Tools:

- Memorize amino acids
- Understand the oxidation state of different functional groups. Each of these categories differ in two electrons that will need to be removed or added (typically by an electron carrier such as NAD+ or FAD)
    - Alkanes
    - Alkenes, alcohols, amines
    - Ketones, aldehydes, hemiacetals, acetals, diols, imines (Schiff base)
    - Carboxylate, ester, amide, thioester
- Decarboxylations (loss of CO2) give off energy
- Oxidations will typically give off energy
- Hydrolysis of a thioester bond gives off energy
- Giving off energy can be used to synthesize a molecule of ATP from ADP and Pi or to form an activated bond (thioester or carboxylation)
- Because these molecules are so common, you should memorize them: pyruvate, lactate, oxaloacetate, acetyl-CoA, glucose, glycerol, glyceraldehyde, glycerate.

Glycolysis:

- Happens In the cytosol
- Objective: obtain ATP without respiration. Fast. Without transport to mitochondrion or need of oxygen.
- Converts glucose into pyruvate
- Consumes 2 ATP, produces 4 ATP, 2 NADH and 2 pyruvate molecules
- PFK-1: step most regulated. The commitment of the 2nd molecules of ATP

Fermentation

- Happens in the cytosol
- Objective: recycle the NADH and convert it into NAD+ so that glycolysis keeps going.
- Consumes 1 pyruvate and 1 NADH and it produces 1 lactate and 1 NAD+
- In yeast pyruvate is turned in to ethanol and 1 CO2 (recycles NADH also)
- See Cori cycle for gluconeogenesis: how lactate is sent to the liver when it accumulates

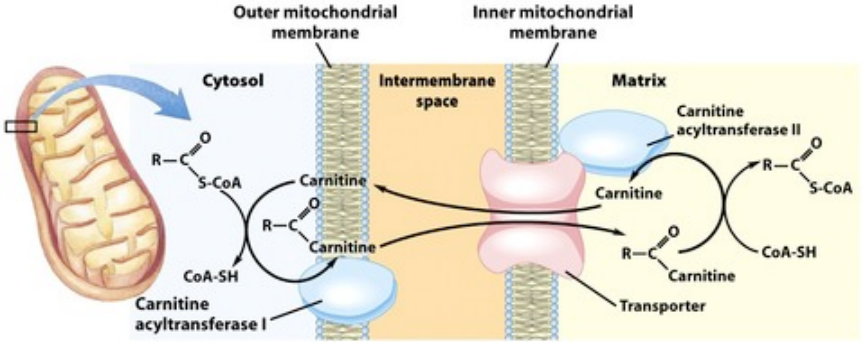
Aerobic catabolism of carbohydrates: PDC + Krebs cycle

- Happens in mitochondria
- Pyruvate is transported inside the mitochondria (this costs energy)
- Pyruvate dehydrogenase complex: pyruvate → acetyl-CoA + NADH + CO2
- Krebs cycle consumes Acetyl-CoA + citrate to give oxaloacetate + 2CO2+ 3NADH+ FADH2+ATP (or GTP)

Fatty acid catabolism

- Triacyl glycerides are hydrolyzed into 3 fatty acids and 1 glycerol. The glycerol is converted through oxidation in the cytosol into one intermediated of glycolysis (DHAP) and it produces 1 NADH. Sometimes this NADH is converted into a FADH2 through the glycerol shuttle.
- Fatty acid needs to be transported inside the mitochondria through the carnitine shuttle: formation of the activated Acyl-CoA bond consumes 1 ATP into AMP in

the cytosol.



- Beta oxidation takes place in the mitochondria
- Each cycle produces two acetyl-CoA or, the last one, produces two (for even # of carbons). Each cycle produces 1 NADH and, if not unsaturated, 1FADH2.

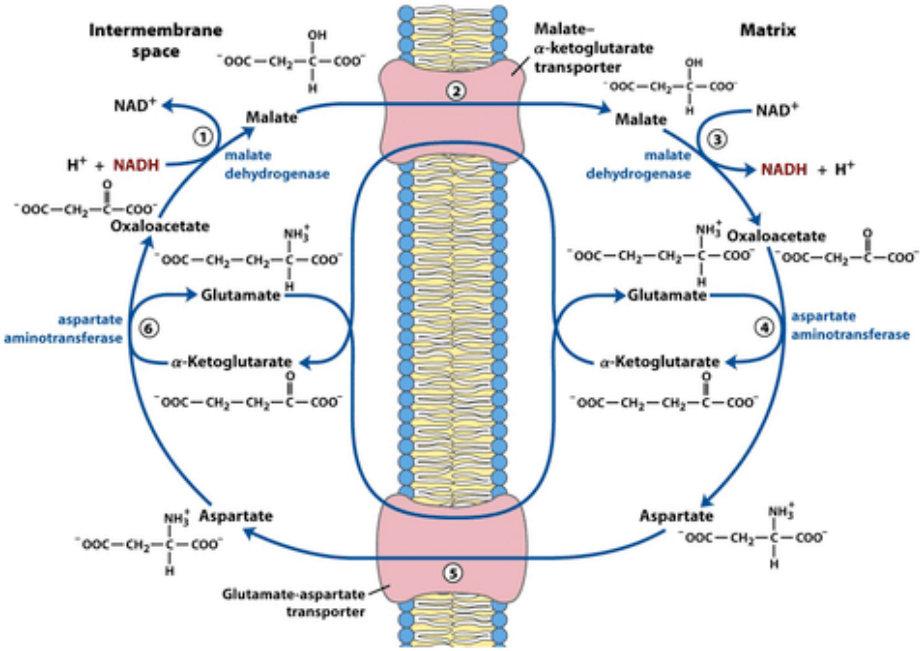
Amino acid catabolism.

- Transamination: the crucial step to convert amino acid into a keto-acid that will be converted into, typically, an intermediate of the Krebs cycle.
- Transamination: Takes place mostly in the mitochondria. Converts an amino acid and alpha-ketoglutarate into the corresponding ketoacid and glutamate.
- It's important to notice that there are some intermediates of the catabolism of carbohydrate that are just one transamination away from some amino acids, such as glutamate, alanine and aspartate.
- Glutamate will accumulate and it will have different fates depending on the tissue:
    - Liver: glutamate dehydrogenase removes the nitrogen and sends it to the Urea cycle
    - Non-muscle tissue: the accumulated glutamate accepts another nitrogen to become glutamine and glutamine is sent to the liver to remove the two nitrogens and use the corresponding alpha-ketoglutarate for energy or biosynthesis
    - Muscle: Alanine cycle: the accumulated glutamate reacts with the also accumulated pyruvate (muscles run a lot of glycolysis) and give as products alanine and alpha-ketoglutarate. The alanine is sent to the liver to get the nitrogen removed that will be sent to the urea cycle and the corresponding pyruvate that will be used for gluconeogenesis.
    - Notice that the Alanine cycle avoids recycling the NADH from glycolysis because it consumes pyruvate and not lactate. Alanine cycle must not work alone, but with in conjunction with fermentation and the Cori Cycle.

Oxidative Phosphorylation

- Respiratory chain: a series of several membrane bound enzymes in the inner membrane of the mitochondria. Their mission is to pass the electrons from NADH or FADH2 into oxygen. The process is done stepwise by different proteins so that each protein can pump protons from the mitochondrion's matrix into the intermembrane space creating a proton gradient.
- It's important to identify the different members of the respiratory chain and their role.
- The proton gradient is used to synthesize ATP in the F0/F1-ATP synthase protein.

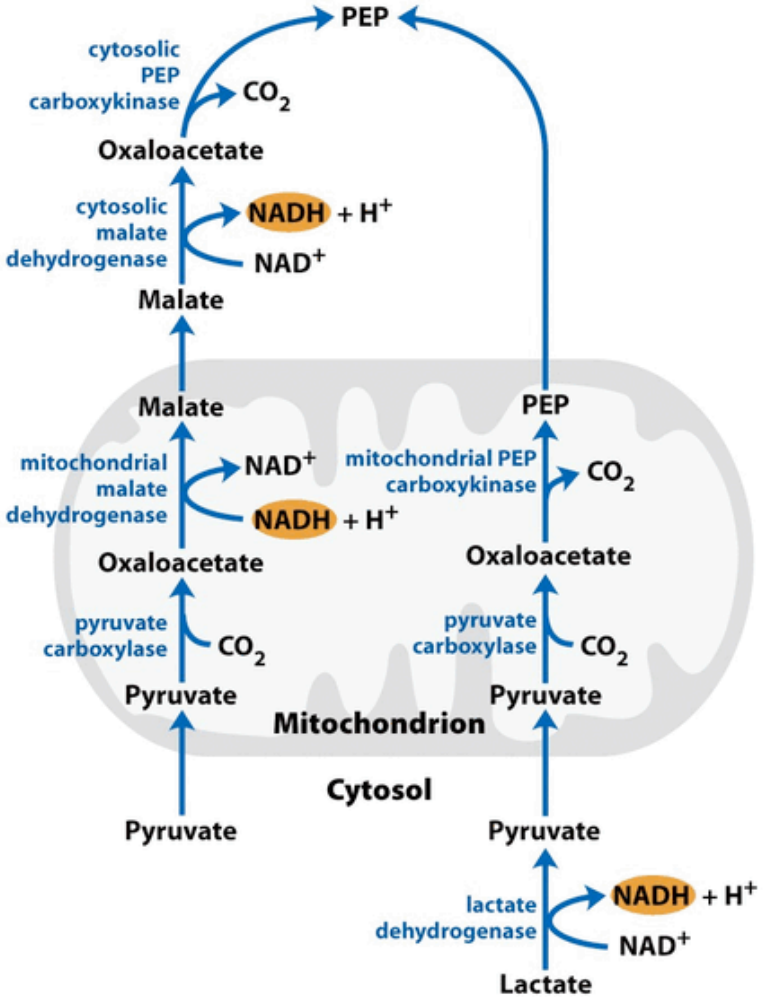
- Most NADH is already inside the mitochondrion, the one in the cytosol needs to be shuttled inside through the malate/aspartate shuttle.



  - NADH is too big to diffuse into the mitochondrial matrix alone
  - This shuttle uses two transporters: malate/alpha-ketoglutarate and glutamate/aspartate
- FADH is a prosthetic group and it cannot travel alone, depending on its source it will enter the respiratory chain from different proteins
  - From the Krebs cycle: Succinate dehydrogenase is also called Complex II and it's already a membrane bound enzyme
  - From the beta oxidation: the acyl dehydrogenase enzyme is in the mitochondria and it will pass the electrons through a series of ETF (electron transferring flavoproteins) which will deliver the electrons to Ubiquinone (complex Q)
  - glycerol-3-phosphate transport system: when glycerol is oxidized to dihydroxiacetone phosphate, this enzyme bound on the intermembrane space of the mitochondrion will store electrons as FADH2 which will be passed to complex Q.
- ATP synthesis
  - 3 protons are used to synthesize one molecule of ATP
  - Since ATP is made inside the mitochondrion it uses an additional proton to be transported to the cytosol.
  - The P/O ratio: Overall, 1 NADH (2 electrons) pumps 10 protons and convert ½ O2 into one water. These 10 protons will be used to synthesize and transport 2.5 molecules of ATP (4 protons per molecule). 1 FADH2 pumps 6 protons and therefore will synthesize 1.5 molecules of ATP

Gluconeogenesis

- It takes place in the cytosol except for the first bypass.



  - Pyruvate is activated inside the mitochondrion and used to transport CO2 and NADH outside of it.
- When starting from lactate, it still gets activated inside the mitochondrion but it does not transfer NADH because lactate is already reduced.
- After the first bypass, the rest of the steps are the reversed steps of glycolysis except for the 2nd and 3rd bypass, which are carried out by phosphatases. Because phosphatases would short-circuit glycolysis they are only found in the endoplasmic reticulum of liver and kidney cells.
- Overall it takes 4ATP and 2GTP to make one molecule of glucose, while out of glycolysis glucose would only provide 2 ATP.
- The Cori cycle is the process through which the glucose consumed to lactate in the muscle is recycled in the liver. While the liver spends the ATP necessary for the synthesis of glucose, no NADH/NAD+ is gained or loss during the cycle.
- Most amino acids are glucogenic, that is, after transamination they become an intermediate of the Krebs cycle which can be converted into oxaloacetate and pyruvate. Therefore, unlike lipids, the cell can synthesize glucose out of amino acids.

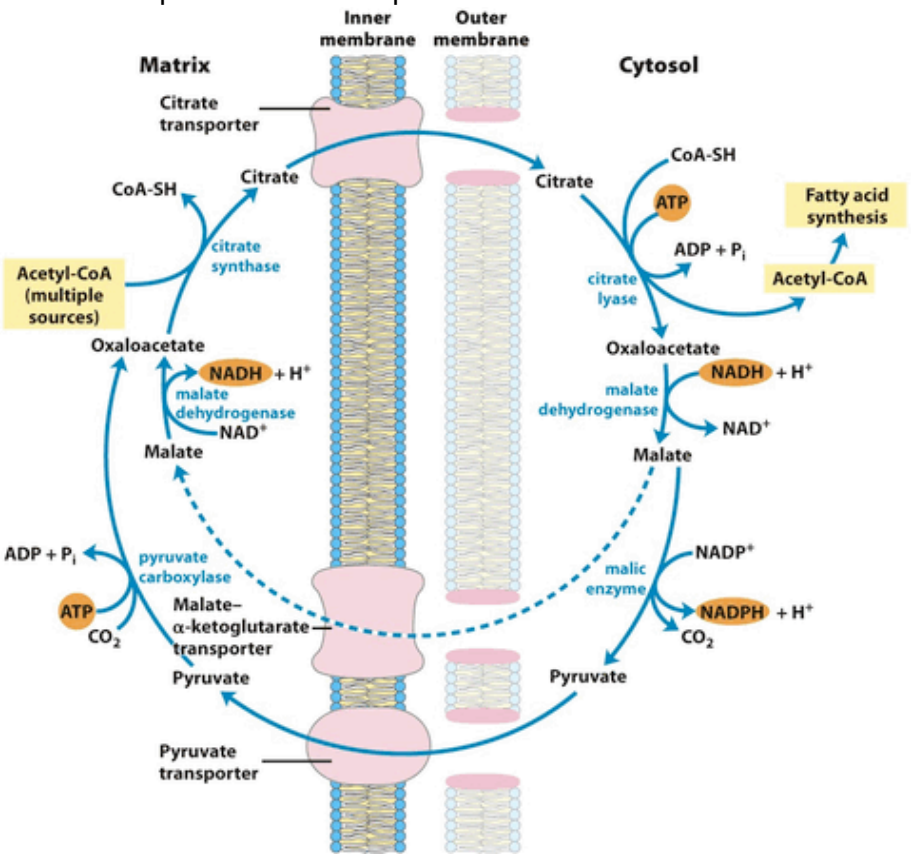
Pentose phosphate pathway

- It takes place in the cytosol and it can have two main functions (it has more)
    - Synthesis of ribose for genetic material: one step called oxidative phase
    - Obtain NADPH for lipid biosynthesis: oxidative phase + nonoxidative phase
- Oxidative phase: it transforms glucose (6-C) into ribose (5-C) and it gives two NADPH and one CO2.
- Nonoxidative phase: the objective is to recover the glucose without having to invest the produced NADPH that will be needed for lipid biosynthesis.
    - It will convert two riboses (5-C) into two intermediates of gluconeogenesis that can later on be converted into the initial glucose.

Fatty acid biosynthesis

- It takes place in the cytosol. Fatty acid synthase is a mulitenzyme complex that starting from acetyl-CoA undoes the same steps of beta oxidation.
- Notice that acetyl-CoA is activated into malonate the same way that in gluconeogenesis, pyruvate is activated into oxaloacetate, that is, with a carboxylation.
- The source of electrons for fatty acid biosynthesis is only NADPH: it makes sense because when an excess of carbohydrates is ingested, the cell will want to convert them into fat, therefore will need to activate both glycolysis and fatty acid biosynthesis, the cell cannot use the same electron carrier for the two tasks because its metabolic homeostasis would be pointing to opposite directions.
- The NADPH comes from the following sources
    - Pentose phosphate pathway
    - Citrate transporter: malate dehydrogenase
        - The malate transporter was used to transport NADH inside the mitochondria for oxidative phosphorylation
        - The same malate transporter had an inverted direction for the first bypasss of gluconeogenesis
        - Now the malate transporter is used to convert the NADH transported from the mitochondria to the cytosol into NADPH

- Citrate transporter: other transports



  - The citrate is hiding the molecule of acetyl-CoA transported from the mitochondria.
  - If the starting point of fatty acid biosynthesis is acetyl-CoA in mitochondria it will take one ATP for converting citrate into oxaloacetate and acetyl-CoA. Plus the a third ATP to activate acetyl-CoA intol malonyl-CoA as the first step of fatty acid biosynthesis.
  - If the starting point of fatty acid biosynthesis is pyruvate in the cytosol, it will take one ATP to convert pyruvate into oxaloacetate (also 1st bypass of gluconeogenesis) and another ATP to convert citrate into oxaloacetate and acetyl-CoA. Plus the a third ATP to activate acetyl-CoA intol malonyl-CoA as the first step of fatty acid biosynthesis.

Insulin and glucagon are two antagonistic hormones. The former is secreted when glucose concentration in blood is high, the latter when glucose concentration in blood is low. Identify if the following processes taking place in the liver will be triggered by the presence of insulin or glucagon.

Process	Triggered by insulin	Triggered by glucagon
Glucose → Glycogen (in liver)		
Triacylglycerol → Fatty acids + glycerol (in adipose tissue)		
Glucose → pyruvate (in liver)		
Fatty acids → Ketone bodies (in liver)		
Amino acids → Pyruvate → Glucose (in liver)		
Acetyl-CoA → Fatty acids (in liver)		

Each of the following events occurs in one or more of the pathways we have studied. Put the correct letter(s) in the pathways below if that statement applies to the pathway. Each letter may be used more than once.

a. Pyruvate is carboxylated
b. Pyruvate is shuttled into the mitochondria
c. Glucose-6-phosphate is oxidized to a 5-carbon sugar.
d. Glucose-6-phosphate is oxidized to a 3-carbon sugar.
e. Acetyl-CoA is shuttled to the cytosol
f. Acetyl-CoA is carboxylated.
g. Takes place in the cytosol (1 step or more)
h. Takes place in the mitochondria (" ")
i. NADPH is a product
j. NADP+ is a product
k. NADH is a product
l. The pathway is activated by insulin in the liver
m. The pathway is activated by glucagon in the liver
n. Is an essential part of the Cori cycle

Pathways

I. Glycolysis (glucose → acetyl-CoA) _____

II. Glycolysis (glucose → lactate) _____

III. Gluconeogenesis (pyruvate → glucose) _____

IV. Fatty acid β-oxidation (acyl-CoA → acetyl-CoA) _____

V. Fatty acid synthesis (acetyl-CoA → acyl-CoA) _____

VI. Pentose phosphate pathway (G-6-P → Ribose-5-P) _____

For each statement, indicate if the statement is true without exception, the statement is true but there are exceptions, or the statement is false by placing an X in the appropriate column. If it is true but there are exceptions, briefly state one exception. If the statement is false, state why

Statement	True with no exceptions	True but there are exceptions	False	If there are exceptions give an example. If false, state why
A step of gluconeogenesis is the reverse of a step of glycolysis.				
In the anaerobic regeneration of NAD^+, pyruvate is converted to ethanol and CO_2.				
A reaction with a positive ΔG in the cell, will proceed in the forward direction in the cell.				
The pentose phosphate pathway is used to synthesize ribose for nucleotide biosynthesis				

1. Show whether **liver** mammalian phosphofructokinase-1 has increased activity, decreased activity or is not affected by each of the conditions shown below by putting an X in the appropriate column.

	Activity		
	Increased	Decreased	Not affected
[Fructose-2,6 bisphosphate] is low.(*)	_____	_____	_____
[Glucagon] in blood is high.	_____	_____	_____
[Insulin] in blood is high.	_____	_____	_____
[Glucose] in blood is low.	_____	_____	_____
A lion just started chasing you.	_____	_____	_____
[ATP] in liver cell is high.	_____	_____	_____
[Citrate] in liver cell is high.	_____	_____	_____
You just ate Thanksgiving dinner.	_____	_____	_____

(*)F-2,6-P has the contrary effect of ATP in modulating PFK-1

1. The following metabolic pathways have specific characteristics. Identify
   a. Glycolysis (glucose → acetyl-CoA)
   b. Glycolysis (glucose → lactate)
   c. Gluconeogenesis (pyruvate → glucose)
   d. Krebs cycle (acetyl-CoA + oxaloacetate)
   e. Fatty acid □-oxidation (saturated acyl-CoA → acetyl-CoA)
   f. Fatty acid synthesis (acetyl-CoA → saturated acyl-CoA)
   g. Pentose phosphate pathway (glucose-6-P → ribose-5-P)

I. All the chemical transformations (not transport) take place in the mitochondria

Pathways:_____

II. All the chemical transformations (not transport) take place in the cytosol

Pathways:_____

III. It uses HCO_3^- to activate a substrate

Pathways:_____

IV. It has NADH as products in the overall reaction

Pathways:_____

V. It has NAD^+ as products in the overall reaction

Pathways:_____

VI. It is activated by insulin in the liver

Pathways:_____

VII. It gives CO_2 as products in the overall reaction

Pathways:_____

VIII. It is an essential process of the Cori cycle

Pathways:_____

IX. The process is activated in the liver between meals

Pathways:_____