Does Fat Really Burn in the Flame of Carbohydrate?

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www.proteinpower.com

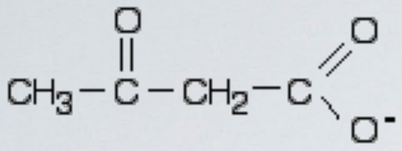
LOW-CARB Breckenridge 2017

February 25, 2017
Breckenridge, Colorado

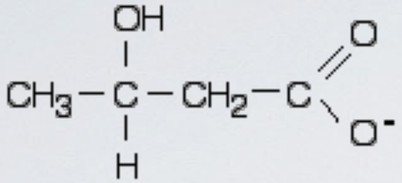
“Fett brennt im Feuer der Kohlenhydrate.”

–Dr Georg Rosenfeld

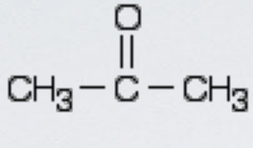
Rosenfeld, G.: Fett- und Kohlenhydrate.
Berlklin. Wchnschr. 43: 978. 1906



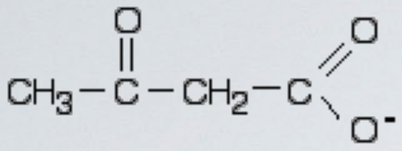
acetoacetate



β-hydroxybutyrate



acetone



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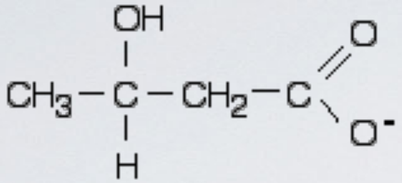

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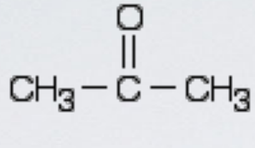

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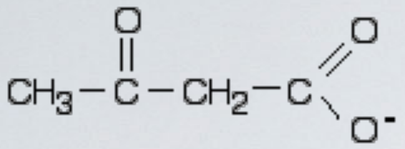

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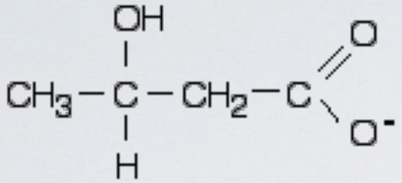

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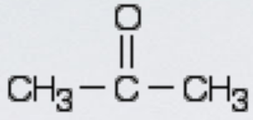

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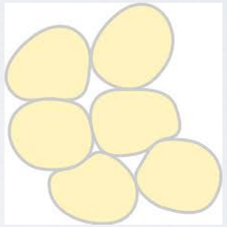

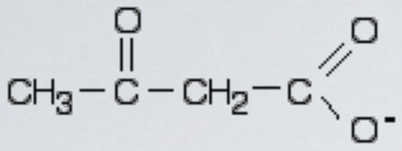

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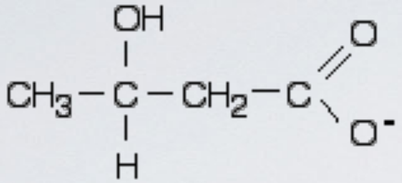
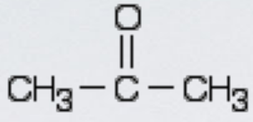


β-hydroxybutyrate



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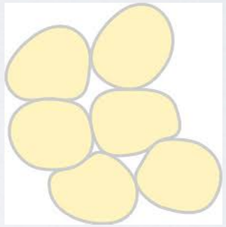

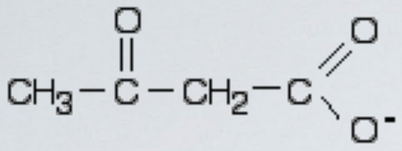

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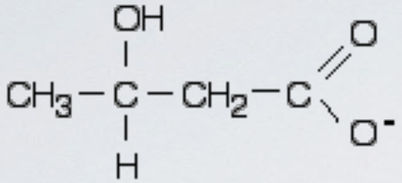

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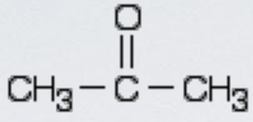

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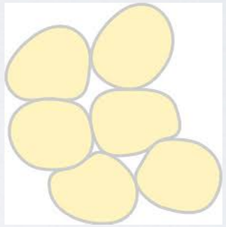

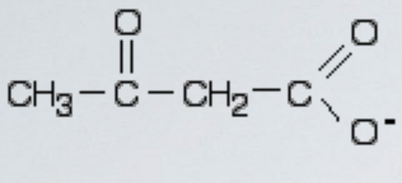

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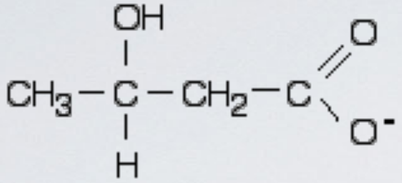

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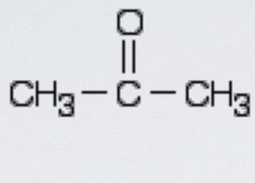
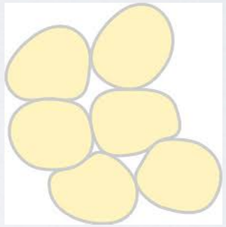


acetone

Ketones: Once thought to be products of incomplete combustion of fat



The acetyl CoA formed in fatty acid oxidation enters the citric acid cycle only if fat and carbohydrate degradation are appropriately balanced. Acetyl CoA must combine with oxaloacetate to gain entry to the citric acid cycle. The availability of oxaloacetate, however, depends on an adequate supply of carbohydrate. Recall that oxaloacetate is normally formed from pyruvate, the product of glucose degradation in glycolysis. If carbohydrate is unavailable or improperly utilized, the concentration of oxaloacetate is lowered and acetyl CoA cannot enter the citric acid cycle. This dependency is the molecular basis of the adage that *fats burn in the flame of carbohydrates.*

In fasting or diabetes, oxaloacetate is consumed to form glucose by the gluconeogenic pathway (Section 16.3) and hence is unavailable for condensation with acetyl CoA. Under these conditions, acetyl CoA is diverted to the formation of acetoacetate and D-3-hydroxybutyrate. Acetoacetate, D-3-hydroxybutyrate, and acetone are often referred to as *ketone bodies.*

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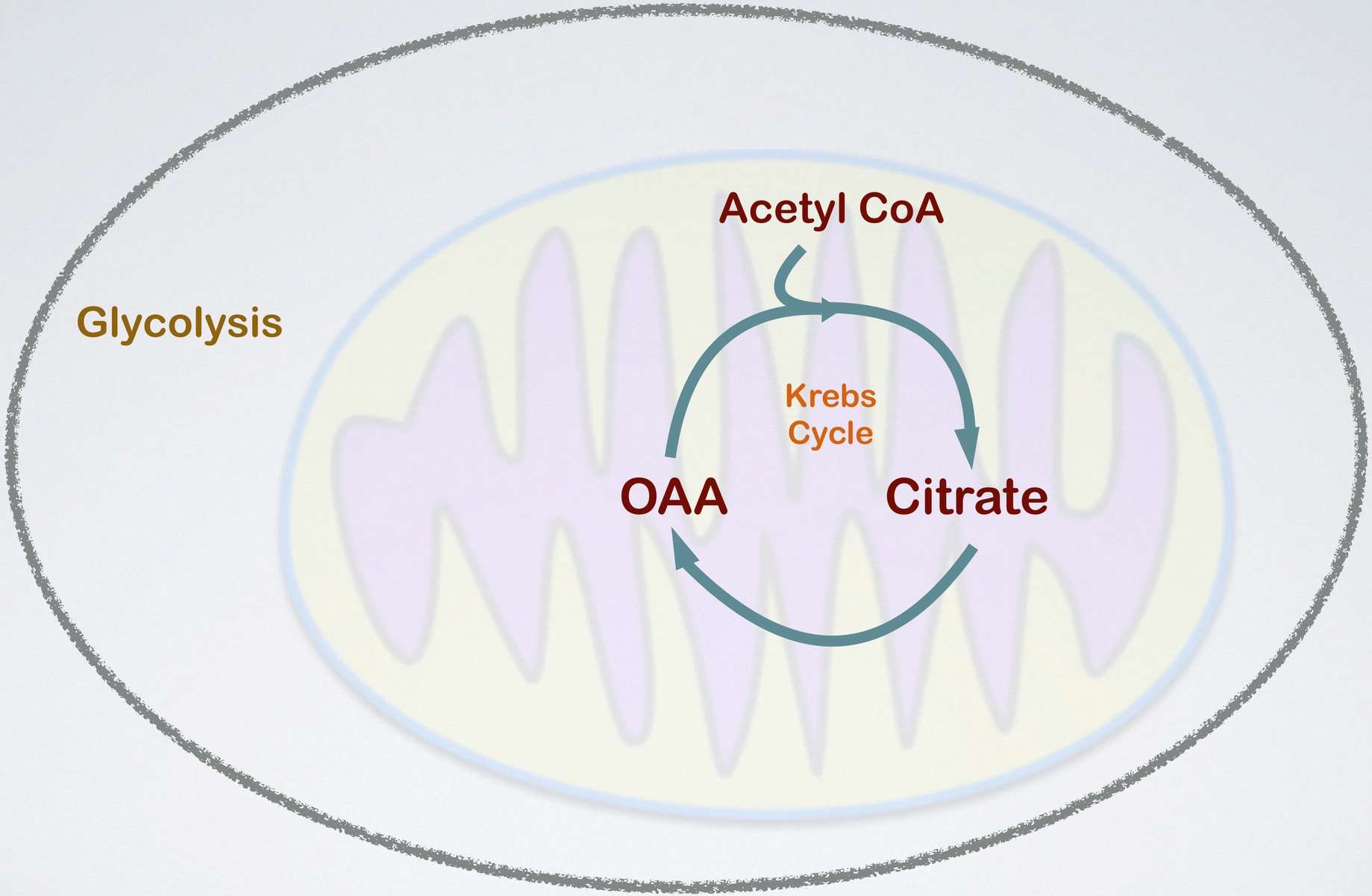
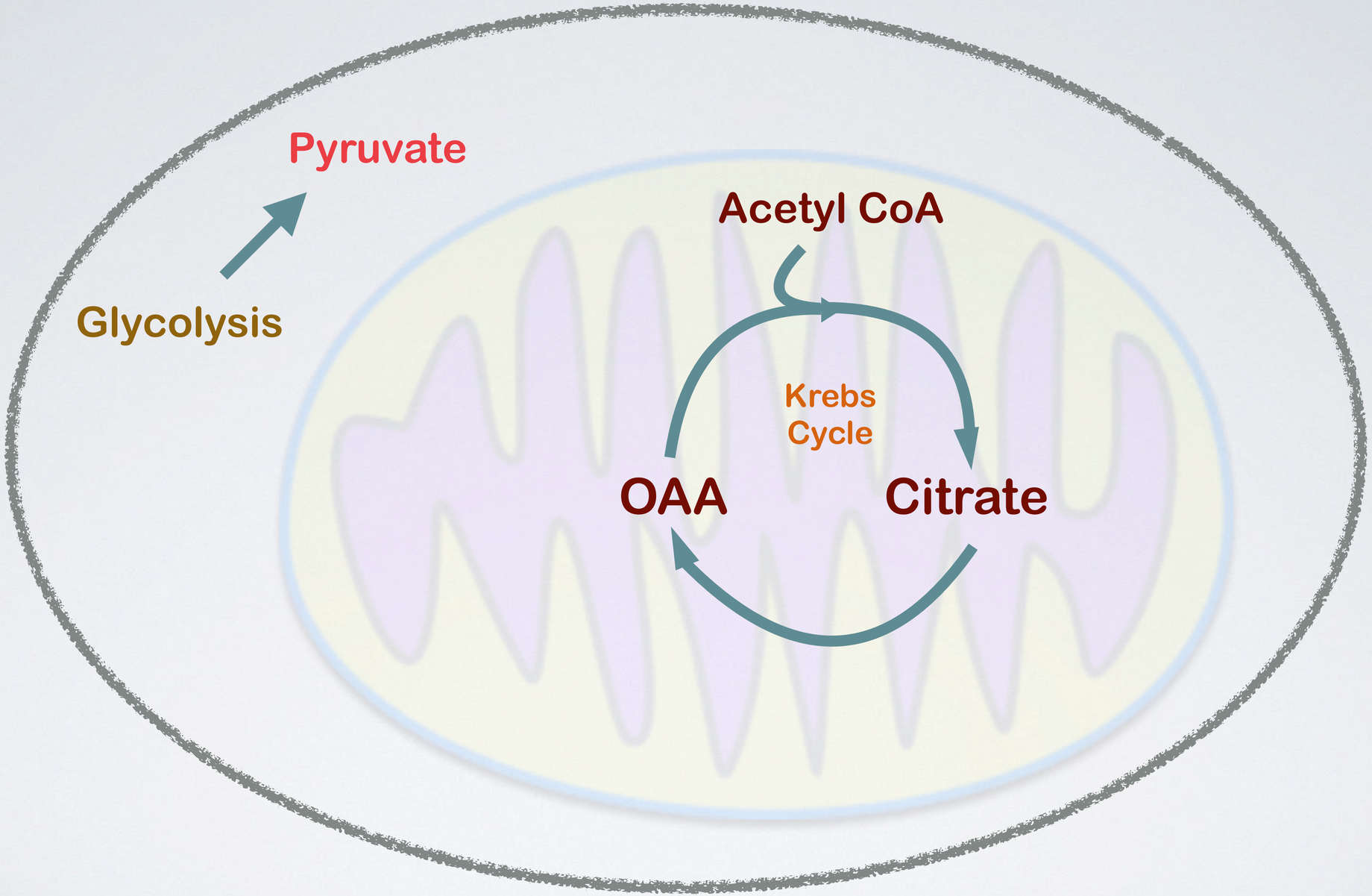
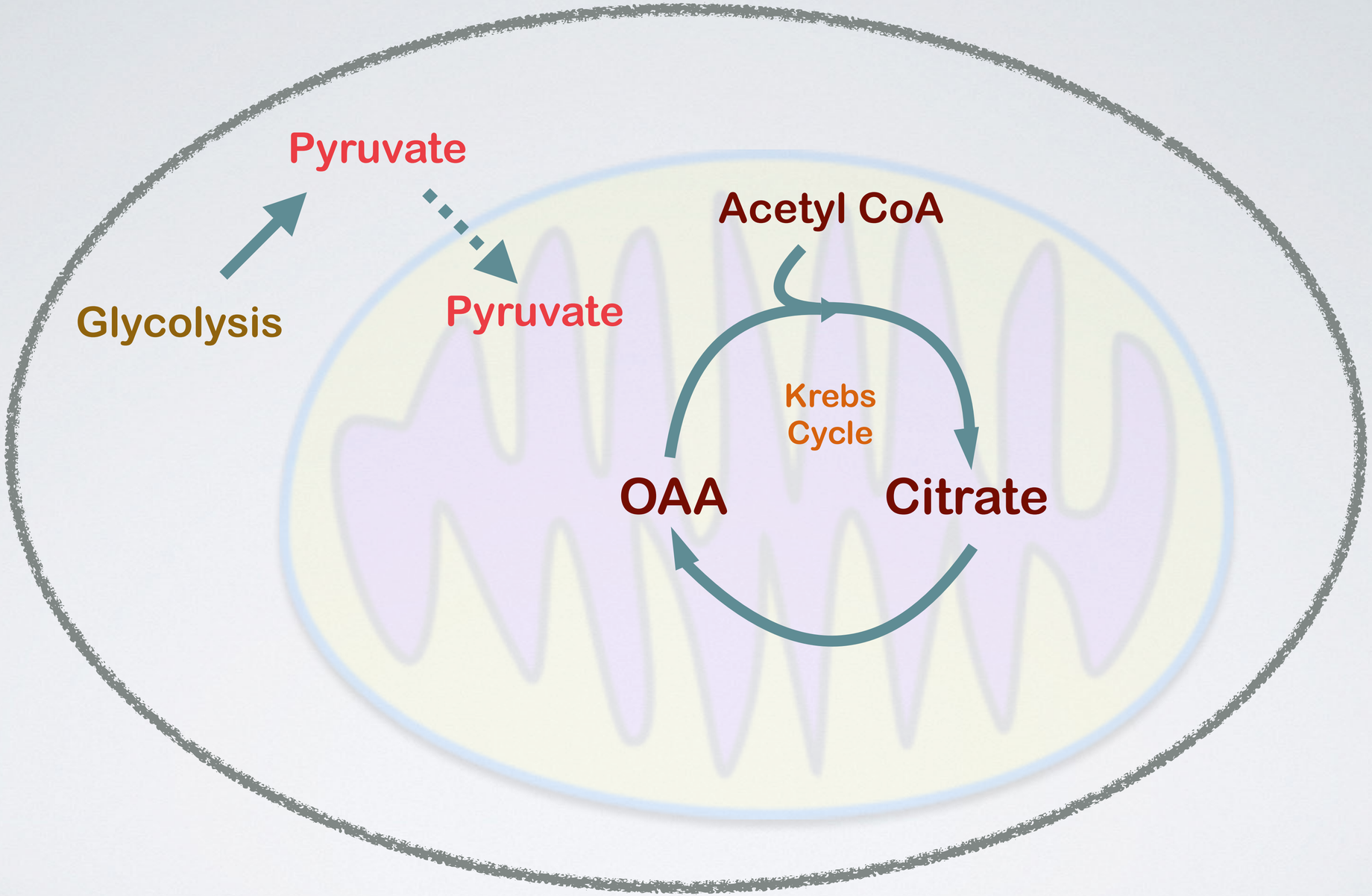

Glycolysis
Acetyl CoA
Krebs
Cycle
OAA
Citrate


Pyruvate
Glycolysis
Acetyl CoA
Krebs
Cycle
OAA
Citrate


Pyruvate
Glycolysis
Pyruvate
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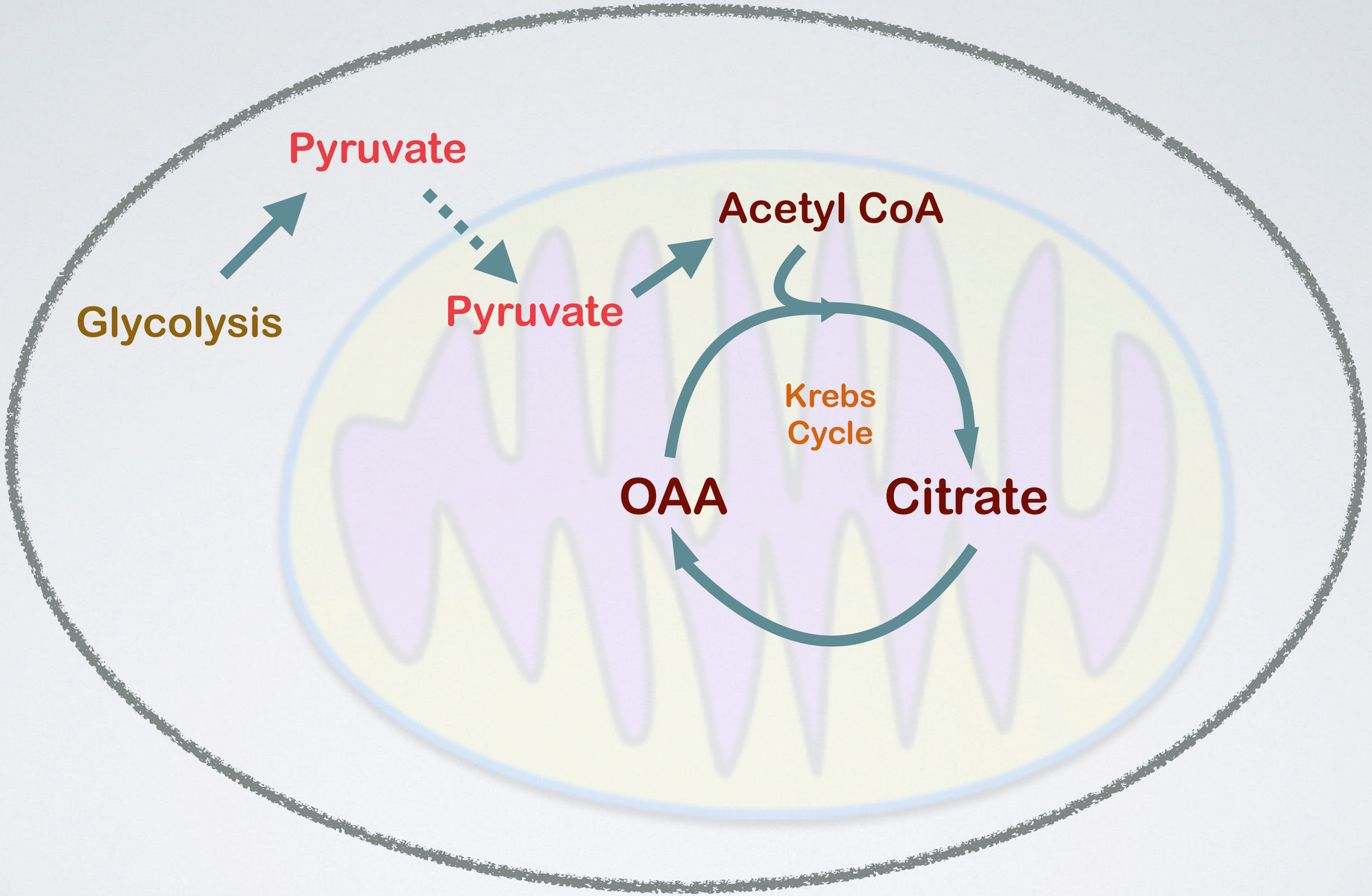
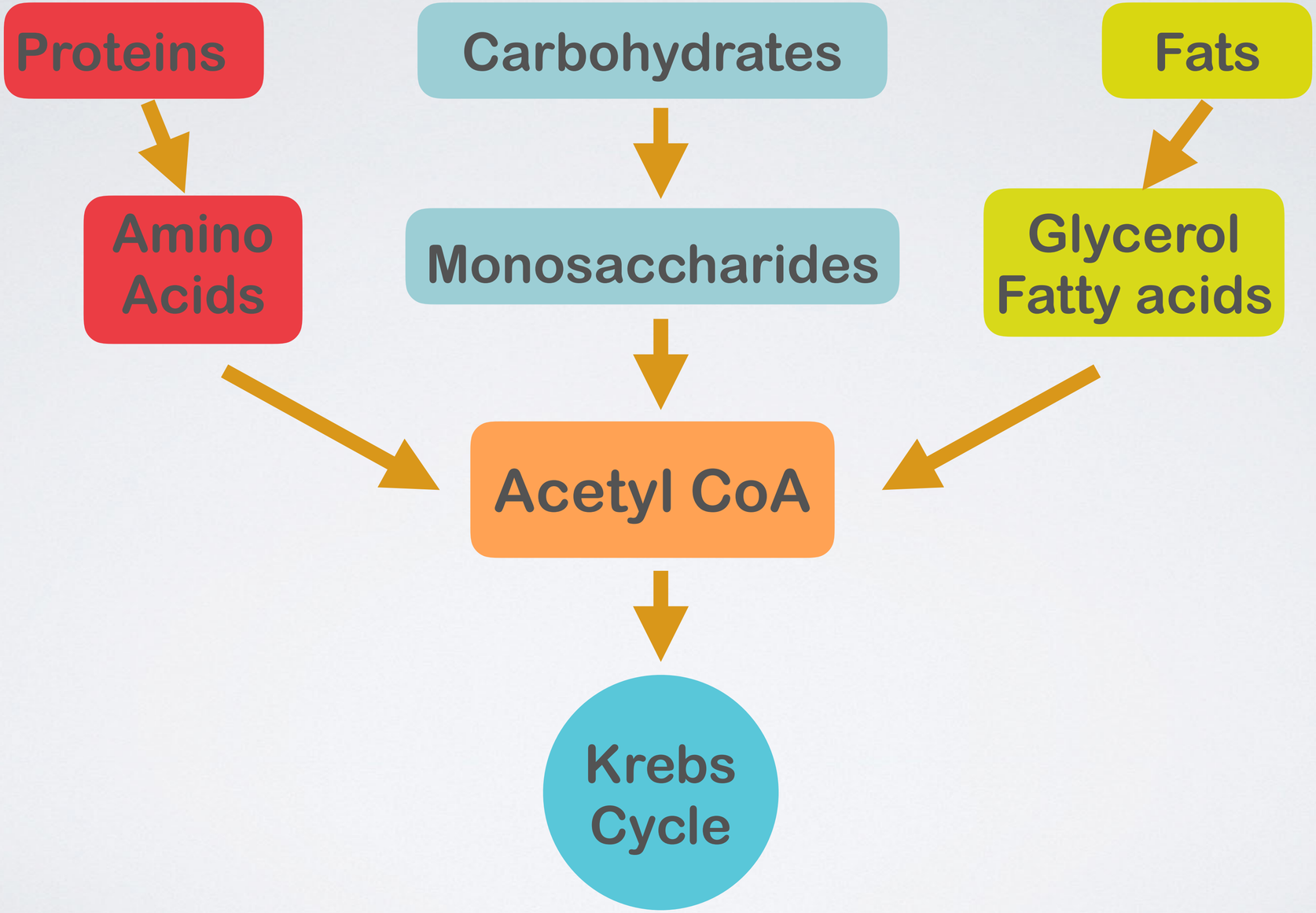
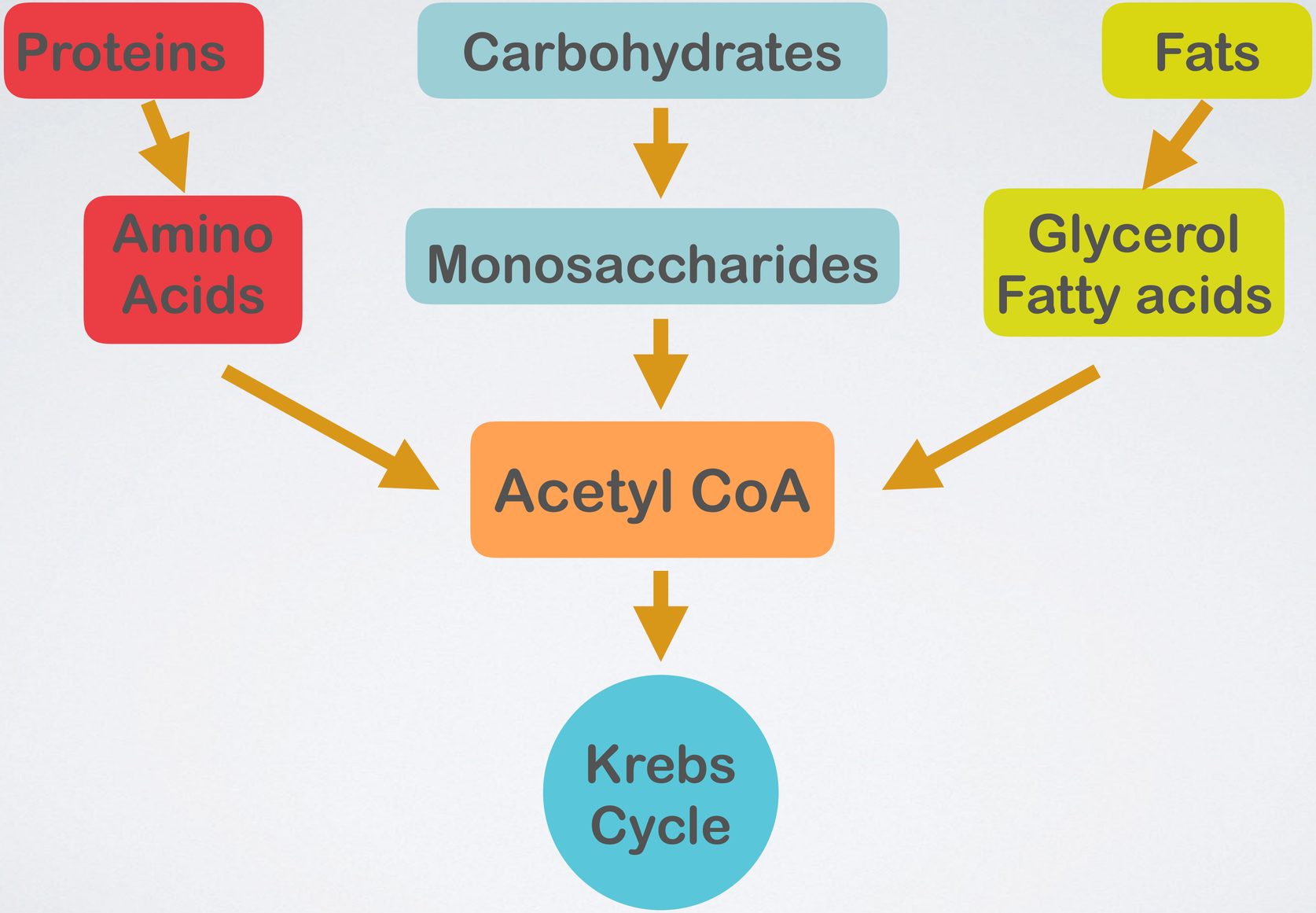
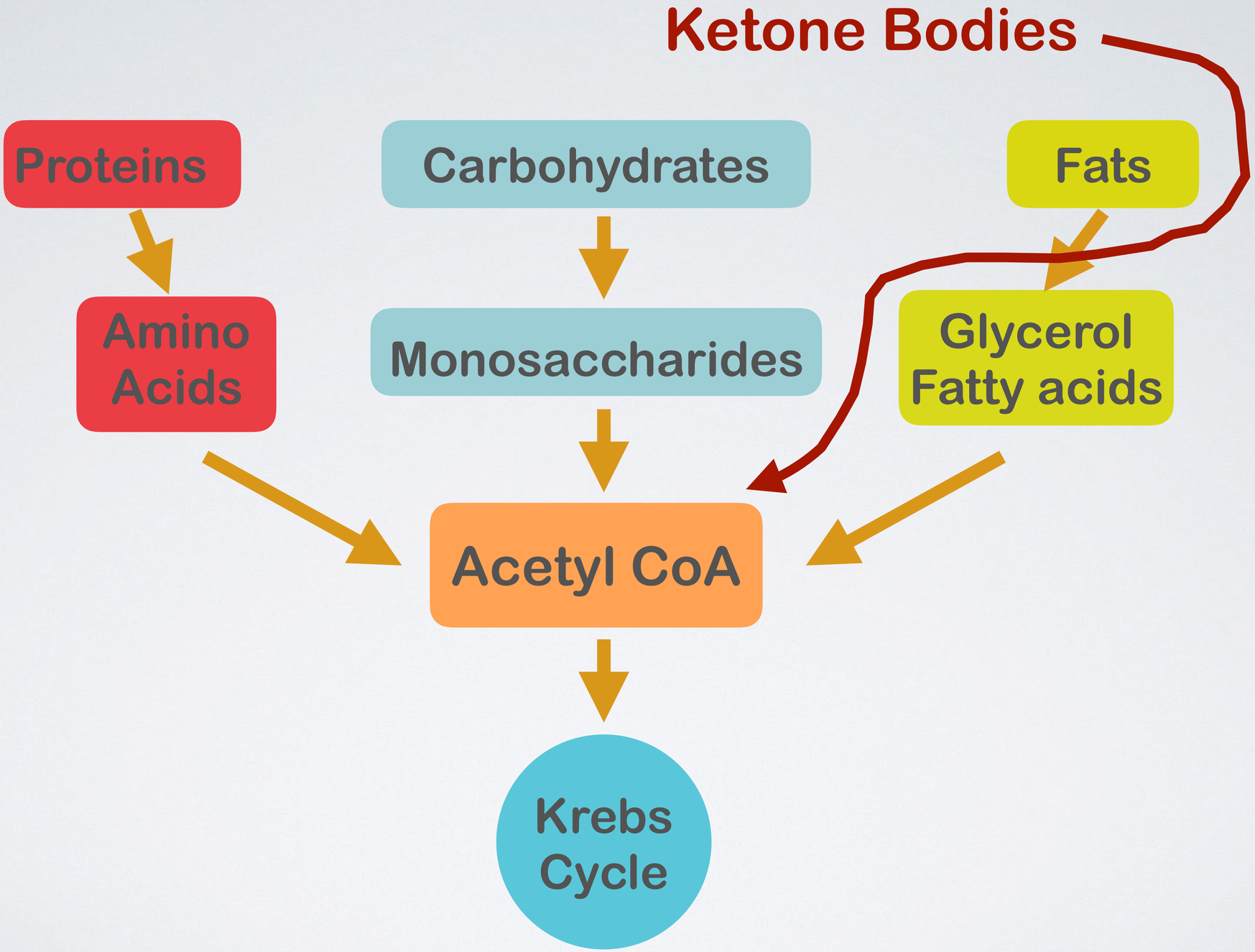
Krebs
Cycle
OAA
Citrate


Pyruvate
Glycolysis
Pyruvate
Acetyl CoA
Krebs
Cycle
OAA
Citrate


Proteins
Carbohydrates
Fats
Amino Acids
Monosaccharides
Glycerol Fatty acids
Acetyl CoA
Krebs Cycle

Ketone Bodies

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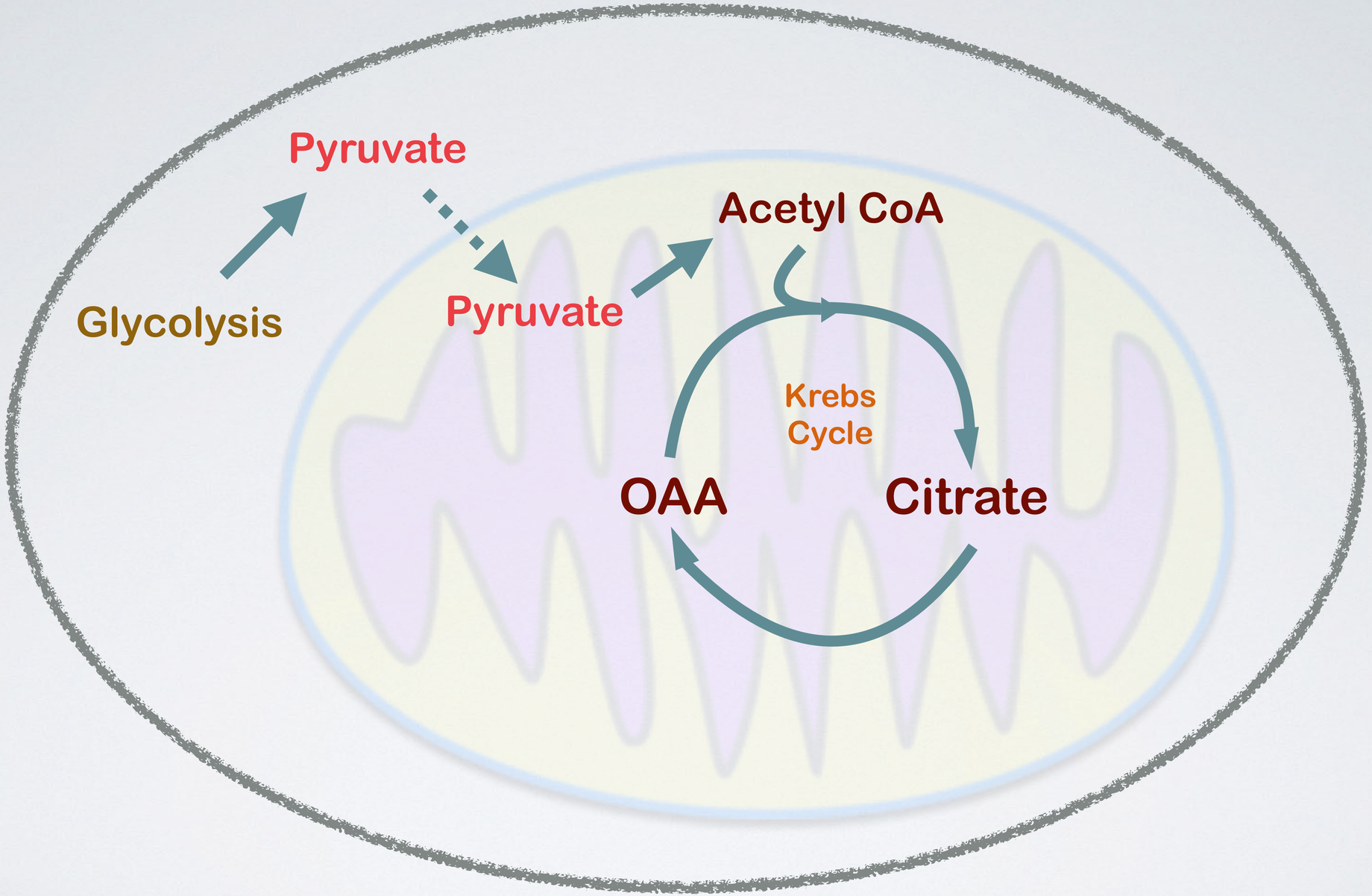
Pyruvate
Glycolysis
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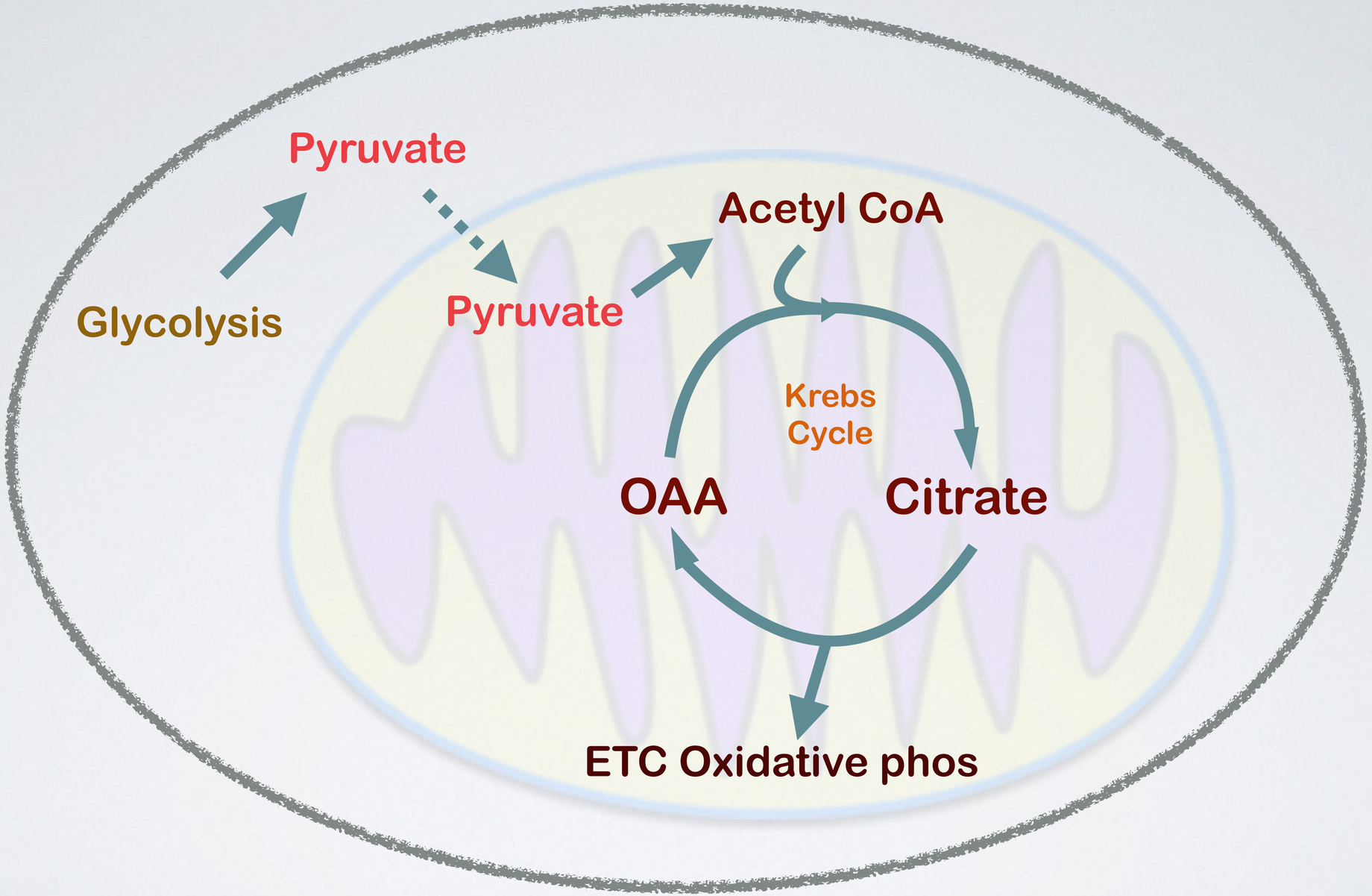
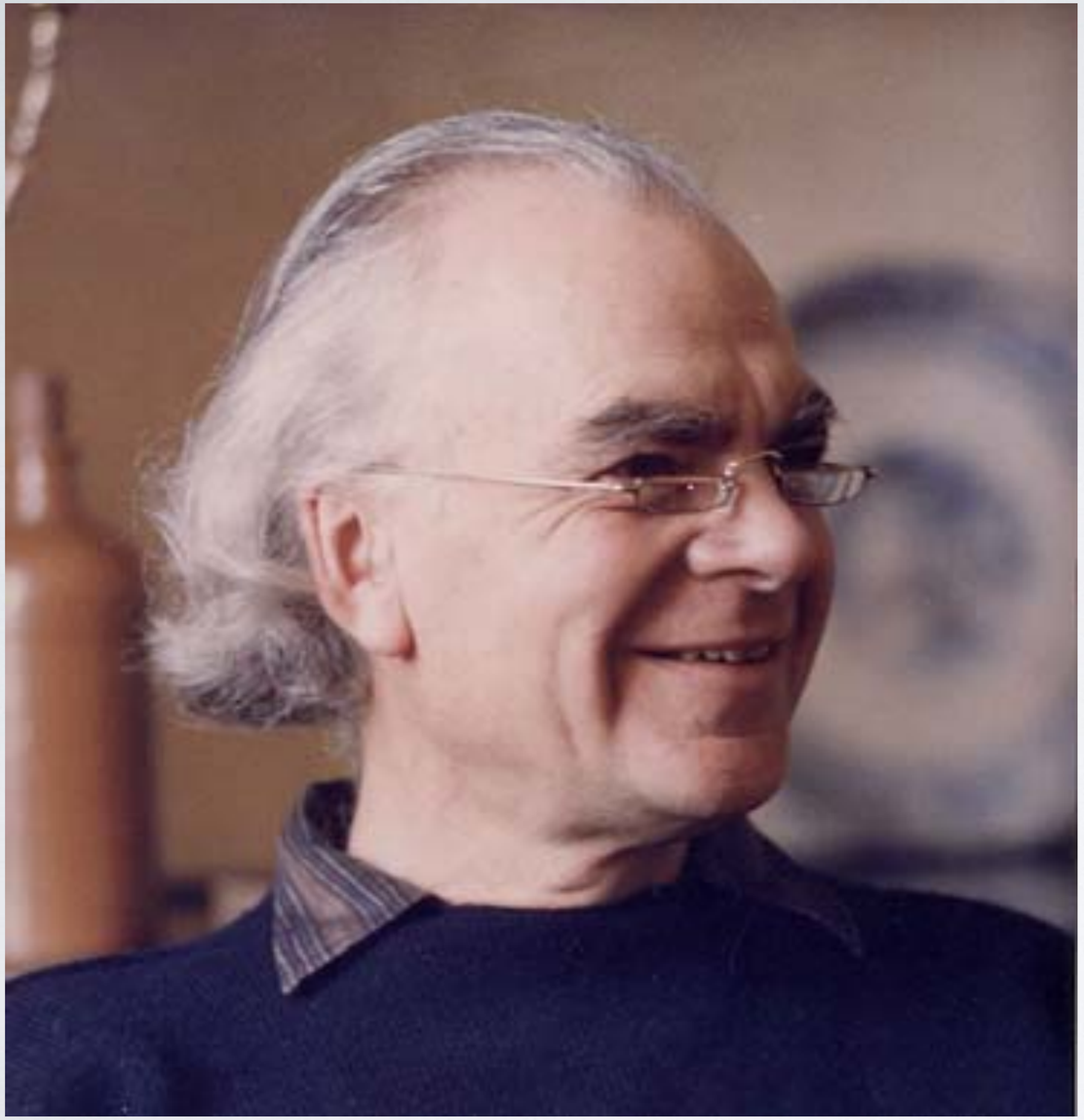
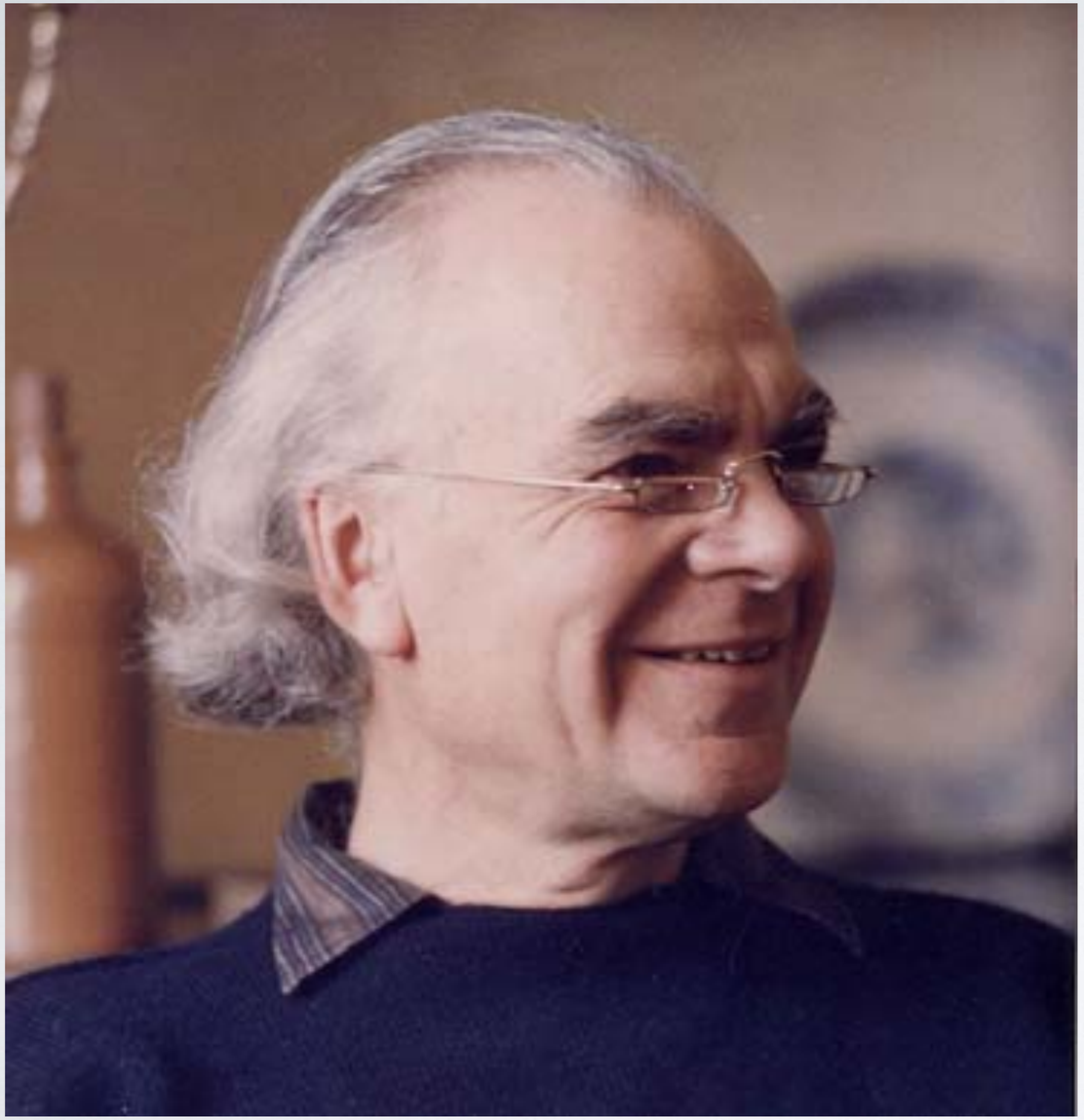
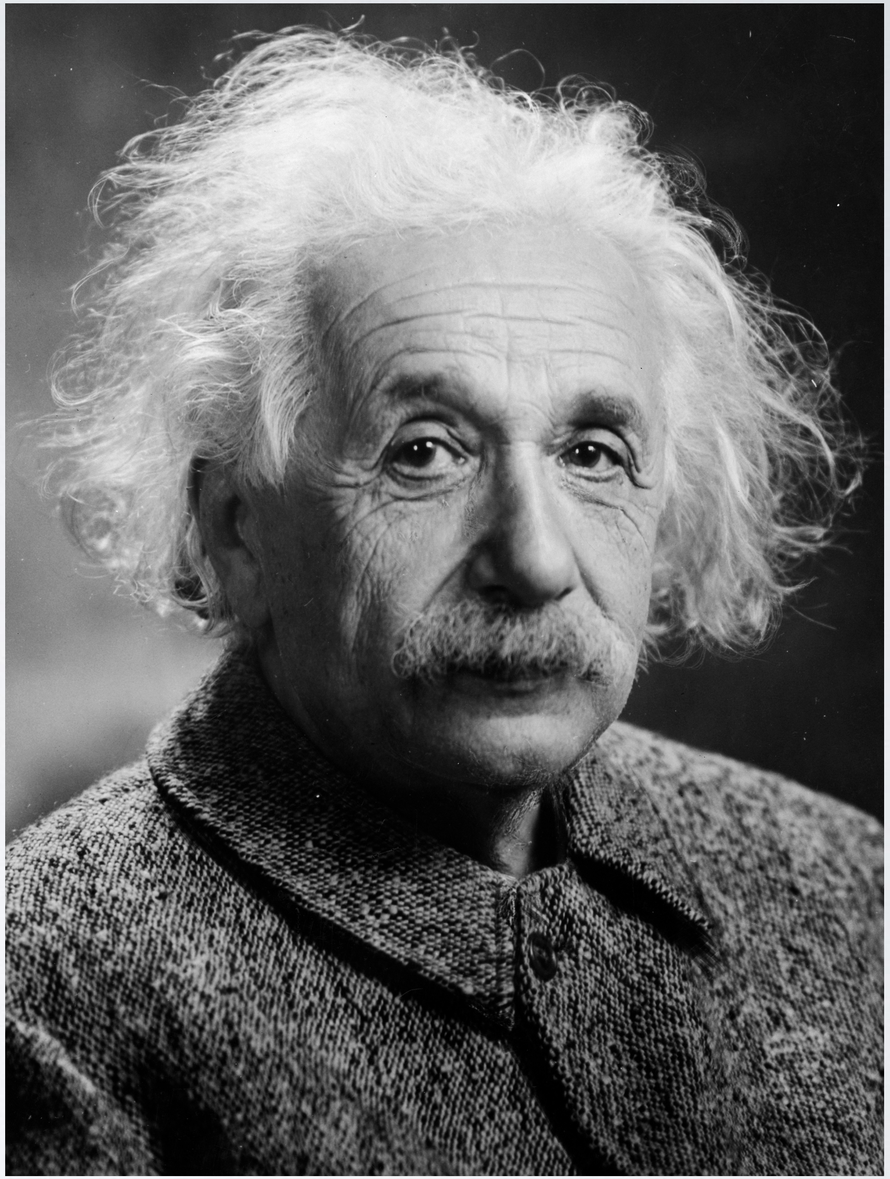
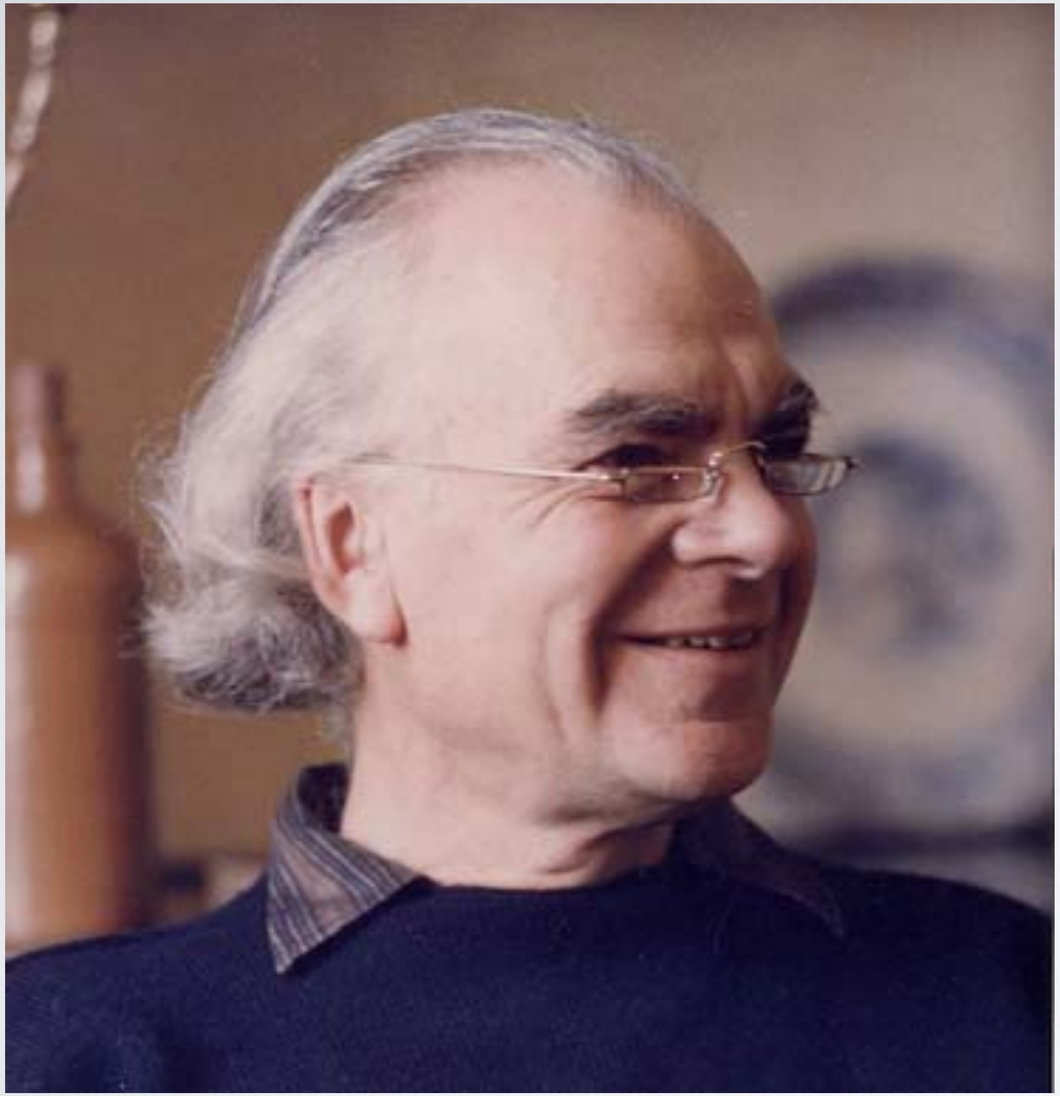
Cycle
OAA
Citrate


Pyruvate
Glycolysis
Pyruvate
Acetyl CoA
Krebs
Cycle
OAA
Citrate
ETC Oxidative phos

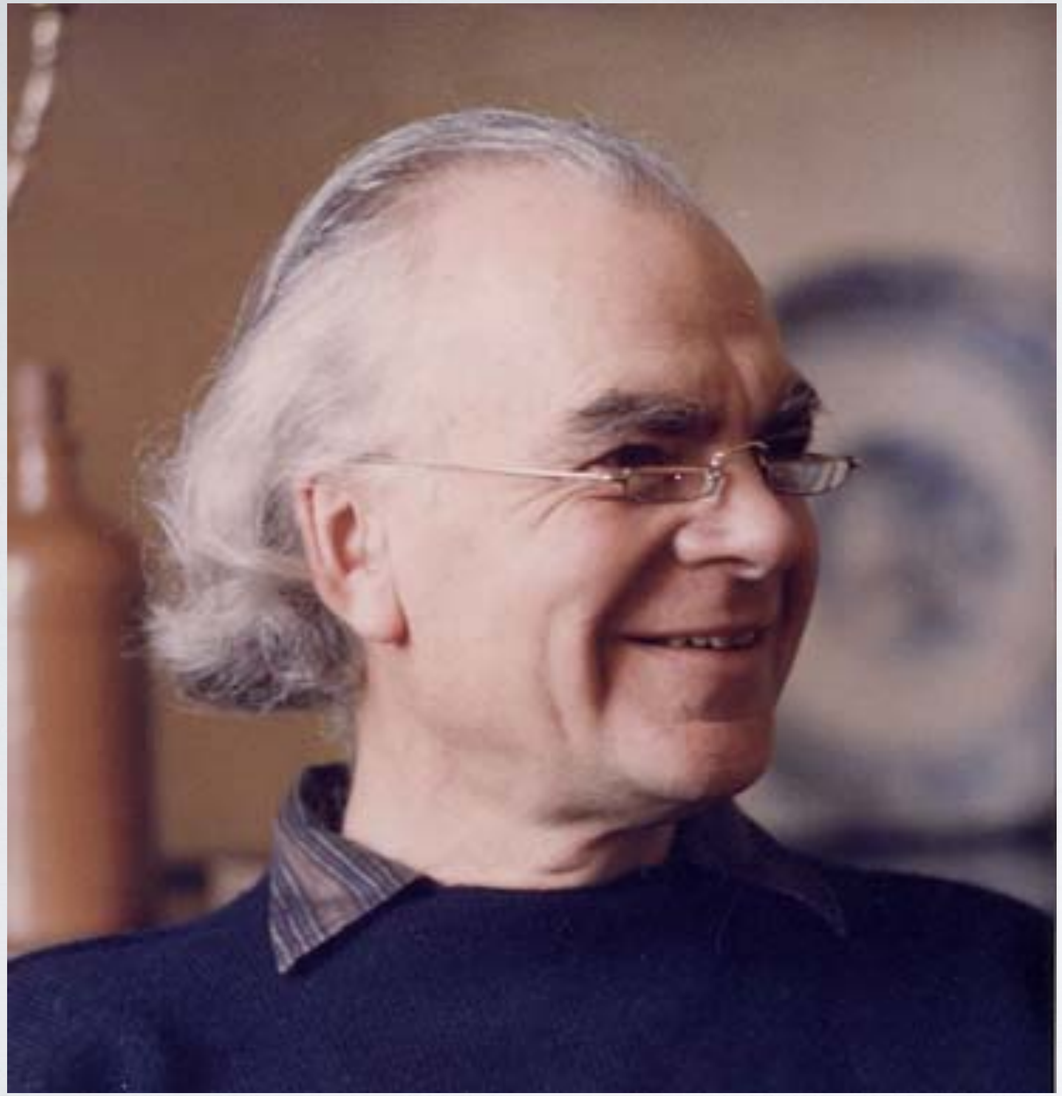






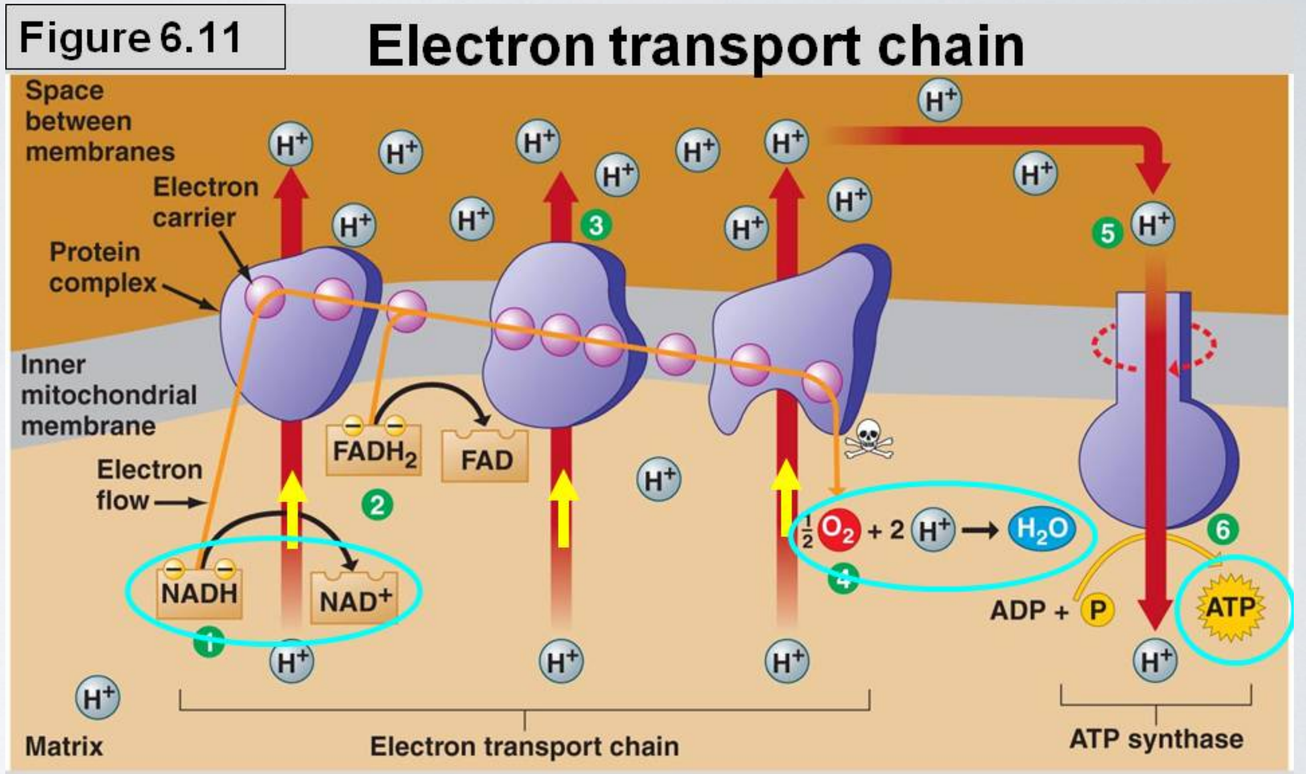


Peter D. Mitchell



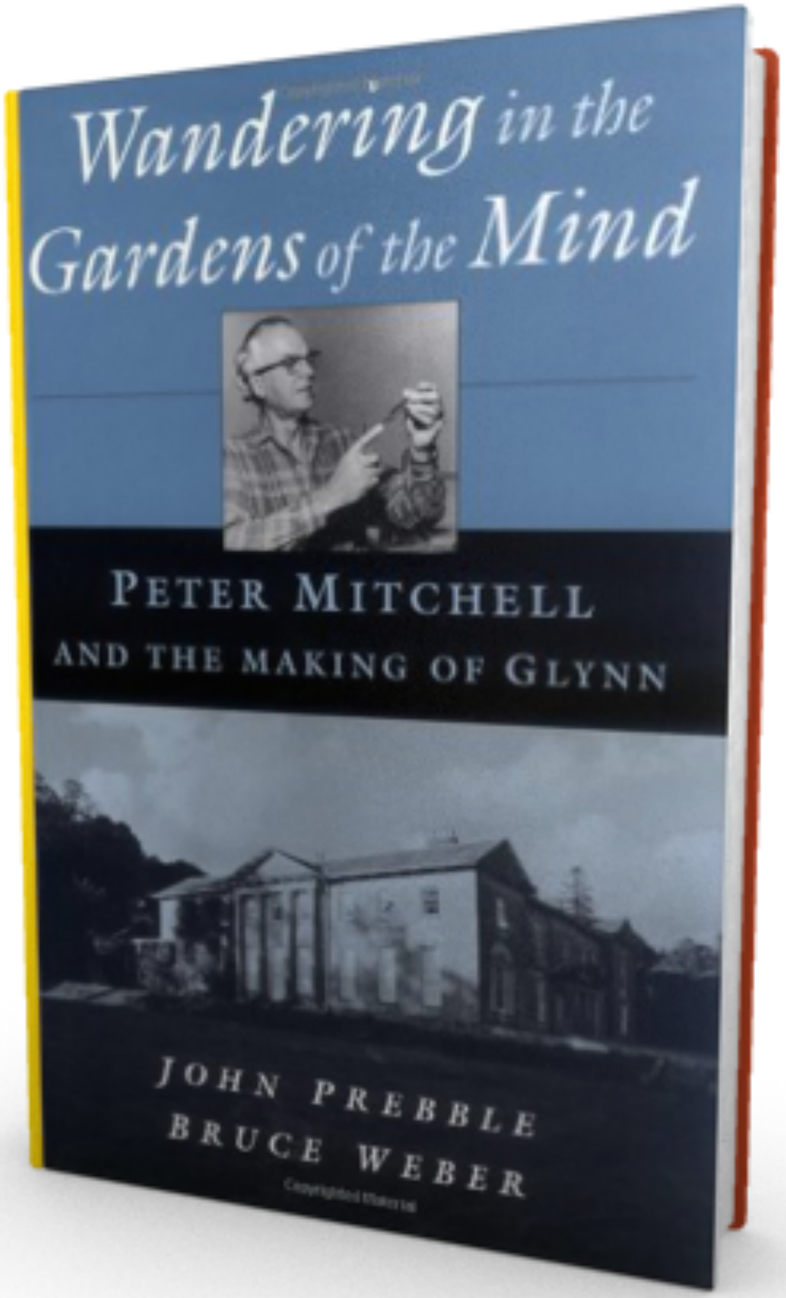
Peter D. Mitchell

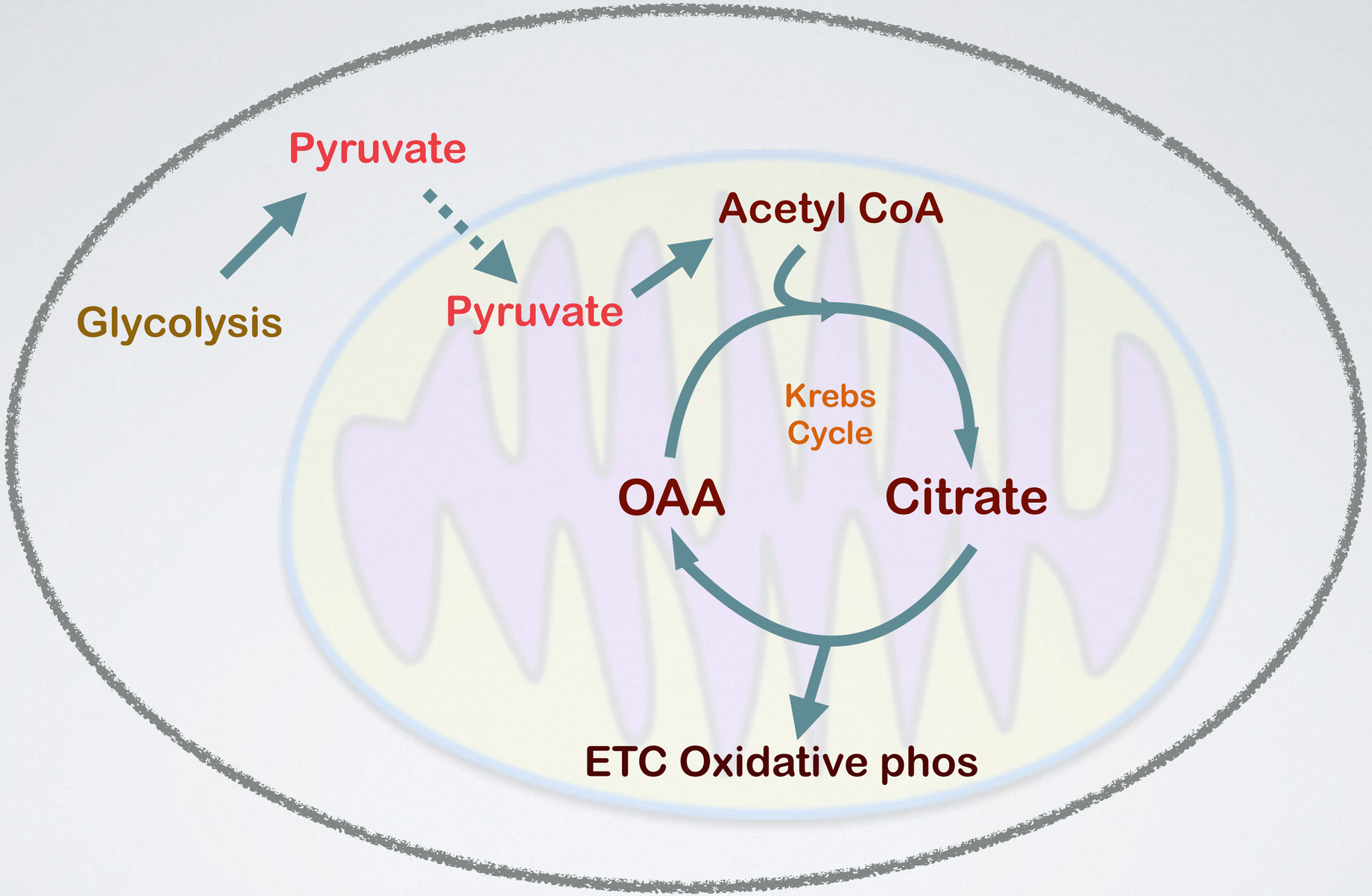
Figure 6.11

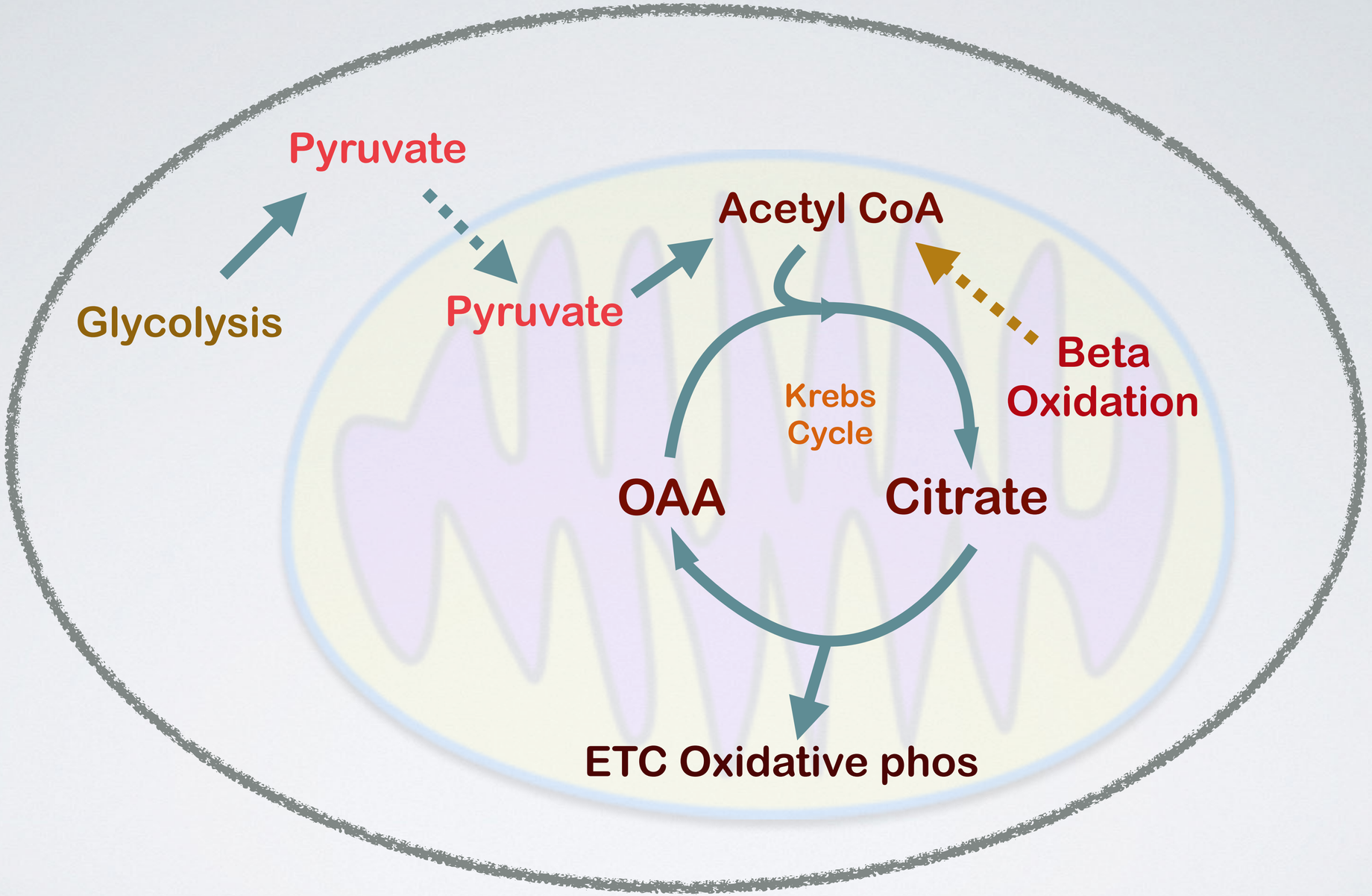


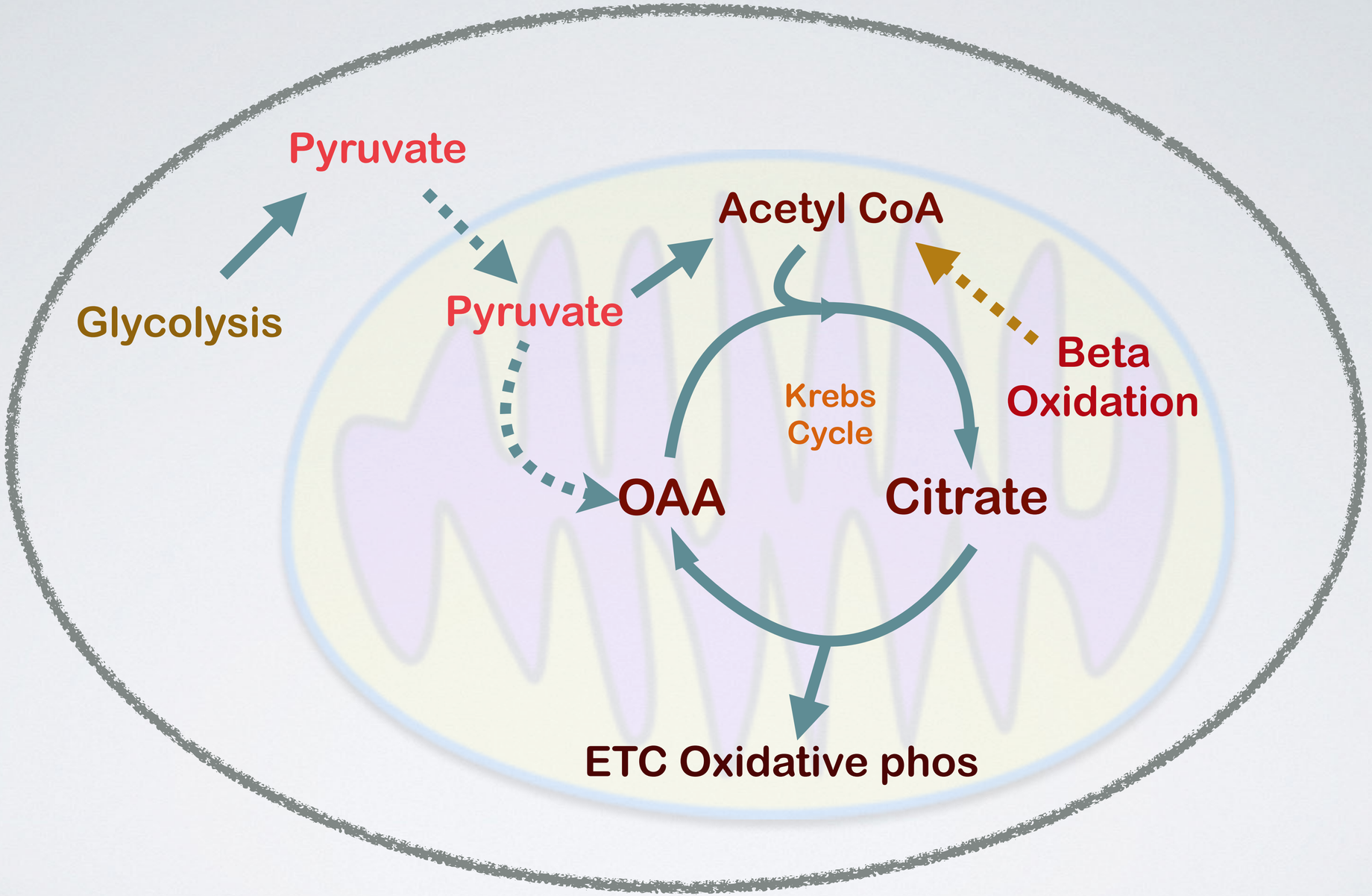
4-5 is sometimes called chemi-osmosis, kinetic energy of H^+ flowing back through ATP synthase powers the synthesis of ATP from ADP (also called oxidative phosphorylation in your book)


Bodrein, "Glynn


Wandering in the Gardens of the Mind
PETER MITCHELL
AND THE MAKING OF GLYNN
JOHN PREBBLE
BRUCE WEBER


Pyruvate
Glycolysis
Pyruvate
Acetyl CoA
Krebs
Cycle
OAA
Citrate
ETC Oxidative phos


Pyruvate
Glycolysis
Pyruvate
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
ETC Oxidative phos


Pyruvate
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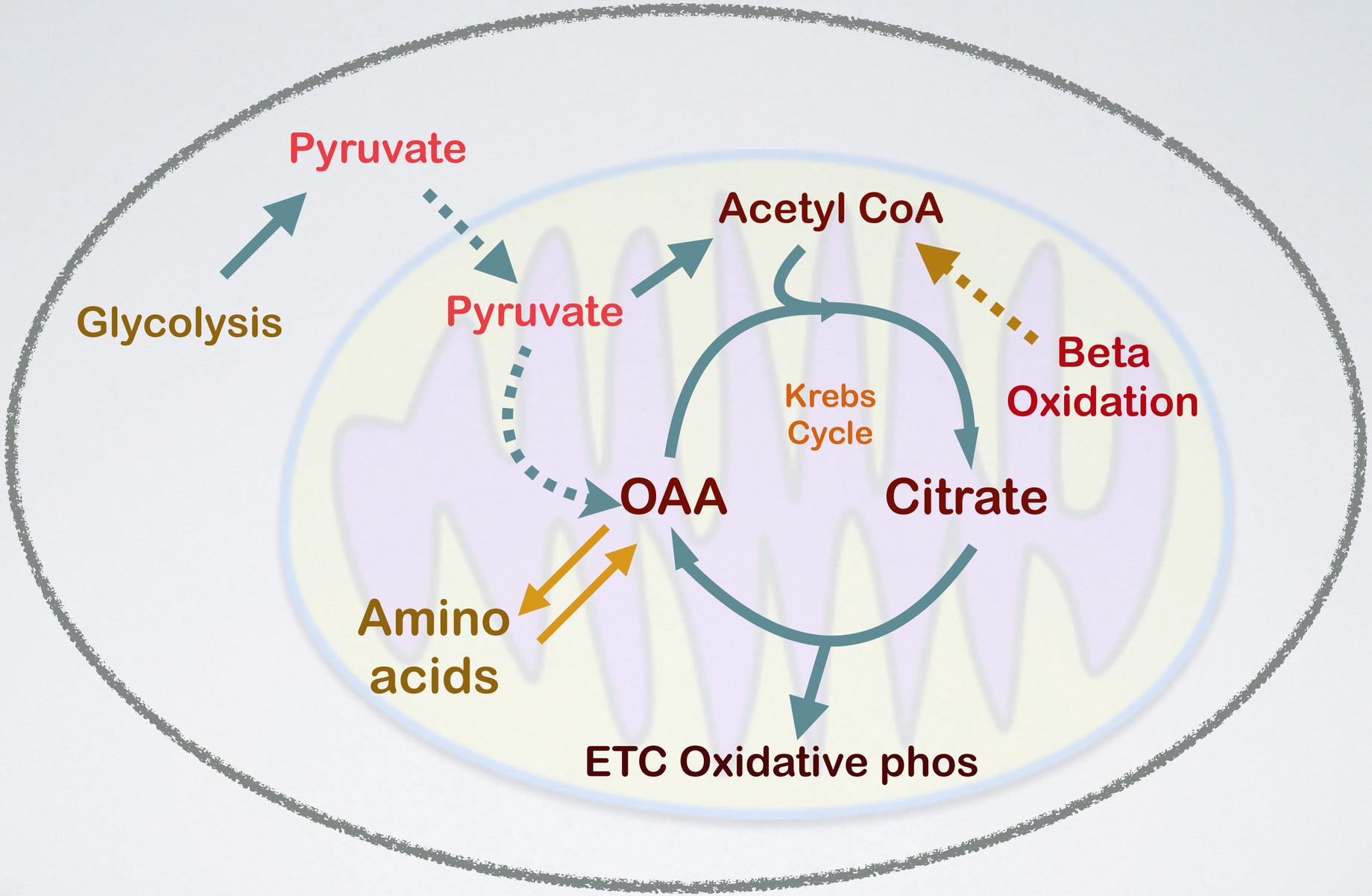
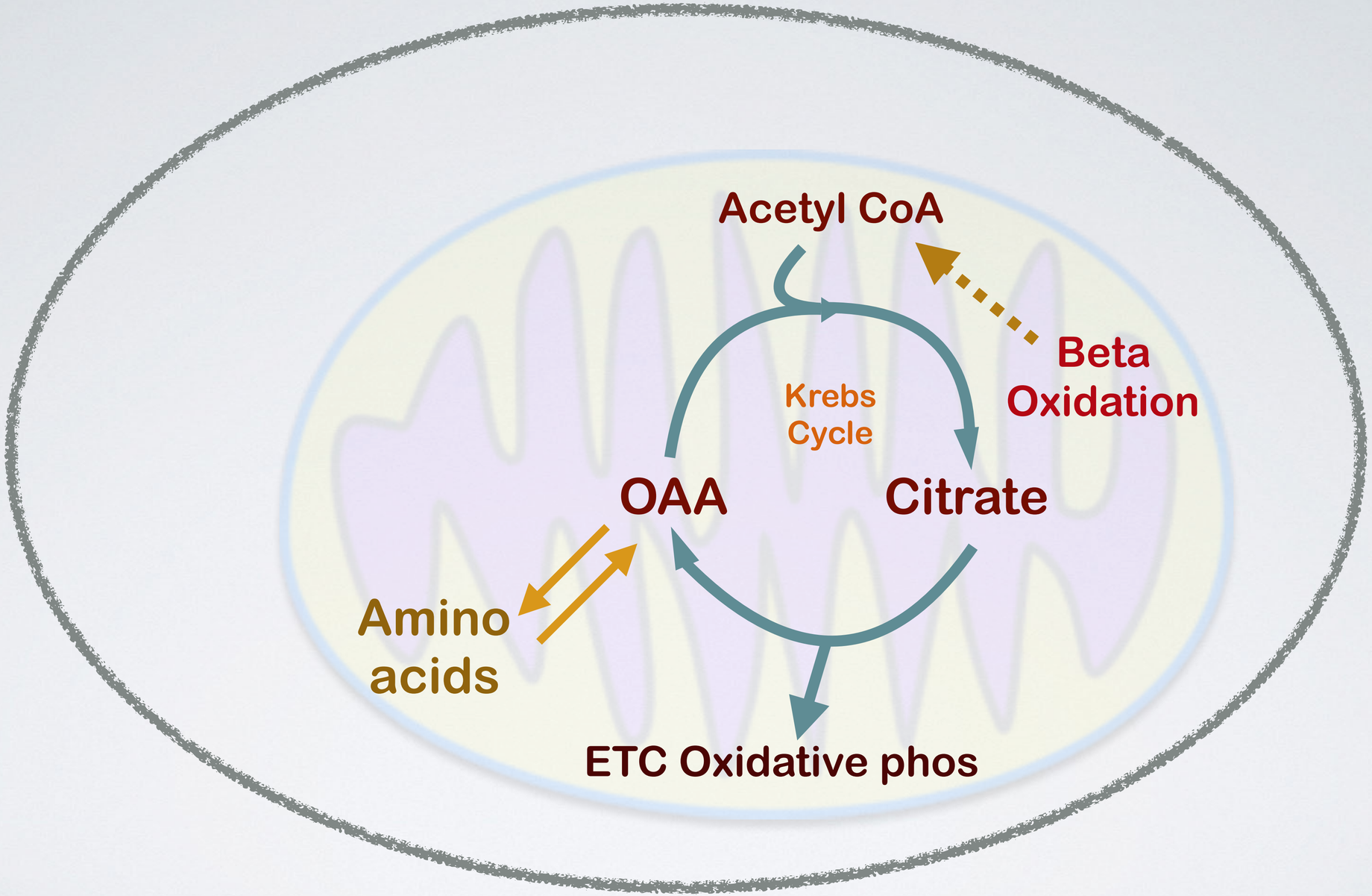
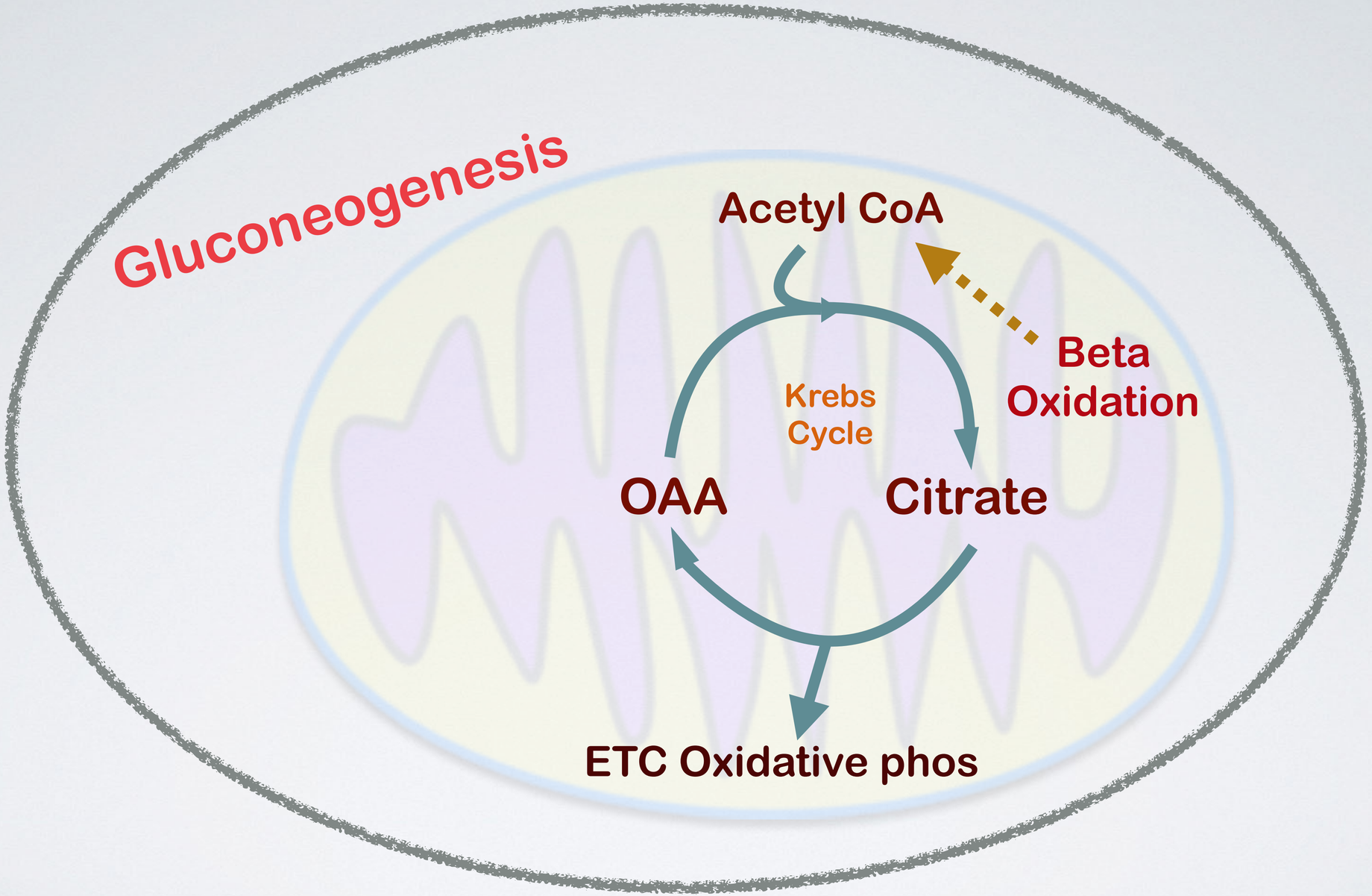

Pyruvate
Glycolysis
Pyruvate
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
Amino
acids
ETC Oxidative phos


Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
Amino
acids
ETC Oxidative phos


Gluconeogenesis
Acetyl CoA
Beta
Oxidation
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Cycle
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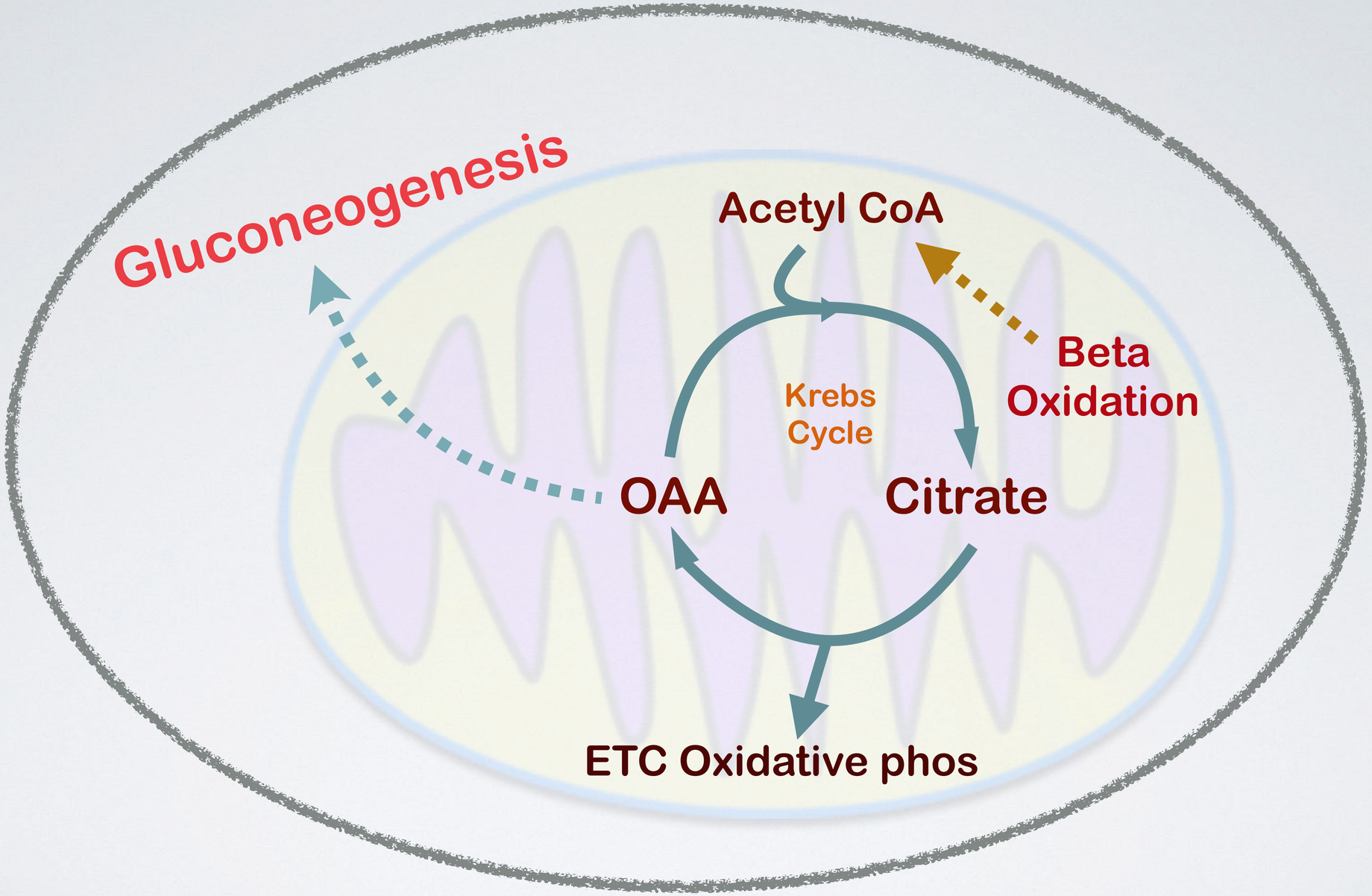
Citrate
ETC Oxidative phos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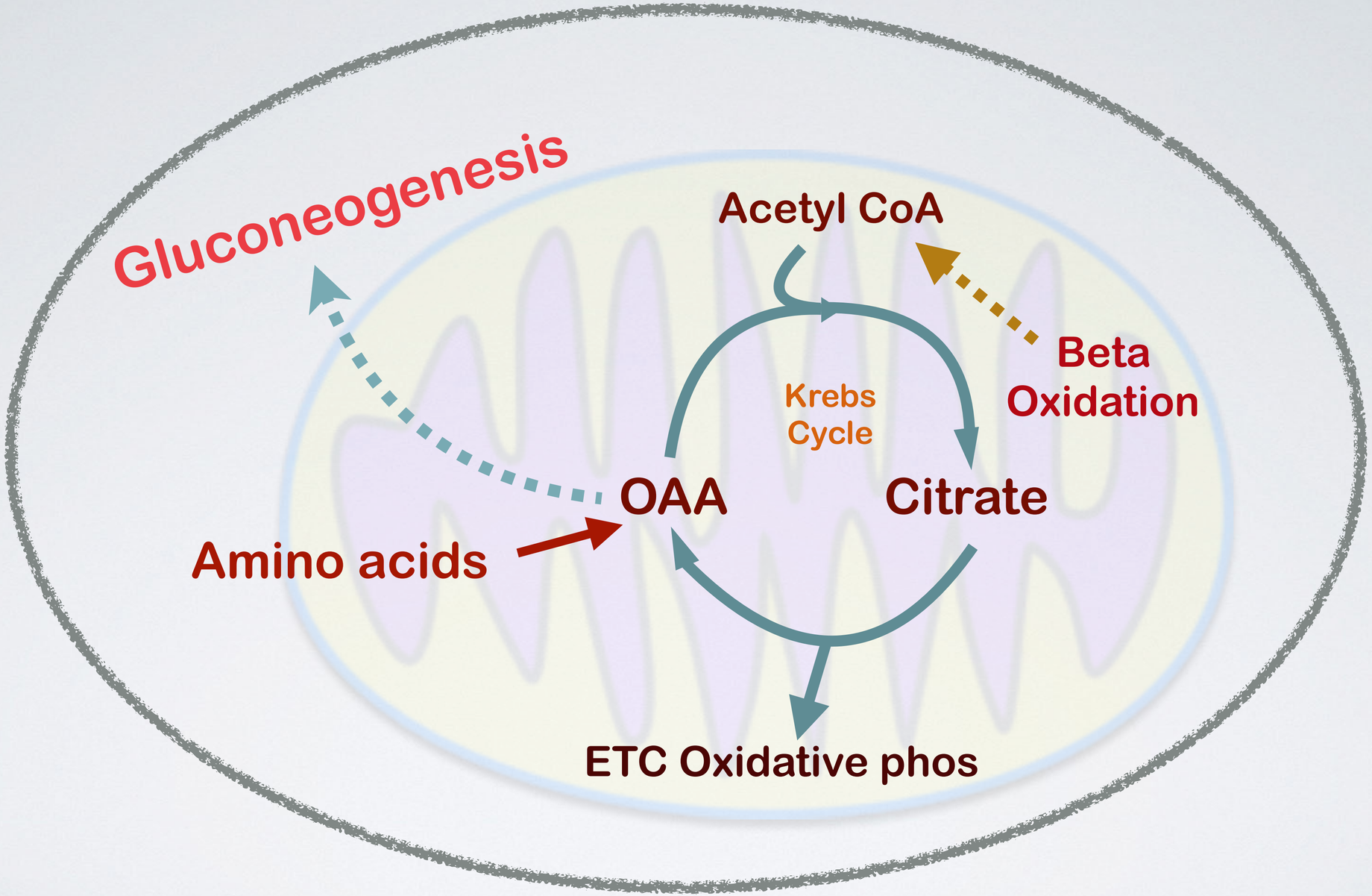
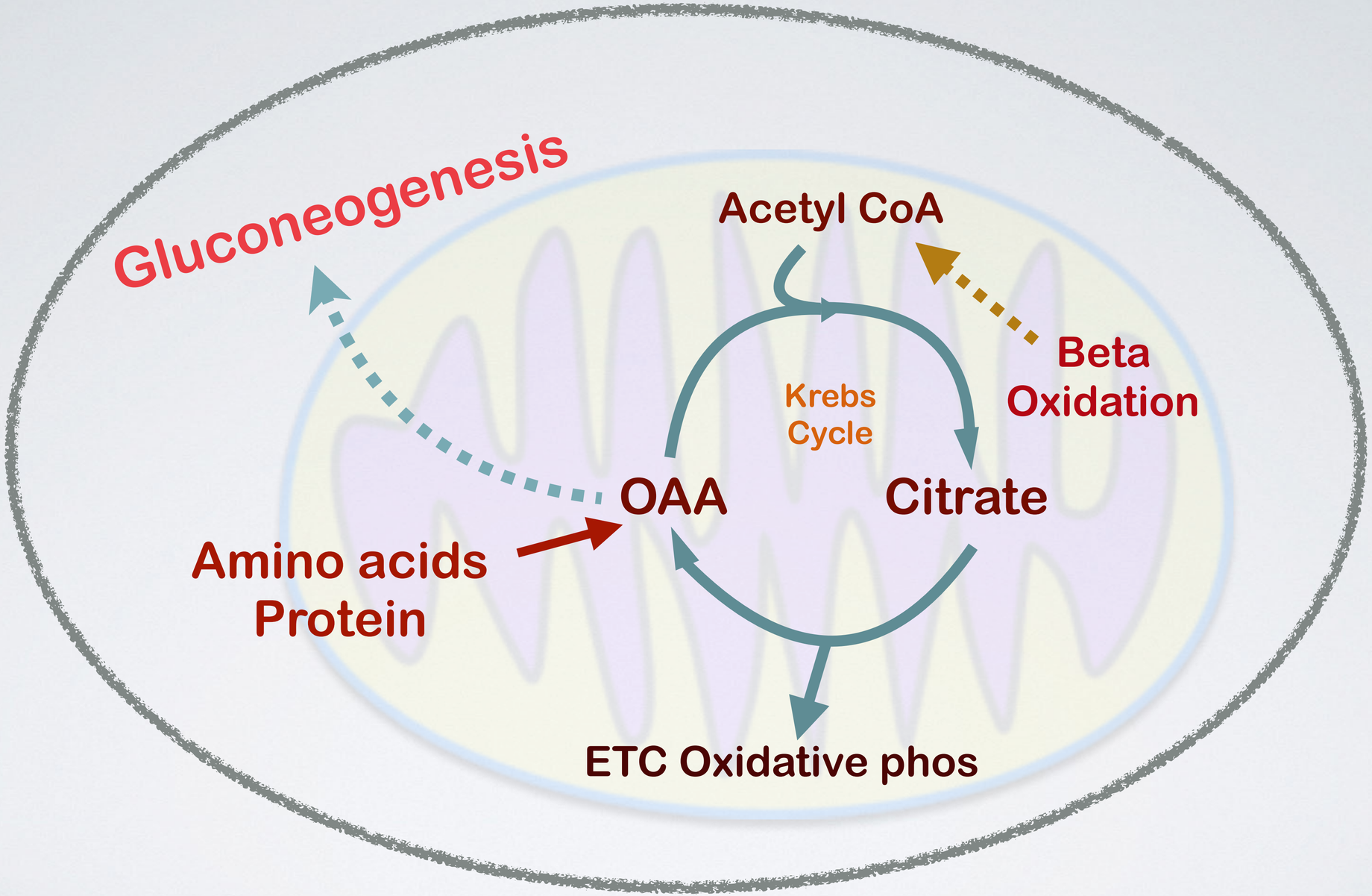
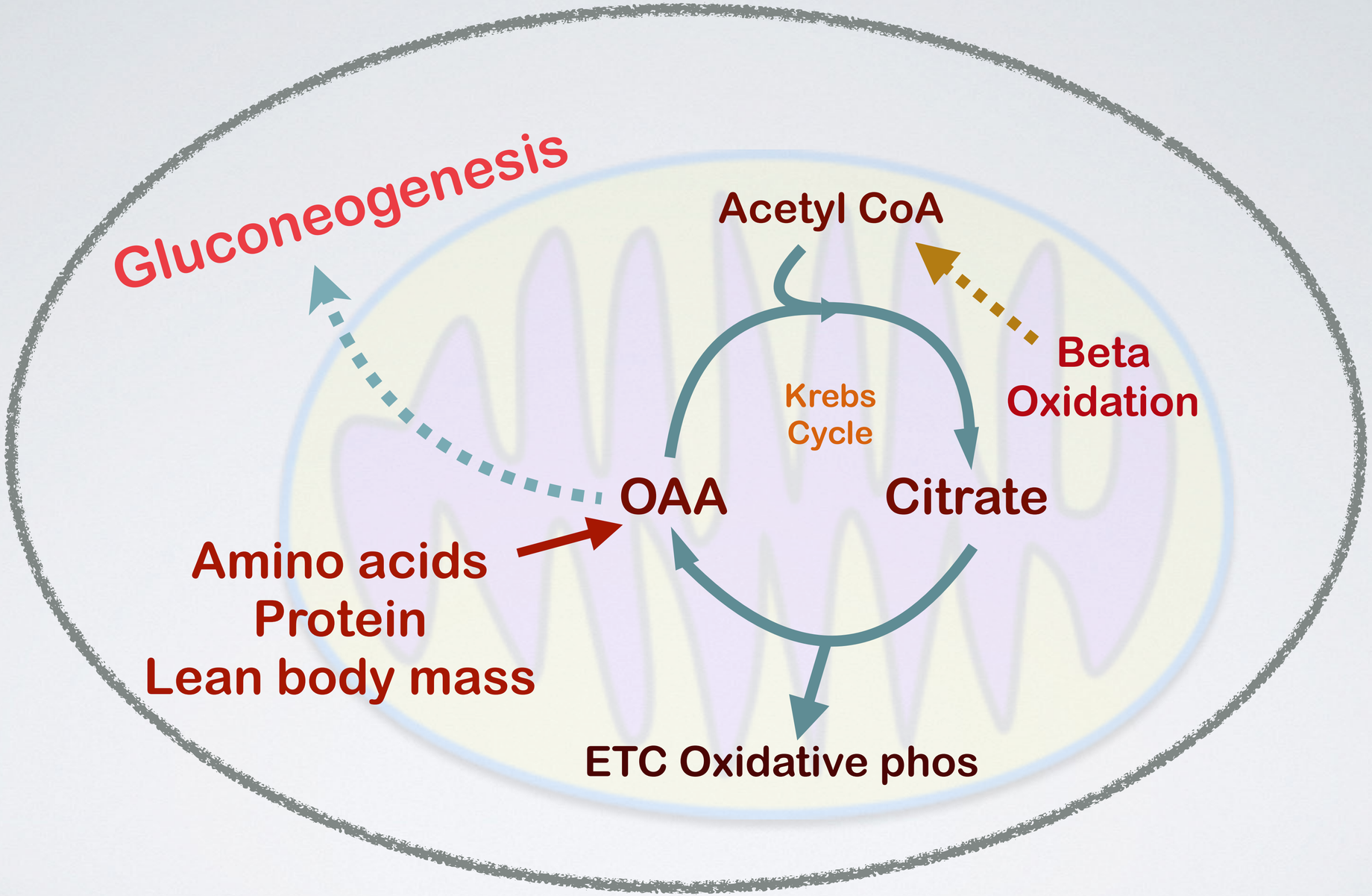
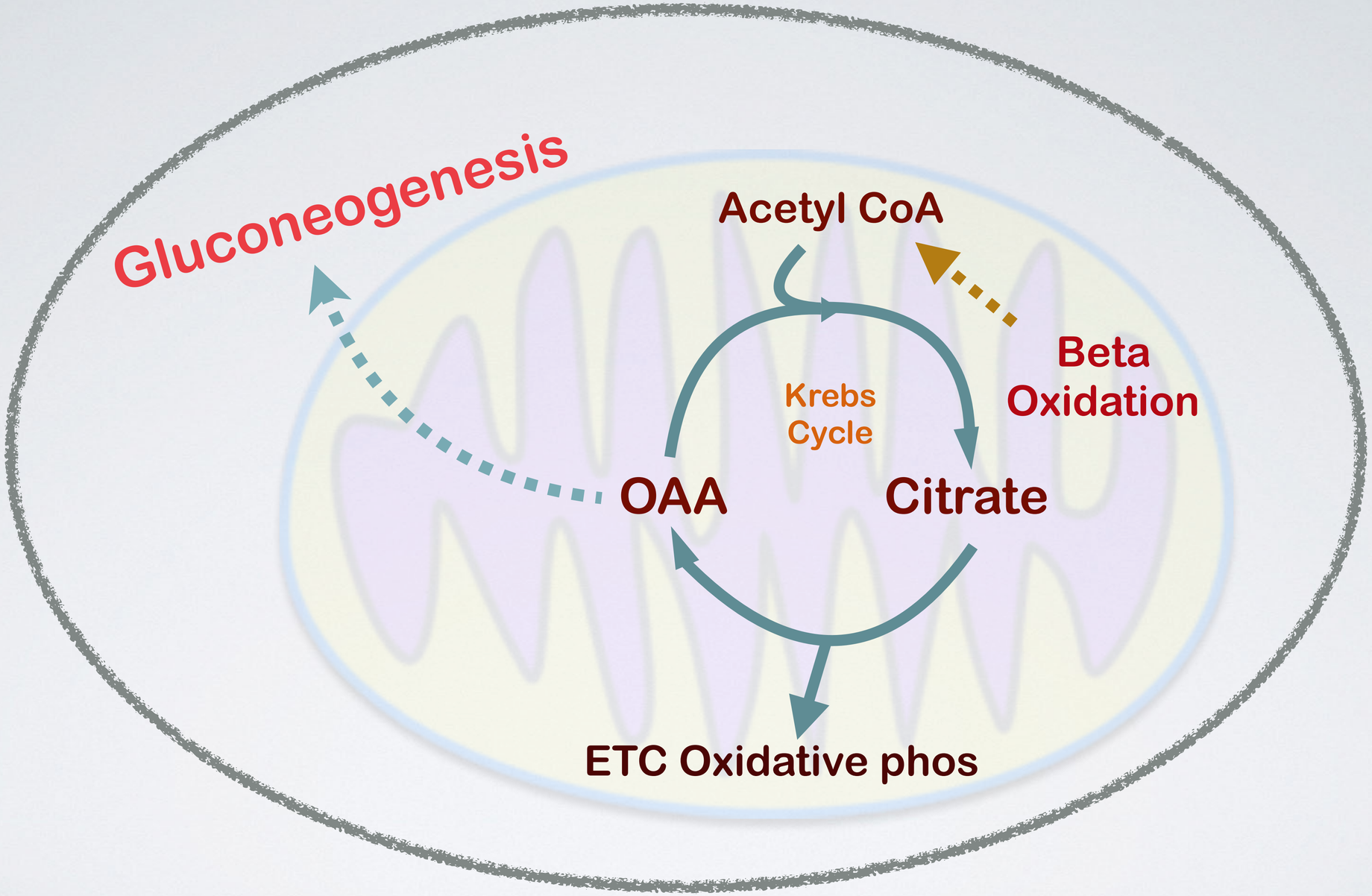
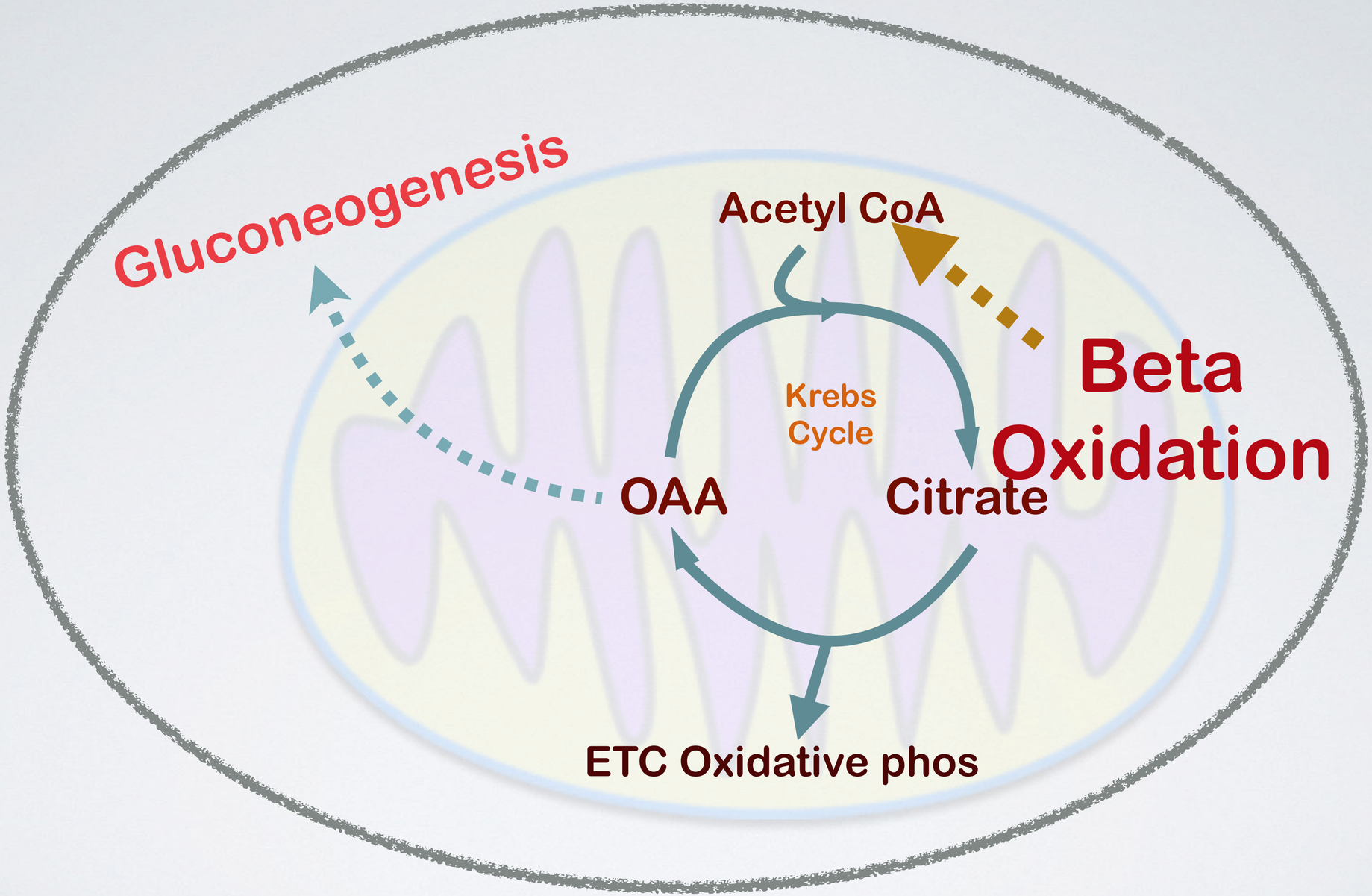
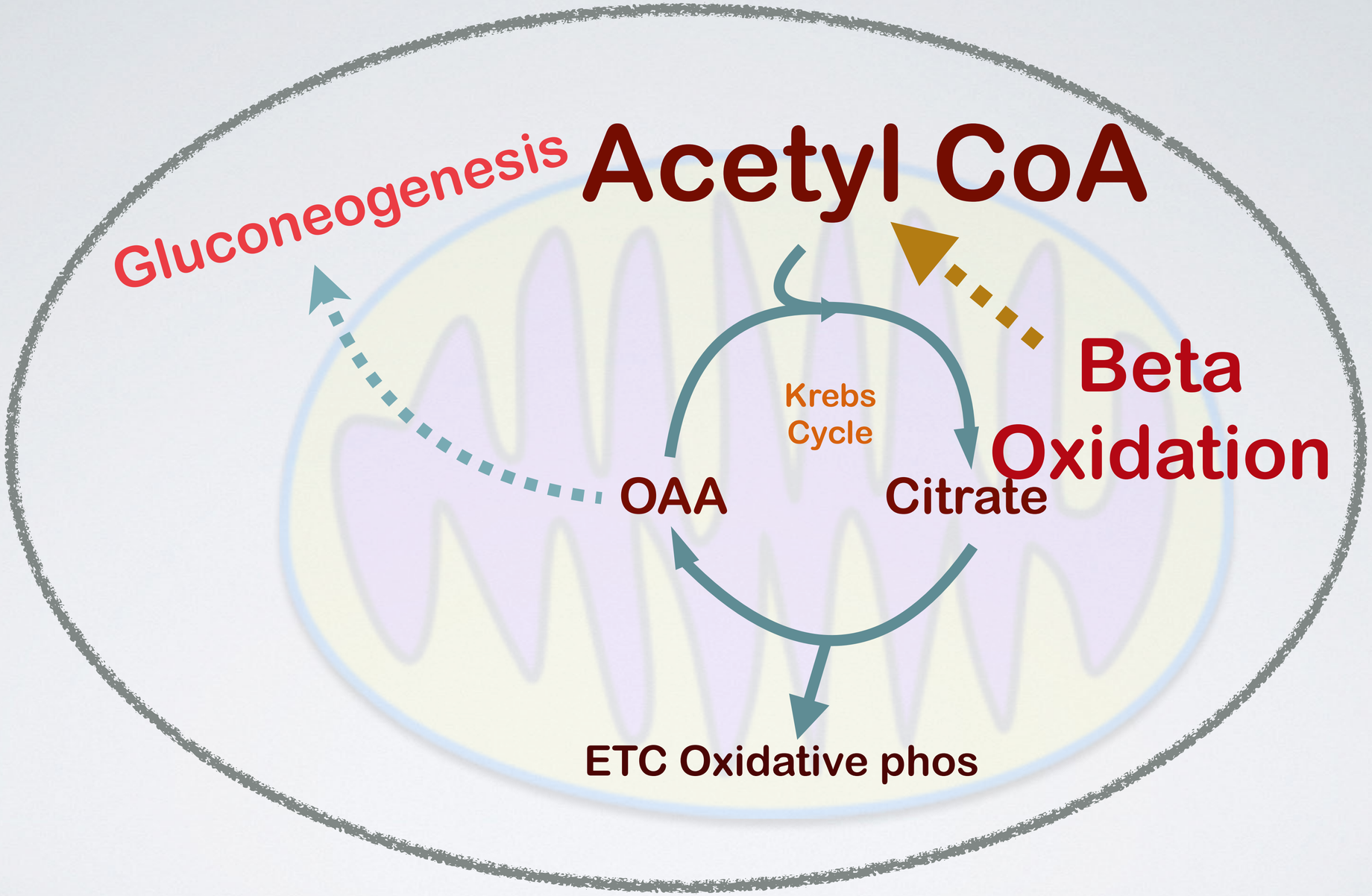

Gluconeogenesis
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
Amino acids
ETC Oxidative phos

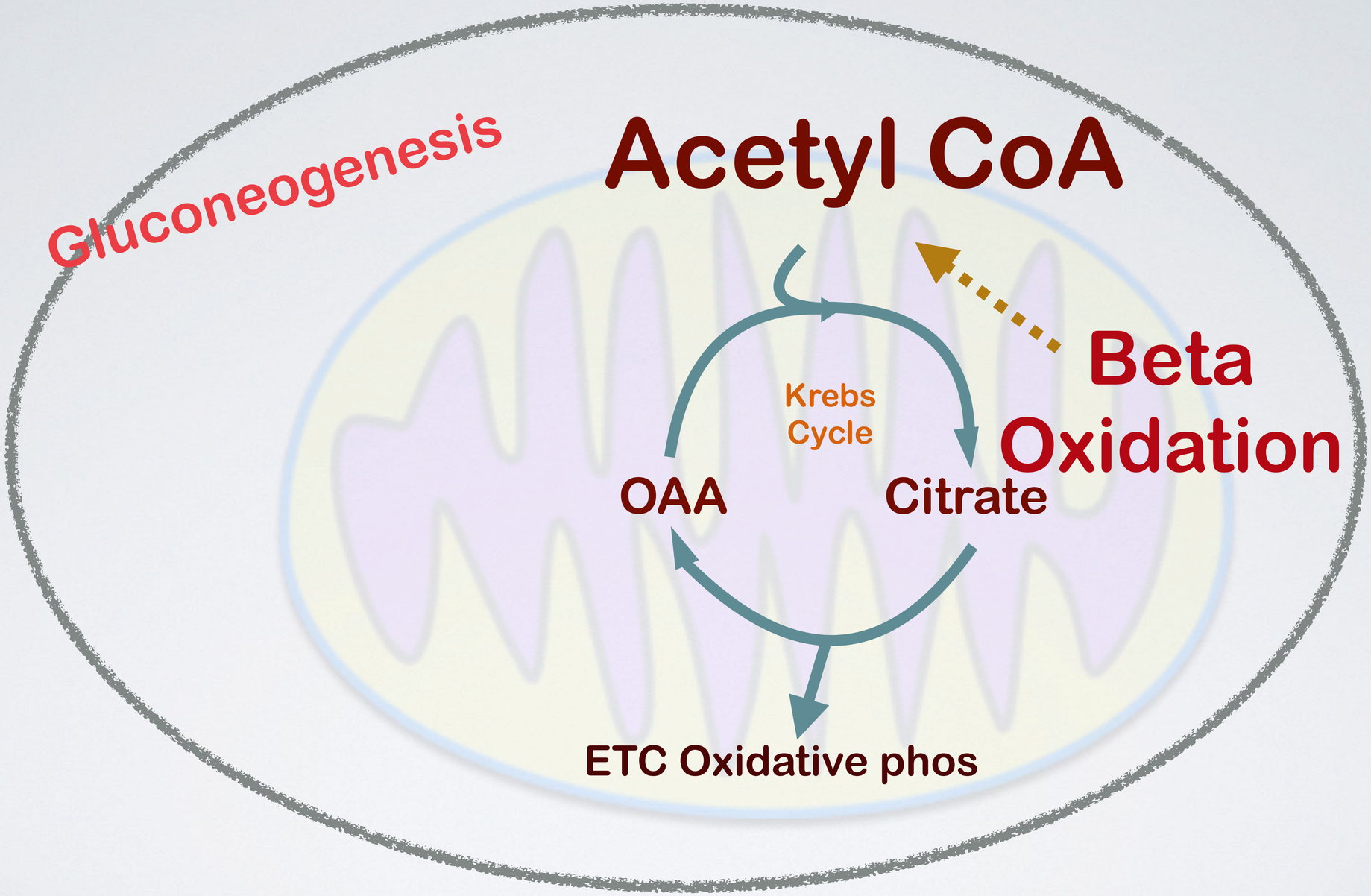

Gluconeogenesis
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
Amino acids
Protein
ETC Oxidative phos

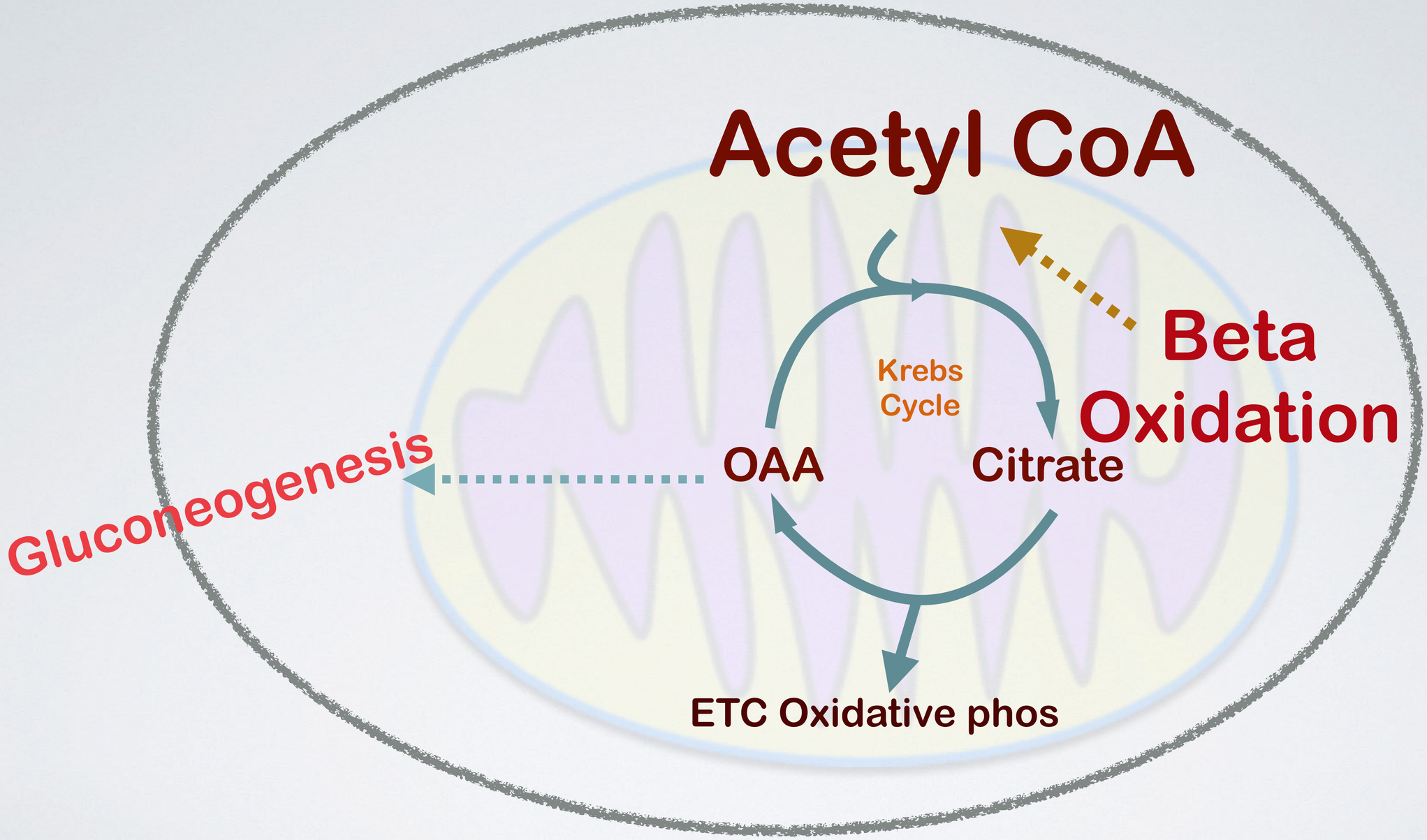

Gluconeogenesis
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
Amino acids
Protein
Lean body mass
ETC Oxidative phos

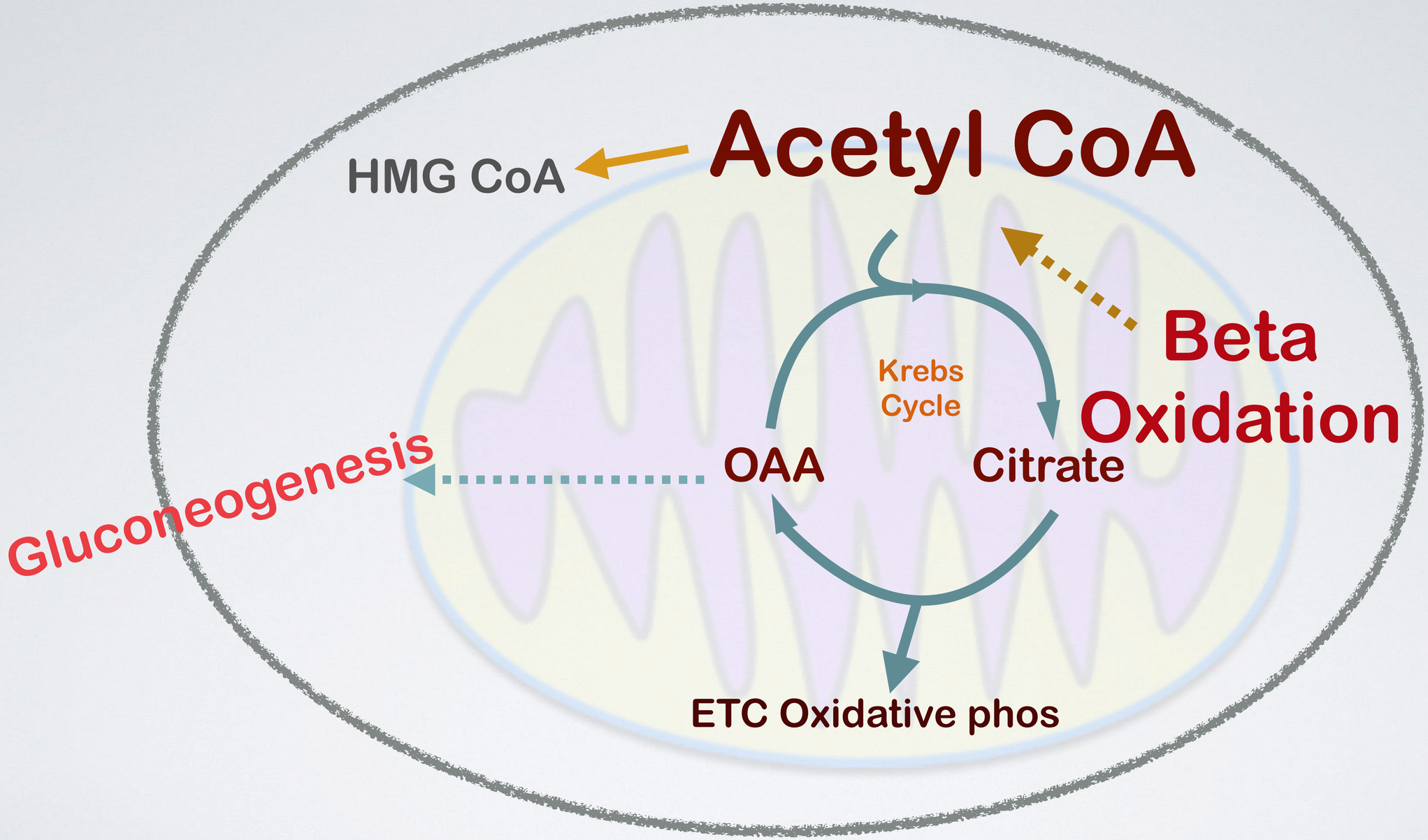

Gluconeogenesis
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
ETC Oxidative phos

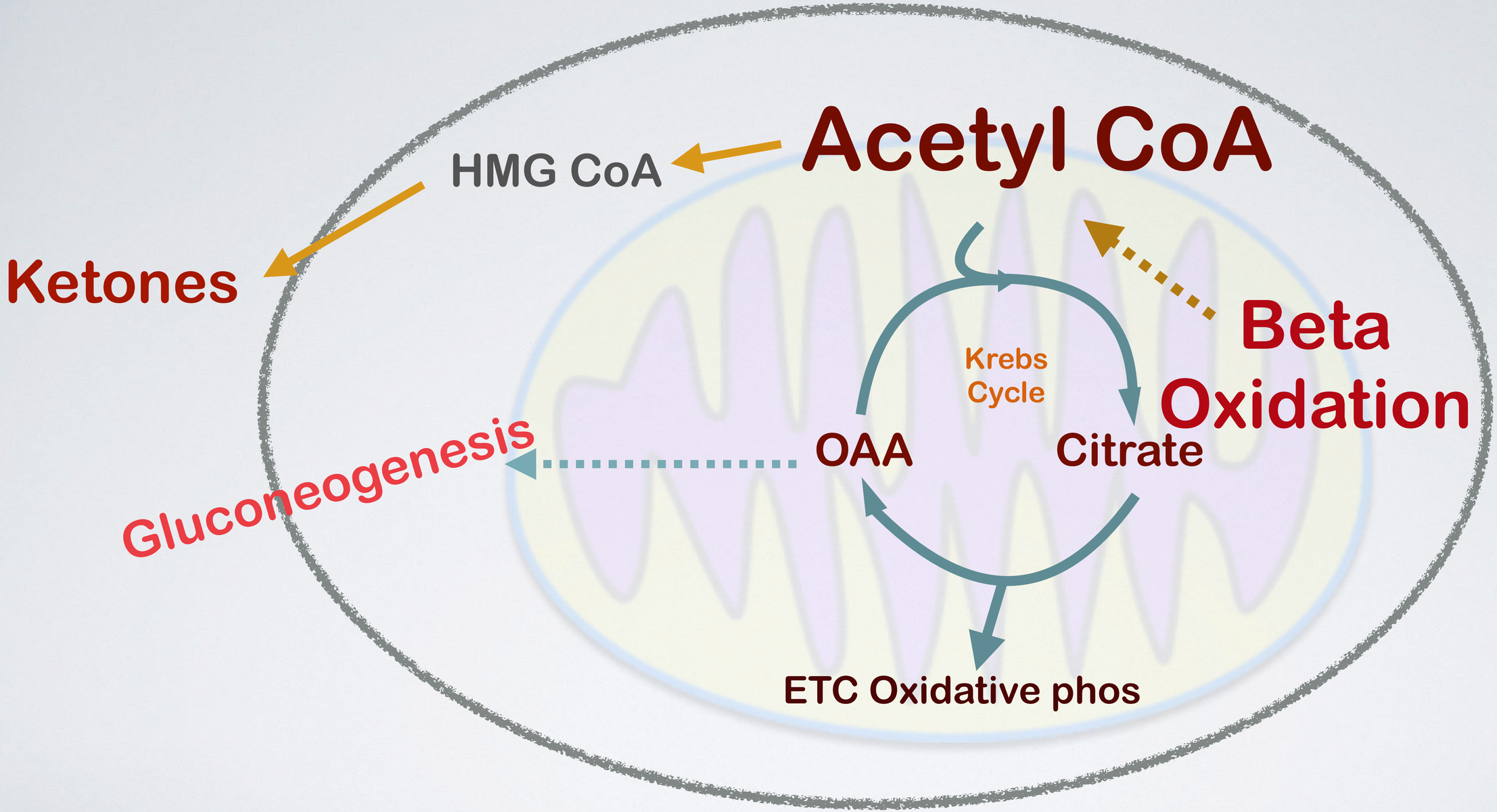

Gluconeogenesis
Acetyl CoA
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
ETC Oxidative phos

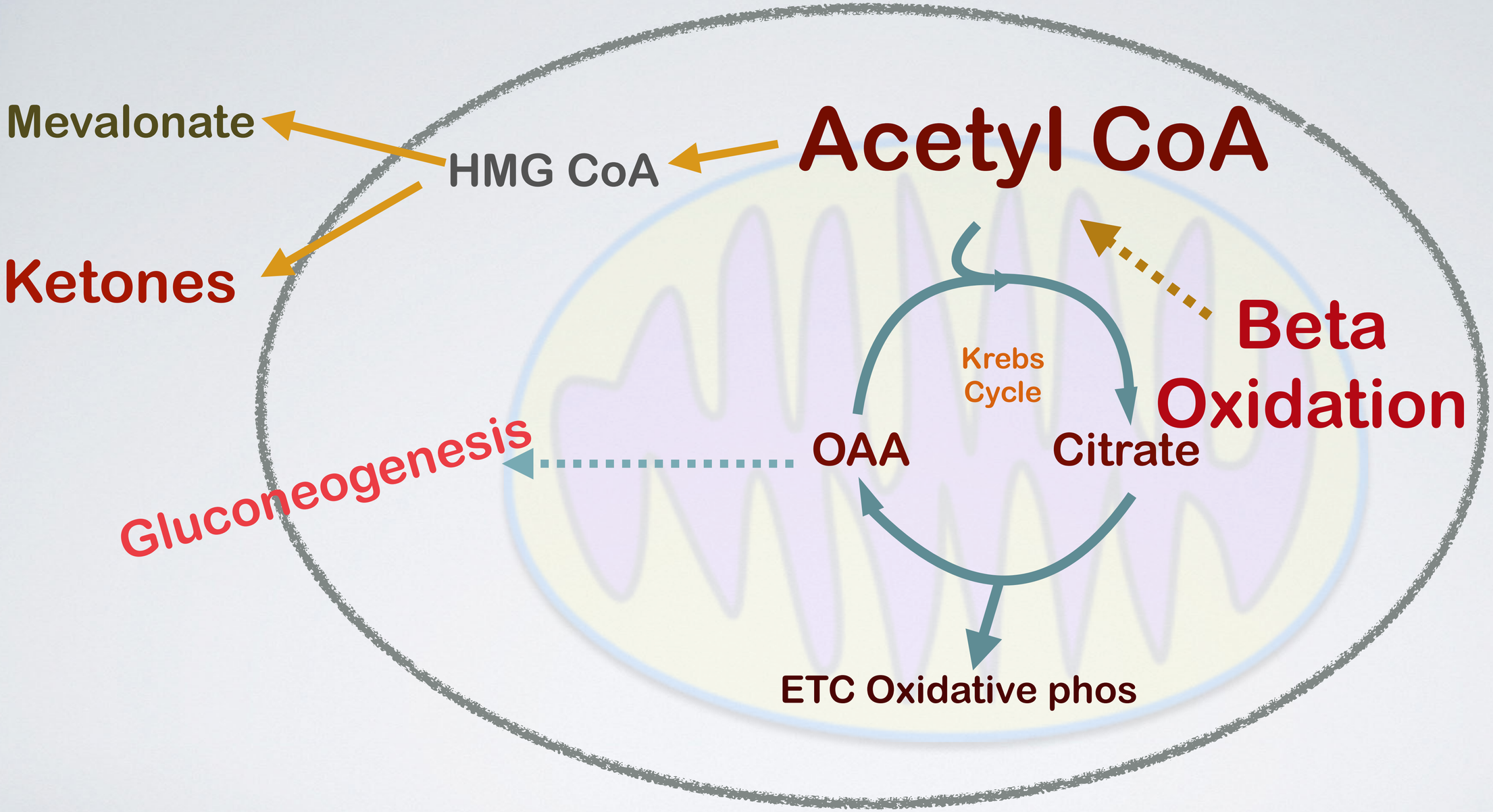

Gluconeogenesis
Acetyl CoA
Beta Oxidation
Krebs Cycle
OAA
Citrate
ETC Oxidative phos

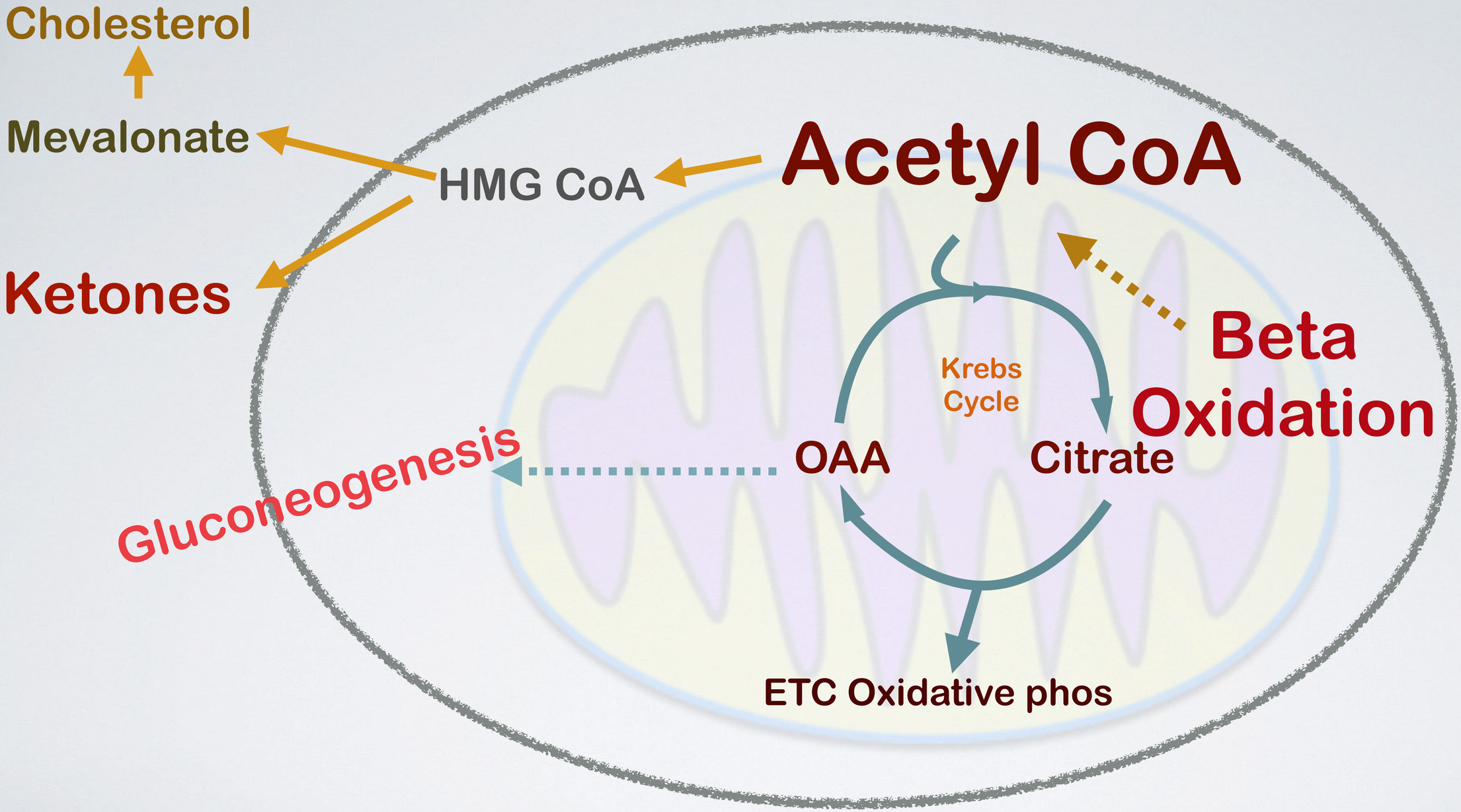

Gluconeogenesis
Acetyl CoA
Beta Oxidation
Krebs Cycle
OAA
Citrate
ETC Oxidative phos

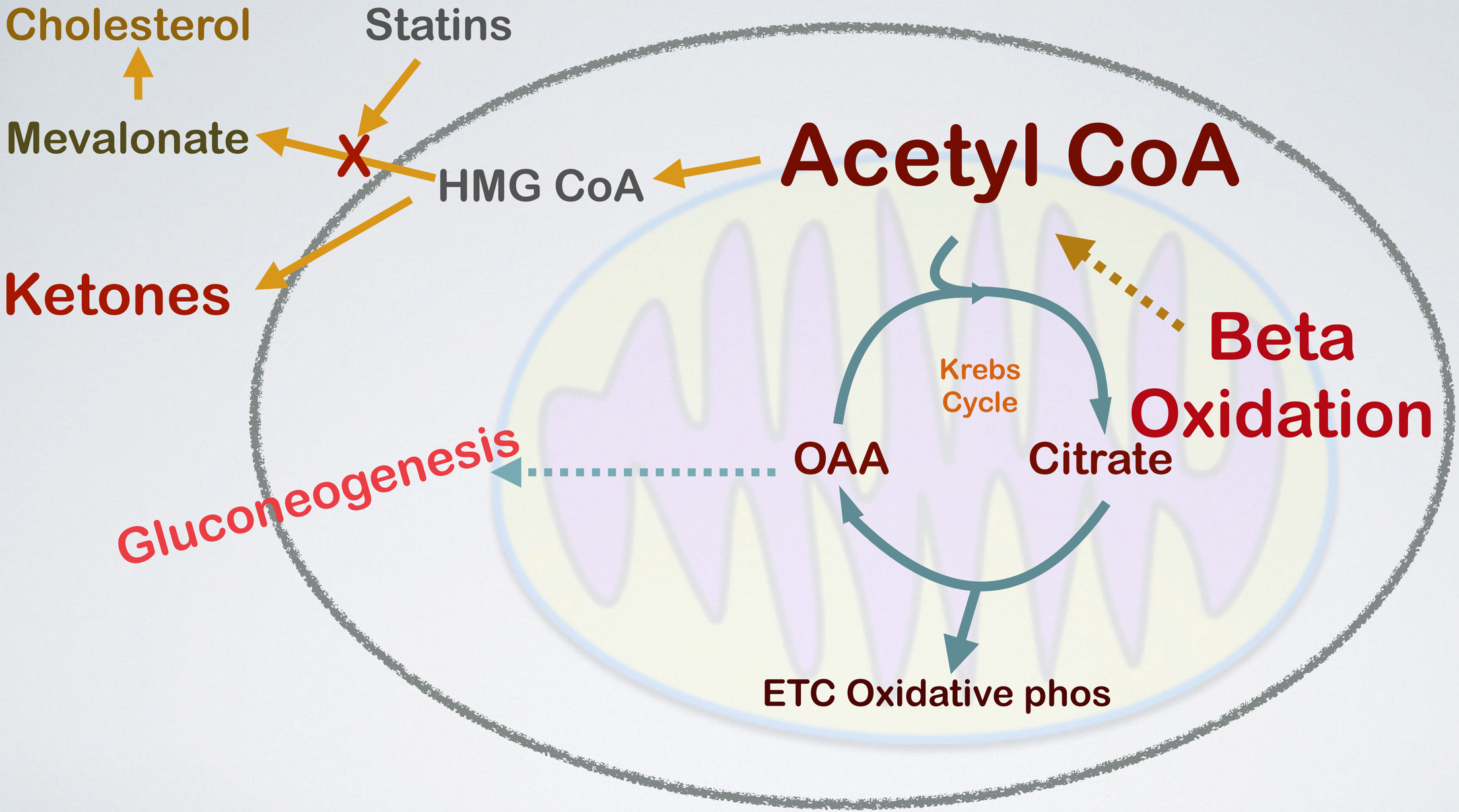

Acetyl CoA
Beta Oxidation
Krebs Cycle
OAA
Citrate
Gluconeogenesis
ETC Oxidative phos

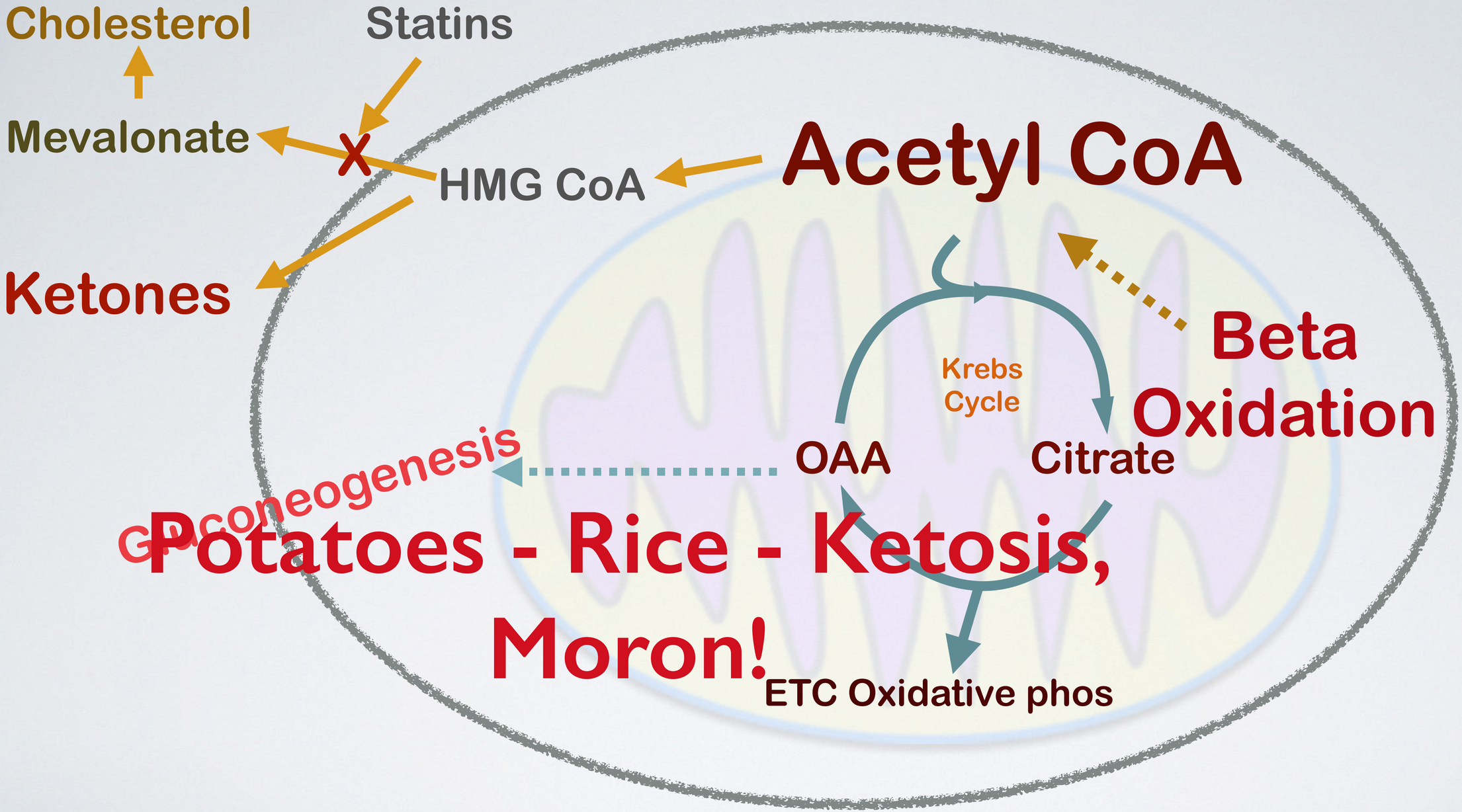

Acetyl CoA
HMG CoA
Beta Oxidation
Krebs Cycle
OAA
Citrate
Gluconeogenesis
ETC Oxidative phos

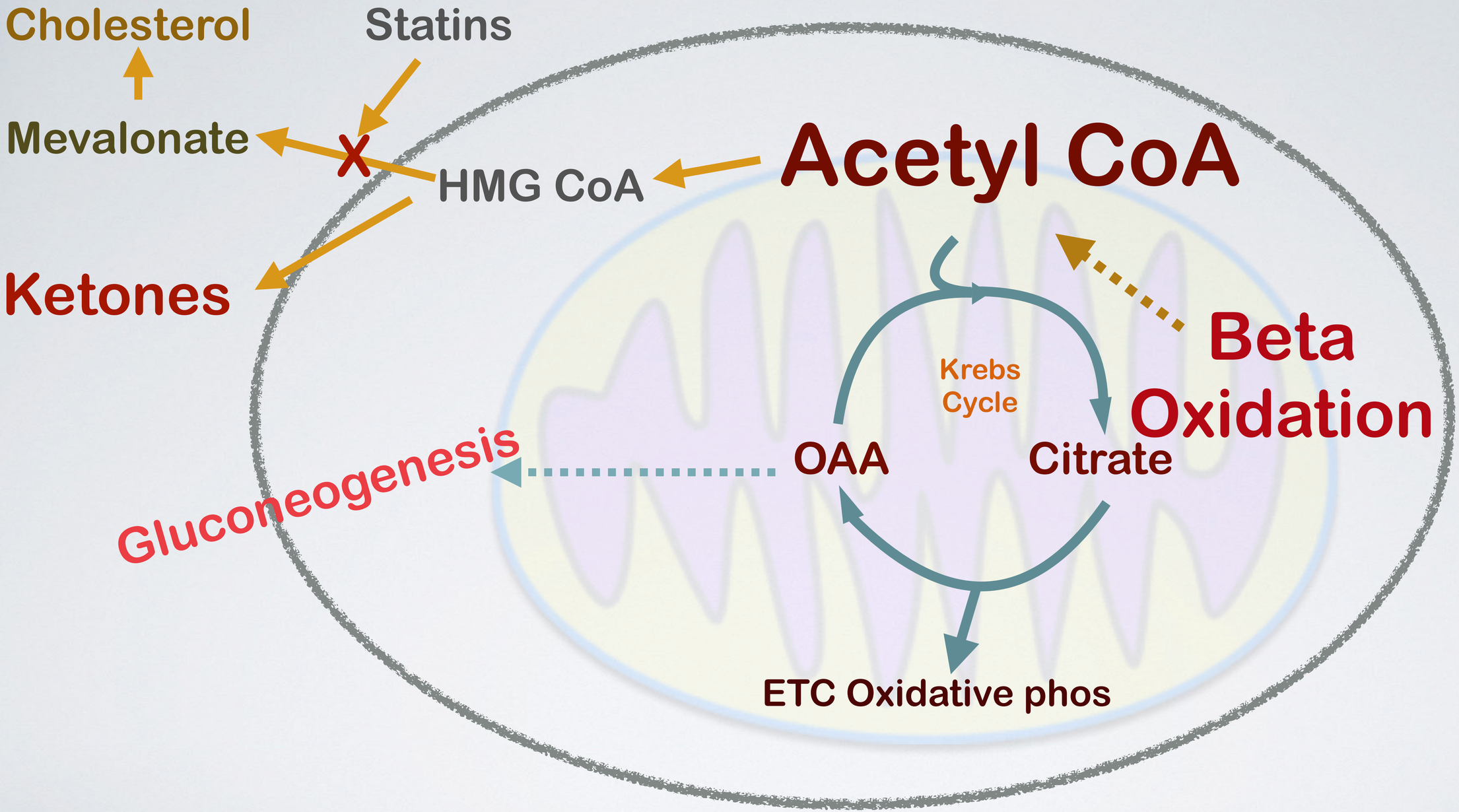

Acetyl CoA
HMG CoA
Ketones
Beta Oxidation
Krebs Cycle
Gluconeogenesis
OAA
Citrate
ETC Oxidative phos


Mevalonate
HMG CoA
Acetyl CoA
Ketones
Beta
Oxidation
Krebs
Cycle
Gluconeogenesis
OAA
Citrate
ETC Oxidative phos


Cholesterol
Mevalonate
HMG CoA
Acetyl CoA
Ketones
Beta Oxidation
Krebs Cycle
Gluconeogenesis
OAA
Citrate
ETC Oxidative phos


Cholesterol
Statins
Mevalonate
HMG CoA
Acetyl CoA
Ketones
Beta Oxidation
Krebs Cycle
Gluconeogenesis
OAA
Citrate
ETC Oxidative phos


Cholesterol
Statins
Mevalonate
HMG CoA
Acetyl CoA
Ketones
Beta Oxidation
Krebs Cycle
OAA
Citrate
Gluconeogenesis
Potatoes - Rice - Ketosis, Moron!
ETC Oxidative phos


Cholesterol
Statins
Mevalonate
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Acetyl CoA
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Beta Oxidation
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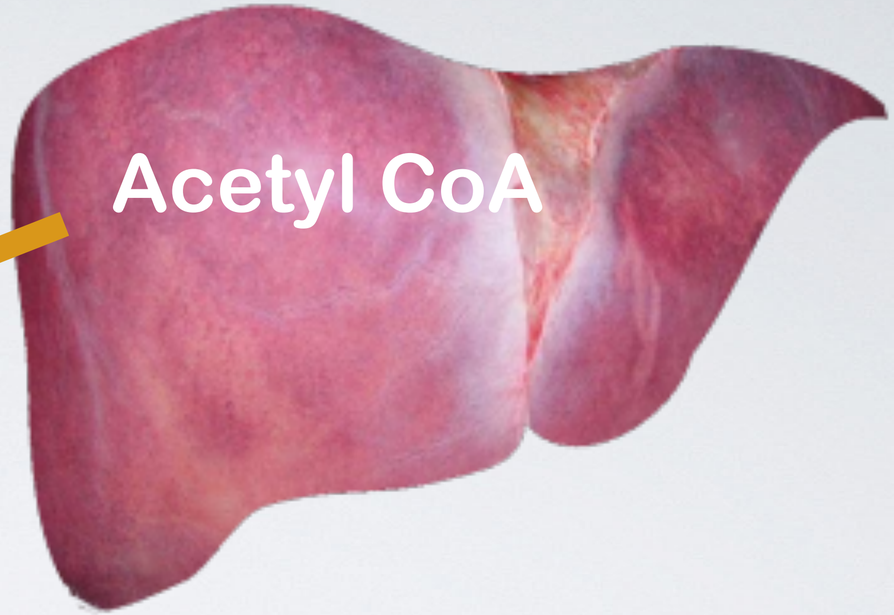
Gluconeogenesis
OAA
Citrate
ETC Oxidative phos

Breath

Urine

Ketones

Acetyl CoA

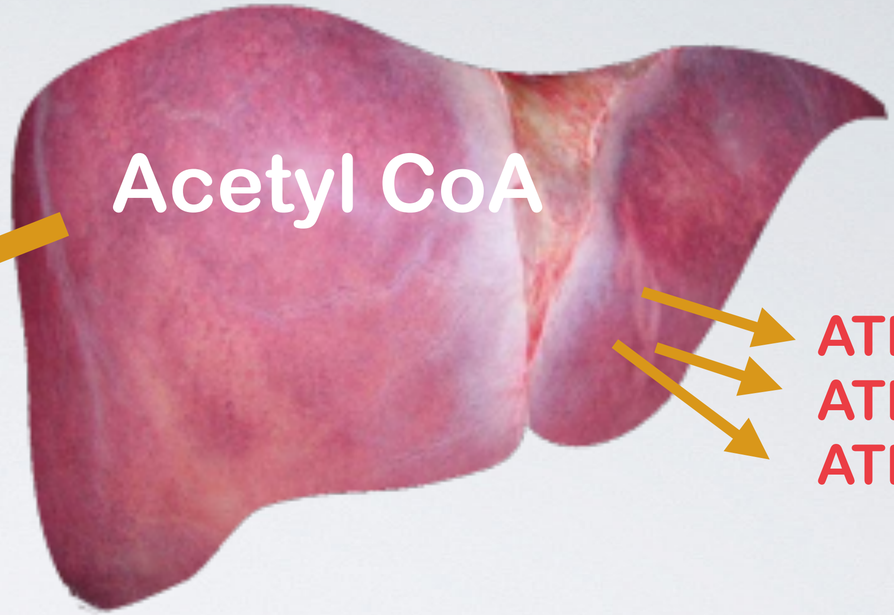


Breath

Urine

Ketones

Acetyl CoA



ATP

ATP

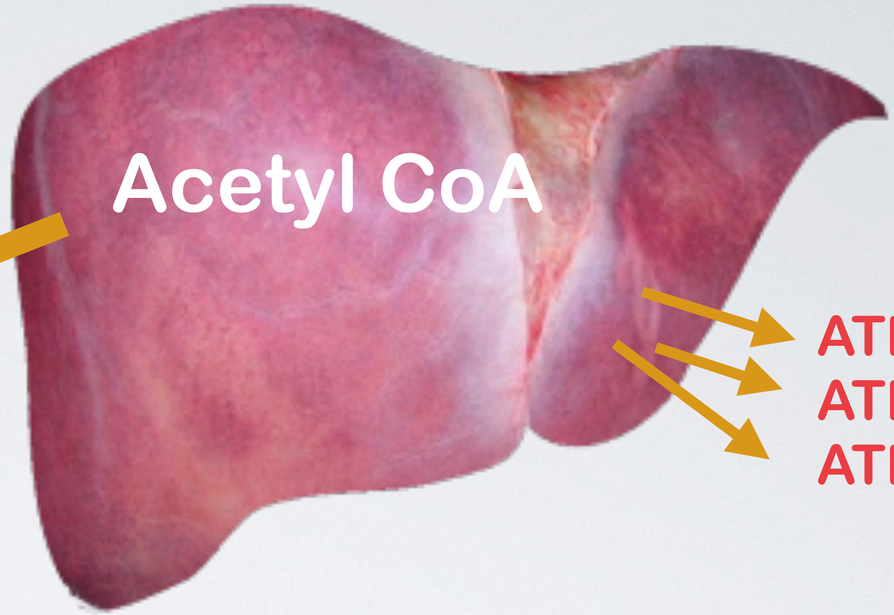
ATP

Breath

Urine

Ketones

Acetyl CoA



ATP

ATP

ATP

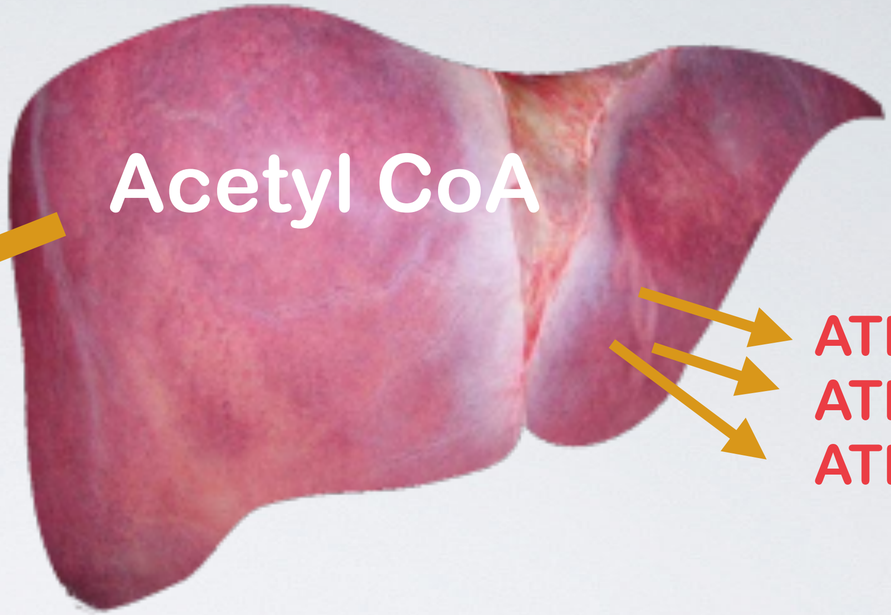
Glycerol 3-phosphate shuttle

Breath

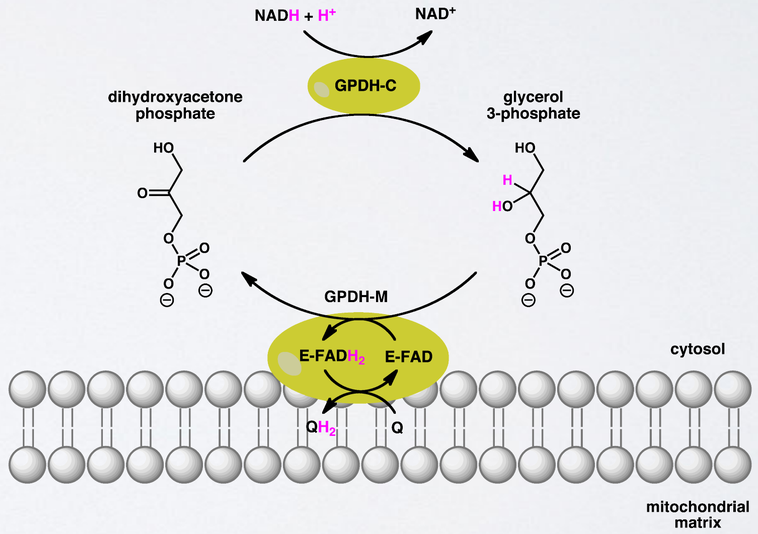
Urine

Ketones

Acetyl CoA



ATP
ATP
ATP



Glycerol 3-phosphate shuttle

Urir

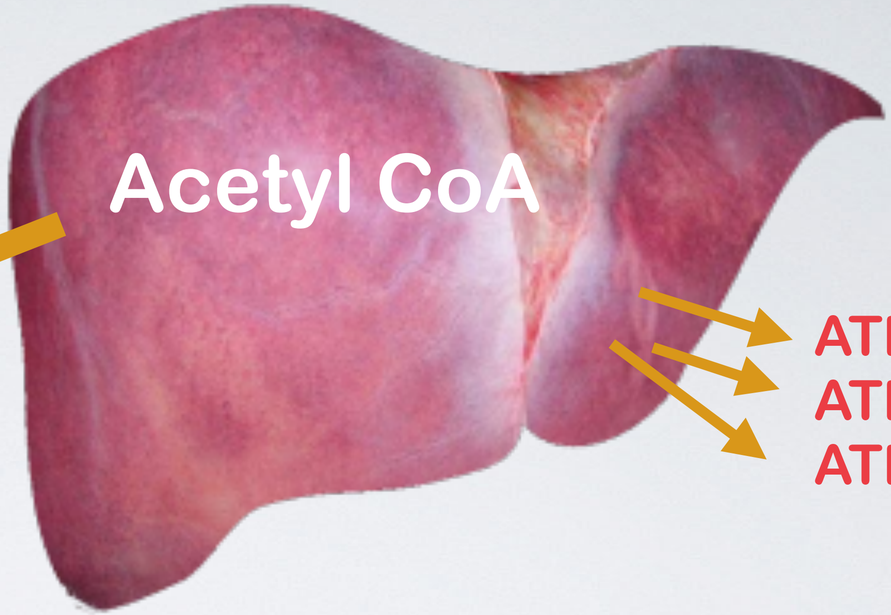
Glycerol 3-phosphate shuttle

Breath

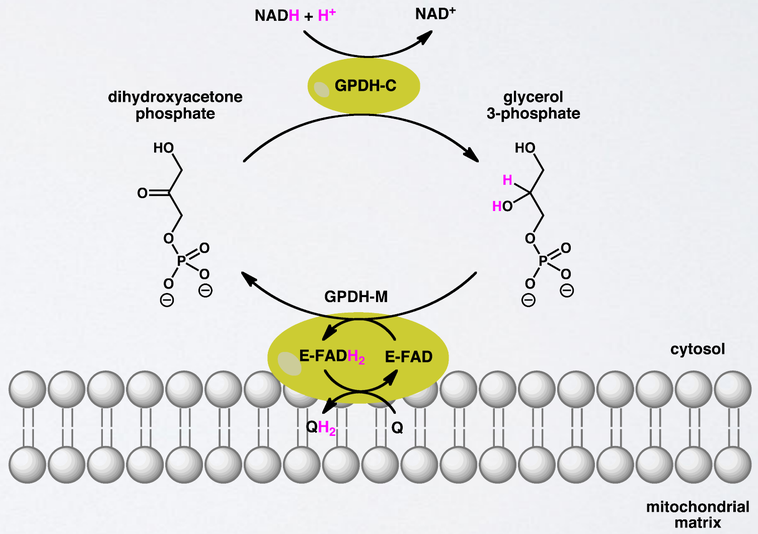
Urine

Ketones

Acetyl CoA



ATP
ATP
ATP



Glycerol 3-phosphate shuttle

Animals cannot convert fatty acids into glucose

A typical human being has far greater fat stores than glycogen stores. However, glycogen is necessary to fuel very active muscle, as well as the brain, which normally uses only glucose as a fuel. When glycogen stores are low, why can't the body make use of fat stores and convert fatty acids into glucose? Because *animals are unable to effect the net synthesis of glucose from fatty acids*. Specifically, acetyl CoA cannot be converted into pyruvate or oxaloacetate in animals. Recall that the reaction that generates acetyl CoA from pyruvate is irreversible (Section 17.1). The two carbon atoms of the acetyl group of acetyl CoA enter the citric acid cycle, but two carbon atoms leave the cycle in the decarboxylations catalyzed by isocitrate dehy-

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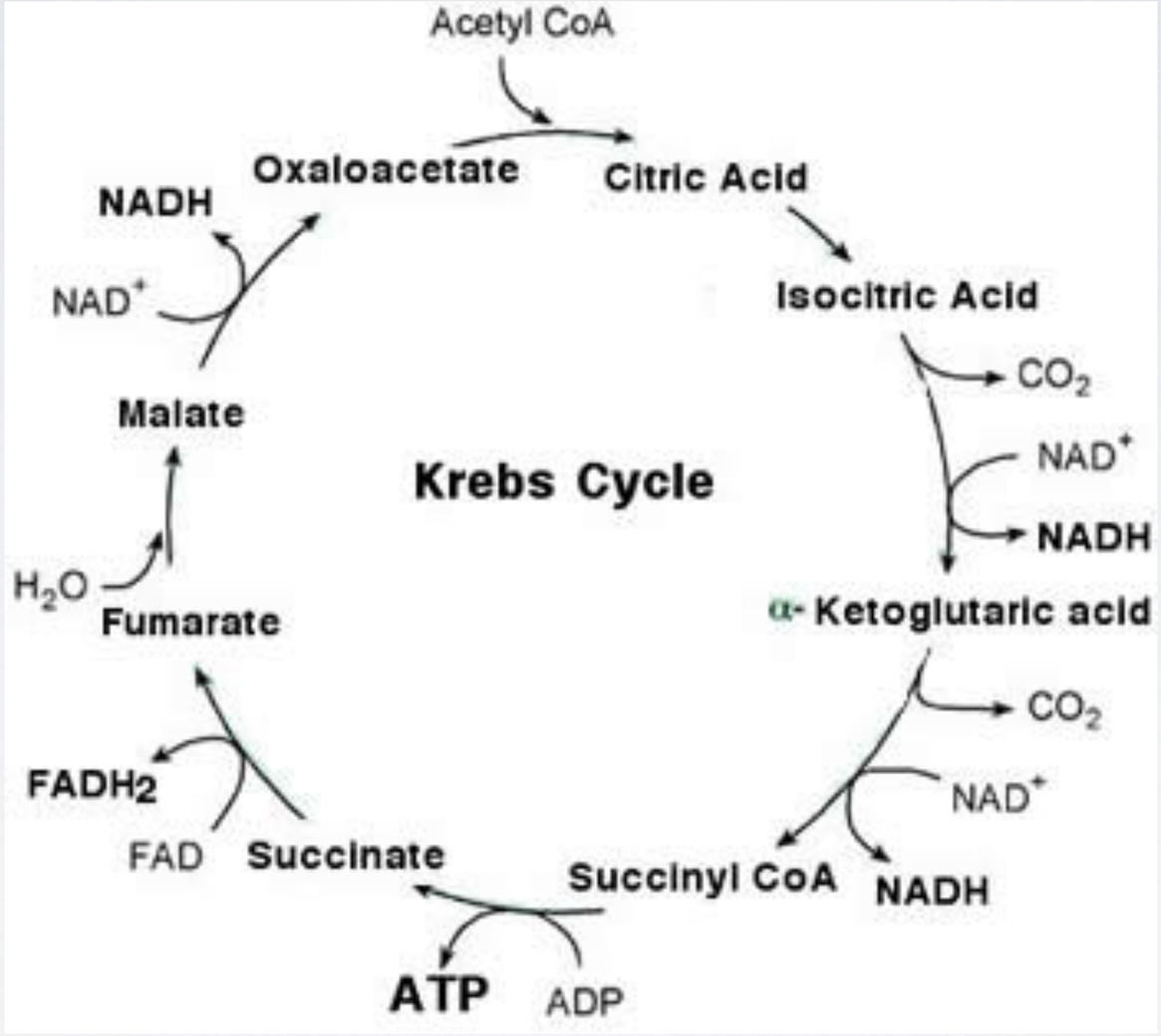
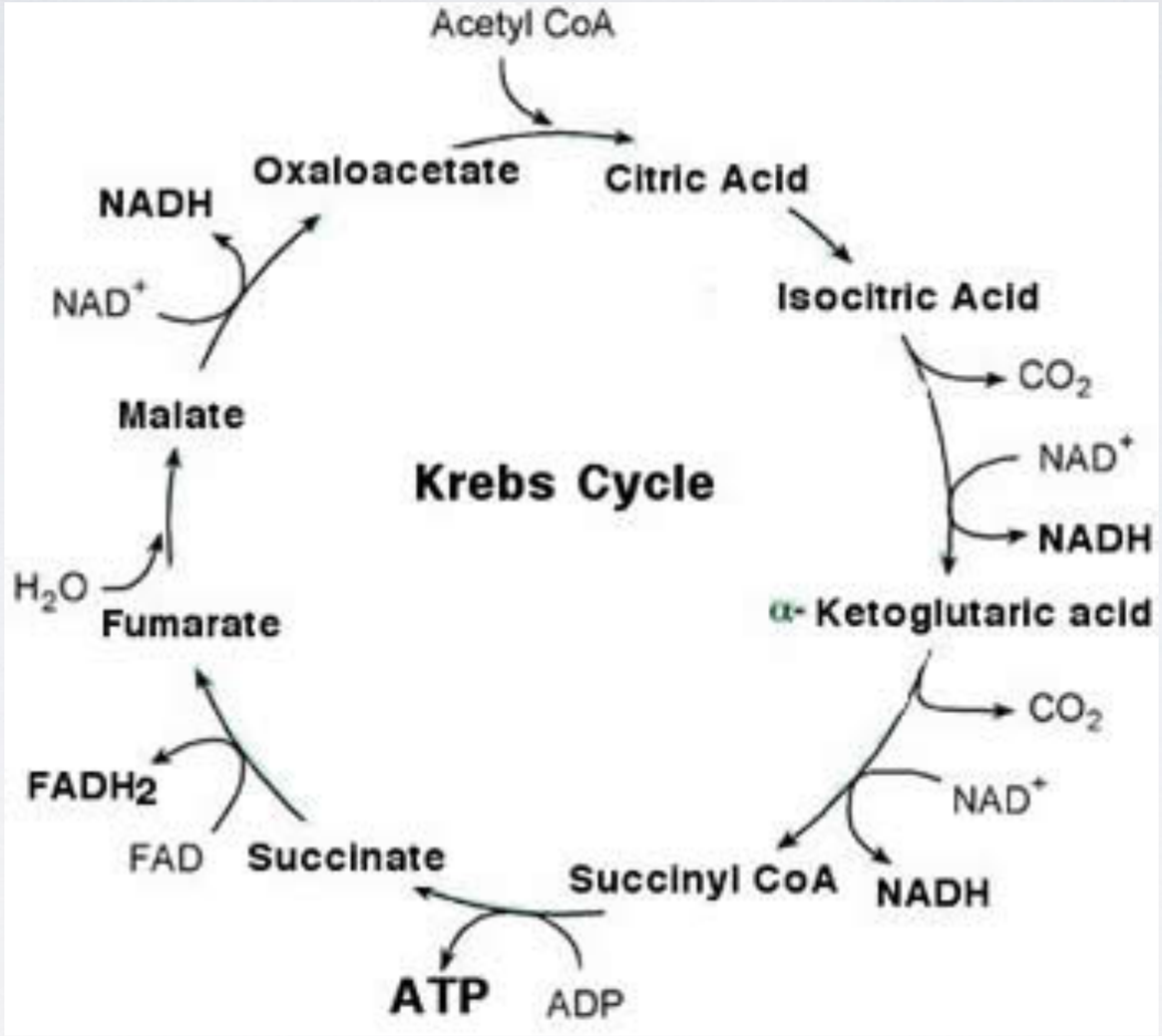
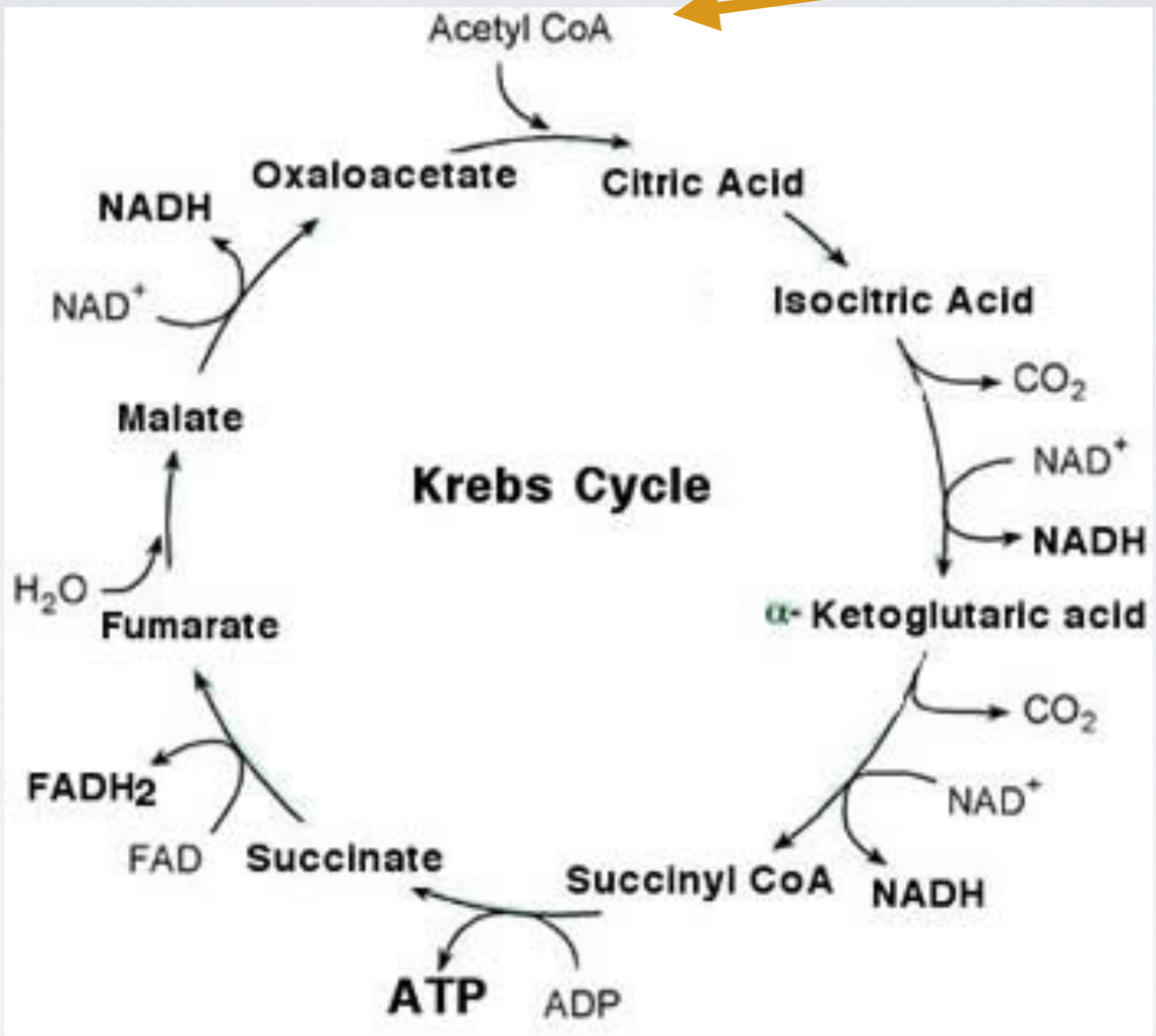

Acetyl CoA
Oxaloacetate
Citric Acid
NADH
NAD+
Isocitric Acid
CO2
Malate
NAD+
Krebs Cycle
NADH
H2O
α- Ketoglutaric acid
Fumarate
CO2
FADH2
NAD+
FAD
Succinate
Succinyl CoA
NADH
ATP
ADP

beta-oxidation



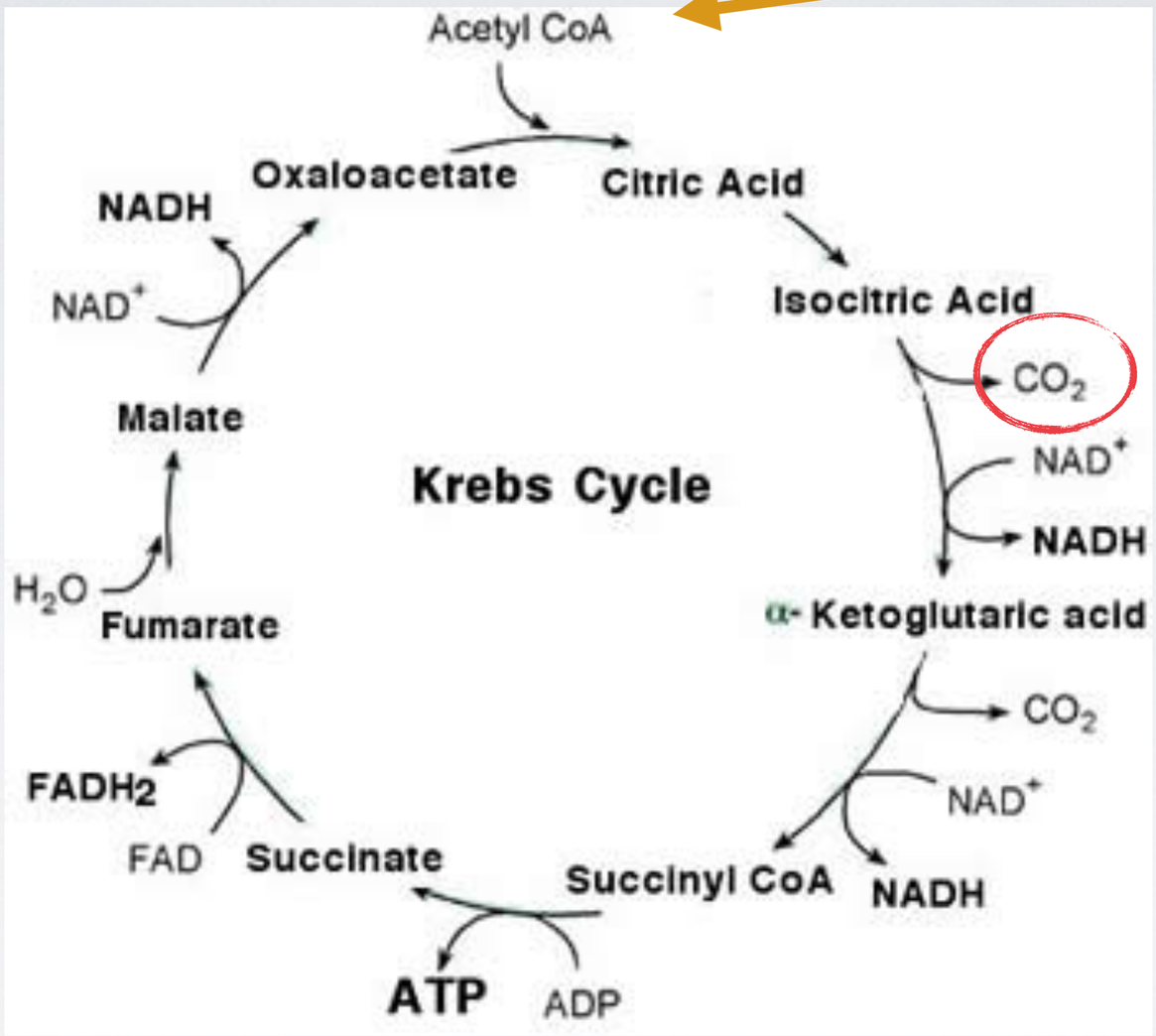
C-C

beta-oxidation



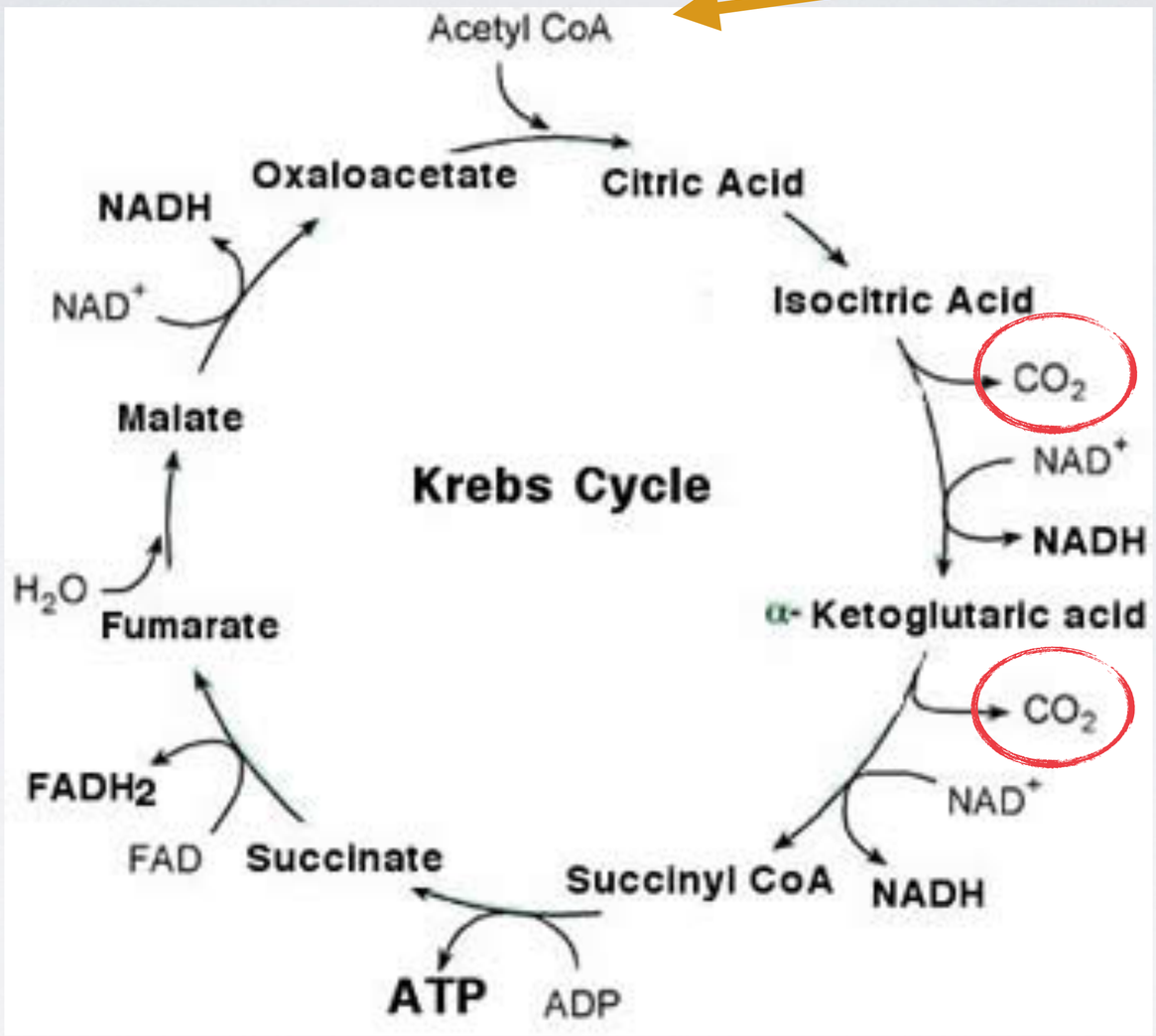
C-C

beta-oxidation



C-C

beta-oxidation



Fuel reserves available in a 70kg male (kcal)

	glucose/glycogen	Triacylglycerols	Mobilizable proteins
Blood	**60**	**45**	**0**
Liver	**400**	**450**	**400**
Brain	**8**	**0**	**0**
Muscle	**1200**	**450**	**24,000**
Adipose tissue	**80**	**135,000**	**40**

After Cahill. (1976) Clin Endocrinol Metab 5:398

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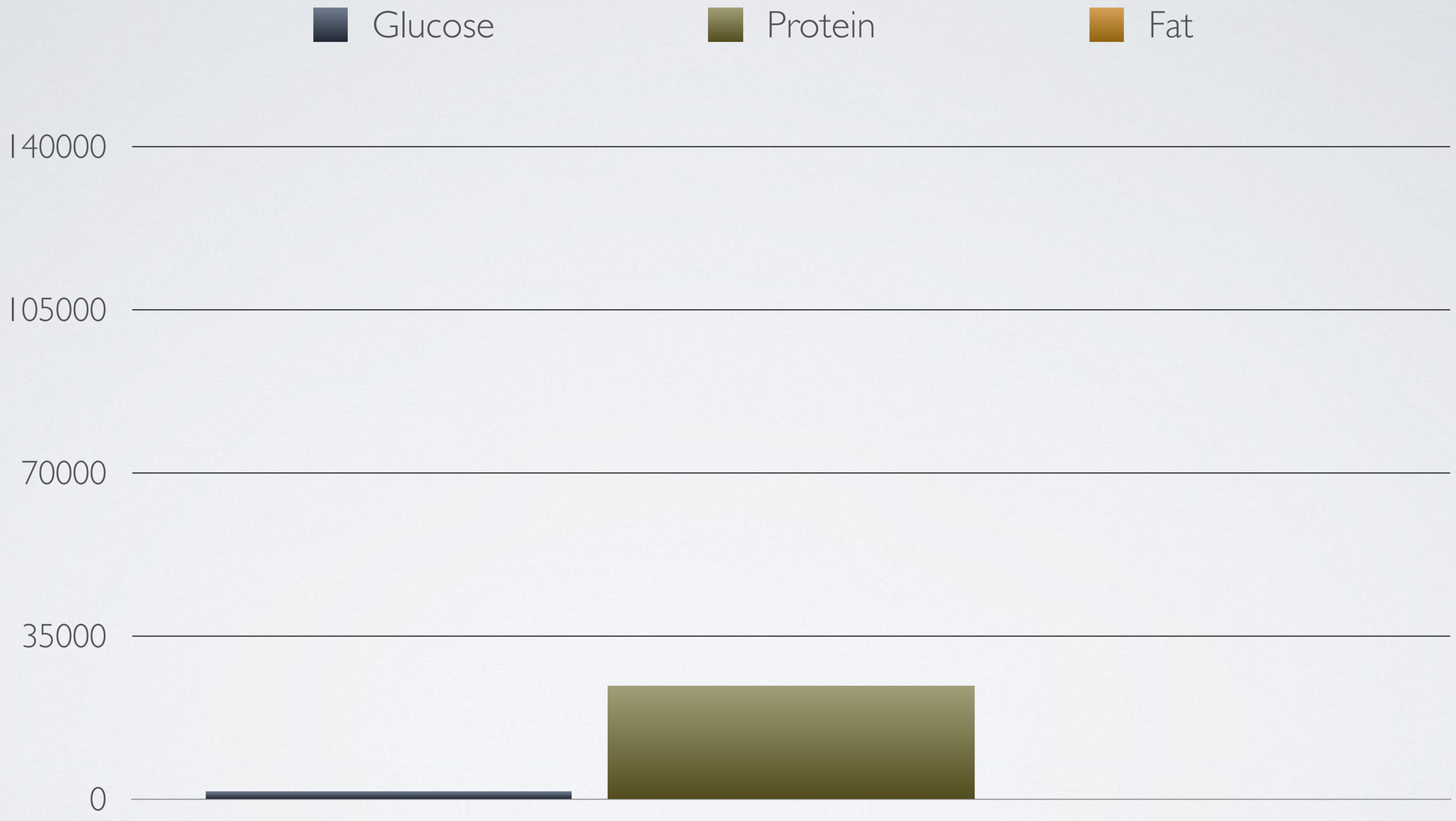

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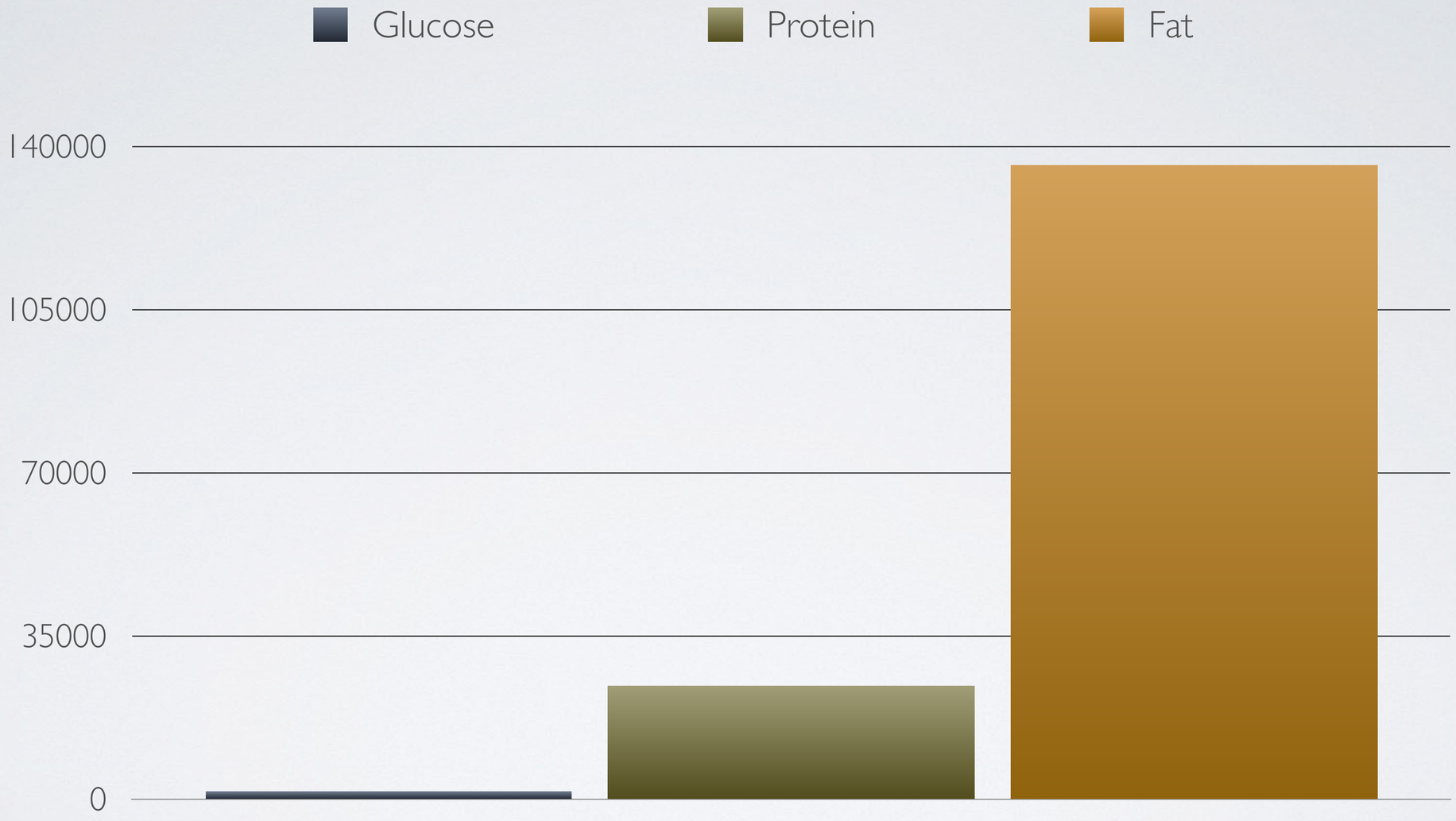

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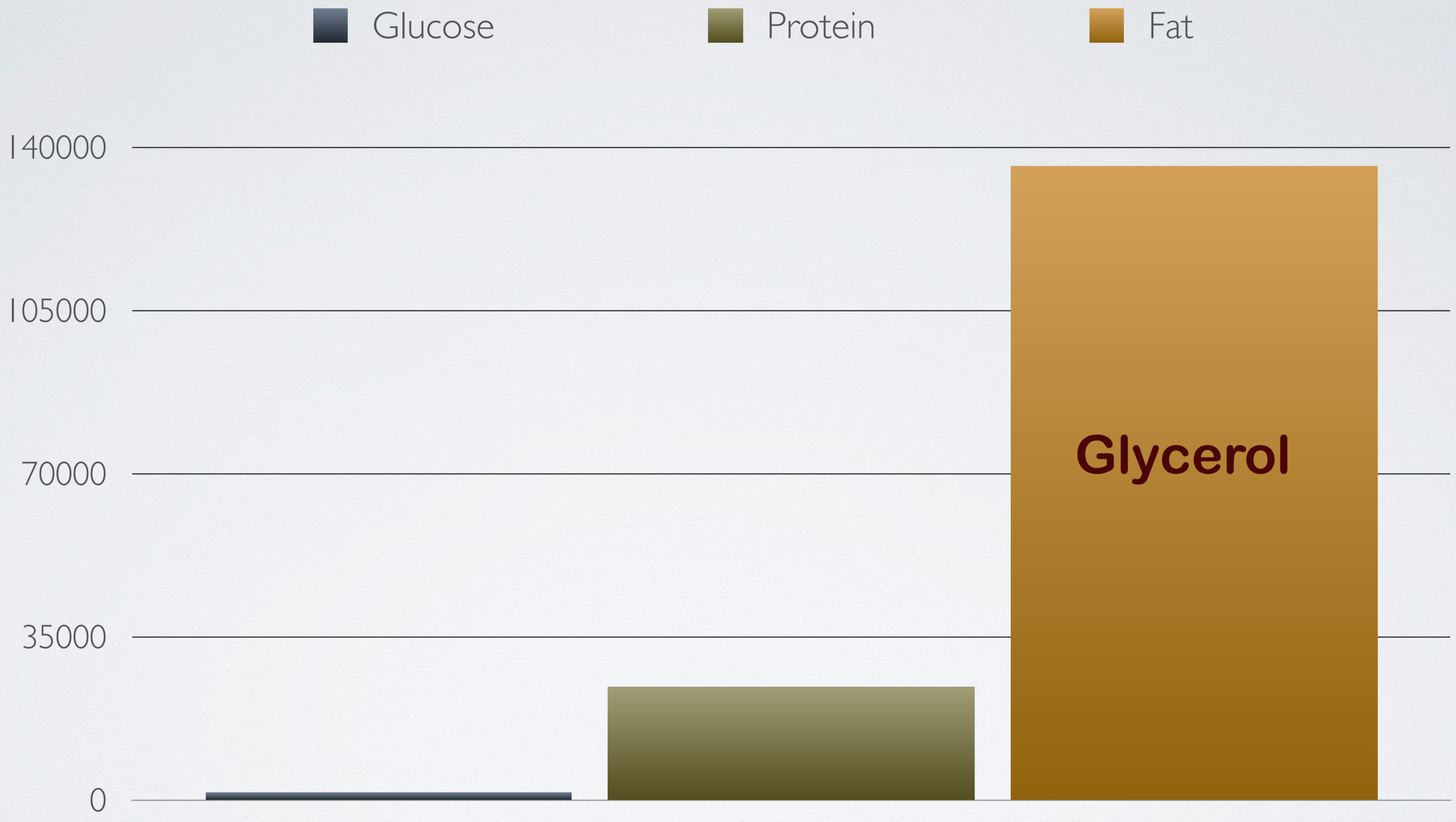

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Fuel reserves available in a 70kg male (kcal)

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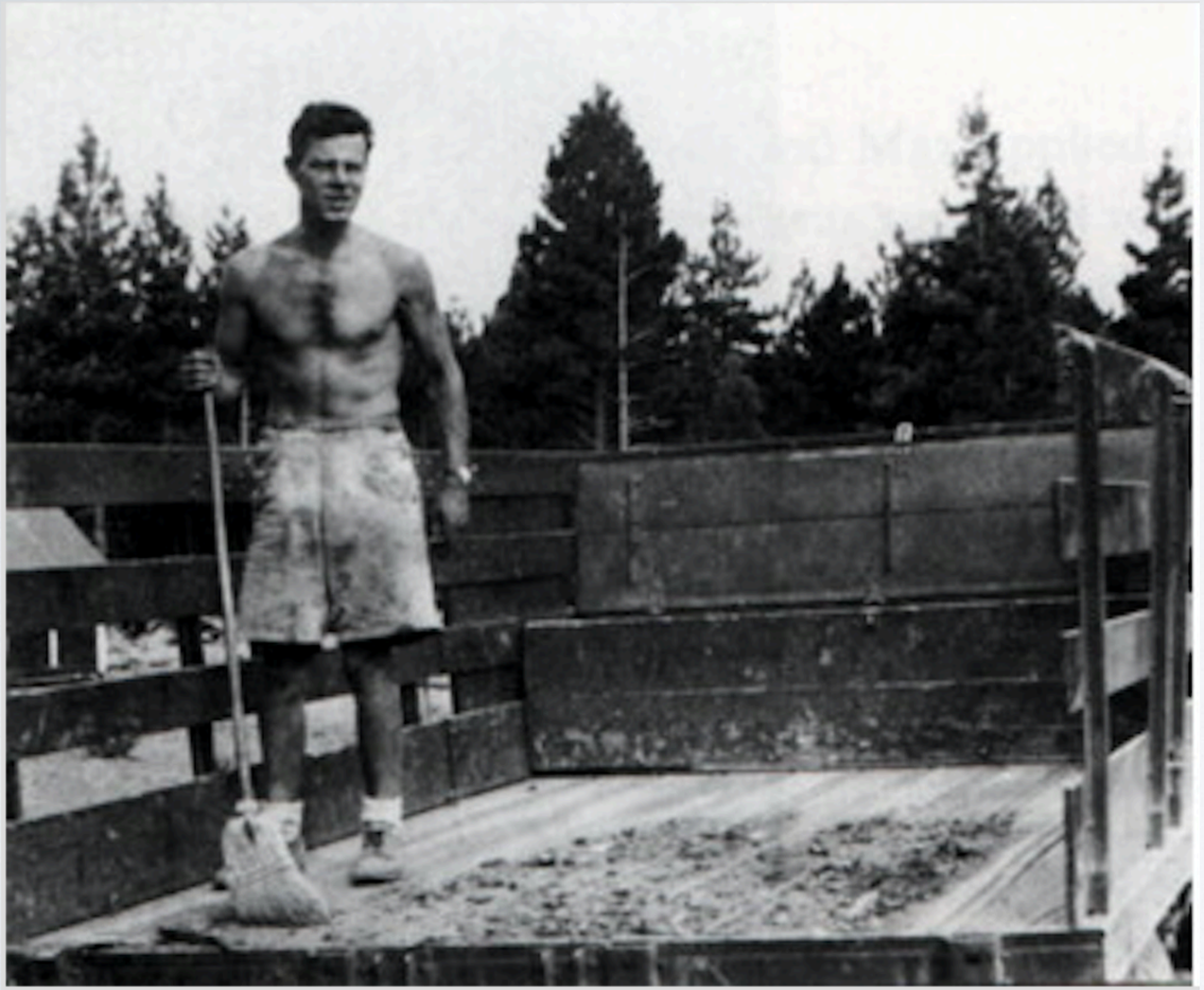
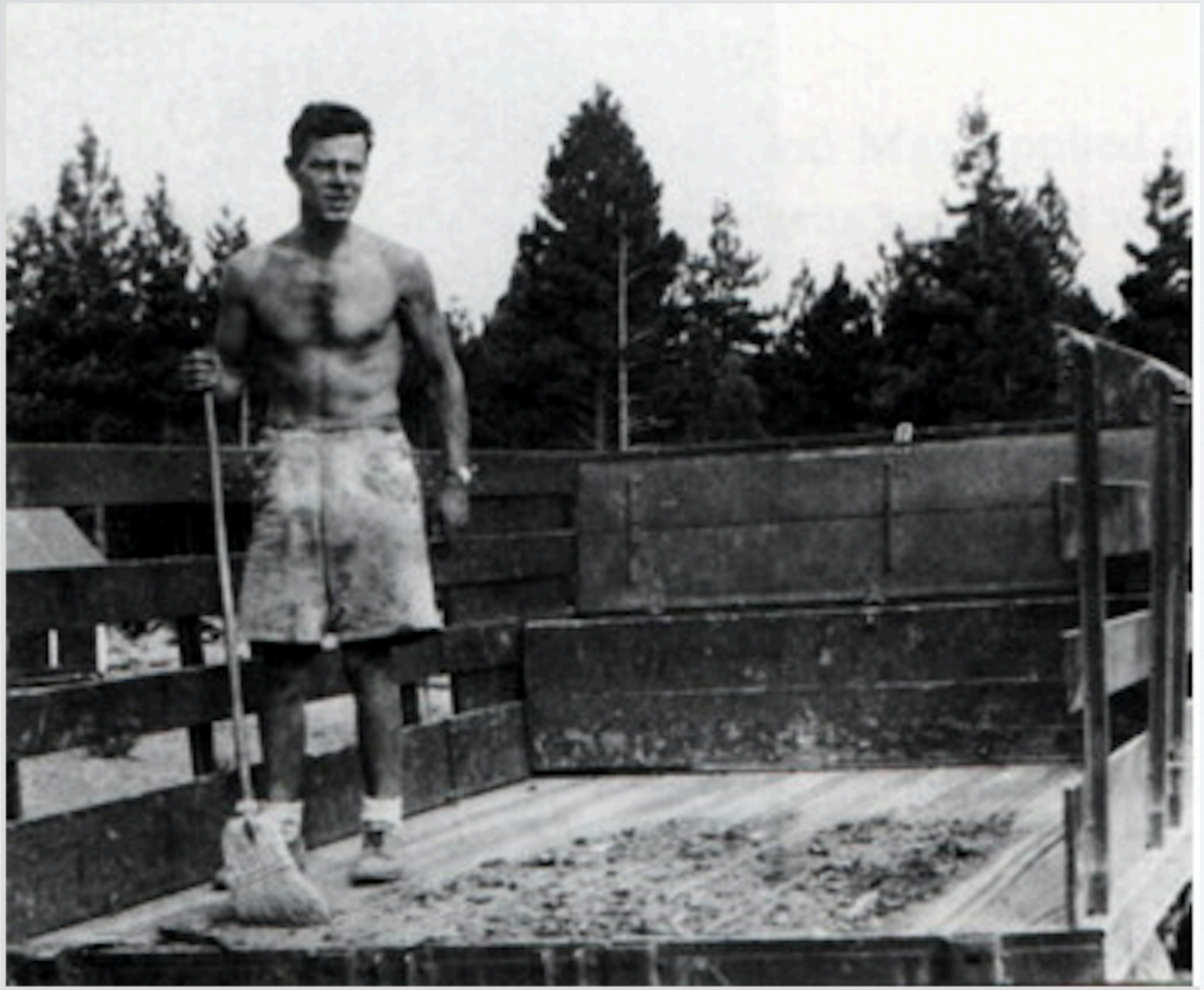


Sam Legg

Fuel reserves available in a 70kg male (kcal)



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Ancel Keys Minnesota Starvation Study 1945

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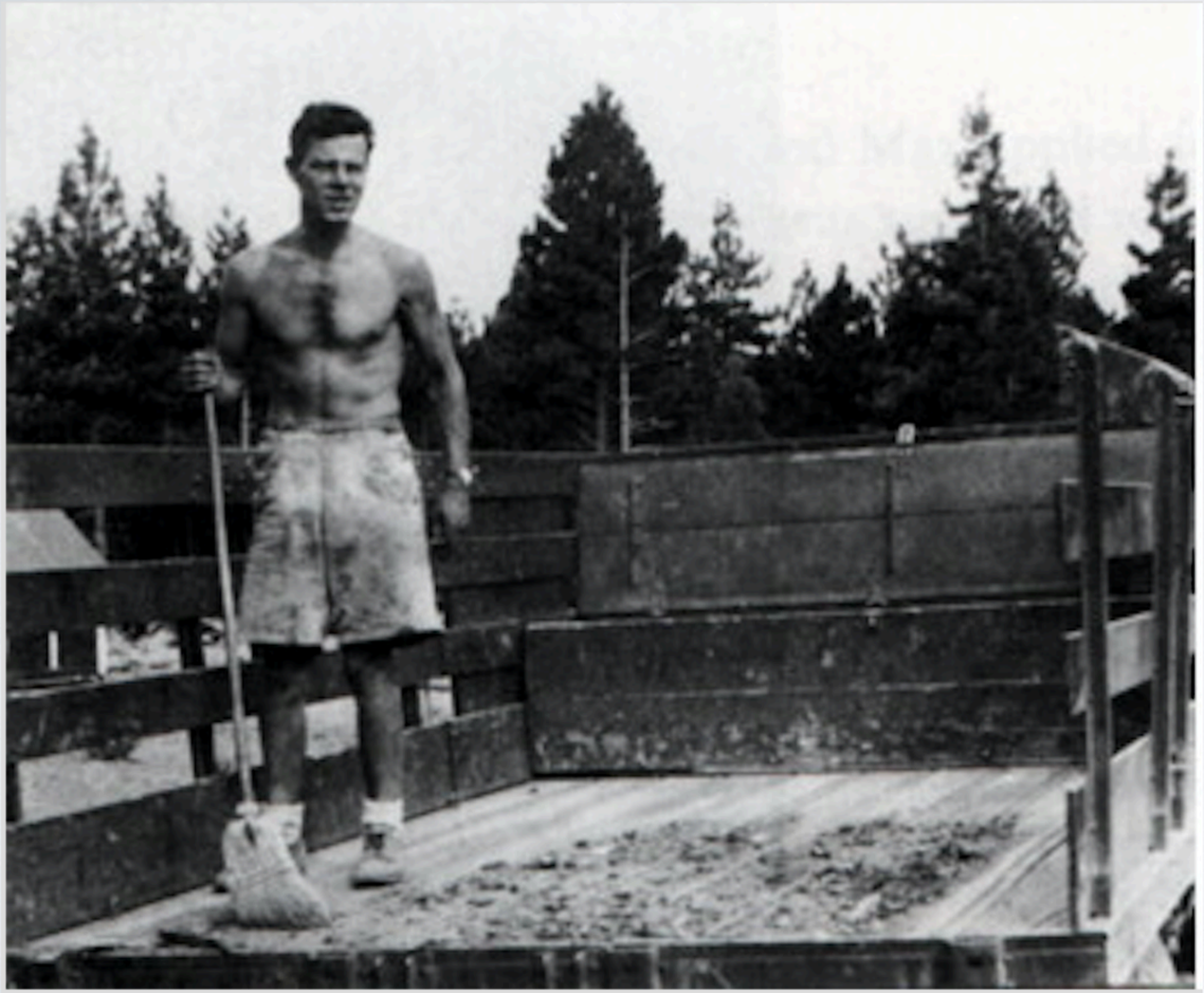

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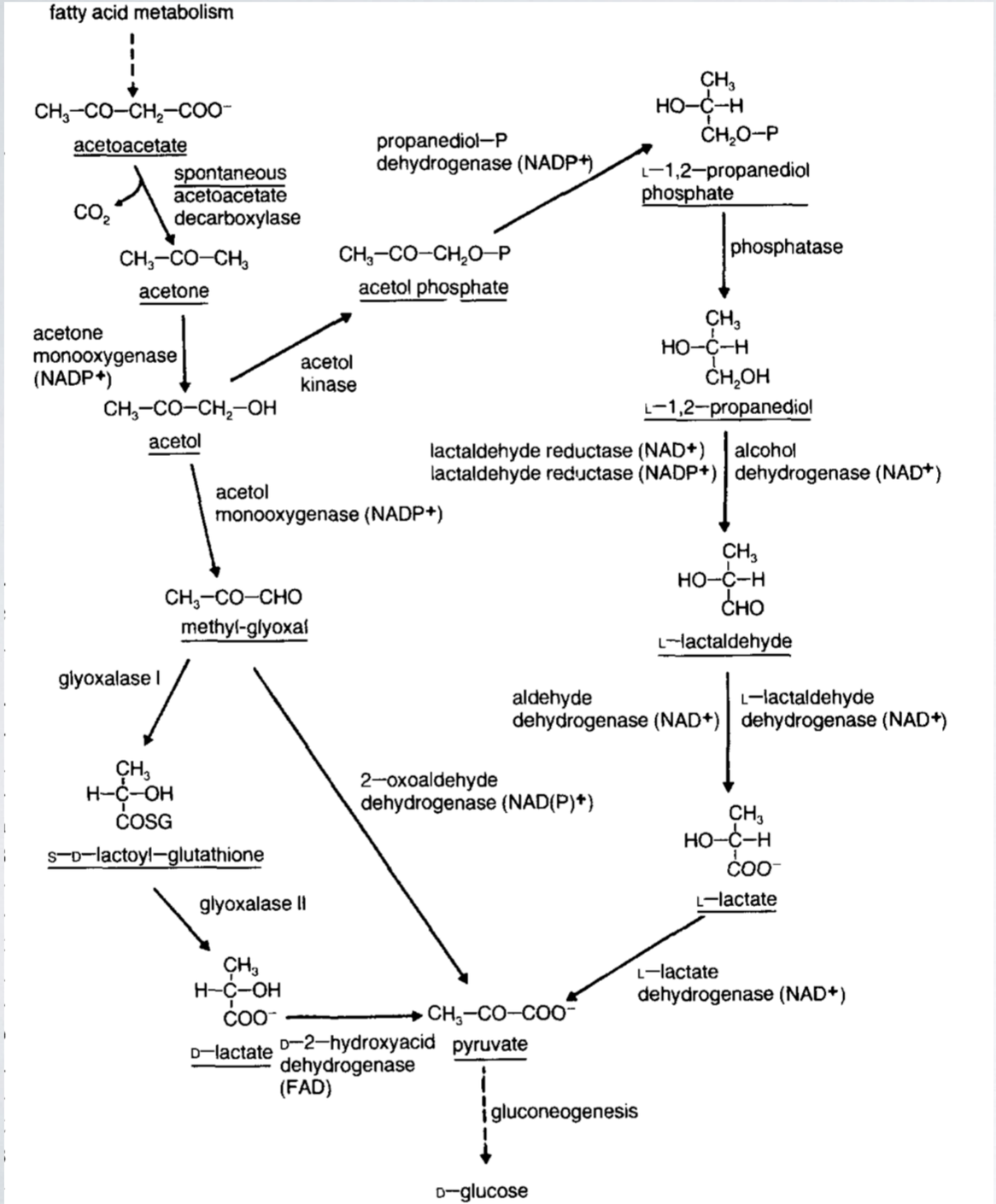


Fat

Acetone

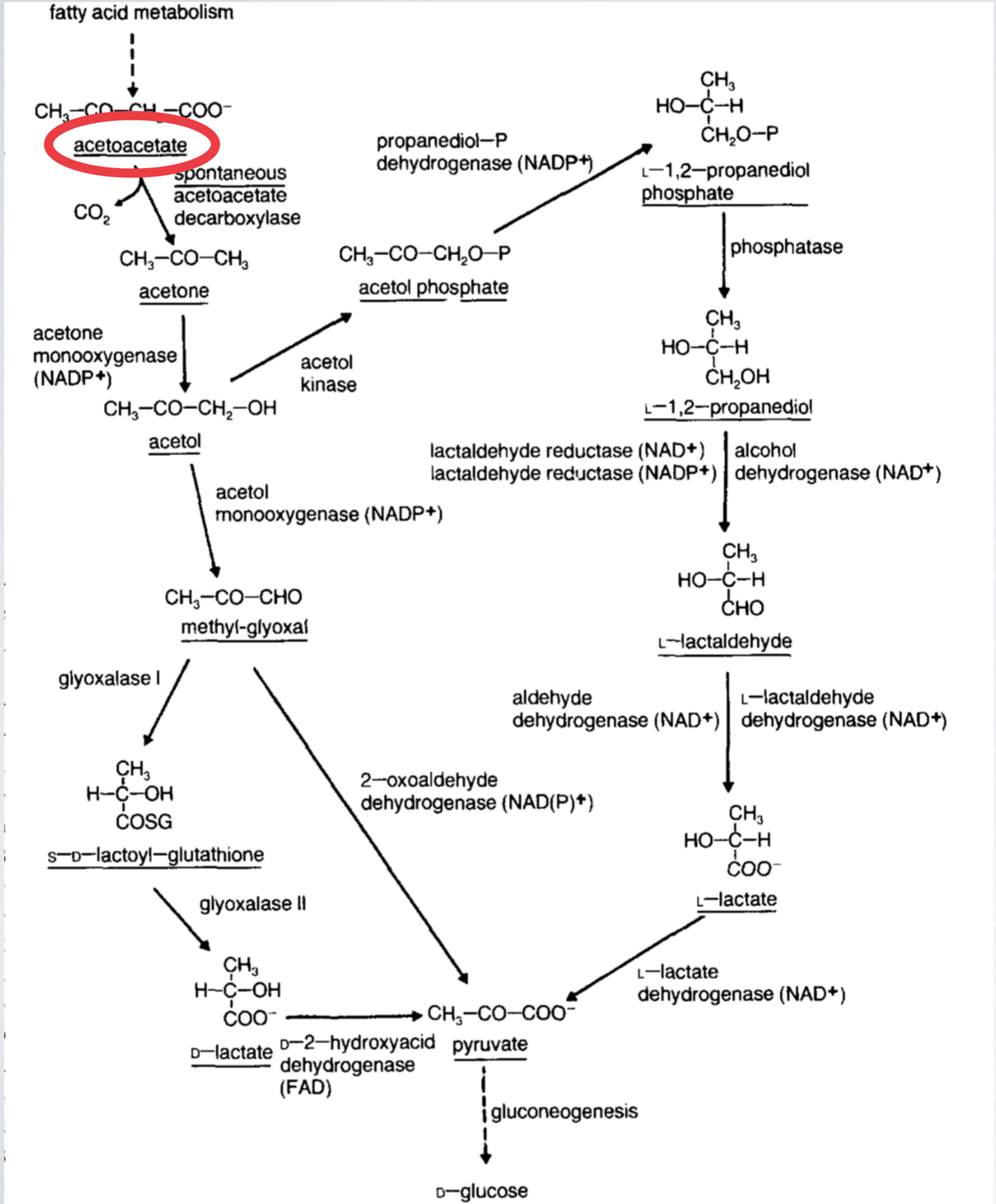
Methylglyoxal

Pyruvate

Oxaloacetate

Glucose

Argilés JM. (1986) Has acetone a role in the conversion of fat to carbohydrate in mammals? Trends in Biochemical Sciences. 11(2):61-63



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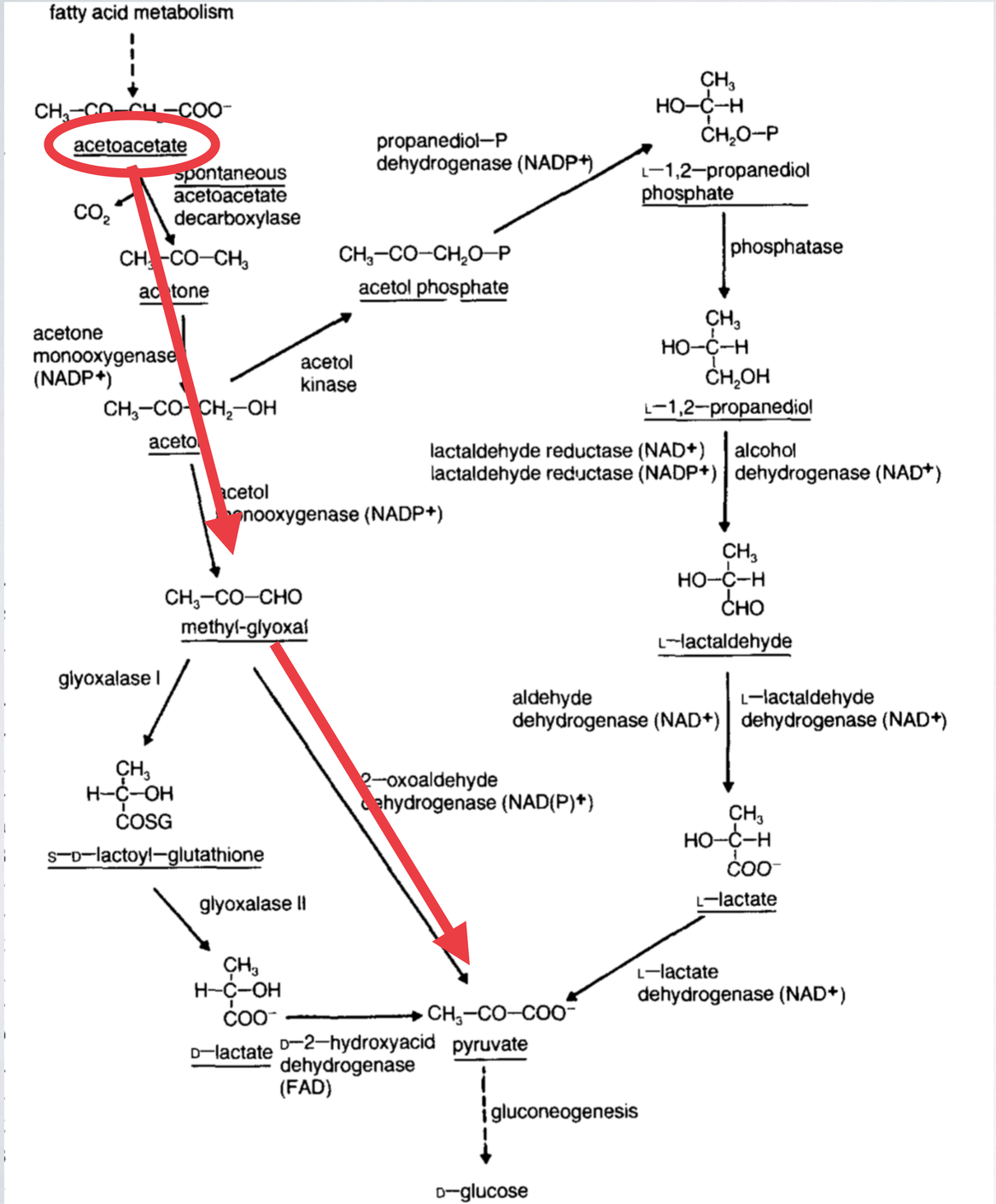

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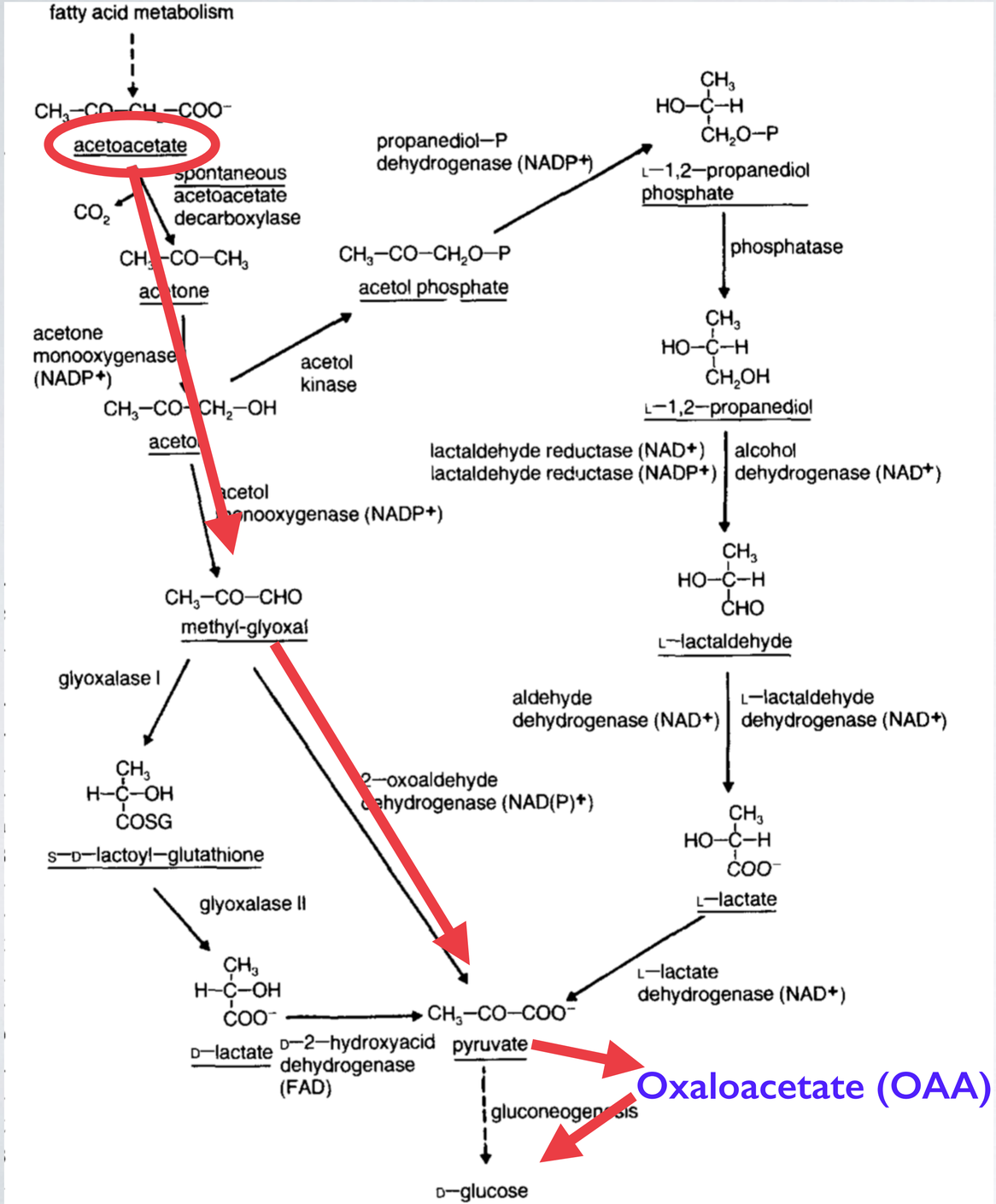

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PLoS COMPUTATIONAL BIOLOGY

In Silico Evidence for Gluconeogenesis from Fatty Acids in Humans

Christoph Kaleta[1]*, Luís F. de Figueiredo[1], Sarah Werner[1], Reinhard Guthke[2], Michael Ristow[3,4], Stefan Schuster[1]

1 Department of Bioinformatics, School of Biology and Pharmaceutics, Friedrich Schiller University of Jena, Jena, Germany, **2** Systems Biology/Bioinformatics Group, Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute, Jena, Germany, **3** Department of Human Nutrition, Institute of Nutrition, University of Jena, Jena, Germany, **4** Department of Clinical Nutrition, German Institute of Human Nutrition, Potsdam-Rehbrücke, Nuthetal, Germany

Abstract

The question whether fatty acids can be converted into glucose in humans has a long standing tradition in biochemistry, and the expected answer is "No". Using recent advances in Systems Biology in the form of large-scale metabolic reconstructions, we reassessed this question by performing a global investigation of a genome-scale human metabolic

Kaleta C et al (2011) In Silico Evidence for gluconeogenesis from fatty acids in humans. PLoS Comput Biol. 2011 Jul;7(7): e1002116

Plasma Acetone Metabolism in the Fasting Human

G. A. Reichard, Jr., A. C. Haff, C. L. Skutches, P. Paul, C. P. Holroyde, and O. E. Owen, *Department of Research, Lankenau Hospital, Philadelphia, Pennsylvania 19151, Department of Medicine and the General Clinical Research Center, Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140*

Abstract The metabolism of acetone was studied in lean and obese humans during starvation ketosis. Acetone concentrations in plasma, urine, and ... niques, we have measured rates of endogenous acetone production, breath, and urinary excretion and conversion ... other biological compounds during starvation-

Richard GA et al (1979) Plasma acetone metabolism in fasting humans. J Clin Invest 63:619-626

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ABSTRACT The metabolism of acetone was studied in lean and obese humans during starvation ketosis. Acet[illegible]e concentrations in plasma, [illegible]ine, and [illegible] niques, we have measured rates of endogenous acetone production, breath, and urinary excretion and conver[illegible] other biological compo[illegible]nds [illegible]uring starvation-

Radioactivity from the C14 acetone…was present in plasma glucose, lipids, and proteins. If glucose synthesis from acetone is possible in humans, this process could account for 11% of the glucose production rate…

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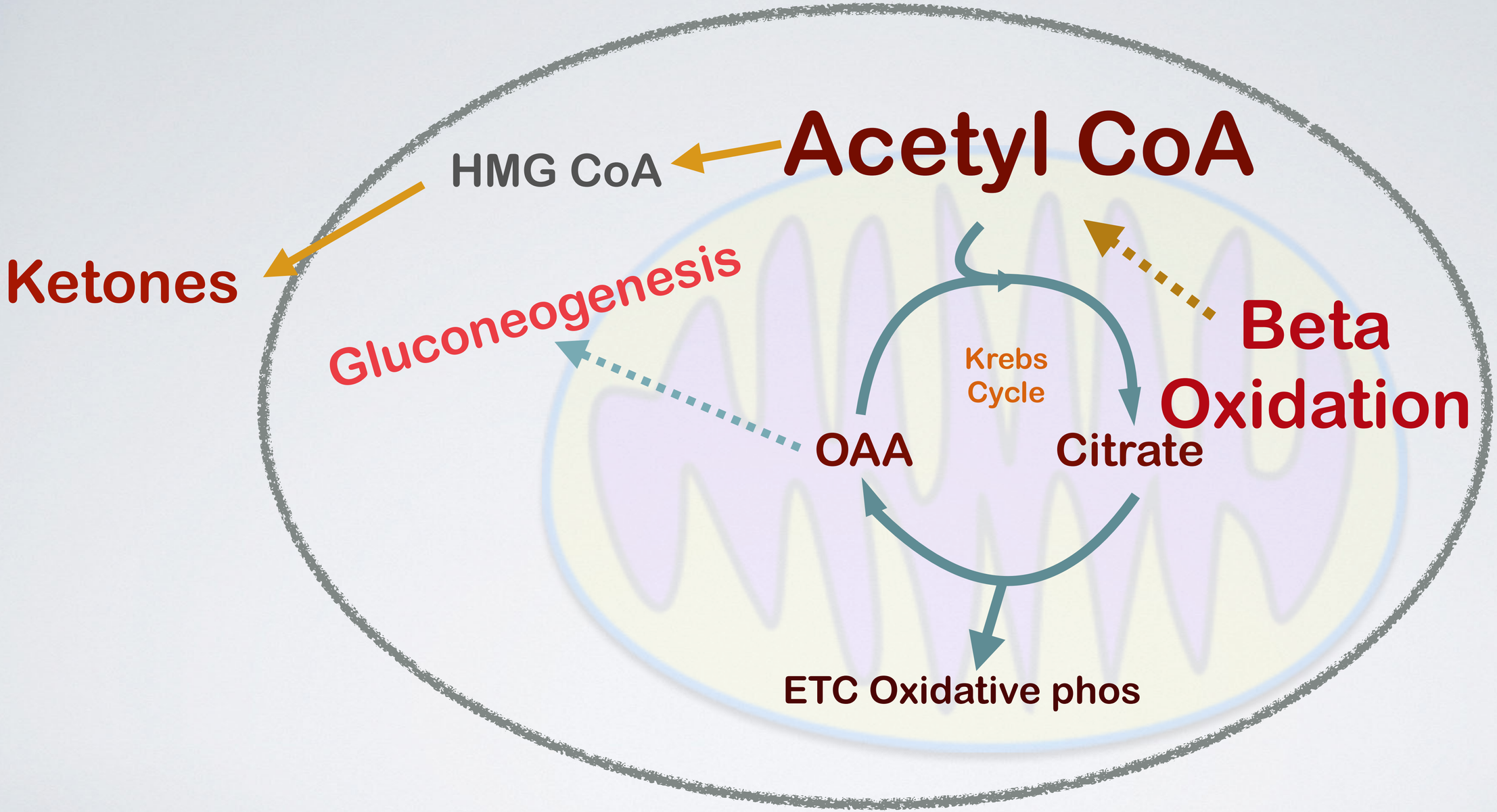
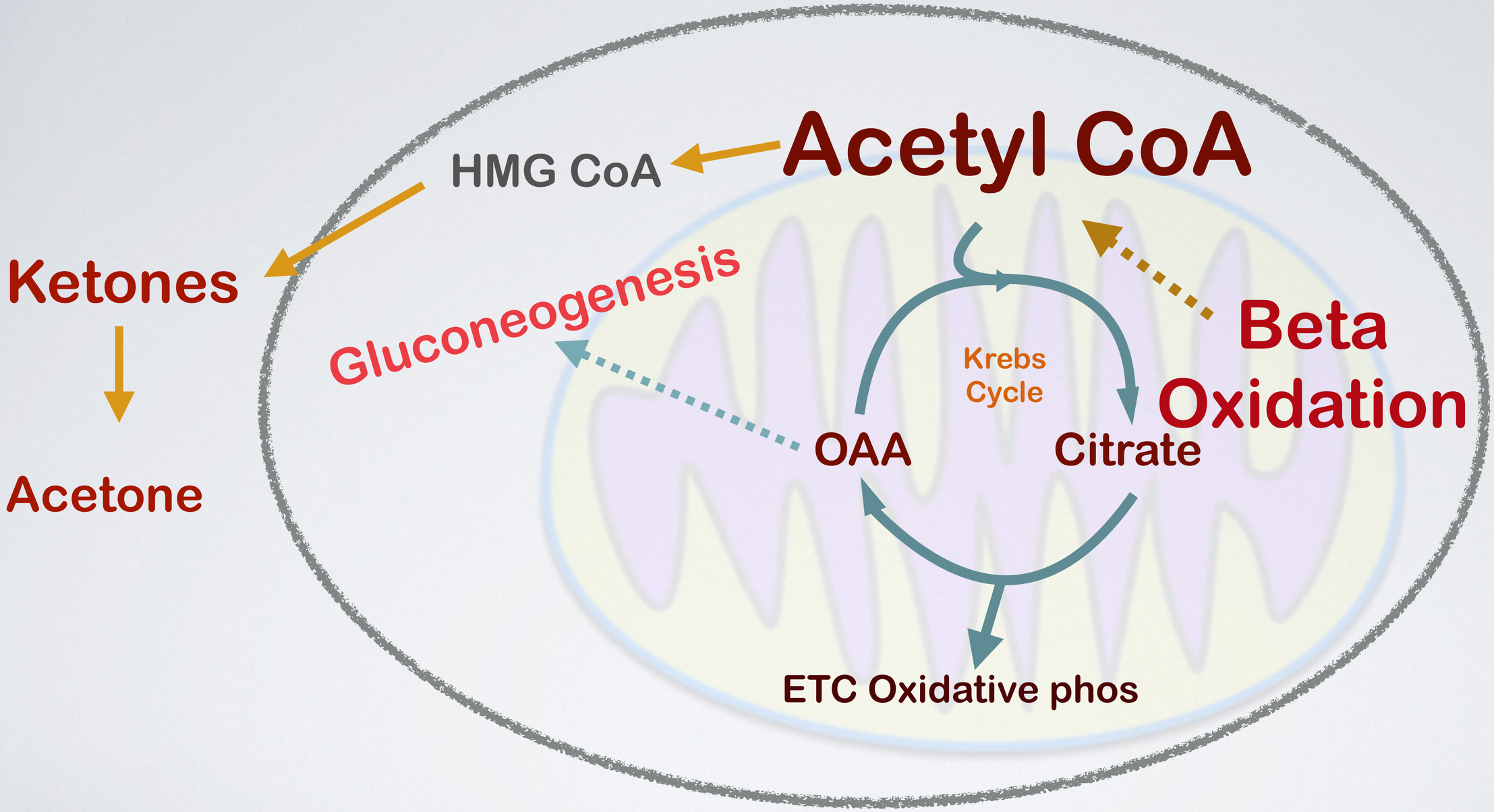

Acetyl CoA
HMG CoA
Ketones
Gluconeogenesis
Beta Oxidation
Krebs Cycle
OAA
Citrate
ETC Oxidative phos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HMG CoA
Ketones
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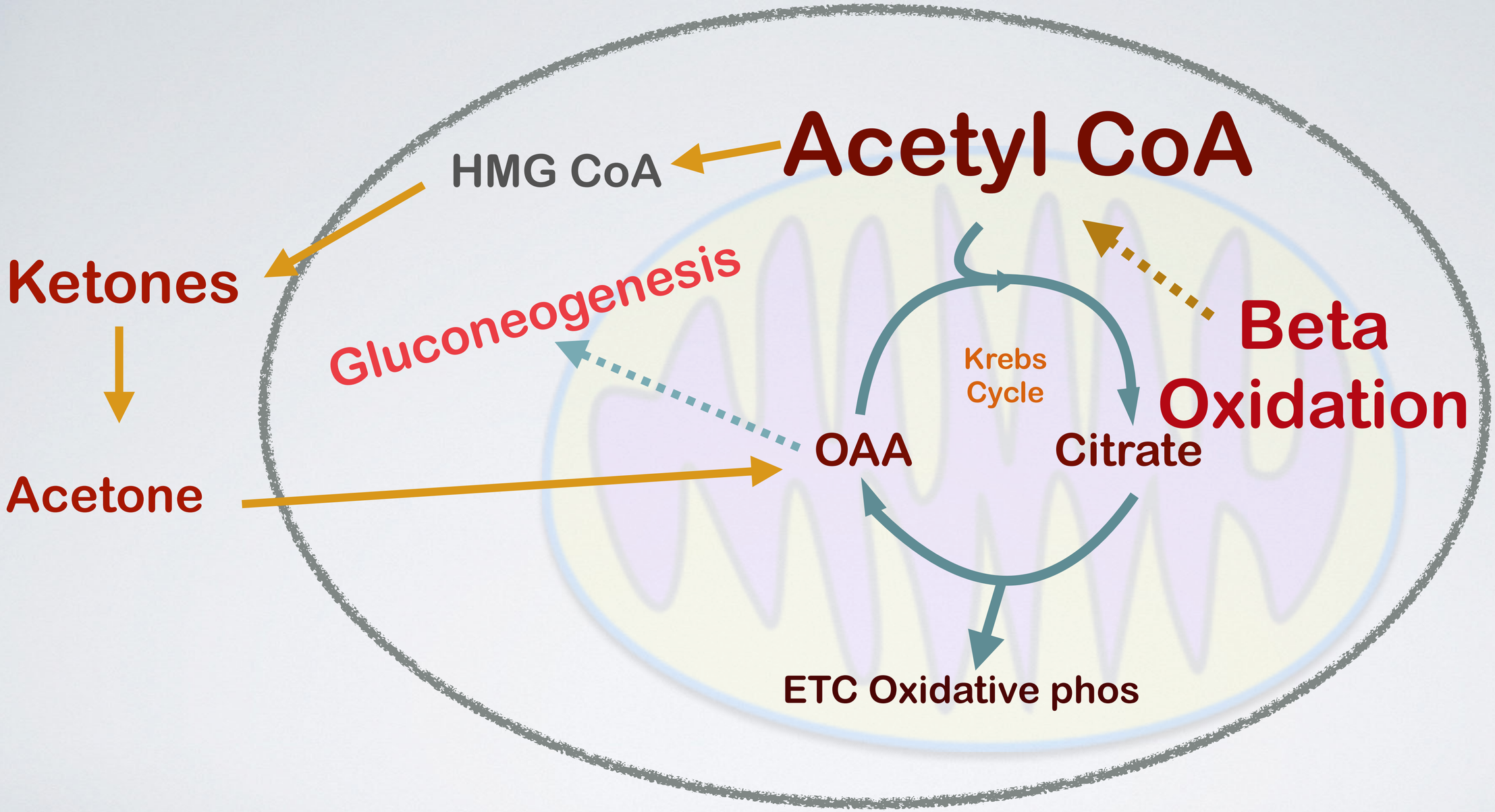
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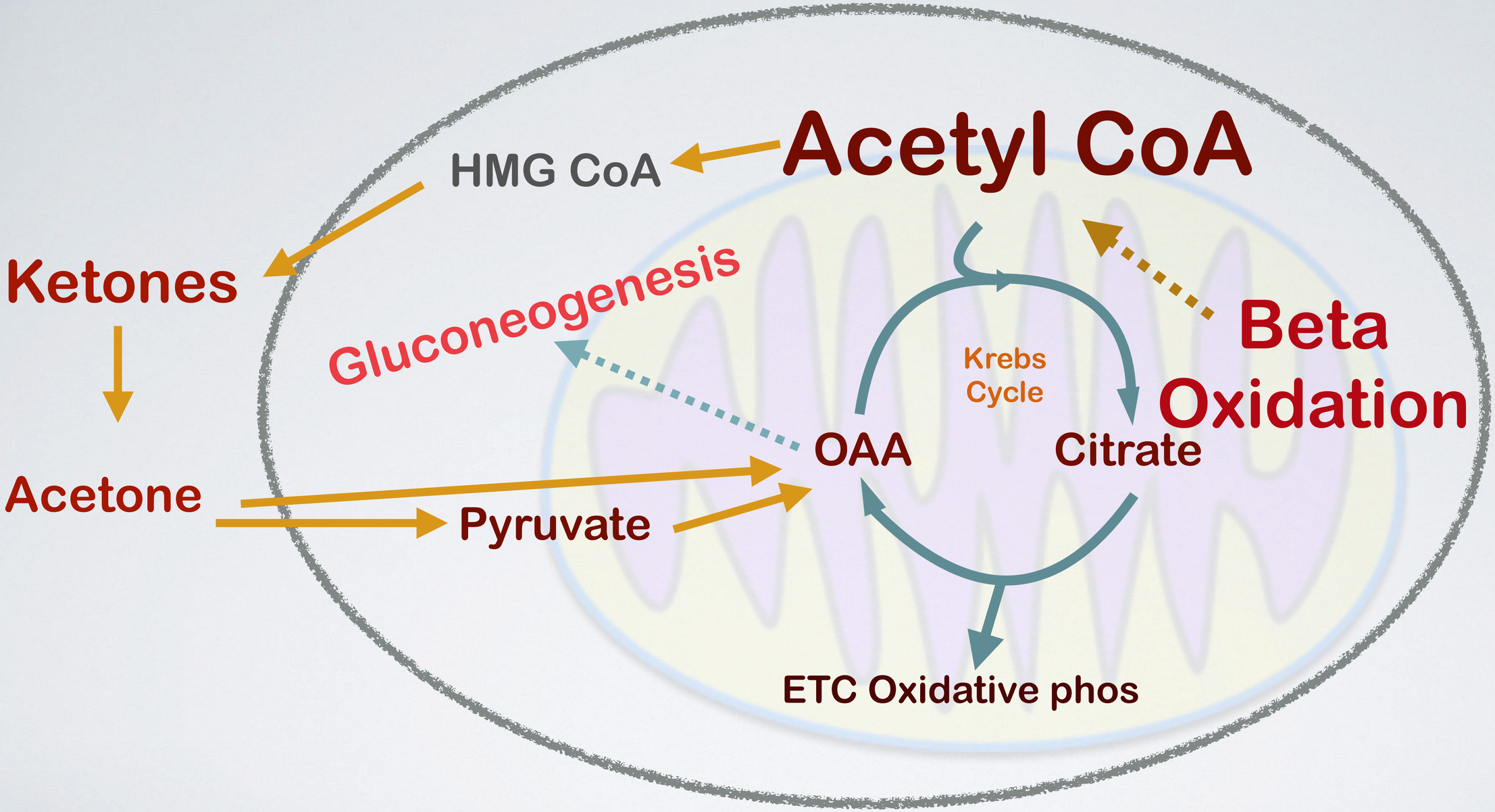
Acetyl CoA
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Acetone
Gluconeogenesis
Pyruvate
Krebs
Cycle
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Citrate
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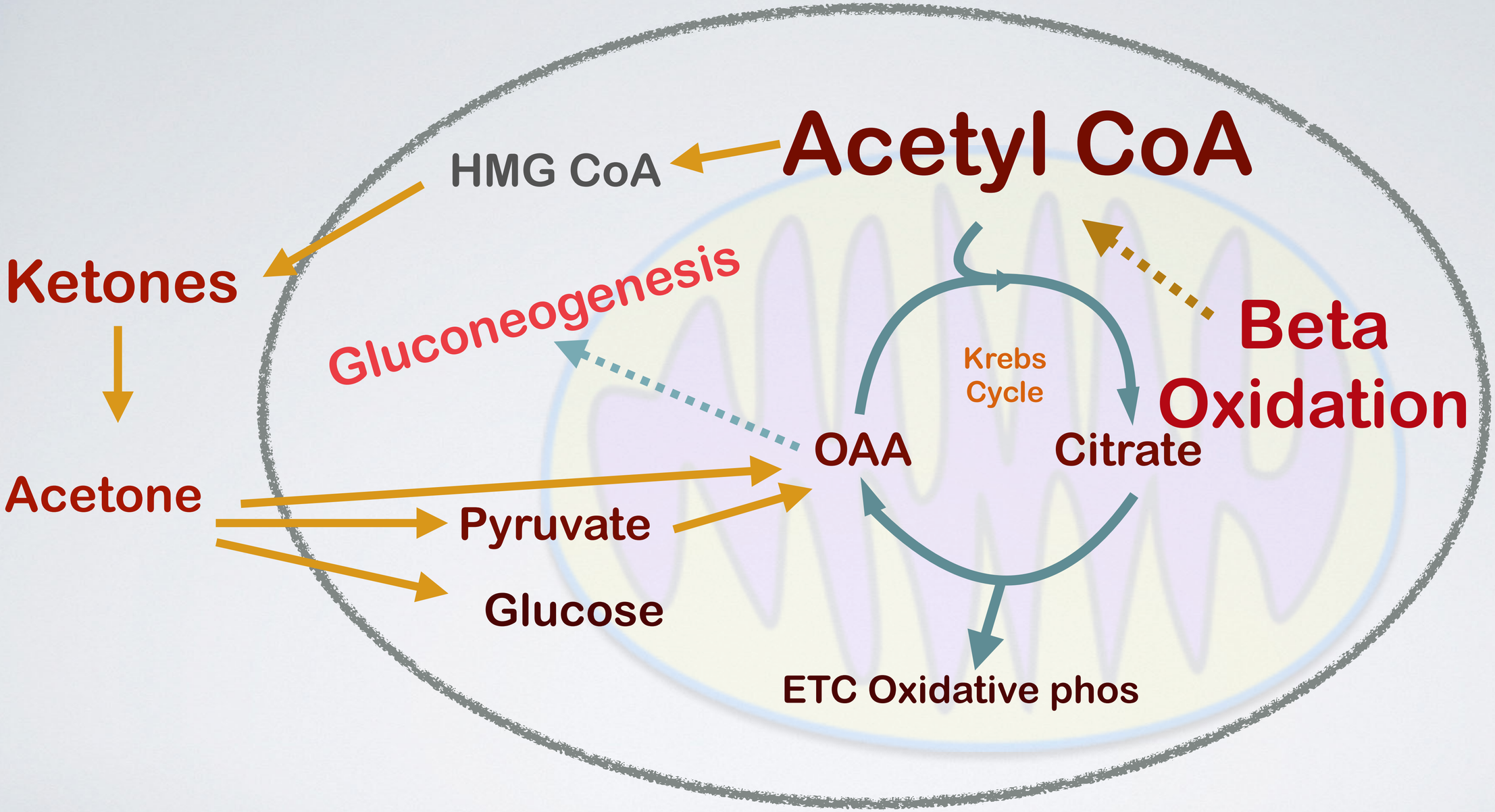
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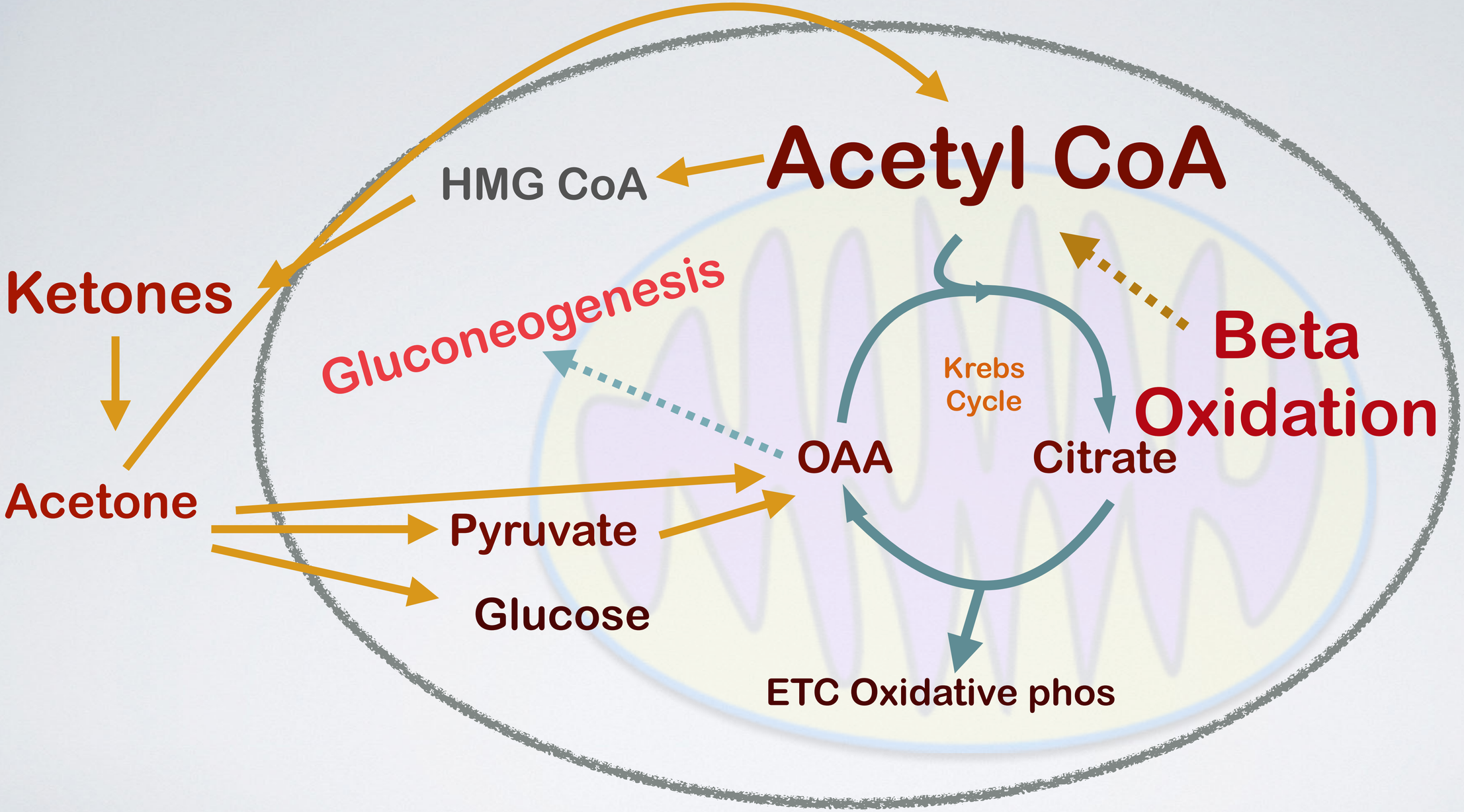
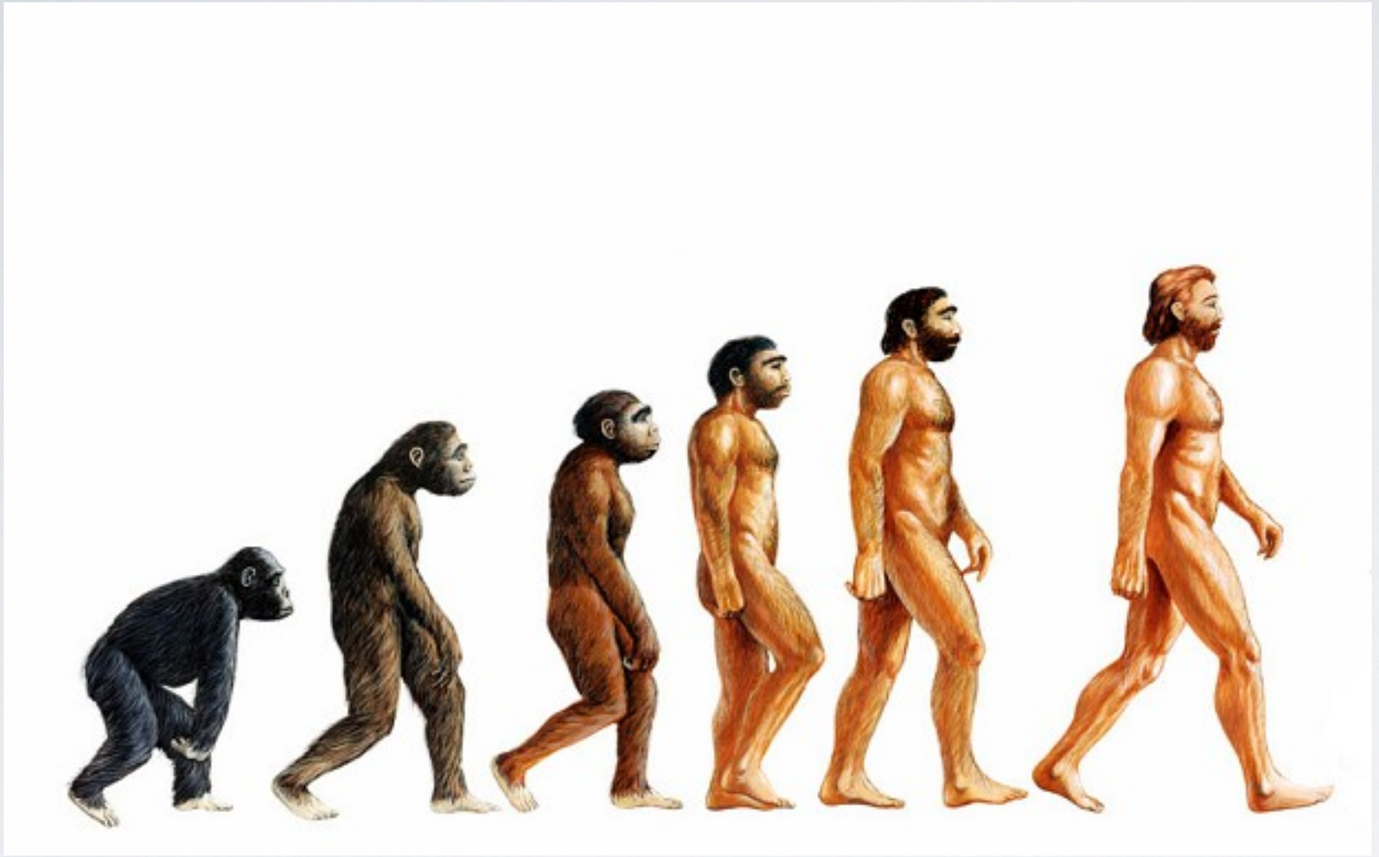
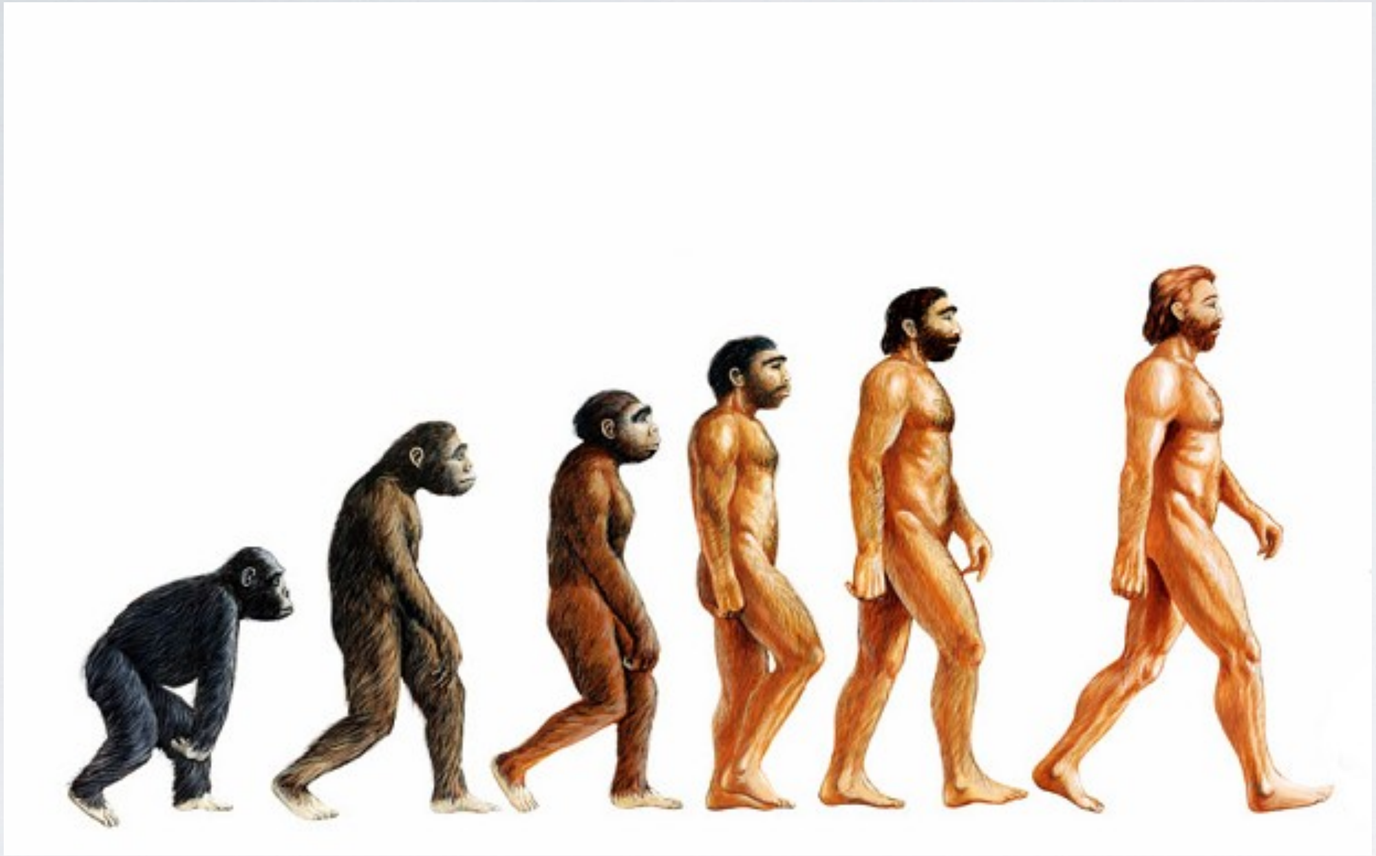
Krebs
Cycle
Beta
Oxidation
OAA
Citrate
Pyruvate
Glucose
ETC Oxidative phos


Acetyl CoA
HMG CoA
Ketones
Gluconeogenesis
Beta
Oxidation
Krebs
Cycle
OAA
Citrate
Acetone
Pyruvate
Glucose
ETC Oxidative phos





Thank God biochemistry textbook writers weren't in charge of evolution!

Nassim Nicholas Taleb

Nassim Nicholas Taleb

“The problem of knowledge is that there are many more books on birds written by ornithologists than books on birds written by birds.”

Thank you very much!

Michael R. Eades, M.D.

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