The mouse as a model to understand peroxisomal disorders
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Peroxisomes are single-membrane bound organelles that are present in all eukaryotic cells with the exception of erythrocytes. In mammals peroxisomes perform a multitude of functions including amongst others, (1) β-oxidation of fatty acids including very-long-chain fatty acids (VLCFA), (2) α-oxidation of phytanic acid, and (3) biosynthesis of plasmalogens. In humans a group of disorders is characterized by lack of peroxisomes or impairment in one of its functions. Collectively these disorders are called Human Peroxisomal Disorders (HPD), and a few examples include: (i) Zellweger syndrome, (ii) Rhizomelic Chondrodysplasia Punctata (RCDP), (iii) X-linked adrenoleukodystrophy, and (iv) Refsum’s disease. Based on the clinical presentation of the different HPD we conclude that peroxisomes are important for the normal well-being and health, as well as, the normal function and development of several tissues including liver, kidney, brain, bone, eye and testis. Although the biochemical and genetic basis of HPD are well characterized, the pathology and the mechanisms behind the pathology remain, in some cases, elusive. Our goal was to continue the characterization of HPD by studying the genetic basis and generate mouse models that would assist in the understanding of the pathology as well as assisting in the development of putative therapies.

Of the different functions performed by peroxisomes we first focused our attention on plasmalogens. Plasmalogens belong to a special class of glycerophospholipids characterized by the presence of an α,β-unsaturated ether-bond (also called vinyl ether bond) at the sn-1 position of the glycerol backbone. Plasmalogens have been implicated in several biological processes where they can affect membrane fluidity, mediate signal transduction and protect against oxidative stress (see Chapter 2). The importance of plasmalogens for human health is highlighted by the observation that plasmalogen deficiency is the biochemical basis of the HPD, RCDP. RCDP is a complex disorder characterized by the presentation of bone, brain and eye abnormalities. Although different genetic forms of RCDP exist, they all share a common clinical presentation and the impaired biosynthesis of plasmalogens. The most frequent form of RCDP, i.e., RCDP type-1, is caused by mutations in the PEX7 gene (see Chapter 3). PEX7 encodes the Peroxin 7, one of the cytosolic receptors involved in the import of proteins from the cytosol to the peroxisomal matrix. As a consequence of the lack or impaired function of Peroxin 7, cells from RCDP type-1 patients cannot import three different proteins into peroxisomes, namely: (1) acetyl-Coenzyme A acyltransferase 1 (ACAA1; also called peroxisomal 3-oxoacyl-Coenzyme A thiolase or thiolase), (2) alkylglycerone phosphate synthase (AGPS; also called alkyl-dihydroxyacetonephosphate synthase, ADHAPS or alkyl-DHAP synthase) and (3) phytanoyl-CoA 2-hydroxylase (PHYH). At the biochemical level RCDP type-1 patients primarily display defects in plasmalogen biosynthesis and phytanic acid α-oxidation. In order to understand the pathophysiological consequences behind RCDP type-1 patients, we generated a mouse model for this disorder by knocking-out part of the mouse Pex7 gene. This mouse model, i.e., the Pex7 knockout mouse, developed all the biochemical and pathologic hallmarks of RCDP type-1 patients (see Chapter 4). Using the Pex7 knockout mouse we were able to evaluate a putative therapy for RCDP patients using an alkyl-glycerol to rescue the plasmalogen defect. It is known for a long time that alkyl-glycerols, i.e., monoalkyl ethers of glycerol (e.g. 1-
O-hexadecylglycerol (chimyl alcohol) or 1-O-octadecylglycerol (batyl alcohol) are able to circumvent the peroxisomal steps involved in the biosynthesis of plasmalogens and normalize the levels of plasmalogens in fibroblasts from RCDP patients. We showed that a batyl alcohol enriched diet, can restore plasmalogen levels in multiple tissues from Pex7 knockout mice and, prevent and rescue the pathology caused by the plasmalogen deficiency (see Chapter 6). This in vivo work should encourage trials in human disorders with plasmalogen defects in which the reduced levels of plasmalogens are the cause of the pathology or may modulate the disease progression. Reduced plasmalogen levels have also been found in non-peroxisomal disorders including Alzheimer’s disease, Gaucher’s disease, dementia and ischemia. We have also studied a possible link between plasmalogens and X-linked adrenoleukodystrophy (X-ALD). X-ALD is a peroxisomal disorder caused by mutations in the ABCD1 gene, encoding the ALD-protein (ALDP) a transmembrane protein belonging to the ATP-binding-cassette (ABC) transporter family, and is characterized by the accumulation of VLCFA in plasma and tissues. The most severe form of X-ALD, called the cerebral ALD variant, is characterized by a severe and rapidly progressing inflammatory demyelination of the brain. It is not fully understood how the accumulation of VLCFA leads to the demyelination and the different presentations of X-ALD. We hypothesized that a deficiency in plasmalogens could play a role in the mechanism through which the accumulation of VLCFA leads to loss of myelin and impaired neuronal function. To test our hypothesis we generated a double knockout mouse lacking plasmalogens and accumulating VLCFA in brain (i.e., the Pex7:Abcd1 double knockout mouse) (see Chapter 5). Our initial results showed that plasmalogens may modulate the pathology caused by VLCFA accumulation. The consequences of VLCFA accumulation were more severe in the absence of plasmalogens, highlighting the importance of these phospholipids for the maintenance of myelin and function of the nervous system. Our results in the mouse have been corroborated by the finding of reduced plasmalogen levels in affected areas of brain samples from X-ALD patients.

Finally, we have also generated a mouse model for Refsum’s disease. Refsum’s disease is a peroxisomal disorder characterized by an impairment in the α-oxidation of phytanic acid, leading to the accumulation of high levels of phytanic acid in plasma and tissues. Clinically, Refsum patients are characterized by: retinitis pigmentosa, peripheral neuropathy, cerebellar atrophy and anosmia. The disorder is caused by mutations in the PHYH gene. The encoded protein, phytanoyl-CoA hydroxylase (PHYH), is the enzyme responsible for the first step in the α-oxidation of phytanic acid. We generated a mouse model for Refsum’s disease by knocking-out part of the mouse Phyh gene (i.e., the Phyh knockout mouse). Our initial characterization of the Phyh knockout mouse showed that, it developed the biochemical and pathologic hallmarks of Refsum’s disease (see Chapter 7). In the Phyh knockout mouse, the accumulation of phytanic acid was correlated with the amount of phytol (the precursor of phytanic acid) in the diet and the accumulation of phytanic acid led to abnormalities in brain, nerve, liver and testis. The continuous characterization of the Phyh knockout mouse should provide us with a better understanding of the pathophysiologic mechanisms behind the accumulation of phytanic acid and should also be useful in evaluating putative therapies for Refsum’s disease.
The use of mouse models to understand human peroxisomal disorders should continue to provide us with important clues related to the biochemistry of impaired peroxisome metabolism and to the ensuing physiological consequences. Although there is a difference between mice and men, which should always be carefully analyzed, studies using mouse models provide us with better tools to achieve experiments of proof-of-principle and test therapeutic approaches that can then be translated to human health.