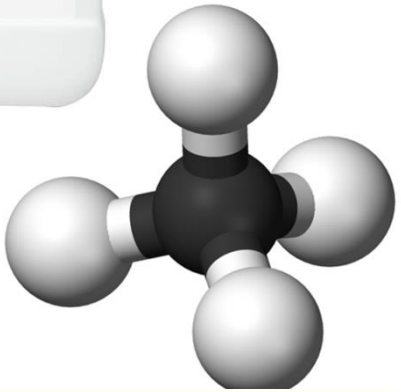
Deutenomics: A Revolution Unfolding in Biology and Medicine

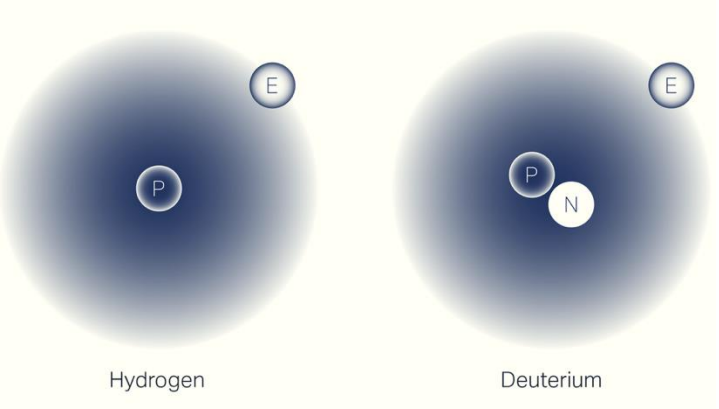
Stephanie Seneff

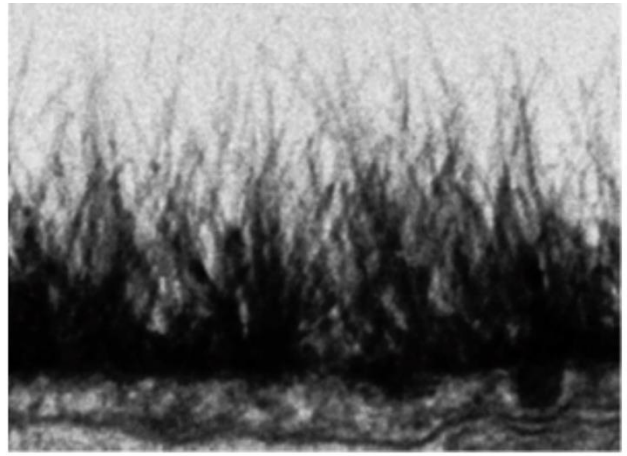
MIT CSAIL

Real Truth About Health Conference

Tuesday, April 9, 2024








Bilicki ©2008 Bilicki.US
RESEARCH CONCLUDES:
WE ARE DESTROYING EARTH.
COULD YOU KINDLY REPHRASE THAT IN EQUIVOCAL, INACCURATE, VAGUE, SELF-SERVING AND ROUNDABOUT TERMS THAT WE CAN ALL UNDERSTAND?
FACTS
GOVERNMENT
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Outline

- Introduction
- Gut Microbes Supply Deuterium-depleted Nutrients to the Host
- Glyphosate Suppresses Dehydrogenases
- Disrupted Glycolysis Leads to Fatty Liver Disease and Hyperlipidemia
- Methionine Deficiency and Methylation Pathways
- Glyphosate Damages Mitochondria
- Collagen, Proline and Deuterium
- Healthy Lifestyle
- Summary

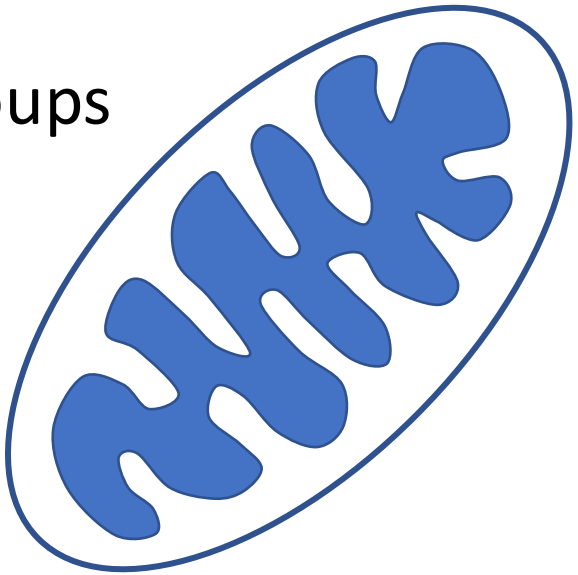
Introduction

A Personal Time Line

- 2007-2012 – Autism
  - Autism is a complex developmental disorder associated with gut dysbiosis and defective methylation and sulfation pathways. Autism rates are alarmingly on the rise in the United States over the past two decades.
- 2012-2019 – Glyphosate
  - Glyphosate is a pervasive herbicide in our food supply. Autism rates in the US have risen exactly in step with glyphosate usage on core crops. Glyphosate disrupts the gut microbiome and methylation and sulfation pathways.
- 2020-2023 – Deuterium
  - Deuterium is a natural heavy isotope of hydrogen. Deuterium is highly damaging to the mitochondria, which produce ATP as an energy source for the cell. Organisms have developed sophisticated strategies to keep deuterium levels low in the mitochondria. These strategies depend critically on gut microbes and sulfation and methylation pathways.

The Big Picture

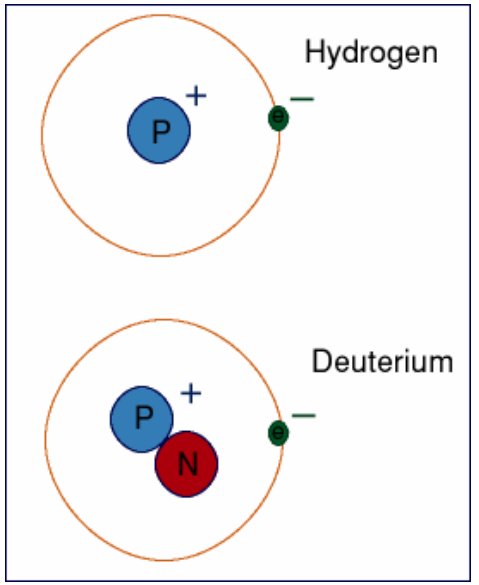
- Deuterium is a natural heavy isotope of hydrogen
  - It is present in the blood at 5x the concentration of calcium
- Deuterium breaks the ATPase pumps in the mitochondria, causing energy loss and generating reactive oxygen species (ROS)
- Nicotinamide Adenine Dinucleotide (NAD) is a major carrier of deuterium-depleted (“deupleted”) hydrogen (as NADH)
- Methylation pathways preserve low-deuterium methyl groups
- *Glyphosate suppresses many proteins involved in deuterium homeostasis*



Deuterium = “Heavy” Hydrogen

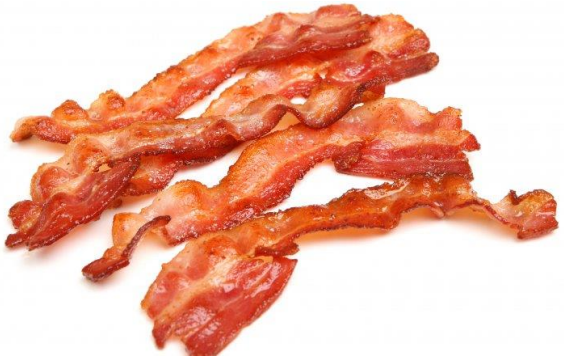
- Hydrogen has one proton and one electron
- Deuterium has one proton, one electron and one neutron
  - ~ Twice as heavy as hydrogen
  - Present in ocean water at 155.8 ppm
  - Has distinct physical and chemical properties compared to hydrogen
  - Fats are low in deuterium compared to other foods

Deuterium management in the body involves trapping deuterium in collagen matrices and invoking specialized enzymes that choose hydrogen over deuterium for their reaction in order to fuel the mitochondria with hydrogen rather than deuterium



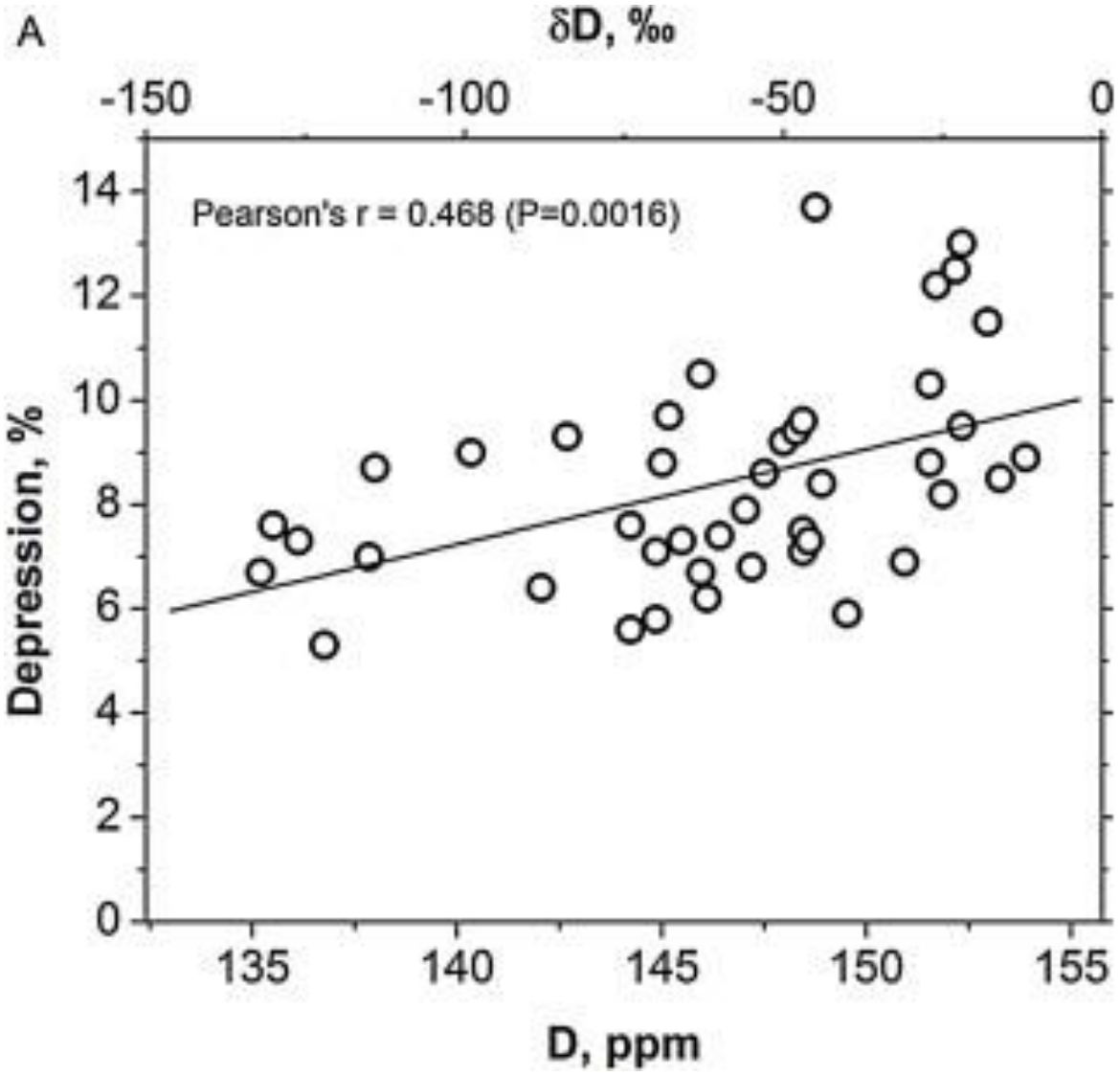
Ketogenic Diet and DDW: Health Benefits*

- *Deuterium depleted water* (DDW) is essential for mitochondria to function properly
- People whose water supply is naturally depleted in deuterium are healthier
- Deuterium depletion maintains strong hydrogen bond networks in DNA (keeps it stable)
- DDW inhibits tumor progression
- A ketogenic diet is a deupleted diet



*Laszlo G Boros et al. Medical Hypotheses 2016; 87: 69-74.

Deuterium in Water and Depression*



B

Prevalence of Depression

C

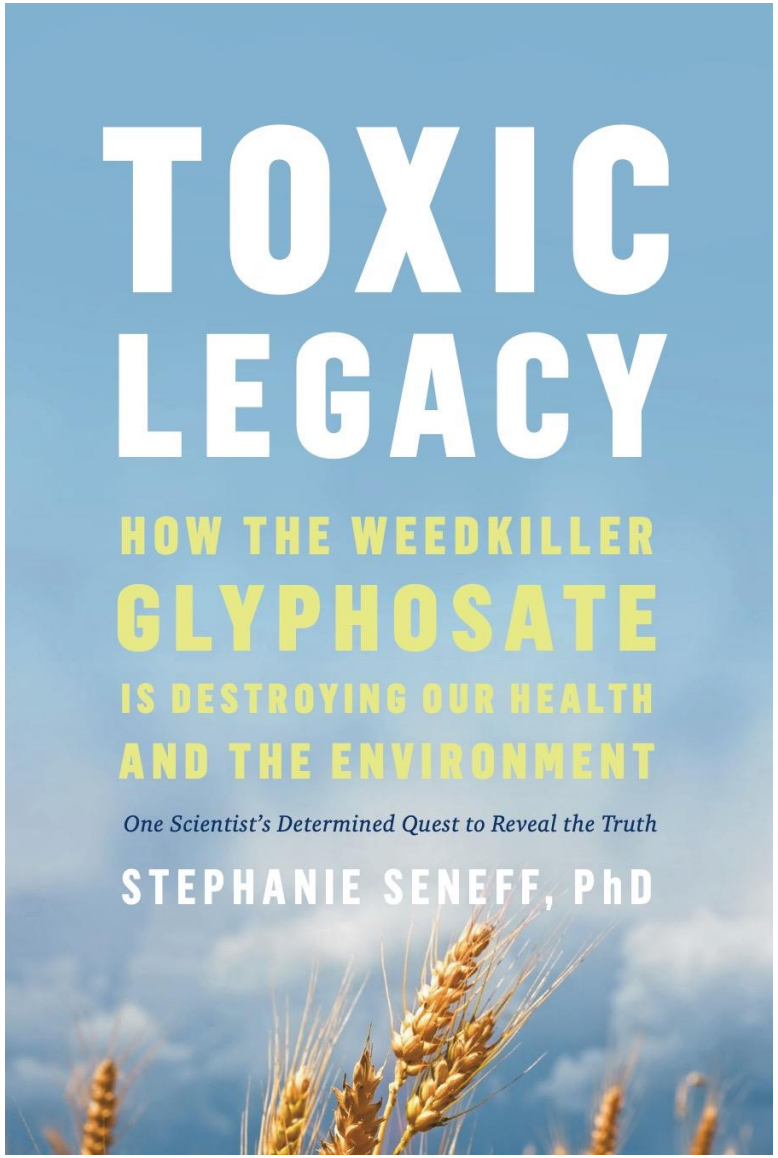
Deuterium levels in tap water

*Tatyana Strekalova et al. Behavioural Brain Research 277 (2015) 237–244.

My Book on Glyphosate

- Released by Chelsea Green in July 2021
- Presents extensive data on glyphosate toxicity to animals and humans
- Shows how glyphosate interferes with sulfate homeostasis
- Argues that glyphosate is insidiously, cumulatively toxic through its diabolical insertion into proteins by mistake in place of the coding amino acid glycine
  - This unique feature explains why it is causal in so many diseases

This book was selected by Kirkus Reviews as one of the top 100 non-fiction books of 2021



Contents lists available at ScienceDirect

Neurotoxicology 2019; 75:1-8.

journal homepage: www.elsevier.com/locate/neuro

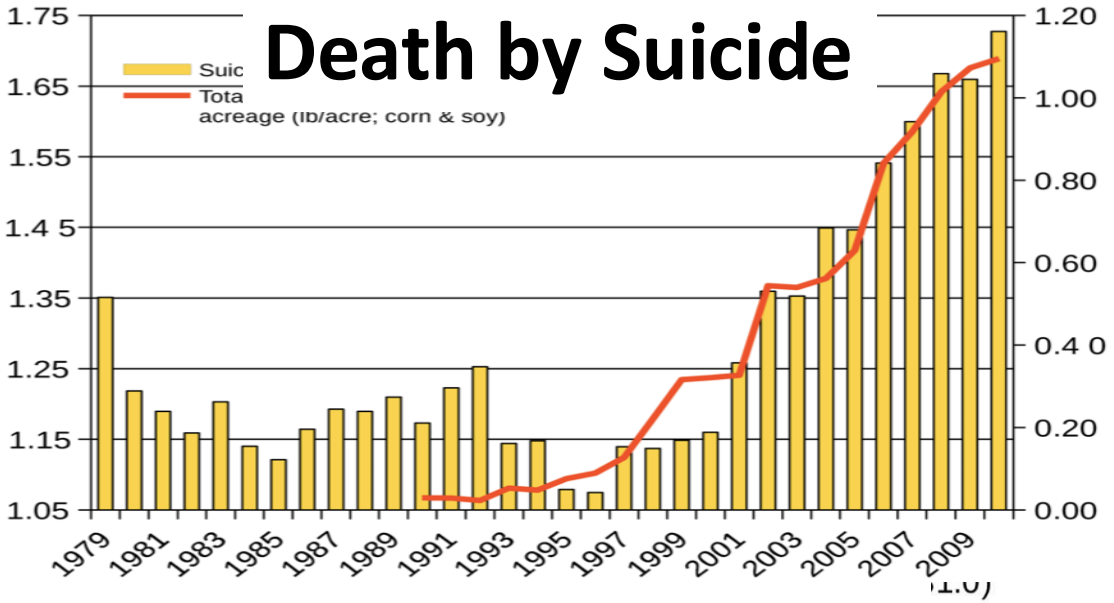
Full Length Article

Gut microbiota and neurological effects of glyphosate

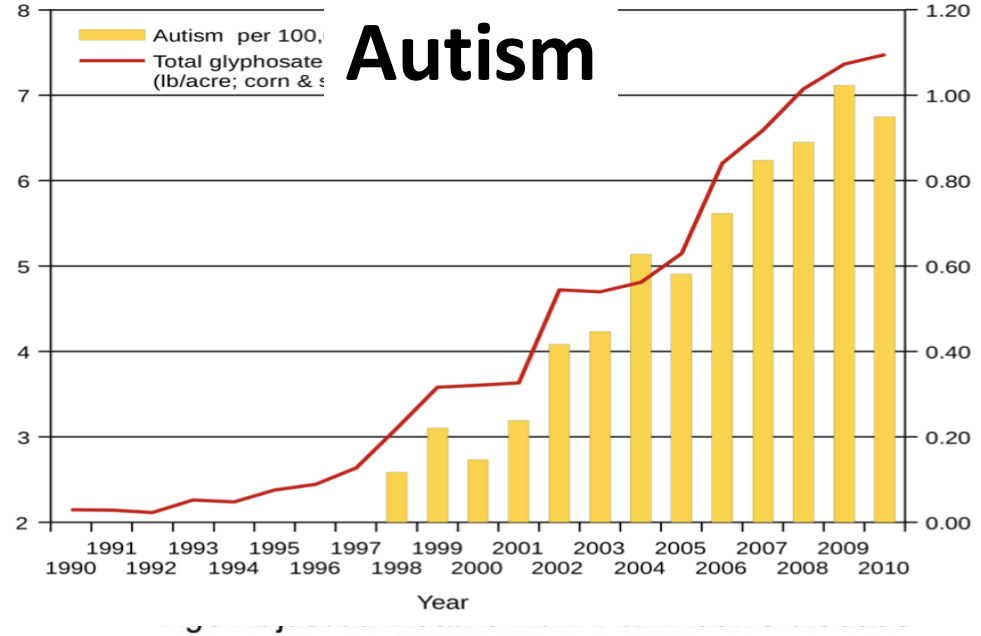
Lola Rueda-Ruzafa[a], Francisco Cruz[b], Pablo Roman[c,d,e,*], Diana Cardona[c,e,f]

"In this work, we state a possible link between Gly[phosate]-induced *dysbiosis* and cognitive and motor aggravations in neurodegenerative and neurodevelopmental pathologies, such as autism spectrum disorder (ASD). Hence, we review the negative impact that Gly-induced dysbiosis may have on *depression/anxiety, autism, Alzheimer's and Parkinson's diseases*."

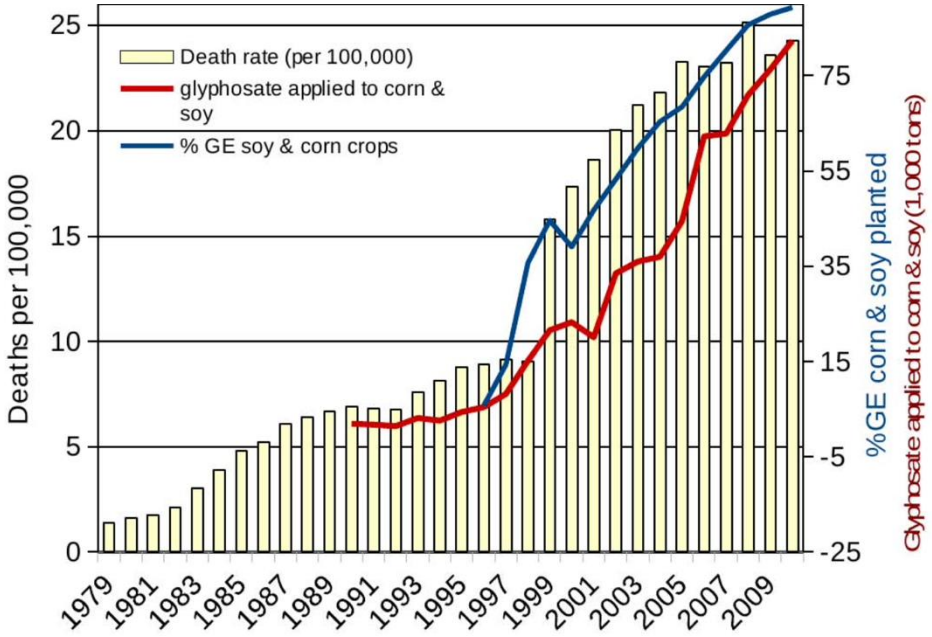
Death by Suicide



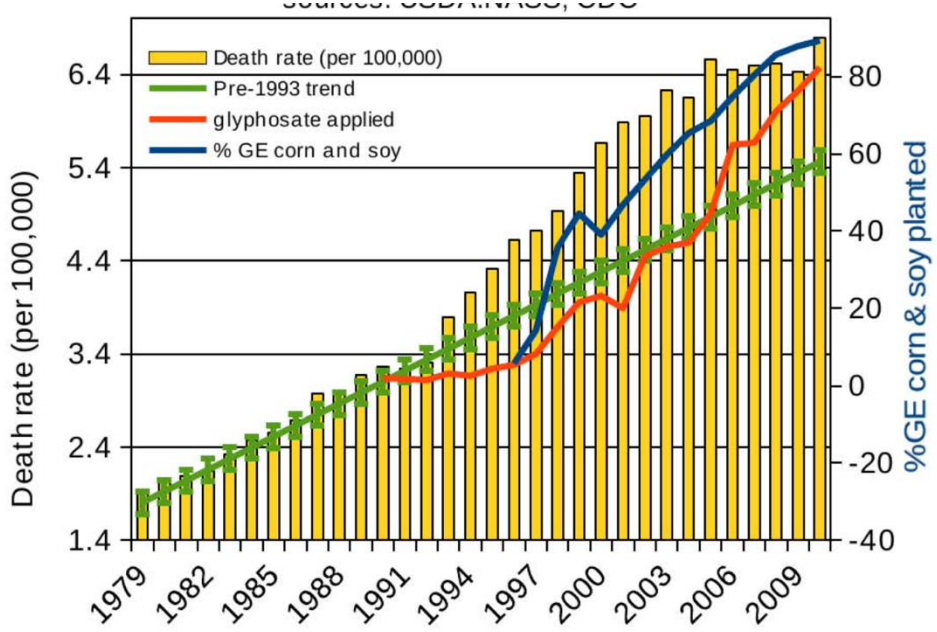
Autism



Alzheimer's



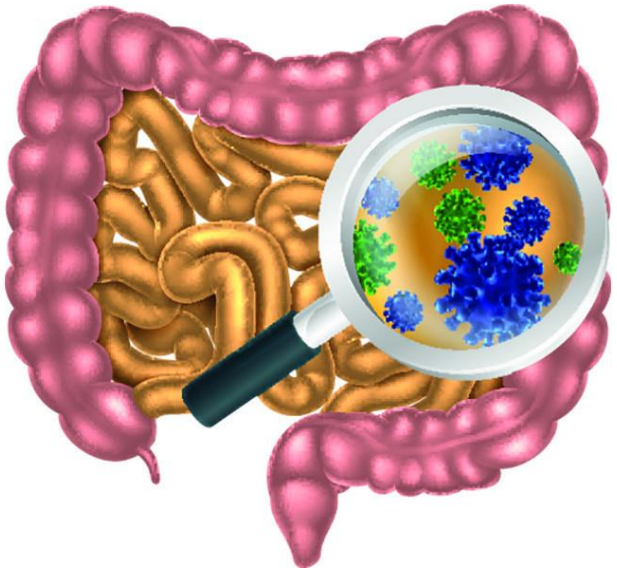
Parkinson's disease



Gut Microbes Supply Deuterium-depleted Nutrients to the Host

The Big Picture

- Gut microbes produce hydrogen gas that is remarkably depleted in deuterium
  - This gas is recycled back into organic nutrients by other microbes → the nutrients are also deuterium depleted
- The enzymes involved have strong dependencies on glycine residues that could be substituted by glyphosate
  - Intestinal bloating and gas pain may be caused by impaired hydrogen recycling due to glyphosate exposure
- Hydrogen enriched water and other hydrogen therapies show therapeutic promise
  - Is the benefit due to the low deuterium in the hydrogen gas?
- DNA methylation may be a storage mechanism for low-deuterium nutrients



Hydrogen gas produced by microbes anaerobically from glucose or formate is depleted down to 30 ppm deuterium*

- "Mass spectrometric analyses of the hydrogen produced by growing cells showed a deuterium content of about 30 ppm. (i.e., depleted by a factor of 4.4 to 5.1…)."
- The same was true whether glucose or formate was the substrate.
- The intracellular water and cellular hydrogen were not significantly depleted in deuterium.

*MI Krichevsky et al. JBC 1961 236(9): 2520-2525.

What happens to the hydrogen gas?

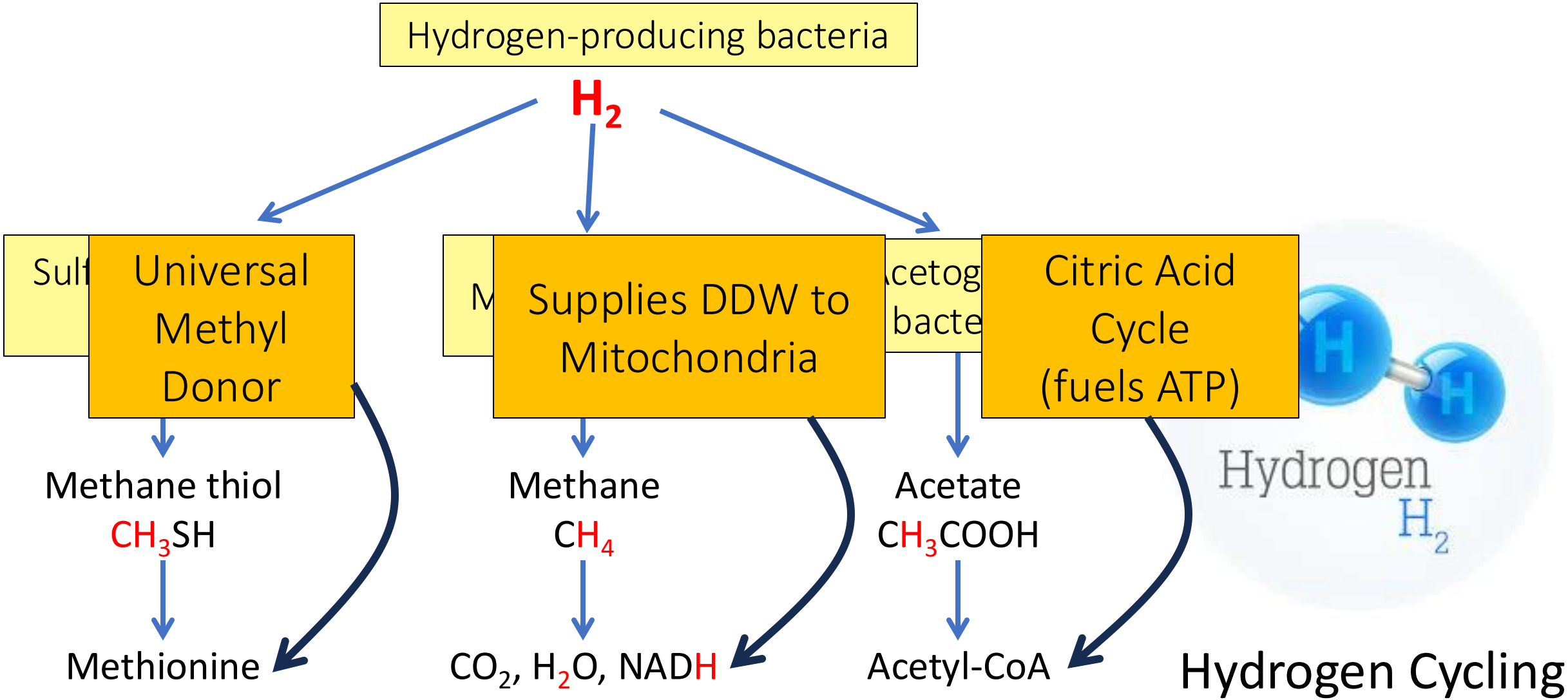
Hydrogen-producing bacteria

H_2

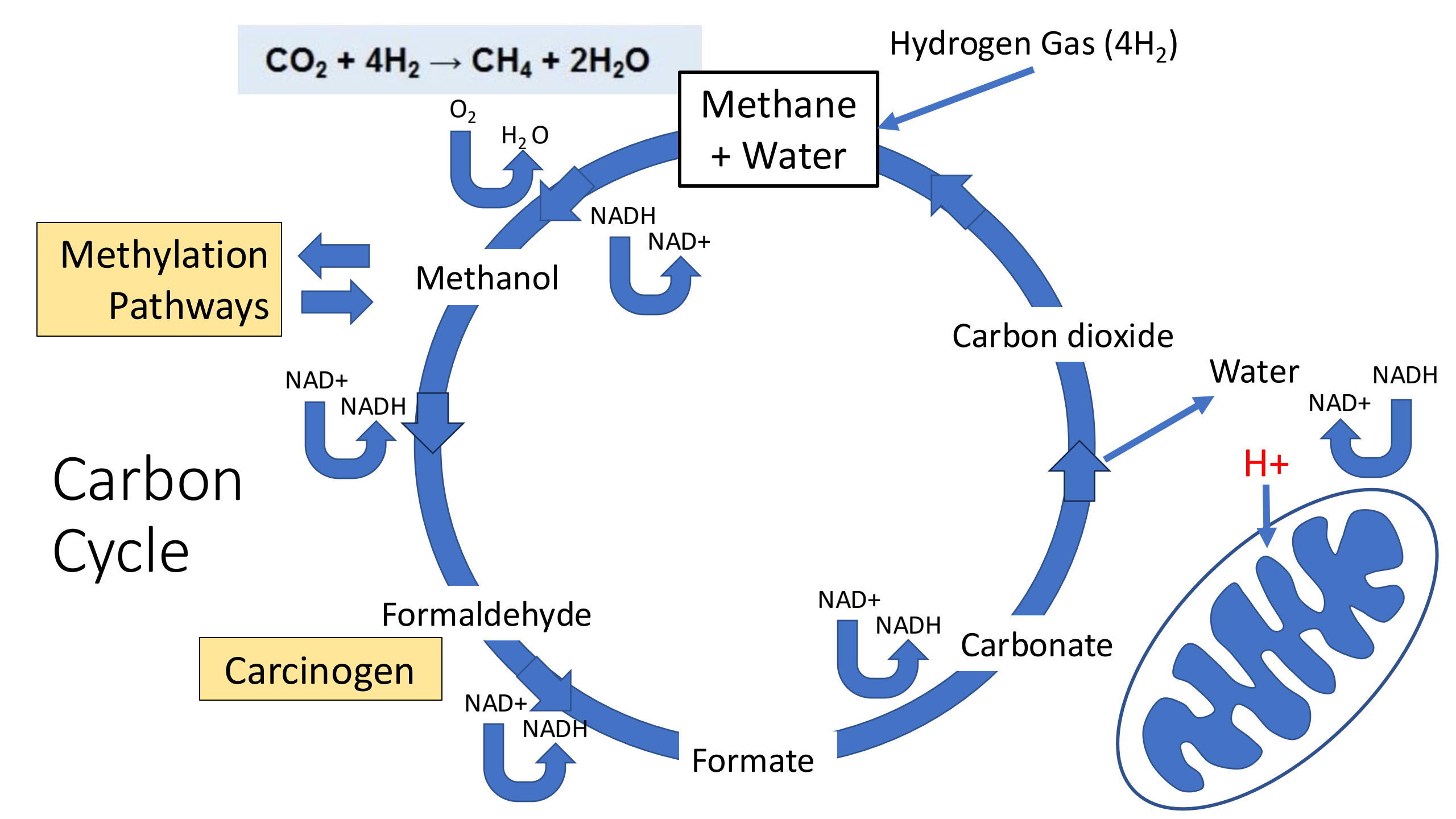
Sulfate-reducing bacteria	Methanogens	Acetogenic bacteria
Methane thiol CH_3SH	Methane CH_4	Acetate CH_3COOH
Methionine	CO_2, H_2O, NADH	Acetyl-CoA

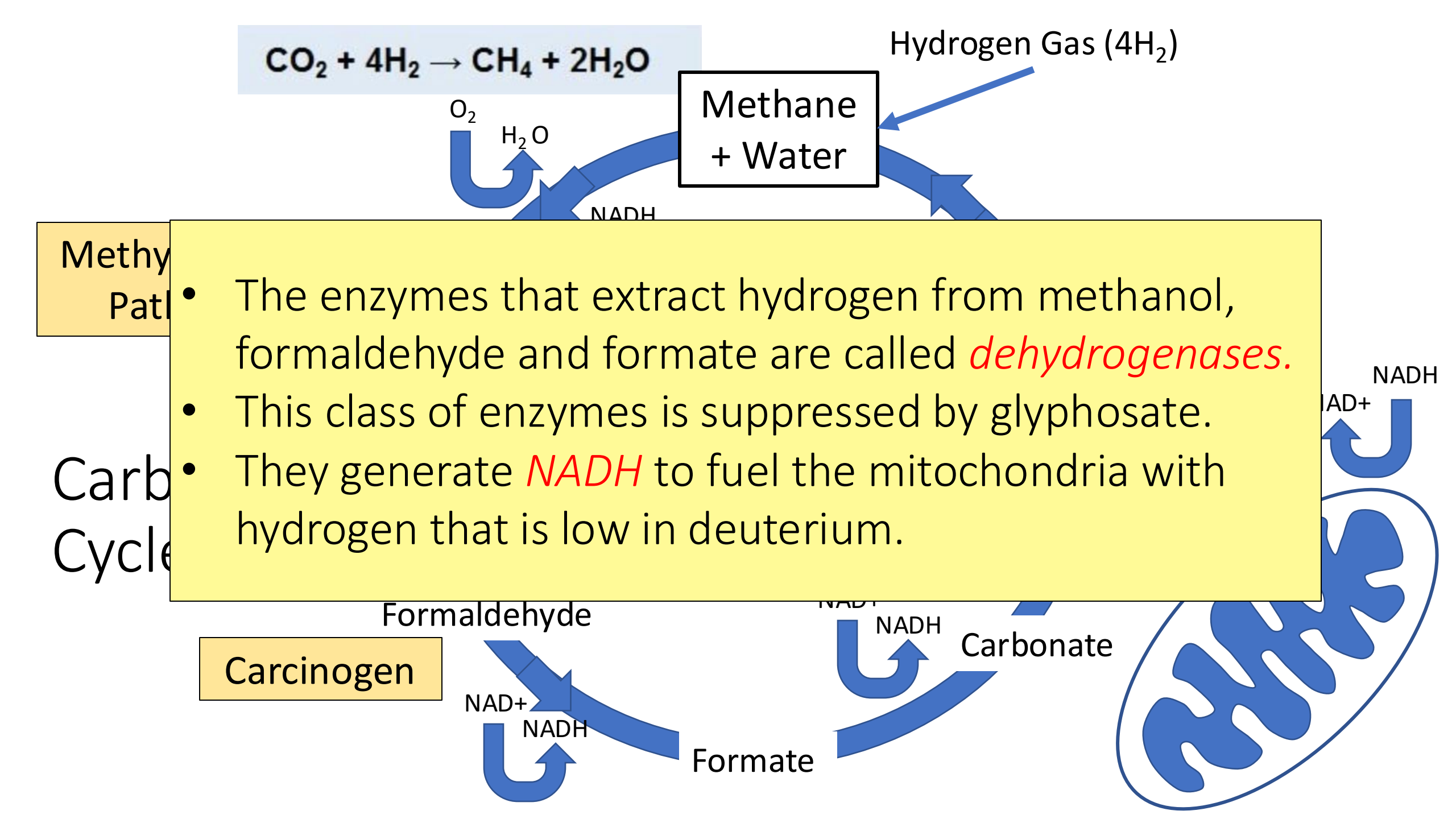
Hydrogen Cycling

What happens to the hydrogen gas?



Hydrogen Cycling


$CO_2 + 4H_2 \rightarrow CH_4 + 2H_2O$
Hydrogen Gas ($4H_2$)
Methane + Water
O_2
H_2O
NADH
NAD+
Methylation Pathways
Methanol
Carbon dioxide
Water
NADH
NAD+
H+
NAD+
NADH
Carbon Cycle
Formaldehyde
Carcinogen
NAD+
NADH
Carbonate
NAD+
NADH
Formate



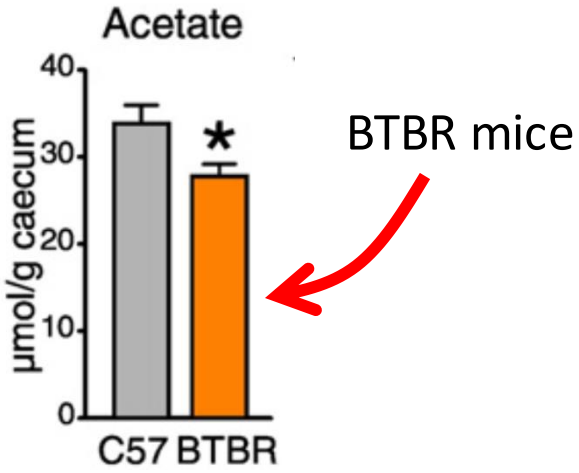
- The enzymes that extract hydrogen from methanol, formaldehyde and formate are called *dehydrogenases.*
- This class of enzymes is suppressed by glyphosate.
- They generate *NADH* to fuel the mitochondria with hydrogen that is low in deuterium.

Dissimilatory sulfate reduction induced by glyphosate

- Multiple enzymes involved in *assimilatory* sulfate reduction in E coli are disrupted by glyphosate (PAPS reductase, APS kinase, sulfite reductase)*
  - Causes deficiency in methionine and other sulfur-containing amino acids
  - Leads to increase in Desulfovibrio and Bilophila wadsworthia species
  - *Dissimilatory* sulfate reduction → excessive hydrogen sulfide gas → brain fog
- Disrupted sulfur assimilation leads to impaired iron absorption**
  - Iron deficiency anemia is an epidemic worldwide

*W Lu et al. Mol Biosyst. 2013 Mar;9(3):522-30.
**BH Hudson et al. PNAS 2018 ePub ahead of print.

BTBR mice have low acetate, and glyphosate disrupts acetate synthesis in the gut*

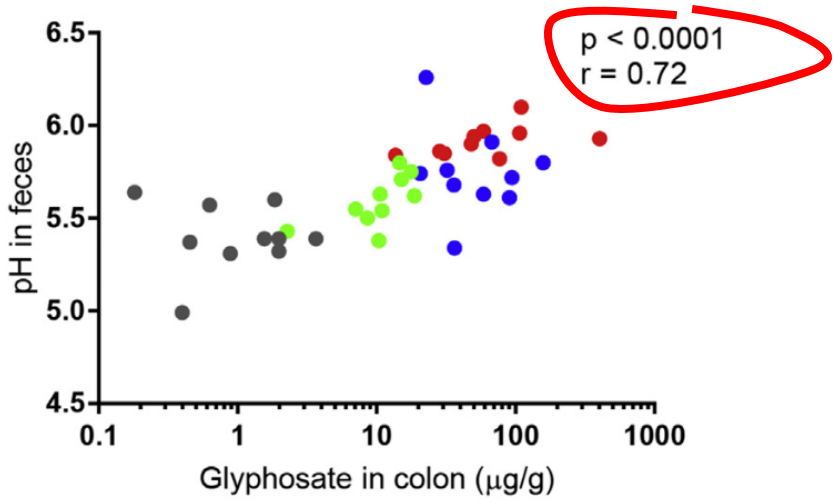


BTBR mice

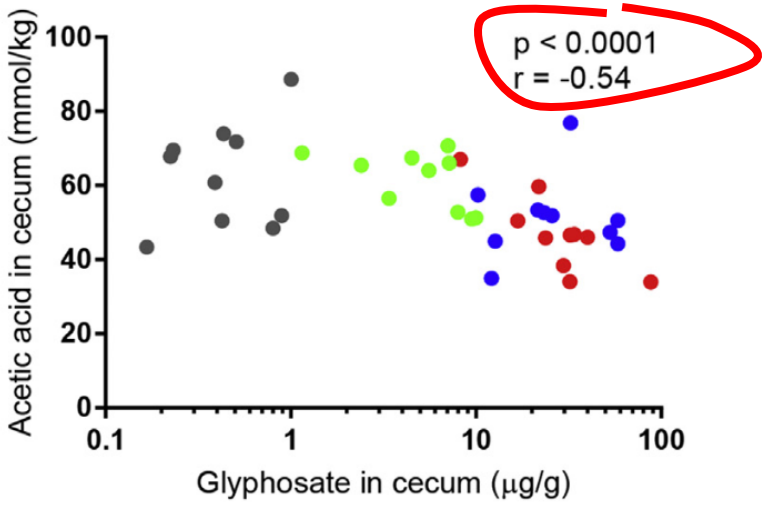
BTBR mice are a well-established mouse model of autism

Children with autism had only 3.5 mg/ml acetate in stool samples compared to 5.1 in controls.**

Glyphosate and pH

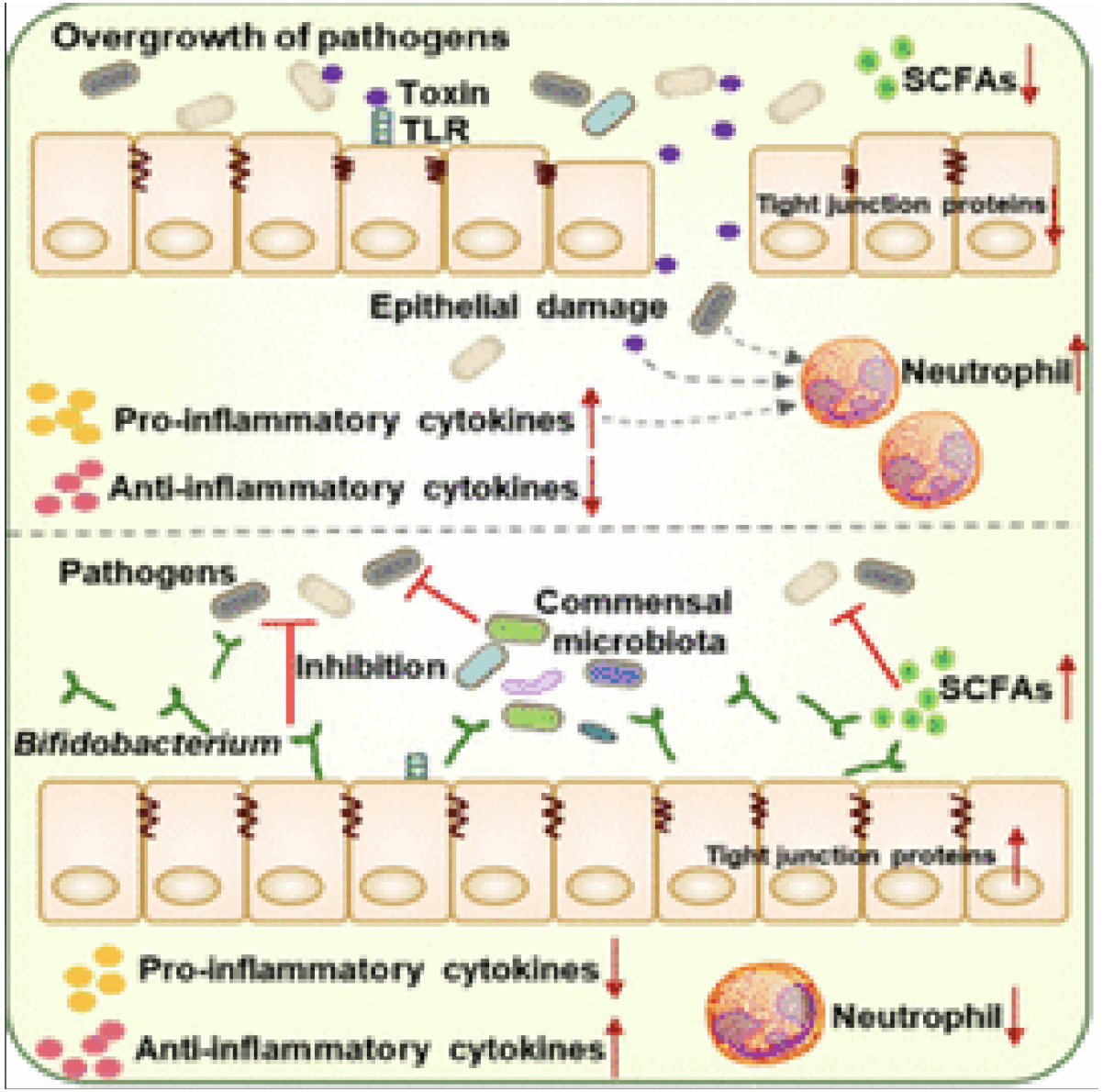


Glyphosate and Acetate



*LN Nielsen et al. Environmental Pollution 2018;233:364e376.

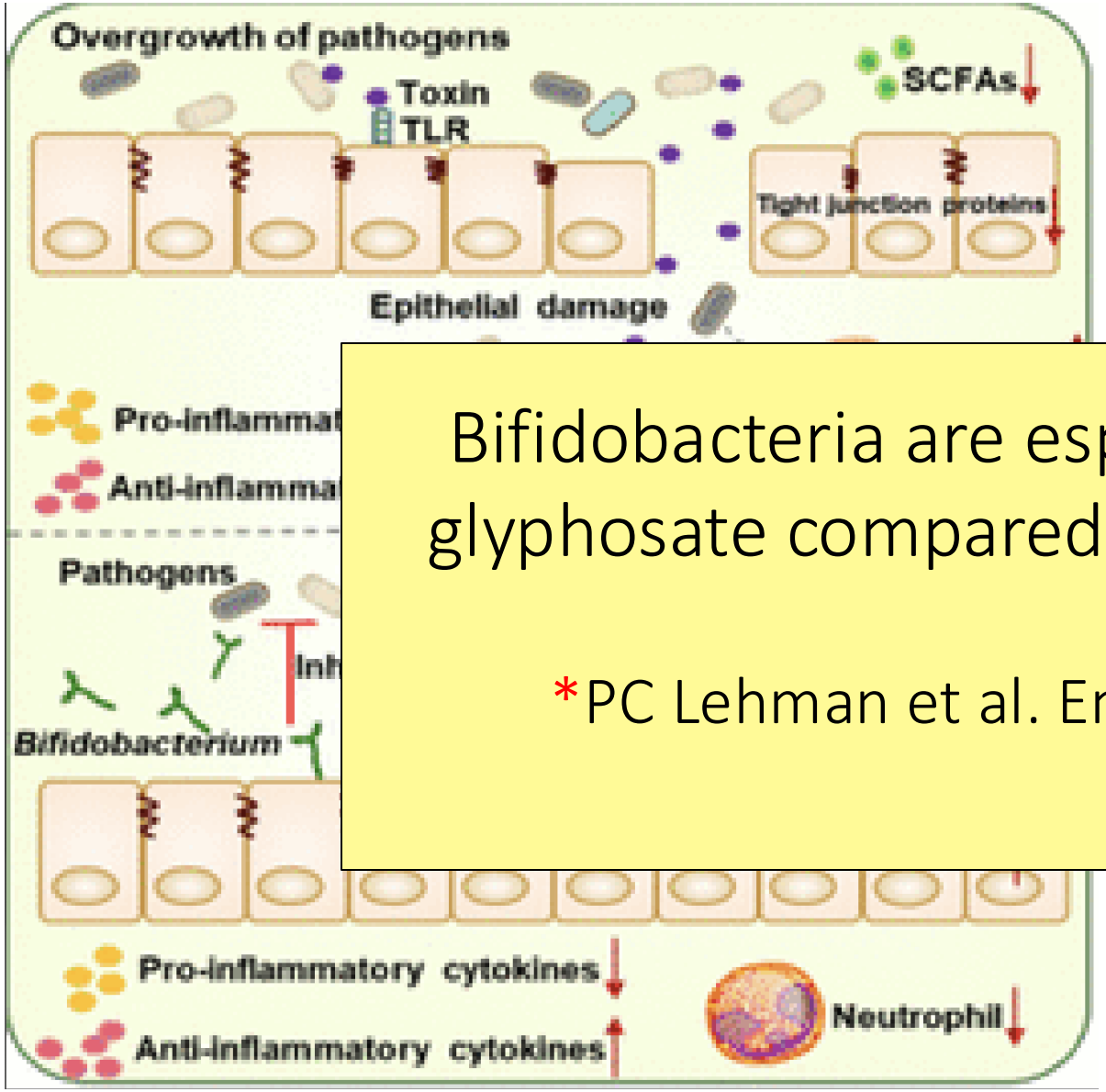
**JB Adams et al. BMC Gastroenterology 2011; 11:22.



Bifidobacteria: Beneficial Role in Colitis

- In a mouse model of colitis, Bifidobacteria bifidum administration alleviated colitis symptoms, reduced proinflammatory cytokine production, reduced neutrophil levels, and enhanced tight junction health
- Bifidobacteria inhibit growth of pathogens and increase production of short chain fatty acids

*Jiacui Shang et al., J. Agric. Food Chem. 2022, 70, 11678−11688.



Bifidobacteria: in Colitis

Bifidobacteria are especially sensitive to glyphosate compared to other microbes*

*PC Lehman et al. Environ Toxicol Pharmacol. 2023 Jun;100:104149.

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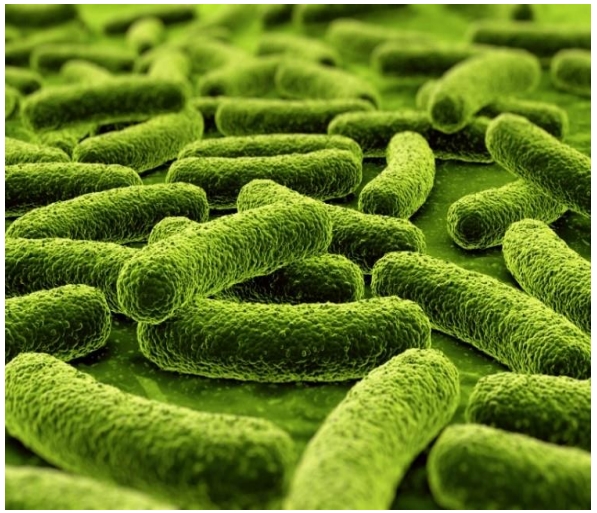
h of pathogens and increase production of short chain fatty acids

*Jiacui Shang et al., J. Agric. Food Chem. 2022, 70, 11678−11688.

Benefits of Bifidobacteria*

- Bifidobacteria metabolize starch to produce lactate and acetate
- Many bacteria, but predominantly Firmicutes and Bacteroidites, produce hydrogen gas from lactate and acetate via hydrogenase enzymes
- Firmicutes are butyrate-producing bacteria that supply the colonocytes with their favorite food
- All these species need to be abundant to support hydrogen recycling
- It is said that approximately 10 liters of hydrogen are produced daily in the human intestines.



- Low hydrogen levels in the breath are linked to Parkinson's disease, rheumatoid arthritis, cardiovascular disease and Crohn's disease

*Yusuke Ichikawa et al., Med Gas Res. 2023 Jul-Sep;13(3):108-111.

Med Gas Res. 2023 Jul-Sep; 13(3): 108–111.
Published online 2022 May 12. doi: 10.4103/2045-9912.344977
PMCID: PMC9979208
PMID: 36571374

The overlooked benefits of hydrogen-producing bacteria

Yusuke Ichikawa, PhD,[1,2,*] Haru Yamamoto,[2,3] Shin-ichi Hirano,[1] Bunpei Sato,[1,2] Yoshiyasu Takefuji,[4,5] and Fumitake Satoh[1,2]

Abstract

Go to: ▸

Intestinal bacteria can be classified into “beneficial bacteria” and “harmful bacteria.” However, it is difficult to explain the mechanisms that make “beneficial bacteria” truly beneficial to human health. This issue can be addressed by focusing on hydrogen-producing bacteria in the intestines. Although it is widely known that molecular hydrogen can react with hydroxyl radicals, generated in the mitochondria, to protect cells from oxidative stress, the beneficial effects of hydrogen are not fully pervasive because it is not generally thought to be metabolized *in vivo*. In recent years, it has become clear that there is a close relationship between the amount of hydrogen produced by intestinal bacteria and various diseases, and this report discusses this relationship.

Hydrogen Gas as a Therapy*

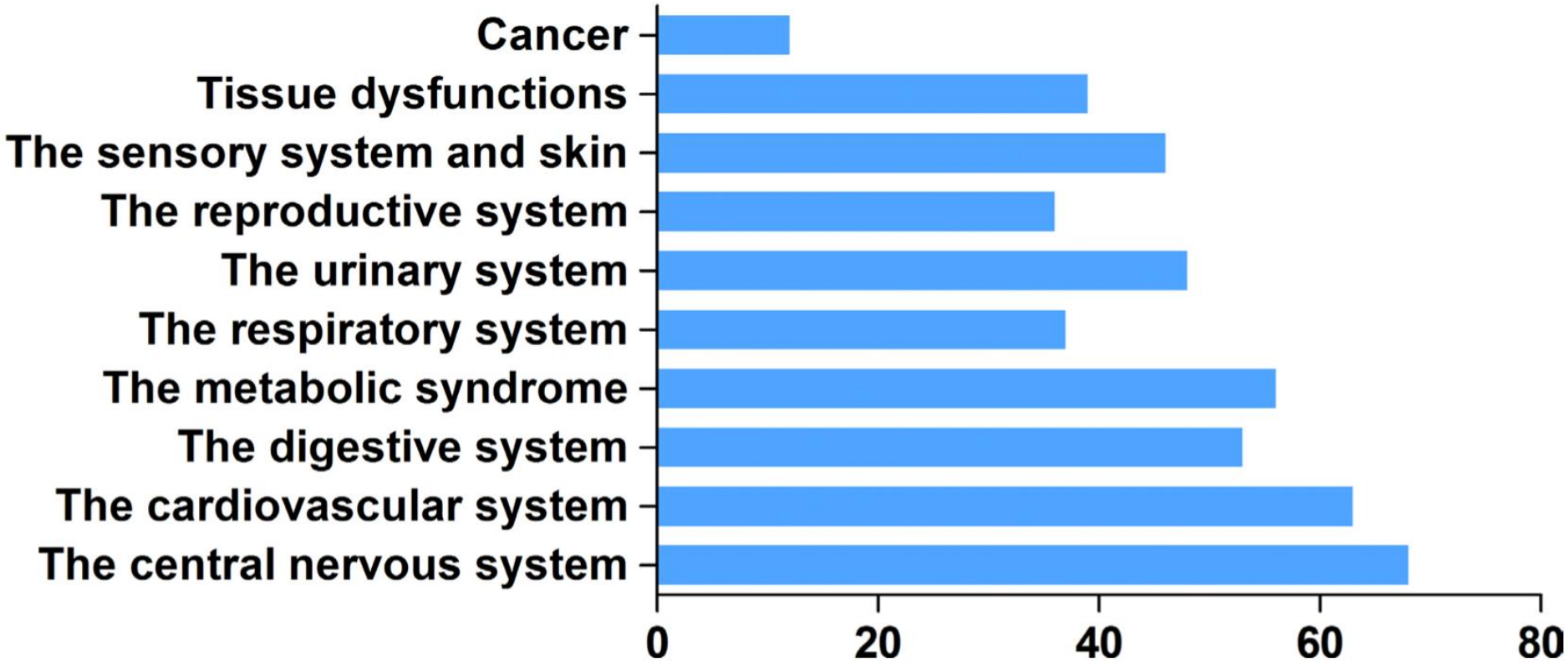


Figure 2: Number of publications on H_2 biological effects in various organ system diseases since 2007.

*L Ge et al. Oncotarget 2017; 8(60): 102653-102673.

"Pilot study of H_2 therapy in Parkinson's disease: a randomized double-blind placebo-controlled trial"*

- Hydrogen water is water with trapped hydrogen gas in it
- It can be created by dropping tablets of elemental magnesium into tap water

$$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$$

"The results indicated that drinking H_2-water was safe and well tolerated, and a significant improvement in total UPDRS [Unified Parkinson's Disease Rating Scale] scores for patients in the H_2-water group was demonstrated."

*Asako Yoritaka et al. Mov Disord 2013; 28(6): 836-9.

Glyphosate Suppresses Dehydrogenases

The Big Picture

- Methane gas is converted by gut microbes in a series of steps into methanol, formaldehyde, formate, and ultimately carbon dioxide
- The enzymes that extract hydrogen from methanol, formaldehyde and formate are called *dehydrogenases.*
  - This class of enzymes is suppressed by glyphosate.
- These enzymes generate *NADH* (H originally from hydrogen gas) to fuel the mitochondria with hydrogen that is low in deuterium
- Methionine's methyl group (derived from methane) is the universal methyl donor
- Many methyl groups are attached to large molecules such as DNA, RNA, histones and other proteins
  - Do these methyls serve as a storage form of low-deuterium hydrogens?

Enzymes Use Hydrogen Tunneling to Avoid Deuterium

- A deuterium kinetic isotope effect (KIE) defines an enzyme's ability to deliver a proton to the product, rather than a deuteron
- Many dehydrogenases have a high deuterium KIE (>>1)
- An essential aspect of enzymatic action involves hydrogen tunneling (quantum physics)
- Protons are far more efficient at tunneling than deuterons

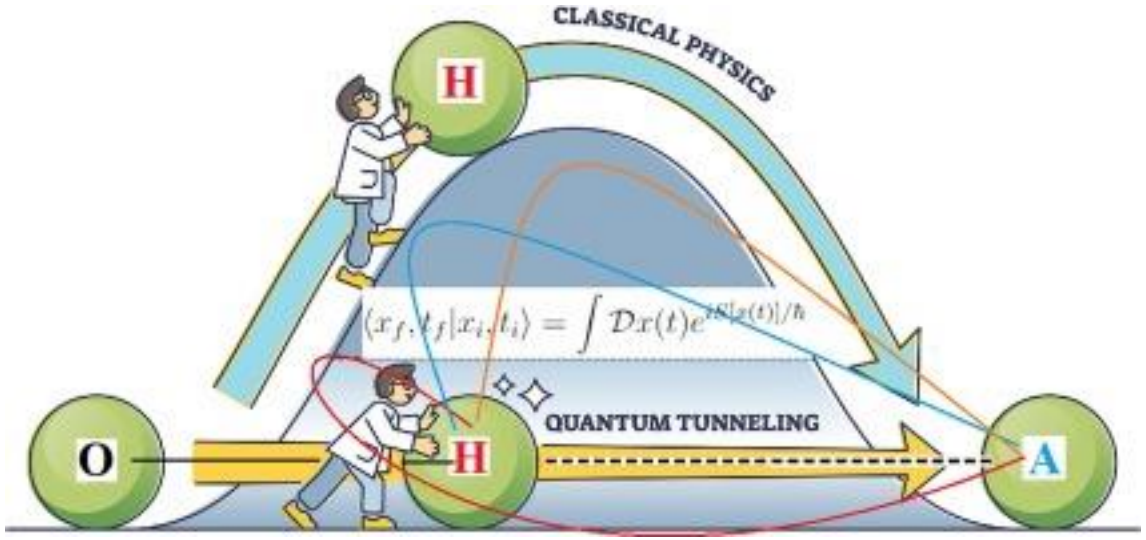


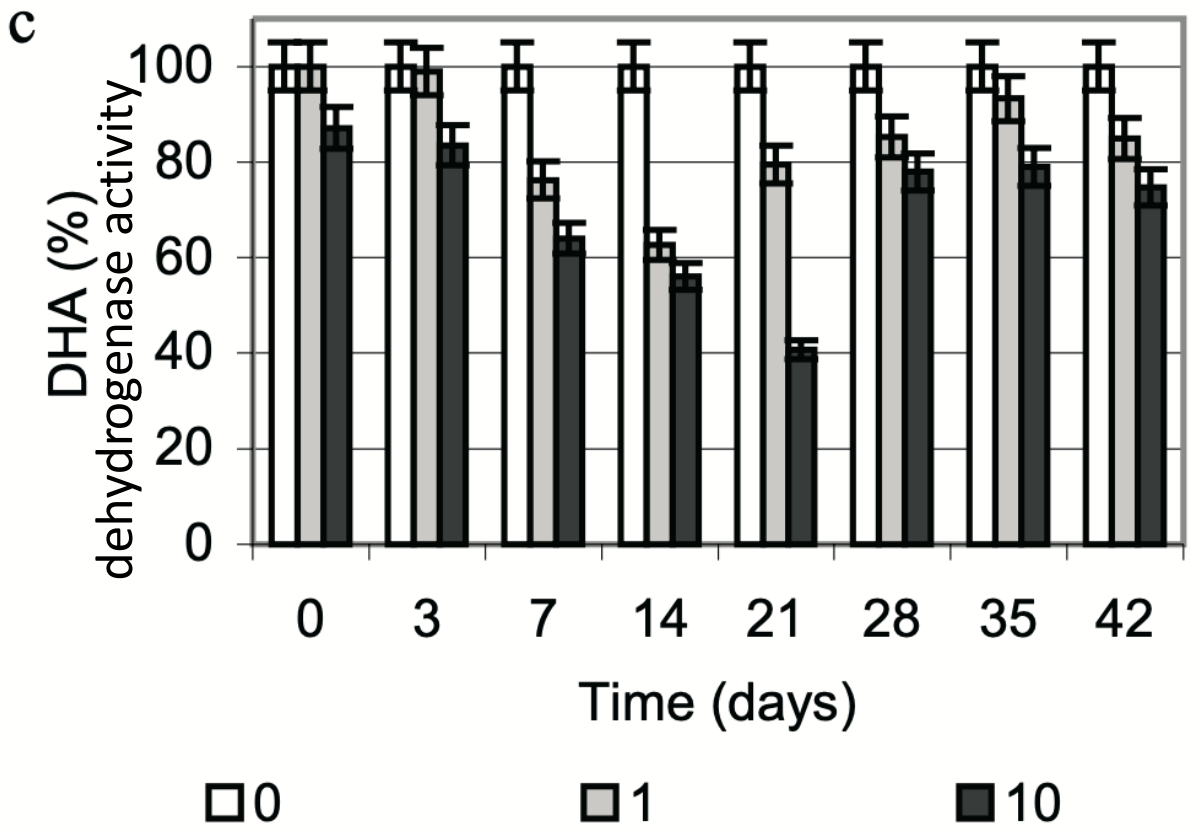
Image credit: Graphical Abstract.
Luca Nanni. Chemical Physics 2023; 574: 112054.

Glyphosate Impairs NAD(P)(H) Pathways*

- NAD(P)(H) is a major carrier of deuterium-depleted protons
- *NAD(P)(H) is derived from tryptophan*
  - Tryptophan is a major product of the shikimate pathway, blocked by glyphosate in plants and microbes
- Glyphosate inhibits *NADH dehydrogenase*, which supplies deuterium-depleted protons to the ATPase pumps in the mitochondria
- Glyphosate inhibits *glucose 6 phosphate dehydrogenase* (G6PD), which restores NADPH from NADP+
- Glyphosate inhibits *succinate dehydrogenase*, the only enzyme that participates in both the citric acid cycle and oxidative phosphorylation in the mitochondria
  - Succinate dehydrogenase deficiency is linked to many cancers

*S Seneff, Toxic Legacy, Chelsea Green Publishers, July 2021.

Glyphosate Suppresses Dehydrogenases in Soil Microbes*



Units: micrograms glyphosate/gram of soil

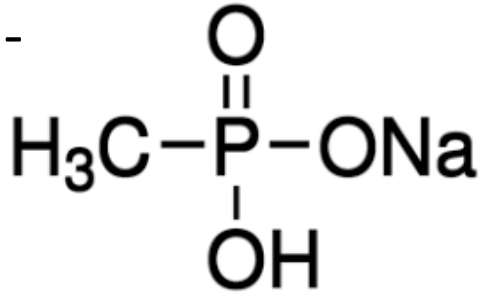
In mollic gleysols (a type of soil prevalent in meadows and river bottoms), the level of microbial dehydrogenase activity decreased steadily over a three-week period following glyphosate exposure

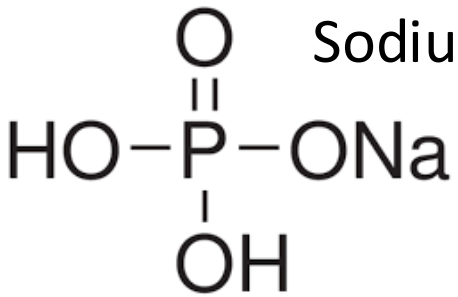
*RP Bennicelli et al. Int. Agrophysics, 2009, 23, 117-122.

Hypothesis: Glyphosate Disrupts Proteins that Bind Phosphate

- Glyphosate is a glycine molecule with a methylphosphonate unit attached to the nitrogen atom
- Glyphosate kills weeds by suppressing EPSP synthase in the shikimate pathway
- Glyphosate blocks EPSP synthase binding to the phosphate in PEP
- The binding site for PEP has a highly conserved glycine residue
  - If this glycine is swapped out for alanine, the enzyme becomes completely insensitive to glyphosate
  - This is the basis for many GMO glyphosate-resistant crops*

Sodium Methyl-phosphonate





Sodium Phosphate

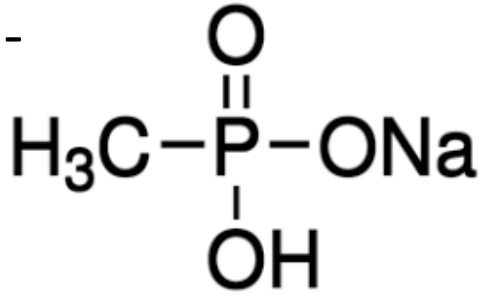
*T Funke et al. Proc Natl Acad Sci U S A 2006; 103(35): 13010-13015

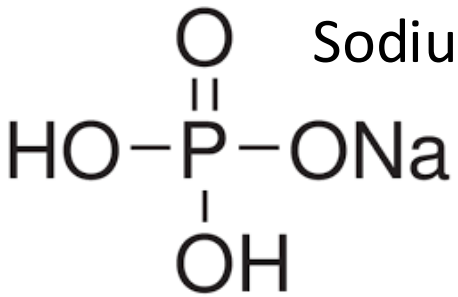
Hypothesis: Glyphosate Disrupts Proteins that Bind Phosphate

- Glyphosate is a glycine molecule with a methylphosphonate unit attached to the nitrogen atom
- Glypho…e shikimate pathw…
- Glypho…e in PEP
- The bi…sidue
  - If th…completely inse…
  - This is the basis for many GMO glyphosate-resistant crops*

Many enzymes that glyphosate has been shown to suppress contain a "glyphosate susceptibility motif": they bind phosphate at a site where there is at least one highly conserved glycine residue

Sodium Methyl-phosphonate





Sodium Phosphate

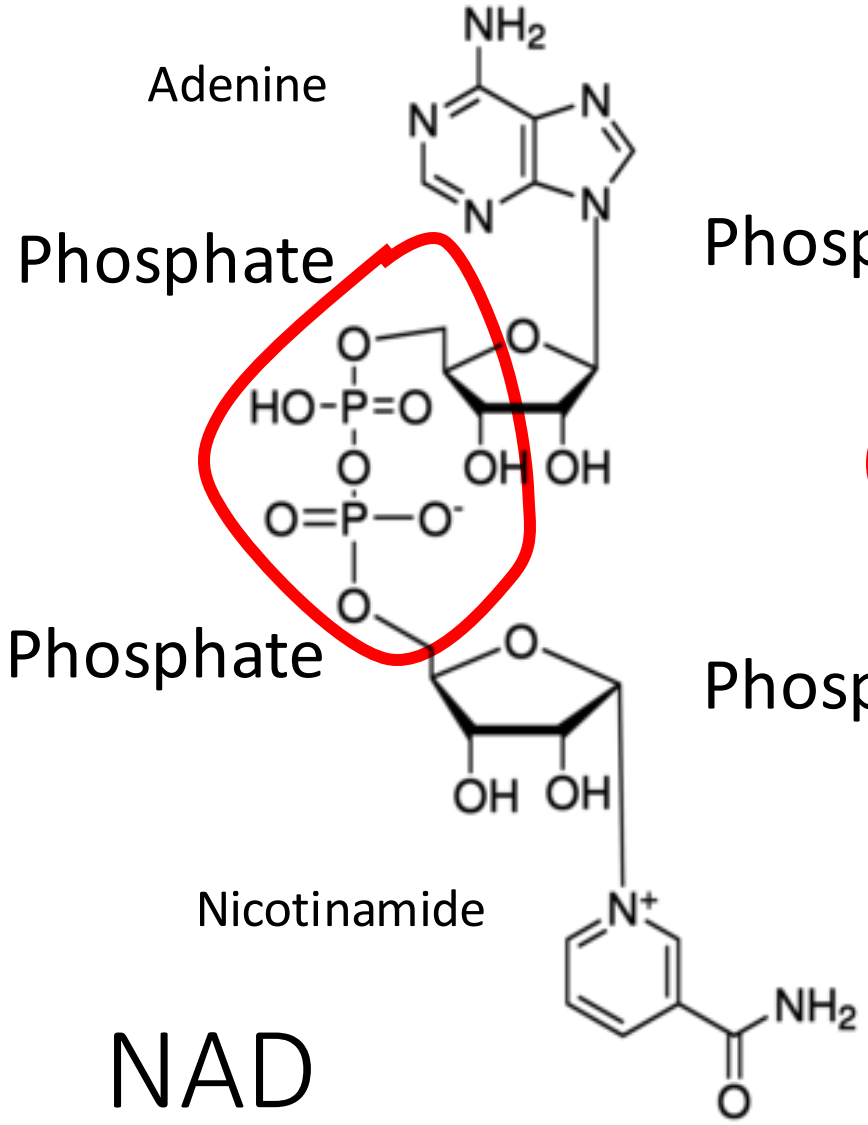
*T Funke et al. Proc Natl Acad Sci U S A 2006; 103(35): 13010-13015

Does Glyphosate Disrupt FAD binding in Dehydrogenases?

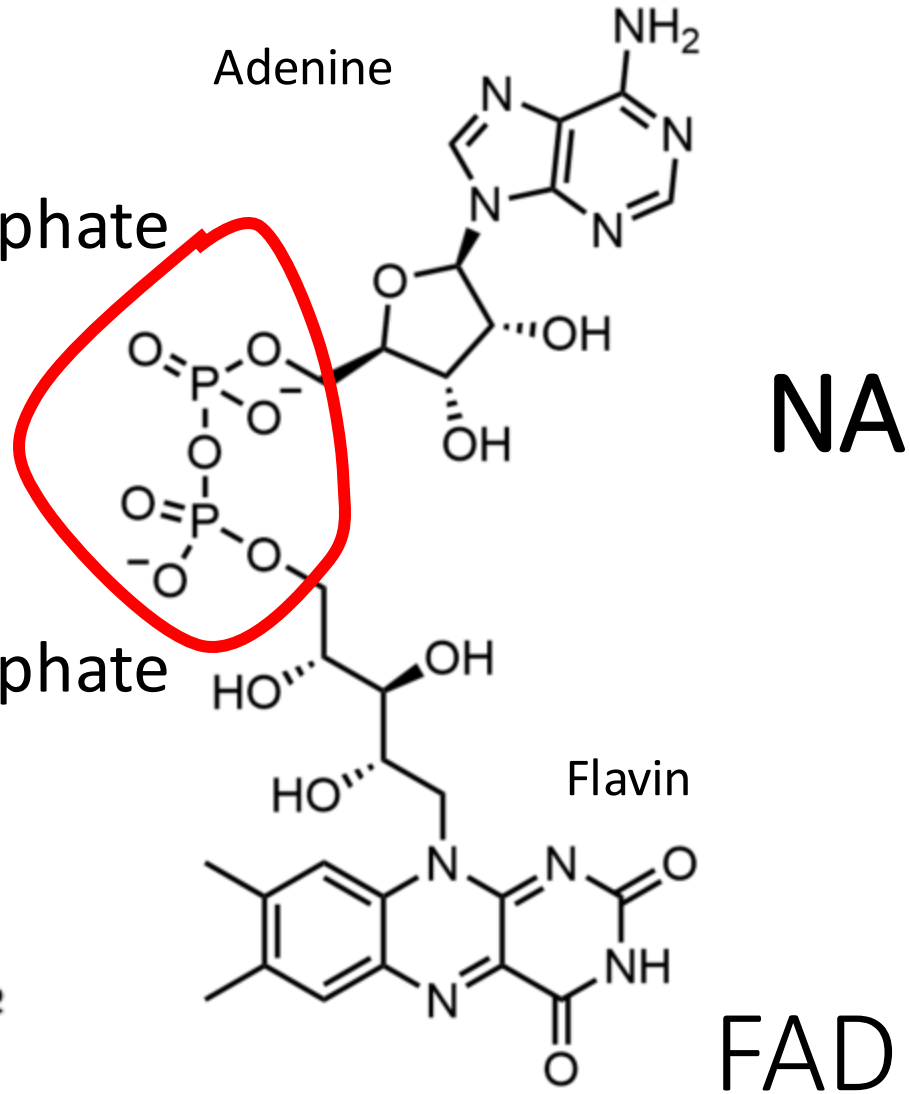
- Many dehydrogenases are *flavoproteins.* They bind flavin-adenine dinucleotide (FAD) at a site with at least one highly conserved glycine residue. FAD facilitates the transfer of protons and electrons
- A region near the carboxyl-terminal segment of FAD-binding dehydrogenases contains a highly conserved glycine-aspartate pair
- Mutation of Gly-478 to alanine in a Bacillus NADH dehydrogenase caused complete loss of activity, due to loss of binding capacity to FAD*
- Gly-478 is preceded by alanine, a small amino acid, leaving room for glyphosate's methylphosphonate unit

*Masato Shiraki and Noriyuki Kayama. Current Microbiology 2003; 46: 432–434.

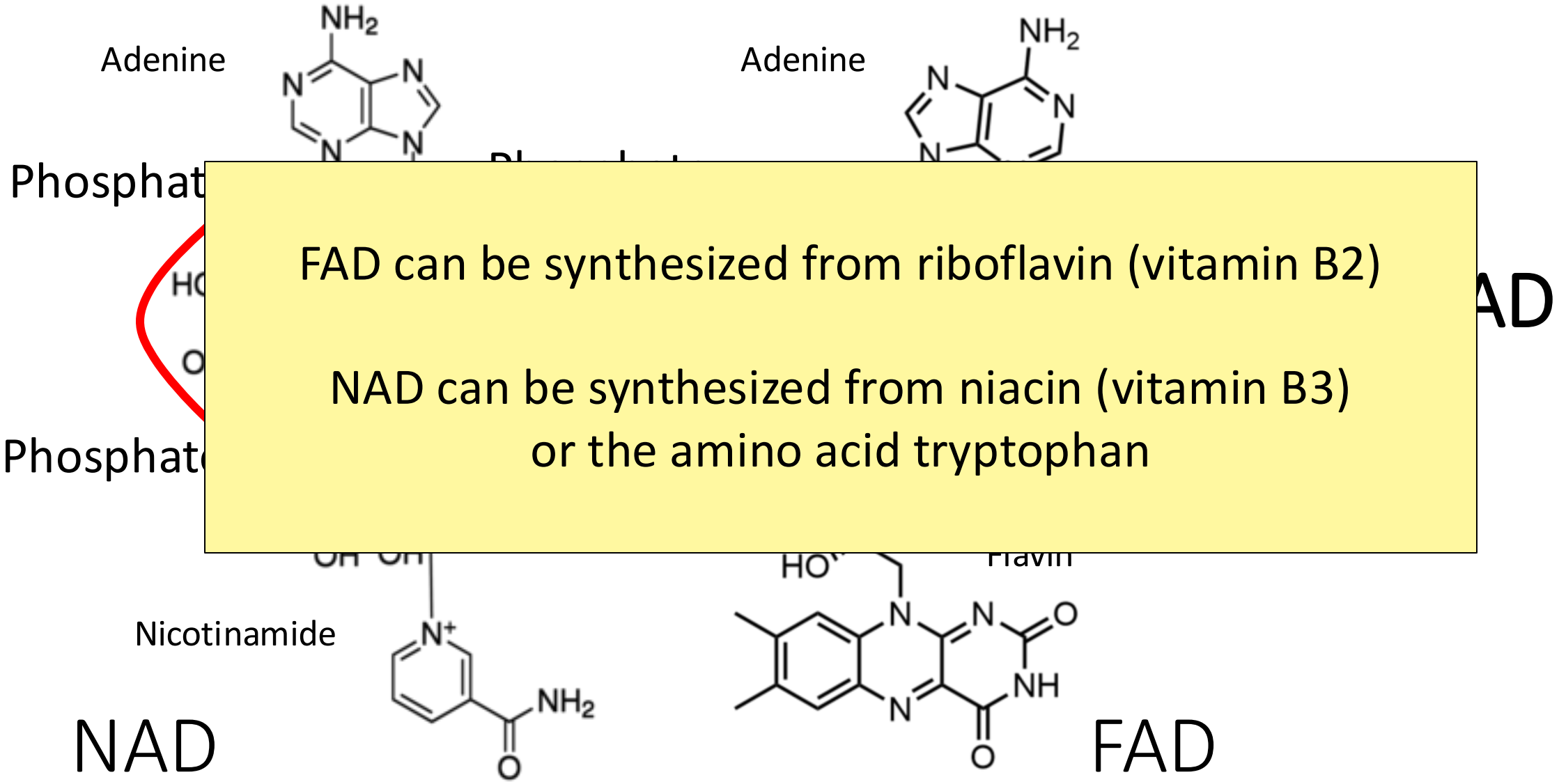
NAD and FAD



NAD



FAD



FAD can be synthesized from riboflavin (vitamin B2)

NAD can be synthesized from niacin (vitamin B3)
or the amino acid tryptophan

Some dehydrogenases that are downregulated in E. coli when exposed to glyphosate*

- NADH dehydrogenase
- glucose-6-phosphate dehydrogenase
- succinate dehydrogenase
- malate dehydrogenase
- α-ketoglutarate dehydrogenase
- 2-deoxy-D-gluconate dehydrogenase
- acetaldehyde-CoA dehydrogenase
- D-amino acid dehydrogenase
- D-lactate dehydrogenase
- NADP-specific glutamate dehydrogenase
- 3-isopropylmalate dehydrogenase
- D-3-phosphoglycerate dehydrogenase

*Wei Lu et al. Molecular BioSystems 2013; 9: 522-530.

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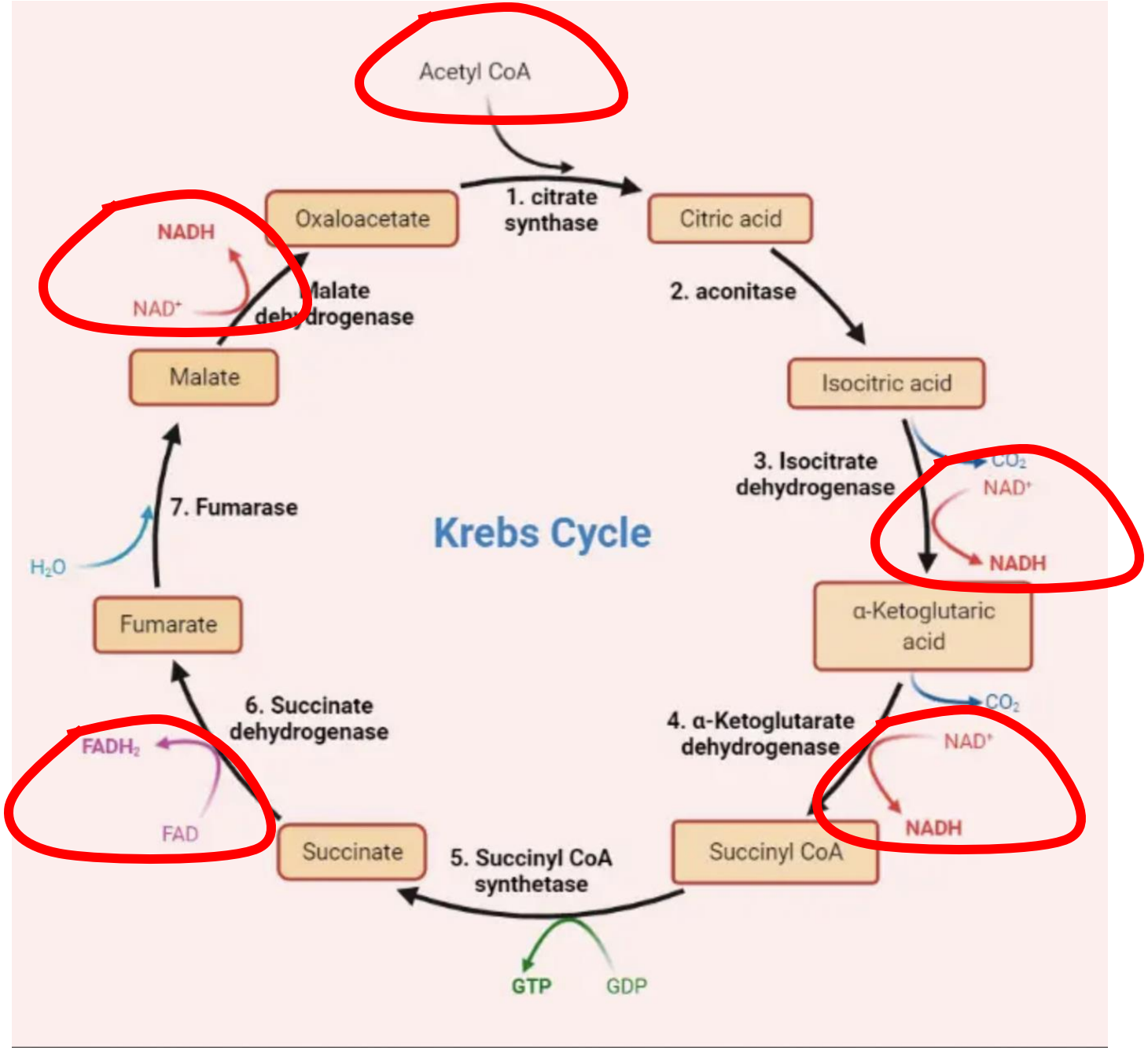
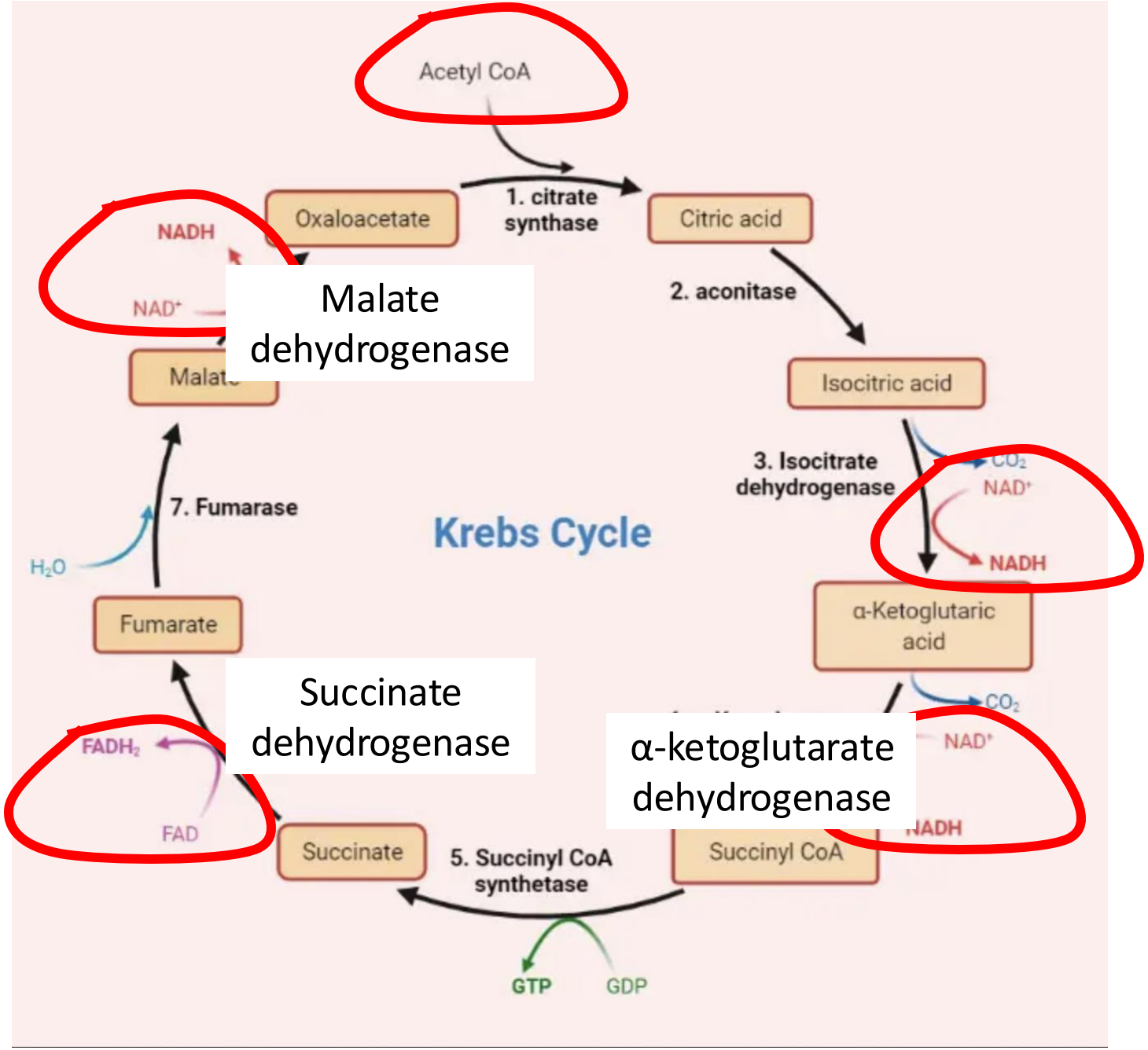


Citric Acid Cycle aka Krebs Cycle: Cellular respiration in the mitochondria



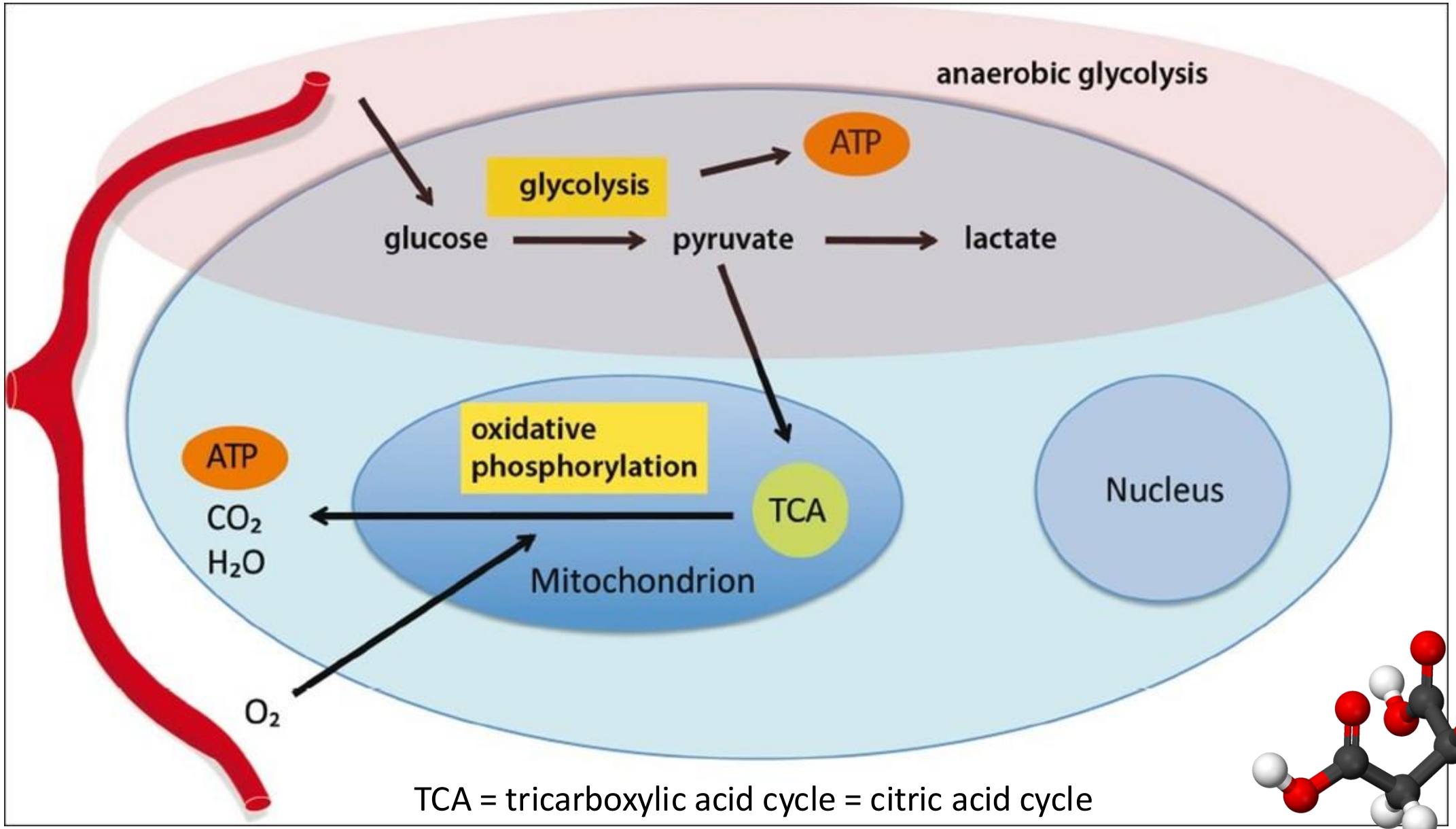
Citric Acid Cycle aka Krebs Cycle: Cellular respiration in the mitochondria

Disrupted Glycolysis Leads to Fatty Liver Disease and Hyperlipidemia

The Big Picture

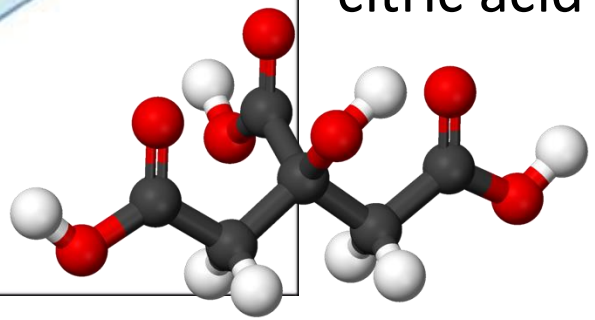
- Glycolysis is the “pre-processing” step that takes place in the cytoplasm and converts glucose into pyruvate
- Many steps in glycolysis help to deplete deuterium in protons
- At least two critical dehydrogenases in glycolysis have strong glyphosate susceptibility motifs
- Genetic mutations in these genes lead to serious health issues, including glycation damage, microcephaly, seizures, cognitive impairment and liver damage

Simplified Glucose Metabolism



TCA = tricarboxylic acid cycle = citric acid cycle

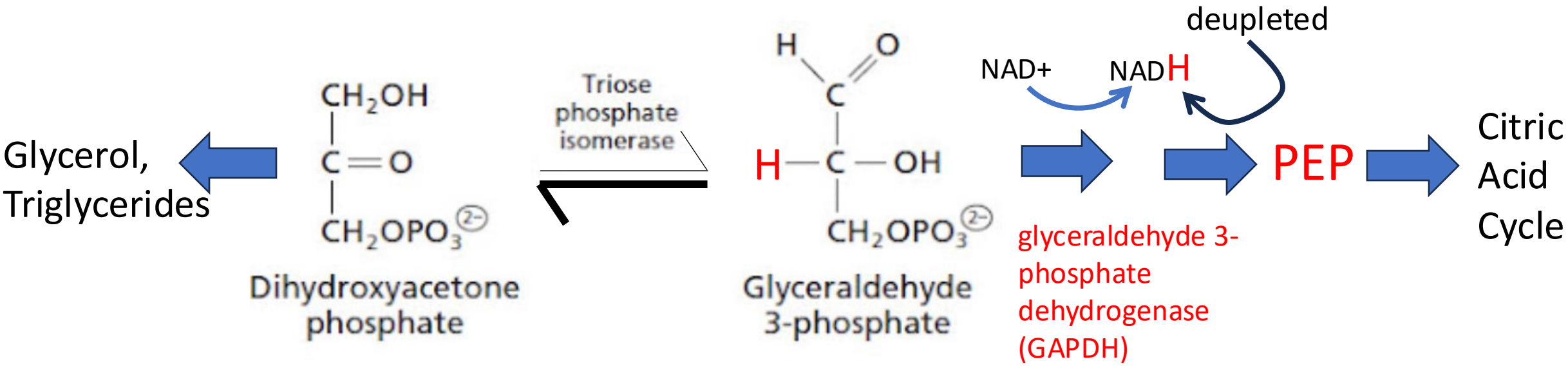
citric acid



Glycolysis and Glyphosate

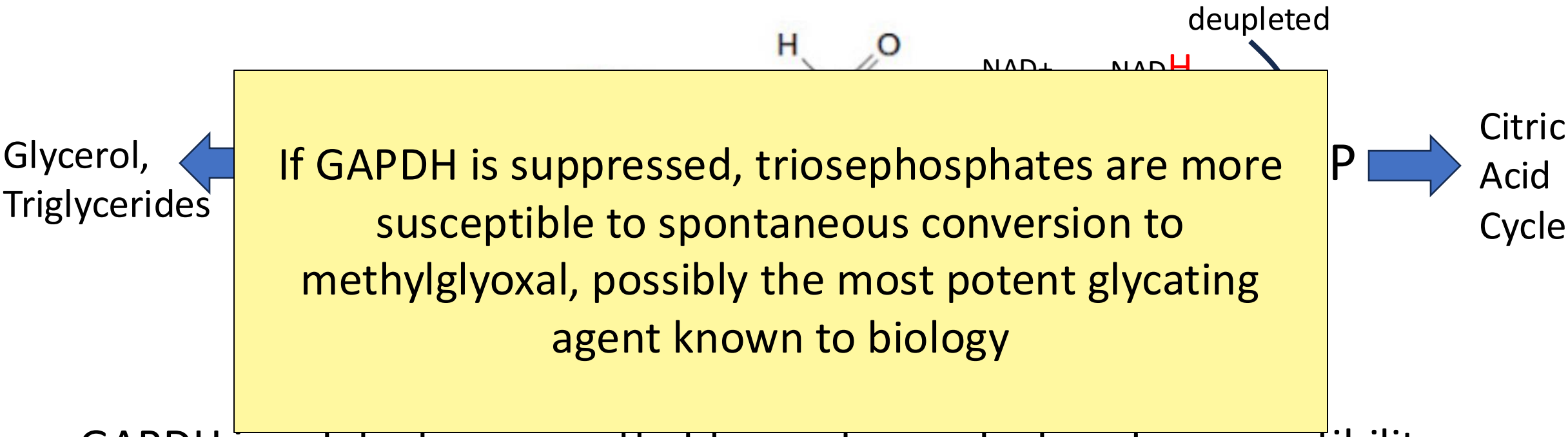
- Glycolysis is the anaerobic pathway in the cytoplasm that converts glucose to pyruvate
- Pyruvate feeds into the citric acid cycle in the mitochondria and gets fully metabolized to carbon dioxide and water
- Glycolysis involves several enzymes that deplete deuterium
- Triosephosphate isomerase is an important enzyme in glycolysis that yields a deupleted proton that is then attached to NAD+ to make NADH
- The dehydrogenase that yields NADH has a strong glyphosate-susceptibility motif

Triosephosphate Isomerase



- GAPDH is a dehydrogenase that has a strong glyphosate-susceptibility motif (highly conserved glycine that binds to NAD)
- PEP = phosphoenolpyruvate – the molecule that EPSPS synthase binds to in the shikimate pathway

Triosephosphate Isomerase



If GAPDH is suppressed, triosephosphates are more susceptible to spontaneous conversion to methylglyoxal, possibly the most potent glycating agent known to biology

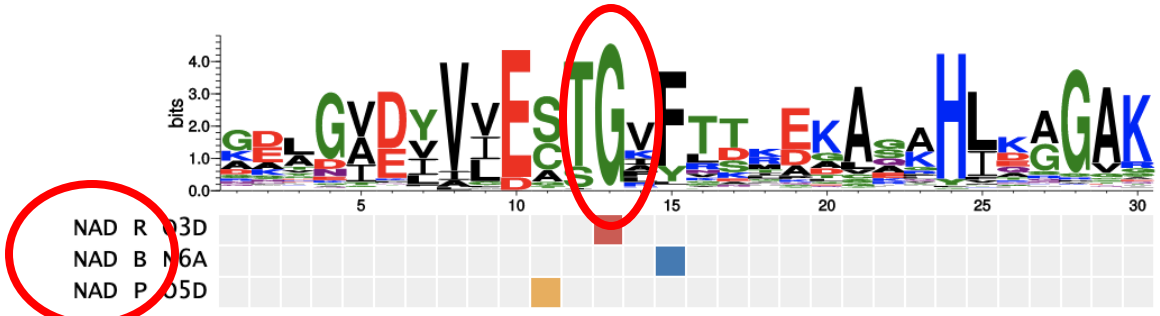
- GAPDH is a dehydrogenase that has a strong glyphosate-susceptibility motif (highly conserved glycine that binds to NAD)
- PEP = phosphoenolpyruvate – the molecule that EPSPS synthase binds to in the shikimate pathway

Highly conserved glycine at NAD binding site of glyceraldehyde 3-phosphate dehydrogenase*

Profile ESTGFH with (dihydro)Nicotinamide adenine dinucleotide

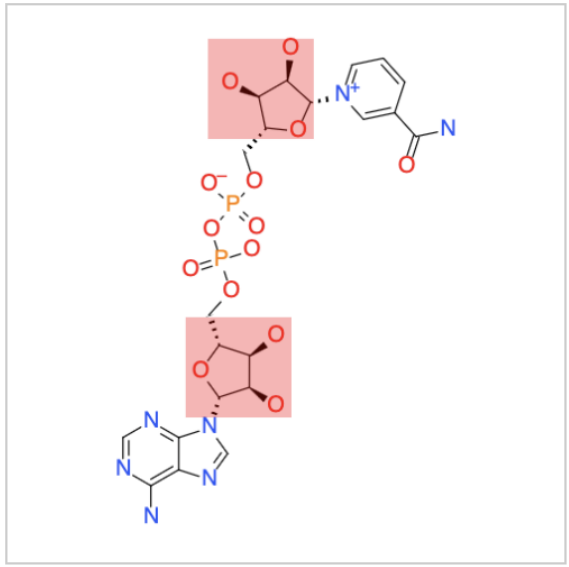
Logo and protein-ligand-atom interactions

Click on a table cell to show interaction with a particular ligand moiety



Download profile data file

NAD(H)



*https://www.uniprot.org/uniprotkb/P04406/entry

*http://nbdb.bii.a-star.edu.sg/search

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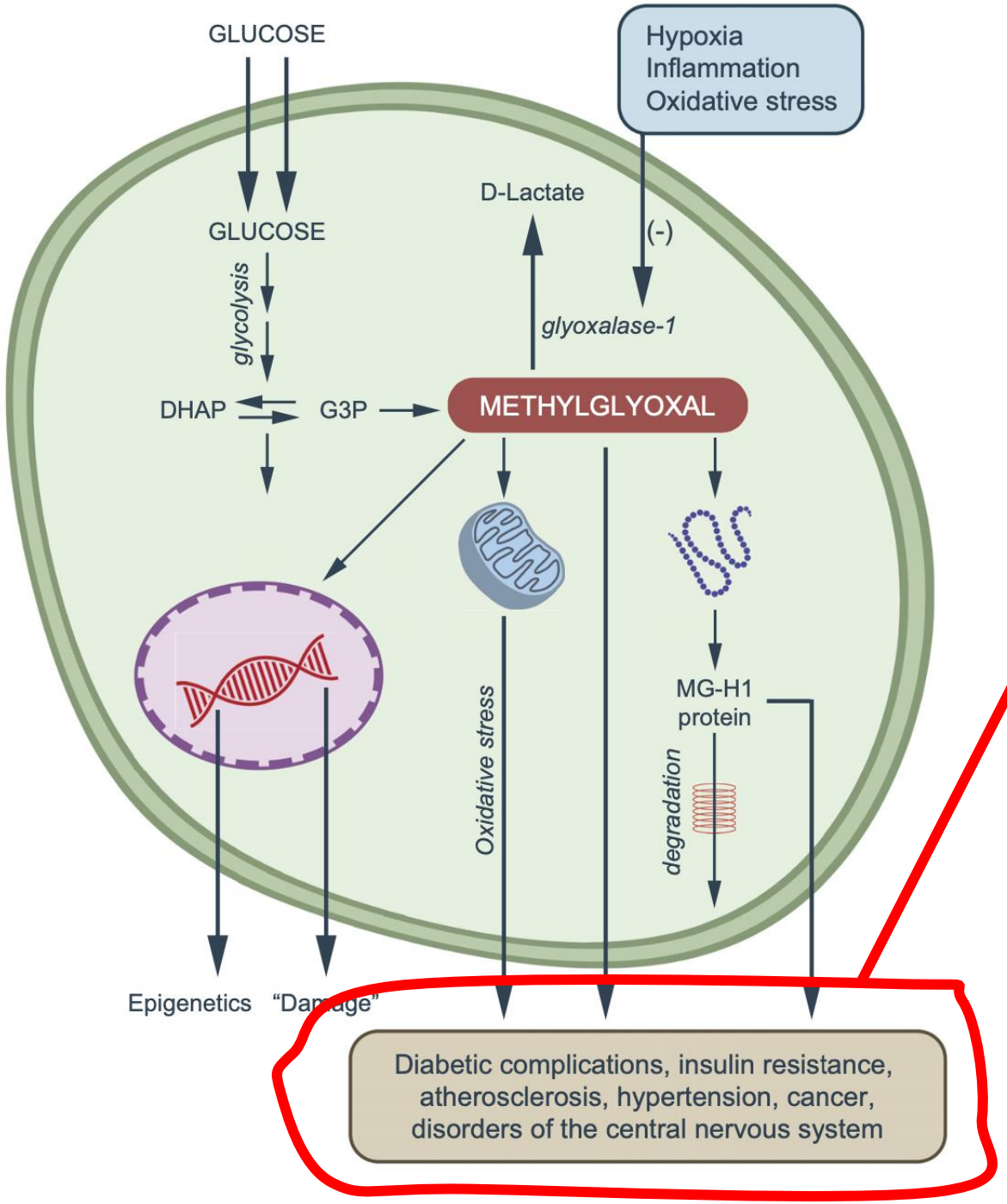
Biochimica et Biophysica Acta 1637 (2003) 98–106

BIOCHIMICA ET BIOPHYSICA ACTA
BBA
www.bba-direct.com

Glyceraldehyde-3-phosphate dehydrogenase activity as an independent modifier of methylglyoxal levels in diabetes

Paul J. Beisswenger*, Scott K. Howell, Kenneth Smith, Benjamin S. Szwergold

79% reduction of GAPDH activity resulted in a sixfold increase in methylglyoxal



"Diabetic complications, insulin resistance, atherosclerosis, hypertension, cancer, disorders of the central nervous system.*"

*Graphical Abstract. CG Schalkwijk and CDA Stehouwer. Physiol Rev 2020; 100:407–461.

Toxicol. Res.
Vol. 30, No. 3, pp. 193-198 (2014)
Open Access http://dx.doi.org/10.5487/TR.2014.30.3.193
pISSN: 1976-8257 eISSN: 2234-2753 **Original Article**

Toxicological Research
Official Journal of
Korean Society of Toxicology
Available Online at http://www.ToxicolRes.org

Methylglyoxal Induces Mitochondrial Dysfunction and Cell Death in Liver

Kyuhwa Seo, Sung Hwan Ki and Sang Mi Shin

- Elevated plasma level of methylglyoxal are associated with diabetes, obesity and fatty liver disease
- Methylglyoxal induces oxidative stress
- Methylglyoxal causes liver toxicity, as indicated by increased levels of ALT and AST
- Methylglyoxal induces mitochondrial impairment and apoptosis in liver cells

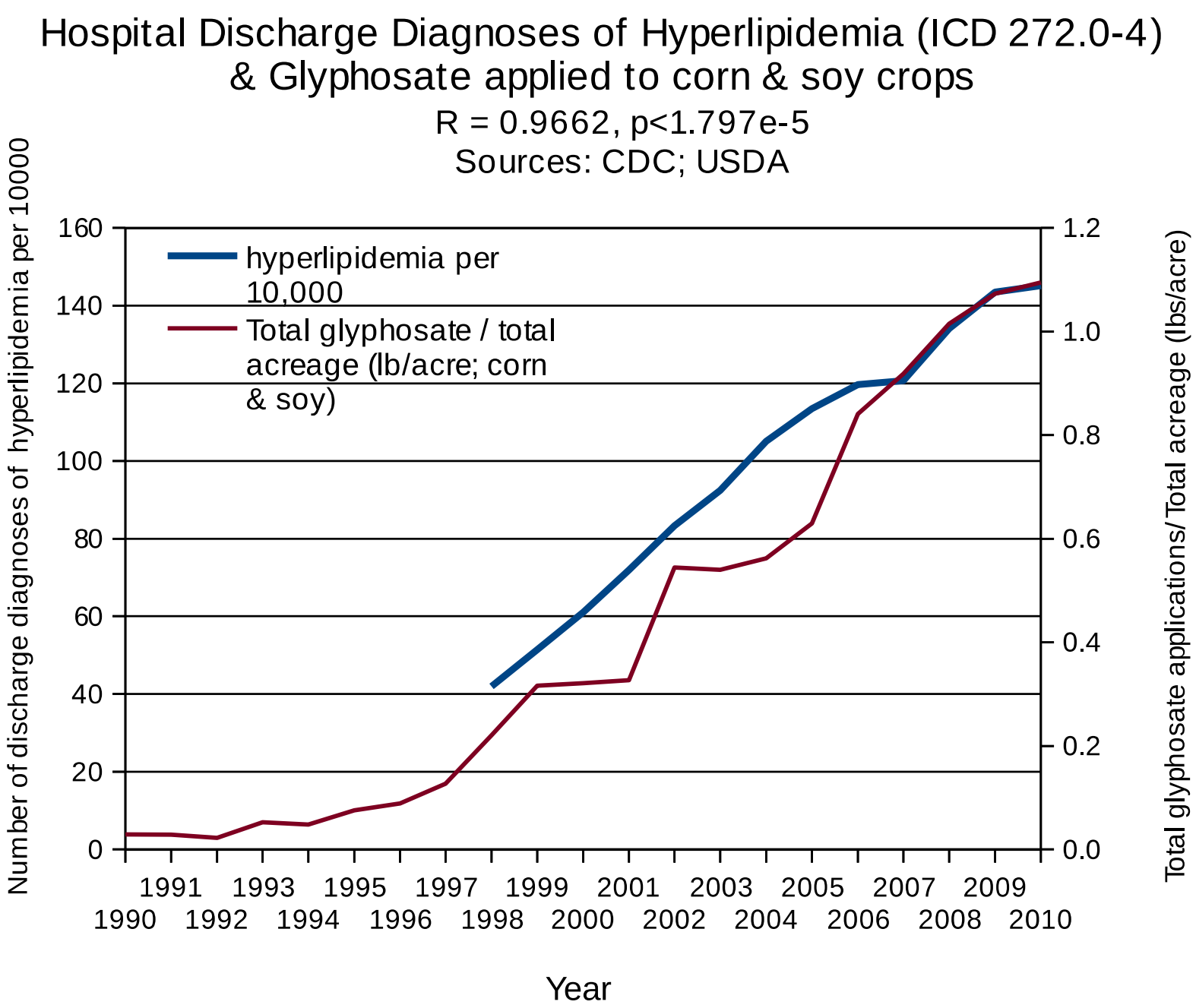
Is Glyphosate Causing an Epidemic in Fatty Liver Disease?

- Worldwide epidemic in fatty liver disease today*
- "Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide"**
- Glyphosate correlated with fatty liver disease in humans***

Non-Alcoholic Fatty Liver Disease (NAFLD)

Hunterdon Gastroenterology Associates
Medical Experts in the Treatment of Digestive Diseases

* Chris Estes et al. Hepatology 2018; 67(1): 123-133.
** Robin Mesnage et al. Sci Rep 2017; 7: 39328.
*** PJ Mills et al. Clinical Gastroenterology and Hepatology 2020;18(3):741-743.



Hyperlipidemia (high blood cholesterol) at hospital discharge is increasing over time, in step with the rise in glyphosate usage on corn and soy crops

*www.westonaprice.org/health-topics/modern-diseases/cholesterol-sulfate-deficiency-coronary-heart-disease/

Some dehydrogenases that are downregulated in E. coli when exposed to glyphosate*

- NADH dehydrogenase
- glucose-6-phosphate dehydrogenase
- succinate dehydrogenase
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- α-ketoglutarate dehydrogenase
- 2-deoxy-D-gluconate dehydrogenase
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- NADP-specific glutamate dehydrogenase
- 3-isopropylmalate dehydrogenase
- D-3-phosphoglycerate dehydrogenase

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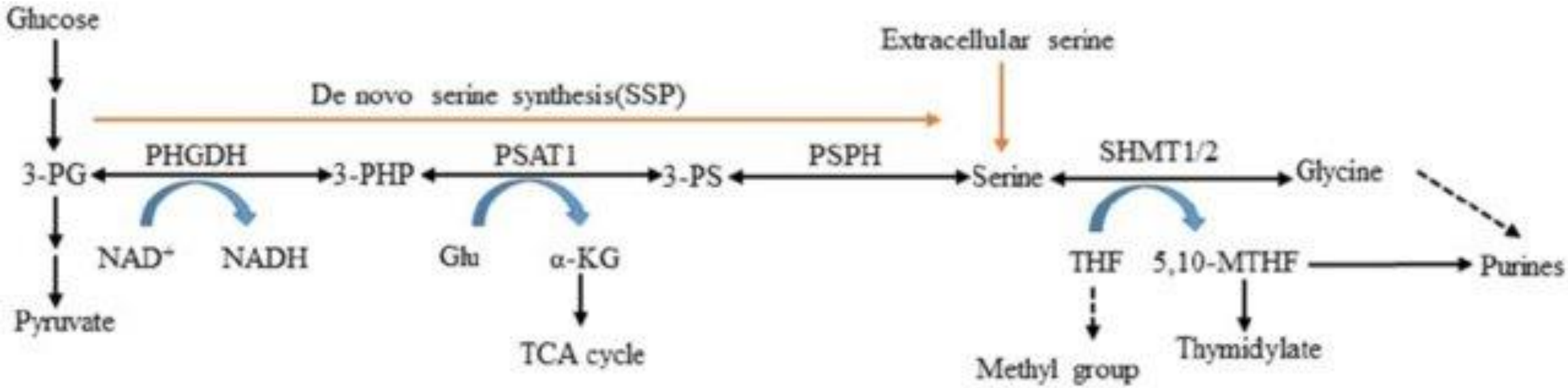
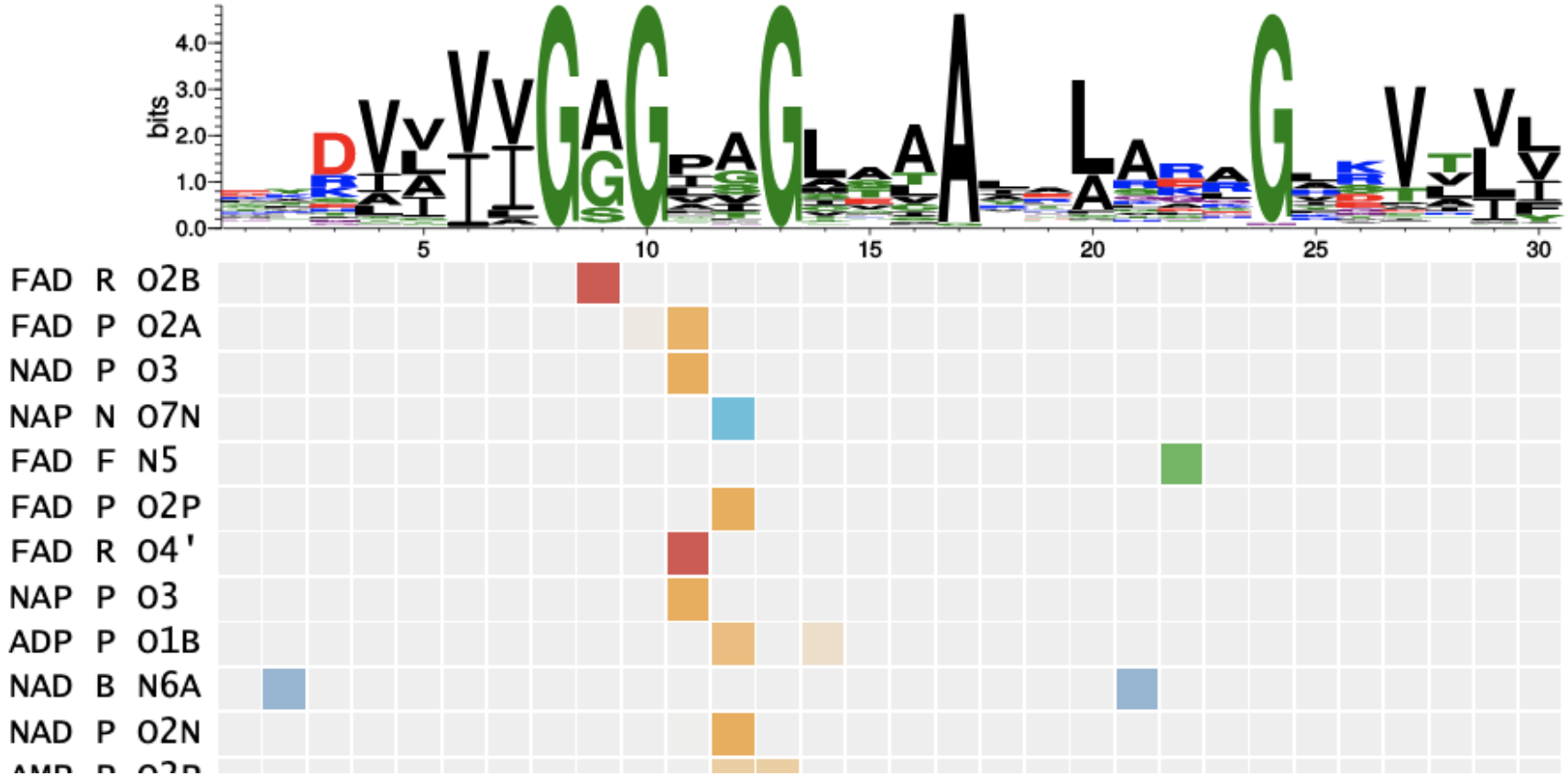
3-phosphoglycerate dehydrogenase



- 3-phosphoglycerate dehydrogenase (PHGDH) pulls an intermediate out of the glyclolysis pathway and initiates serine synthesis
- Genetic defects in PHGDH lead to microcephaly, intractable seizures, and motor and cognitive impairments*
- PHGDH has a highly conserved GxGxxG motif at the NAD binding site

*Koning T. Journal of Inherited Metabolic Disease 2006; 29: 347-351.

GxGxxG Motif at NAD binding site in 3-phosphoglycerate dehydrogenase



Methionine Deficiency and Methylation Pathways

The Big Picture

- Methylation pathways attach methyl groups to histones and to the cytosines in DNA molecules
- The methylation pattern of histones and DNA greatly influences gene expression
- Cancer is associated with hypomethylated DNA
- Methyls are metabolized while still attached to DNA, and the reaction yields succinate, an important source of protons in the mitochondria
- Methionine is the original source of the methyls, so they are normally severely depleted in deuterium content
- Supplemental methionine is problematic because it is usually synthesized in the chemistry lab rather than biologically synthesized
- Rat studies have shown that methionine deficiency leads to longevity, but these studies are fatally flawed

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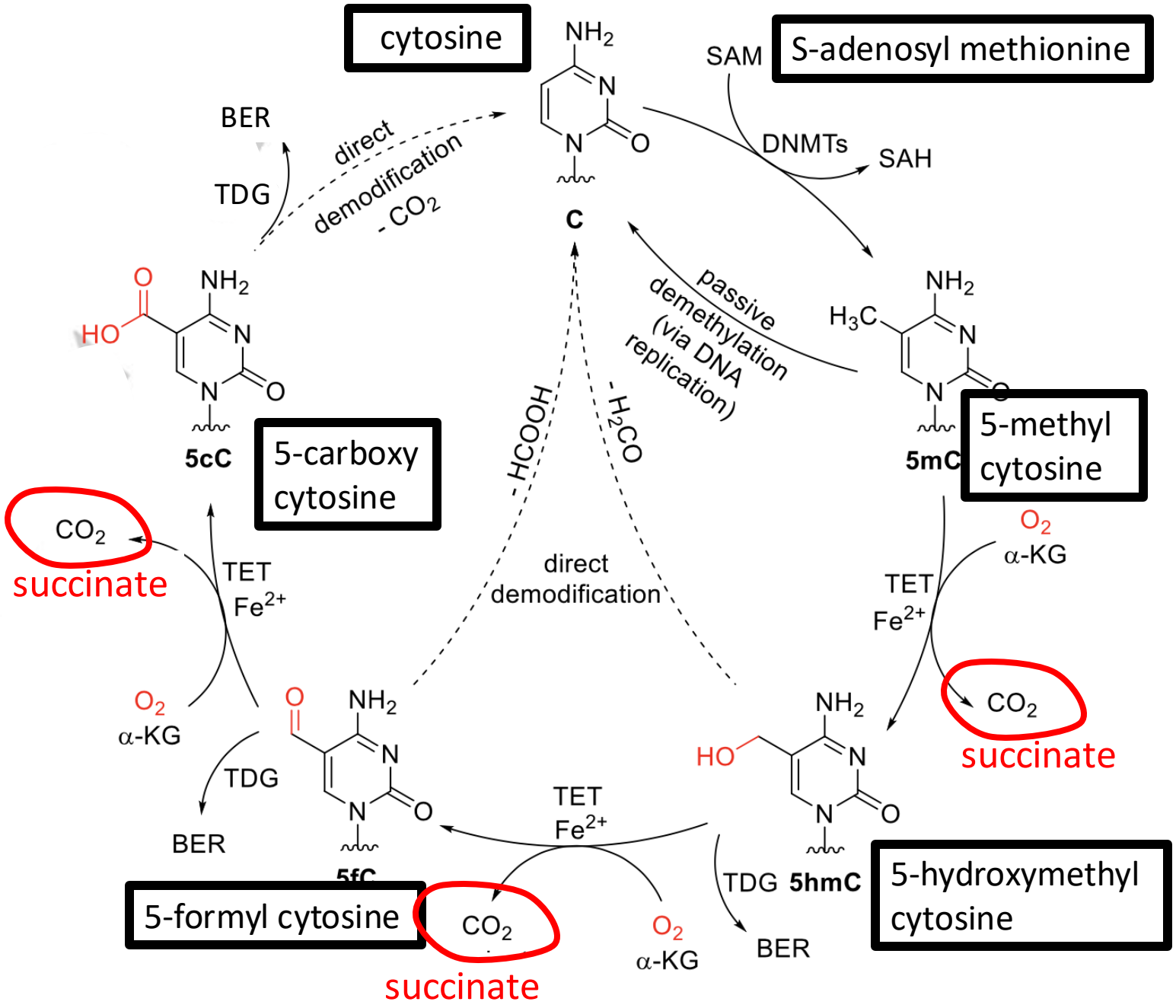
Epigenomics. 2009 December ; 1(2): 239–259. doi:10.2217/epi.09.33.

DNA hypomethylation in cancer cells

Melanie Ehrlich
Hayward Genetcs Program, Department of Biochemistry, and Tulane Cancer Center, Tulane Medical School, 1430 Tulane Ave., New Orleans, LA 70112, USA, Tel.: +1 504 988 2449, Fax: +1 504 988 1763, ehrlich@tulane.edu

- DNA hypomethylation is a ubiquitous feature of carcinogenesis
- DNA hypomethylation can be found early in carcinogenesis, but can also be associated with tumor progression

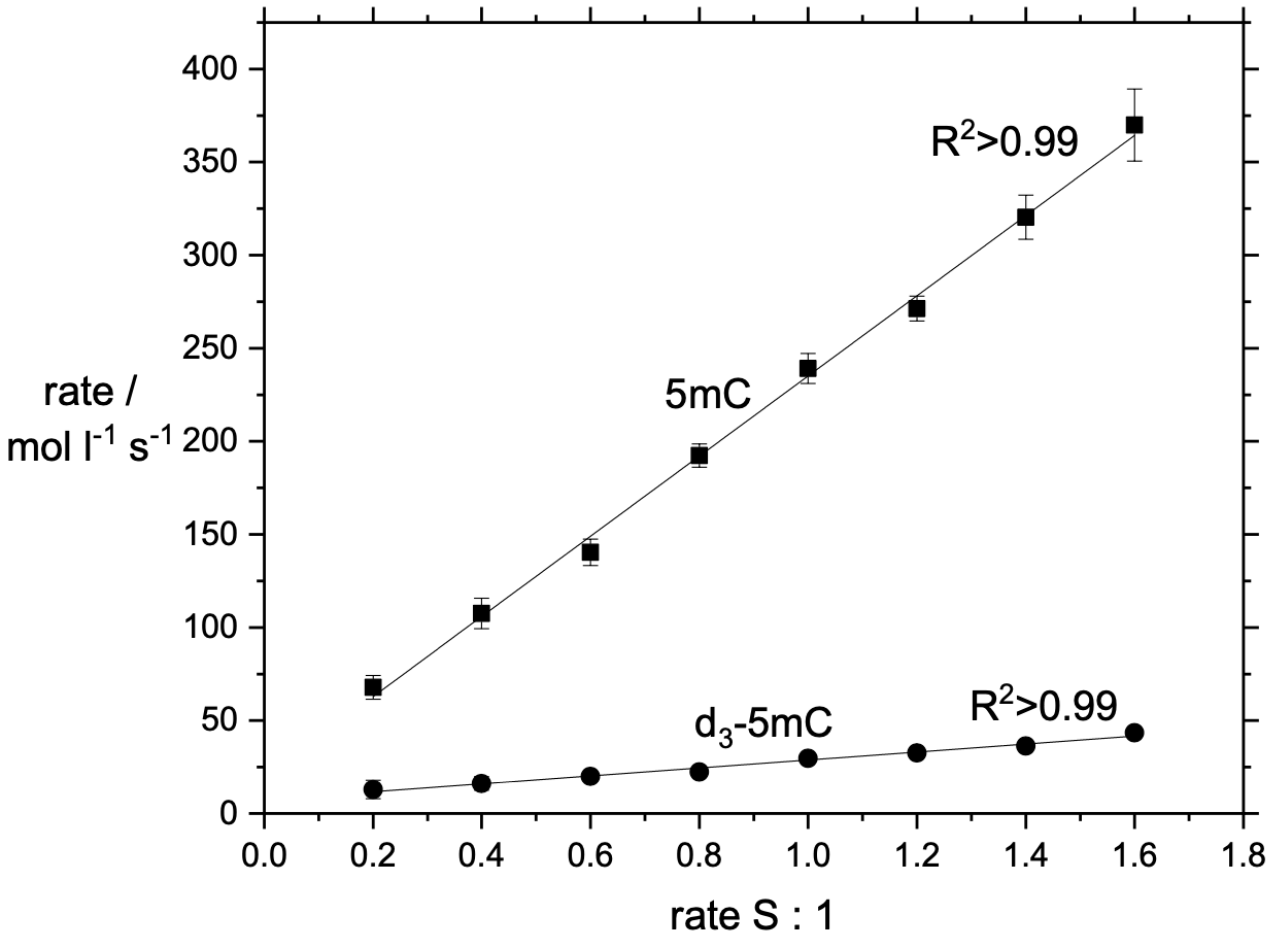


Demethylation of Cytosines in DNA*

- Protons are removed one by one from the methyl group originally attached to the nucleotide cytosine.
- α-ketoglutarate (α-KG) is converted to succinate, which can then feed low-deuterium protons to the mitochondrial intermembrane space
- The enzymes that achieve this feat are called ten eleven translocation (TET) family enzymes

*Figure 1. Niko Jonasson and Lena Daumann. Chemistry 2019; 25(52): 12091-12097.

TET has a high deuterium kinetic isotope effect (KIE)*



When the three protons attached to the methyl group in 5-methyl cytosine are all replaced with deuterium, the reaction rate decreases dramatically

*Figure 6. Niko Jonasson and Lena Daumann. Chemistry 2019; 25(52): 12091-12097.

Fibromalgia linked with DNA Hypomethylation*

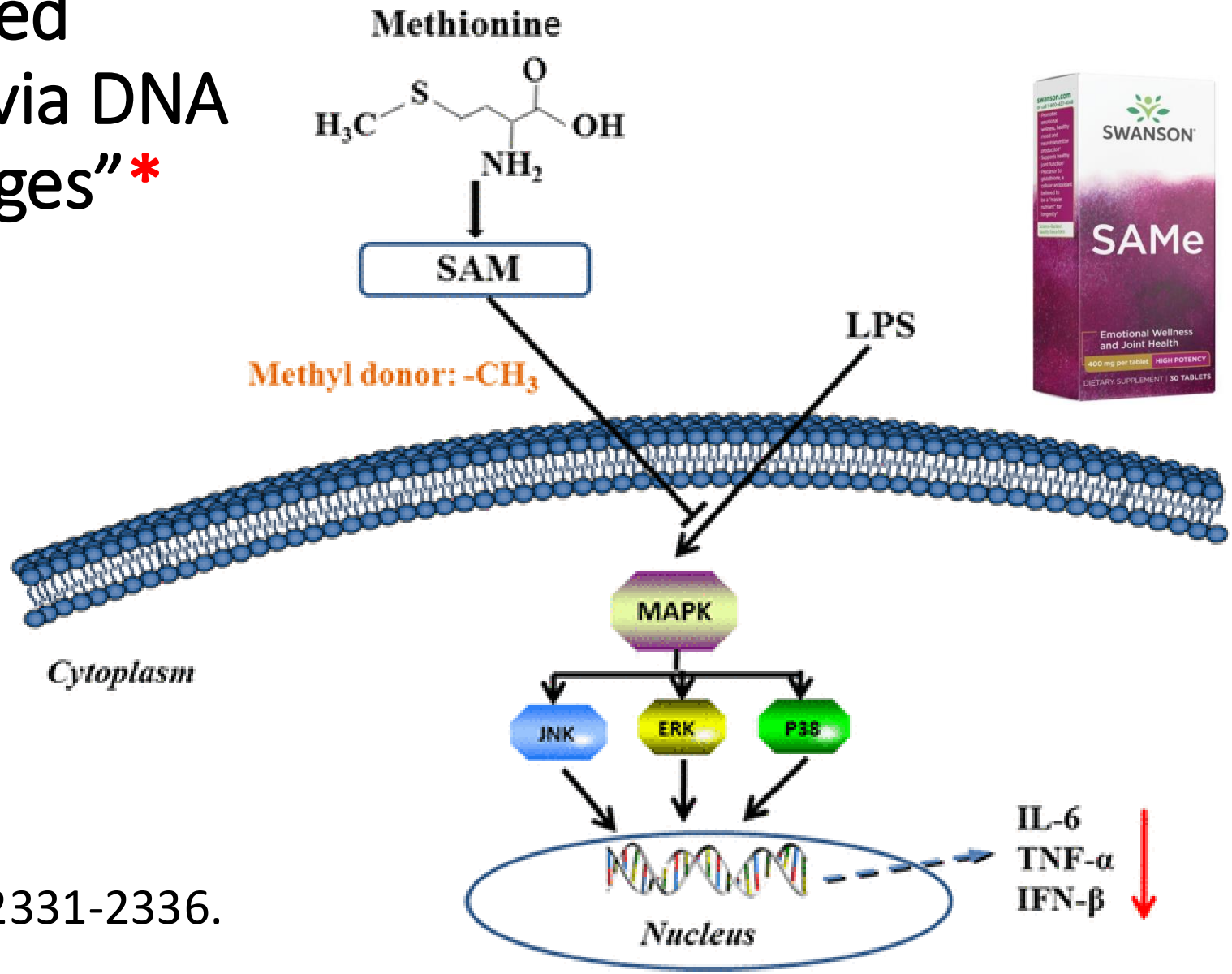
- Fibromalgia has a hypomethylation DNA pattern
- Enriched in genes implicated in stress response and DNA repair/free radical clearance
- This set of genes is also enriched for other disorders, including schizophrenia, mood disorders, bulimia, hyperphagia, and obesity.

Is depletion of methyl groups in DNA an indicator of mitochondrial dysfunction due to excess deuterium?

*Daniel Ciampi de Andrade et al. Pain. 2017 Aug;158(8):1473-1480.

“Methionine Attenuates Lipopolysaccharide-Induced Inflammatory Responses via DNA Methylation in Macrophages”*

- Methionine suppresses MAPK signaling via TLR4 through DNA methylation, and reduces production of inflammatory markers
- Reduces inflammatory response to both COVID-19 and the mRNA vaccines

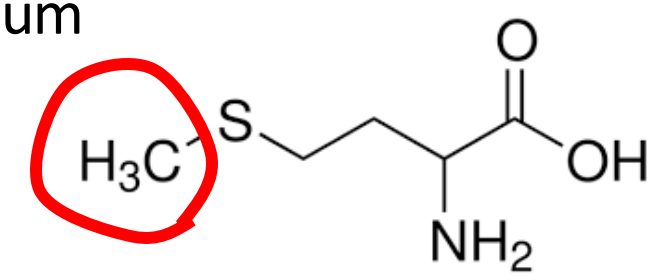


*Jian Ji et al. ACS Omega 2019; 4(1): 2331-2336.

“Dietary” Methionine Deficiency Induces Longevity

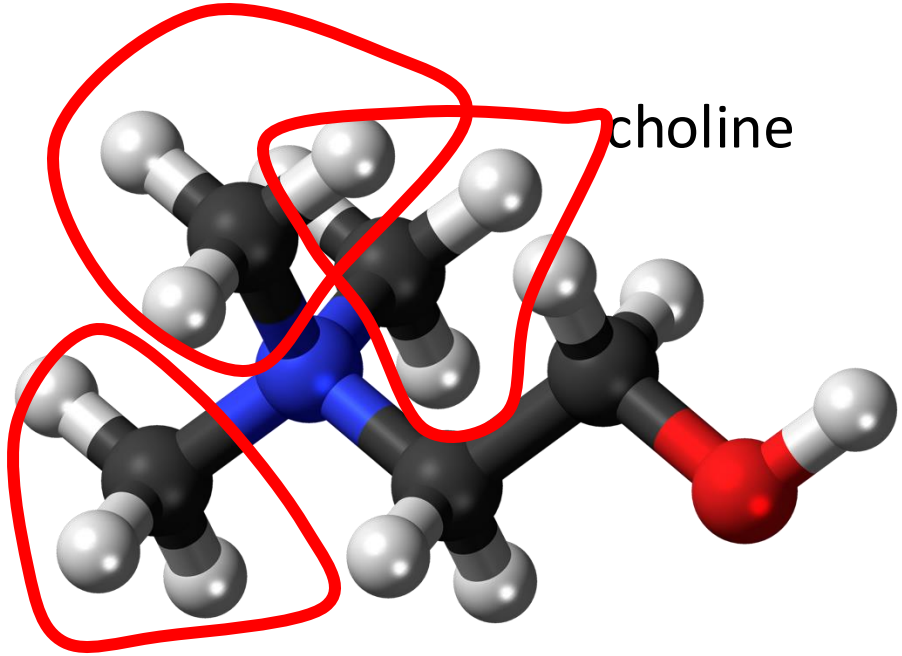
“Forty percent methionine restriction decreases mitochondrial oxygen radical production and leak at complex I during forward electron flow and lowers oxidative damage to proteins and mitochondrial DNA in rat kidney and brain mitochondria.”*

- Rats were fed synthetic amino acids instead of natural proteins
- Treated group got 40% reduced supply of synthetic methionine
  - They relied on methionine synthesized by the gut microbes
  - Their methyl groups were therefore greatly reduced in deuterium
  - Less deuterium in the mitochondria led to reduced ROS

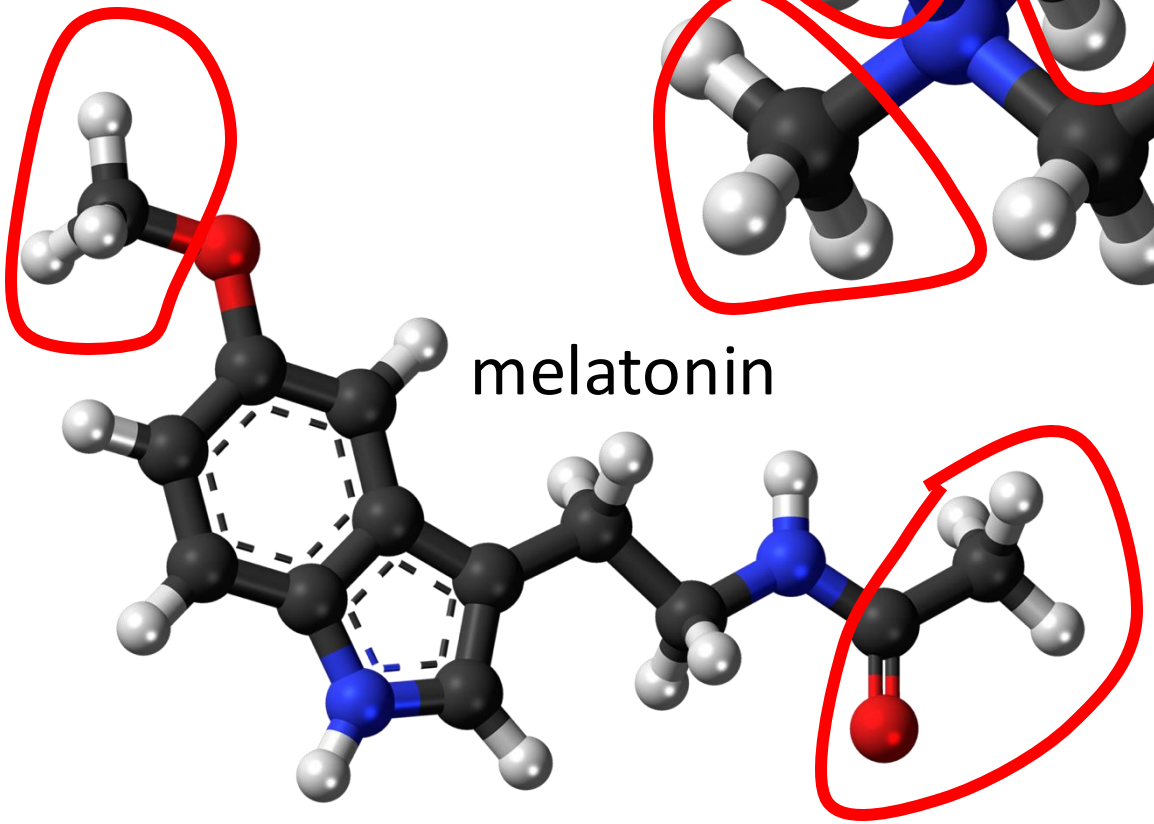


*P Caro et al. Rejuvenation Res. 2009; 12(6): 421-34.

Problematic Supplements

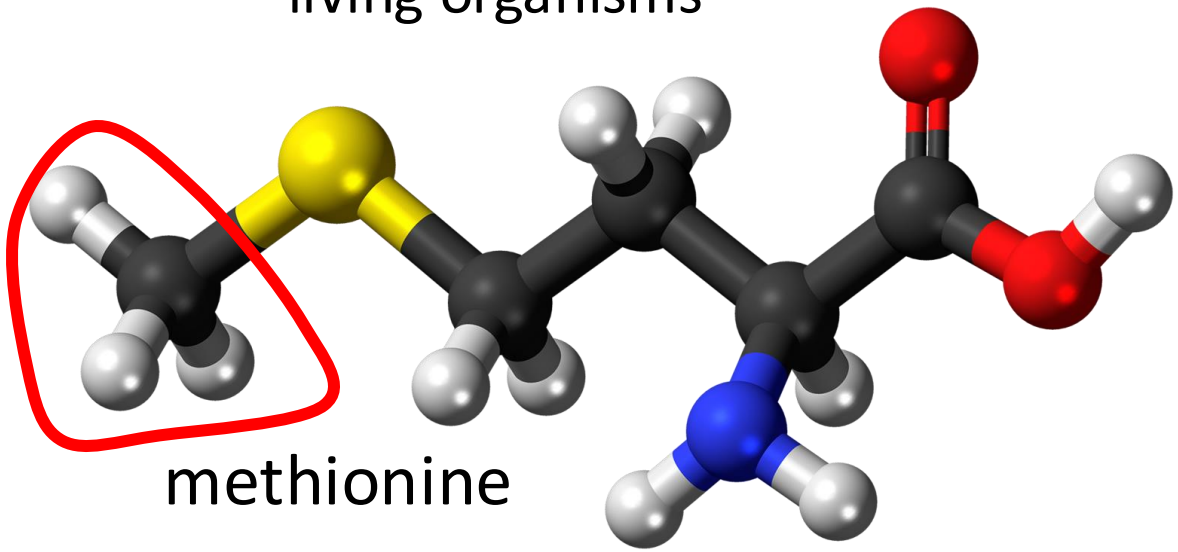


choline



melatonin

When these nutrients are taken as supplements, they are likely not depleted in deuterium, because they were synthesized in the chemistry lab instead of by living organisms



methionine

Glyphosate Damages Mitochondria

Glyphosate Suppresses Succinate Dehydrogenase

- Study on glyphosate's effects on E. coli proteins found that glyphosate significantly suppressed three different components of the succinate dehydrogenase complex*
- In vitro study on rat liver mitochondria in isolation exposed to Roundup found significant suppression of succinate dehydrogenase**
- Analysis of mechanism of glyphosate suppression suggested it disrupted *binding of succinate dehydrogenase to FAD****
- Succinate dehydrogenase has the sequence "GAGGAG" (Gly-Ala-Gly-Gly-Ala-Gly) at the site where it binds FAD

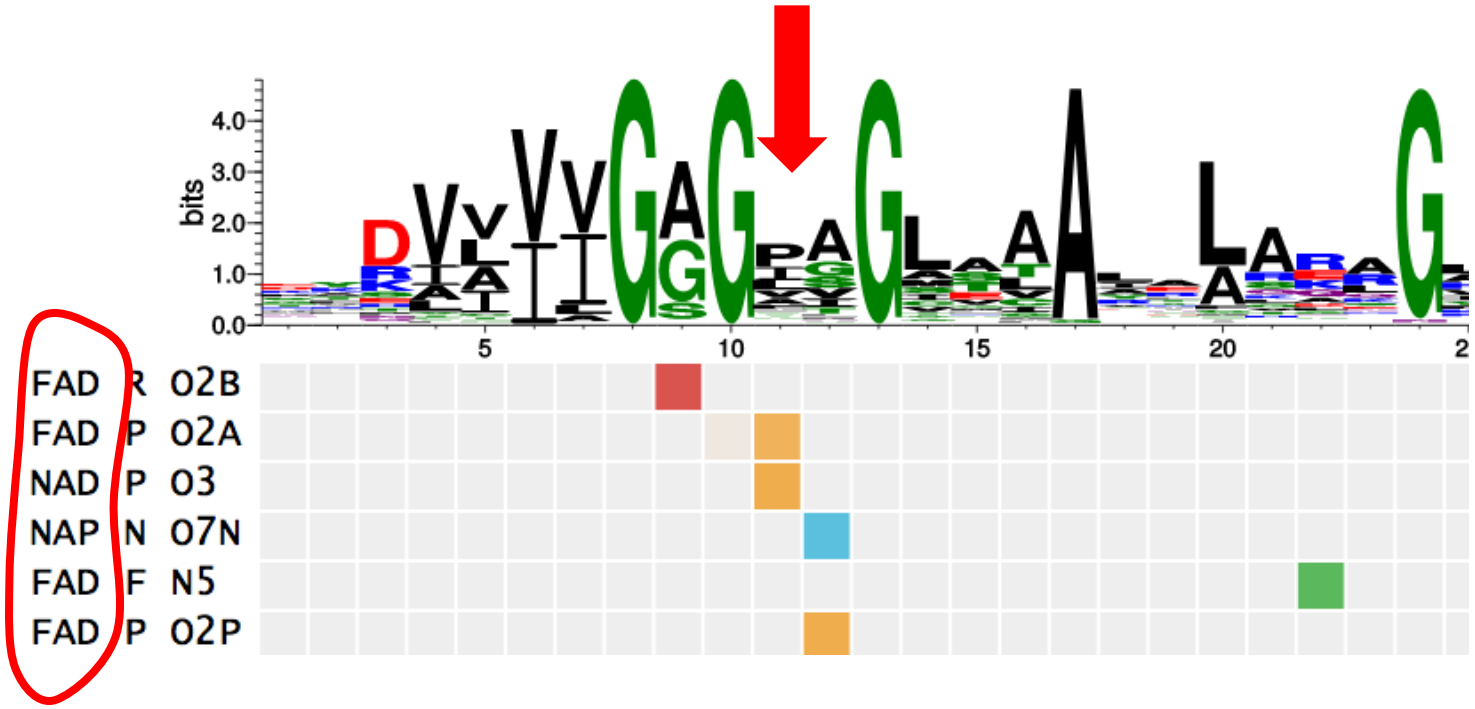
*W Lu et al., Mol. Biosys. 9 (2013) 522–530.

**Francisco Peixoto Chemosphere 61 (2005) 1115-1122.

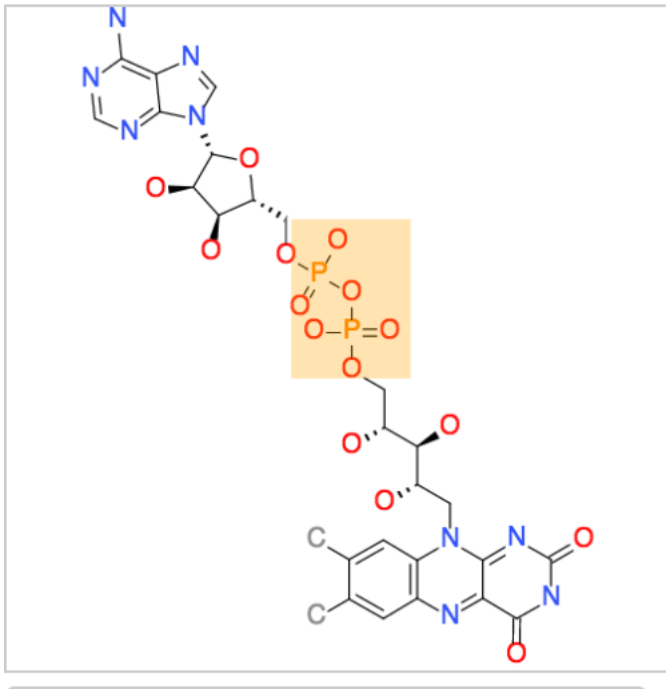
***R Ugarte. Computational Theor. Chem. 1043 (2014) 54–63.

Succinate Dehydrogenase: GxGGxG Motif*

GAGGAG

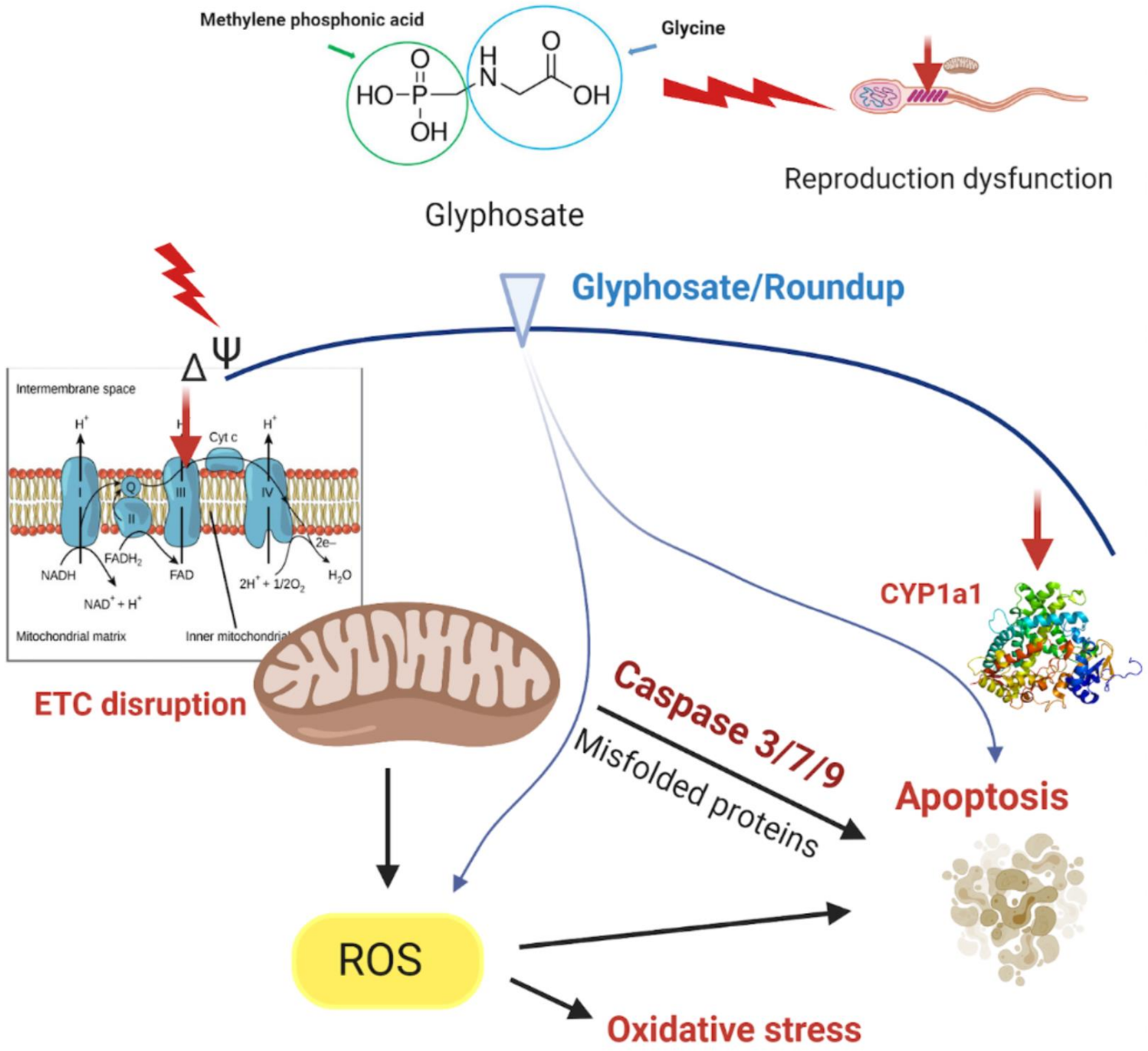


FAD(H)



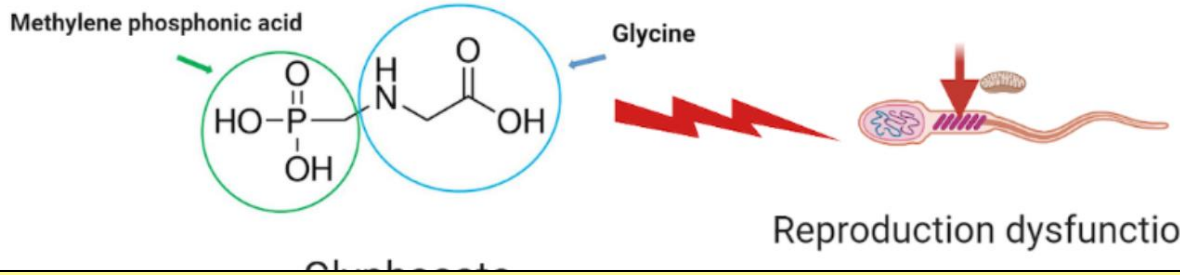
Binds FAD as a cofactor to catalyze electron transport in the mitochondria

*http://nbdb.bii.a-star.edu.sg/search



"The Effects of Low-toxic Herbicide Roundup and Glyphosate on Mitochondria"*

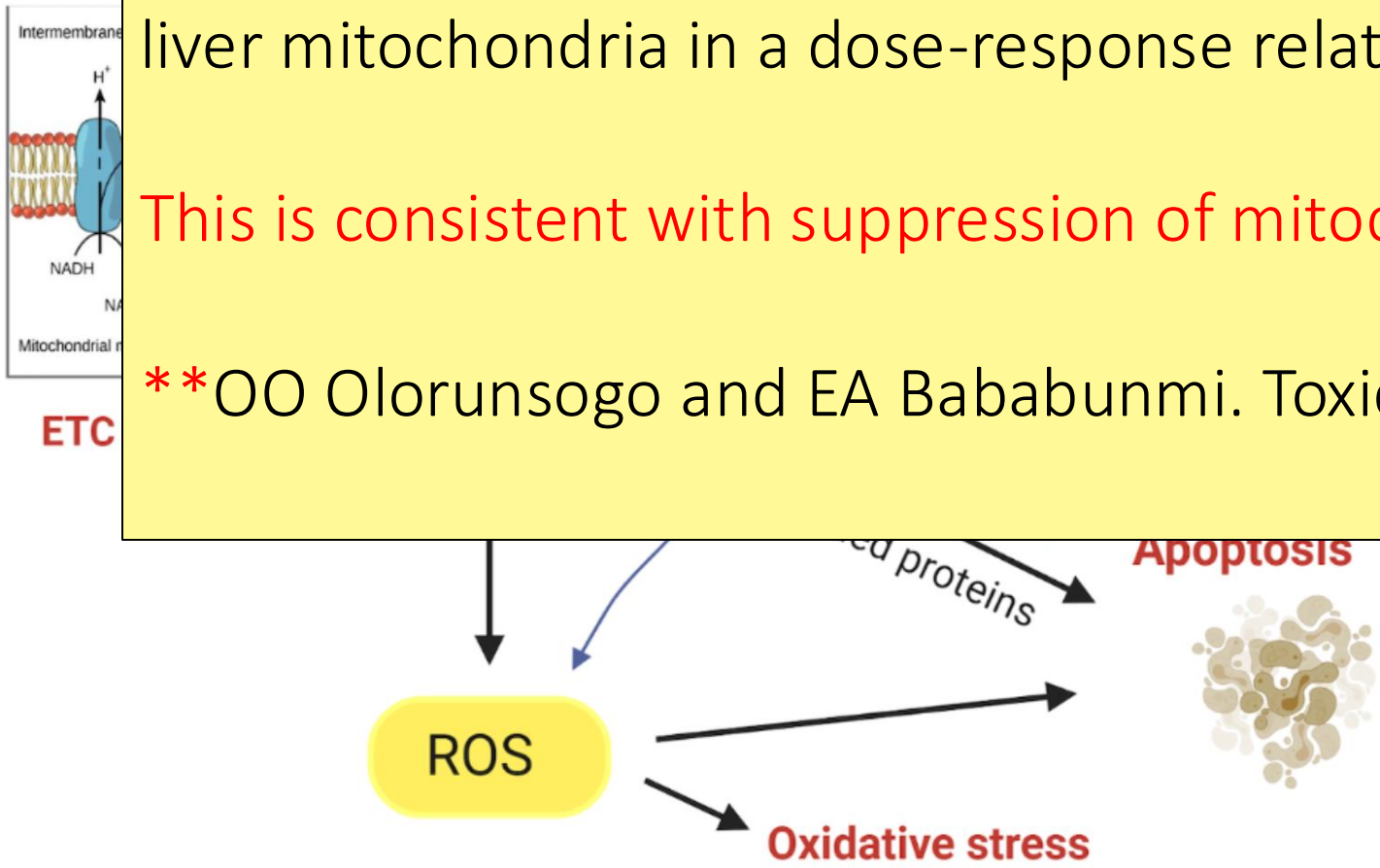
*Figure 2. Olha M. Strilbyska et al. EXCLI Journal 2022;21:183-196.



Glyphosate reduced conversion of NAD+ to NADH by up to 45% in rat liver mitochondria in a dose-response relationship**

This is consistent with suppression of mitochondrial dehydrogenases

**OO Olorunsogo and EA Bababunmi. Toxicol Lett. 1980;7:149-52.



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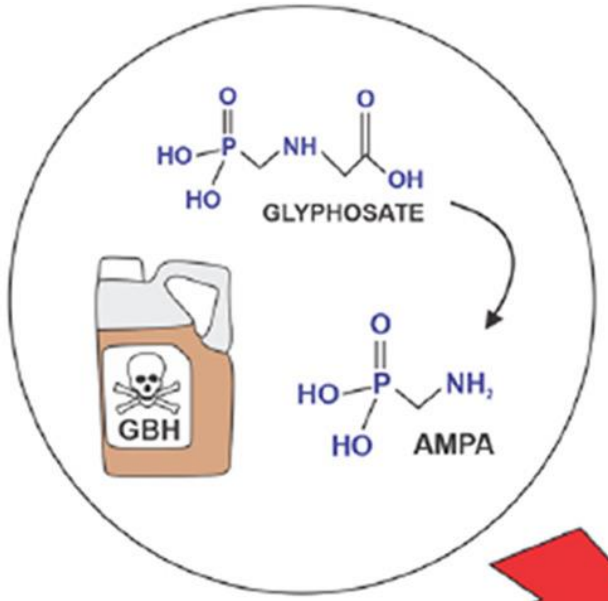
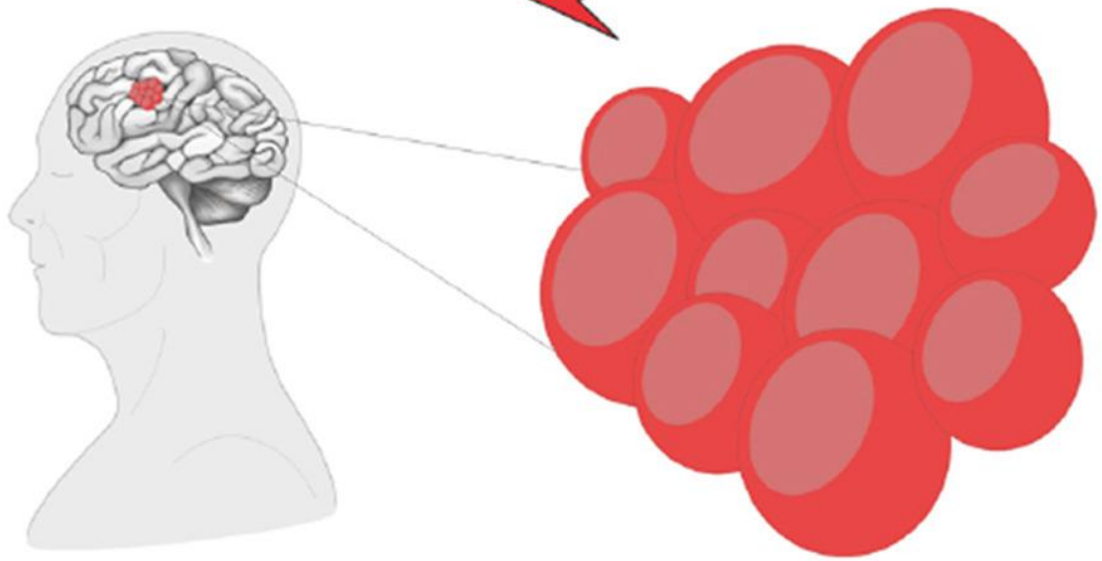


- Increased clonogenic growth
- Genomic instability
- Cell cycle deregulation
- Sustained proliferative signaling
- Oxidative stress
- Mitochondrial dysfunction
- Inflammation modulation



Glyphosate caused increased proliferation and mitochondrial dysfunction in human glioblastoma cells.*

Legend
AMPA: Aminomethylphosphonic acid
GBH: Glyphosate-based herbicide

*Claudia Daniele Bianco et al. Environmental Pollution 2023; 338: 122695.

Collagen, Proline and Deuterium

The Big Picture

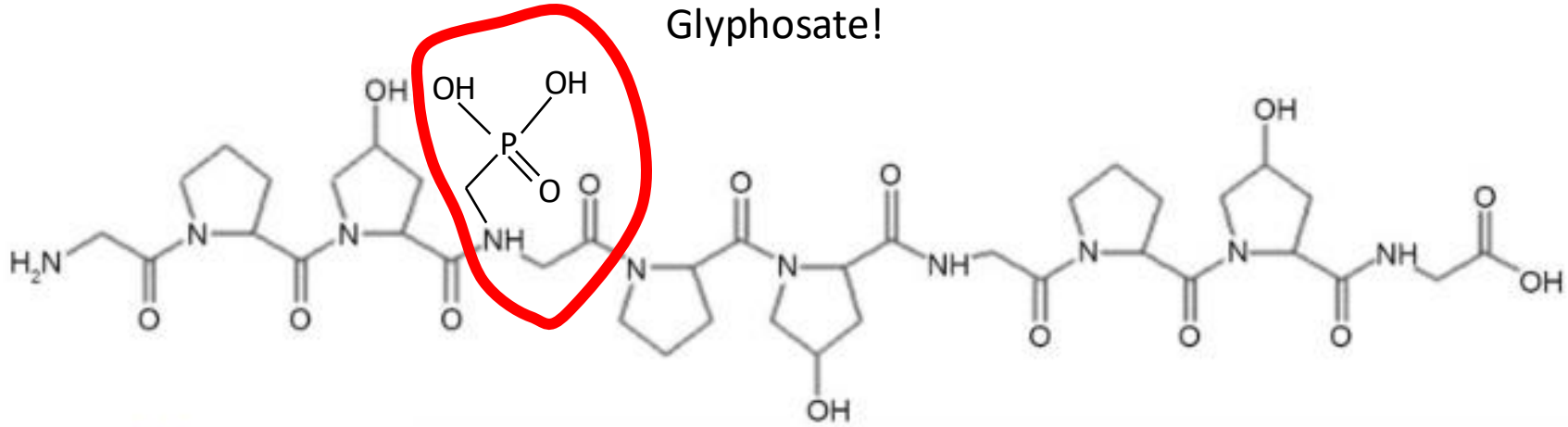
- One third of the proteins in the human body are collagen molecules!
- Collagen forms the glue that holds the body together
- Collagen's triple helix structure gives it strength and elasticity
- Collagen has long sequences of GxyGxy… that are susceptible to glyphosate substitution
  - Many glycine mutations lead to connective tissue disorders
- Collagen is highly enriched in proline and hydroxyproline as well
- Proline has special properties that allow collagen to trap and sequester deuterium
- Peptidyl prolyl isomerase (PPIase) is a crucial class of enzymes that orchestrate collagen folding and trap deuterium in the endoplasmic reticulum
- Proline plays a major role in cancer cell metabolism

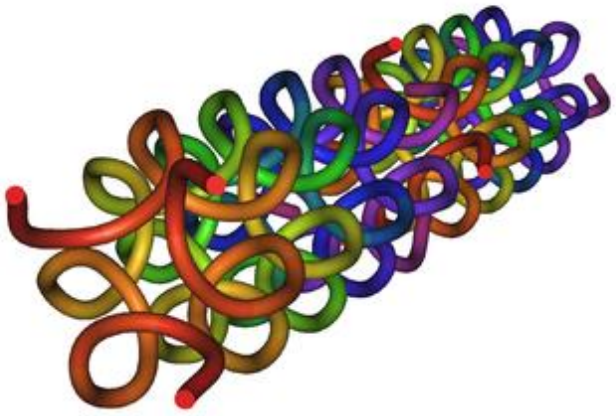
A

Gly-Pro-Hyp-Gly-Pro-Hyp-Gly-Pro-Hyp-Gly

Glyphosate!

B





Common sequence in collagen

Joint Hypermobility Syndrome

- Joint Hypermobility Syndrome is a relatively common genetic condition that often involves mutations in glycine residues in collagen
  - Connective tissue fragility, joint hypermobility, delayed wound healing, thin stretchy skin, abnormal scarring, vascular fragility, risk of aortic aneurism
- Specific heritable disorders include Marfan syndrome (MFS), osteogenesis imperfecta (OI) and Ehlers–Danlos syndrome (EDS)
- A mutation in a single glycine residue can lead to severe disease*
- Caused by impaired folding of the collagen molecule leading to collagen deficiency

*R Inokuchi et al. Medicine (Baltimore). 2014 Dec;93(28):e291.

Proline Tightly Binds Deuterium*

- "A sample of proline containing 17 atom percent D was boiled with 20% hydrochloric acid for 72 hours."
- "The proline isolated from this solution was found to contain 16.2% D."
- "Thus, even under these relatively drastic conditions exchange, if there is any, is very slow."

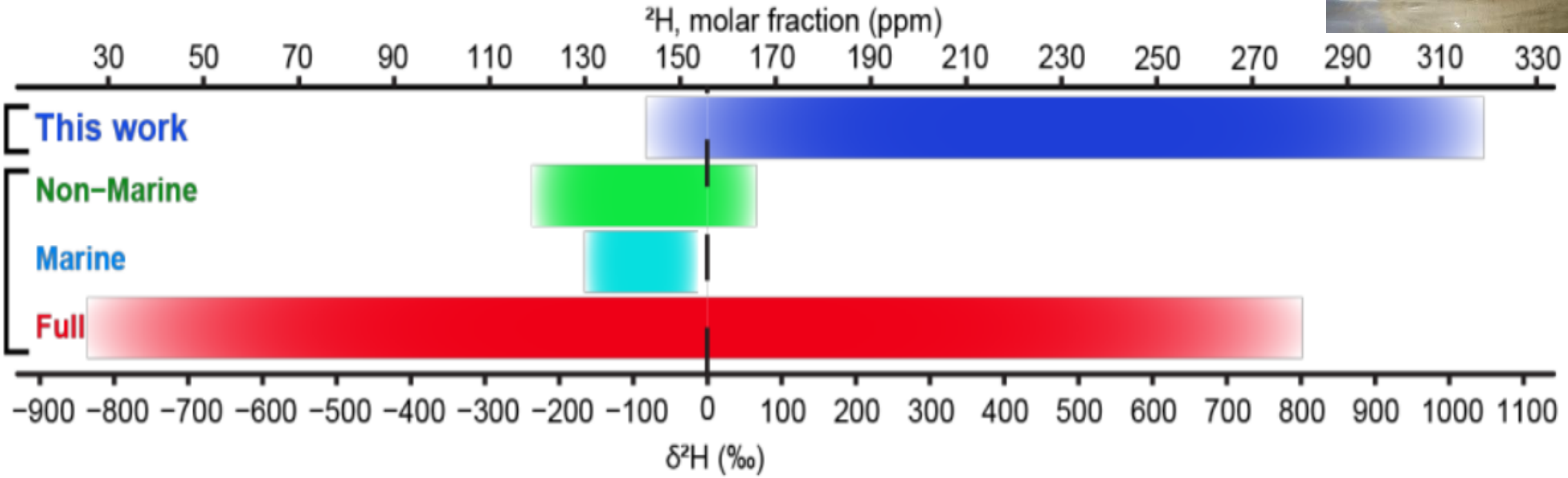
Hypothesis:

- Collagen folding in the endoplasmic reticulum involves trapping deuterium in proline molecules and ultimately sequestering it in the extracellular matrix and bone.
- This reduces deuterium loading in other proteins.

*Marjorie Roloff Stetten. Doctoral Thesis. Columbia University, 1943.

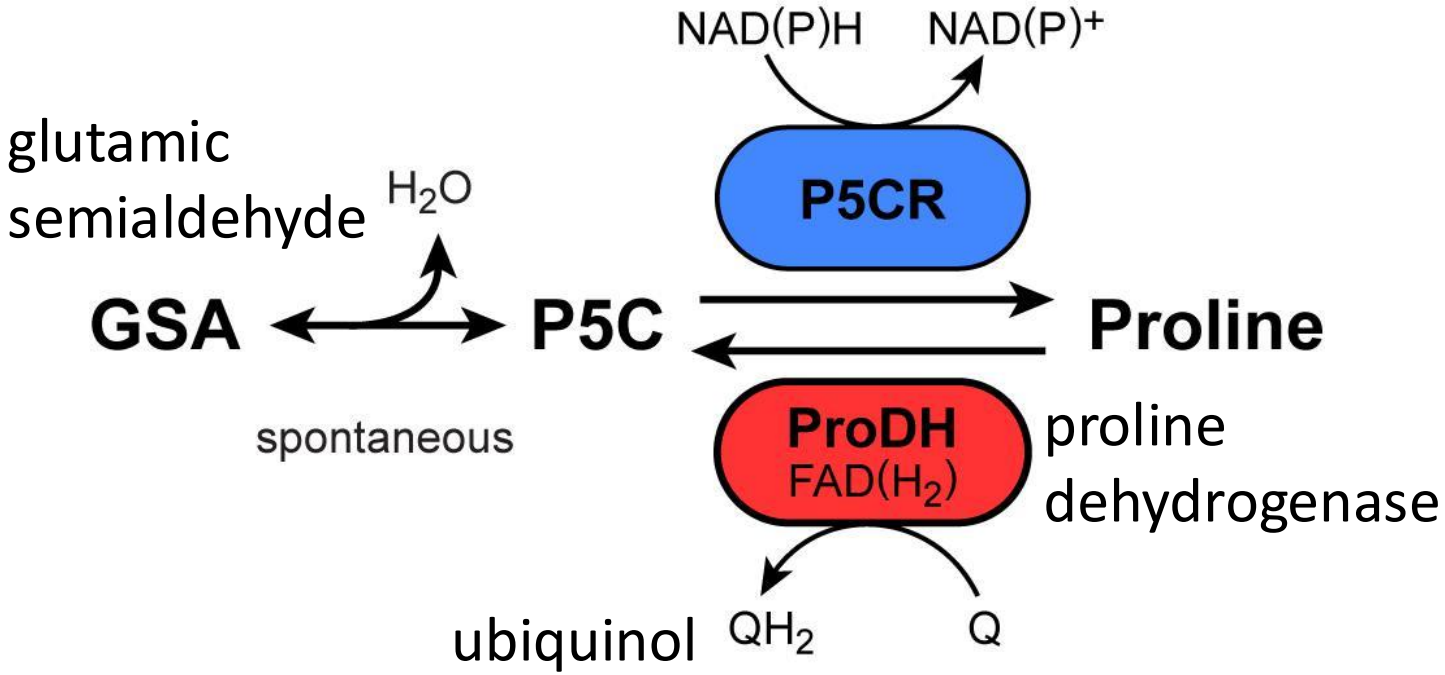
Bone Collagen from Seals*

- More than twice as much deuterium in proline and hydroxy-proline in the collagen of seals than is found in seawater
- Anomalously high deuterium levels are also found in proline and hydroxyproline in other biological sources



*Hassan Gharibi et al. J. Am. Chem. Soc. 2022, 144, 6, 2484-2487.

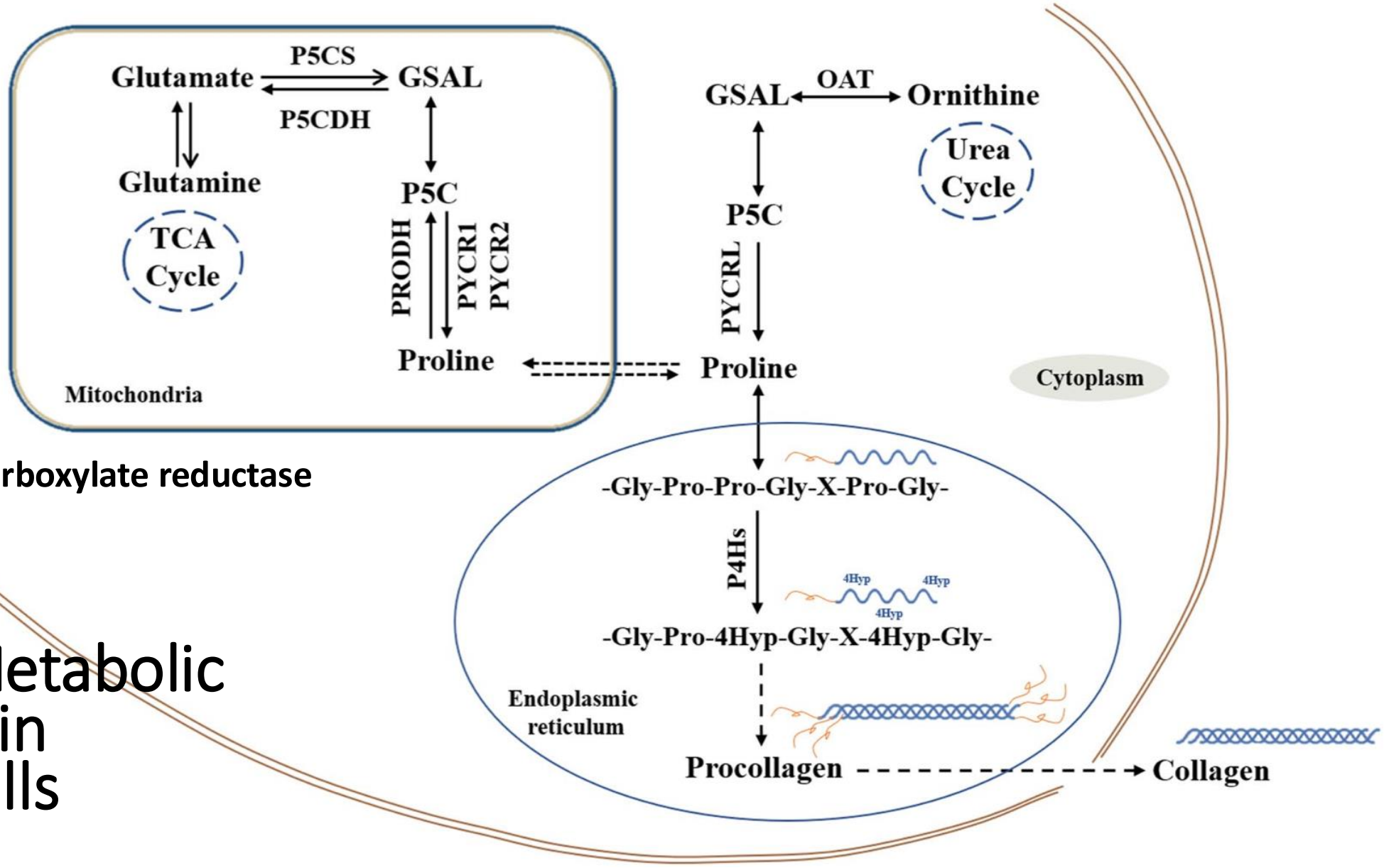
Proline dehydrogenase replaces succinate dehydrogenase in cancer cells



P5CR = pyrroline-5-carboxylate reductase

- Proline dehydrogenase (ProDH) substitutes for succinate dehydrogenase in the mitochondria when that enzyme is defective
- This also increases the demand for glutamate in cancer cells, or they can steal proline from the extracellular matrix

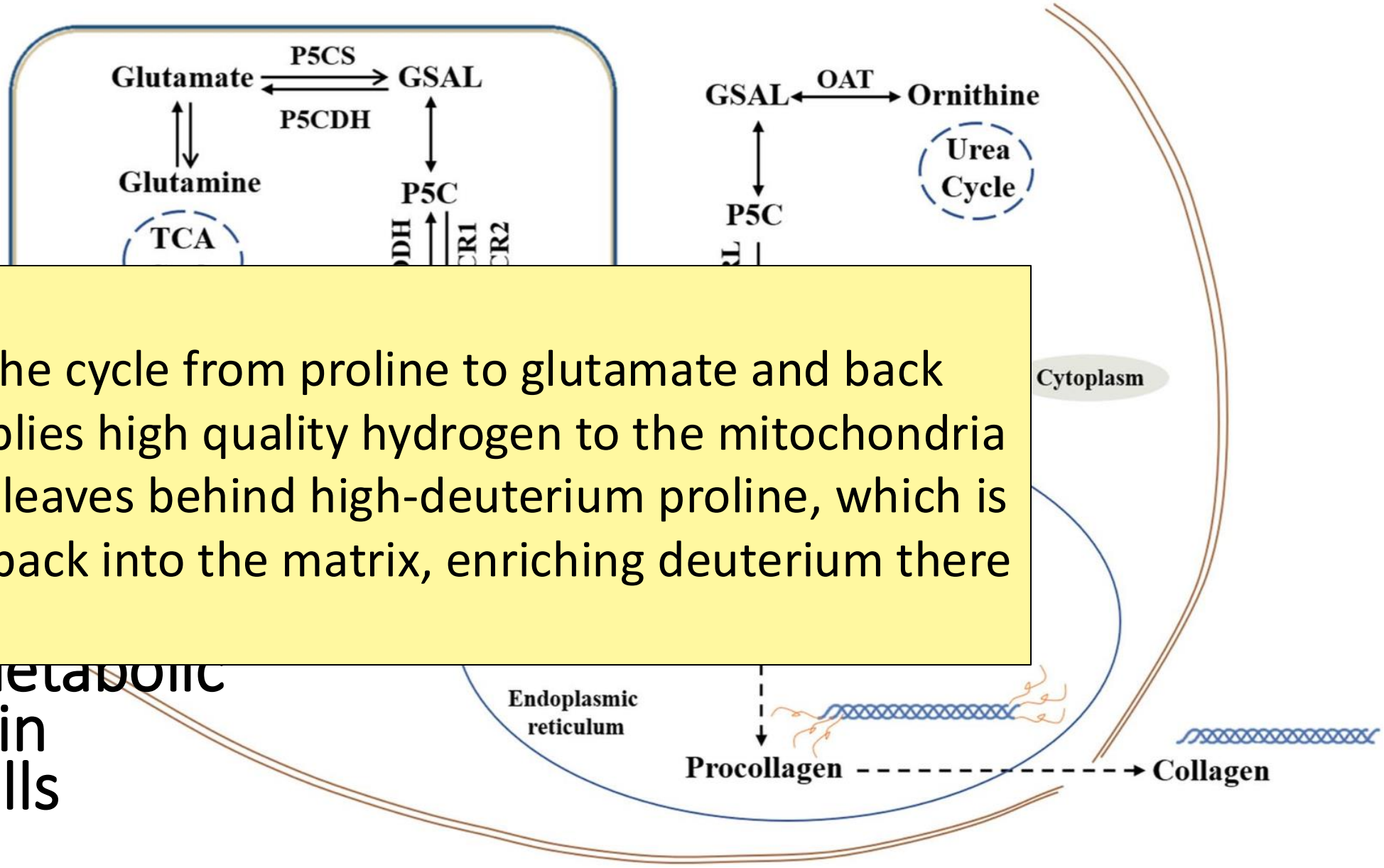
Proline Metabolic Pathways in Cancer Cells



PYCR = pyrroline-5-carboxylate reductase

*Figure 1. Pengyu Geng et al. Amino Acids (2021) 53:1769-1777.

Proline Metabolic Pathways in Cancer Cells



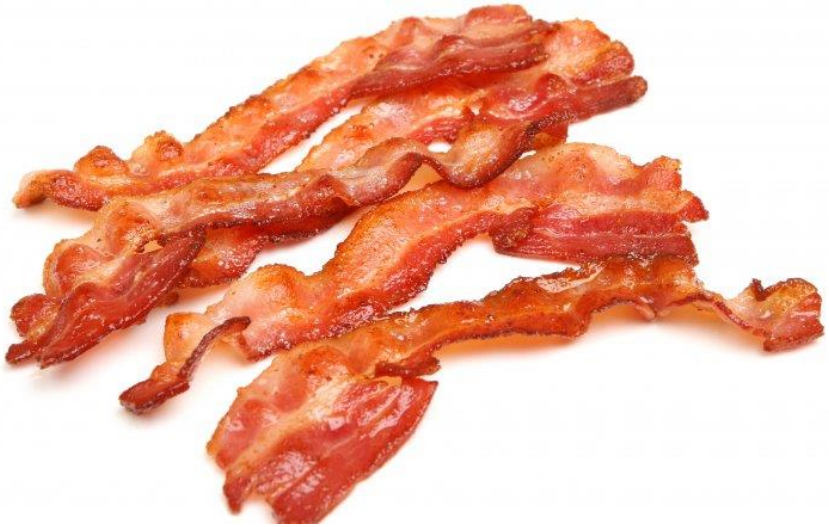
The cycle from proline to glutamate and back supplies high quality hydrogen to the mitochondria and leaves behind high-deuterium proline, which is put back into the matrix, enriching deuterium there

*Figure 1. Pengyu Geng et al. Amino Acids (2021) 53:1769-1777.

Healthy Lifestyle

A High-Fat Diet is a Low-Deuterium Diet

- Butter, lard and coconut oil were among the foods with the lowest detected levels of deuterium among foods tested
- The synthesis of fats involves transfer of hydrogen from NADPH into the growing fatty acid chain



Amounts of Deuterium in Various Foods

Flour: 150 ppm

Sugar: 146 ppm

Cottage Cheese: 136 ppm

Olive Oil: 130 ppm

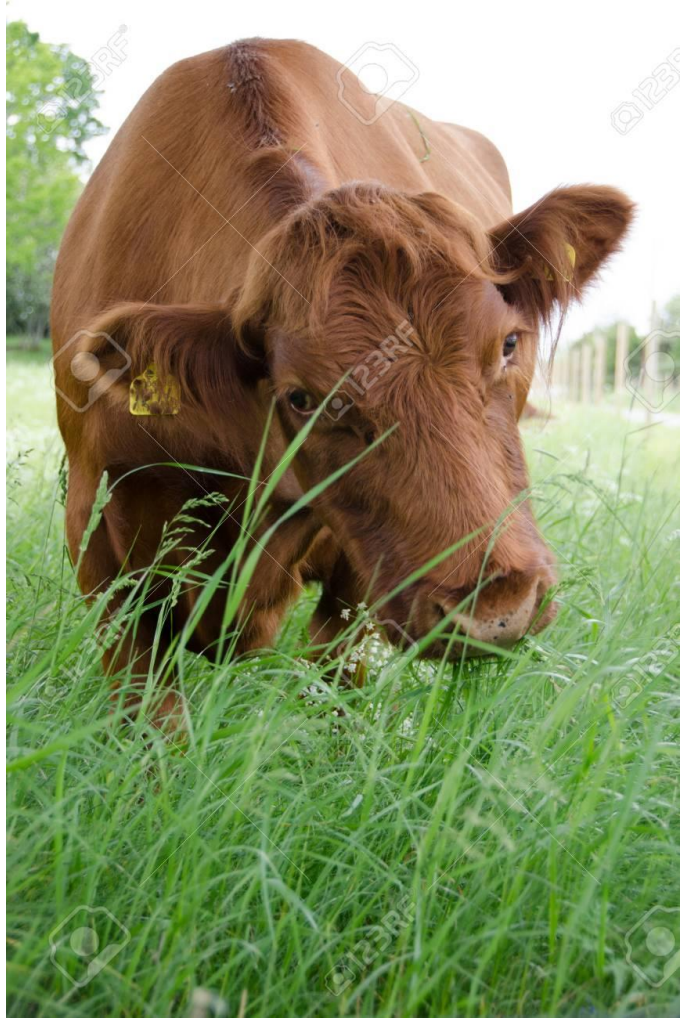
Coconut Oil: 110 ppm

Ghee: 112 ppm

Butter: 124 ppm

Deuterium in Foods and Mast-Cell Activation Syndrome*

- Mast cells release histamines during an allergic reaction
- Deuterium increases histamine release from mast cells
- Plants get rid of deuterium by storing it in sugar and starch
  - Fruits, root vegetables (potato) and grains are high in deuterium
  - Meats from grain-fed animals are high in deuterium
- Leafy green vegetables, animal fats (lard, tallow, butter) and plant fats (avocado, coconut, olive oil) are low in deuterium
- Grass-fed beef and the dairy products derived from pastured cows are excellent sources of low-deuterium fat



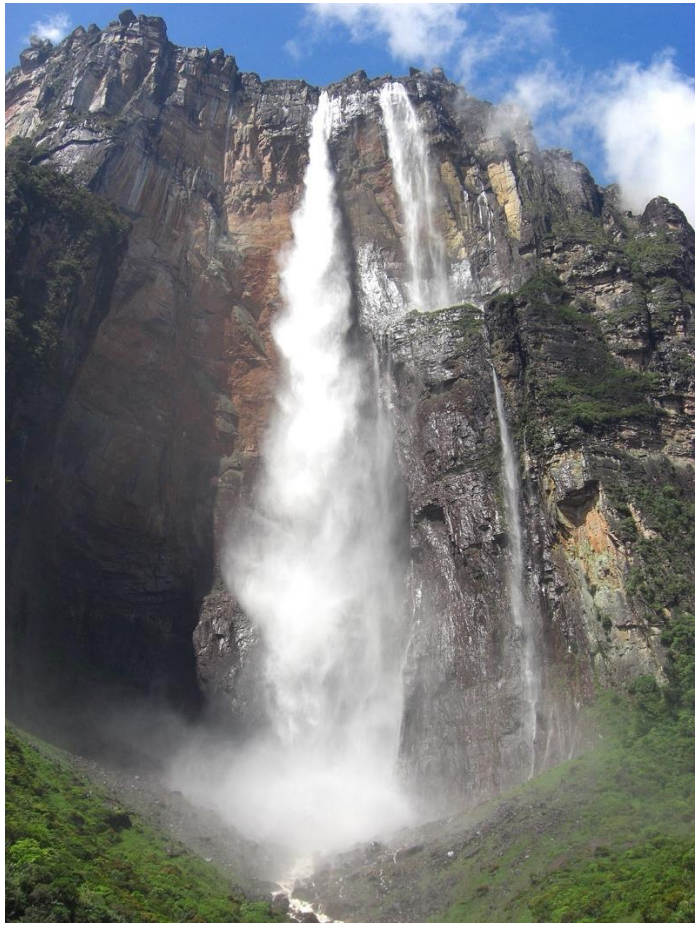
*https://healinghistamine.com/deuterium-histamine-intolerance/

Waterfalls are Therapeutic!*

- Waterfalls produce inhalable, negatively charged nano-water particles known as “Lenard ions” or ballo-electric ions
- These particles are likely to be deuterium depleted

“Conclusions: Our study provides new data, which strongly support an “added value” of exposure to waterfall microclimate when combined with a therapeutic sojourn at high altitude including regular physical activity.”

- Ocean waves probably have a similar effect



*C Grafetstätter et al. Physiol Anthropol. 2017; 36: 10.

"Life expectancy in Iceland among the highest in Europe, infant mortality rate is lowest”*

"In 2015 the infant mortality rate in Iceland was 1.9 per 1,000 live births”

“The average in the European Union is 4.0, while the US has an infant mortality rate of 5.87"

Sólheimajökull Glacier

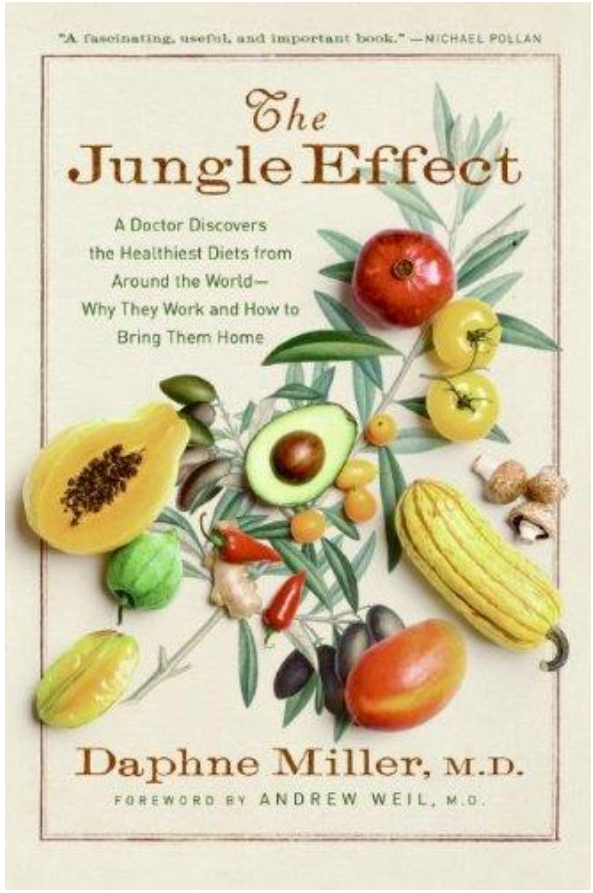
Smoked puffin

black sand beach of town Vík í Mýrdal in Iceland.

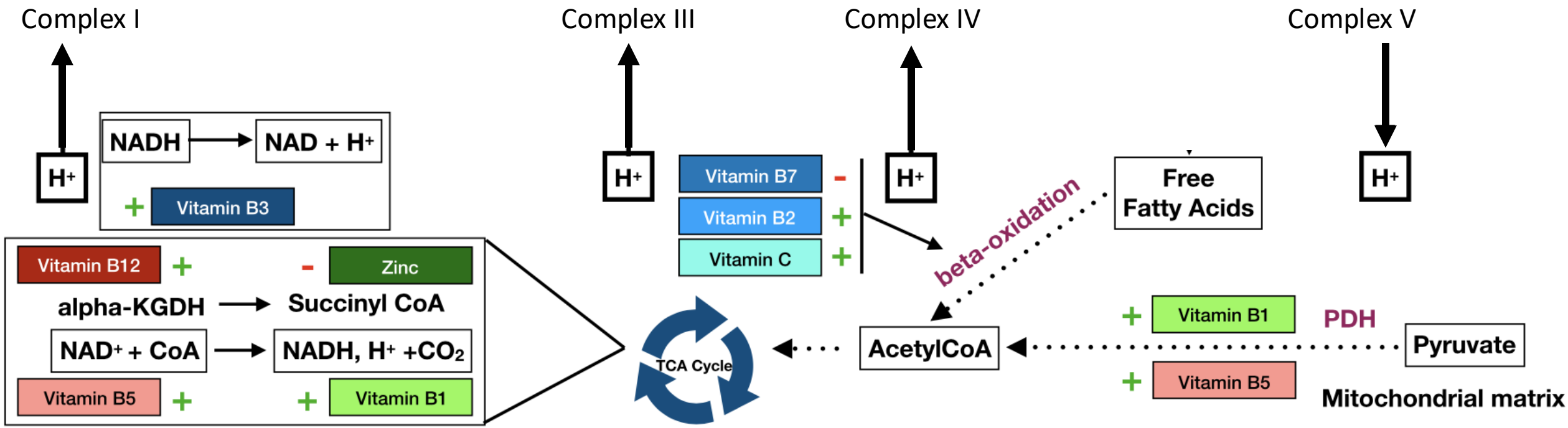
*https://icelandmag.is/article/life-expectancy-iceland-among-highest-europe-infant-mortality-rate-lowest

“The Jungle Effect: Healthiest Diets from Around the World” by Daphne Miller, MD

- Iceland was one of the places she studied
- Diet consists of fish, sheep, seabirds, potatoes, and other simple vegetables
- Iceland also has glacier water which is low in deuterium, and basalt which is high in sulfur (maintain sulfate levels)
  - Many sulfur hot springs with therapeutic benefit
- After a major eruption in the 1800’s, many islanders moved to northern Canada
  - They lost their health benefits



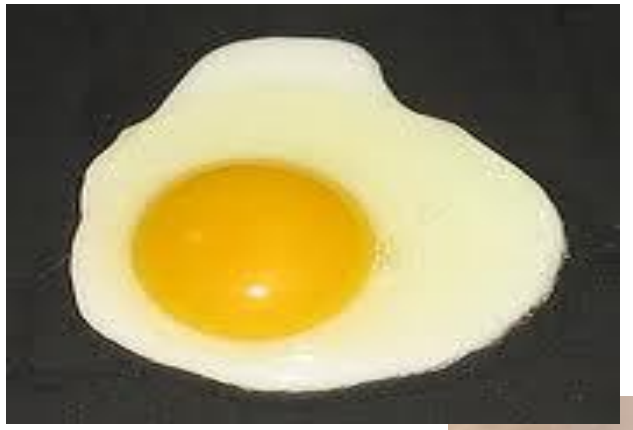
Many Nutrient Deficiencies Contribute to Mitochondrial Dysfunction*

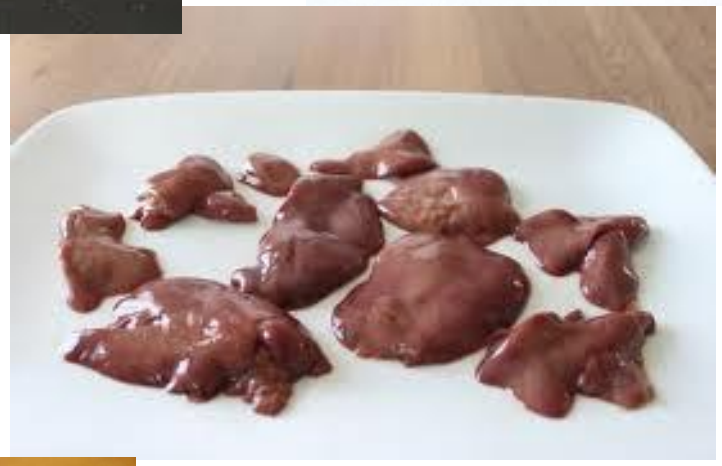


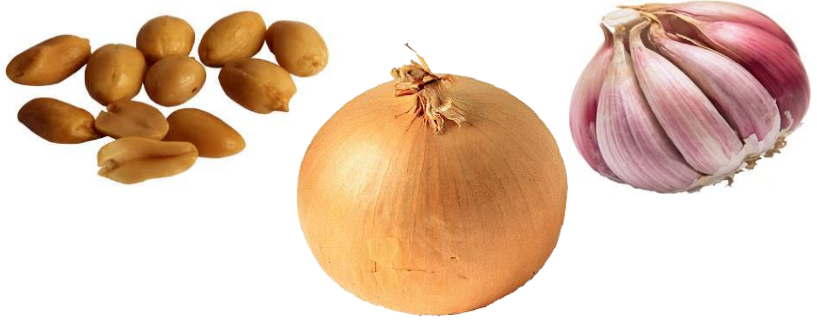
B1 = thiamine
B2 = riboflavin
B3 = niacin
B5 = pantothenic acid
B12 = cobalamin

*E. Wesselink et al. Clinical Nutrition 2019; 38: 982e995.

Eat Foods Containing Sulfur







Supplemental Sources of Sulfur*

- glucosamine sulfate
- chondroitin sulfate
- glutathione
- N-acetylcysteine
- alpha lipoic acid
- taurine
- DMSO, MSM
- S-adenosylmethionine (SAMe)
- Epsom salts (Mg-sulfate)

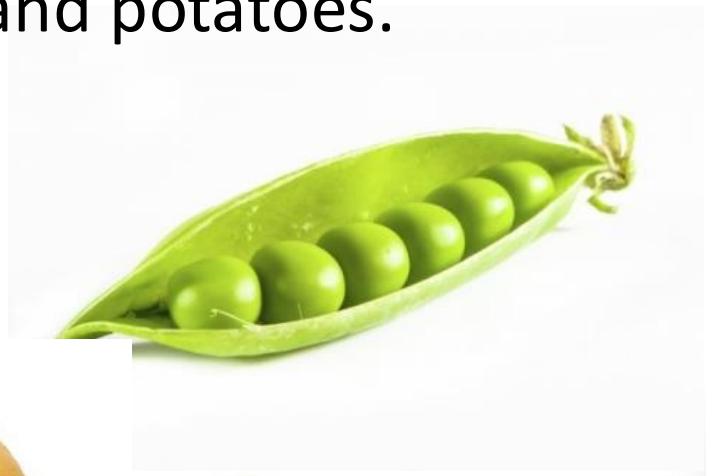
These can have many beneficial effects and are nearly nontoxic

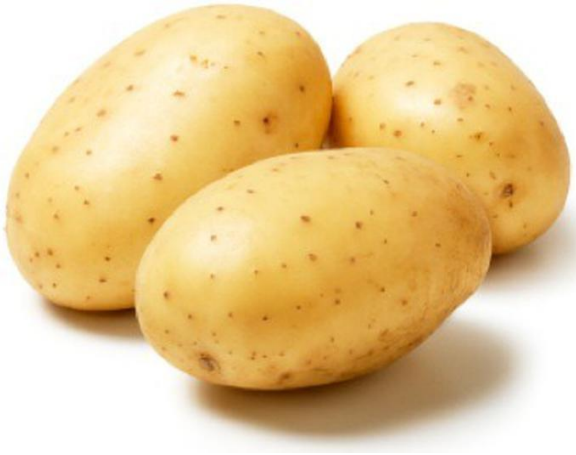
My personal favorite is Epsom salt baths: Magnesium sulfate uptake through the skin

*S Parcell, Alternative Medicine Review 7(1), 2002, 22-44

Foods High in Niacin (B3) → NAD(P)(H)

- Many foods are rich in niacin (B3), especially animal products like meat, fish and poultry.
- Vegetarian sources include avocado, peanuts, whole grains, mushrooms, green peas and potatoes.





Riboflavin (B2): Source for FAD in Flavoproteins

Foods high in riboflavin (B2) include beef, tofu, milk, fish, mushrooms, pork, spinach, almonds, avocados, and eggs

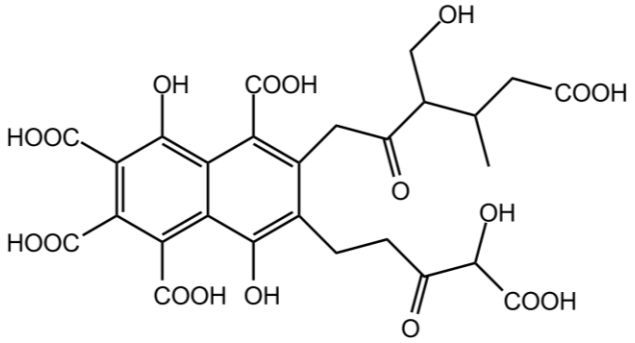
DDW, Glacier Water and Hydrogen Water

Flavonoids and Polyphenols!

Treating Glyphosate Poisoning in Cows*

Bentonite Clay

Activated charcoal, bentonite clay, humic and fulvic acids, and sauerkraut juice have been shown to be effective in reducing urinary levels of glyphosate and improving animal health



Fulvic Acid

Activated Charcoal

*H Gerlach et al., J Environ Anal Toxicol 2014, 5:2

Go Organic!


QUE PASA
TORTILLA CHIPS
ORGANIC
Original Handcooked Recipe
Gluten-Free
Stone Ground
ORGANIC CORN STARCH
RAPUNZEL
ORGANIC CORN STARCH
ORGANIC BEST ALE
SAM SMITH
OLDE BREWERY
ORGANIC SHOYU
NATURALLY BREWED SOY SAUCE
PASTURE-RAISED
Organic HALF & HALF
ULTRA PASTEURIZED GRADE A
Pasture-Raised
ORGANIC VALLEY
FARMER-OWNED
Organic
HALF & HALF
Organic Sweet Cream
ORGANIC VALLEY
4 QUARTERS
Salted Butter
FARMER-OWNED

Summary

- The herbicide glyphosate is pervasive in our food supply, and it is far more toxic than our regulators are willing to admit
- Glyphosate's mechanism of toxicity is unique, and it likely involves substituting for the amino acid glycine by mistake during protein synthesis in susceptible proteins
- Glyphosate disrupts sulfation and methylation pathways, which results in mitochondrial dysfunction due to excessive deuterium accumulation
- Mitochondria exposed to too much deuterium become dysfunctional, spewing out reactive oxygen species and producing insufficient ATP
- Collagen traps deuterium in proline residues, but is highly susceptible to glyphosate toxicity
- Many modern diseases are associated with mitochondrial dysfunction