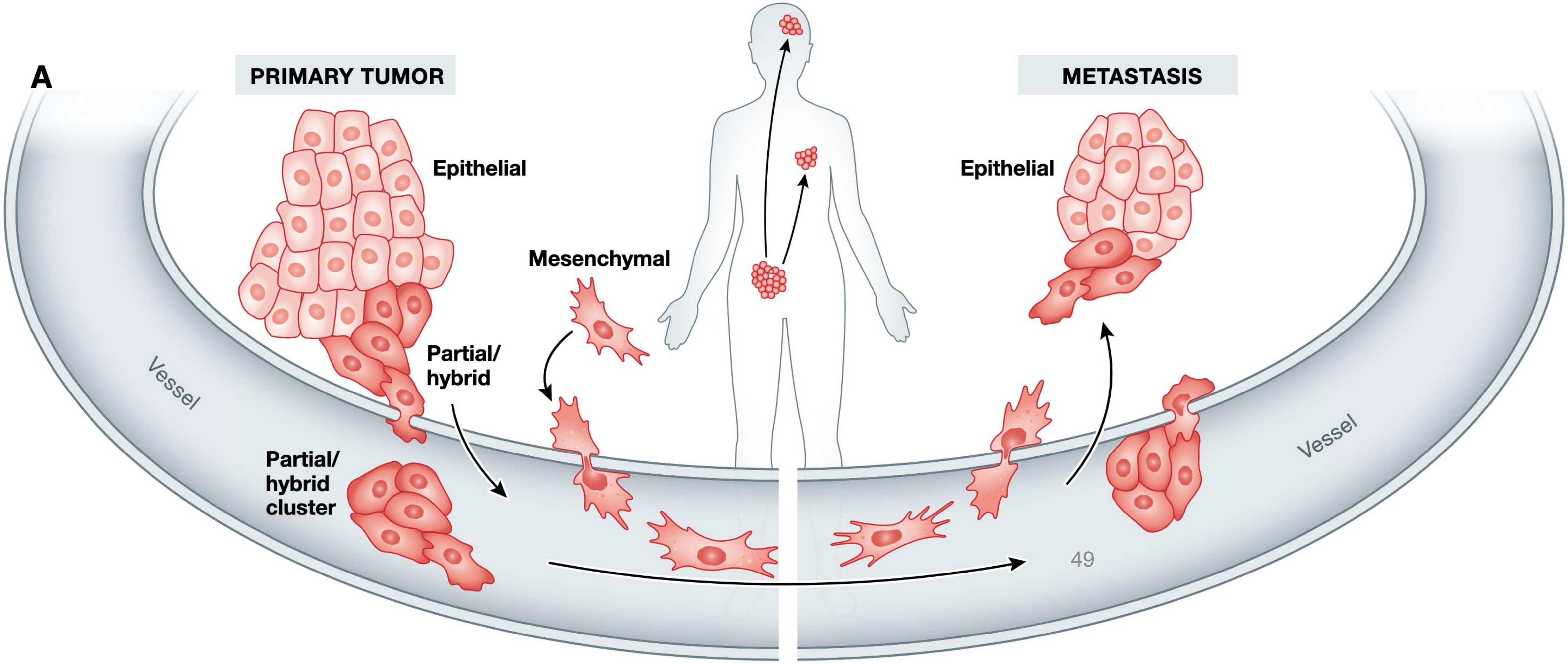
L-asparaginase in the treatment of acute lymphoblastic leukemia (ALL)



Selective starvation of ALL

Asparagine-non essential in normal cells essential in ALL

Metastatic Cascade

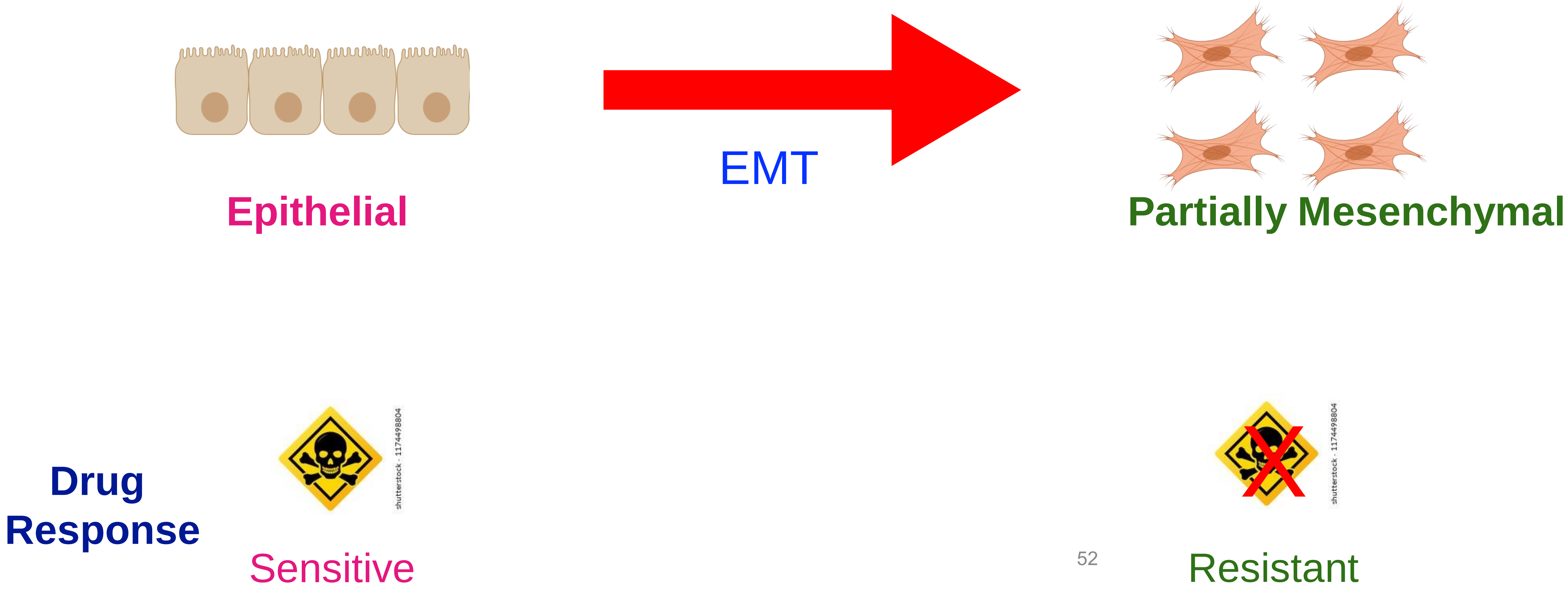


1. S. Brabletz, H. Schuhwerk, T. Brabletz, M. P. Stemmler, Dynamic EMT: a multi-tool for tumor progression. *Embo J*, e108647 (2021).

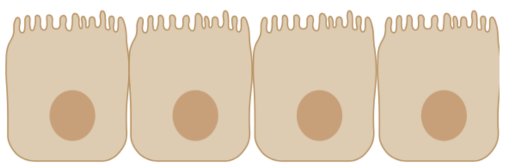
What makes the cell leave the tumor?

In order to execute the journey the cells needs to change

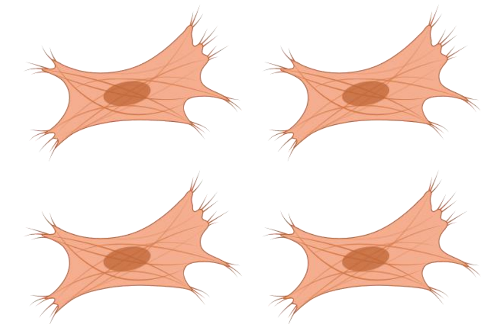
Epithelial-Mesenchymal Transition (EMT)



Epithelial-Mesenchymal Transition (EMT)



EMT



Epithelial

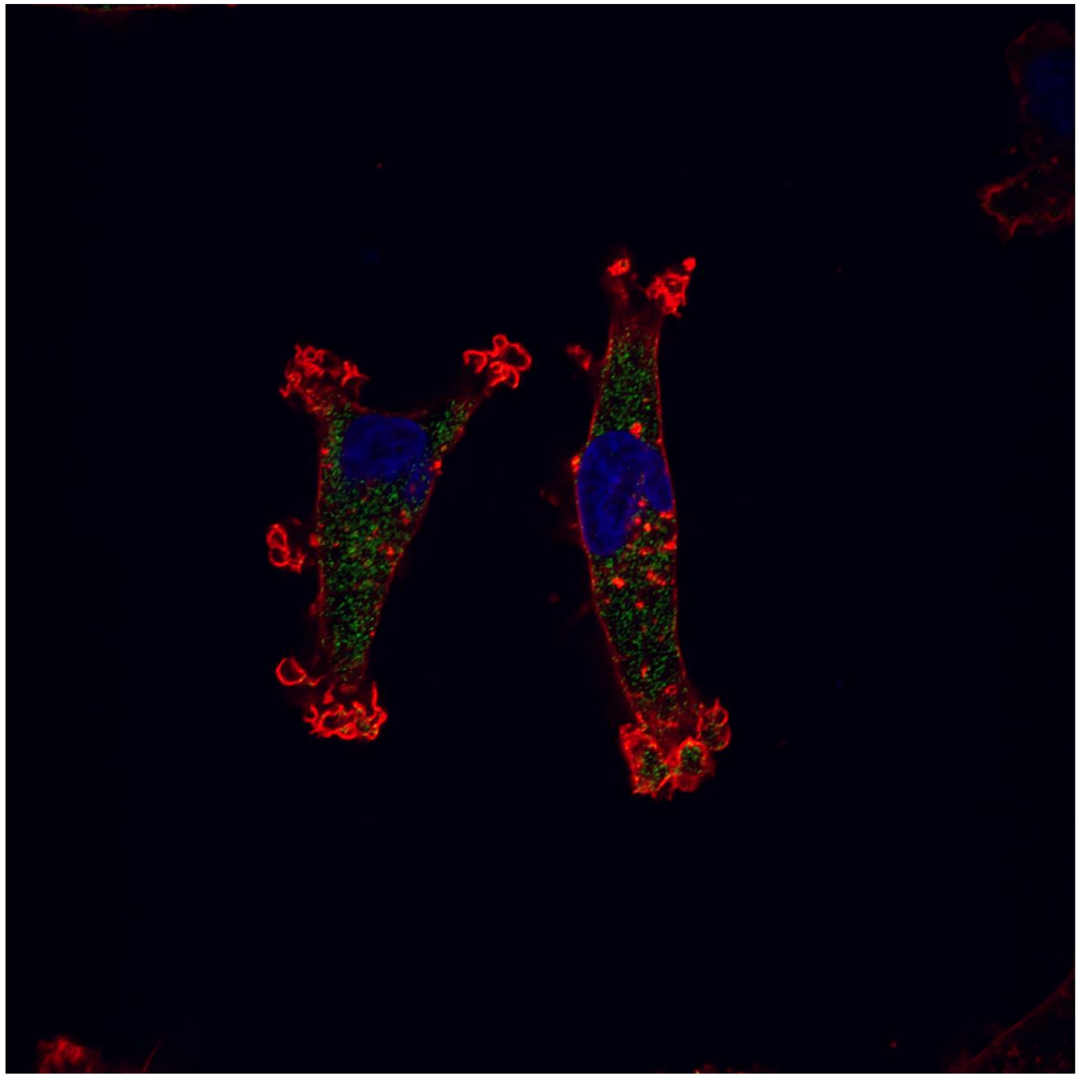
Partially Mesenchymal

Cell Migration

Slow

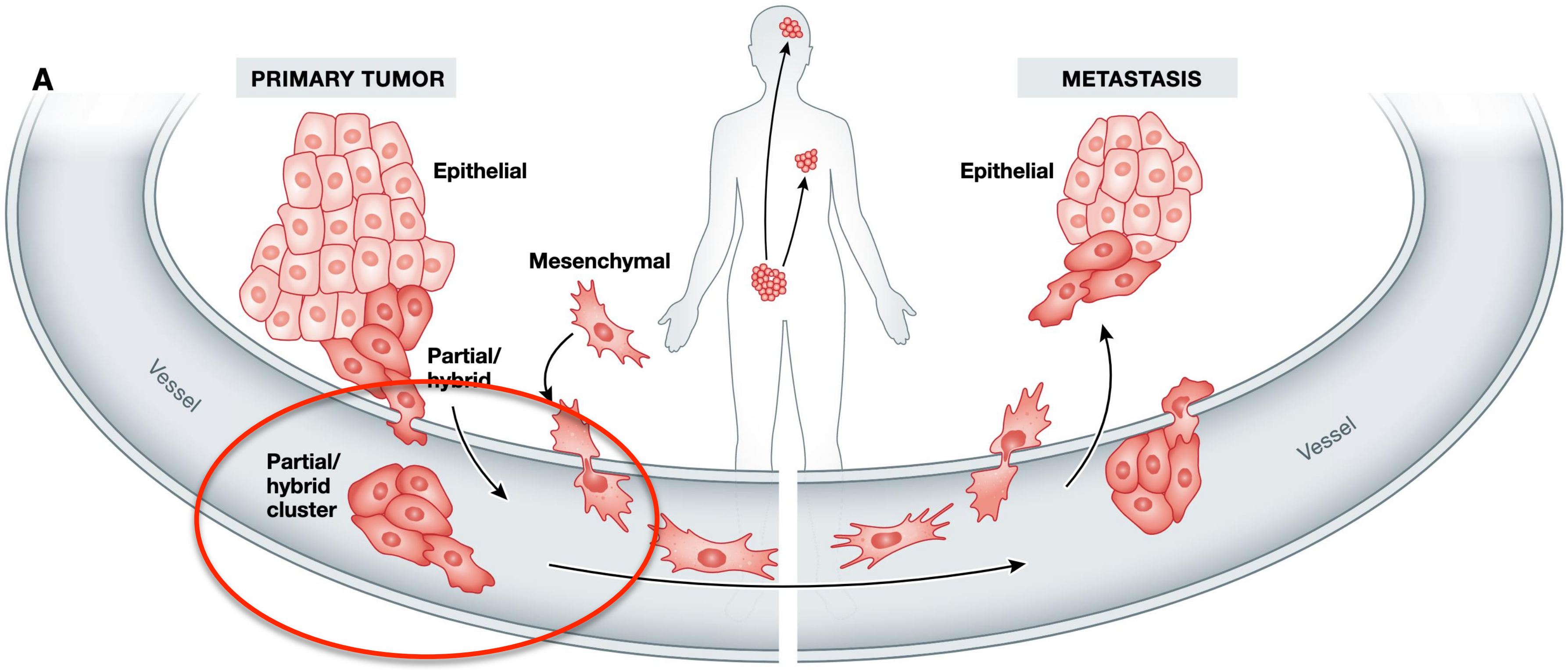
Fast

The migrating cells contains “hands” that help them migrate



A picture taken in our lab

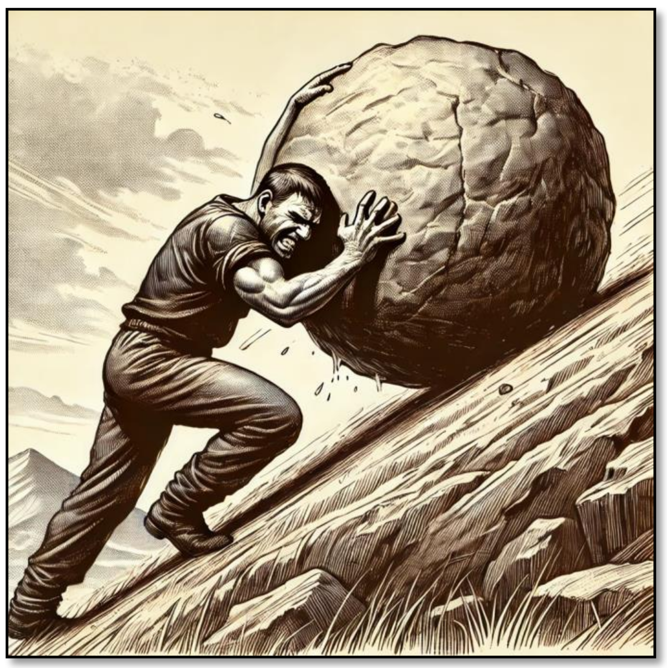
Metastatic Cascade

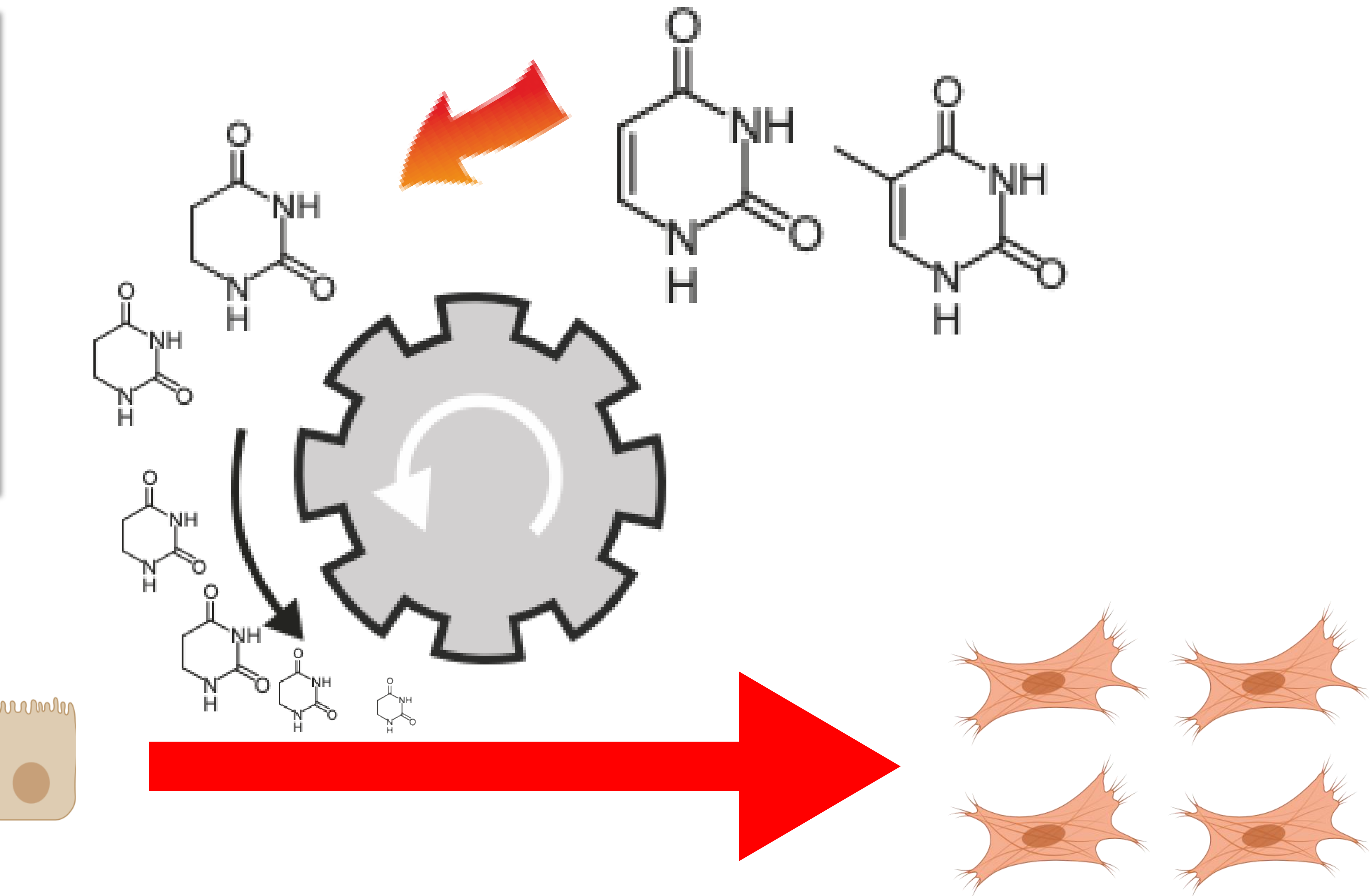


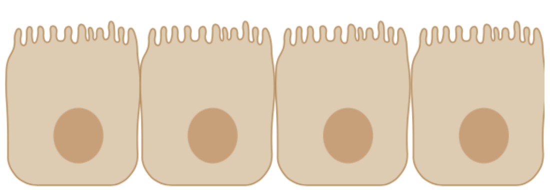
Currently, as far as we know, there are no available anti-EMT drugs.

1. S. Brabletz, H. Schuhwerk, T. Brabletz, M. P. Stemmler, Dynamic EMT: a multi-tool for tumor progression. *Embo J*, e108647 (2021).

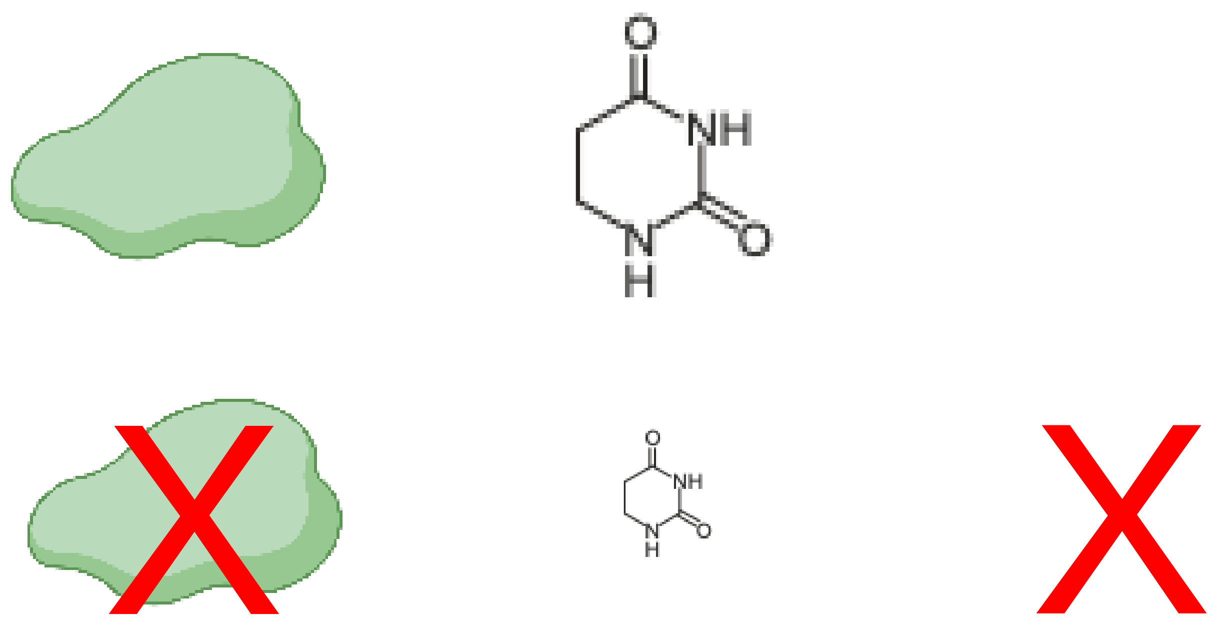
My lab interest is to identify metabolic processes that push cancer cells to become aggressive





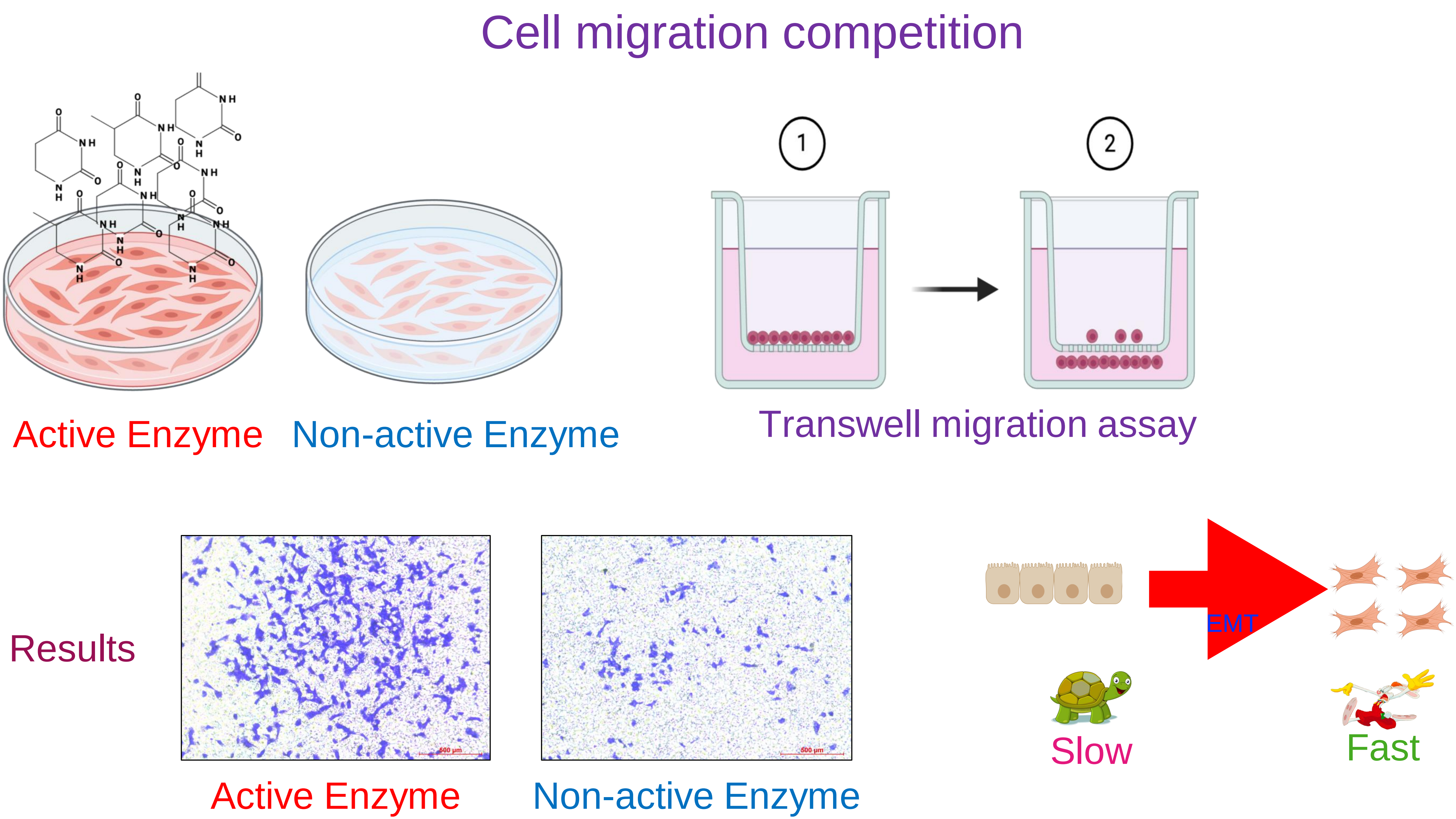


How do we study?



Active Enzyme

Non-active Enzyme


Cell migration competition
1
2
Active Enzyme
Non-active Enzyme
Transwell migration assay
Results
Active Enzyme
Non-active Enzyme
EMT
Slow
Fast

Email: yoavsh@ekmd.huji.ac.il

My Team