

Peroxisomal disease

Peroxisomes

These organelles are abundant in tissues where lipid metabolism is active (they are most abundantly present in the cytoplasm of hepatocytes, in the epithelial cells of kidney canals or in oligodendroglia (brown fat). There are on average around a hundred to a thousand of them in one cell). They are structurally similar to lysosomes and mitochondria. While mitochondria have a double membrane (see mitochondria), peroxisomes have a simple trilaminar membrane , which is relatively well permeable to hydrophilic molecules, surrounding a finely granular matrix. Peroxisomes are present in all cell types except erythrocytes and spermatozoa and are 0.05–2 micrometers in size.

Enzyme substrates, smaller than 800 daltons, pass through the membrane through non-specific pores - two proteins with molecular weights of 22 and 28 kDa are associated here. While lysosomes are characterized by acid phosphatase, peroxisomes are characterized by the enzyme catalase (catalyzes the reaction of decomposition of hydrogen peroxide into water and oxygen).

The human peroxisomal proteome includes the products of approximately 80 nuclear gDNA -encoded genes . These are both membrane and peroxisomal matrix proteins. The overwhelming majority of these proteins are associated with metabolic pathways located in peroxisomes . The last third of the proteins are called peroxins and play essential roles in the biogenesis and maintenance of the peroxisomal organelle population. The marker (exclusively represented and usable for detection in tissues) enzyme of peroxisomes is catalase , which can be detected either histochemically (using enzymatic activity) or immunohistochemically (specific antibody).

Peroxisome biogenesis

Peroxisome biogenesis (growth and fission) is still an undefined field in many aspects; especially regarding the recent hypothesis of de-novo synthesis of peroxisomes in the endoplasmic reticulum. Another open question remains the sharing of some protein components of biogenesis between peroxisomes and mitochondria (especially proteins associated with the cleavage of the networks of these organelles).

Compared to mitochondria, peroxisomes do not contain their own genetic information in the form of any form of nucleic acid . The entire peroxisomal proteome is encoded by nuclear gDNA, and most peroxisomal proteins (matrix proteins and membrane protein fractions) are synthesized on free cytosolic ribosomes or polyribosomes. The targeting of these proteins to pre-existing peroxisomes is mediated by short specific signal sequences of amino acids (the so-called peroxisomal targeting signal - PTS). Unlike proteins of the endoplasmic reticulum and mitochondria, peroxisomal proteins are transported across the limiting organelle membrane in a folded state, however, the exact molecular mechanism of this transfer has not been definitively established.

The rest of the peroxisomal membrane proteins are targeted to peroxisomes from the ER , most likely by vesicular transport. Recently, it has also been shown that some proteins enter peroxisomes from mitochondria. What has not yet been reliably documented is retrograde transport from peroxisomes to the ER or mitochondria.

The import of proteins into peroxisomes leads to volume expansion of the organelle, which subsequently results in peroxisomal fission.

Peroxisomes are degraded by microautophagy.

Peroxisomal metabolism

A number of anabolic and catabolic processes take place in peroxisomes. They primarily synthesize plasmalogens (phospholipids in which the fatty acid is bound by an ether bond, not an ester bond; they contain, for example, vinyl ethers of fatty acids). Peroxisomes further synthesize cholesterol and bile acids; they also undergo gluconeogenesis from amino acids and the formation of oxalic acid catalyzed by alanine:glyoxalate aminotransferase.

Of the catabolic reactions, it is mainly the degradation of hydrogen peroxide, by the effect of catalase (the most represented enzyme in peroxisomes) and the β -oxidation of fatty acids with a very long chain, with more than 24 carbons.

Oxidation of polyamines, ethanol, degradation of purines, hydroxylation of phytanic acid and degradation of pipecolic acid also take place here. Peroxisomes contain various antioxidant enzymes (catalase, glutathione-peroxidase, superoxide-dismutase), as well as fatty acid oxidases (saturated and unsaturated, and fatty acids with a very long chain). Fatty acid oxidation is analogous to that in the mitochondria, but while peroxisomes only break down about 10% of palmitic acid, 90% of the oxidation takes place in the mitochondria; longer and very long chain fatty acids are broken down exclusively in peroxisomes. The final products of β -oxidation are C6–C12 fragments (most often C8), which are further transferred to the mitochondria, where oxidation continues.

α -oxidation of fatty acids is also important, which enables the splitting of, for example, phytanic acid, which is produced by oxidation from phytol - part of chlorophyll. This substance contains a methyl radical on the beta carbon, which blocks classical β -oxidation; in humans, the intake of this substance is about 50-100 mg/day from various dairy products. However, the peroxisome also oxidizes D-amino acids and L-dihydroxy acids.

Peroxisomes contain aminotransferases, acyltransferases, as well as enzymes for the synthesis of cholesterol or dolichol (alcohol with a large number of carbons, which transfers carbohydrate molecules to proteins during the construction of various proteoglycans and glycoproteins). While in the mitochondria about 90% of the oxygen is converted to water and only the rest to superoxide, in the peroxisome the main product is peroxide. However, in both cases, the various reactive oxygen forms must be removed by CuZn- or Mn-superoxide dismutases, catalase and glutathione peroxidase, in order to prevent cell damage.

Peroxisomal disease

All peroxisomal functions are directly dependent on continuous peroxisomal biogenesis, i.e. on the import of components of the peroxisomal matrix and membranes. This feature of peroxisomal biology significantly distinguishes - among others - peroxisomal and mitochondrial disorders from each other. To date, approximately 24 different human diseases causally related to peroxisomal dysfunction have been described. In addition to relatively rare hereditary peroxisomal diseases, there are also more common disorders, such as some types of non-alcoholic steatohepatitis (steatosis of the liver associated with its inflammation), which are caused by abnormal peroxisomal function.

There are a number of hereditary metabolic defects that are the result of either a defect in the biogenesis and subsequent arrangement of the peroxisome or a defect in one or more peroxisomal enzymes. Therefore, two categories of disorders were classified:

1. Disorders of peroxisomal biogenesis with impairment of all functions

- Disruption of the import of peroxisomal matrix proteins resulting in complete loss of all peroxisomal functions.
- Zellweger's syndrome, adrenoleukodystrophy, infantile Refsum's disease - they form the Zellweger spectrum - they flow smoothly into each other.
- Diagnosis - massively increased plasma concentration of very long-chain fatty acids, limited plasmalogen biosynthesis, absence of intact peroxisomes in cultured fibroblasts, increased concentration of phytanic acid in rhizomelic chondrodysplasia punctata and classical Refsum's disease.

Prenatal diagnosis is possible for all forms.

- Zellweger syndrome - the most severe AR hereditary form of perox. The basis of the disease are defects in the genes of the PEX family, which code for peroxins (see above). Since the cell is unable to create peroxisomes, they are sometimes called "peroxisomal ghosts". Due to the lack of their functions, fatty acids with a very long chain accumulate in the brain, among other things. Children are characterized by craniofacial dysmorphism with a high forehead, hypertelorism (excessive distance between the eyes), sunken nose root and epicanthum, (skin fold above the upper eyelid) eye deviations are common (cataract, glaucoma, optic nerve dysplasia). Neurological syndromes include severe muscle hypotonia, neonatal convulsions, and arrest of psychomotor development. There is always a characteristic disorder of neuronal migration in the brain, cholestatic liver involvement with early development of cirrhosis is also common. Most patients have small cysts in the kidneys. There is no effective therapy yet. Patients die in infancy.
- Neonatal adrenoleukodystrophy (NALD) - here, too, the basis is a disorder of the genes encoding peroxins. A protracted course is characteristic. Dysmorphism is less pronounced, neonatal convulsions are a very common symptom, severe psychomotor retardation occurs, hepatomegaly with impaired liver function is often found, retinitis pigmentosa and deafness are characteristic, symptoms of adrenal insufficiency are fatigue, vomiting and pigmentation of the skin eyelashes. Survival into the second decade of life is possible. There is no effective therapy. Patients most often die before the age of 6.
- Infantile Refsum's disease - likewise, this disease is caused by defects in genes encoding peroxins. It probably has the easiest course. Manifestation occurs later, signs of facial dysmorphism are mild or absent. Achieved motor skills 1.-3. year they slowly regress. Neurological symptoms of a milder manifestation. Peroxisomes may be present. We regularly find hepatomegaly and adrenal atrophy, retinitis pigmentosa and deafness. Patients survive on average slightly longer than Zellweger syndrome and NALD (8 years of life). There is no therapy yet.
- Rhizomelic chondrodysplasia punctata - the basis for this disease is a defect in the PEX7 gene, which codes for factor seven of peroxisomal biogenesis. Characteristic symptoms are shortening of the proximal parts of the limbs, craniofacial dysmorphism, cataracts, psychomotor retardation, changes in the vertebral bodies and calcification of the epiphyses. There is no successful therapy.
- Other: Hyperpipecolic aciduria, Leber's amaurosis.

2. Diseases caused by individual protein deficits

- X-linked adrenoleukodystrophy - X-linked recessively inherited diseases are among the most common perox. peroxisome deficiency. The ABC-transporter ABCD1 leads to the accumulation of very long-chain fatty acids, to inflammatory demyelination of the CNS, to peripheral neuropathy, as well as to adrenal and testicular insufficiency. 6 forms with different clinical courses are described, and different phenotypes occur with an identical genotype even within the same family. Mostly boys are affected. More than half of female carriers show neurological problems.

- Children's cerebral form - the most severe clinical form with rapid progression of neurological symptoms. At the beginning of the disease, children are completely inconspicuous, symptoms start from 3-10. years of age with behavioral disorders, deterioration of vision and hearing. Over the course of several months, a vegetative stage develops with spastic tetraparesis, cerebral convulsions, and dementia. Patients die within three years of diagnosis.
- Cerebral form of adolescents - differs only in the age of manifestation.
- Cerebral form of adults - differs only in the age of manifestation.
- Adrenomyeloneuropathy – symptoms begin in the third decade, demyelination of the spinal cord and peripheral neurons leads to spastic paraparesis of the lower limbs, incontinence and somatosensory disorders.
- Addison-only form - isolated adrenal insufficiency.
- Asymptomatic form - without clinical symptoms.
- Diagnosis – increased plasma concentration of fatty acids with a very long chain, demyelinating deposits in the CNS mainly periventricular and occipital, mutation analysis , adrenal insufficiency (increased ACTH, decreased cortisol).
- Treatment - in the very early stages, bone marrow transplantation is the method of choice, which leads to complete recovery. In boys younger than 6 years, a special diet can delay the onset of neurological symptoms (administration of Lorenzo's oil - monounsaturated MK), which normalizes the plasma concentration of VLCAD. The prognosis depends significantly on the clinical form.
- classic Refsum's syndrome – a breakdown of phytanic acid leads to its accumulation in tissues and plasma. The disease manifests itself mainly in adolescence with peripheral neuropathy, cerebellar ataxia, retinitis pigmentosa (dysmorphia, mental retardation and liver function disorders are mostly absent). ichthyosis and insomnia.
 - Diagnosis - reduced nerve fiber conduction velocity, abnormal acoustic and visual evoked potentials, pathological electroretinogram, increased protein in the cerebrospinal fluid, increased serum phytanic acid, evidence of an enzyme defect in fibroblasts.
 - Treatment – diet (reduction of phytanic acid intake), treatment can stop tissue demyelination.
- Other: Peroxisomal acyl-CoA oxidase deficiency, Peroxisomal 3-oxoacyl-CoA thiolase deficiency, Akatalasemia (hydrogen peroxide oxidoreductase deficiency).

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References

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- MASOPUST, Jaroslav. Skripta *Patobiochemie buňky*
- http://www.sekk.cz/ELM_ukonceni.pdf[encyklopedie/A/AJEJK.htm](http://www.sekk.cz/ELM_ukonceni.pdfencyklopedie/A/AJEJK.htm)

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