REVIEW ARTICLE

The roles of prosaposin in neurological disorders: current understandings and prospects

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Abstract: Prosaposin is a multifunctional protein known for its regulatory role in lysosomal physiological functions and its involvement as a secreted protein in various physiological processes. It has been identified as a factor in several major neurological disorders, including Parkinson's Disease (PD), Alzheimer's disease (AD), Frontotemporal dementia (FTD), schizophrenia, and nerve injury. A comprehensive understanding of prosaposin's involvement in the pathological processes of these diseases and exploring their commonalities among different diseases could shed light on new strategies for understanding the mechanisms and treating various neurological disorders. This review summarizes the role of prosaposin in the pathogenesis of multiple neurological diseases and discusses its commonalities across these diseases, offering an outlook on future research directions regarding the diagnosis and treatment.

Keywords: Prosaposin; Saposin; Neurodegenerative disease; Neuropsychiatric disorders; Lysosome.

INTRODUCTION

Human prosaposin is an evolutionarily conserved 524 amino acid protein that primary sequence contains multiple conserved domains, including a signal peptide, four saposin-like domains (A, B, C, and D), and a lysosomal targeting signal (van Leent *et al.*, 2021; Zhao & Morales, 2000). The protein exhibits a high level of evolutionary conservation, ranging from avian to mammals, indicating its importance across species.

Prosaposin expression extends across various cell types, encompassing central nervous system cells (neurons, astrocytes, and microglia), and cells in the spinal cord (nerve cells, satellite cells, oligodendrocytes, and macrophages). The distribution of prosaposin in the nervous system lacks strong regional specificity and extends throughout the brain (including the cortex, hippocampus, substantia nigra, cingulate cortex, cerebellum, etc.) and spinal cord. Within the central nervous system, neurons exhibit high prosaposin expression compared to other cells like glia (Mendsaikhan *et al.*, 2019). Prosaposin is released as a secretory factor into various secretory fluids such as cerebrospinal fluid, semen, milk, pancreatic juice, and bile (Rebecca C Meyer, Michelle M Giddens, Brilee M Coleman, & Randy A Hall, 2014). However, the specific cellular origins of prosaposin in these substances and their relationship with diseases remain unexplored, necessitating further investigation into cell types.

Intracellularly, proteolytic processing of prosaposin leads to the formation of four sphingolipid activator proteins, known as saposins A, B, C, and D, which are situated within lysosomes, initiating

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sphingolipid hydrolysis by lysosomal hydrolases (Rebecca C. Meyer, Michelle M. Giddens, Brilee M. Coleman, & Randy A. Hall, 2014). Saposin A enhances galactocerebroside breakdown by activating β-galactosylceramidase. Additionally, it has been associated with the regulation of lysosomal enzymes and providing neuroprotection to glial cells. (Swift *et al.*, 2020). Saposin B is essential for the breakdown of cerebroside sulfates within lysosomes (Ahn, Faull, Whitelegge, Fluharty, & Privé, 2002). It acts as an enhancer of activity for various glycosphingolipid hydrolases and is involved in the degradation of several glycosphingolipids, including galactosylceramide and sulfatide (Sun *et al.*, 2008). Saposin C can protect β-glucosidase (Gcase) from proteolytic degradation (Sun *et al.*, 2009), whereas saposin D is known to specifically stimulate acid sphingomyelinase activity. Saposin dysfunction or loss leads to lysosomal storage disorders, leading to severe neurological deficits and complex glycosphingolipid accumulation in both neuronal and visceral tissues (Sun *et al.*, 2013). It is reported that a deficiency in saposin is linked to neurodegenerative lysosomal storage disorders in children, which led to early mortality within the first three months of life (Hindle, Hebbar, Schwudke, Elliott, & Sweeney, 2017). Moreover, reports suggest that a deficiency in saposin B leads to a lysosomal storage disorder, exhibiting clinical features akin to those observed in metachromatic leukodystrophy (Qi *et al.*, 1999). Furthermore, saposin C deficiency has been associated with Gaucher disease, resembling the characteristics of neuronopathic acid β-glucosidase deficiency variants (Champagne, Lamontagne, & Potier, 1994). These findings underscore the critical role of saposins in maintaining cellular homeostasis and lysosomal function, and their dysfunction can lead to severe pathological conditions.

In addition, full-length prosaposin also has neuroprotective effects, and increasing evidence supports that prosaposin exerts its protective role as a secreted factor. *In vitro* experiments have demonstrated that exogenous prosaposin promotes the survival and proliferation of neurons (Jiang *et al.*, 2019), and prevents programmed cell death in cultured neurons and neuroglial cells (Meyer, Giddens, Schaefer, & Hall, 2013). In astrocytes, prosaposin exerts its neuroprotective effects by activating its receptors, GPR37 and GPR37L1 (Meyer *et al.*, 2013). *In vivo* experiments have found that intraperitoneal injection of prosaposin in rats offers protective effects on the ischemic hippocampus, and significantly safeguards hippocampal neurons from kainic acid-induced neurotoxicity (Nabeka, 2021). These studies underscore the neuroprotective role of full-length prosaposin as a secreted protein.

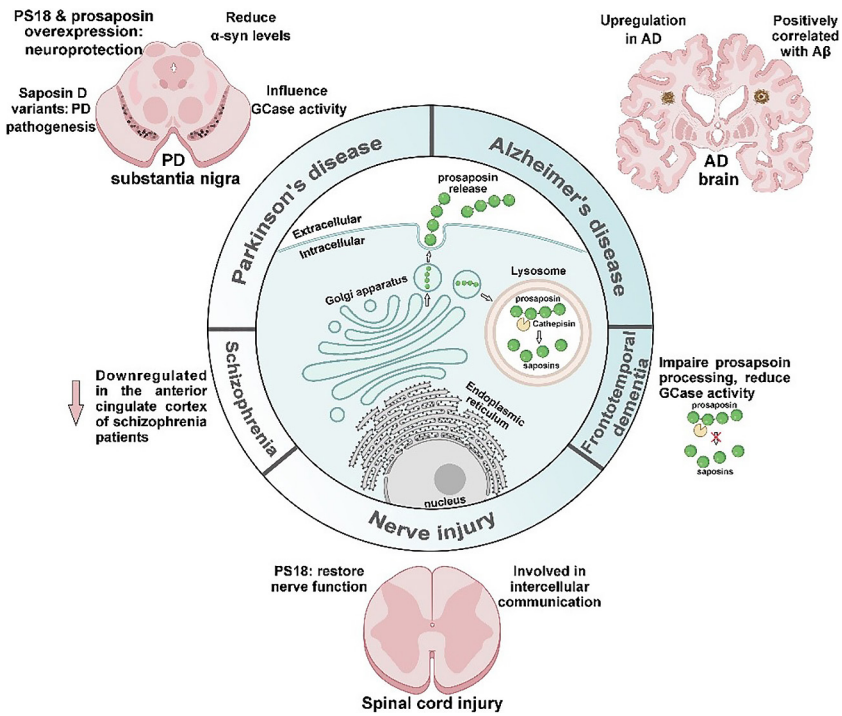

Figure 1. The biological processes of prosaposin and its role in neurological disorders.

This review elucidates the roles of prosaposin and saposins in neurological disorders, including Parkinson's Disease (PD), Alzheimer's Disease (AD), Frontotemporal dementia (FTD) and nerve injury (Fig. 1, Table 1). It explores common research themes regarding prosaposin and saposins across different neurological conditions. Additionally, the review offers a perspective on the future applications of prosaposin and saposins in the diagnosis and treatment of these diseases, highlighting their potential as a significant biomarker and therapeutic agent.

1. THE ROLES OF PROSAPOSIN AND SAPOSINS IN NEUROLOGICAL DISORDERS

Neurological disorders result from the combined influences of genetic and environmental factors and involve complex interrelationships among various cell types within them. Mutations in prosaposin or saposins, along with the abnormal regulation of prosaposin and saposins at the organismal, cellular, and organelle levels, intricately interconnect with diseases. For example, some of these diseases are related to intracellular lysosome dysfunction and disrupted glycosphingolipid metabolism. For example, neurological diseases are associated with intracellular lysosomal dysfunction and disturbances in glycosphingolipid metabolism. As a key player in maintaining cellular homeostasis and lysosomal function, prosaposin plays a key role in the pathogenesis and progression of such diseases. The specific role of prosaposin in neurological diseases will be explained below.

1.1. PD

PD is an intricate neurodegenerative condition, marked by the gradual demise of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the aggregation of intracellular Lewy bodies (LBs) and Lewy neurites (LNs). Intraneuronal buildup of LBs/LNs with misfolded α-synuclein (α-Syn) and selective destruction of midbrain dopamine (DA) neurons in the SNpc contribute to PD's primary motor symptoms, including bradykinesia, tremor, and postural instability (Luk *et al.*, 2012). The aberrant accumulation of pathologic α-syn as the primary constituent of Lewy bodies and neurites is intricately involved in the pathogenesis of PD through a multitude of pathways. Research suggests that saposin and full-length prosaposin play crucial roles in PD, including their impact on α-syn.

For prosaposin, it was reported that the protein levels of prosaposin were notably reduced in individuals with PD and exhibited a correlation with elevated levels of α-syn, indicating a potential protective role of prosaposin in PD (Ruz *et al.*, 2022). Recent animal experiments have also demonstrated the protective effects of prosaposin against PD. In 6-hydroxydopamine (6-OHDA) PD models, the administration of prosaposin-derived 18-mer peptide (PS18) which had trophic effects *in vitro* and *in vivo* (Kotani *et al.*, 1996), was found to significantly enhance motor behavior. PS18 exerts a protective effect against 6-OHDA-mediated neurodegeneration in PD animal models. This protective effect may be due to the resistance of PS18 to endoplasmic reticulum stress (Wu *et al.*, 2023). Moreover, in the 6-OHDA PD model, overexpression of prosaposin via adeno-associated virus (AAV) injection also alleviated dopaminergic degeneration in mice and reduced contralateral rotation in behavioral experiments (Y. He *et al.*, 2023). Taking into account that prosaposin is a secreted protein, delivering prosaposin to the brains of rats overexpressing α-syn via extracellular delivery revealed that it protected rats from α-syn-induced dopaminergic loss and hypolocomotion (Y. He *et al.*, 2023). In turn, mice lacking sufficient prosaposin in dopaminergic systems showed reduced dopaminergic markers, disrupted synaptic plasticity in the striatum, and behavioral deficits. In summary, prosaposin has demonstrated protective effects against PD in both patients and animal models, suggesting its potential in PD therapeutic interventions.

For saposins, they play a dual role in PD. On one hand, variants in saposin are linked to PD. Analysis based on both familial and sporadic PD cohorts indicated the presence of pathogenic mutations in saposin D, and further validation in mouse models confirmed that mutations in saposin D led to progressive motor decline and dopaminergic neurodegeneration (Oji *et al.*, 2020). On the other hand, saposins themselves, similar to prosaposin, exhibit protective effects against PD, which are closely linked to α-syn. α-syn aggregation in PD has been closely linked to lysosomal dysfunction, as emphasized in several investigations (Bellomo, Paciotti, Gatticchi, & Parnetti, 2020; Decressac *et al.*, 2013; Freeman *et al.*, 2013). Saposin C is known to interact with lysosomal enzyme GCase and enhance its enzymatic activity, thereby facilitating the degradation of glycosphingolipids within the lysosome (Tamargo, Velayati, Goldin, & Sidransky, 2012).

GCase has been identified as a significant genetic risk factor for the development of PD and related synucleinopathies, and its deficiency has been associated with α-syn accumulation and aggregation, which are key pathological features of PD (Do, McKinney, Sharma, & Sidransky, 2019; Menozzi & Schapira, 2020). The current research indicated that prosaposin was cleaved by cathepsin B to generate saposin C, jointly activating GCase activity. However, this process was disrupted in a PD genetic model (Kim, Jeong, & Krainc, 2022). Moreover, saposin C safeguarded GCase from α-syn inhibition by displacing α-syn from lipid membranes (Yap, Gruschus, Velayati, Sidransky, & Lee, 2013). These results demonstrated that saposins potentially exert their effects on PD by influencing GCase activity. Besides its involvement in lysosomal function associated with α-syn, saposins also participate in the clearance of α-syn. Saposin C effectively displaced α-syn from artificial glucosylceramide-enriched vesicles within lysosome. This suggests that saposin C acts as a neuroprotective agent, partially impeding α-syn aggregation by substituting it on the lysosomal membrane (Kojima *et al.*, 2022). To sum up, prosaposin and saposins play crucial roles in the pathology of PD. Besides, mutations in saposin are also considered as factors contributing to PD. This research suggests the potential involvement of both in the mechanisms of study and treatment of PD.

1.2. AD

AD progresses as a neurological condition marked by diminishing cognitive function and memory. It stands as the predominant form of dementia, accounting for the majority of dementia cases. The pathological features of AD include amyloid-beta (Aβ; derived from amyloid precursor protein) extracellular deposits in senile plaques, the intracellular creation of neurofibrillary tangles (NFTs; comprised of an anomalously phosphorylated tau protein), and the depletion of neurons and synapses (Scheltens *et al.*, 2021). Previous research results have indicated that posaposin and saposins influence the aforementioned three aspects of AD pathological features.

The accumulation of Aβ plaques is a prominent pathological feature of AD, contributing to the neurodegenerative process (Corti *et al.*, 2020). Aβ peptides, particularly $A\beta_{1\text{-}42}$, are known to aggregate and form fibrillar plaques. These plaques are considered a key contributor in the widespread neurodegenerative processes and memory impairment linked with AD (Hashimoto *et al.*, 2012). Prosaposin expression was mainly detected in Aβ plaques. Furthermore, in cases without dementia and low plaque density, Aβ plaques with prosaposin deposits were observed, suggesting that this constitutes an early stage in the formation of plaques. In AD patients, elevated expression of prosaposin has been observed, and the levels of prosaposin are positively correlated with Aβ (Mendsaikhan *et al.*, 2019). This human brain-based study illustrates prosaposin interactions in AD pathology. In AD mouse models, the association between saposins with plaques has also been observed (Sharoar, Palko, Ge, Saido, & Yan, 2021). Specifically, saposin C was localized around the dystrophic neurites surrounding Aβ plaque core in mouse models. During plaque growth, an increase in Saposin C expression was observed in younger model mice, while an apparent elevation in prosaposin expression occurred in the brains of older mice. This suggests distinct patterns of interaction between saposins and prosaposin with Aβ plaques.

NFTs are a defining pathological feature of AD, characterized by the intracellular accumulation of abnormally hyperphosphorylated tau protein. These tangles are observed in the neuronal cell bodies and processes, leading to disrupted neuronal function and eventual cell death. The presence of NFTs is strongly correlated with the cognitive deterioration and neurodegeneration observed in AD. It was reported that the immunoreactivity of prosaposin in neurons containing NFTs is weaker compared to neurons without NFTs, and was negatively correlated with the area occupied by phosphorylated tau (p-Tau) (Mendsaikhan, Tooyama, Serrano, Beach, & Walker, 2021). Research shows the autophagy-lysosomal pathway as the foremost route for the degradation of p-Tau in neurons (Mendsaikhan *et al.*, 2019). Simultaneously, prosaposin is an essential protein within the lysosomes. Therefore, it is speculated that prosaposin might play a role in the degradation of p-Tau. The continuous decline of prosaposin in the pathological process of AD suggests that it could potentially serve as a regulatory factor in AD pathology.

The loss of neurons and synapses is also one of the pathological features of AD. Recent research indicated that prosaposin, by promoting the activation of astrocytes, leads to neuronal synaptic loss, synaptic functional impairment, and morphological abnormalities, and prosaposin might be a potential regulatory factor in the pathological process of AD (Luo *et al.*, 2023).

Type	Disease	Model	Alteration	Function	References
Prosaposin	PD	White blood cells of PD patients	Downregulation	—	(Ruz *et al.*, 2022)
Prosaposin	PD	The postmortem brains of PD patients	Downregulation in DA neurons from PD patients	—	(Y. He *et al.*, 2023)
Prosaposin	PD	Plasma from PD patients	Upregulation in PD	—	(Freeman *et al.*, 2013)
Prosaposin	PD	6-OHDA mouse models injection of AAV for prosaposin overexpression; cell biodelivery of prosaposin in rat models overexpressing α-syn	—	Neuroprotective effect	(Y. He *et al.*, 2023)
Prosaposin	PD	SH-SY5Y cell line overexpressing prosaposin	—	Reduce α-syn levels	(Kojima *et al.*, 2022)
Prosaposin	AD	The postmortem brains of AD patients	Upregulation	The levels of prosaposin are positively correlated with Aβ	(Mendsaikhan *et al.*, 2019)
Prosaposin	AD	The postmortem brains of AD patients	—	The levels of prosaposin are negatively correlated with p-Tau	(Mendsaikhan *et al.*, 2021)
Prosaposin	AD	The postmortem brains of AD patients	Upregulation	—	(Luo *et al.*, 2023)
Prosaposin	FTD	The postmortem brains of FTD patients	—	The processing of saposin C by prosaposin results in impaired GCase activity	(Valdez *et al.*, 2020)
Prosaposin	Schizophrenia	The postmortem brains of schizophrenia patients	Downregulation	—	(Y. C. He *et al.*, 2022)
Prosaposin	Spinal cord injury	Mice with spinal cord injury	—	Participate in communications among oligodendrocytes	(Z. Wu *et al.*, 2023)
Prosaposin	Traumatic brain injury	Traumatic brain injury mouse models	Upregulation (prosaposin signaling pathway)	—	(Qiu *et al.*, 2023)
PS18	PD	6-OHDA rat PD models; primary dopaminergic neuron; SH-SY5Y cell line	—	Neuroprotective effect	(K. J. Wu *et al.*, 2023)
PS18	Neural tube defect	Chick embryos with spina bifida aperta	—	Enhance the regeneration/restoration process	(Khan *et al.*, 2023)
Saposin C	PD	White blood cell of PD patients	Downregulation	—	(Ruz *et al.*, 2022)
Saposin C	PD	Parkin KO cells	Downregulation	—	(Kim *et al.*, 2022)
Saposin C	AD	AD mouse brains	Upregulation	—	(Sharoar *et al.*, 2021)
Saposin D	PD	Familial and sporadic PD cohorts; mice with the saposin D variant	Variants in saposin D domain	—	(Menozzi & Schapira, 2020)

Table 1. Recent research on the association between prosaposin and neurological disorders.

It is noteworthy that research on prosaposin and saposins has primarily focused on exploring its relationship with AD pathology. However, whether changes in prosaposin are the cause of AD or a result of AD pathological alterations remains unclear. This may explain the seemingly contradictory results of prosaposin being positively correlated with Aβ and negatively correlated with NFTs. To elucidate the relationship between prosaposin and AD pathology, it is essential to combine prosaposin knockout models with AD animal models to explore the pathogenic mechanisms.

1.3. FTD

FTD encompasses a group of neurodegenerative diseases characterized by progressive impairments in behavior, executive function, or linguistic capabilities. The hallmark of FTD is the atrophy of the frontal and temporal lobes (Jee Bang, Salvatore Spina, & Bruce L. Miller, 2015). Mutations in *GRN*, the gene encoding progranulin (PGRN), were discovered in individuals diagnosed with FTD. These mutations typically result in decreased expression of the PGRN protein (Sephton, Cenik, Herz, & Yu, 2012). Both PGRN and prosaposin serve as crucial lysosomal proteins and exhibit a close association between them. Previous studies showed that PGRN assists in transporting prosaposin to the lysosome, where prosaposin is then cleaved into saposin A-D (Simon, Logan, DeVos, & Di Paolo, 2023). In FTD-PGRN patient cortical tissues and iPSC-derived PGRN mutant neurons, the processing of prosaposin to saposin C was significantly impaired within lysosome, resulting in reduced GCase activity (Valdez, Ysselstein, Young, Zheng, & Krainc, 2020). Targeting GCase as a potential therapeutic approach for numerous neurological disorders, such as PD (as previously mentioned), this study investigates the viability of GCase as a possible treatment strategy for FTD patients with PGRN mutations. Therefore, elucidating the function of prosaposin is particularly crucial in FTD, and future research should further focus on these molecules for investigation.

1.4. Schizophrenia

Schizophrenia, a multifaceted and impairing mental health condition, impacts around 1% of people worldwide (Shrivastava, Sousa, & Rao, 2016). The disorder is marked by various symptoms like hallucinations, delusions, disorganized thought patterns, and impaired cognition. The neurobiological basis of schizophrenia is thought to involve abnormalities in brain development, plasticity, and neurotransmitter systems (Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). Dysfunctions in the anterior cingulate gyrus are implicated in the pathological mechanisms of schizophrenia (Takahashi *et al.*, 2003). Protein analysis of the anterior cingulate cortex revealed a notable reduction in prosaposin levels observed solely in individuals diagnosed with schizophrenia when compared to the healthy control group. Mice with prosaposin knockout in the anterior cingulate cortex exhibited elevated anxiety-like behavior and impaired sensorimotor gating, which are manifestations of schizophrenia. Moreover, the absence of prosaposin in mouse brains leads to an upregulation of early gene expressions associated with schizophrenia, including Early growth response protein 1 (EGR-1) along with the activity-dependent cytoskeleton-associated protein (ARC) (He, Zhang, Flais, & Svenningsson, 2022). This suggests an important role of prosaposin in schizophrenia pathophysiology, but the specific mechanisms and clinical significance require further investigations.

1.5. Nerve injury

It has been reported that prosaposin is related to injuries in both the central and peripheral nervous systems. Current research indicates the involvement of the prosaposin/GPR37 and prosaposin/GPR37L1 ligand-receptor pairs in nerve injury and regeneration. Prosaposin has been associated with the G protein-coupled receptors GPR37 and GPR37L1, which are implicated in various neurological and neurodegenerative diseases. Through single-cell analysis of spinal cord injury models, the pivotal roles of prosaposin/GPR37 and prosaposin/GPR37L1 ligand-receptor pairs were identified among oligodendrocyte lineage cells. This finding indicates the involvement of prosaposin in cell communications following spinal cord injury, suggesting that prosaposin may play a potential role in the process of spinal cord injury (Z. Wu *et al.*, 2023). Similarly, in single cell analysis of traumatic brain injury, an upregulation of the prosaposin signaling pathway was identified. Prosaposin can promote neural progenitor cell proliferation and neurite growth, and may play potential roles

in neural regeneration (Qiu *et al.*, 2023). Another study focused on investigating the therapeutic role of prosaposin in central nervous system injury. It is shown that the prosaposin-derived peptide PS18 has a protective effect on the spinal cord, preserving it from secondary damage and aiding in the restoration of neural function (Khan *et al.*, 2023). This study targeted neural tube defects (NTDs), which are a group of congenital anomalies that result from the incomplete development of the neural tube. NTDs lead to mortality in fetuses and children, or result in lifelong neurological disabilities (Greene & Copp, 2014). Conducting functional experiments based on a chicken model of spina bifida aperta, which involved surgically manipulating the neural plate in chicken embryos by opening the neural tube, while simultaneously injecting PS18 into the embryo's amniotic cavity. Intra-amniotic treatment with PS18 reconstituted the neural tube, recovered postnatal motor functions, and protected neurons in the spinal cord. Based on the results, PS18 exhibits promise as a therapeutic agent for NTDs and holds potential for the treatment of various other forms of spinal cord injuries.

In the peripheral nervous system, the involvement of prosaposin/GPR37 and prosaposin/GPR37L1 is also observed. Prosaposin and its receptors GPR37/GPR37L1 were found upregulated in the developing DRG (Taniguchi *et al.*, 2021). By employing single-cell analysis targeting macrophages in the DRG, which are believed to aid in nerve repair and neuropathic pain, it was discovered that macrophages express prosaposin, and communicate with macrophage-like satellite glial cells through the prosaposin receptor GPR37L1 (Feng, Muraleedharan Saraswathy, Mokalled, & Cavalli, 2023). These studies showed the potential involvement of prosaposin in the development and neural repair within the DRG, yet there is currently a lack of mechanistic research.

Based on analyses across various injury models in the central and peripheral nervous systems, the signaling pathways involving prosaposin and its receptors GPR37/GPR37L1 deserve attention. Previous intracellular mechanism studies have demonstrated that prosaposin and its active fragment, prosaptide, mediate ERK signaling and cell protection by activating the orphan G protein-coupled receptors, GPR37 and GPR37L1 (Liu *et al.*, 2018; Meyer *et al.*, 2013). This provides certain indications for subsequent investigations into the mechanisms of nerve injury.

2. COMMONALITY STUDIES OF PROSAPOSIN AND SAPOSINS IN NEUROLOGICAL DISORDERS

Neurological disorders, while distinct in their characteristics, share commonalities in certain pathogenic mechanisms and pathological presentations. For example, previous findings indicated a convergence in clinical, pathological, and genetic aspects among FTD and prevalent neurodegenerative conditions like AD and PD (Jee Bang, Salvatore Spina, & Bruce L Miller, 2015). Studies in epidemiology have documented elevated incidences of PD among individuals with schizophrenia (Kuusimäki *et al.*, 2021; H.-L. Lin, Lin, & Chen, 2014). In turn, among individuals diagnosed with PD, symptoms related to schizophrenia, such as depression, sleep disturbances, and cognitive impairments, are commonly observed (Schapira, Chaudhuri, & Jenner, 2017). Genome-wide association study also revealed shared associated genomic loci between PD and schizophrenia (Smeland *et al.*, 2021), suggesting that shared molecular genetic mechanisms may underlie the common pathophysiological and clinical characteristics across these diseases. Besides, based on a prospective cohort study in the population, individuals with FTD-PGRN have been found to concurrently experience Lewy body disease (Forrest *et al.*, 2019). These studies suggest a potential pathological connection among neurological disorders.

Given the interconnections among various diseases, understanding the roles of prosaposin and saposins in these diseases and performing an in-depth analysis of the commonality of prosaposin in diseases offer potential therapeutic targets for drug development and treatment strategies. Analyzing the fundamental functions of prosaposin and saposins may provide insights into their common roles across various diseases.

For saposins, their fundamental function lies in promoting sphingolipid hydrolysis. Sphingolipids are prevalent in the brain, forming distinct profiles specific to different cell types that undergo characteristic modifications during developmental stages, aging, and in response to brain pathological changes. These changes in sphingolipid composition have been implicated in various neurological disorders, including AD, PD, and Huntington's disease (van Kruining *et al.*, 2020). Due to the heightened sensitivity of neurons to lipid accumulation, the absence or mutation of saposins leads to decreased

sphingolipid hydrolase activity, resulting in sphingolipid accumulation and causing neuronal damage, which could be a cause of these neurological disorders (Hindle *et al.*, 2017). On the other hand, Saposin C plays a protective role in GCase activity during sphingolipid hydrolysis (Morimoto, Yamamoto, O'Brien, & Kishimoto, 1990). Specifically, in FTD and other neurodegenerative diseases, the reduction in PGRN levels may contribute to the cleavage of prosaposin into saposin C within lysosomes, thereby reducing GCase activity, promoting the accumulation of tau and α-syn (Takahashi *et al.*, 2022; Valdez *et al.*, 2020). This indicates that the lysosomal PGRN-saposin C-GCase pathway could be a shared therapeutic target in various neurodegenerative diseases, such as FTD, AD and PD. Future research could focus on saposin function to prevent excessive sphingolipid accumulation and incorporate saposin-related pathways into studies of other diseases, providing insights into the mechanisms of these conditions.

For prosaposin, its fundamental role lies in serving as a secreted protein, exerting neuroprotective functions. It was reported that prosaposin stimulates intracellular signaling through its cell membrane surface receptors, GPR37 and GPR37L1, and elicits neuroprotective actions (Meyer *et al.*, 2013). Evidence has supported the engagement of GPR37 and GPR37L1 in neurological conditions, demonstrating their potential role in seizure susceptibility (Giddens *et al.*, 2017). Furthermore, a recent study reported impaired aversive memory formation in GPR37L1 knockout mice, indicating the involvement of GPR37L1 in cognitive processes (Veenit, Zhang, Paslawski, Mantas, & Svenningsson, 2022). Currently, there is limited research on the signaling pathways of prosaposin and GPR37/GPR37L1 in neurological disorders. Further investigation is required to determine whether this pathway could be applied in disease therapeutics in the future.

3. FUTURE PERSPECTIVES

In different types of neurological disorders, prosaposin and saposins exhibit their respective functions, as mentioned above. While current research mostly remains in the experimental stages, exploring prosaposin and saposins has become a highly promising issue. As research progresses, targeting prosaposin and saposins for disease diagnosis and treatment appears increasingly feasible.

In terms of diagnosing the disease, previous research investigating the potential role of prosaposin in disease diagnosis examined small-sample clinical data. The study indicated elevated prosaposin expression in the plasma of PD patients. Furthermore, PD patients were categorized into mild cognitive impairment PD (MCI PD) and cognitively normal PD groups, revealing increased plasma prosaposin expression in MCI PD cases (He *et al.*, 2023). Similarly, significant increases in prosaposin levels were noted in the AD patients' cerebrospinal fluid (CSF), as well as in preclinical AD cohorts. It highlights the potential of prosaposin in early disease diagnosis. Take AD as an example, $A\beta_{42}$, p-tau, and total tau protein are considered typical diagnostic targets. Pathological diagnosis based on a combination of magnetic resonance imaging and CSF markers ($A\beta_{42}$, p-tau, and total tau protein) has become the gold standard in clinical AD diagnosis, yet the accuracy of CSF diagnostics stands at 85%-90% (Weller & Budson, 2018). As research advances, the incorporation of novel CSF or blood markers in the future could aid in adjunctive AD diagnosis. To ascertain prosaposin's suitability as a diagnostic marker, large-scale clinical case testing is required, coupled with the integration of clinical data using artificial intelligence machine learning algorithms to determine if prosaposin enhances the diagnostic efficiency of AD. In other neurological disorders, further exploration is needed to understand the diagnostic role of prosaposin.

In terms of treating the disease, in various neurological disorders such as PD and NTD (Khan *et al.*, 2023; Kotani *et al.*, 1996; K. J. Wu *et al.*, 2023), prosaposin or its derived peptides have demonstrated the potential to alleviate pathology and improve behavior in animal models. Similarly, the neuroprotective and therapeutic effects of prosaposin can be extrapolated to other neurological disorders and might exhibit analogous functions in corresponding animal models. Prosaposin could potentially have clinical applications in neurological diseases through protein or peptide-based drug delivery in the future. Moreover, the research on the mechanisms and biological functions of prosaposin in diseases still offers substantial scope for exploration. Recently, in the human neuron genome-wide CRISPRi/a screen, prosaposin was implicated in lysosomal lipid dysregulation, leading to neuronal ferroptosis. Prosaposin loss resulted in lipofuscin and iron accumulation (Tian *et al.*, 2021). Although this study broadened the biological functions of

prosaposin, there remains a lack of association research with neurological disorders. Significantly, the buildup of lipofuscin is linked to the selective depletion of dopaminergic neurons in the substantia nigra, possibly linking prosaposin to PD (Lin & Zhang, 2021). Further investigation is needed to explore how prosaposin might mitigate lipofuscin accumulation, dampen neuronal ferroptosis, and mitigate the loss of dopaminergic neurons in models of PD disease. Currently, clinical trials have reported the use of iron chelators for treating PD (Martin-Bastida *et al.*, 2017). Considering the relationship between prosaposin and ferroptosis, prosaposin could emerge as a potential therapeutic approach for PD in the future, offering new insights into the treatment of other diseases as well.

CONCLUSION

In conclusion, prosaposin and saposins, as a multifunctional protein, play various roles in the pathogenesis, diagnosis, and treatment of neurological disorders. Mutations in saposins contribute to the pathogenesis of certain diseases (such as PD); however, prosaposin (or its derived peptides) and saposins also hold the potential for treating various disorders. The dual functionality of prosaposin and saposins underscores their involvement in complex disease processes, necessitating further elucidation of their pathophysiological functions. Additionally, the role of prosaposin in the diagnosis and treatment of multiple neurological diseases has been preliminarily reported, suggesting its potential as an auxiliary target in disease diagnosis and treatment.

List of abbreviations

AAV: adeno-associated virus
AD: Alzheimer's disease
Aβ: amyloid-beta
CSF: cerebrospinal fluid
DA: dopamine
FTD: frontotemporal dementia
Gcase: β-glucosidase
LB: Lewy body
LN: Lewy neurite
MCI PD: mild cognitive impairment PD
NFT: neurofibrillary tangle
NTD: neural tube defect
PD: Parkinson's disease
PGRN: progranulin
PS18: prosaposin-derived 18-mer peptide
p-Tau: phosphorylated tau
SNpc: substantia nigra pars compacta
α-Syn: α-synuclein
6-OHDA: 6-hydroxydopamine

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Conflict of interest

The authors declare no conflict of interest.

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