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REVIEW

Crosstalk 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 acid 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 great plasticity and high potency to adapt their form and number according to cell requirements. Their functions are connected, and any alteration in the function of mitochondria may induce changes in peroxisomal physiology. The objective of this paper was to highlight the interconnection and the crosstalk existing between mitochondria and peroxisomes. Special emphasis was placed on the best known connections between these organelles: origin, structure, and metabolic interconnections.

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

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 cell of higher organisms. They share some properties (such as size and function), but differ in terms of origin, structure, and physiological roles. With the current knowledge of the subject, 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, while peroxisomes are bordered by a single membrane system. In the cell, the number of peroxisomes and mitochondria varies according to the cell type (*e.g.*, mitochondria are very abundant in brown adipose tissue, but relatively scarce 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 high plasticity and are able to adopt various shapes depending on the cell's 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 supposedly of endosymbiotic origin[1]. However, this theory is no longer considered, as many reports have suggested that peroxisomes are instead derived from the endoplasmic reticulum[2]. This has been especially shown in experiments in which cells with no peroxisomes were able to engender new peroxisomes[3]. In fact, several studies have established that peroxisomes can be formed from pre-existing peroxisomes, as well as *de novo* from the endoplasmic reticulum (ER) under certain circumstances[4,5].

When looking at the origin of proteins present in peroxisomes, two categories of proteins can be described: those of a prokaryotic origin and those of an eukaryotic origin[6]. Eukaryotic originating proteins are essentially involved in peroxisomal biogenesis, while peroxisomal proteins originating from bacteria appear to be 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]. About 25% of proteins in peroxisomes have an origin that is difficult to precisely define. This suggested that some peroxisomal proteins have evolved from mitochondrial proteins. Many proteins are present in both organelles, which suggests that these enzymes may be retargeted from mitochondria to peroxisomes[8]. This would indicate that peroxisome formation is influenced by mitochondria.

However, if peroxisomes are derived from ER, why are mitochondrial proteins included in the organelle and why are mitochondria not assuming these functions? What are the links between ER and mitochondria/peroxisomes? These questions remain as yet 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 entered eukaryotic cells and became organelles. However, this theory has not always been accepted by the scientific community; it was first proposed for plastids at the beginning of the 20th century, but was only accepted for mitochondria for a few years before being rejected by cell biologists. It was not until the 1960's that the theory was reconsidered and more widely accepted[9].

This theory is based on several facts: (1) endosymbiotic organelles retain a small genome encoding several dozen proteins. Regardless of this genome reduction, mitochondria harbor at least 2000 proteins[10] 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.,* and (2) the endosymbiotic gene transfer. This process of gene transfer occurs during the evolution of the organism and, in time, will become a protein import mechanism, such as the mitochondrial import system for proteins. This closes the endosymbiotic process circle; the organelle carries out functions that the eukaryotic cell is unable to realize, while the eukaryotic cell provides extra proteins for the organelle. This process gives evolutionary advantages to both the eukaryotic cell and the "new" organelle[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 peroxisomes: Proteins present in the peroxisome are strictly dependent on nuclear genes and to an import system. Peroxisomes do not possess any DNA sequences and are not able to synthesize any proteins. They rely on cytosolic synthesis from nuclear genes and on the import of these proteins into the peroxisome. This protein import 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 (Pex)[12]. Pex proteins control peroxisome structure, division, and inheritance. Over a dozen peroxins have

been described[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]. 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[15,16]. This is a method of peroxisomal import unique to several species, such as the nematode *Caenorhabditis elegans*[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].

Protein import into mitochondria: Mammalian mitochondria possess their own genome, which is a circular DNA chain of about 16000 base pairs. In animal mitochondria, the genetic code is slightly different from the "universal" code[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 rRNA, 22 tRNA, and 13 polypeptides involved in mitochondrial respiration[20].

All proteins synthesized from the mitochondrial genome participate in the respiratory chain (complex Ⅰ, Ⅲ, Ⅳ, and Ⅴ) and are located in the inner membrane of the mitochondria[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, although mitochondrial proteins 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 involved in the transport of the precursors to specific receptors on the mitochondrial surface. This mechanism also depends on cytosolic factors[22]. The most common mitochondrial targeting signal is a positively-charged sequence, known as the presequence, which is located at the N-terminus of the protein[23]. The presequence addresses proteins to 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, although many proteins of the inner membrane and the intermembrane space do not possess the classical presequence, and instead 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 that allows for the crossing of the outer membrane[24].

Dynamic

Contrarily to the nucleus that is present as a single organelle in almost all cells, numerous peroxisomes and mitochondria are present, with the actual number depending 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].

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

Mitochondrial dynamic: Mitochondria are also dynamic organelles that permanently change their morphology, size, and number. This dynamic is associated with the processes of fusion/fission that permit the fusion of two mitochondria or the division of a mitochondrion to give rise to two mitochondria, respectively[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 in mtDNA repair, complementation of proteins, and in the balance of metabolites. Fission also participates in the dynamic of mitochondria, as this process participates in mtDNA segregation. It may also participate in the removal of altered mitochondria through the process of mitophagy. Additionally, these mechanisms of fission/fusion participate in the positive segregation 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]. 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 outer mitochondrial membrane. Although initially only two proteins were described as docking proteins for Drp1 (Fis1 and Mff), another two (MiD49 and MiD51) were later discovered[30,31].

Drp1 is a very controlled enzyme. Its intracellular level and activity are regulated through various mechanisms, including SUMOylation and phosphorylation[32,33]. A recent review has listed and analyzed all of the factors that participate in the regulation of mitochondrial

fission[34]. The authors emphasized the regulatory role played by Bcl2 family proteins and the regulatory role of TNF-alpha and PKA.

Mitochondrial fusion involves Mfn1 and Mfn2 proteins[35]. These mitofusins are large proteins located in the mitochondrial outer membrane. They exhibit GTPase activity and allow the fusion of two outer mitochondrial membranes coming from two distinct mitochondria[35]. OPA1, on the other hand, is used in the fusion of mitochondrial inner membranes, and is located in the outer side of the inner mitochondrial membrane[36,37]. 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, with the resulting homozygous mice dying during gestation[38]. Mfn1- and Mfn2-deficient mice were made, which die during midgestation. Similarly, animal models carrying a deletion of the *Drp1* gene also died at the embryonic stage in mice[39].

Comparison: While it seems clear that mitochondria and peroxisomes do not derive from a common ancestor, it may be 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 an altered structure[39,40]. The docking proteins Mff and Fis1 are also important for both organelles[41]. This suggests that whatever the origin of these organelles, they are able to interact with each other.

Organelle degradation

Autophagy is a genetically programmed process that degrades and removes proteins present in the cell, as well as participating in 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 have their content degraded[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 the formation of the autophagosome; (4) Fusion between the autophagosome and lysosomes; and (5) Degradation of the autophagosome content[43]. The overall mechanism is similar in yeast and mammalian cells. In the yeast *Saccharomyces cerevisiae*, nearly 30 autophagy-related proteins have been identified[44,45].

Pexophagy: An autophagic process called pexophagy is responsible for regulating the number of peroxisomes in the cell[46]. While, in mammalian cells, all aspects of this programmed peroxisome death are not yet fully characterized, 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 upon it[47].

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

Mitophagy: Mitophagy is a biological process that allows the elimination of mitochondria using an autophagic process[49]. During mitophagy, mitochondria are initially integrated into an autophagosome, which subsequently fuses with lysosomes and leads to the degradation of its content. This mechanism was initially described in cells undergoing starvation, but mitophagy also participates in the regulation of mitochondrion numbers[50].

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) through physiological and extraphysiological processes. ROS are able to activate the inflammasome system, which is a multiprotein system coupled with the caspase and interleukin activating systems. The activation of inflammasome leads to a programmed cell death process, and its dysregulation may play a significant role in various diseases[51].

On the other hand, both mitochondria and peroxisomes possess biological tools that allow for the scavenging of damaging reactive oxygen species[52]. It is important to note that ROS scavenging is crucial in limiting the cellular damage that these compounds may induce. It should also be noticed that ROS physiologically contribute to various pathways, including those involved in metabolism and signaling.

ROS production in peroxisomes: Many oxidases that produce several kinds of ROS (including nitric oxide, superoxide radicals, hydroxyl radicals, and hydrogen peroxide) are present in peroxisomes. H_2O_2 is mainly produced by oxidases that use many different types of substrates, such as lactate, urate, or oxalate[53]. Peroxisomes are also potential sources of $O_2\bullet^-$ and NO•, *via* the enzymatic activity of xanthine oxidase and nitric oxide synthase[54]. Xanthine oxidase also produces H_2O_2 and $O_2\bullet^-$ as byproducts[54]. Nitric oxide synthases (NOS) are a broad family of enzymatic proteins, with the inducible form of NOS catalyzing the oxidation of L-arginine to NO• and citrulline in response to induction by cytokines or endotoxins. This reaction requires O_2, FAD, tetrahydrobiopterin, NADPH, and FMN and, in the absence of adequate amounts of substrates, the enzyme can also produce important amounts of $O_2\bullet^-$[55]. Mammalian peroxisomes do not seem to contain enzymes that directly produce •OH or $ONOO^-$[54]. However, these ROS might be able to produce them as secondary products from H_2O_2, $O_2\bullet^-$, and NO•.

ROS production in 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.

ROS can induce a vicious cycle that may lead to cell death. Excessive production of ROS is able to damage many macromolecules. Lipids, proteins, and DNA can become targets for 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 ultimately increase the production of ROS. In addition, overproduction of ROS in mitochondria may lead to the release of cytochrome c and the triggering of apoptosis[56].

Scavenging of ROS in peroxisomes: Several anti-oxidant systems are present in peroxisomes: catalase, Mn-SOD, Cu/Zn-SOD, peroxiredoxin Ⅰ, epoxide hydrolase, peroxisomal membrane protein 20, and glutathione peroxidase are present in the peroxisomal matrix and contribute to the defense against excessive 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]. This common marker for peroxisomes metabolizes both H_2O_2 (catalytic function) and many other substrates, such as ethanol, methanol, phenol, and nitrites, through its peroxidatic activity[58]. Catalase is targeted to peroxisomes, as it possesses modified PTS1.

The relationship between oxidative stress and the 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]. 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 oxidative stress (*i.e.*, UV irradiation or exposure to H_2O_2) induces pronounced elongation of peroxisomes[60], with antioxidant treatment blocking this elongation process. This elongation step seems a prerequisite for peroxisome division[61]. This suggests that peroxisomes can be activated when oxidative stress occurs, indicating that peroxisomes may actively participate in 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]. Enzymes with antioxidant 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 damage; these aspects have been extensively reviewed by Andreyev *et al*[62]. Exposure of cells to a overproduction of ROS induces an increase in activity of the mitochondrial defense system[62].

Scavenging of ROS mobilizes both mitochondria and peroxisomes, as both organelles possess similar systems for counteracting 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 acid oxidation. Fatty acids play many important role in energy production, inflammation and its resolution[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 yeasts and plants, fatty acid oxidation occurs uniquely in peroxisomes[64], as 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 enzymatic reactions. Furthermore, the metabolic implication and final products are not the same in mitochondria and peroxisomes[65] (Table 1).

The overall pathways are essentially the same in both mitochondria and peroxisomes: Fatty acids are first activated as acyl-CoA and then the activated fatty acid (acyl-CoA) is dehydrogenated. This represents the first step of beta-oxidation. Hydration of the double bound then occurs, and is followed by dehydrogenation and cleavage. This allows for the removal of 2 C from C:n acyl-CoA, leading to the formation of C:n-2 acyl-CoA.

Peroxisomal fatty acid oxidation: In peroxisomes, the very first step of fatty acid oxidation is the conversion reaction of fatty acid into acyl-CoA. The thus-formed acyl-CoA can be directed to the peroxisomal matrix after crossing the peroxisomal membrane, with the intervention of an ABC transporter (ABCD1) being implied[66]. Once in the peroxisomal matrix, beta-oxidation starts *via* a reaction catalyzed by acyl-CoA oxidase (ACOX), an enzyme that is often considered a key element of the process. During the reaction catalyzed by ACOX, electrons provided by FAD are transferred to oxygen, thereby leading to the formation of H_2O_2. In the mitochondrial pathway, the reaction is essentially the same, with the exception that the electrons are transferred to the respiratory chain instead. ACOX isoforms have been described in mammals and are all dimeric proteins. The next reaction is catalyzed by an enzyme known as the multifunctional enzyme (MFE), which realizes both the second and the third reactions of peroxisomal beta-oxidation. In the peroxisomal matrix, two MFE are present: MFE-1 [L-bifunctional protein (LBP)] and MFE-2 [D-bifunctional protein (DBP)]; both

Table 1 Comparison between mitochondrial and peroxisomal beta-oxidation

	Mitochondrial	Peroxisomal
Substrates	LCFA	VLCFA, branched FA, leukotrienes
Entry system	Carnitine system (including CPT1, CACT and CPT2)	ABC transporters
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.

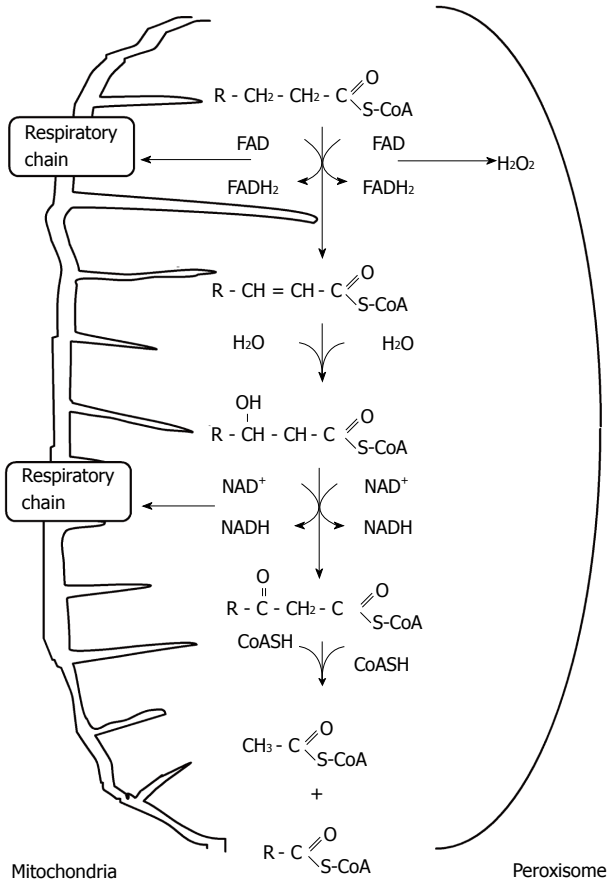

Figure 1 Mitochondrial and peroxisomal beta-oxidations. The reactions involved in mitochondria are presented on the left side of the figure, while the reactions occurring in peroxisome are on the right side of the figure.

catalyze the formation of 3-ketoacyl-CoA intermediates from substrate mirror image stereochemistry. Although the two enzymes catalyze the same reaction, they do not show any similarities in terms of structure[67]. The final reaction in this pathway is catalyzed by thiolase. This enzyme catalyzes the thiolytic cleavage of 3-ketoacyl-CoA to acetyl-CoA and Cn-2-acyl-CoA[68]. The peroxisomal beta-oxidation is incomplete, as it climaxes with shortened acyl-CoA (medium chain, with one of the common being octanoyl-CoA). These compounds are converted into acylcarnitine by carnitine octanoyl transferase, and can then leave the peroxisome[69].

Peroxisomal beta-oxidation mainly concerns very long chain fatty acids (> C22) and 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 the mitochondrial pathway is related to catabolism and energy production. The end product of peroxisomal oxidation of fatty acid is H_2O_2, while mitochondrial beta-oxidation is coupled with the production of ATP (Figure 1).

Mitochondrial fatty acid oxidation: Mitochondrial beta-oxidation mainly involves long chain fatty acids provided by foodstuff. This pathway supplies the 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 acyl-CoA into the mitochondrial matrix. The activation of fatty acid into acyl-CoA is catalyzed by acyl-CoA synthases, which are ATP-dependent enzymes located in the cytosol. According to the size of the fatty acid, several acyl-CoA synthases with various affinities for different types of substrates carry out these reactions. The following 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 of two acyl-transferases (carnitine palmitoyltransferase 1 and 2) and the transporter carnitine acylcarnitine translocase. The presence of L-carnitine is also required as an essential part of this system[70].

Four enzymatic reactions compose the mitochondrial beta-oxidation. The initial reaction is catalyzed by acyl-CoA dehydrogenase, while the subsequent steps are catalyzed by 2-enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and 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 of successive cycles (consisting of the four aforementioned enzymatic reactions) leading to the removal of 2C from C: n acyl-CoA, thereby generating C: n-2 acyl-CoA. The end-product of this pathway is acetyl-CoA, while mitochondrial beta-oxidation is metabolically coupled with the respiratory chain and tricarboxylic acid

cycle[71].

CONCLUSION

While peroxisomes and mitochondria do not derive from a common ancestor (the origin of mitochondria is endosymbiotic, while peroxisomes derive from the endoplasmic reticulum), 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 and use identical factors and enzymes. This suggests efficient crosstalk between peroxisomes and mitochondria.

However, the physiological function of the two 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, while peroxisomal beta-oxidation is more involved in anabolic processes. However, the two organelles work together for the metabolism of fatty acids. Peroxisomes and mitochondria are independent organelles but their interaction is necessary for optimal function of the cell.

REFERENCES

1 **de Duve D**. The peroxisome: a new cytoplasmic organelle. *Proc R Soc Lond B Biol Sci* 1969; **173**: 71-83 [PMID: 4389354 DOI: 10.1098/rspb.1969.0039]

2 **Dimitrov L**, Lam SK, Schekman R. The role of the endoplasmic reticulum in peroxisome biogenesis. *Cold Spring Harb Perspect Biol* 2013; **5**: a013243 [PMID: 23637287 DOI: 10.1101/cshperspect.a013243]

3 **South ST**, Gould SJ. Peroxisome synthesis in the absence of preexisting peroxisomes. *J Cell Biol* 1999; **144**: 255-266 [PMID: 9922452 DOI: 10.1083/jcb.144.2.255]

4 **Tam YY**, Fagarasanu A, Fagarasanu M, Rachubinski RA. Pex3p initiates the formation of a preperoxisomal compartment from a subdomain of the endoplasmic reticulum in Saccharomyces cerevisiae. *J Biol Chem* 2005; **280**: 34933-34939 [PMID: 16087670 DOI: 10.1074/jbc.M506208200]

5 **Hoepfner D**, Schildknegt D, Braakman I, Philippsen P, Tabak HF. Contribution of the endoplasmic reticulum to peroxisome formation. *Cell* 2005; **122**: 85-95 [PMID: 16009135 DOI: 10.1016/j.cell.2005.04.025]

6 **Gabaldón T**, Snel B, van Zimmeren F, Hemrika W, Tabak H, Huynen MA. Origin and evolution of the peroxisomal proteome. *Biol Direct* 2006; **1**: 8 [PMID: 16556314 DOI: 10.1186/1745-6150-1-8]

7 **Kim PK**, Hettema EH. Multiple pathways for protein transport to peroxisomes. *J Mol Biol* 2015; **427**: 1176-1190 [PMID: 25681696 DOI: 10.1016/j.jmb.2015.02.005]

8 **Tabak HF**, Hoepfner D, Zand Av, Geuze HJ, Braakman I, Huynen MA. Formation of peroxisomes: present and past. *Biochim Biophys Acta* 2006; **1763**: 1647-1654 [PMID: 17030445]

9 **Bölker M**. Editorial overview: growth and development: eukaryotes. *Curr Opin Microbiol* 2014; **22**: v-vii [PMID: 25467419 DOI: 10.1016/j.mib.2014.10.006]

10 **Meisinger C**, Sickmann A, Pfanner N. The mitochondrial proteome: from inventory to function. *Cell* 2008; **134**: 22-24 [PMID: 18614007 DOI: 10.1016/j.cell.2008.06.043]

11 **Martin W**, Hoffmeister M, Rotte C, Henze K. An overview of endosymbiotic models for the origins of eukaryotes, their ATP-producing organelles (mitochondria and hydrogenosomes), and their heterotrophic lifestyle. *Biol Chem* 2001; **382**: 1521-1539 [PMID: 11767942 DOI: 10.1515/BC.2001.187]

12 **Shimozawa N**, Imamura A, Zhang Z, Suzuki Y, Orii T, Tsukamoto T, Osumi T, Fujiki Y, Wanders RJ, Besley G, Kondo N. Defective PEX gene products correlate with the protein import, biochemical abnormalities, and phenotypic heterogeneity in peroxisome biogenesis disorders. *J Med Genet* 1999; **36**: 779-781 [PMID: 10528859]

13 **Fujiki Y**, Nashiro C, Miyata N, Tamura S, Okumoto K. New insights into dynamic and functional assembly of the AAA peroxins, Pex1p and Pex6p, and their membrane receptor Pex26p in shuttling of PTS1-receptor Pex5p during peroxisome biogenesis. *Biochim Biophys Acta* 2012; **1823**: 145-149 [PMID: 22079764 DOI: 10.1016/j.bbamcr.2011.10.012]

14 **Otera H**, Okumoto K, Tateishi K, Ikoma Y, Matsuda E, Nishimura M, Tsukamoto T, Osumi T, Ohashi K, Higuchi O, Fujiki Y. Peroxisome targeting signal type 1 (PTS1) receptor is involved in import of both PTS1 and PTS2: studies with PEX5-defective CHO cell mutants. *Mol Cell Biol* 1998; **18**: 388-399 [PMID: 9418886]

15 **Gunkel K**, van Dijk R, Veenhuis M, van der Klei IJ. Routing of *Hansenula polymorpha* alcohol oxidase: an alternative peroxisomal protein-sorting machinery. *Mol Biol Cell* 2004; **15**: 1347-1355 [PMID: 14699075 DOI: 10.1091/mbc.E03-04-0258]

16 **Gatto GJ**, Maynard EL, Guerrerio AL, Geisbrecht BV, Gould SJ, Berg JM. Correlating structure and affinity for PEX5: PTS1 complexes. *Biochemistry* 2003; **42**: 1660-1666 [PMID: 12578380 DOI: 10.1021/bi027034z]

17 **Motley AM**, Hettema EH, Ketting R, Plasterk R, Tabak HF. *Caenorhabditis elegans* has a single pathway to target matrix proteins to peroxisomes. *EMBO Rep* 2000; **1**: 40-46 [PMID: 11256623 DOI: 10.1038/sj.embor.embor626]

18 **Mukai S**, Fujiki Y. Molecular mechanisms of import of peroxisome-targeting signal type 2 (PTS2) proteins by PTS2 receptor Pex7p and PTS1 receptor Pex5pL. *J Biol Chem* 2006; **281**: 37311-37320 [PMID: 17040904]

19 **Osawa S**, Jukes TH, Watanabe K, Muto A. Recent evidence for evolution of the genetic code. *Microbiol Rev* 1992; **56**: 229-264 [PMID: 1579111]

20 **Christian BE**, Spremulli LL. Mechanism of protein biosynthesis in mammalian mitochondria. *Biochim Biophys Acta* 2012; **1819**: 1035-1054 [PMID: 22172991 DOI: 10.1016/j.bbagrm.2011.11.009]

21 **Taanman JW**. The mitochondrial genome: structure, transcription, translation and replication. *Biochim Biophys Acta* 1999; **1410**: 103-123 [PMID: 10076021]

22 **Yogev O**, Pines O. Dual targeting of mitochondrial proteins: mechanism, regulation and function. *Biochim Biophys Acta* 2011; **1808**: 1012-1020 [PMID: 20637721 DOI: 10.1016/j.bbamem.2010.07.004]

23 **Harbauer AB**, Zahedi RP, Sickmann A, Pfanner N, Meisinger C. The protein import machinery of mitochondria-a regulatory hub in metabolism, stress, and disease. *Cell Metab* 2014; **19**: 357-372 [PMID: 24561263 DOI: 10.1016/j.cmet.2014.01.010]

24 **Romero-Ruiz M**, Mahendran KR, Eckert R, Winterhalter M, Nussberger S. Interactions of mitochondrial presequence peptides with the mitochondrial outer membrane preprotein translocase TOM. *Biophys J* 2010; **99**: 774-781 [PMID: 20682254 DOI: 10.1016/j.bpj.2010.05.010]

25 **Reddy PH**, Reddy TP, Manczak M, Calkins MJ, Shirendeb U, Mao P. Dynamin-related protein 1 and mitochondrial fragmentation in neurodegenerative diseases. *Brain Res Rev* 2011; **67**: 103-118 [PMID: 21145355 DOI: 10.1016/j.brainresrev.2010.11.004]

26 **Schrader M**, Bonekamp NA, Islinger M. Fission and proliferation of peroxisomes. *Biochim Biophys Acta* 2012; **1822**: 1343-1357 [PMID: 22240198 DOI: 10.1016/j.bbadis.2011.12.014]

27 **Bonekamp NA**, Grille S, Cardoso MJ, Almeida M, Aroso M, Gomes S, Magalhaes AC, Ribeiro D, Islinger M, Schrader M. Self-interaction of human Pex11pβ during peroxisomal growth and division. *PLoS One* 2013; **8**: e53424 [PMID: 23308220 DOI: 10.1371/journal.pone.0053424]

28 **Polyakov VY**, Soukhomlinova MY, Fais D. Fusion, fragmentation, and fission of mitochondria. *Biochemistry* (Mosc) 2003; **68**: 838-849 [PMID: 12948383]

29 **Wang L**, Ye X, Zhao Q, Zhou Z, Dan J, Zhu Y, Chen Q, Liu L.

Drp1 is dispensable for mitochondria biogenesis in induction to pluripotency but required for differentiation of embryonic stem cells. *Stem Cells Dev* 2014; **23**: 2422-2434 [PMID: 24937776 DOI: 10.1089/scd.2014.0059]
30 **Palmer CS**, Elgass KD, Parton RG, Osellame LD, Stojanovski D, Ryan MT. Adaptor proteins MiD49 and MiD51 can act independently of Mff and Fis1 in Drp1 recruitment and are specific for mitochondrial fission. *J Biol Chem* 2013; **288**: 27584-27593 [PMID: 23921378 DOI: 10.1074/jbc.M113.479873]
31 **Losón OC**, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. *Mol Biol Cell* 2013; **24**: 659-667 [PMID: 23283981 DOI: 10.1091/mbc.E12-10-0721]
32 **Wasiak S**, Zunino R, McBride HM. Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death. *J Cell Biol* 2007; **177**: 439-450 [PMID: 17470634]
33 **Cribbs JT**, Strack S. Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death. *EMBO Rep* 2007; **8**: 939-944 [PMID: 17721437]
34 **Dhingra R**, Kirshenbaum LA. Regulation of mitochondrial dynamics and cell fate. *Circ J* 2014; **78**: 803-810 [PMID: 24647412 DOI: 10.1253/circj.CJ-14-0240]
35 **Chen H**, Detmer SA, Ewald AJ, Griffin EE, Fraser SE, Chan DC. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. *J Cell Biol* 2003; **160**: 189-200 [PMID: 12527753 DOI: 10.1083/jcb.200211046]
36 **Song Z**, Chen H, Fiket M, Alexander C, Chan DC. OPA1 processing controls mitochondrial fusion and is regulated by mRNA splicing, membrane potential, and Yme1L. *J Cell Biol* 2007; **178**: 749-755 [PMID: 17709429]
37 **Mishra P**, Carelli V, Manfredi G, Chan DC. Proteolytic cleavage of Opa1 stimulates mitochondrial inner membrane fusion and couples fusion to oxidative phosphorylation. *Cell Metab* 2014; **19**: 630-641 [PMID: 24703695 DOI: 10.1016/j.cmet.2014.03.011]
38 **Davies VJ**, Hollins AJ, Piechota MJ, Yip W, Davies JR, White KE, Nicols PP, Boulton ME, Votruba M. Opa1 deficiency in a mouse model of autosomal dominant optic atrophy impairs mitochondrial morphology, optic nerve structure and visual function. *Hum Mol Genet* 2007; **16**: 1307-1318 [PMID: 17428816]
39 **Ishihara N**, Nomura M, Jofuku A, Kato H, Suzuki SO, Masuda K, Otera H, Nakanishi Y, Nonaka I, Goto Y, Taguchi N, Morinaga H, Maeda M, Takayanagi R, Yokota S, Mihara K. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. *Nat Cell Biol* 2009; **11**: 958-966 [PMID: 19578372 DOI: 10.1038/ncb1907]
40 **Kobayashi S**, Tanaka A, Fujiki Y. Fis1, DLP1, and Pex11p coordinately regulate peroxisome morphogenesis. *Exp Cell Res* 2007; **313**: 1675-1686 [PMID: 17408615 DOI: 10.1016/j.yexcr.2007.02.028]
41 **Mohanty A**, McBride HM. Emerging roles of mitochondria in the evolution, biogenesis, and function of peroxisomes. *Front Physiol* 2013; **4**: 268 [PMID: 24133452 DOI: 10.3389/fphys.2013.00268]
42 **Köchl R**, Hu XW, Chan EY, Tooze SA. Microtubules facilitate autophagosome formation and fusion of autophagosomes with endosomes. *Traffic* 2006; **7**: 129-145 [PMID: 16420522]
43 **Tanida I**. Autophagosome formation and molecular mechanism of autophagy. *Antioxid Redox Signal* 2011; **14**: 2201-2214 [PMID: 20712405 DOI: 10.1089/ars.2010.3482]
44 **Ma J**, Bharucha N, Dobry CJ, Frisch RL, Lawson S, Kumar A. Localization of autophagy-related proteins in yeast using a versatile plasmid-based resource of fluorescent protein fusions. *Autophagy* 2008; **4**: 792-800 [PMID: 18497569 DOI: 10.4161/auto.6308]
45 **Klionsky DJ**, Cregg JM, Dunn WA, Emr SD, Sakai Y, Sandoval IV, Sibirny A, Subramani S, Thumm M, Veenhuis M, Ohsumi Y. A unified nomenclature for yeast autophagy-related genes. *Dev Cell* 2003; **5**: 539-545 [PMID: 14536056 DOI: 10.1016/S1534-5807(03)00296-X]
46 **Sakai Y**, Oku M, van der Klei IJ, Kiel JA. Pexophagy: autophagic degradation of peroxisomes. *Biochim Biophys Acta* 2006; **1763**: 1767-1775 [PMID: 17005271]
47 **Li X**, Gould SJ. The dynamin-like GTPase DLP1 is essential for peroxisome division and is recruited to peroxisomes in part by PEX11. *J Biol Chem* 2003; **278**: 17012-17020 [PMID: 12618434 DOI: 10.1074/jbc.M212031200]
48 **Till A**, Lakhani R, Burnett SF, Subramani S. Pexophagy: the selective degradation of peroxisomes. *Int J Cell Biol* 2012; **2012**: 512721 [PMID: 22536249 DOI: 10.1155/2012/512721]
49 **Burman C**, Ktistakis NT. Autophagosome formation in mammalian cells. *Semin Immunopathol* 2010; **32**: 397-413 [PMID: 20740284 DOI: 10.1007/s00281-010-0222-z]
50 **Kanki T**, Klionsky DJ. Mitophagy in yeast occurs through a selective mechanism. *J Biol Chem* 2008; **283**: 32386-32393 [PMID: 18818209]
51 **Ajith TA**, Jayakumar TG. Mitochondria-targeted agents: Future perspectives of mitochondrial pharmaceutics in cardiovascular diseases. *World J Cardiol* 2014; **6**: 1091-1099 [PMID: 25349653]
52 **Matés JM**, Segura JA, Alonso FJ, Márquez J. Oxidative stress in apoptosis and cancer: an update. *Arch Toxicol* 2012; **86**: 1649-1665 [PMID: 22811024 DOI: 10.1007/s00204-012-0906-3]
53 **Antonenkov VD**, Grunau S, Ohlmeier S, Hiltunen JK. Peroxisomes are oxidative organelles. *Antioxid Redox Signal* 2010; **13**: 525-537 [PMID: 19958170 DOI: 10.1089/ars.2009.2996]
54 **Fransen M**, Nordgren M, Wang B, Apanasets O. Role of peroxisomes in ROS/RNS-metabolism: implications for human disease. *Biochim Biophys Acta* 2012; **1822**: 1363-1373 [PMID: 22178243 DOI: 10.1016/j.bbadis.2011.12.001]
55 **Stuehr D**, Pou S, Rosen GM. Oxygen reduction by nitric-oxide synthases. *J Biol Chem* 2001; **276**: 14533-14536 [PMID: 11279231 DOI: 10.1074/jbc.R100011200]
56 **Akopova OV**, Kolchinskaya LI, Nosar VI, Bouryi VA, Mankovska IN, Sagach VF. Cytochrome C as an amplifier of ROS release in mitochondria. *Fiziol Zh* 2012; **58**: 3-12 [PMID: 22586905]
57 **Siraki AG**, Pourahmad J, Chan TS, Khan S, O'Brien PJ. Endogenous and endobiotic induced reactive oxygen species formation by isolated hepatocytes. *Free Radic Biol Med* 2002; **32**: 2-10 [PMID: 11755311 DOI: 10.1016/S0891-5849(01)00764-X]
58 **Kodydková J**, Vávrová L, Kocík M, Žák A. Human catalase, its polymorphisms, regulation and changes of its activity in different diseases. *Folia Biol* (Praha) 2014; **60**: 153-167 [PMID: 25152049]
59 **van der Valk P**, Gille JJ, Oostra AB, Roubos EW, Sminia T, Joenje H. Characterization of an oxygen-tolerant cell line derived from Chinese hamster ovary. Antioxygenic enzyme levels and ultrastructural morphometry of peroxisomes and mitochondria. *Cell Tissue Res* 1985; **239**: 61-68 [PMID: 3967286 DOI: 10.1007/BF00214903]
60 **Schrader M**, Wodopia R, Fahimi HD. Induction of tubular peroxisomes by UV irradiation and reactive oxygen species in HepG2 cells. *J Histochem Cytochem* 1999; **47**: 1141-1148 [PMID: 10449535 DOI: 10.1177/002215549904700906]
61 **Itoyama A**, Honsho M, Abe Y, Moser A, Yoshida Y, Fujiki Y. Docosahexaenoic acid mediates peroxisomal elongation, a prerequisite for peroxisome division. *J Cell Sci* 2012; **125**: 589-602 [PMID: 22389399 DOI: 10.1242/jcs.087452]
62 **Andreyev AY**, Kushnareva YE, Starkov AA. Mitochondrial metabolism of reactive oxygen species. *Biochemistry* (Mosc) 2005; **70**: 200-214 [PMID: 15807660 DOI: 10.1007/s10541-005-0102-7]
63 **Demarquoy J**, Le Borgne F. Biosynthesis, metabolism and function of protectins and resolvins. *Clinical Lipidology* 2014; **9**: 683-693 [DOI: 10.2217/clp.14.44]
64 **Smith JJ**, Brown TW, Eitzen GA, Rachubinski RA. Regulation of peroxisome size and number by fatty acid beta-oxidation in the yeast *Yarrowia lipolytica*. *J Biol Chem* 2000; **275**: 20168-20178 [PMID: 10787422 DOI: 10.1074/jbc.M909285199]
65 **Le Borgne F**, Demarquoy J. Interaction between peroxisomes and mitochondria in fatty acid metabolism. *Open J Mol Integr Physiol* 2012; **2**: 27-33 [DOI: 10.4236/ojmip.2012.21005]
66 **Pujol A**, Ferrer I, Camps C, Metzger E, Hindelang C, Callizot N, Ruiz M, Pàmpols T, Giròs M, Mandel JL. Functional overlap between ABCD1 (ALD) and ABCD2 (ALDR) transporters: a therapeutic target for X-adrenoleukodystrophy. *Hum Mol Genet* 2004; **13**: 2997-3006 [PMID: 15489218 DOI: 10.1093/hmg/ddh323]

67 **Matsuoka S**, Saito T, Kuwayama H, Morita N, Ochiai H, Maeda M. MFE1, a member of the peroxisomal hydroxyacyl coenzyme A dehydrogenase family, affects fatty acid metabolism necessary for morphogenesis in *Dictyostelium* spp. *Eukaryot Cell* 2003; **2**: 638-645 [PMID: 12796309 DOI: 10.1128/EC.2.3.638-645.2003]

68 **Mannaerts GP**, Debeer LJ. Mitochondrial and peroxisomal beta-oxidation of fatty acids in rat liver. *Ann N Y Acad Sci* 1982; **386**: 30-39 [PMID: 6953849 DOI: 10.1111/j.1749-6632.1982.tb21405.x]

69 **Le Borgne F**, Ben Mohamed A, Logerot M, Garnier E, Demarquoy J. Changes in carnitine octanoyltransferase activity induce alteration in fatty acid metabolism. *Biochem Biophys Res Commun* 2011; **409**: 699-704 [PMID: 21619872 DOI: 10.1016/j.bbrc.2011.05.068]

70 **Demarquoy J**. l-carnitine: Structure and Function. eLS: John Wiley & Sons, Ltd, 2011

71 **Eaton S**, Bartlett K, Pourfarzam M. Mammalian mitochondrial beta-oxidation. *Biochem J* 1996; **320** (Pt 2): 345-357 [PMID: 8973539]

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