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**Cross talk between mitochondria and peroxisomes**

Demarquoy J *et al*. Cross talk between mitochondria and peroxisomes

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**Abstract**

Mitochondria and peroxisomes are small ubiquitous organelles. They both play major roles in cell metabolism, especially in terms of fatty acids metabolism, reactive oxygen species (ROS) production and ROS scavenging and it is now clear that they metabolically interact with each other. These two organelles share some properties such as a great plasticity and a high potency to adapt their form and number according to cell requirements. Their functions are connected and alteration in the function of mitochondria may induce changes in the peroxisomal physiology. The objective of this paper was to highlight the interconnection and the crosstalks existing between mitochondria and peroxisomes. Special emphasis was put on the best known connections between these organelles: origins, structure and metabolic interconnections.

**Key words:** Peroxisome; Mitochondrion; Reactive oxygen species; Beta oxidation; Dynamic; Fatty acids

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**Core tip:** The goal of this review was to highlight the links between mitochondria and peroxisomes in terms of dynamic and metabolism. This review of the literature shows that these two organelles even if they derive from distinct ancestors share several common functions and coordinate their activities. The division of peroxisomes and mitochondria uses similar mechanisms and autophagic processes are used to limit the number of both organelles. The metabolic implication of mitochondria and peroxisomes in fatty acid metabolism is remarkable as these organelles use closely related pathways for oxidizing fatty acid but with different metabolic goals. All together, the available data suggest a major interconnection between these organelles.

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**INTRODUCTION**

Mitochondria and peroxisomes are small organelles present in almost every cells of higher organisms. They share properties such as size and functions but differ in terms of origin, structure and physiological roles. Today, it seems clear that these two organelles communicate in the cell and in some cases participate at the same biosynthetic pathways. They share many enzymes and mitochondrial function has been shown to regulate peroxisomal activity.

Peroxisomes and mitochondria share a common range size of 0.1 to 1 µm. However, they differ in terms of structure: mitochondria are surrounded by a double membrane, peroxisomes, on the other hand, are bordered by a single membrane system. In the cell, the number of peroxisomes and mitochondria varies according to the cell type. For instance, mitochondria are very abundant in brown adipose tissue and on the contrary very few mitochondria are present in white adipocytes. Peroxisomal and mitochondrial abundance is regulated by several cellular parameters: (1) organelle formation; (2) organelle dynamic; and (3) organelle death.

**ARE MITOCHONDRIA AND PEROXISOME DERIVED FROM A COMMON ANCESTOR?**

***Origin***

Both, peroxisomes and mitochondria are very dynamic organelles. They show a high plasticity and are able to adopt various shapes depending on the cell requirements: their number and morphology can change according to the metabolic needs of the cell and/or the physiopathological environment.

**Peroxisomal origin:** The origin of peroxisomes is still not fully understood. From the early days of peroxisome discovery, peroxisomes were supposed to be of an endosymbiotic origin[[1](#_ENREF_1)]. Today, this theory is not considered anymore; many reports suggest that peroxisomes are derived from the endoplasmic reticulum[[2](#_ENREF_2)]. This has especially been shown by the experiments in which cells with no peroxisomes were able to engender new peroxisomes[[3](#_ENREF_3)]. In fact, several studies have established that peroxisomes can be formed from pre-existing peroxisomes and also, under certain circumstances, *de novo,* from endoplasmic reticulum (ER)[[4](#_ENREF_4),[5](#_ENREF_5)].

When looking at the origin of proteins present in the peroxisome, two categories of proteins can be described: proteins from a prokaryotic origin and proteins from an eukaryotic origin[[6](#_ENREF_6)]. Roughly, proteins of eukaryotic origin are essentially involved in peroxisomal biogenesis and peroxisomal proteins originated from bacteria appear to be proteins initially targeted to mitochondria. In accordance with the finding that peroxisomes are derived from the ER, many conserved proteins involved in peroxisome biogenesis and repairs are homologous to proteins present in the ER[[7](#_ENREF_7)]. In the peroxisome, there are about 25% of proteins whose origin is difficult to define precisely. This suggested that some peroxisomal proteins have evolved from mitochondrial proteins. Many proteins are present in both organelles: this suggests that these enzymes may be retargeted from mitochondria to peroxisomes[[8](#_ENREF_8)]. This would indicate that peroxisomes formation is influenced by mitochondria.

This leads to unsolved questions. If the peroxisome derives from ER, why mitochondrial proteins were included in the organelle and why mitochondria are not assuring these functions? What are the links between ER and mitochondria/peroxisomes? Today, these questions remain unanswered.

### The origin of mitochondria: The origin of mitochondria is more likely to be endosymbiotic. The endosymbiotic theory indicates that mitochondria were initially free-living prokaryotes that enter eukaryotic cell becoming organelles. This theory has not always been accepted by the scientific community. It was first proposed for plastid at the beginning of the 20th century and was a few years ago used for mitochondria. This theory was rejected by cell biologists the following years and reconsidered in the 60s[[9](#_ENREF_9)].

This theory is based on several facts: (1) endosymbiotic organelles retain a small genome encoding several dozens of proteins. Regardless of this genome reduction, mitochondria harbor at least 2000 proteins[[10](#_ENREF_10)] which are involved in many biochemical pathways and, in particular, in energy production. The difference between the number of proteins encoded by the mitochondrial genome and the number of proteins located in this organelle is usually explained by another aspect of endosymbiotic mechanisms, *i.e.,* (2) the endosymbiotic gene transfer. This process of gene transfer occurs during the evolution of the organism and in fine will ends up as a protein import mechanism such as the mitochondrial import system for proteins. This closes the endosymbiotic process circle where the organelle will carry out functions that the eukaryotic cell was unable to realize and on the other hand the eukaryotic cell will provide extra proteins for the organelle. This process gives evolutionary advantages to both the eukaryotic cell and the “new” organelle[[11](#_ENREF_11)].

Even if they share a few similarities, mitochondria and peroxisomes do not derive from the same evolutionary process with mitochondria deriving from an endosymbiotic process and peroxisomes from an intracellular maturation process.

## *Protein import*

### Protein import in peroxisome: Proteins present in the peroxisome are strictly dependent on nuclear genes and to an import system. The peroxisomes do not possess any DNA sequence and are not able to synthesize any protein. It relies on a cytosolic synthesis from nuclear genes and on the import of these proteins in the peroxisome. The import of proteins into the peroxisome relies on the presence of a peroxisomal targeting signal in the protein sequence: either PTS1 or PTS2. The import of proteins into the peroxisomal matrix is a coordinated process involving the intervention of many proteins known as peroxins (or Pex)[[12](#_ENREF_12)]. Pex proteins control peroxisome structure, division and inheritance. Over a dozen of peroxins have been described[[13](#_ENREF_13)].

PTS1 is composed of the consensual sequence SKL (or their conserved variants) and is located at the C terminal domain of the protein. It is mostly used by proteins located in the peroxisomal matrix[[14](#_ENREF_14)]. PTS1-containing proteins are recognized by Pex5 protein whose C-terminal domain (and in rare cases its N-terminal domain) interacts with the PTS1 sequence[[15](#_ENREF_15),[16](#_ENREF_16)]. This is the unique way for peroxisomal import in several species such as C. elegans[[17](#_ENREF_17)]. In mammals, several proteins contain another type of PTS: type 2 PTS. This motif is recognized by the Pex7 protein, and proteins carrying this PTS2 signal are transported into the peroxisome with the same mechanisms[[18](#_ENREF_18)].

### Protein import into mitochondria: Mammalian mitochondria possess their own genome. It is a circular DNA chain of about 16000 base pairs. In animal mitochondria, the genetic code is slightly different from the “universal” code[[19](#_ENREF_19)]. The structure of this genome is simple: there are virtually no non-coding regions and the genes are mostly adjacent to each other. The mitochondrial genome encodes for 2 rRNAs, 22 tRNAs and 13 polypeptides involved in mitochondrial respiration[[20](#_ENREF_20)].

All the proteins synthesized from the mitochondrial genome participate at the respiratory chain (complex I, III, IV and V) and are located in the inner membrane of the mitochondria (MIM)[[21](#_ENREF_21)]. Among these 13 proteins, 7 are present in Complex I (NADH:ubiquinone oxidoreductase), 1 is part of Complex III (ubiquinone:cytochrome c oxidoreductase), 3 belong to Complex IV (cytochrome c:oxygen oxidoreductase) and 2 are part of Complex V (ATP synthase).

This means that the other proteins present in the mitochondria: *i.e.,* around 2000 proteins are the products of nuclear genes. As for any nuclear genes, the corresponding proteins are synthesized in the cytosol but for mitochondrial protein they are subsequently imported into the mitochondria. The import of these proteins requires that they find their way to the mitochondria. The journey of these precursors throughout the cytosol is supported by mitochondrial targeting elements that are involved in the transport of the precursors to specific receptors on the mitochondrial surface. This mechanism also depends on cytosolic factors[[22](#_ENREF_22)]. The most common mitochondrial targeting signal is a positively charged sequence that is located at the N-terminus of the protein[[23](#_ENREF_23)]. This sequence is named presequence. It addresses proteins to either the mitochondrial matrix, the inner membrane or the mitochondrial intermembrane space. This process is universal as an important part of proteins located in the mitochondrial outer membrane and many proteins of the inner membrane and the intermembrane space do not possess the classical presequence, but enclose internal cryptic targeting sequences in their amino acid sequence.

Once onto the mitochondrial outer membrane, mitochondrial protein precursors go through the lipid of this membrane with the intervention of the TOM complex (mitochondrial outer membrane preprotein translocase). The TOM complex is made of seven subunits and forms a channel allowing the crossing of the outer membrane[[24](#_ENREF_24)].

## *Dynamic*

Contrarily to the nucleus that is present as a single organelle in almost all cells, numerous peroxisomes and mitochondria are present and this number depends on the metabolic needs of the cells. The shape and the interconnection among and between these organelles also change depending on the metabolic environment[[25](#_ENREF_25)].

### Peroxisomal dynamic: The peroxisomes show high plasticity and a high capacity of adaptation in response to developmental, metabolic and environmental alterations. Their number, their protein content and their shape can be modulated. Peroxisomes number can increase either by division of pre-existing organelles or, at least under certain circumstances, from a de novo biosynthesis from the ER[[26](#_ENREF_26)]. While most of the biochemical processes involved in this dynamic process, the basic mechanisms and the nature of the control of these processes are still poorly understood[[27](#_ENREF_27)].

### Mitochondrial dynamic: Mitochondria are also dynamic organelles that permanently change their morphology, their size and their number. This dynamic is associated with the processes of fusion/fission that permit the fusion of 2 mitochondria or the division of a mitochondrion to give rise to 2 mitochondria, respectively[[28](#_ENREF_28)].

In the cell, mitochondrial fusion and fission participate in maintaining an adequate mitochondrial number. The fusion process allows mitochondria to combine their whole content. This process participates at the repair of mtDNA repair, the complementation of proteins and in the balance of metabolites. Fission also participates at the dynamic of mitochondria as this process participates in mtDNA segregation. It also may participate in the removal of altered mitochondria through the mitophagy process. Thus these mechanisms of fission/fusion also participate at a positive segregation of mitochondria.

#### (1) Fission of mitochondria. The key enzyme for fission of mitochondria is Drp1. This enzyme has a GTPase activity that promotes the fission of mitochondrial lipid membrane[[29](#_ENREF_29)]. Drp1 is the ortholog of Dnm1, a yeast enzyme. The action of Drp1 requires the translocation of this protein onto specific sites located in the OMM. Initially 2 proteins were described as docking proteins for Drp1, these first 2 proteins (Fis1 and Mff) are now joined by MiD49 and MiD51[[30](#_ENREF_30),[31](#_ENREF_31)].

Drp1 is a very controlled enzyme. Its intracellular level and its activity are regulated through various mechanisms including SUMOylation and phosphorylation[[32](#_ENREF_32),[33](#_ENREF_33)]. A recent review has listed and analyzed all the factors that participate at the regulation of mitochondrial fission[[34](#_ENREF_34)]. The authors emphasized on the regulatory role played by Bcl2 family proteins, and on the regulatory role of TNF-alpha and PKA.

#### (2) Fusion. Mitochondrial fusion involves Mfn1 and Mfn2 proteins[[35](#_ENREF_35)]. These mitofusins are large proteins located in the mitochondrial outer membrane. They exhibit a GTPase activity and allow the fusion of 2 MOM coming from 2 distinct mitochondria[[35](#_ENREF_35)]. OPA1, on the other hand, serves for the fusion of mitochondrial inner membrane[[36](#_ENREF_36)]. OPA1 is located in the outer side of the MIM[[37](#_ENREF_37)]. This process of fusion is highly regulated. To identify the physiological roles of these proteins mouse mutants have been realized. Mice carrying mutations in the *Opa1* gene were created and the resulting homozygous mice die during gestation[[38](#_ENREF_38)]. Mfn1- and Mfn2-deficient mice were made, these animals died at midgestation. Similarly, animal model carrying a deletion of the *Drp1* gene also died at the embryonic stage in mice[[39](#_ENREF_39)].

#### Comparison: While it seems clear that mitochondria and peroxisomes do not derive from a common ancestor, it may look surprising that the fission machinery is in a good part conserved between these organelles. The genetic deletion of Drp1 leads to peroxisomes and mitochondria with altered structure[[39](#_ENREF_39),[40](#_ENREF_40)]. The docking protein Mff and Fis1 are also important for both organelles[[41](#_ENREF_41)]. This suggest that whatever the origin of these organelles, they are able to interact with each other.

## *Organelle degradation*

Autophagy is a genetically programmed process that degrade and remove proteins present in the cell and also participate at the removal of damaged or excessive organelles through the initial formation of a structure known as the autophagosome; these structures will then fuse with lysosomes and their content degraded[[42](#_ENREF_42)].

The process of autophagy can be divided into five major steps: (1) development of the isolation membrane; (2) elongation of this membrane; (3) closure of the isolation membrane with formation of the autophagosome; (4) fusion between the autophagosome and lysosomes; and (5) Degradation of the autophagosome content[[43](#_ENREF_43)]. The overall mechanism is similar in yeast and in mammalian cells. In the yeast *Saccharomyces cerevisiae* nearly 30 autophagy related proteins (ATGs) have been identified[[44](#_ENREF_44),[45](#_ENREF_45)].

### Pexophagy: An autophagic process called pexophagy is responsible for regulating the number of peroxisomes in the cell[[46](#_ENREF_46)]. While, in mammalian cells, all the aspects of this programmed death of peroxisomes are not fully characterized yet, some aspects of this process have been described. It has been shown that Pex11p, Pex25p and Pex27p positively control this mechanism. It was also reported that Drp1 was directly involved in peroxisome division. The implication of Drp1a and Pex11 is not clear yet. Drp1 and Pex11-beta are overexpressed during this process but they did not seem to act directly in this process[[47](#_ENREF_47)].

The mechanisms involved have been extensively studied in yeast and have been recently reviewed[[48](#_ENREF_48)].

**Mitophagy:** Mitophagy is a biological process that allows the elimination of mitochondria using an autophagic process[[49](#_ENREF_49)]. During mitophagy, mitochondria are initially integrated into an autophagosome. Subsequently the autophagosome will fuse with lysosomes: this will lead to the degradation of its content. This mechanism was initially described in cells submitted to starvation but mitophagy also participate at the regulation of the number of mitochondria[[50](#_ENREF_50)].

# THE METABOLIC CROSSTALK

## *Reactive oxygen species production and scavenging*

Intense oxidation activities occur in both mitochondria and peroxisomes. These organelles are also directly implicated in the production of reactive oxygen species (ROS) trough physiological and extraphysiological processes. ROS are able to activate the inflammasome system. Inflammasome is a multi protein system that is coupled with caspase and interleukin activating systems. The activation of the inflammasome leads to a programmed cell death process and its dysregulation may play significant roles in various diseases[[51](#_ENREF_51)].

On the other hand, both the mitochondria and peroxisomes possess biological tools able to scavenge damaging reactive oxygen species[[52](#_ENREF_52)]. It is important to remind that ROS scavenging is crucial to limit cellular damage that these compounds may induce. It should also be notices that ROS physiologically contribute to various pathways from metabolism to signalling.

**ROS production in the peroxisome:** Many oxidases that produce several kinds of ROS including nitric oxide, superoxide radicals, hydroxyl radicals and hydrogen peroxide are present in the peroxisomes. H2O2 is mainly produced by oxidases that use many different types of substrates such as lactate, urate or oxalate[[53](#_ENREF_53)]. Peroxisomes are also potential sources of O2•− and NO•, through the enzymatic activity of xanthine oxidase and nitric oxide synthase[[54](#_ENREF_54)]. Xanthine oxidase also produces H2O2 and O2•− as byproducts[[54](#_ENREF_54)]. Nitric oxide synthases (NOS) are a broad family of enzymatic proteins: among those, the inducible form of NOS catalyzes the oxidation of L-arginine to NO• and citrulline in response to an induction by cytokines or endotoxins. This reaction requires O2, FAD, tetrahydrobiopterin, NADPH and FMN, and in the absence of adequate amount of substrates the enzyme can also produce important amounts of O2•−[[55](#_ENREF_55)]. Mammalian peroxisomes do not seem to contain enzymes that directly produce •OH or ONOO−[[54](#_ENREF_54)]. However, these ROS might be produce as secondary products from H2O2 and O2•− and NO•.

### ROS production in the mitochondria: The mitochondrial electron transport chain is also an important source of ROS. At the complex 1 level, superoxide ions are produced; these ions can be subsequently transformed into more potent ROS.

All together ROS can induce a vicious cycle that may lead to cell death. An excessive production of ROS is able to damage many macromolecules. Lipids, proteins and DNA can become targets for the ROS and an inadequate production of ROS will damage mitochondrial enzymes and mitochondrial DNA. Subsequently, these initial damages will induce an altered functioning of the electron transport system and finally increase the production of ROS. In addition, an overproduction of ROS in mitochondria may lead to the release of cytochrome c that will trigger apoptosis[[56](#_ENREF_56)].

### Scavenging of ROS in peroxisomes: Several antioxidant systems are present in the peroxisomes: catalase, Mn-SOD, Cu/Zn-SOD, peroxiredoxin I, epoxide hydrolase, peroxisomal membrane protein 20 (PMP 20) and glutathione peroxidase are present in the peroxisomal matrix and contribute to the defense against excessive amounts of ROS.

Catalase is the “historic” marker of peroxisomal activity and has a crucial protective function against the peroxides generated in peroxisomes and their toxicity[[57](#_ENREF_57)]. This common marker for peroxisomes metabolizes both H2O2 (catalytic function) and many other substrates such as ethanol, methanol, phenol and nitrites through its peroxidatic activity[[58](#_ENREF_58)]. Catalase is targeted to peroxisomes as it possesses a modified PTS1.

The relationship between oxidative stress and peroxisomal ROS scavenging system has been studied. It has been shown that an increase in oxygen concentration induced a moderate increase in the activity of enzymes involved in the scavenging of ROS[[59](#_ENREF_59)]. On the other hand, low levels of enzymes involved in ROS scavenging such as catalase, glutathione peroxidase and Mn-SOD are commonly observed in malignant cells. In cultured cells, it has been observed that an oxidative stress (UV irradiation, exposure to H2O2) induces a pronounced elongation of peroxisomes[[60](#_ENREF_60)] and a treatment with antioxidants blocked this elongation process. This elongation step seems a prerequisite for peroxisome division[[61](#_ENREF_61)]. This suggests that peroxisomes can be activated when an oxidative stress occurs arguing that peroxisomes may actively participate at the control of ROS accumulation in the cell.

### Scavenging of ROS in mitochondria: Mammalian mitochondria possess enzymes and non-enzymatic antioxidants systems for ROS scavenging[[62](#_ENREF_62)]. Enzymes with anti-oxidant activities such as MnSOD, glutathione reductase, glutathione-S-transferase and molecules with anti-oxidant properties such as thioredoxin, glutaredoxin, peroxiredoxins, cytochrome c, glutathione and NADH are present in the mitochondria and participate in limiting oxidative damages. These aspects have been extensively reviewed by Andreyev *et al*[[62](#_ENREF_62)] and the exposure of cells to a overproduction of ROS induces an increase in the activity of the mitochondrial defence system[[62](#_ENREF_62)].

#### Scavenging of ROS mobilizes both mitochondria and peroxisomes, both organelles possess similar systems for counteracting an excessive production of ROS. However, the underlying mechanisms involved in the recruitment of either system remain unknown.

## *Fatty acid metabolism in peroxisome and mitochondria*

One of the most remarkable common features between mitochondria and peroxisome is the cooperative function for fatty acids oxidation. Fatty acids play many important role in energy production, in inflammation and its resolution[[63](#_ENREF_63)], *etc*. In mammalian cells, both peroxisomes and mitochondria contain a beta-oxidative pathway. Beta oxidation is a key pathway for the breakthrough of fatty acids. In yeast and in plant, fatty acids oxidation occurs uniquely in peroxisomes[[64](#_ENREF_64)], mitochondria are not able to catabolize fatty acids. In mammalian cells, both peroxisomes and mitochondria can beta-oxidize fatty acids. These two pathways share many similarities especially in terms of enzymatic reactions but they differ in terms of substrates and of enzymatic reactions. Furthermore, the metabolic implication and the final products are not the same in mitochondria and in peroxisomes[[65](#_ENREF_65)] (Table 1).

The overall pathways are pretty much the same in both the mitochondria and the peroxisomes: fatty acids are first activated as acyl-CoA and then the activated fatty acid (acylCoA) is dehygrogenated. This represents the first step of the beta oxidation. Then the hydration of the double bound occurs and is followed by a dehydrogenation and a cleavage. This allows to remove 2 C from C:n acyl CoA leading to the formation of a C:n-2 acyl CoA.

**Peroxisomal fatty acid oxidation:** In peroxisomes, the very first step of fatty acid oxidation is the reaction of conversion of the fatty acid into acyl-CoA. The so-formed acylCoA can be directed to the peroxisomal matrix after crossing the peroxisomal membrane, this implies the intervention of an ABC transporter (ABCD1)[[66](#_ENREF_66)]. Once in the peroxisomal matrix, the beta oxidation starts by a reaction catalyzed by an acyl-CoA oxidase (ACOX), an enzyme that is often considered as a key element. During the reaction catalyzed by ACOX, electrons provided by FAD are transferred to oxygen, this leads to the formation of H2O2. In the mitochondrial pathway, the reaction is pretty much the same except that the electrons are transferred to the respiratory chain. ACOX isoforms of ACOX have been described in mammals, all are dimeric proteins. The next reaction is catalyzed by an enzyme known as the multifunctional enzyme (MFE), this enzyme realizes both, the second and the third reactions of the peroxisomal beta oxidation. In the peroxisomal matrix, two MFE are present: MFE-1 (also named L-bifunctional protein, LBP) and MFE-2 (D-bifunctional protein, DBP). Both catalyzed the formation of 3-ketoacyl-CoA intermediates from substrates mirror image stereochemistry. These two enzymes catalyse the same reaction but do not show any similarities in terms of structure[[67](#_ENREF_67)]. Finally, the last reaction in this pathway is catalyzed by the thiolase. This enzyme catalyzes the thiolytic cleavage of 3-ketoacyl-CoA to acetyl-CoA and Cn-2-acyl-CoA[[68](#_ENREF_68)]. The peroxisomal beta oxidation is incomplete, *i.e.,* it ends up with shortened acyl-CoA (medium chain, one of the common being the octanoyl-CoA). These compounds are converted into acyl-carnitine by the carnitine octanoyl transferase and can leave the peroxisome[[69](#_ENREF_69)].

Peroxisomal beta oxidation mainly concerns very long chain fatty acids (> C22), branched fatty acids, as well as some prostaglandins and leukotrienes. While mitochondrial beta oxidation relies on the energy needs of the cells, peroxisomal beta oxidation does not. Peroxisomal beta oxidation is essentially involved in biosynthesis pathways while mitochondrial pathway is related to catabolism and energy production. The end product of peroxisomal oxidation of fatty acid is H2O2, in the same time the mitochondrial beta oxidation is coupled with the production of ATP (Figure 1).

### Mitochondrial fatty acid oxidation: Mitochondrial beta oxidation mainly interests long chain fatty acid provided by food stuff. This pathway allows to supply acetyl-CoA used, at least in part, for ATP synthesis (Figure 1).

As for the peroxisomal pathway, mitochondrial fatty acid beta oxidation requires the initial esterification of fatty acids into acyl-CoA and then the entry of the acyl CoAs into the mitochondrial matrix. The activation of fatty acid into acyl-CoA is catalyzed by acylCoA synthases. These are ATP-dependent enzymes located in the cytosol. According to the size of the fatty acid, several acyl-CoA synthases with various affinity for different types of substrates carry these reactions. Are present in the cytosol: short-chain acyl-CoA, medium-chain acyl-CoA and long-chain acyl-CoA. Once converted into acyl-CoA, these compounds can cross the mitochondrial membranes: short and medium-chain acyl-Coas seem to be able to freely cross the mitochondrial membrane while for long chain acyls, the crossing of the mitochondrial double membrane system requires the intervention of the carnitine system. This system consists in two acyl-transferases: the carnitine palmitoyltransferase 1 and 2 and a transporter the carnitine acylcarnitine translocase. It also strictly requires the presence of L-carnitine as an essential part of this system[[70](#_ENREF_70)].

Four enzymatic reactions compose the mitochondrial beta oxidation. The initial reaction is catalyzed by the acyl-CoA dehydrogenase, and the following steps are catalyzed by the 2-enoyl-CoA hydratase, the 3-hydroxyacyl-CoA dehydrogenase and the 3-oxoacyl-CoA thiolase, successively. The overall goal of mitochondrial beta oxidation is the production of energy (mainly as ATP). The beta oxidation itself consists in successive cycles (consisting in the 4 enzymatic reactions described above) leading to the removal of 2C from a C:n acyl-CoA, generating a C:n-2 acyl-CoA. The end-product of this pathways is acetyl-CoA and the mitochondrial beta oxidation is metabolicaly coupled with the respiratory chain and the tricarboxyilic acid cycle[[71](#_ENREF_71)].

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# CONCLUSION

Peroxisomes and mitochondria do not derive from a common ancestor, the origin of mitochondria is endosymbiotic, while peroxisomes derive from endoplasmic reticulum, however several proteins are common among these organelles and they share not only a few enzymes but also full metabolic pathways. Their divisions are closely related: using identical factors and enzymes. This suggests an efficient crosstalk between peroxisomes and mitochondria.

However, the physiological function of the 2 organelles are different. In terms of fatty acid metabolism, mitochondria degrade the majority of long-chain fatty acids to supply acetyl-CoA for the production of ATP and for anabolic reactions, peroxisomal beta oxidation on the other hand is more involved in anabolic processes, but together, they work together for the metabolism of fatty acids. Peroxisomes and mitochondria are independent organelles but their interaction is necessary for an optimal function of the cell.

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**Figure 1 Mitochondrial and peroxisomal beta oxidations.** The reactions involved in mitochondria are presented on the left side of the figure and the reactions occurring in peroxisome in the right part of the figure.

**Table 1 Comparison between mitochondrial and peroxisomal beta oxidations**

|  |  |  |
| --- | --- | --- |
|  | **Mitochondrial** | **Peroxisomal** |
| Substrates | LCFA | VLCFA, branched FA, leukotrienes |
| Entry system | Carnitine system (including CPT1, CACT and CPT2) | ABC tranporters |
| End products | Acetyl-CoA(and subsequently ATP) | Acetyl-CoA and MCFA(and subsequently H202) |
| Physiological implications | Energy production  | Biosynthesis of specific fatty acids *e.g.*, DHA |

LCFA: Long-chain fatty acids; VLCFA: Very long chain fatty acids; FA: Fatty acids; CPT: Carnitine palmitoyltransferase; CACT: Carnitine-acylcarnitine translocase; ABC: ATP-binding cassette; MCFA: Medium-chain fatty acids; DHA: Docosahexaenoic acid.