DOCTOR 2020 | JU

METABOLISM

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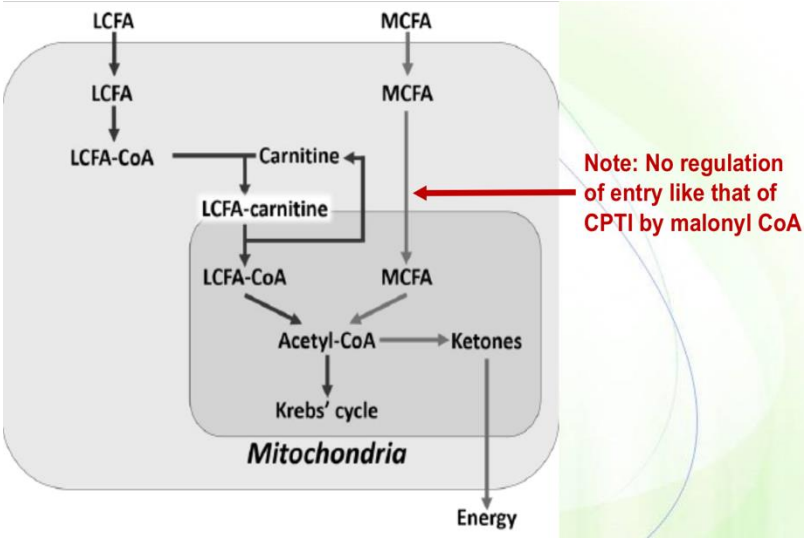
We will complete the topic of oxidation of fatty acids in this lecture

Last thing that we talked about was medium chain fatty acids and short chain fatty acids , these don't need carnitine to be transported to the mitochondria, so once they are in the mitochondria they are activated by attaching to CoA to them, and then they can be degraded so they are different from long chain fatty acids (in long chain fatty acids they get activated first in cytosol and they need carnitine to transport them Vs short and medium chain fatty acids they get activated in mitochondria and don't need carnitine to transport them to the mitochondria).



Let's talk now about Medium Chain Fatty Acyl Dehydrogenase Deficiency:

Basically, this medium chain fatty acyl dehydrogenase is the enzyme that catalyses the first reaction (creating the double bond), there are 4 isozymes of this enzyme, each one is specific for a fatty acid with certain length, so there is a dehydrogenase for short chain fatty acids (SCFA) there is another one for medium chain fatty acids (MCFA), third for long chain fatty acids (LCFS) and fourth one for very long chain fatty acids (VLCFA).

Certain people have deficiency in medium chain fatty acyl CoA dehydrogenase, so they are not able to oxidise these medium chain fatty acids, it is the most common inborn error of beta oxidation, (1 of 14,000 infants), it has higher incidence in Caucasians of north European descent (If you do to Sweden, Norway and Denmark, such countries you might diagnose people with this condition more often than Jordan),**this is an Autosomal-recessive disorder,** meaning (**you have two types of chromosomes: 1. Autosomal chromosomes 2. Sex chromosomes (X & Y)**, autosomal chromosomes are those that are numbered from 1 to 22) so they follow an autosomal inheritance pattern, which is different than sex-linked disorders (we will learn that in genetics إن شاء الله).

Recessive means: متنحي you need to have 2 mutated Alleles to have the condition, rather than being dominant سائد where one mutated Allele is enough.

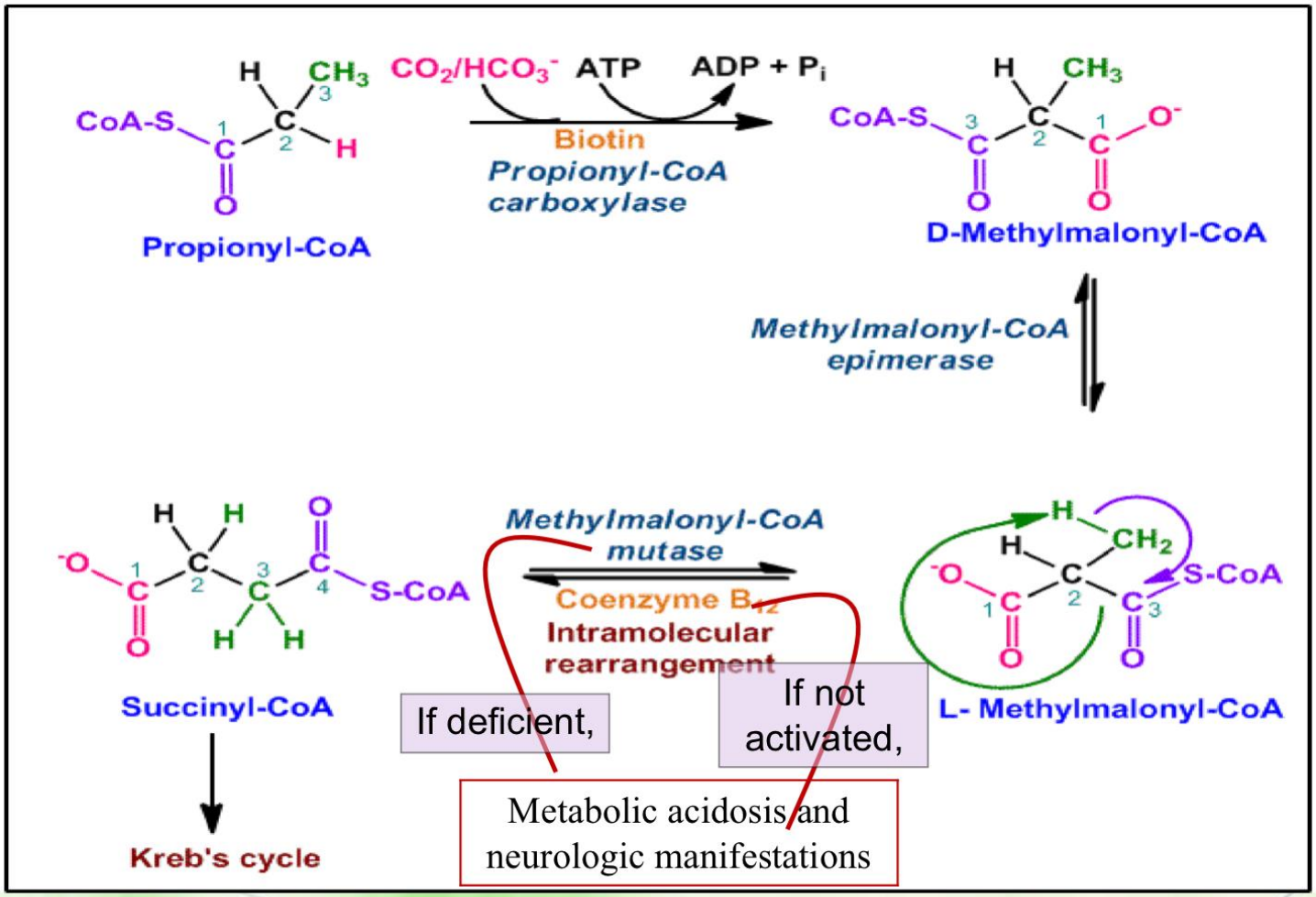
So, people can't oxides medium chain fatty acids, they suffer from lack of energy, even though most of fatty acids (especially mothers' milk) are mainly long chain fatty acids. However, 25% almost of fatty acids in mothers' milk are MCFAs, so they still have a significance, so people who have this deficiency suffer from lack of energy also they have severe hypoglycemia because there is reliance and dependence on glucose for metabolism rather than these fatty acids, and they also suffer from hypoketonemia (low level of ketone bodies… we will talk about his next).

Treatment: basically, avoidance of fasting.

All that we have talked about was really about the classical fatty acid oxidation which such as oxidation of palmitate (16C), stearate (18C saturated fatty acid) for example but these are saturated fatty acids, they are within certain length range and they have even number of carbons, but there are exceptions (in this lecture we will talk about these exceptions).

Palmitate or stearate for example these are even number fatty acid, they have 16 carbons or 18 carbons and so on, how do cells handle odd numbered fatty acids (15, 17, 19 carbons)? That's how it goes:

1. It starts normally with beta oxidation (removing 2 Acetyl CoA molecules at a time)
2. once they reach the end (having a 3 carbons molecule) it is called (propionyl CoA) now what happens with this molecule right here is that it must be carboxylated **(so the enzyme is carboxylase. The enzyme that is called carboxylase requires Biotin (vitamin B7) which is involved in carboxylation reactions)** for carboxylation you need a carbon which comes from HCO3- **(there are some textbooks put it as CO2, but what really happens is that bicarbonate molecule is the source of the carbon)** we are talking about a condensation reaction, so energy is needed (from ATP)
3. You end up with a 4-carbon molecule (propionyl-CoA 3 carbon molecule which is methylated, so the total is 4 carbons) it is in D conformation.
4. You have an epimerase which is called (methylmalonyl-CoA epimerase or methylmalonyl-CoA racemase) that changes it to L-conformation the result is L- methylmalonyl-CoA
5. Then you have intramolecular rearranging of groups forming succinyl-CoA (catalyzed by methylmalonyl-CoA mutase) it requires B12, there are cases where this isomerase can be mutable so it is deficient or if there is deficiency in B12 or inability to activate vitamin B12 that would result in a conditions such as metabolic acidosis **(because of dependance on ketone bodies)** as well as neurological manifestations, so notice that whenever you have these inborn metabolic errors whether it is lipids or sugars it leads to neurological manifestations mainly.
6. You have succinyl-CoA at the end, it's an intermediate in Krebs cycle, and it enters Krebs cycle, except of that there is a loss of electrons, why? Because you are skipping a reaction that generates NADH that is the reaction that converts isocitrate to Alpha ketoglutarate, so there is a loss of electrons and loss of ATP as well.



Note: Loss of electrons

Try to match between the six steps with this photo

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Let's take about Monounsaturated fatty acids

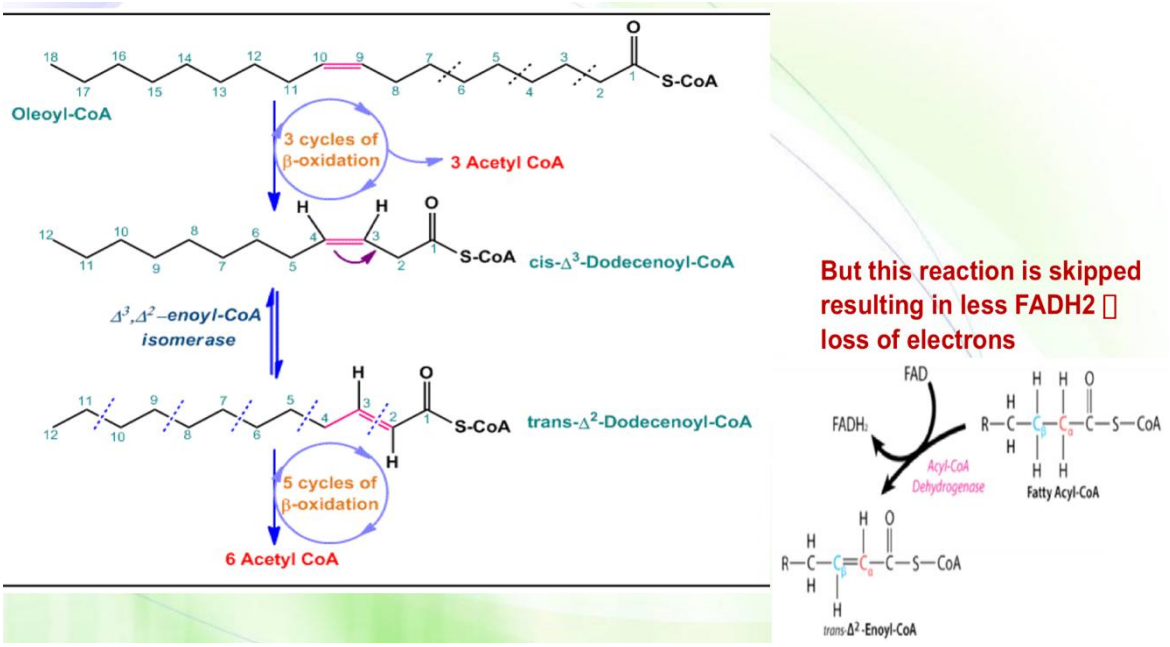
How do cells handle double bond in fatty acids?

Well, an example is oleic acid:

1. oleic acid undergoes beta oxidation just like any other fatty acid (you have removal of Acetyl CoA one at a time "2 carbons at a time").
2. Until you get near to the double bond, what's important that where this double bond is existing **(does it exist at even numbered carbon or an odd numbered carbon)**, now in this case, it exists in odd numbered carbon that is number 9 (look at the photo below), and down to it a fatty acid with double bond in carbon number 3 **(we get it after 3 cycles of beta oxidation that was applied on the original fatty acid which has the double bond on carbon 9).**
3. What happens here is that you need an isomerase enzyme, and what this enzyme does that it changes the location of the double bond from cis 3-4 carbons bond to trans 2-3 carbons bond, the result (the last molecule in the photo below) is very similar to the product of the first reaction of beta oxidation, (remember: the first reaction in the lower right part of the photo below, it is an oxidation reaction of fatty acyl CoA molecule

creating the double bond, so the result of first reaction of beta oxidation looks exactly like the molecule that result from the isomerization of the odd numbered 3-4 double bond fatty acid). “We don’t start with the original compound rather we start with the compound that looks like the product of first reaction in beta oxidation”.

4. Since this reaction (first reaction in beta oxidation) results in the production of FADH2 and we skipped this reaction because our compound looks like the product of this reaction, so we have a loss of FADH2 (meaning we loss 1.5 ATP).

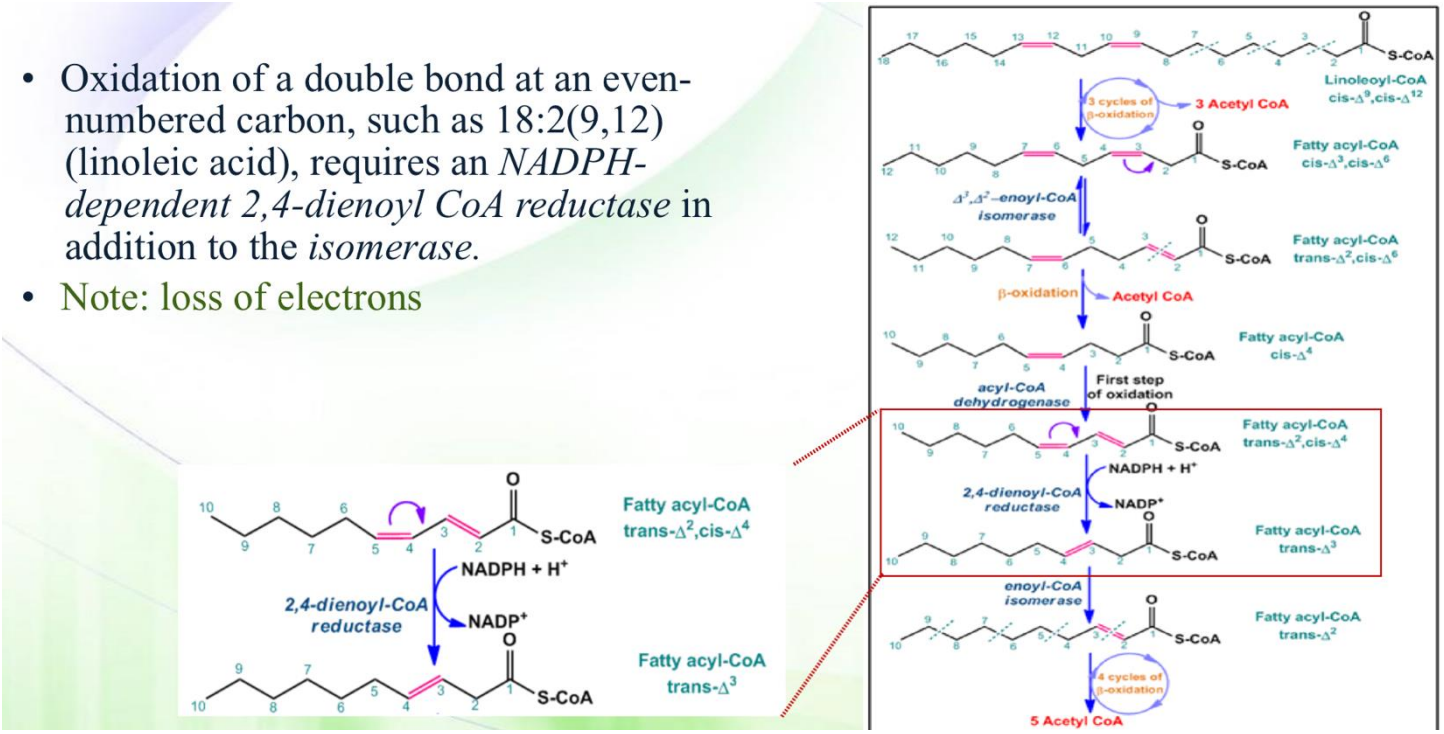


How about polyunsaturated fatty acids?

Each polyunsaturated fatty acid has at least 2 double bond one on odd-numbered carbon and another one on even-numbered carbon. The odd numbered is the same thing as oleic acid, but the even numbered double bond oxidation requires extra steps with their enzymes. Let’s take linoleic acid as an example:

1. You start with beta oxidation (removing Acetyl CoA).
2. Once we get to the odd-numbered double bond, you need an isomerase enzyme that moves the double bond from carbon number 3-4 to carbon number 2-3 (just like oleic acid).
3. Remember that you have the removal of Acetyl CoA but you have skipped the oxidation reaction of beta oxidation process and loss FADH2.
4. Then beta oxidation continues. Once you get to the second double bond (fourth compound at the following photo) you need this additional reaction (and this reaction is catalyzed by dehydrogenase enzyme, by creation of double bond (look at the photo), so you have 2 double bonds, notice their locations.

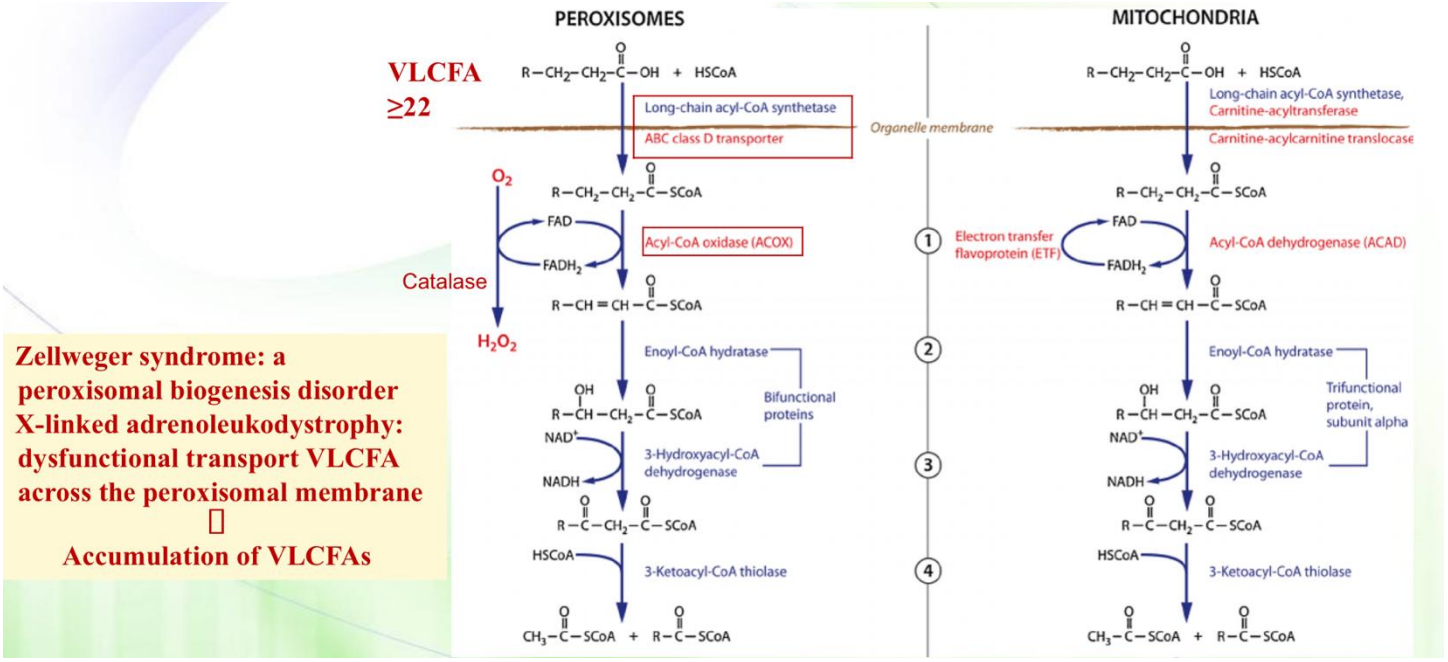
5. You need a reductase enzyme, what reductase does is it saturate one of them and change the location of the another, it combines these two double bonds into one between carbons 3-4 using NADPH.
6. This is followed by the same isomerase that is needed for oleic acid, so you need this enzyme to move the double bond from carbons 3-4 to 2-3.
7. Again, you can continue with beta oxidation starting from the second reaction not the first because the compound looks like the product of first reaction of beta oxidation.



So again we will talk about exceptions: How cells metabolize very long chain fatty acids (22 carbons or more)….

1. (Peroxisomes) are needed, what first happens is that you need to activate these fatty acids, just like mitochondrial beta oxidation to allow fatty acids enter the mitochondria, and for VLCFAs you need activation by attaching CoA to them to allow them to enter the peroxisomes and they need special transporter for that known as ABC class D transporter
2. Once they are in the peroxisomes they undergo oxidation, it is known as Peroxisomal Beta Oxidation, it's just like the mitochondrial beta oxidation (oxidation, hydration, oxidation and thiolytic cleavage).
3. What happens, is oxidation of fatty acid (formation a double bond just like mitochondrial beta oxidation and you need the electron carrier FAD) look at the photo below, same as mitochondrial beta oxidation but with different enzymes (we use acyl-CoA oxidase (ACOX) in peroxisomal which produces FADH2 that must be regenerated again to FAD), regeneration of FAD is linked to the reduction of molecular oxygen to H2O2 then to H2O which is catalyzed by catalase

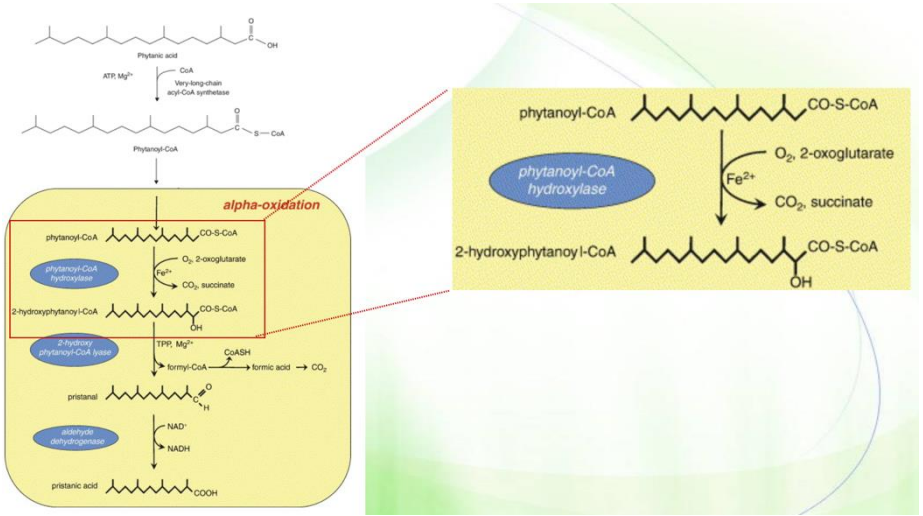
4. The other reactions continue as the mitochondrial beta oxidation, and eventually you will get Acetyl CoA and you will get shorter fatty acid.
5. What happens to the Shortened fatty acids that they get attached to carnitine in Peroxisomes, they leave the Peroxisomes and they get into the mitochondria where you have a continuation of beta oxidation of the fatty acyl CoA, and the entry of Acetyl CoA in Krebs cycle.



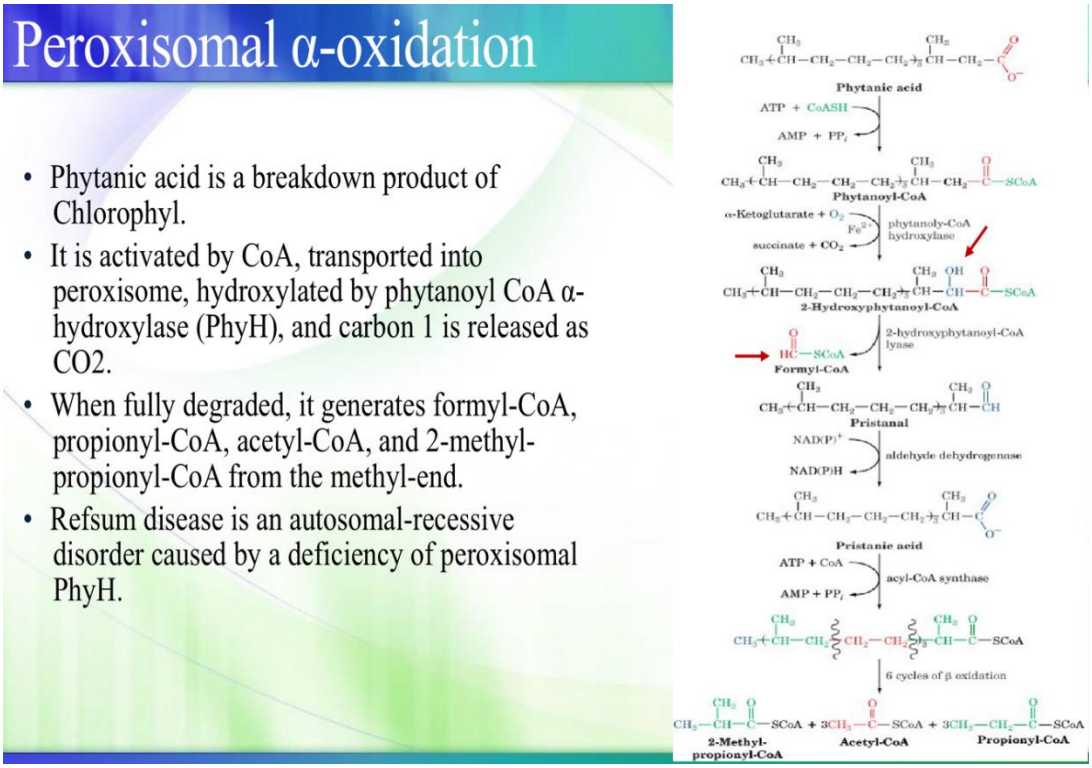
There are some pathological conditions that are related to peroxisomal beta oxidation, we will talk about two of them:

1. Zellweger syndrome, it is related to biogenesis of the Peroxisomes (the creation of Peroxisomes in cells), so the very long fatty acids will be excreted without metabolizing
2. X-linked adrenoleukodystrophy: it is related to deficiency or abnormality in the transport of fatty acids into the Peroxisomes and that leads to accumulation of these fatty acids in the blood and tissues

The doctor has skipped this figure



There is another thing known as peroxisomal Alpha oxidation, it is related to Alpha carbon.



Peroxisomal Alpha oxidation is basically the metabolism of chlorophyll, if you eat green leaves there is chlorophyll inside them

The product of breaking down of chlorophyll is phytanic acid (look at its structure in the photo below) it is branched (there is a methyl group branched from the beta carbon), there is an enzyme that is necessary in metabolism of phytanic acid.

1. Phytanic acid needs to be activated, by attaching a CoA.
2. It gets hydroxylated at Alpha carbon (there is a hydroxylase enzyme that is needed for this reaction).
3. Another reaction that results in the removal of Alpha carbon (that is why we call it alpha oxidation) and you have the formation of byproduct known as formyl CoA.
4. We have the continuation of breaking down of phytanic acid, until there is another methylated carbon.

The products of metabolism of phytanic acid are:

1. Formyl acid (Formyl CoA)
2. Methylpropionyl CoA
3. Acetyl CoA
4. Propionyl CoA (it follows the metabolism of odd numbered fatty acids and gets converted to succinyl CoA)

Finally we have something that is called **Omega oxidation**

It is related to oxidation that starts from omega carbon which is the very last carbon in the fatty acid chain.

And that's why we say omega 3 omega 6, we are talking about methyl group right here.

It is a minor not a major pathway in the smooth endoplasmic reticulum SER.

What happens is that the methyl group is converted into a carboxylic group, so you have 2 carboxylic groups at this fatty acid molecule (one at either end).

It is upregulated in conditions like MCAD deficiency (medium chain fatty acyl dehydrogenase deficiency).

ω-Oxidation is a minor pathway of the SER

It generates dicarboxylic acids.

It is upregulated in certain conditions such as MCAD deficiency.