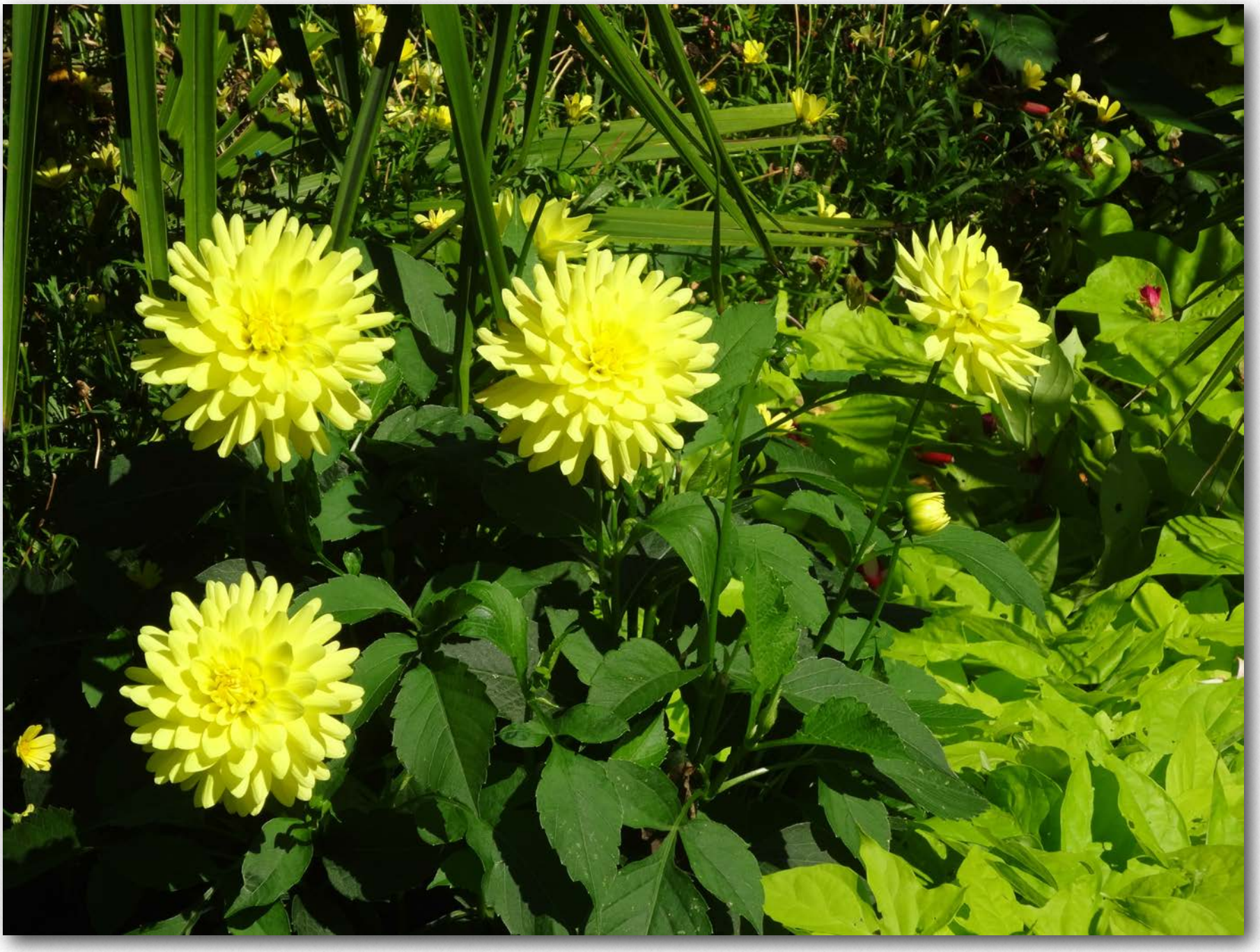
Metabolism: Citric Acid Cycle & Related Pathways



Citric acid cycle

The primary catabolic pathway in the body is the citric acid cycle because it is here that oxidation to carbon dioxide occurs for breakdown products of the cell's major building blocks - sugars, fatty acids, and amino acids. The pathway is cyclic (Figure 6.63) and thus, doesn't really have a starting or ending point. All of the reactions occur in mitochondria, though one enzyme is embedded in the organelle's inner membrane. As needs change, cells may use a subset of the reactions of the cycle to produce a desired molecule rather than to run the entire cycle (see HERE).

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Acetyl-CoA

The molecule "feeding" the citric acid cycle is acetyl-CoA and it can be obtained from pyruvate (from glycolysis), from fatty acid β-oxidation, from ketone bodies, and from amino acid metabolism. Molecules from other pathways feeding into the citric acid cycle for catabolism make the

citric acid cycle 'cataplerotic'. It is worth noting that acetyl-CoA has very different fates, depending on the cell's energy status/needs (see HERE). The description below describes oxidation (catabolism) in citric acid cycle.

Anabolically, acetyl-CoA is also very important for providing building blocks for synthesis of fatty acids, ketone bodies, amino acids and cholesterol. Other citric acid cycle intermediates are also important in amino acid metabolism (Figure 6.63), heme synthesis, electron shuttling, and shuttling of acetyl-CoA across the mitochondrial inner membrane. The ability of the citric acid cycle to supply intermediates to pathways gives rise to the term 'anaplerotic.' It means 'to fill up.' Before discussing the citric acid cycle, it is important to first describe one important enzyme complex that is a major source of acetyl-CoA for the cycle.

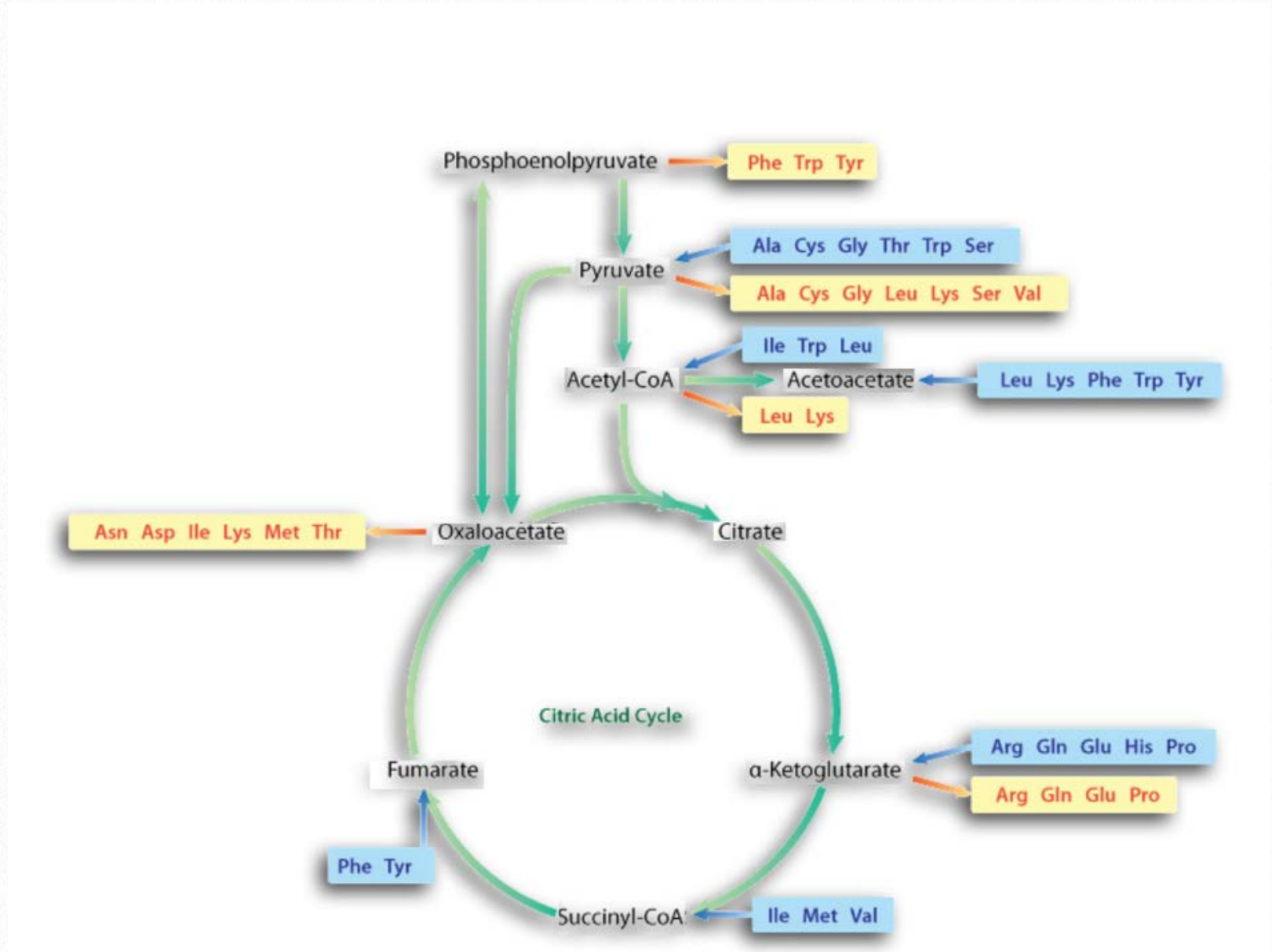

Figure 6.63 - Amino acid metabolism and the citric acid cycle. Amino acids boxed in yellow are made from the indicated intermediate. Amino acids in blue are made into the intermediate in catabolism.

Image by Aleia Kim

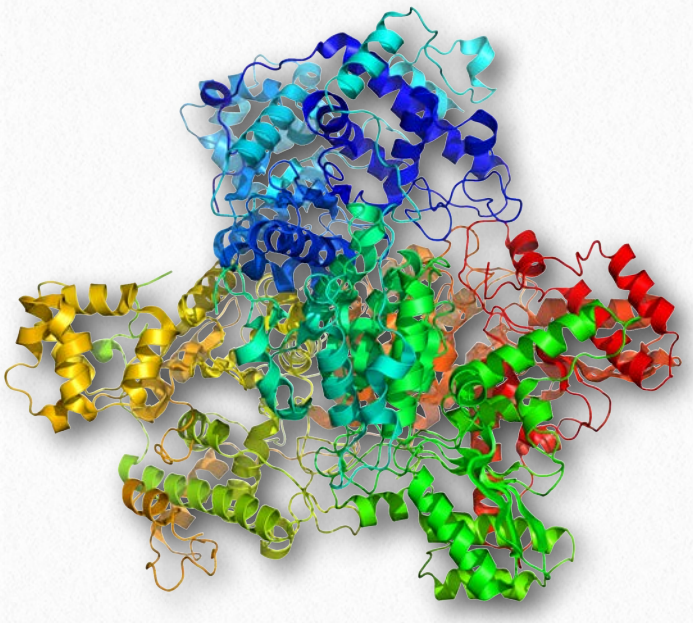

Figure 6.64 - E1 Subunit of Pyruvate Dehydrogenase

Wikipedia

Pyruvate decarboxylation

The pyruvate dehydrogenase enzyme is a complex of multiple copies of three subunits that catalyze the decarboxylation of pyruvate to form acetyl-CoA. The reaction mechanism requires use of five coenzymes. Pyruvate dehydrogenase is an enormous complex in mammals with a size five times greater than ribosomes.

Subunits

The three subunits are designated by E_1, E_2, and E_3. E_2 is also referred to as dihydrolipoamide acetyltransferase and E_3 is more precisely called dihydrolipoyl dehydroge-

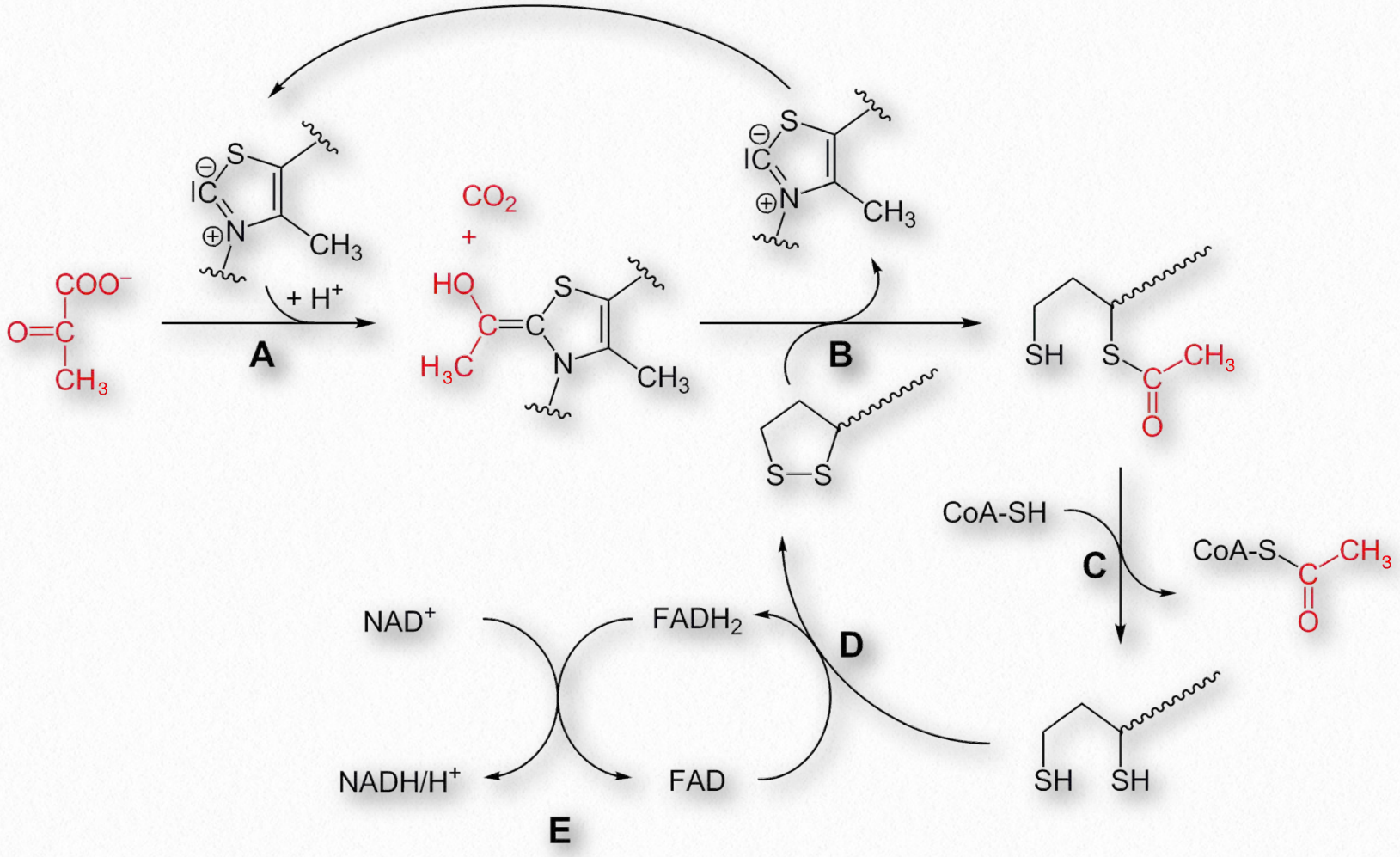

Figure 6.65 - Mechanism of action of pyruvate decarboxylation and oxidation by pyruvate dehydrogenase.

nase. Confusion arises with the name for E_1. Some call it pyruvate dehydrogenase and others give it the name pyruvate decarboxylase. We will use pyruvate decarboxylase solely to refer to E_1 and pyruvate dehydrogenase only to refer to the complex of E_1, E_2, and E_3.

The catalytic actions of pyruvate dehydrogenase can be broken down into three steps, each taking place on one of the subunits. The steps, sequentially occurring on E_1, E_2, and E_3, are 1) decarboxylation of pyruvate; 2) oxidation of the decarboxylated product; and 3) transfer of electrons to ultimately form NADH (Figure 6.65).

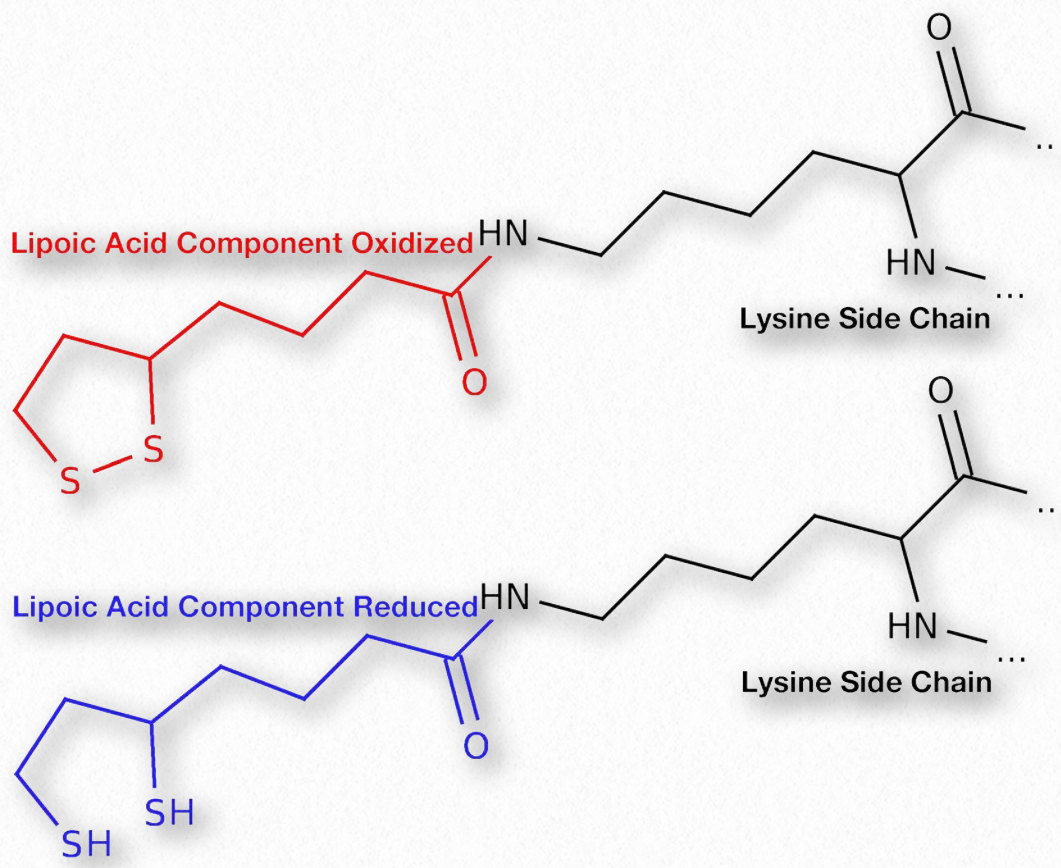

Figure 6.66 - Oxidized and reduced structures of lipoamide (lipoic acid linked to lysine)

Catalysis

The catalytic process begins after binding of the pyruvate substrate with activation of the thiamine pyrophosphate coenzyme through formation of an ylide intermediate. The nucleophilic carbanion of the ylide attacks the electrophilic ketone carbon on the pyruvate, releasing carbon dioxide and creating an enol that loses a proton on the carbon to become a 1,3 dipole that includes the positively charged nitrogen of the thiamine. The reaction (step A in Figure 6.65) is a non-oxidative decarboxylation. Oxidation of the two carbon hydroxyethyl unit occurs in the transfer to the lipoamide.

Reductive acetylation

Reductive acetylation occurs next (Step B) as the 2-carbon hydroxyethyl unit is transferred to lipoamide on E_2. (Lipoamide is the name for a molecule of lipoic acid covalently attached to a lysine side chain in the E_2 subunit). In prokaryotes in the absence of oxygen, the hydroxyethyl group is not passed to lipoamide, but instead is released as free acetaldehyde , which can accept electrons from NADH (catalyzed by alcohol dehydrogenase) and become ethanol in the process of fermentation. In the presence of oxygen in almost all aerobic organ-

isms, the process continues with transfer of the hydroxyethyl unit to E_2 and continuation of the cycle below.

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Oxidation step

Transfer of the hydroxyethyl group from E_1 to the lipoamide coenzyme in E_2 is an oxidation, with transfer of electrons from the hydroxyethyl group to lipoamide's disulfide (reducing it) and formation on the lipoamide of an acetyl-thioester (oxidizing it).

The acetyl group is then transferred from lipoamide to coenzyme A in E_2 (Step C in Figure 6.65), forming acetyl-CoA, which is released and leaving reduced sulfhydryls on the lipoamide. In order for the enzyme to return to its original state, the disulfide bond on lipoamide must be re-formed. This occurs with transfer of electrons from reduced lipoamide to an FAD covalently bound to E_3 (Step D). This reduces FAD to $FADH_2$.

Formation of NADH

In the last step in the process, electrons from $FADH_2$ are transferred to external NAD^+, forming NADH (Step E) and completing the overall cycle. Then enzyme can then begin another catalytic round by binding to a pyruvate.

Pyruvate dehydrogenase regulation

Pyruvate deyhdrogenase is regulated both allosterically and by covalent modification - phosphorylation / dephosphorylation.

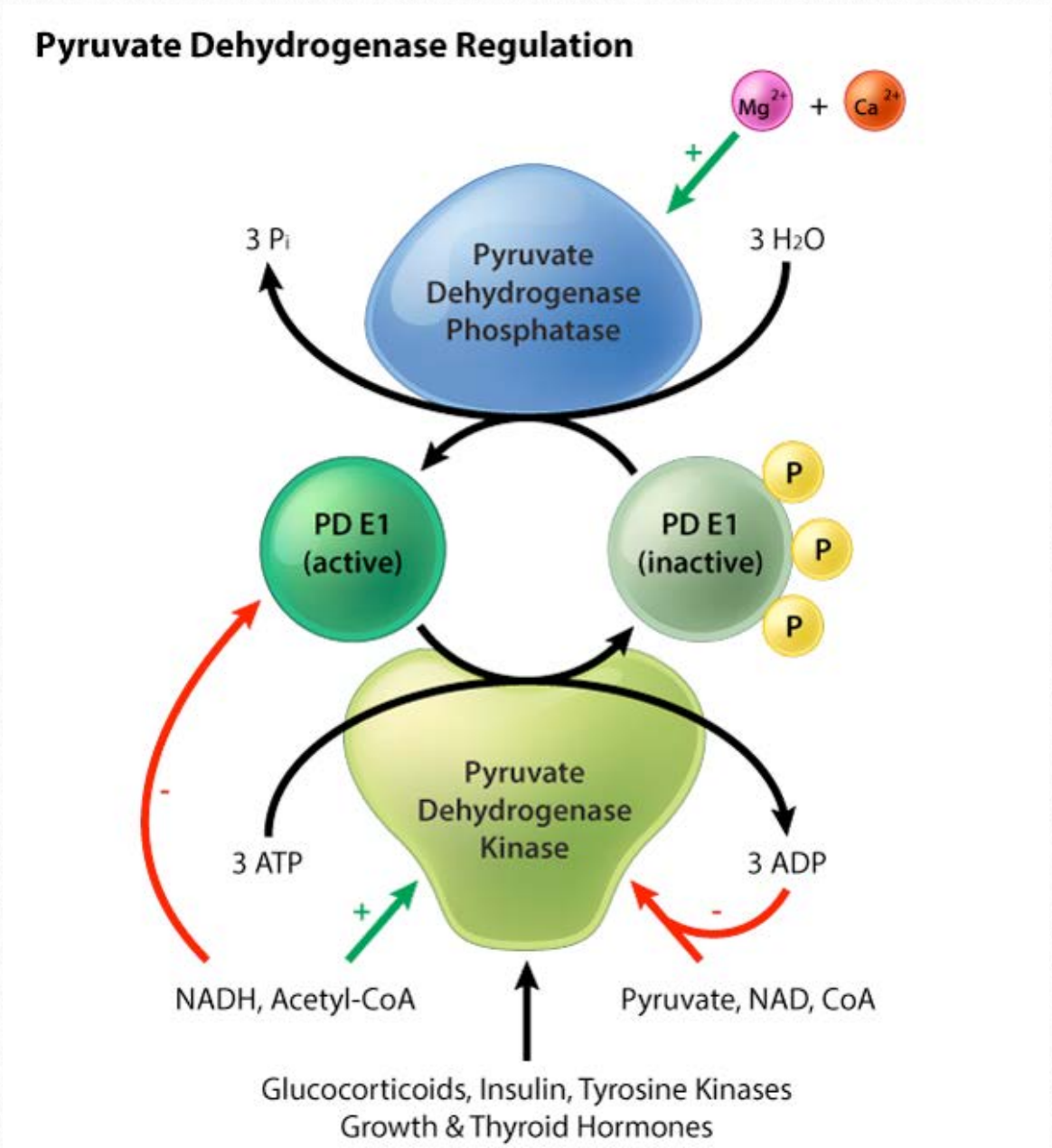

Figure 6.67 - Regulation scheme for pyruvate dehydrogenase (PD)

Image by Aleia Kim

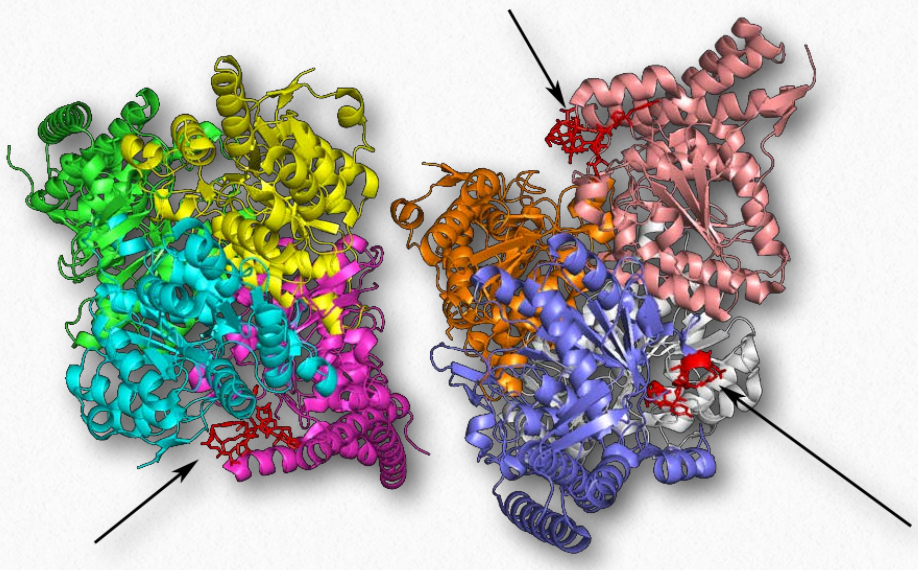

Figure 6.68 - Pyruvate dehydrogenase complex with three phosphorylation sites in red marked by arrows.

Wikipedia

tion. Regulation of pyruvate dehydrogenase, whether by allosteric or covalent mechanisms has the same strategy. Indicators of high energy shut down the enzyme, whereas indicators of low energy stimulate it. For allosteric regulation, the high energy indicators affecting the enzyme are ATP, acetyl-CoA, NADH, and fatty acids, which inhibit it. AMP, Coenzyme A, NAD^+, and calcium, on the other hand, stimulate it (Figure 6.67).

Covalent modification

Covalent modification regulation of pyruvate dehydrogenase is a bit more complicated. It occurs as a result of phosphorylation by pyruvate dehydrogenase kinase (PDK - Figure 6.67) or dephosphorylation by pyruvate dehydrogenase phosphatase (PDP).

PDK puts phosphate on any one of three serine residues on the E_1 subunit, which causes pyruvate kinase to not be able to perform its first step of catalysis - the decarboxylation of pyruvate. PDP can remove those phosphates. PDK is allosterically activated in the mitochondrial matrix when NADH and acetyl-CoA concentrations rise.

Product inhibition

Thus, the products of the pyruvate dehydrogenase reaction inhibit the production of more products by favoring its phosphorylation by PDK. Pyruvate, a substrate of pyruvate dehydrogenase, inhibits PDK, so increasing concentrations of substrate activate pyruvate dehydrogenase by reducing its phosphorylation by PDK. As concentrations of NADH and acetyl-CoA fall, PDP associates with pyruvate kinase and removes the phosphate on the serine on the E_1 subunit.

Low concentrations of NADH and acetyl-CoA are necessary for PDP to remain on the enzyme. When those concentrations rise, PDP dissociates and PDK gains access to the serine for phosphorylation. Insulin and calcium can also activate the PDP. This is very impor-

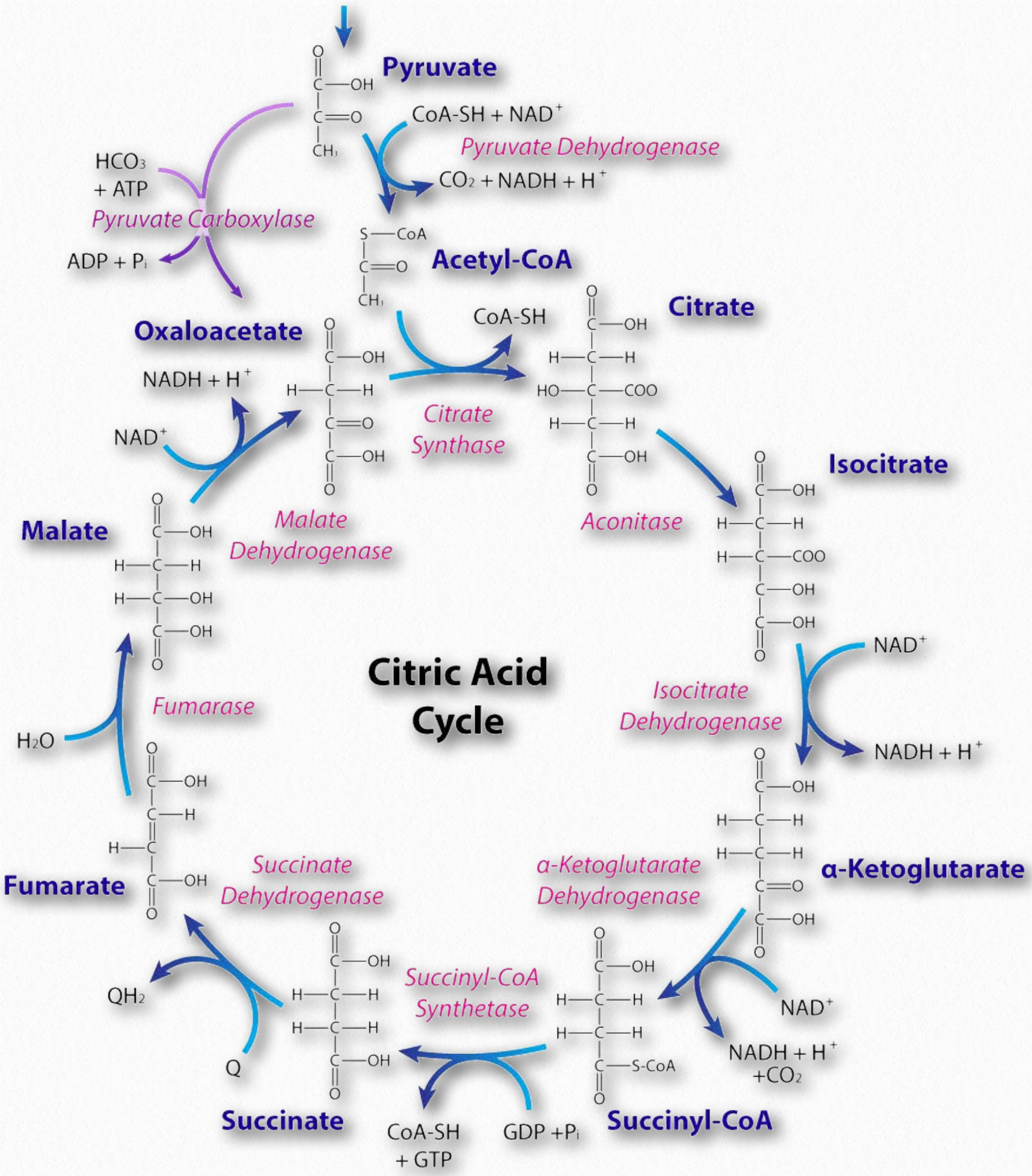

Figure 6.69 - The citric acid cycle

image by Aleia Kim

tant in muscle tissue, since calcium is a signal for muscular contraction, which requires energy.

Insulin also also activates pyruvate kinase and the glycolysis pathway to use internalized glucose. It should be noted that the cAMP phosphorylation cascade from the β-adrenergic receptor has no effect on pyruvate kinase, though the insulin cascade does, in fact, affect PDP and pyruvate kinase.

Citric acid cycle reactions

Focusing on the pathway itself (Figure 6.69), the usual point to start discussion is addition of acetyl-CoA to oxaloacetate (OAA) to form citrate.

Acetyl-CoA for the pathway can come from a variety of sources. The reaction joining it to OAA is catalyzed by citrate synthase and the $\Delta G^{\circ\prime}$ is fairly negative. This, in turn, helps to "pull" the malate dehydrogenase reaction preceding it in the cycle.

Acetyl-CoA + Oxaloacetate

⇅

Citrate + CoA-SH

In the next reaction, citrate is isomerized to isocitrate by action of the enzyme called aconitase.

Citrate

⇅

Isocitrate

Isocitrate is a branch point in plants and bacteria for the glyoxylate cycle (see HERE). Oxidative decarboxylation of isocitrate by

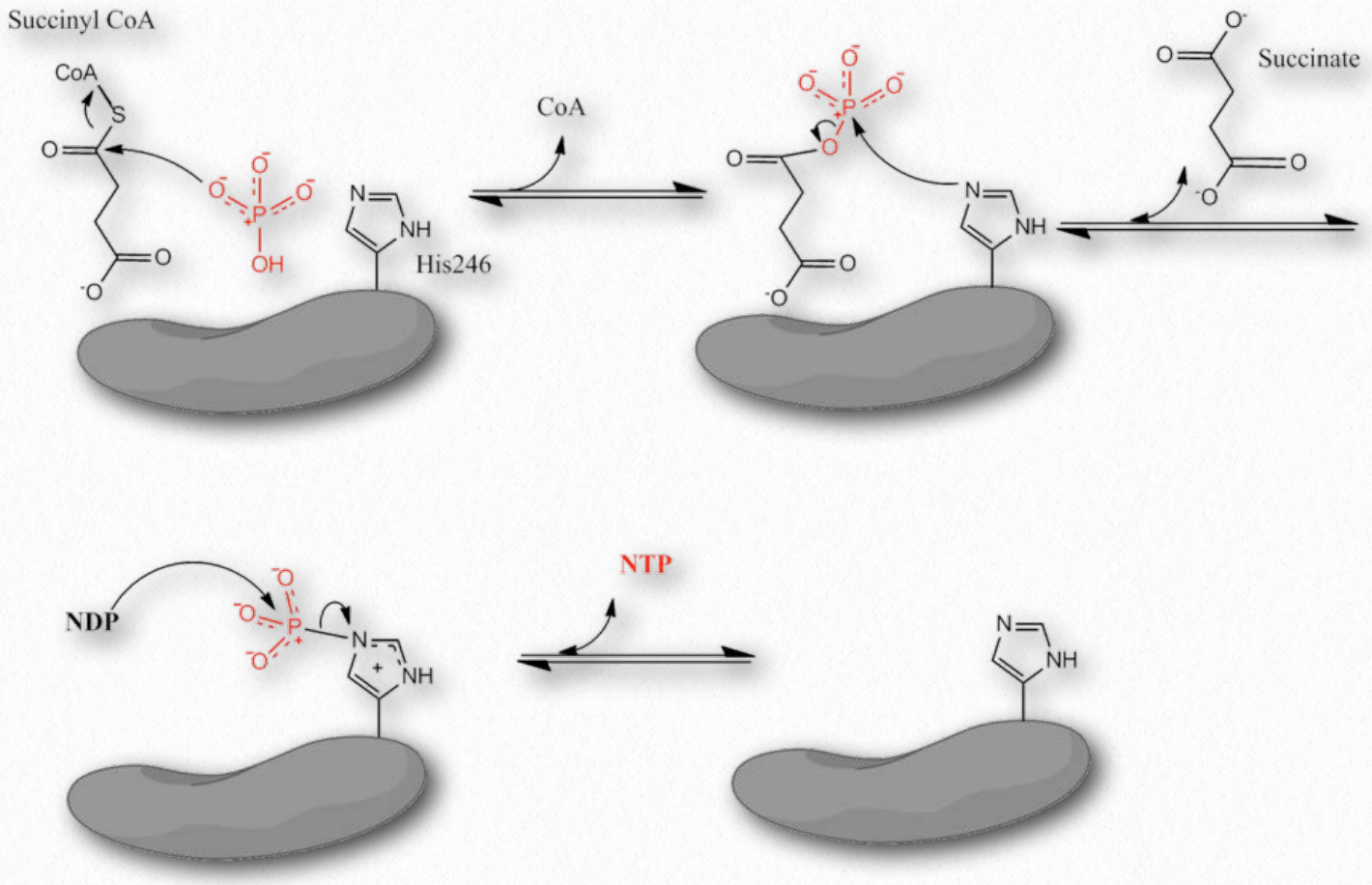

Figure 6.70 - Succinyl-CoA synthetase mechanism

isocitrate dehydrogenase produces the first NADH and yields α-ketoglutarate.

Isocitrate + NAD^+

⇅

α-ketoglutarate + NADH + CO_2

This five carbon intermediate is a branch point for synthesis of the amino acid glutamate. In addition, glutamate can also be made easily into this intermediate in the reverse reaction. Decarboxylation of α-ketoglutarate produces succinyl-CoA and is catalyzed by α-ketoglutarate dehydrogenase.

α-ketoglutarate + NAD^+ + CoA-SH

⇅

Succinyl-CoA + NADH + CO_2

The enzyme α-ketoglutarate dehydrogenase is structurally very similar to pyruvate dehydrogenase and employs the same five coenzymes – NAD^+, FAD, CoA-SH, thiamine pyrophosphate, and lipoamide.

Regeneration of oxaloacetate

The remainder of the citric acid cycle involves conversion of the four carbon succinyl-CoA into oxaloacetate. Succinyl-CoA is a branch point for the synthesis of heme (see HERE). Succinyl-CoA is converted to succinate in a reaction catalyzed by succinyl-CoA synthetase (named for the reverse reaction) and a GTP is produced, as well – the only substrate level phosphorylation in the cycle.

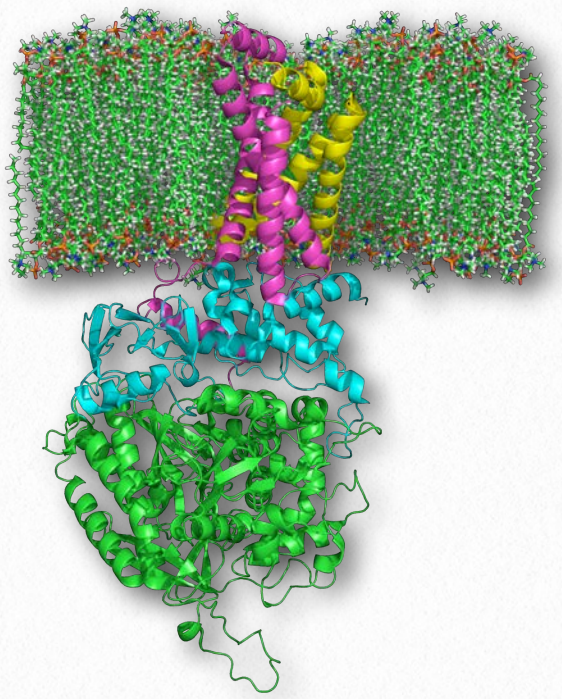

Figure 6.71 - Succinate dehydrogenase embedded in the mitochondrial inner membrane (top)
Wikipedia

Succinyl-CoA + GDP + P_i

⇅

Succinate + GTP + CoA-SH

The energy for the synthesis of the GTP comes from hydrolysis of the high energy thioester bond between succinate and the CoA-SH. Evidence for the high energy of a thioester bond is also evident in the citrate synthase reaction, which is also very energetically favorable. Succinate is also produced by metabolism of odd-chain fatty acids (see HERE).

Succinate Oxidation

Oxidation of succinate occurs in the next step, catalyzed by succinate dehydrogenase.

Succinate + FAD

⇅

Fumarate + $FADH_2$

This interesting enzyme both catalyzes this reaction and participates in the electron transport system, funneling electrons from the $FADH_2$ it gains in the reaction to coenzyme Q. The product of the reaction, fumarate, gains a water across its *trans* double bond in the next reaction, catalyzed by fumarase to form malate.

Fumarate + H_2O

⇅

L-Malate

Fumarate is also a byproduct of nucleotide metabolism and of the urea cycle. Malate is important also for transporting electrons across membranes in the malate-aspartate shuttle (see HERE) and in ferrying carbon dioxide from mesophyll cells to bundle sheath cells in C_4 plants (see HERE).

YouTube Lectures by Kevin HERE & HERE

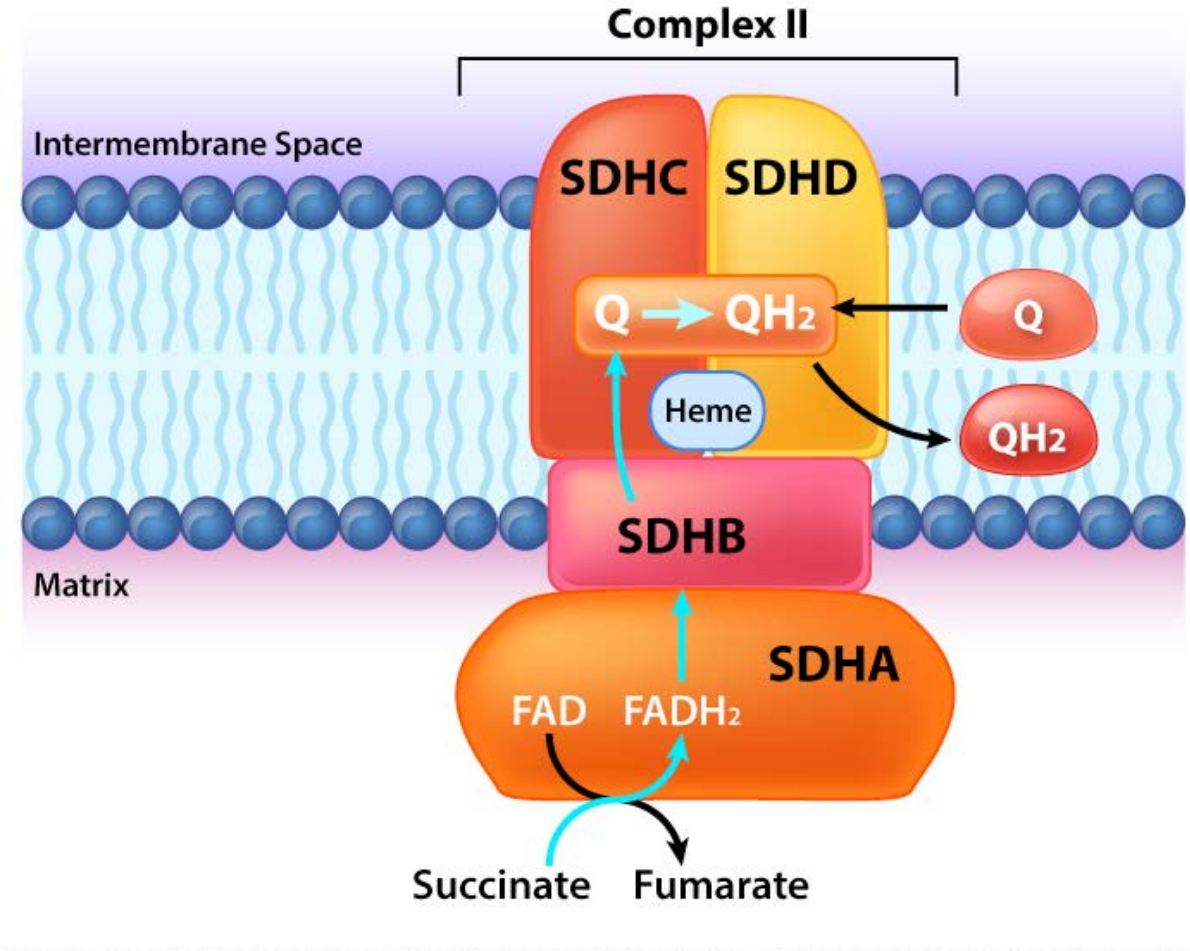

Figure 6.72 - Succinate dehydrogenase reaction

Image by Aleia Kim

Rare oxidation

Conversion of malate to oxaloacetate by malate dehydrogenase is a rare biological oxidation that has a $\Delta G°'$ with a positive value (29.7 kJ/mol).

L-Malate + NAD^+

⇅

Oxaloacetate + NADH

The reaction is 'pulled' by the energetically favorable conversion of oxaloacetate to citrate in the citrate

synthase reaction described above. Oxaloacetate intersects other important pathways, including amino acid metabolism (readily converted to aspartic acid), transamination (nitrogen movement) and gluconeogenesis.

It is worth noting that reversal of the citric acid cycle theoretically provides a mechanism for assimilating CO_2. In fact, this reversal has been noted in both anaerobic and microaerobic bacteria, where it is called the Arnon-Buchanan cycle (Figure 6.73).

Regulation of the citric acid cycle

Allosteric regulation of the citric acid cycle is pretty straightforward. The molecules involved are all substrates/products of the pathway or molecules involved in energy transfer. Substrates/products that regulate or affect the pathway include acetyl-CoA and succinyl-CoA .

Inhibitors and activators

High energy molecular indicators, such as ATP and NADH will tend to inhibit the cycle and low energy indicators (NAD^+, AMP, and ADP) will tend to activate the cycle. Pyruvate dehydrogenase, which catalyzes formation of acetyl-CoA for entry into the cycle is allosterically inhibited by its product (acetyl-CoA), as well as by NADH and ATP.

Regulated enzymes

Regulated enzymes in the cycle include citrate synthase (inhibited by NADH, ATP, and succinyl-CoA), isocitrate dehydrogenase (inhibited by ATP, activated by ADP and

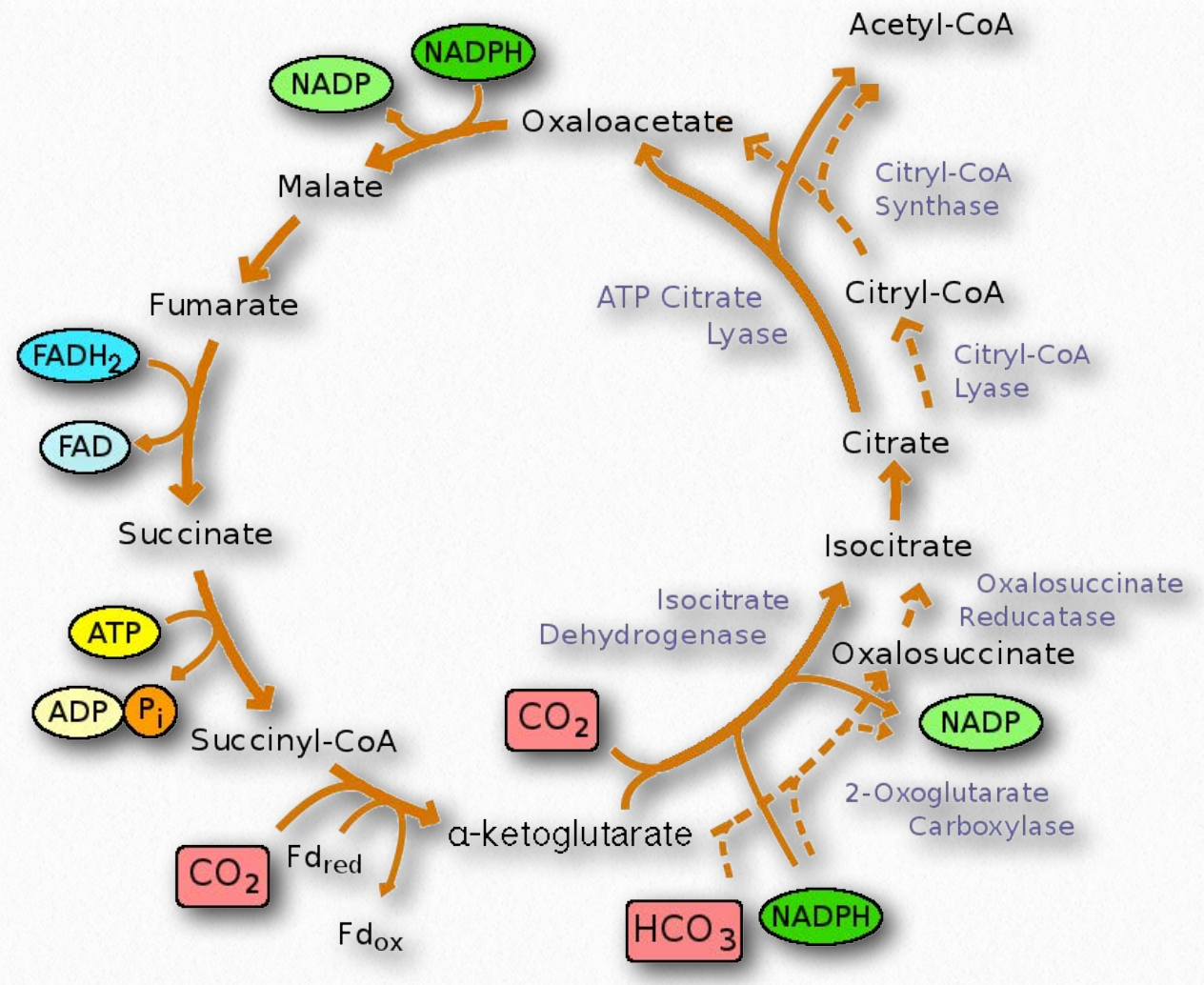

Figure 6.73 - Arnon-Buchanon cycle. Alternative enzymes shown on right in lavender. Fd = ferredoxin

Wikipedia

NAD^+), and α-ketoglutarate dehydrogenase (inhibited by NADH and succinyl-CoA and activated by AMP).

Anaplerotic/ cataplerotic pathway

The citric acid cycle is an important catabolic pathway oxidizing acetyl-CoA into CO_2 and generating ATP, but it is also an important source of molecules needed by cells and a mechanism for extracting energy from amino acids in protein breakdown and other breakdown products. This ability of the citric acid cycle to supply molecules as needed and to absorb metabolic by-products gives great flexibility to cells. When citric acid cycle intermediates are taken from the pathway to make other molecules, the term used to describe this is cataplerotic, whereas when molecules are added to the pathway, the process is described as anaplerotic.

I love my citrate synthase
It really is first rate
Adds O-A-A to Ac-Co-A
Producing one citrate

Aconitase is picky
Binds substrates specially
Creating isocitrate
Which has no symmetry

Then CO_2 gets lost from it
Released in the next phase
The secret weapon - Isocitrate
Dehydrogenase

The alpha K–D-H is next
It gets my admiration
For clipping CO_2 in one more
Decarboxylation

Succ-CoA synthetase steps up
Reacting most absurd
It's named for a catalysis
That simply runs backward

Suc -CIN-ate de-hyd-ROG-en-ase
Pulls H from succinate
Creating $FADH_2$
As well as fumarate

The fumarate gains water
O-H configured L
The fumarase's product?
Some malate for the cell

With one last oxidation
Malate de-hyd-ROG-en-ase
Expels its two creations
N-A-D-H / O-A-A

Kevin Ahern

Cataplerotic molecules

The citric acid cycle's primary cataplerotic molecules include **α**-ketoglutarate, succinyl-CoA, and oxaloacetate. Transamination of α-ketoglutarate and oxaloacetate produces the amino acids glutamate and aspartic acid, respectively. Oxaloacetate is important for the production of glucose in gluconeogenesis.

Glutamate plays a very important role in the movement of nitrogen through cells via glutamine and other molecules and is also needed for purine synthesis. Aspartate is a precursor of other amino acids and for production of pyrimidine nucleotides. Succinyl-CoA is necessary for the synthesis of porphyrins, such as the heme groups in hemoglobin, myoglobin and cytochromes.

Citrate is an important source of acetyl-CoA for making fatty acids. When the citrate concentration is high (as when the citric acid cycle is moving slowly or is stopped), it gets shuttled across the mitochondrial

membrane into the cytoplasm and broken down by the enzyme citrate lyase to oxaloacetate and acetyl-CoA. The latter is a precursor for fatty acid synthesis in the cytoplasm.

Anaplerotic molecules

Anaplerotic molecules replenishing citric acid cycle intermediates include acetyl-CoA (made in many pathways, including fatty acid oxidation, pyruvate decarboxylation, amino acid catabolism, and breakdown of ketone bodies), α-ketoglutarate (from amino acid metabolism), succinyl-CoA (from propionic acid metabolism), fumarate (from the urea cycle and purine metabolism), malate (carboxylation of PEP in plants), and oxaloacetate (many sources, including amino acid catabolism and pyruvate carboxylase action on pyruvate in gluconeogenesis)

Glyoxylate cycle

A pathway related to the citric acid cycle found only in plants and bacteria is the glyoxylate cycle (Figures 6.74 & 6.75). The glyoxylate cycle, which bypasses the decarboxylation reactions while using most of the non-decarboxylation reactions of the citric acid cycle, does not operate in animals, because they lack two enzymes necessary for it – isocitrate

I'm thinking I could lose some weight
If I could make glyoxylate
Combined with acetyl-CoA
Malate would then form OAA
The excess OAA in turn
Would give more glucose to be burned
Converting fat to glucose, see
Expends it glycolytically

lyase and malate synthase. The cycle occurs in specialized plant peroxisomes called glyoxysomes. Isocitrate lyase catalyzes the conversion of isocitrate into succinate and

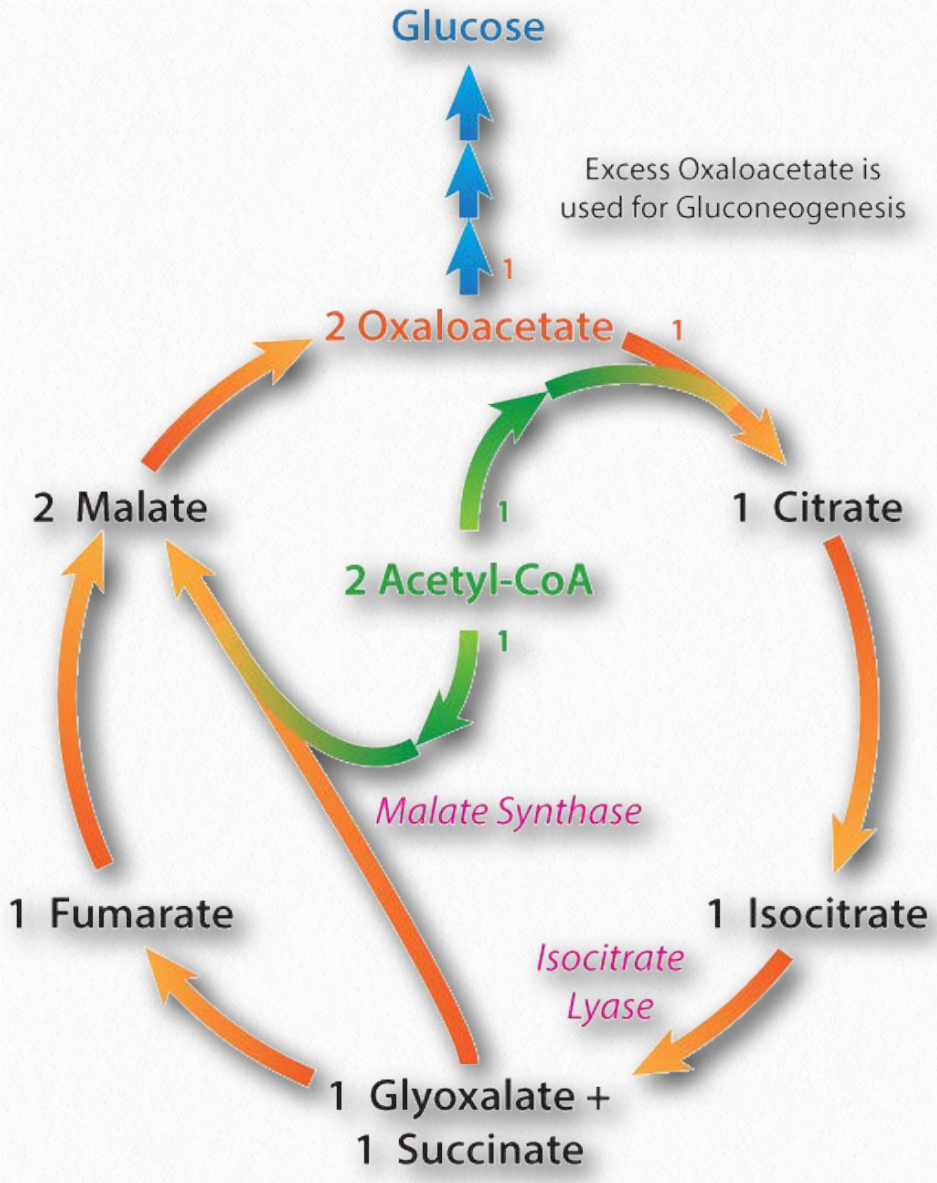

Figure 6.74 - Overview of the glyoxylate cycle
Image by Aleia Kim

glyoxylate. Because of this, all six carbons of the citric acid cycle survive each turn of the cycle and do not end up as carbon dioxide.

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Succinate continues through the remaining reactions to produce oxaloacetate. Glyoxylate combines with another acetyl-CoA

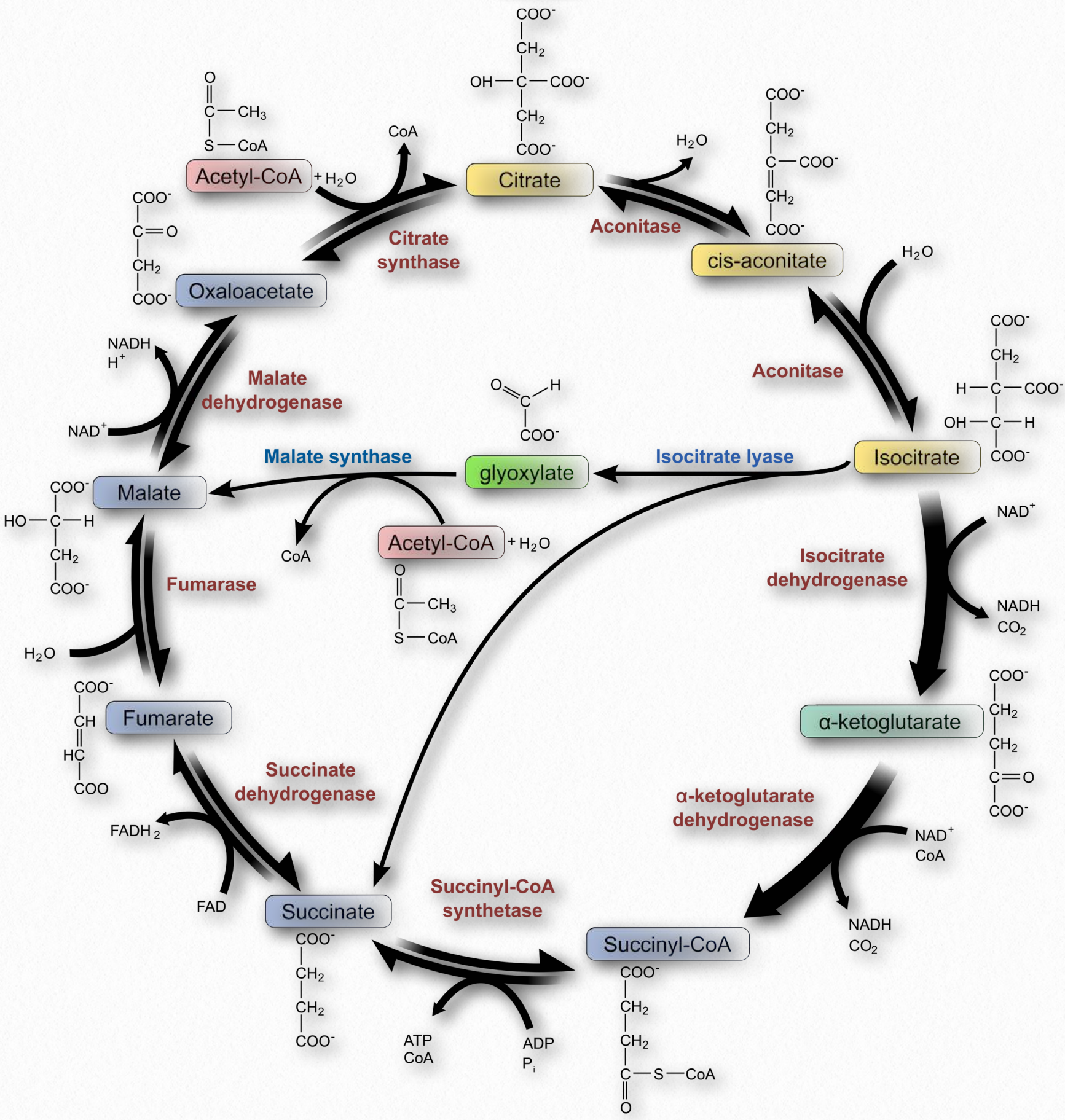

Figure 6.75 - Reactions of the glyoxylate cycle

Wikipedia

Figure 6.76 - A gingko seed embryo
Wikipedia

(one acetyl-CoA was used to start the cycle) to create malate (catalyzed by malate synthase). Malate can, in turn, be oxidized to oxaloacetate.

It is at this point that the glyoxylate pathway's contrast with the citric acid cycle is apparent. After one turn of the citric acid cycle, a single oxaloacetate is produced and it balances the single one used in the first reaction of the cycle. Thus, in the citric acid cycle, there is no net production of oxaloacetate in each turn of the cycle.

Net oxaloacetate production

On the other hand, thanks to assimilation of carbons from two acetyl-CoA molecules, each turn of the glyoxylate cycle results in two oxaloacetates being produced, after starting with one. The extra oxaloacetate of the glyoxylate cycle can be used to make other molecules, including glucose in gluconeogenesis. This is particularly important for plant seed germination (Figure 6.76), since the seedling is not exposed to sunlight. With the glyoxylate cycle, seeds can make glucose from stored lipids.

Because animals do not run the glyoxylate cycle, they cannot produce glucose from acetyl-CoA in net amounts, but plants and bacteria can. As a result, plants and bacteria can turn acetyl-CoA from fat into glucose, while animals can't. Bypassing the oxidative decarboxylations (and substrate level phosphorylation) has energy costs, but, there are also benefits. Each turn of the glyoxylate cycle produces one $FADH_2$ and one NADH instead of the three NADHs, one $FADH_2$, and one GTP made in each turn of the citric acid cycle.

Carbohydrate needs

Organisms that make cell walls, such as plants, fungi, and bacteria, need large quantities of carbohydrates as they grow to support the biosynthesis of the complex structural polysaccharides of the walls. These include cellulose, glucans, and chitin. Notably, each of the organisms can operate the glyoxylate cycle using acetyl-CoA from β-oxidation.

Coordination of the glyoxylate cycle and the citric acid cycle

The citric acid cycle is a major catabolic pathway producing a considerable amount of

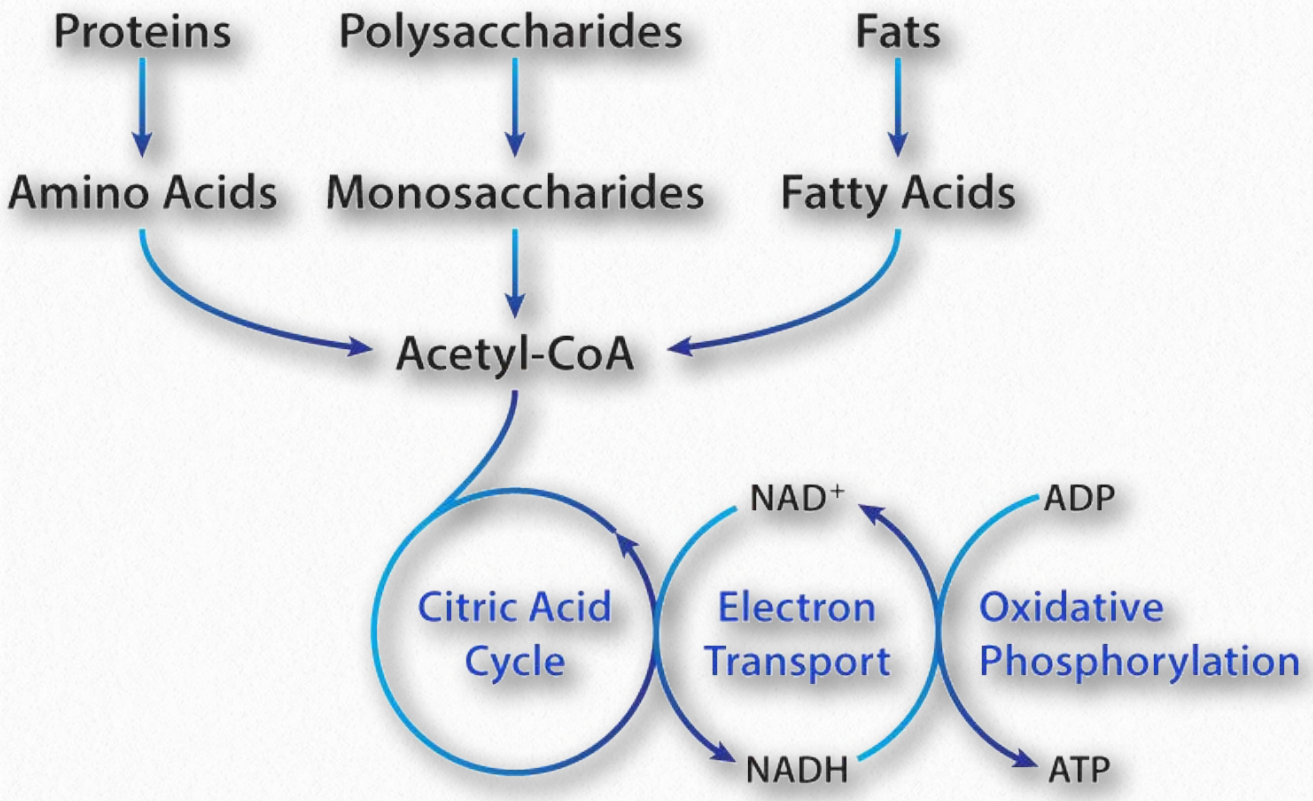

Figure 6.77 - Acetyl-CoA metabolism

Image by Aleia Kim

energy for cells, whereas the glyoxylate cycle's main function is anabolic - to allow production of glucose from fatty acids in plants and bacteria. The two pathways are physically separated from each other (glyoxylate cycle in glyoxysomes / citric acid cycle in mitochondria), but nonetheless a coordinated regulation of them is important.

The enzyme that appears to provide controls for the cycle is isocitrate dehydrogenase. In plants and bacteria, the enzyme can be inactivated by phosphorylation by a kinase found only in those cells. Inactivation causes isocitrate to accumulate in the mitochondrion and when this happens, it gets shunted to the glyoxysomes, favoring the glyoxylate cycle.

Removal of the phosphate from isocitrate dehydrogenase is catalyzed by an isocitrate dehydrognease-specific phosphoprotein phosphatase and restores activity to the enzyme.

When this happens, isocitrate oxidation resumes in the mitochondrion along with the rest of the citric acid cycle reactions.

In bacteria, where the enzymes for both cycles are present together in the cytoplasm, accumulation of citric acid cycle intermediates and glycolysis intermediates will tend to favor the citric acid cycle by activating the phosphatase, whereas high energy conditions will tend to favor the glyoxylate cycle by inhibiting it.

Acetyl-CoA metabolism

Acetyl-CoA is one of the most "connected" metabolites in biochemistry, appearing in fatty acid oxidation/synthesis, pyruvate oxidation, the citric acid cycle, amino acid anabolism/catabolism, ketone body metabolism, steroid/bile acid synthesis, and (by extension from fatty acid metabolism) prostaglandin synthesis . Most of these pathways

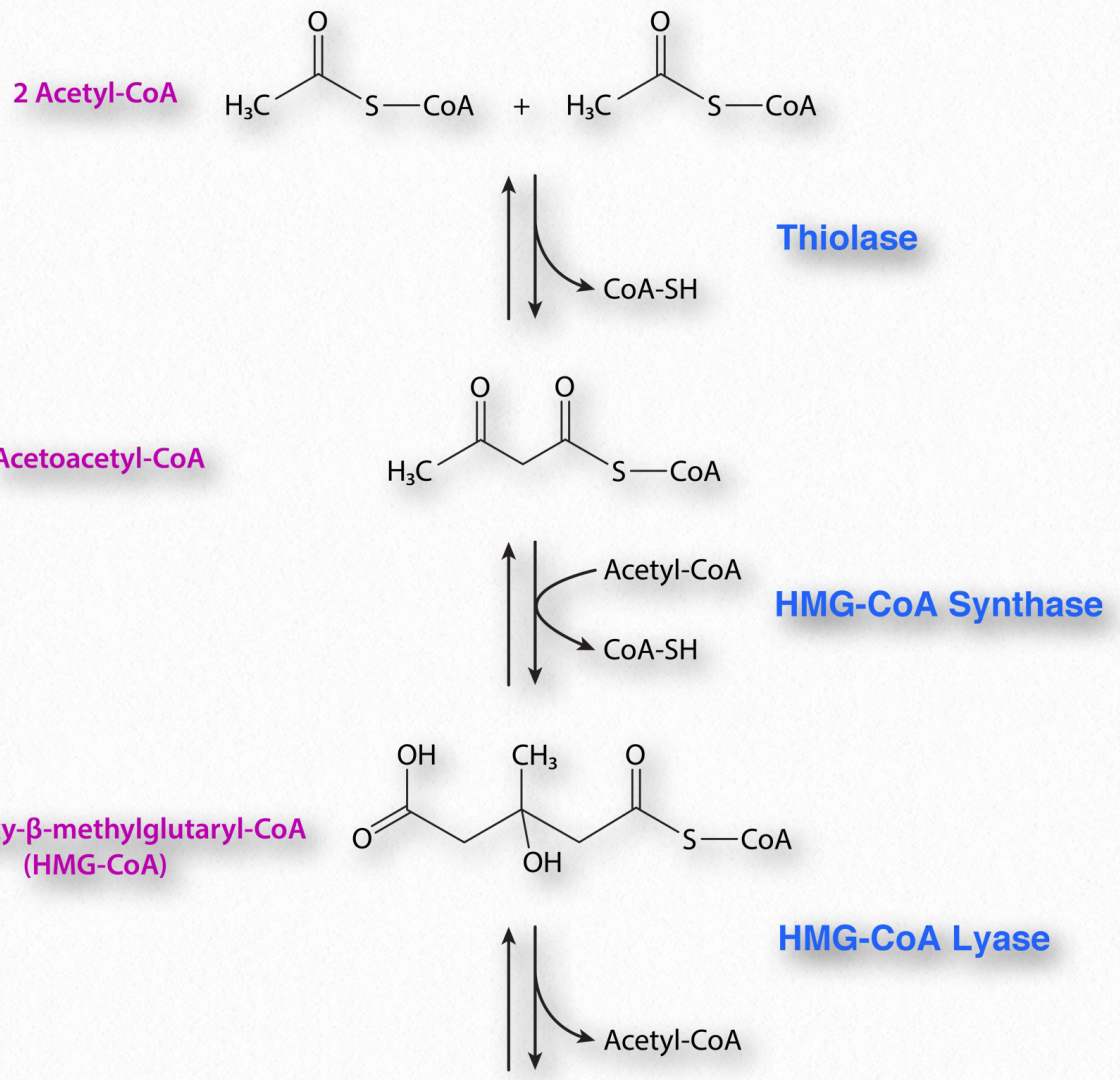

Figure 6.78 Ketone body metabolism

Image by Pehr Jacobson

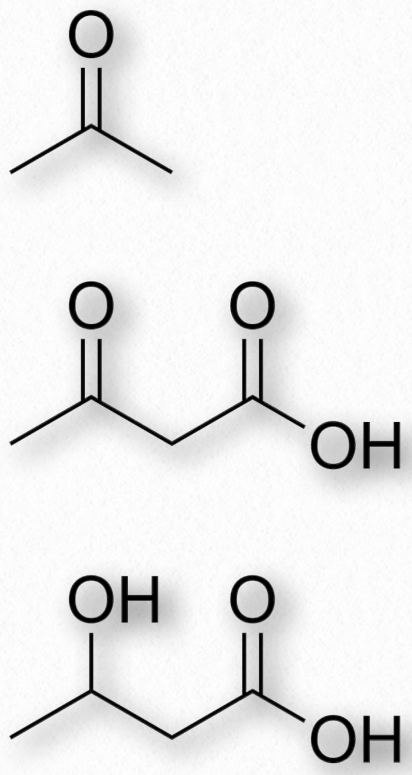

Figure 6.79 - Three ketone bodies - acetone (top), acetoacetic acid (middle), and β-hydroxybutyrate (bottom)

will be dealt with separately. Here we will cover ketone body metabolism.

Ketone body metabolism

Ketone bodies are molecules made when the blood levels of glucose fall very low. Ketone bodies can be converted to acetyl-CoA by reversing the reaction of the pathway that makes them (Figure 6.78). Acetyl CoA, of course, can be used for ATP synthesis via the citric acid cycle. People who are very hypoglycemic (including some diabetics) will produce ketone bodies (Figure 6.79) and these are often first detected by the smell of acetone on their breath.

Overlapping pathways

The pathways for ketone body synthesis and cholesterol biosynthesis (Figure 6.80

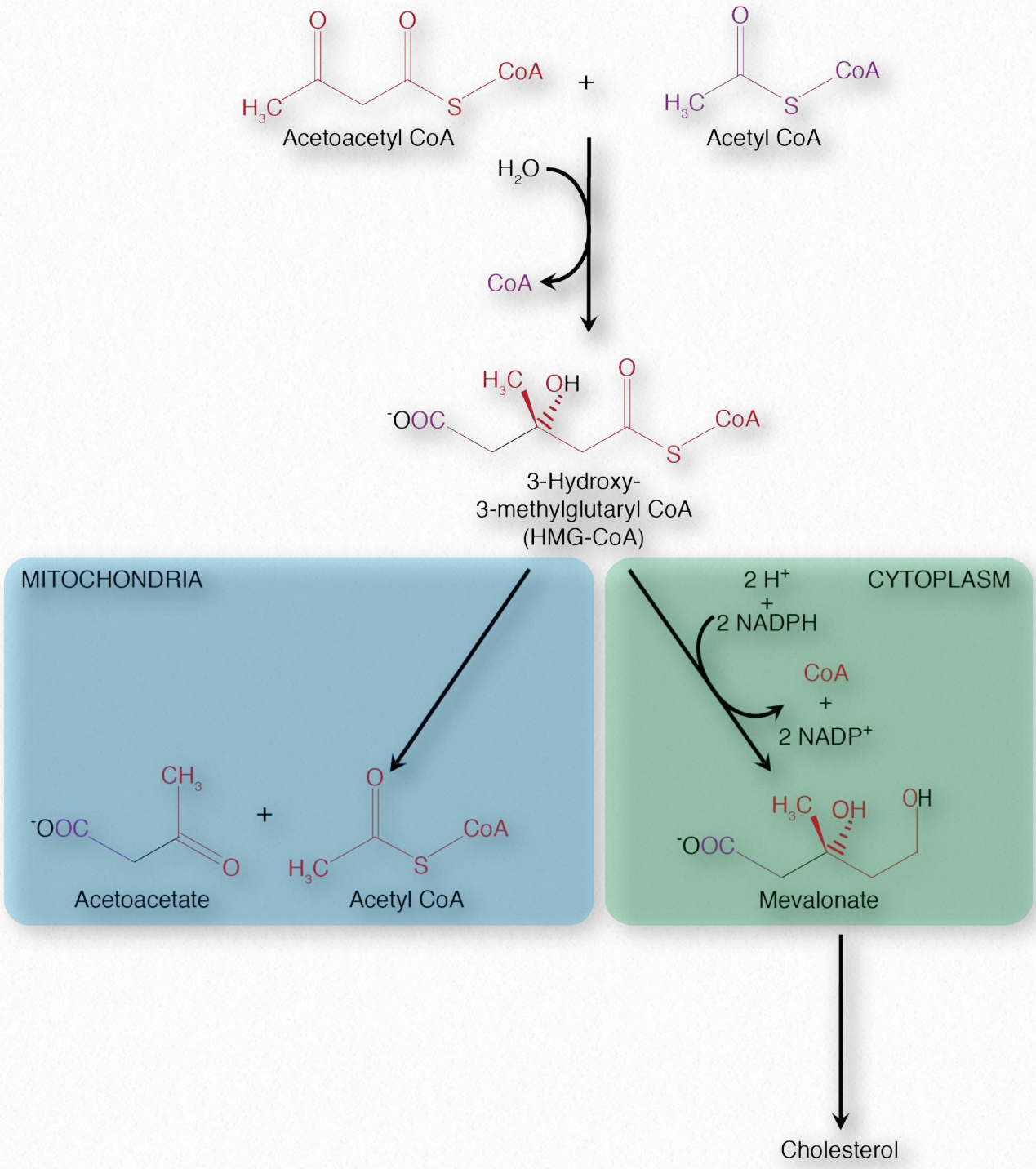

Figure 6.80 - Diverging biosynthetic pathways for ketone bodies (left) and cholesterol biosynthesis (right)

Image by Penelope Irving

and see HERE) overlap at the beginning. Each of these starts by combining two acetyl-CoAs together to make acetoacetyl-CoA. Not coincidentally, that is the next to last product of β-oxidation of fatty acids with even numbers of carbons (see HERE for fatty acid oxidation). In fact, the enzyme that catalyzes the joining is the same as the one that catalyzes its breakage in fatty acid oxidation – thiolase. Thus, these pathways start by reversing the last step of the last round of fatty acid oxidation.

YouTube Lectures by Kevin HERE & HERE

HMG-CoA formation

Both pathways also include addition of two more carbons to acetoacetyl-CoA from a third acetyl-CoA to form hydroxy-methyl-glutaryl-CoA, or HMG-CoA, as it is more commonly known. It is at this point that the two pathways diverge. HMG-CoA is a branch point between the two pathway and can either go on to become cholesterol or ketone bodies. In the latter pathway, HMG-CoA is broken down into acetyl-CoA and acetoacetate.

Acetoacetate is itself a ketone body and can

be reduced to form another one, D-β-hydroxybutyrate (not actually a ketone, though). Alternatively, acetoacetate can be converted into acetone. This latter reaction can occur either spontaneously or via catalysis by acetoacetate decarboxylase. Acetone can be converted into pyruvate and pyruvate can be made into glucose.

D-β-hydroxybutyrate travels readily in the blood and crosses the blood-brain barrier. It can be oxidized back to acetoacetate, converted to acetoacetyl-CoA, and then broken down to two molecules of acetyl-CoA for oxidation in the citric acid cycle.

Ketosis

When a body is producing ketone bodies for its energy, this state in the body is known as ketosis. Formation of ketone bodies in the liver is critical. Normally glucose is the body's primary energy source. It comes from the diet, from the breakdown of storage carbohydrates, such as glycogen, or from glucose synthesis (gluconeogenesis). Since the primary stores of glycogen are in muscles and liver and since gluconeogenesis occurs only in liver, kidney, and gametes, when the supply of glucose is interrupted for any reason, the liver must supply an alternate energy source.

From fatty acid breakdown

In contrast to glucose, ketone bodies can be made in animals from the breakdown of fat/fatty acids. Most cells of the body can use ketone bodies as energy sources. Ketosis may arise from fasting, a very low carbohydrate diet or, in some cases, diabetes.

Acidosis

The term acidosis refers to conditions in the body where the pH of arterial blood drops be-

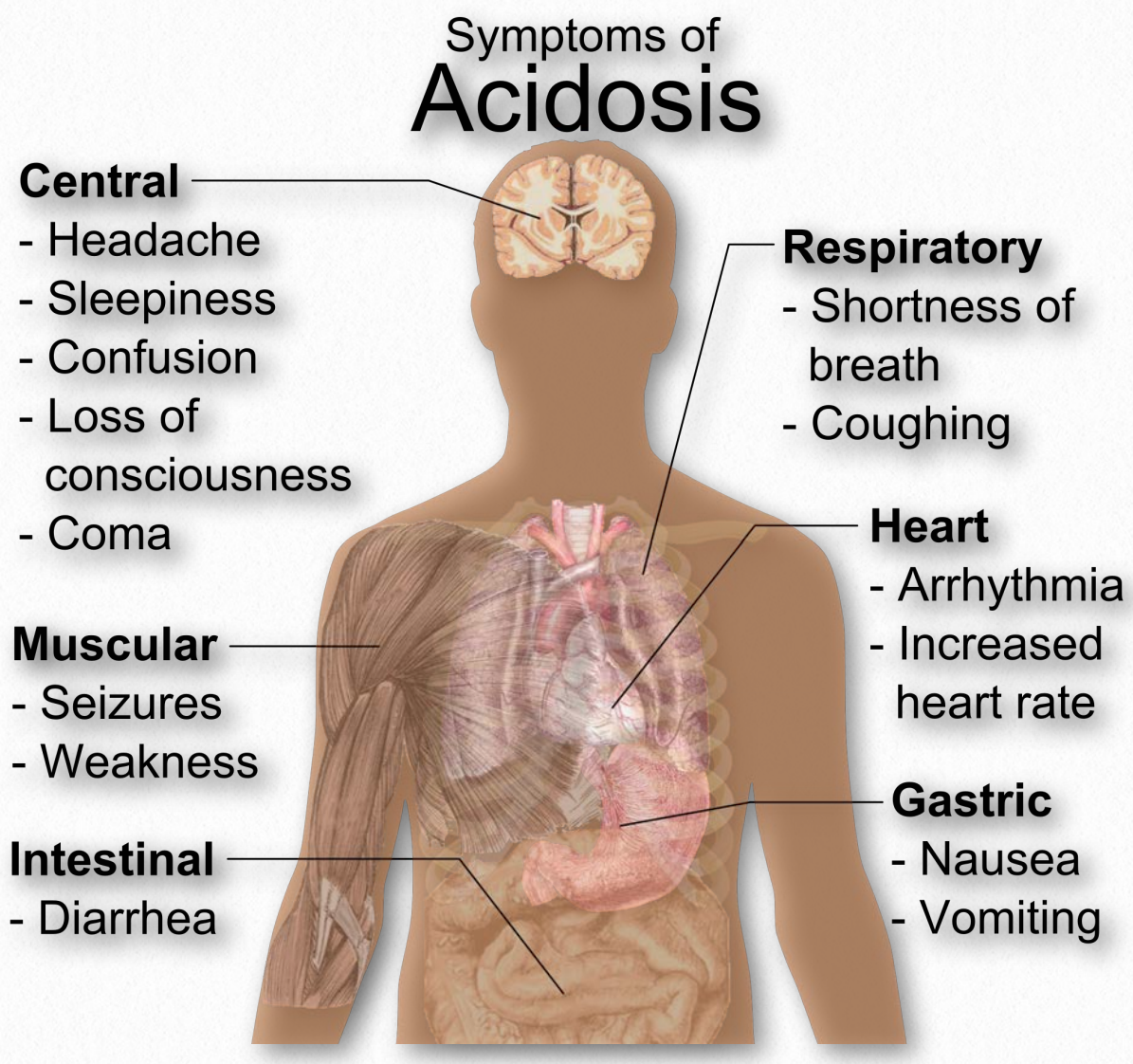

Figure 6.81 - Symptoms of acidosis

low 7.35. It is the opposite of the condition of alkalosis, where the pH of the arterial blood rises above 7.45. Normally, the pH of the blood stays in this narrow pH range. pH values of the blood lower than 6.8 or higher than 7.8 can cause irreversible damage and may be fatal. Acidosis may have roots in metabolism (metabolic acidosis) or in respiration (respiratory acidosis).

There are several causes of acidosis. In metabolic acidosis, production of excess lactic acid or failure of the kidneys to excrete acid can cause blood pH to drop. Lactic acid is produced in the body when oxygen is limiting, so anything that interferes with oxygen delivery may create conditions favoring production of excess lactic acid. These may include restrictions in the movement of blood to target tissues, resulting in hypoxia (low oxygen conditions) or decreases in blood volume. Issues with blood movement can result from heart problems, low blood pressure, or hemorrhaging.

Strenuous exercise can also result in production of lactic acid due to the inability of the blood supply to deliver oxygen as fast as tissues require it (hypovolemic shock). At the end of the exercise, though, the oxygen supply via the blood system quickly catches up.

Respiratory acidosis arises from accumulation of carbon dioxide in the blood. Causes include hypoventilation, pulmonary problems, emphysema, asthma, and severe pneumonia.

Graphic images in this book were products of the work of several talented students. Links to their Web pages are below

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Click HERE for Pehr Jacobson's Web Page

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The Citric Acid Cycle

To the tune of "*When Irish Eyes Are Smiling*"

Metabolic Melodies Website HERE

(This song uses only the chorus of the original song)

The citric acid cycle
Is a source of energy
It gets electrons moving
While reducing NAD

It starts with citric acid
Turning to aconitate
Which becomes an isocitrate
On the way to glutarate

The loss of one more carbon
Gives succinyl-CoA
And then succinic acid
When the CoA goes away

A further oxidation
Gives one *trans* fumarate
Which gains a water on the
Next step to make malate

One simple oxidation
Makes O-A-A you see
Which combined with Ac-Co-A
Returns us cyclically

Recording by David Simmons
Lyrics by Kevin Ahern

The Mellow Woes of Testing

To the tune of "*Yellow Rose of Texas*"

Metabolic Melodies Website HERE

The term is almost at an end
Ten weeks since it began
I worried how my grade was cuz
I did not have a plan

The first exam went not so well
I got a sixty three
'Twas just about the average score
In biochemistry

I buckled down the second time
Did not sow my wild oats
I downloaded the videos
And took a ton of notes

I learned about free energy
And Delta Gee Naught Prime
My score increased by seven points
A C-plus grade was mine

I sang the songs, I memorized
I played the mp_3s
I learned the citrate cycle
And I counted ATPs

I had electron transport down
And all of complex vee
I gasped when I saw my exam
It was a ninety three

So heading to the final stretch
I crammed my memory
And came to class on sunny days
For quizzing comedy

I packed a card with info and
My brain almost burned out
'Twas much to my delight I
Got the 'A' I'd dreamed about

So here's the moral of the song
It doesn't pay to stew
If scores are not quite what you want
And you don't have a clue

The answers get into your head
When you know what to do
Watch videos, read highlights and
Re-

Recording by David Simmons
Lyrics by Kevin Ahern