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Review

The importance of ether-phospholipids: A view from the perspective of mouse models ☆

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ABSTRACT

Ether-phospholipids represent an important group of phospholipids characterized by an alkyl or an alkenyl bond at the sn-1 position of the glycerol backbone. Plasmalogens are the most abundant form of alkenyl-glycerophospholipids, and their synthesis requires functional peroxisomes. Defects in the biosynthesis of plasmalogens are the biochemical hallmark of the human peroxisomal disorder Rhizomelic Chondrodysplasia Punctata (RCDP), which is characterized by defects in eye, bone and nervous tissue. The generation and characterization of mouse models with defects in plasmalogen levels have significantly advanced our understanding of the role and importance of plasmalogens as well as pathogenetic mechanisms underlying RCDP. A review of the current mouse models and the description of the combined knowledge gathered from the histopathological and biochemical studies is presented and discussed. Further characterization of the role and functions of plasmalogens will contribute to the elucidation of disease pathogenesis in peroxisomal and non-peroxisomal disorders. This article is part of a Special Issue entitled: Metabolic Functions and Biogenesis of Peroxisomes in Health and Disease.

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1. Introduction

The discovery of the relationship between lack of peroxisomes and the Zellweger syndrome [1,2] was the initial driving force to unravel the intricacies behind peroxisome biogenesis, protein import into peroxisomes and peroxisomal functions [3–5]. The knowledge gained in the last three decades allowed a better understanding of the Zellweger syndrome, the identification of new peroxisomal disorders and methods to perform pre- and post-natal diagnosis. Peroxisomes are mostly known for their ability to perform (1) β-oxidation of very-long-chain fatty acids, (2) α-oxidation of phytanic acid, (3) degradation of hydrogen peroxide, and (4) the biosynthesis of ether-phospholipids [6,7]. Nevertheless, the determination of the peroxisomal proteome is still unraveling new peroxisomal proteins [8], which increases the functions performed by these organelles and potentially the number of human peroxisomal disorders.

The complexity of human peroxisomal disorders is emphasized by (1) the lack of a unique or specific clinical presentation, (2) the variable degrees of biochemical defects, (3) the multitude of genes that can affect peroxisome biogenesis, (4) the absence of genotype–phenotype correlations, and by (5) the variety of organs and tissues affected. These features combined with a general unavailability of postmortem material have in some cases, hindered a detailed characterization of the tissue pathology and the mechanisms behind disease progression. To circumvent some of these problems mouse models for human peroxisomal disorders have been generated. Mouse models have been generated for most peroxisomal disorders including the Zellweger spectrum (*i.e.*, the Pex5, Pex2, Pex11 and Pex13 knockout mice; [9–13]), X-linked adrenoleukodystrophy (the ATP-binding cassette, sub-family D, member 1 (Abcd1) knockout mouse; [14–17]), Refsum disease (the phytanoyl-CoA 2-hydroxylase (PHYH) knockout mouse; [18]), and D-bifunctional protein deficiency (the DBP or MFP2 knockout mouse; [19,20]). For further reading and a comprehensive listing of the current mouse models with either peroxisome biogenesis defects or β-oxidation defects see the chapter in this issue by Baes and Van Veldhoven [21].

In this review we present the combined knowledge obtained from the generation and characterization of mouse models for Rhizomelic Chondrodysplasia Punctata (RCDP). RCDP is a complex disorder in terms of clinical presentation, pathology and genetics. The disorder is caused by an impairment in the biosynthesis of ether-phospholipids of which plasmalogens play crucial roles that are further delineated in this review.

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2. Characteristics and functions of plasmalogens

In mammalian cells ether-phospholipids represent an important group of phospholipids. In distinction to diacyl-glycerolphospholipids, which contain two acyl chains linked to the glycerol backbone by ester bonds, in ether-phospholipids the acyl chain in position 1 is linked to the glycerol backbone by either an alkyl- or an alkenyl-bond [22]. Plasmalogens are the most abundant form of ether-phospholipids and are alkenyl-glycerophospholipids containing either an ethanolamine or a choline moiety in the polar headgroup of the glycerol backbone [23]. Alkyl-glycerophospholipids are less abundant, although platelet-activating factor is abundant in neutrophils [24]. The biosynthesis of plasmalogens is initiated in peroxisomes through the activity of two enzymes namely, glyceronephosphate O-acyltransferase (GNPAT) and alkylglycerone phosphate synthase (AGPS), and is finalized in the endoplasmic reticulum (reviewed in [25]).

The structure and composition of plasmalogens, and in particular the vinyl-ether bond at the sn-1 position, are thought to dictate their role in cellular membranes. Plasmalogens have been found to serve as (a) endogenous antioxidants, since the vinyl-ether bond is prone to attack by oxidants, (b) mediators of membrane structure and dynamics, since they exhibit a tendency to form nonbilayer lipid phases, reduce surface tension and viscosity and, (c) storages of polyunsaturated fatty acid and lipid mediators, since the sn-2 position usually contains docosahexaenoic acid and arachidonic acid, whose metabolism produces leukotrienes and prostaglandins. Recent reviews on the functions and roles of plasmalogens are recommended for further reading [26,27]. Although most experimental settings have been performed *in vitro*, some studies were performed in cells derived from plasmalogen-deficient patients. Based on the growing number of cells and tissues with defects caused by a plasmalogen deficiency, and the availability of mouse models with defects in plasmalogens the aim should now be to investigate the attributed roles and functions of plasmalogens in target cells and tissues from plasmalogen deficient mice.

3. Plasmalogen deficiency in humans

The clinical presentation of RCDP typifies the consequences of a plasmalogen deficiency. The clinical features of RCDP patients include, shortening of femur and humerus, cataracts, contractures, hypotonia, atypical facial appearance (*e.g.*, prominent forehead, anteverted nares, long philtrum) and mental and growth retardation [28–30]. On X-ray imaging the ectopic stippled calcifications, flared epiphyses and coronal clefts in vertebral bodies further denote the defects in endochondral ossification present in RCDP patients [28,31,32]. Magnetic resonance imaging (MRI) may reveal delayed myelination, ventricular enlargement, cerebellar atrophy, and rarely neuronal migration defects, which may contribute to the poor neurologic prognosis of RCDP patients [30,33–37].

In RCDP patients the impairment in plasmalogen biosynthesis can be caused by three different defects. These defects also denote the three forms of RCDP depending on which gene is mutated. In RCDP type 1, mutations in *PEX7* [38,39], encoding the cytosolic receptor for peroxisomal proteins carrying the peroxisomal targeting signal 2 (PTS2), impair the import of three proteins (reviewed in [40,41]), of which AGPS, is the cause of the impaired plasmalogen biosynthesis. In RCDP type 2, mutations in *GNPAT*, encoding the first enzyme in the plasmalogen biosynthesis pathway, are responsible for the inability to synthesize plasmalogens [42]. In RCDP type 3, mutations in *AGPS*, encoding the second enzyme in the plasmalogen biosynthesis, are the cause of the plasmalogen defect [43–45]. Despite this genetic heterogeneity, all forms of RCDP share the same clinical presentation, which indicates that the presentation of RCDP type 1patients is primarily caused by the plasmalogen defects, although the defects in β- and α-oxidation may worsen or modulate the disease state [46,47]. Although there is no obvious genotype–phenotype correlation in any of the RCDP types, atypical presentations (usually lacking the bone defects and the shortening of proximal bones) have been described and linked to high residual levels of plasmalogens [33,38,48–50].

In Zellweger patients the lack of functional peroxisomes also leads to a defect in the biosynthesis of plasmalogens [51]. The clinical presentation of Zellweger patients shares some features with that of RCDP patients, but the disease severity is greater (including hypotonia, cranial and facial dysmorphism, hepato- and splenomegaly) since all peroxisomal functions are impaired in Zellweger patients [52–54]. MRI finding may include dysmyelination, and a severe defect in neuronal migration seen as cerebral cortical microgyria and pachygyria, cerebral and cerebellar neuronal heterotopias and dysplasias of the inferior olive [55–58]. Given the multitude of biochemical abnormalities it becomes difficult to attribute a given symptom or tissue pathology to one of the biochemical defects.

Recently, reduced levels of plasmalogens have been found in X-linked adrenoleukodystrophy (ALD) and D-bifunctional protein (DBP) deficiency, two peroxisomal disorders etiologically unrelated to RCDP [59,60]. ALD is primarily characterized by adrenal insufficiency, testicular atrophy and inflammatory demyelination of the central nervous system [61–65]. At the biochemical level ALD is characterized by the accumulation of very-long-chain fatty acids due to impaired β-oxidation [66–68]. The molecular basis of ALD lies in mutations in the *ABCD1* gene, encoding a peroxisomal transmembrane protein belonging to the ATP-binding-cassette (ABC) transporter family, which is thought to function as a transporter of fatty acids [69–71]. ALD has a complex presentation and variable onset of disease (see chapters in this issue by S. Kemp and A. Pujol). Recently, a detailed study in affected areas of the brain from ALD patients has revealed low levels of plasmalogens [59]. The deficiency in plasmalogens in active demyelinating areas may act synergistically with the accumulation of VLCFA and thereby exacerbate the pathology and accelerate disease progression.

The clinical presentation of D-bifunctional protein (DBP) deficiency is characterized by neonatal hypotonia, seizures, craniofacial dysmorphism and visual and hearing impairment [72,73]. At the biochemical level the disorder is characterized by a defect in peroxisomal β-oxidation with accumulation of VLCFA, branched-chain fatty acids (*e.g.* pristanic acid) and bile acid intermediates (di- and trihydroxycholestanoic acids) [72,73]. Phospholipid analyses in the brain of a DBP patient revealed a decreased amount of plasmalogens in gray matter [60]. These findings warrant further analyses in other DBP patients, and the investigation if the observed defects are related to an impairment in the biosynthesis of plasmalogens or an increased degradation. Previous work has shown that acyl-CoA generated in peroxisomes through β-oxidation can be used in the biosynthesis of plasmalogens [74]. This link between two distinct peroxisomal pathways, may suggest that impairments in peroxisomal β-oxidation can affect plasmalogen levels as seen in ALD and DBP patients. Nevertheless, studies in mice with defects in peroxisomal β-oxidation did not show a correlation between impaired peroxisomal β-oxidation and abnormalities in plasmalogen levels [21,75]. Similarly to what has been observed in ALD, a plasmalogen deficiency may increase the nervous tissue pathology in DBP patients, although in DBP the plasmalogen deficiency seems to be more pronounced in gray matter, whereas in ALD the deficiency in plasmalogens is localized to affected white matter regions.

Interestingly, reduced plasmalogen levels have also been found in non-peroxisomal disorders. These include Alzheimer's disease [76–80], Parkinson's disease [81], Gaucher disease [82] and Pelizaeus–Merzbacher disease (PMD) [83]. In PMD, a leukodystrophy caused by mutations in the *PLP1* gene encoding the myelin proteolipid protein-1, levels of plasmalogens are reduced in fibroblasts and lymphocytes from PMD patients [83]. In Alzheimer's disease, reduced levels of

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