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Review

The Overlooked Transformation Mechanisms of VLCFAs: Peroxisomal β-Oxidation

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Abstract: Beta-oxidation(β-oxidation) is an important metabolic process involving multiple steps by which fatty acid molecules are broken down to produce energy. The very long-chain fatty acids (VLCFAs), a type of fatty acid (FA), are usually highly toxic when free in vivo, and their oxidative metabolism depends on the peroxisomal β-oxidation. For a long time, although β-oxidation takes place in both mitochondria and peroxisomes, most studies have been keen to explore the mechanism of β-oxidation in mitochondria while ignoring the importance of peroxisomal β-oxidation. However, current studies indicate that it is hard to provide effective treatment for diseases caused by the disorder of peroxisomal β-oxidation, such as X-ALD, SCOX deficiency, and D-BP deficiency; thus, actions should be taken to solve this problem. Based on existing research results, this review will summarize the importance of peroxisomal β-oxidation and help further learning.

Keywords: peroxisome; very long-chain fatty acids; beta-oxidation

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1. Introduction

Fatty acids (FAs) can be divided into four types according to the length of the carbon chain, namely short-chain fatty acids (containing 2–4 carbon atoms, SCFAs), medium-chain fatty acids (containing 6–12 carbon atoms, MCFAs), long-chain fatty acids (containing 13–18 carbon atoms, LCFAs) and very long-chain fatty acids (containing 20 or more carbon atoms, VLCFAs) [1]. In this review, we will refer to VLCFAs, including C20:0, C20:1, C22:0, and others. Any of these VLCFAs have important functions that cannot be substituted by LCFAs, such as skin barrier formation, retinal functions, resolution of inflammation, maintenance of myelin, sperm development and maturation, and liver homeostasis.

Most carbon saturated fatty acids (SFAs) are metabolized by β-oxidation in mitochondria. However, some specific FAs, such as unsaturated fatty acids (UFAs), branched-chain fatty acids (BCFAs), and VLCFAs, require different oxidation processes, including isomerization, alpha-oxidation (α-oxidation), omega-oxidation (ω-oxidation), and the oxidation process in peroxisomes. Similar to β-oxidation in mitochondria, four sequential reactions also occur in peroxisomal β-oxidation [2]. Despite similarities in the reactions, mitochondria and peroxisomes still have different catalytic proteins, electron transport chains, and orientations of metabolites, all of these suggest that research on mitochondria cannot be applied to peroxisomes (Figure 1).

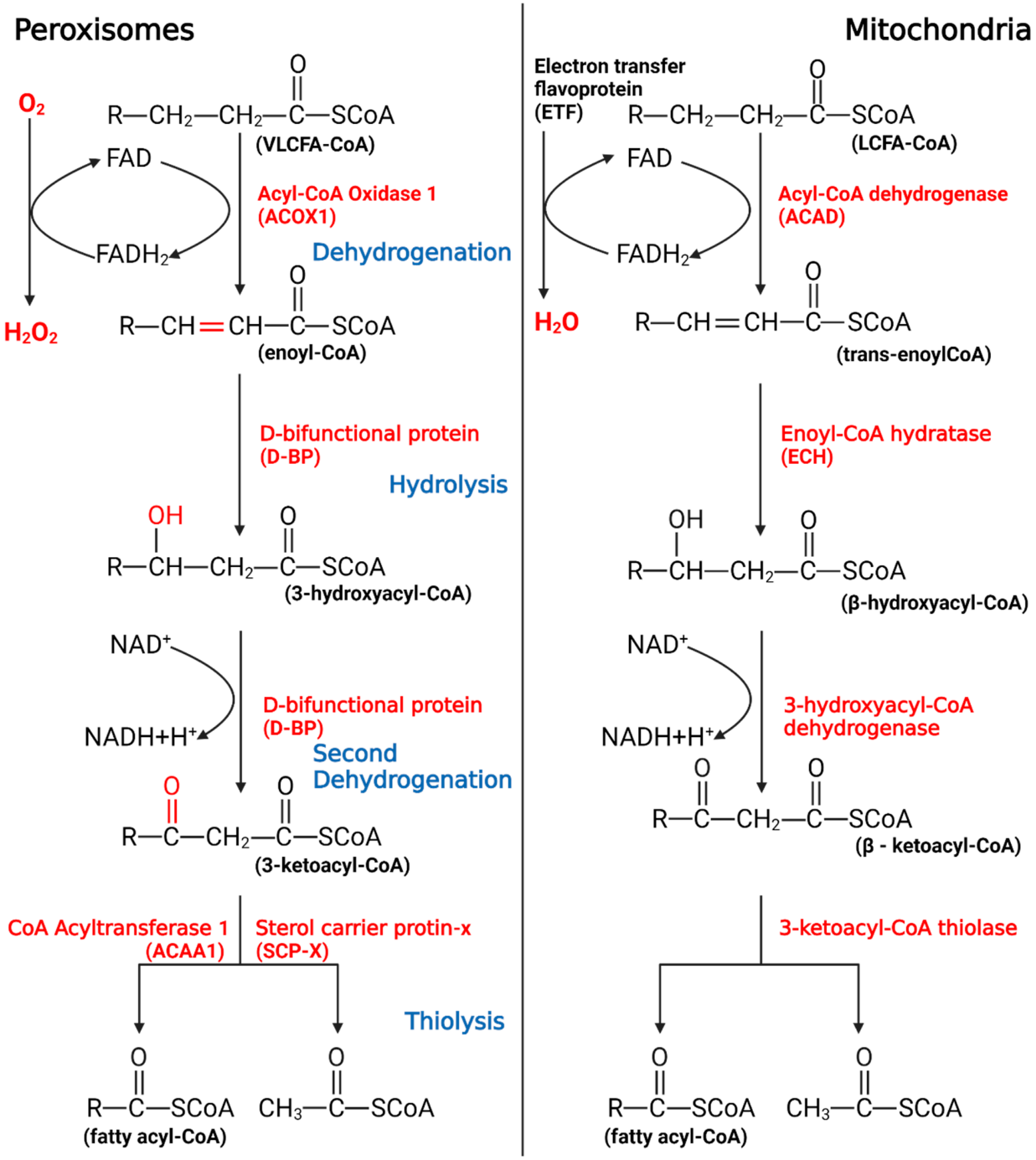

Figure 1. The process of peroxisomal β-oxidation.

VLCFAs enter the peroxisome in the form of -CoA, start the β-oxidation from the first oxidation, undergo hydrolysis, begin the second oxidation, undergo thiolysis, and remove two C atoms. If VLCFAs are still present, they will enter the cycle again until the number of carbon chains is less than 18, after which the products will enter the mitochondria to continue metabolism.

While peroxisomal β-oxidation plays a role in fat metabolism, researchers habitually look for solutions in mitochondria when encountering problems associated with fat metabolism, especially cancer. Taking prostate cancer (PCa) as an example, multiple studies have demonstrated that the occurrence of PCa is related to free FAs and oxidative stress in the body [3], whereas most studies focus on regulating mitochondria to avoid or treat

PCa; thus, peroxisomes have not been taken seriously yet. Interestingly, since 2015, certain studies have proposed to locate some relevant biomarkers in PCa cells peroxisome, such as monocarboxylate transporter 2 [4]. Some studies have also indicated that the expression of peroxisomal β-oxidation changes with PCa proliferation, and the rate of β-oxidation might affect the homeostasis of PCa cells [5]. By contrast, the specific mechanism of action between peroxisome and PCa and how to treat PCa through peroxisome remained unclear. It can be seen that peroxisome β-oxidation may also be the target scheme in many problems, but it is always overlooked. These days most studies focus on the interaction between peroxisome and mitochondria, whereas fewer studies have been done on its independent role. So, does it have research significance?

2. The Significance of Peroxisomal β-Oxidation

As alluded to above, it is not paradoxical that what has been overlooked tends to be of great importance. Peroxisomes, the widely distributed organelles in the body, play irreplaceable roles in cellular metabolism, especially in fatty acid oxidation (FAO) and the generation and elimination of reactive oxygen species (ROS).

In FAO, the oxidation of VLCFAs is an aspect of peroxisome that differs from mitochondria. The mitochondrial β-oxidation pathway has long been considered to play a central role in lipid degradation [6,7], and any blockage of the oxidative pathway leads to increased lipid levels in tissues, yet the role of peroxisomes has been considered. Dysregulation of VLCFAs, essential components in the body, can lead to the occurrence of many diseases [8]. In humans, studies have shown that the accumulation of VLCFAs is the main cause of many neurological diseases, such as Alzheimer's disease, multiple sclerosis, and dementia. In addition, studies of sexually transmitted diseases have found that VLCFAs are associated with ichthyosis, myopathy, and demyelination [9]. To be specific, VLCFAs accumulate in the plasma and tissue of patients, resulting in a fatal neurodegenerative phenotype, including childhood-onset cerebral adrenoleukodystrophy (CCALD) and adrenomyeloneuropathy (AMN) [10]. AMN is the milder phenotype characterized by a slowly progressive axonopathy. Thus, VLCFAs are not only an indispensable part of the body but also a substance that, if dysregulated in vivo, may result in strong toxicity.

In living organisms, free FAs, generally with low concentration, are mainly bound to fatty acid-binding proteins [11,12]. In this case, FAs in vivo are usually produced by the degradation of deposited fat and basically do not contain VLFCAs, and mitochondrial β-oxidation is the primary way of FAO. However, when the toxic VLCFAs enter the body or are in a free state, the peroxisome immediately activates the transport capacity through the transporter; in turn, acyl-CoA oxidase 1 (ACOX1) functions to ensure that peroxisomes can preferentially process VLCFAs that are not suitable for the internal environment. It is this timely processing mechanism that makes the intoxication caused by VLCFAs rare in the body. Of course, this may also be part of the reason why peroxisomal β-oxidation is easily overlooked.

Peroxisomal β-oxidation also plays an irreplaceable role in coping with oxidative stress. When the body is subjected to various harmful stimuli, highly active molecules such as ROS and reactive nitrogen species (RNS) generate excessive free radicals, and the oxidation degree exceeds the antioxidant capacity of cells to remove oxides. The oxidative and antioxidant systems are unbalanced, leading to tissue damage. This is related to the ratio of $FADH_2$/NADH (F/N) (an electron transport chain involved in the transfer of free hydrogen ions and electrons) entering the electron transport chain. In short, the length of the FA carbon chain will affect the saturation and the F/N ratio, which in turn affects ROS production. If VLCFAs are metabolized in mitochondria, the ROS formed can cause severe oxidative stress in mitochondria. Special oxidation products generated during peroxisomal β-oxidation effectively reduced the occurrence of oxidative stress (Figure 2). In peroxisomes, the high-energy electrons stored in $FADH_2$ are directly transferred from O_2 to H_2O_2, and subsequently decomposed into H_2O and O_2. Therefore, the oxidation of VLCFAs in peroxisomes can reduce the amount of β-oxidation in mitochondria, thereby reducing the

F/N ratio and ROS formation. Of course, peroxisomal β-oxidation inevitably causes ATP loss, and the energy carried by $FADH_2$ is not used to synthesize ATP but is dissipated in the form of thermal energy. However, this heat loss is not a physiologically ineffective behavior, since studies have shown that peroxisomes accelerate the decomposition of FAs in BAT under cold stress conditions to help the body quickly adapt [13]. Therefore, peroxisomal β-oxidation is an important metabolic activity during nonshivering thermogenesis. Correspondingly, there is noise stimulation. In an extremely noisy environment, ROS production increases and causes oxidative damage, and peroxisomes can also regulate disorders caused by these stimuli through β-oxidation. Current research shows that this oxidative feedback regulation mechanism is activated by PEX5 [14].

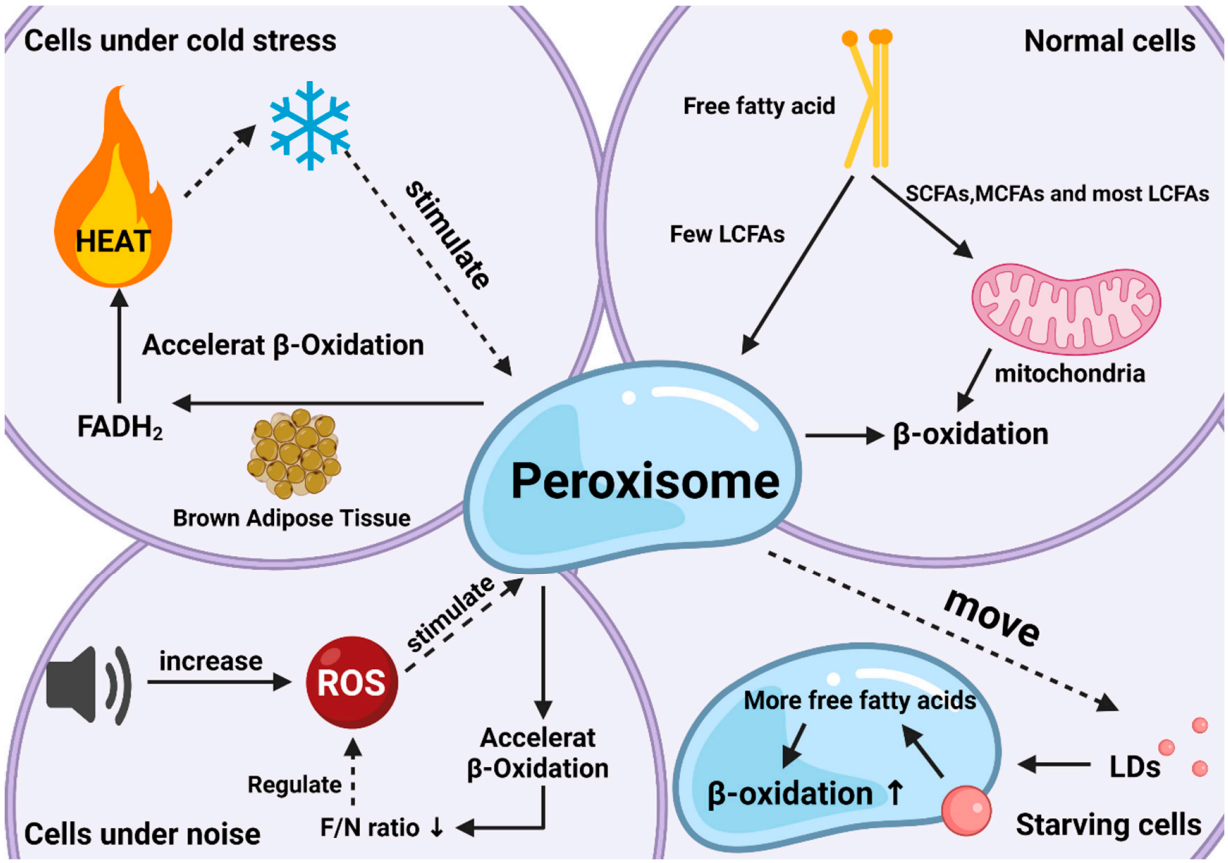

Figure 2. The roles of peroxisomal β-oxidation under various conditions. Responses and effects of peroxisomal β-oxidation in cells under normal (**top right**), starvation (**bottom right**), cold stress (**top left**), and noise (**bottom left**) conditions.

Another neglected effect is related to lipid droplets (LDs). LDs are lipid-storing organelles present in nearly all organisms, from bacteria to mammals, and their degradation provides metabolic energy for different cellular processes, such as membrane synthesis and molecular signaling [15]. Studies have shown that LDs and peroxisomes are generated at the same place in the endoplasmic reticulum with close subcellular localization after maturation, implying the possibility of interaction between the two organelles [16]. Indeed, researchers have found that when the body is starving, peroxisomes can move to and contact LDs with the help of kinesin KLFC3, and then transfer lipids from lipid droplets into the β-oxidation process more quickly to promote their degradation and maintain energy balance [17]. The latest research also authenticates this conclusion and gives a more specific explanation for "starvation" this condition arises to protect the body from ROS, since starvation increases fatty acid peroxidation as does the production of ROS [18].

Among mammals, peroxisomes also play an important role in ruminants, especially dairy cows. In other non-ruminant mammals, where FAO occurs mainly in mitochondria

(76%), in ruminants, FAO occurs in mitochondria and peroxisomes (approximately 50% in each organelle) [19]. As dairy livestock are important, many studies have focused on the different lactation stages and butterfat percentage of dairy cows. Consumer choices today are based not only on the nutritional aspects of the food but also on products known to promote better health or prevent disease [20,21]. In this regard, the proportion of VLCFAs in milk is a concern. Dairy cows have a complete pathway for the synthesis and utilization of VLCFAs, through ELOVL protein synthesis and peroxisome utilization [22]. In actual production, high-producing dairy cows are subject to constant oxidative stress due to a high metabolic rate and physiological adaptation to intensive farming [23]. During the perinatal period of dairy cows, the body will undergo complex physiological changes, among which ketosis often occurs [24]. The occurrence of ketosis is often accompanied by fat deposition in the liver [25]. The essence is that after excess NEFAs (nonesterified fatty acid, fatty acids above C10, mainly VLCFAs) enter the liver, part of NEFAs enter the ketone body synthesis pathway to generate ketone bodies [26,27]. Study showed a greater level of ROS in mammary epithelial cells of ketotic cows, and greater oxidant indices, indicating increased oxidative stress status [28,29]. Although there is no direct research to prove that the occurrence of ketosis is related to peroxisomes, many studies have proved that factors related to peroxisomal β-oxidation are involved in the occurrence and control of the disease, such as PPARα, and AMPK, combined with the presence of VLCFAs, we think this is very possibly related to peroxisomes [30,31]. Also, many diseases in dairy cows can be attributed to oxidative stress, such as mastitis and breast edema [32–35]. Although some studies use extrinsic drugs to treat diseases from oxidative stress [36–38], authors believe that the harm caused by oxidative stress can be alleviated by intrinsically regulating the rate of peroxisomal β-oxidation. Unfortunately, at present, few studies have linked peroxisomal β-oxidation to these diseases.

Overall, current research on peroxisomal β-oxidation has demonstrated its importance as a major factor in regulating lipid metabolism disorders in the internal environment and maintaining the balance of lipids and ROS. Unfortunately, most research on these functions has focused on understanding how they operate, and the current understanding of molecular-level mechanisms of functions remains limited.

3. Factors Involved in the Regulation of the Peroxisomal β-Oxidation

Although it attracts less research than mitochondria, the importance of the peroxisomal β-oxidation molecular mechanism can still be spotted from some mechanisms involved in upstream regulation.

3.1. PPAR

Peroxisome proliferation activating nuclear receptors (PPARs), members of the steroid hormone nuclear receptor ligand-dependent transcription factor superfamily, can regulate peroxisome proliferation by regulating the peroxisome proliferation β-oxidation process [39]. PPARs have three subunits, namely PPARα, PPARβ/δ, and PPARγ (Figure 3), which differ in tissue distribution, ligand affinity, and target genes. Surprisingly, they are all related to peroxisomal β-oxidative metabolism [40]. Activation of PPARα promotes fatty acid entry into peroxisomes, and PPARα participates in the regulation of energy homeostasis. By contrast, activation of PPARγ causes insulin sensitization and enhances glucose metabolism, whereas activation of PPARβ/δ enhances FAO.

3.1.1. PPARα

The effect of peroxisome proliferators on the synergistic induction of the peroxisomal β-oxidation system enzymes has been well established, which is regulated by PPARα. As a lipid sensor, PPARα can coordinate and promote the expression of a large number of target genes in the process of FAO, especially in starvation or high-fat diet conditions [41]. Studies have shown that PPARα induces the translation of downstream genes under the stimulation of VLCFAs: it promotes the proliferation of peroxisomes, and it specifically

upregulates the expression of peroxisomal β-oxidative proteins and coenzymes [42]. At present, research on PPARα mainly focuses on its targeted ligands. For example, synthetic lipid-lowering drugs have been shown to activate PPARα and then regulate the peroxisomal β-oxidation [43]. And in the ruminants, some studies have found that PPARα has different expression levels in the mammary between the dry and lactation period [19,44]. Further, the study also showed that PPARα plays an important role in regulating milk fat synthesis in ruminants [45]. In addition to this, PPARα is also involved in the regulation of fat in the liver [46,47]. Interestingly, PPARα also plays an important role in ruminant reproduction [48,49], but it is not known whether this role is related to peroxisomal β-oxidation, which is a direction worth exploring. Simply put, regardless of whether the drugs are endogenous or exogenous ligands, their activation mechanism to bind the PPARα further increases transcriptional activity.

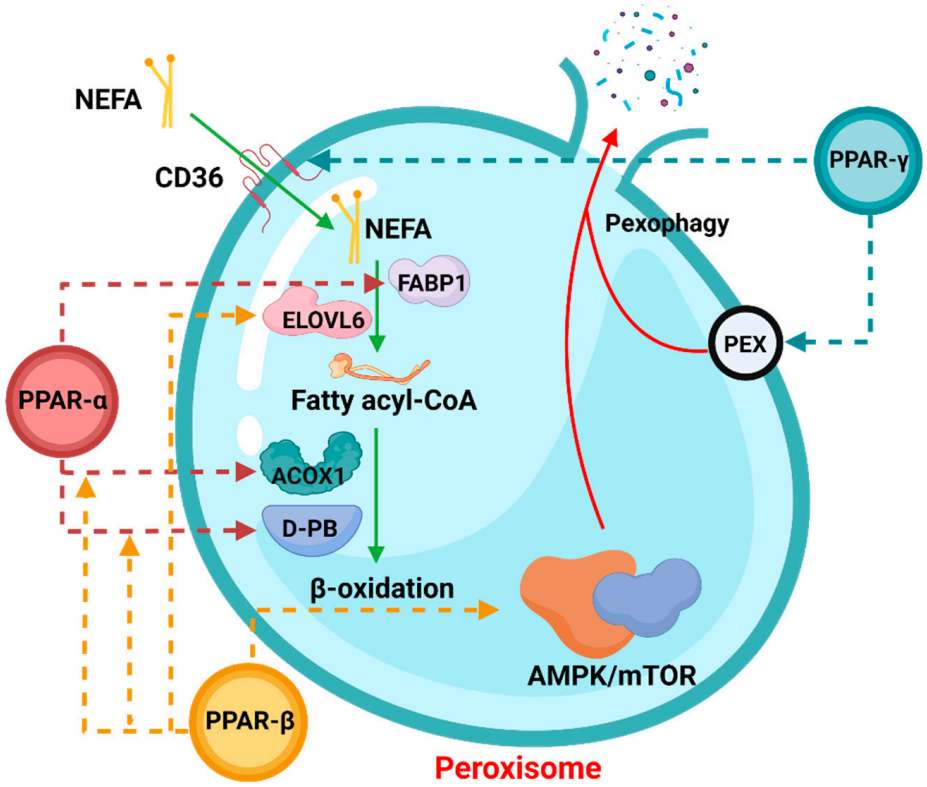

Figure 3. The role of PPARs in peroxisomal β-oxidation.

In the process of peroxisomal β-oxidation, PPARs are actively involved in various processes. The dotted arrows in the figure indicate that the corresponding PPAR members participate in the regulation of the process. Among them, NEFA: non-esterified fatty acid, FABP1: fatty acid binding protein 1, ELOVL6: ELOVL Fatty Acid Elongase 6, ACOX1: Acyl-CoA Oxidase 1. The process involving pexophagy was complicated, and "PEX" was only a general reference. For details, please refer to Section 3.3.

3.1.2. PPARγ

As one of the key transcriptional regulators of adipocyte differentiation, PPARγ also plays an important role in mediating peroxisomal β-oxidation and lipid metabolisms [50]. Studies have shown that a variety of genes involved in FA transport and metabolism are regulated by PPARγ at the transcriptional level, such as FA translocases, implying that PPARγ can stimulate peroxidase by increasing the expression of FA transporters and FA transportases [51,52]. The initiation of β-oxidation in vivo has also been proven. By knocking out PPARγ in mice, it was found that they had obvious lipid metabolism disorders [53].

In dairy cows, PPARγ plays an important role which is the critical mediator of lipogenesis [54]. One of the significant roles it plays in dairy cows from the point of view of economic interest is controlling the synthesis of milk fat in dairy cows, not only in mitochondria but also with ELVOL participating in the regulation of peroxisomal β-oxidation. PPARγ expression increases during changes in the lactation period [55,56], thereby regulating peroxisomal β-oxidation to prevent metabolic stress. Research further confirmed the importance of PPARγ in regulating milk fat production [57,58]. Similarly, as milk-producing ruminants, goats and sheep are also regulated by PPARγ. Many studies indicate that PPARγ is involved in adipocyte differentiation and adipogenesis in sheep/goats [59–63], though, in addition to fat regulation, PPARγ was previously thought to be involved in the regulation of hormones in goats and sheep [64,65]. However, there has been some relevant research in recent years. Some studies have pointed out that the role of PPARγ and hormones is only a servo-assist mechanism [66]. In the author's opinion, there is no obvious evidence to prove either statement; thus, this is also a worthy question.

3.1.3. PPARβ/δ

Compared with PPARα and PPARγ, PPARβ/δ is more widely distributed in various tissues in vivo. Aline et al. showed that PPARβ/δ could participate in the activation of FAO in BATs, but genes involved in processes such as lipogenesis were not significantly correlated [67]. This demonstrates that PPARβ/δ is a thermogenic transcription factor in vivo, which bears great resemblance to the purpose of peroxisomal β-oxidation. Furthermore, Tong et al. studied PPARβ/δ-induced autophagy, although the study assessed expression changes in mitochondria and revealed the PPARβ/δ-AMPK/mTOR pathway by searching for a signaling pathway (mTOR, one of the important factors of peroxisomal β-oxidation), which further demonstrated that PPARβ/δ has a regulatory effect on peroxisomal β-oxidation [68]. Recent studies have shown that PPARβ/δ is indispensable for the upregulation of autophagic behavior [43,69–72], making the relationship between PPARβ/δ and peroxisomal β-oxidation more explicit. When the body is under certain conditions, PPARβ/δ frees more VLCFAs by upregulating cellular autophagy, which in turn regulates the initiation and enhancement of peroxisomal β-oxidation. However, a lot of research is still needed to confirm what certain conditions are and whether this speculation is correct.

Regardless of which subunit of PPARs is involved in the regulation of peroxisomal β-oxidation, as PPAR is often reported to be associated with the occurrence of diseases like type 2 diabetes, PPAR-associated peroxisomal β-oxidation changes may also be involved. A study pointed out that inhibition of peroxisome biosynthesis can interrupt β-oxidation through the action of PPAR, thereby effectively preventing the occurrence of type 2 diabetes [13]. Nevertheless, the molecular mechanism underlying this phenomenon has not been elucidated. In addition, the prevalence of some diseases is different by gender [73], and many experiments also show that PPARs are different in function by gender. PPARα expression is more abundant in native and activated male T cells than in female cells [74,75], suggesting that PPARα has a more substantial role in male T cells than in female T cells. Likewise, multiple studies have shown that the male hormone androgen has been suggested to influence the expression of PPARα in male T cells [76–78]. A study of sex-specific differences in the role of PPARγ in T cell survival has shown that male PPARγ-deficient T cells have increased apoptosis and contain a greater proportion of apoptotic cells than female PPARγ-deficient T cells [79]. Some studies have also validated similar conclusions, suggesting that PPARγ plays an important role in T cell survival [80–83]. Although more convincing data are needed to resolve this discrepancy, PPARγ may act as a survival factor in female T cells. Unlike others, the regulatory role of PPARβ/δ in T cells has not been well studied, but sex-specific differences in PPARβ/δ regulation should be considered in future studies.

3.2. PGC-1α

Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) is a powerful transcriptional coactivator that regulates a broad range of physiological and energy homeostasis responses at the transcriptional level in diverse mammalian tissues. In the past, scholars focused more on the regulatory mechanism of PGC-1α in controlling mitochondrial function [84,85]. In 2010, Bagattin et al. found that PGC-1α coordinates not only mitochondrial remodeling but also peroxisome specialization and biogenesis [86], which stimulated an upsurge in the function study of peroxisome PGC-1α. Moreover, Huang et al. studied peroxisomes in human skeletal muscle cells. They found that overexpression of PGC-1α induced the expression of AOCX1, and that the levels of some proteins associated with peroxisome activity also substantially increased [87]. In addition, some studies have also demonstrated the importance of PGC-1α in peroxisomes [88,89].

In conclusion, the regulatory relationship between PGC-1α and peroxisomal β-oxidation deserves further research because of the critical functionality of PGC-1α, and we wonder whether PGC-1α could be used as a novel chemical modulator for the treatment of Zellweger syndrome symptoms and other diseases. PGC-1α has not been studied much in ruminants and has mostly focused on regulating fatty acids [90,91]. But there is one direction worth mentioning. Zhou et al. found that PGC-1α seems to play a role in the skeletal muscles of goats, and it can also maintain metabolic rhythm through the phosphorylation of upstream regulators [92]. We speculate that this is related to peroxisomal β-oxidation.

3.3. PEX

In 1996, the term peroxin was coined for proteins in peroxisome biogenesis, including peroxisomal matrix protein import, membrane biogenesis, peroxisome proliferation, and peroxisome inheritance [93]. Peroxins are encoded by PEX genes, also known as PEX proteins. To date, 37 PEX proteins have been discovered and studied. Some are highly conserved, while others only occur in a limited number of species, such as PEX17, which only distributes in Fungi, and PEX35, which only distributes in *Saccharomycetaceae* [94]. Most PEX proteins have been shown to play a significant role in peroxisomal β-oxidation (Figure 4).

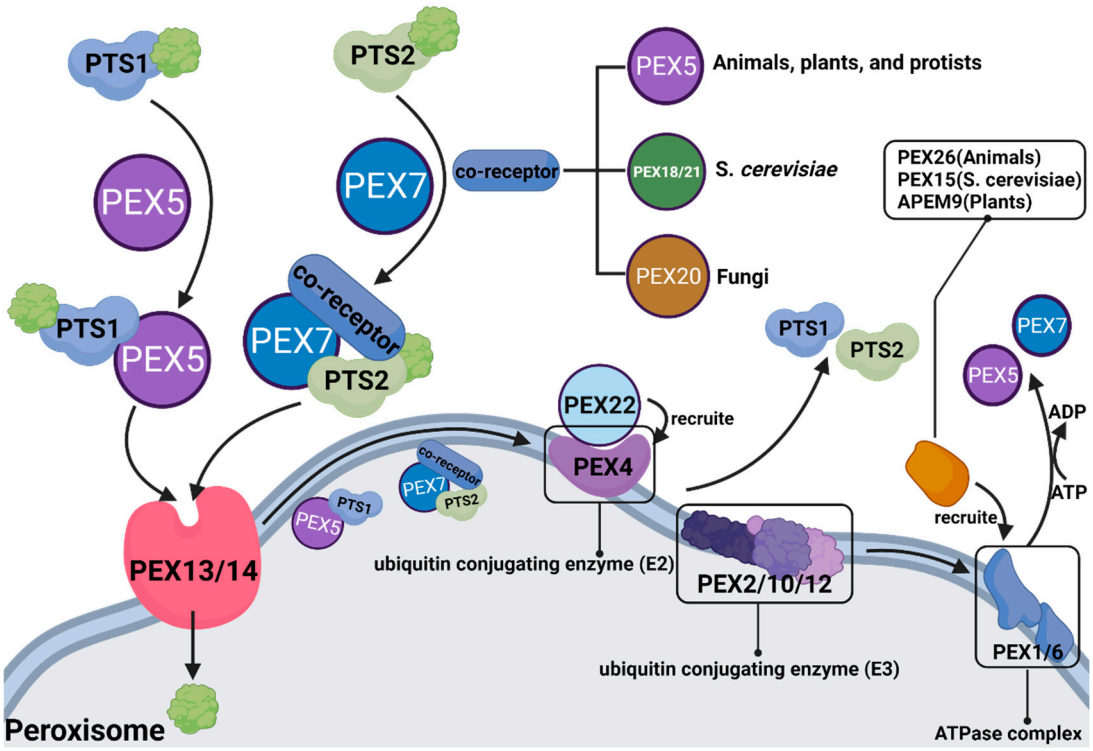

Figure 4. The role of different PEX proteins in peroxisomal β-oxidation.

PEX5 is the most commonly studied object in eukaryotes. As mentioned above, peroxisomes are very sensitive to ROS, whereas multiple organelles in the internal environment can produce ROS. Consequently, peroxisomes themselves are susceptible to the influences of other metabolic processes and become dysfunctional. A study found that PEX5 can respond to the expression of ROS and induce cell autophagy after ubiquitination to prevent damage from excessive or defective peroxisomes from cellular β-oxidation [95].

More research on PEX has focused on diseases caused by mutation or dysfunction of the PEX gene, including peroxisome biogenesis disorders in the Zellweger spectrum (PBD-ZSD) and rhizomelic chondrodysplasia punctata (RCDP). Studies have pointed out that PBD-ZSD is caused by PEX gene mutation that results in insufficient peroxisomal β-oxidation, which increases levels of VLCFAs in plasma and cells. However, so far, there is no treatment for PBD-ZSD, and researchers have tried to treat it from the perspective of autophagy, but the effect is not ideal [96]. Does this imply that there are unknown mechanisms other than autophagy regulating the relationship between PEX and β-oxidation? It reminds us that long-term neglect makes it impossible for us to have precise treatment for diseases caused by peroxisomal β-oxidation disorders, that we can't find the therapeutic target, and thus further exploration is urgently needed.

Substances entering peroxisomes for β-oxidation need to form receptor cargo complexes with PTS (PTS: peroxisome targeting sequence, whose role is to locate peroxisomes to ensure accurate transport of carried substances) and PEX, in which PTS1 is transported by PEX5, and PTS2 is transported by PEX7 and coreceptors (coreceptors are PEX5, PEX18/21 and PEX20, depending on the species). After the substance enters the peroxisome, PTS and PEX must be ubiquitinated and recovered.

3.4. ATP-Binding Cassette (ABC)

In peroxisomes, VLCFAs are mainly introduced as CoA through ABCD1–3 (Figure 5). Studies have shown that peroxisomal β-oxidation is dysfunctional after the deletion of ABCD1/ALDP in vivo, resulting in the expression levels of VLCFAs in both plasma and tissues being increased [97,98]. ABCD1 and ABCD2 share a high degree of sequence homology, except that ABCD2 plays a central role in the metabolism of monounsaturated and polyunsaturated VLCFAs, rather than saturated VLCFAs, and may be involved in the regulation of oxidative stress and DHA synthesis [99]. ABCD3/PMP70 plays a major role in transporting 2-methylacyl-CoA esters [100]. In addition, despite the distinct functions of peroxisomal ABC transporters, in vitro and in vivo studies have clearly identified that there is at least partial functional redundancy between these transporters [101,102]. In ruminants, ABC is equally important. Ahmad et al. found that the expression of ABC varies significantly among different milk yields by RNA-seq [103]. Since the expression of ABC is also different between different breeds of cattle, the difference in immunity may also be related to ABC. And Lopez et al. further verified this conclusion, ABC is indeed related to the immune system of cattle [104]. Although this conclusion was obtained by RNA-seq, we speculate that this is caused by the different content of VLCFAs in vivo and the autophagy function of peroxisome; the latest research also suggests that ABC is involved in intracellular cholesterol-mediated autophagy [105]. In addition, the role of ABC was also found in the reproductive system of sheep [106], revealing that ABC may be related to the degeneration of germ cells. Although researchers have paid more attention to the transport function of ABCD, we would like to emphasize that the X-linked adrenoleukodystrophy (X-ALD) remains a matter of concern because it lacks peroxisomal β-oxidation caused by ABCD deletion. At present, the only effective treatment is hematopoietic stem cell transplantation (HSCT), but the risk of death remains high. Some studies have pointed out that the β-oxidation defects can be restored by overexpressing ABCD1/2 in cells, whereas the understanding of its mechanism is still incomplete [28,30,35]. As mentioned above, a comprehensive understanding of peroxisomal β-oxidation is urgently needed.

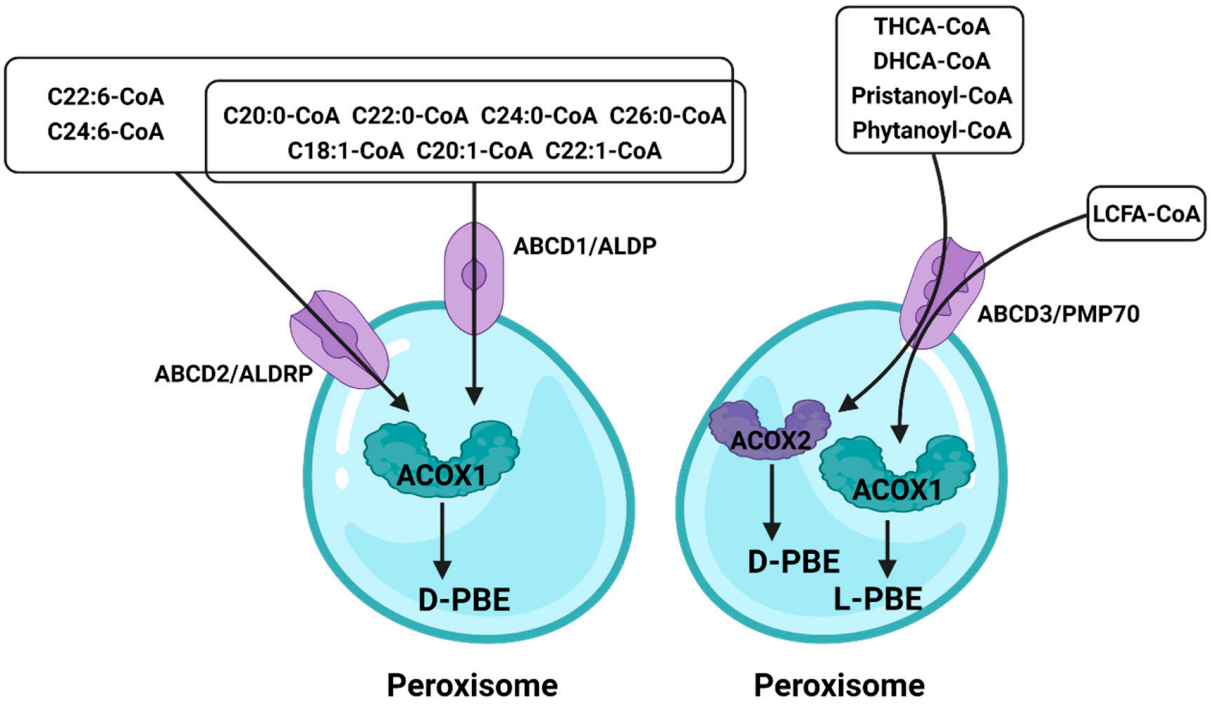

Figure 5. The role of the ATP-binding cassette in peroxisomal β-oxidation.

Different fatty acids enter peroxisome through different ATP-binding cassettes, and ABCD2 has a broader role. Fatty acids that enter peroxisomes through ABCD3 are processed by different enzymes to achieve oxidation results.

3.5. Others

New regulators involved in the regulation of peroxisomal β-oxidation have constantly been identified. AMPK, for example, promotes FAO by activating the expression of PPARα and ACOX1 [107,108], whereas mTOR promotes the accumulation of FAs by shutting down β-oxidation [109,110]. Hence, these are considered the AMPK-mTOR pathway for regulating β-oxidation [111]. The NAD-dependent protein lysine deacylases of the sirtuin family regulate various physiological functions, from energy metabolism to stress responses [112]. Numerous studies have found that Sirtuin has a variety of catalytic activities [113]. These pleiotropic enzymatic activities give sirtuins their far-reaching functions in maintaining genome integrity, regulating metabolism homeostasis, and promoting organismal longevity. And a recent study found that sirtuin 5 (SIRT5) functions similarly to mTOR, which shuts down peroxisomal β-oxidation by inhibiting the activity of ACOX1 [114]. Other reports have studied CoA in the process of β-oxidation and found that Nudt7 and Nudt19 in the Nudt superfamily can exert positive effects on CoA substrates in certain metabolic processes to promote the metabolic process [115,116]. With the upsurge of research on non-coding RNAs (ncRNAs), some play positive or inhibitory roles in peroxisomal β-oxidation, such as miR-222, miR-25-3p, circ_0005379, and others [117–122], which mainly target the rate-limiting enzyme ACOX1. Recently, Li et al. analyzed the ACOX1 transcript and found that miR-532-3P could regulate the expression of ACOX1 by targeting the complementary sequence in the 3′-UTR, thereby participating in lipid metabolism [117].

Moreover, other enzymes involved in peroxisomal β-oxidation were also regulated. Several studies have demonstrated that phosphatidylserine (PS) can bind to D-bifunctional protein (D-BP) and localize to peroxisomes, implying that PS can also affect the β-oxidation process [123]. It is worth noting that some studies have pointed out that acetylation is important for the normal functioning of D-BP [124,125], but related studies are not common; thus, we do not know which factors affect its acetylation process. Another key regulatory enzyme of peroxisomal β-oxidation, Acetyl-CoA acyltransferase 1 (ACAA1), has been

extensively studied. In the breeding of livestock and poultry, researchers often explore its effects on adipocytes; for example, in goats and sheep, ACAA1 is involved in regulating adipogenesis. Studies have shown that ACAA1 deficiency increased lipid accumulation and the triglyceride content and promoted sheep preadipocyte differentiation [126]. At the same time, the study also proved a regulatory relationship between ACAA1 and PPARγ. Although the study does not point out the relationship between such a phenomenon and peroxisomal β-oxidation, it is not difficult to speculate that peroxisomal β-oxidation plays an important role. And in humans or model animals, researchers have focused on the diseases caused by it [127]. At present, it is generally believed that the expression of PPAR affects the expression of ACCA1, which in turn affects the process of β-oxidation.

4. Discussion and Future Perspectives

In 1954, peroxisomes were first identified as important organelles capable of β-oxidation in living organisms. Compared to mitochondria, there have been few studies on peroxisomes, and the reason why they are always ignored may be that they have fewer tasks in the body. As the entire process runs correctly, it makes people ignore their presence. However, disease can quickly emerge when peroxisomal β-oxidation is abnormal, particularly in human-related studies, such as X-ALD, SCOX deficiency, and D-BP deficiency [128–130] (Table 1). It is undeniable that fewer therapeutic options once again demonstrate that many functional and molecular mechanisms in metabolic processes remain undetermined. Of course, due to its unique subcellular localization, its extraction may not be carried out smoothly. Fortunately, peroxisomes are attracting the attention of scholars, and an increasing number of related studies have begun to appear. In a new study, McGill University studied the origin of the peroxisome and found two origins, suggesting that in addition to the endoplasmic reticulum, mitochondria may also be involved in the formation of new peroxisomes [131]. We do not yet know whether this finding points to a compensatory mechanism on the other side when peroxisomal or mitochondrial β-oxidation is defective. Still, it is most likely that this research will have a major impact on the field of peroxisome biology and ultimately on understanding human disease progression. Ding et al. showed peroxisomal β-oxidation functions as a novel sensor of FAs that regulates lipolysis through a complex pathway and modulates the interaction between peroxisomes and LDs. They described a previously unimaginable interpretation of the relationship [132]. This also means that the relationship between peroxisomes and lipid droplets has not been thoroughly studied, and their interdependent functions remain to be determined (Figures 6 and 7).

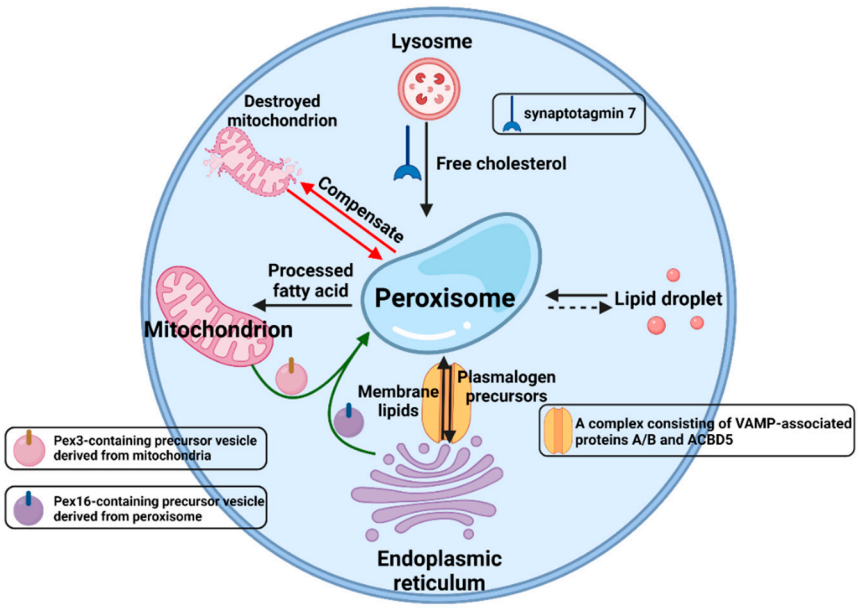

Figure 6. Interactions of peroxisomes with other intracellular organelles.

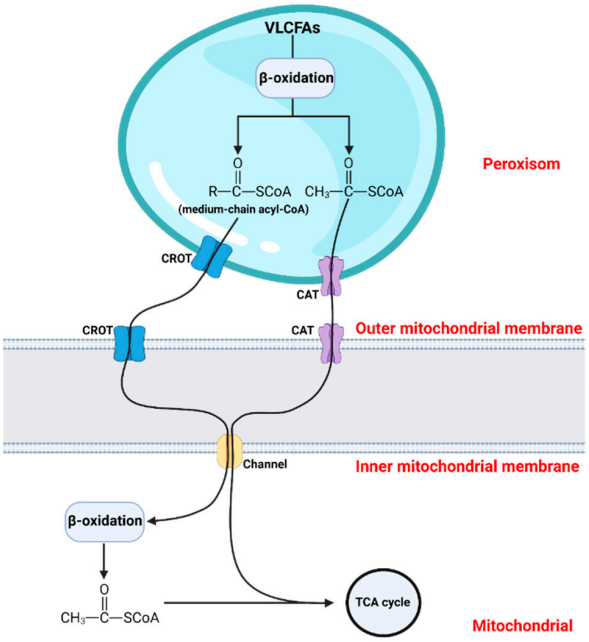

Figure 7. The transfer of fatty acids from peroxisomes to mitochondria.

With the continuous emergence of new technologies (such as employing omics) and the expansion of research fields [30,35,133], this is indeed an exciting time to comprehensively explore the peroxisome itself and its β-oxidation mechanism, a research hotspot with plenty of opportunities and challenges ahead.

The converging green arrow lines in the figure indicate the biogenesis of the peroxisome, and the red arrow lines indicate that when one side of the peroxisome/mitochondrion undergoes oxidative damage/other damage, the other side performs functional compensation. The black arrow lines represent normal material transport.

When fatty acids are processed in peroxisomes into fatty acyl-CoA with 18 carbons or less, they enter the mitochondria through CROT for further processing until they finally become acetyl-CoA, and enter the TCA cycle to provide energy for the body. Among them are CROT: Carnitine O-Octanoyltransferase, CAT: Catalase from Micrococcus lysodeikticus, TCA cycle: tricarboxylic acid cycle.

Table 1. Major diseases in peroxisome.

Peroxisome Biogenesis Disorders (PBDs)	Incentive	References
Zellweger spectrum disorders (ZSDs)	Genetic disorders caused by mutations in PEX genes	[134–139]
Zellweger syndrome (ZS)	Mutations in peroxisome biogenesis or mutations in PEX gene	[140–147]
Neonatal adrenoleukodystrophy (NALD)	Mutations in PEX gene	[148,149]
Infantile Refsum disease (IRD)	A medical condition within the ZSDs	[150–153]
Heimler syndrome (HS)	Biallelic mutations in PEX1 or PEX6	[154–156]
Rhizomelic chondrodysplasia punctata (RCDP)	A peroxisome biogenesis disorder, may be related to PEX gene	[157–161]
X-linked adrenoleukodystrophy (X-ALD)	Mutations in ABCD1 gene	[130,162–166]
Acyl-CoA oxidase deficiency	Deletion or mutation of ACOX1 gene	[167–169]
D-Bifunctional protein deficiency	Deletion or mutation of D-BP protein	[170,171]
3-Ketoacyl-CoA thiolase deficiency	Deletion or mutation of THIO enzyme	[172,173]
α-Methylacyl-CoA racemase deficiency	Biallelic mutations in AMACR gene	[174–177]
Mevalonate kinase deficiency	Mutations in peroxisome biogenesis or deletion or mutation of MK	[178–182]
Glutaric aciduria type 3 (glutaryl-CoA oxidase deficiency)	Deficiency of succinyl-CoA	[183–185]
Acatalasemia	Homozygous mutations in the catalase gene	[186–188]

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