Pexophagy and Peroxisomes in Neurological Disorders

Hala Abdullateef*
Synapse, Neuroscience Institute, Pakistan

*Corresponding Author**

Hala Abdullateef
Synapse, Neuroscience Institute, Pakistan
E-mail: shifaqureshi11@gmail.com

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Abstract

Endoplasmic Reticulum (ERs), lipid bodies, and mitochondria are all in communication with peroxisomes. varied parts of the brain have varied types, sizes, and forms of them. Additionally, peroxisomes are crucial for maintaining oxidative equilibrium, lipid synthesis, and degradation in the Central Nervous System (CNS), and their failure results in a number of neurological disorders. Pexophagy, which is the selective elimination of malfunctioning or unnecessary peroxisomes, has neuroprotective effects, suggesting a possible therapeutic target. However, the role of pexophagy in neurological diseases is mainly unstudied. The mechanisms of pexophagy crosstalk in neurological pathology require more research.

Keywords: Peroxisome• Pexophagy• Autophagy• Neurological diseases • Neuroprotection

Introduction

In the 1960s, Christian De Duve made the initial discovery of peroxisomes, which are tiny, membrane-bound organelles with a single membrane. They are versatile and all-pervasive. The peroxisomes also have direct interactions with other organelles, including the Endoplasmic Reticulum (ER), mitochondria, and lysosomes. Through both catabolic and anabolic routes, peroxisomes perform distinct activities in various cells. Reactive Oxygen Species (ROS) metabolism, lipid metabolism, and ether-phospholipid production might be considered the three main functions of peroxisomes. Additionally, peroxisomes are crucial for the innate immune system and inflammatory signaling. Peroxisomes play a crucial role in the formation of cellular membranes and myelin sheaths in the Central Nervous System (CNS). Additionally, peroxisome-produced ether phospholipids are crucial for maintaining the proper activities of glia and neurons [1]. Naturally, peroxisome malfunction is linked to neurological diseases including Peroxisome Biogenesis Disorders (PBDs), stroke, Parkinson's Disease (PD), etc. and is said to have caused terrible damage to the neural cells. Particularly in the CNS, peroxisomes are crucial organelles for preserving cellular homeostasis. By creating a variety of complex systems to regulate their quality and quantity, peroxisomes are able to retain their usual functions. The expansion and division of pre-existing peroxisomes or de novo synthesis from mitochondria and ER are two ways that new peroxisomes are produced. Pexophagy, a form of selective autophagy, is used to destroy excess or malfunctioning peroxisomes. Peroxisomal Membrane Proteins (PMPs) and Peroxins (PEXs), which are peroxisome biogenesis factors, mediate each production and degradation process. A crucial process that sustains homeostasis throughout diverse internal and external stress responses is selective autophagy of cellular organelles. In order to maintain peroxisome homeostasis, pexophagy, the selective autophagy of peroxisomes, is crucial. Additionally, a growing body of research has shown that pexophagy is crucial to the pathophysiology of neurological illnesses. The CNS's lipid metabolism and cellular redox homeostasis are both maintained in large part by peroxisomes. In contrast to other organelles, peroxisomes' physiological and pathological functions in the CNS are still poorly known [2].

Protein import from peroxisomes

Nuclear genes encode peroxisome-specific proteins, which are then synthesised on free cytosolic polyribosomes and transferred to peroxisomes. Freshly made proteins are bound in the cytosol by the cytosolic receptor proteins PEX5S, PEX5L, and PEX7, which subsequently direct them to the peroxisomal membrane. PEX5S and PEX5L are produced through alternative splicing of the *PEX5* gene's primary transcript. PEX7 must interact with PEX5L in order to be guided to the peroxisomal membrane. The receptor proteins are docked with matrix proteins in the peroxisomal docking complex, which is composed of the peroxisomal membrane proteins PEX14 and PEX13 [3].

Formation, division and proliferation of peroxisomes

Following membrane formation and the import of matrix proteins, peroxisomes divide concurrently with a number of processes, including elongation, constriction, and fission. Peroxisomal morphogenesis and division depend on a membrane peroxin called PEX11. Mammal peroxisomal division also requires the proteins Mitochondrial Fission Factor (Mff), fission 1, and Dynamin-Like Protein 1 (DLP1). Ectopic PEX11 expression causes peroxisome proliferation, whereas PEX11 deletion in mice and genetic flaws in human PEX11 cause peroxisome abundance to decrease. The protein's morphogenic activity is thought to be fueled by homo-oligomerization of PEX11 through its N-terminal domain. The homo-oligomerization of PEX11 and their interaction with membrane phospholipids, which results in peroxisomal membrane deformation, require amphipathic helixes in the N-terminal region of PEX11. Unexpectedly, membranes rich in PEX11 and peroxisomes both stretch in response to DHA, a polyunsaturated fatty acid abundant in peroxisomal -oxidation metabolites [4]. According to these results, PEX11 is required for the peroxisome elongation process and that in order for it to operate; PEX11 must interact with phospholipids that contain DHA in its N-terminal amphipathic region. DLP1, a member of the dynamin GTPase family, is essential for the membrane fission of peroxisomes and mitochondria by travelling to the sites of membrane constriction. DLP1 is predicted to facilitate the fission stage by generating large multimeric spirals. According to an increasing body of research, PEX11 forms a ternary fission machinery complex with Mff and DLP1 in the constricted membrane region of elongated peroxisomes, which promotes fission during peroxisome division. PEX11 promotes the GTPase activity of DLP1, highlighting the variety of functions performed during peroxisome division procedures [5].

Conclusion

Different tissues and cell types contain peroxisomes of various sorts, sizes, and forms. Uncertainty exists regarding the precise effects of these variations on peroxisome function in diverse cell types. The nervous system and brain are highly diverse, particularly in terms of shape, quantity, and function. As previously mentioned, peroxisomes are now understood to be responsible for a number of brain-related illnesses. Peroxisomes are crucial for lipid production, oxidative homeostasis, and breakdown. Both changed peroxisome activity and diminished peroxisome function are associated with neurological disorders. However, a detailed examination of the consequences and molecular specifics is required. Pexophagy, despite playing a critical role in cell physiology, has not been extensively studied in neurological illnesses. Studies have revealed the roles of adaptors in mediating pexophagy, including p62 and NBR1. These adaptors, however, are involved in other selective autophagic processes, such as xenophagy and mitophagy, and do not only contribute to pexophagy. Understanding the functions of peroxisomal proteins and pexophagy adaptors would make it possible to better comprehend the molecular mechanisms of pexophagy in neurological illnesses. Furthermore, the majority of the evidence is based on

preclinical animal studies, therefore we lack any clinical proof that pexophagy contributes to neurological illnesses.

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