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Peroxisomes in brain development and function☆

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ABSTRACT

Peroxisomes contain numerous enzymatic activities that are important for mammalian physiology. Patients lacking either all peroxisomal functions or a single enzyme or transporter function typically develop severe neurological deficits, which originate from aberrant development of the brain, demyelination and loss of axonal integrity, neuroinflammation or other neurodegenerative processes. Whilst correlating peroxisomal properties with a compilation of pathologies observed in human patients and mouse models lacking all or individual peroxisomal functions, we discuss the importance of peroxisomal metabolites and tissue- and cell type-specific contributions to the observed brain pathologies. This enables us to deconstruct the local and systemic contribution of individual metabolic pathways to specific brain functions. We also review the recently discovered variability of pathological symptoms in cases with unexpectedly mild presentation of peroxisome biogenesis disorders. Finally, we explore the emerging evidence linking peroxisomes to more common neurological disorders such as Alzheimer's disease, autism and amyotrophic lateral sclerosis. This article is part of a Special Issue entitled: Peroxisomes edited by Ralf Erdmann.

1. Introduction

Peroxisomes are single membrane-bound organelles, which harbor a variety of biochemical reactions and metabolic pathways that contribute to different physiological functions in eukaryotic organisms. Peroxisomes are found ubiquitously, but their number, shape and enzymatic content appear variable and differ between organisms and tissues and even upon changes in the environment [1]. In this review, we restrict the discussion to peroxisomal functions in the mammalian nervous system, with a specific focus on human physiology and pathophysiology supplemented by observations made in various mouse models. In mammals, peroxisomes contain around 50 different proteins [2], which exert a variety of catabolic and anabolic reactions as, for example, the degradation of very long-chain fatty acids (VLCFA)[1], dicarboxylic acids, branched-chain fatty acids, or parts of the biosynthesis of ether phospholipids or specific polyunsaturated fatty acids [3].

The importance of peroxisomes for mammalian physiology is highlighted by the existence of a variety of severe inherited human diseases caused by the complete or partial loss of peroxisomal functions. These diseases have been subdivided into *peroxisome biogenesis disorders* (PBD), in which the formation of functional peroxisomes is disturbed, and *single enzyme and transporter deficiencies* lacking individual enzymatic activities that are performed by peroxisomes. Patients suffering from PBD show a broad spectrum of symptoms summarized as Zellweger spectrum disorders and rhizomelic chondrodysplasia punctata (RCDP) type 1. The genetic basis for each PBD is a mutation in one of 14 *PEX* genes, which encode proteins termed peroxins (PEX proteins or peroxisome biogenesis factors), which are involved in the biogenesis of the organelle (Table 1). All peroxisomal enzymes and membrane proteins contain a targeting signal, which is necessary and sufficient to mediate the interaction of the encoding protein with a receptor protein that translocates its cargo to peroxisomes and initiates the import. These processes are carried out by the PEX proteins (Fig. 1), which are either involved in the import of matrix proteins (PEX1, 2, 5, 6, 7, 10, 12, 13, 14, 26) or of membrane proteins (PEX3, 16 and 19) [4]. Soluble proteins harbor such peroxisome targeting signal (PTS) sequences either at their extreme C-terminus (type 1, PTS1) or close to their N-terminus (type 2, PTS2), whereas membrane proteins contain targeting signals for membrane proteins (mPTS). PTS1 is required for the interaction with the cytoplasmic receptor PEX5, PTS2 for the interaction with PEX7 and the mPTS for the interaction with PEX19. This is the reason why in Zellweger spectrum patients, on the cellular level, peroxisomes are either absent or empty (ghosts).

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[1] Abbreviations: Aβ, amyloid-β; ABC, ATP-binding cassette; ACAA, acetyl-CoA acyltransferase; ACOX, acyl-CoA oxidase; AD, Alzheimer's disease; ADHAPS, alkyldihydroxyacetone phosphate synthase; ALS, amyotrophic lateral sclerosis; AMACR, 2-methylacyl-CoA racemase; AMN, adrenomyeloneuropathy; CALD, cerebral X-ALD; CNS, central nervous system; CT, computed tomography; DAO, D-amino acid oxidase; DBP, D-bifunctional protein; DDO, D-aspartate oxidase; DHA, docosahexaenoic acid; DHAPAT, dihydroxyacetone phosphate acyltransferase; DHCA/THCA, di-/trihydroxycholestanoic acid; ER, endoplasmic reticulum; FAR, fatty acyl-CoA reductase; IDE, insulin-degrading enzyme; KO, knockout; MRI, magnetic resonance imaging; PBD, peroxisome biogenesis disorders; PEX, peroxin; PHYH, phytanoyl-CoA hydroxylase; PMP, peroxisomal membrane protein; PNS, peripheral nervous system; PTS, peroxisomal targeting signal, RCDP, rhizomelic chondrodysplasia punctata; ROS, reactive oxygen species; SCPx, sterol carrier protein X; VLCFA, very long-chain fatty acids; X-ALD, X-linked adrenoleukodystrophy.

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Table 1
Genetic basis of peroxisomal disorders.

Gene	Protein	Disease	Phenotype MIM	Reference
Peroxisome biogenesis disorders				
		Zellweger syndrome spectrum disorder		
PEX1	Peroxin 1 (PEX1)	Zellweger syndrome,	214100	[316]
		neonatal adrenoleukodystrophy, infantile Refsum disease	601539	
PEX2	Peroxin 2 (PEX2)	Zellweger syndrome,	614866	[46]
		infantile Refsum disease	614867	[317]
PEX3	Peroxin 3 (PEX3)	Zellweger syndrome	614882	[318]
PEX5	Peroxin 5 (PEX5)	Zellweger syndrome,	214110	[319]
		neonatal adrenoleukodystrophy	202370	
PEX6	Peroxin 6 (PEX6)	Zellweger syndrome,	614862	[320]
		neonatal adrenoleukodystrophy, infantile Refsum disease	614863	[321]
PEX10	Peroxin 10 (PEX10)	Zellweger syndrome,	614870	[322]
		neonatal adrenoleukodystrophy	614871	
PEX12	Peroxin 12 (PEX12)	Zellweger syndrome,	614859	[323]
		neonatal adrenoleukodystrophy, infantile Refsum disease	266510	[324]
PEX13	Peroxin 13 (PEX13)	Zellweger syndrome,	614883	[325]
		neonatal adrenoleukodystrophy	614885	[326]
PEX14	Peroxin 14 (PEX14)	Zellweger syndrome	614887	[327]
PEX16	Peroxin 16 (PEX16)	Zellweger syndrome	614876	[328]
		Mild Zellweger syndrome spectrum disorder	614877	[58]
PEX19	Peroxin 19 (PEX19)	Zellweger syndrome	614886	[329]
PEX26	Peroxin 26 (PEX26)	Zellweger syndrome,	614872	[330]
		neonatal adrenoleukodystrophy, infantile Refsum disease	614873	
PEX11β	Peroxin 11β (PEX11β)	Mild Zellweger syndrome spectrum disorder	614920	[331,332]
PEX7	Peroxin 7 (PEX7)	**Rhizomelic chondrodysplasia punctata type 1**	215100	[176–178]
			614879	[190]
Single peroxisomal enzyme and transporter deficiencies				
Fatty acid β-oxidation				
ACOX1	Acyl-CoA oxidase 1 (ACOX1)	Acyl-CoA oxidase deficiency	264470	[333]
HSD17B4	D-Bifunctional protein[a]	D-Bifunctional protein deficiency	261515	[334]
		Perrault syndrome 1	233400	[85]
SCP2	Sterol carrier protein 2 (SCP2)[b]	Sterol-carrier-protein X deficiency	613724	[102]
AMACR	α-Methylacyl-CoA racemase	α-Methylacyl-CoA racemase deficiency	614307	[93]
		Congenital bile acid synthesis defect 4	214950	
ABCD1	ATP-binding cassette transporter, subfamily D, member 1 (ABCD1)	X-linked adrenoleukodystrophy	300100	[108]
ABCD3	ATP-binding cassette transporter, subfamily D, member 3 (ABCD3)	ATP-binding cassette transporter, subfamily D, member 3 deficiency	616278	[335]
Fatty acid α-oxidation				
PHYH/PAHX	Phytanoyl-CoA hydroxylase (PHYH, PAHX)	Refsum disease	266500	[170,336]
Ether phospholipid biosynthesis				
GNPAT	Dihydroxyacetone phosphate acyltransferase (DHAPAT)	Rhizomelic chondrodysplasia punctata type 2	222765	[179]
AGPS	Alkyl-dihydroxyacetone phosphate synthase (ADHAPS)	Rhizomelic chondrodysplasia punctata type 3	600121	[180]
FAR1	Fatty acyl-CoA reductase 1 (FAR1)	Rhizomelic chondrodysplasia punctata type 4/peroxisomal fatty acyl-CoA reductase 1 deficiency	616154	[183]
PEX5	Peroxin 5 long isoform (PEX5L)	Rhizomelic chondrodysplasia punctata type 5	–	[185]
Bile acid maturation				
BAAT	Bile acid CoA:amino acid N-acyl-transferase (BAAT)	Familiar hypercholanemia/bile acid-CoA: amino acid N-acyltransferase deficiency	607748	[337]
Glyoxylate metabolism				
AGXT	Alanine-glyoxylate aminotransferase (AGXT, AGT)	Primary hyperoxaluria type I	259900	[338]
Hydrogen peroxide metabolism				
CAT	Catalase	Acatalasemia	614097	[339]
Others				
ALDH3A2	Fatty aldehyde dehydrogenase (FALDH)[c]	Sjögren–Larsson syndrome	270200	[340]
DAO	D-Amino acid oxidase (DAO, DAAO)	Amyotrophic lateral sclerosis	105400	[254]

[a] Alternative names: 17-β-hydroxysteroid dehydrogenase IV (HSD17B4)/multifunctional protein 2 (MFP2).
[b] Alternative name: sterol carrier protein X (SCPX).
[c] Two isoforms are known residing in peroxisomes and the ER, which precludes attribution of the disease to a particular variant.

The symptoms of patients with peroxisomal single enzyme and transporter deficiencies have a broad heterogeneity, related to differences in the physiological role of the affected metabolic pathway or reaction [5]. In this group of inherited diseases, mutations have been identified in 13 different genes encoding peroxisomal enzymes and in two genes encoding peroxisomal transporter proteins (Table 1; Fig. 1).

The brain is the most elaborate organ of the mammalian body and consists of a variety of tissue-specific cell types: neurons (with hundreds of different subtypes), oligodendrocytes, astrocytes and microglia. These differ in structure and function but cooperate tightly to perform all the tasks attributed to the brain. Moreover, the structural complexity of brain organization requires a precisely coordinated developmental process to accomplish its proper formation. The central nervous system (CNS; brain and spinal cord) and the peripheral nervous system (PNS) use the same mechanisms for communication between neurons, which transmit information by chemical synapses between cells. In addition, efficient propagation of the electrical signal (action

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