Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

VPS35-Retromer: Multifunctional Roles in Various Biological Processes – A Focus on Neurodegenerative Diseases and Cancer

Xiaoyang Fan, Yuqi Xie, Sitong Cao, Li Zhu, Xueting Wang

Institute of Special Environmental Medicine, Co-Innovation Center of Neuroregeneration, Nantong University, Nantong, People's Republic of China

Correspondence: Xueting Wang; Li Zhu, Institute of Special Medicine, Nantong University, No. 9, Seyuan Road, Chongchuan District, Nantong City, Jiangsu, 226009, People's Republic of China, Email wangxueting@ntu.edu.cn; zhulizhou@ntu.edu.cn

Abstract: The Vacuolar Protein Sorting 35 (VPS35)-Retromer complex plays a pivotal role in intracellular protein trafficking and recycling. As an integral component of the Retromer complex, VPS35 selectively recognizes and retrogradely transports membrane protein receptors to the trans-Golgi network, thereby preventing the degradation of transmembrane proteins by lysosomes after they have fulfilled their physiological functions, and facilitating their continued activity. VPS35 regulates autophagy, mitophagy, mitochondrial homeostasis, and various other biological processes, including epidermal regeneration, neuronal iron homeostasis, and synaptic function. Studies have shown that mutations or dysfunctions in VPS35 disrupt the normal operation of Retromer, impair neuronal health and survival, and contribute to the onset of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Additionally, VPS35 modulates tumor growth and metastasis in cancers such as liver and breast cancer through the regulation of multiple signaling pathways. Targeting VPS35 might be a potential therapy in clinic treatment of neurodegenerative diseases and cancers.

Keywords: vacuolar protein sorting 35, retromer, endosome-lysosome pathway, autophagy, mitochondrial homeostasis, Parkinson's disease, Alzheimer's disease, retinal ganglion cell degeneration, cancer, anemia

Introduction

The Retromer complex, a multi-subunit protein assembly, is primarily responsible for the retrograde transport of specific membrane protein cargos from endosomes to the trans-Golgi network (TGN) or plasma membrane. It is composed of five highly conserved subunits from the vacuolar protein sorting (VPS) family: VPS26, VPS29, VPS35, VPS5, and VPS17, with VPS5 and VPS17 contributing to membrane recognition. Among these, VPS35 is particularly essential. As a core component of the Retromer complex, VPS35 is essential for the recognition and binding of specific cargo proteins.[1] With a molecular weight of approximately 40 kDa, VPS35 features an N-terminal α-helix domain, a central β-pleated sheet region, and a C-terminal α-helix domain. These structural domains collectively form the three-dimensional architecture of VPS35, enabling its interaction with other subunits to establish a stable Retromer complex. Specifically, the N-terminus of VPS35 binds to VPS26, while the C-terminus interacts with VPS29, forming the core scaffold of the Retromer assembly.[2,3]

Structurally, the C-terminal region of VPS35 is composed of 13 α-helices, adopting a horseshoe-shaped, right-handed α-solenoid configuration.[2,4] This conformation not only extends the length of VPS35, providing additional binding sites for sorting nexins and receptor cargos, but also allows the structure to flexibly adjust its curvature, accommodating the curved membrane of vesicles.[5] In contrast, the N-terminal region of VPS35 comprises 20 α-helices, forming a slightly curved structure that binds to VPS26 and the sorting nexin dimer 3 (SNX3), thereby contributing to the formation of a T-shaped configuration.[6] The trimeric structure of the Retromer complex (VPS26, VPS29, and VPS35) is highly conserved across species. In organisms ranging from unicellular eukaryotes like Saccharomyces cerevisiae[7] and Schizosaccharomyces pombe[8] to more complex eukaryotic organisms such as Drosophila melanogaster,[2] Xenopus laevis,[2,9] mice,[10,11] rats, and humans, the sequences of the Retromer trimer exhibit substantial homology. For example,

Received: 6 December 2024
Accepted: 23 March 2025
Published: 3 April 2025

human *VPS35* shares 92.7% homology with Xenopus laevis *Vps35*, 99.4% homology with mouse and rat *Vps35*, and 99.5–100% homology with non-human primate *Vps35*.[1] The assembly of the Retromer complex occurs in multiple steps. Initially, VPS26 and VPS29 form a stable dimer through their N-terminal interactions, which constitutes the core scaffold of the complex. Subsequently, VPS35 binds to the VPS26/VPS29 dimer via its C-terminal α-helical domain, completing the Retromer complex. During this process, the N-terminal α-helix of VPS35 may also play a role in recognizing and binding specific cargo proteins. VPS35 is widely expressed across various human tissues, with expression levels varying between tissues.[1] This widespread distribution underscores the critical function of the VPS35-Retromer complex in maintaining cellular homeostasis and overall cellular function.

Cytological Functions of the VPS35-Retromer Complex

Cargo Recognition and Transport: The Core Role of VPS35 in the Retromer Complex

Intracellular cargo recognition and transport is a highly precise and coordinated process, with VPS35 playing a pivotal role as the core subunit of the Retromer complex. Initially, VPS35 interacts with VPS26 and VPS29 to form a stable trimeric structure of the Retromer complex.[12] This complex specifically recognizes and binds cargo proteins on endosomal membranes, typically through domains containing retrograde transport signal sequences.[13] This recognition process is the first step in cargo selection, ensuring that only the correct cargo is transported. Upon binding to the cargo, the Retromer complex induces membrane curvature, facilitating the formation of tubular or vesicular structures. This membrane deformation is facilitated by the cooperative action of the Retromer complex with other endosomal proteins, such as sorting nexins (SNXs), and cytoskeletal elements like microtubules.[14] This synergy not only promotes the formation of membrane tubes and vesicles but also provides the structural and dynamic support necessary for efficient cargo transport. Simultaneously with the formation of these membrane structures, the Retromer complex ensures the precise sorting of cargo proteins, selectively encapsulating them within the vesicles or tubules. This highly specific sorting process guarantees the accurate delivery of cargo proteins to their designated destinations. The resulting membrane tubes or vesicles then travel along the microtubule network toward the TGN or plasma membrane.[15] This transport process is a critical component of intracellular material cycling, which is essential for maintaining normal cellular function (Figure 1).

Upon reaching their target membranes, the vesicles fuse with them, releasing the cargo proteins into their final locations. This fusion process requires the involvement of several membrane fusion proteins and GTPases, ensuring both precision and efficiency in cargo delivery.[16] The accuracy of this membrane fusion event is critical for ensuring that cargo proteins reach their intended sites and perform their physiological functions. Following cargo delivery, the Retromer complex dissociates from the target membrane and, through a series of intricate molecular mechanisms, returns to the endosome to prepare for the next cycle of cargo transport.[17] This recycling of the complex is an essential aspect of intracellular material cycling, allowing cells to continuously perform cargo transport and maintain homeostasis. VPS35 is central to this process. As the core scaffold protein of the Retromer complex, VPS35 not only participates in the recognition and binding of cargo proteins but also stabilizes the complex and maintains its functionality through interactions with other subunits and accessory proteins. Mutations or dysfunctions in VPS35 disrupt the retrograde transport function of the Retromer complex, leading to the accumulation and mis-sorting of cargo proteins within the endosomes. This misrouting triggers cellular dysfunctions and contributes to various disease states.[18]

The functions of VPS35 extend beyond cargo transport; it also plays a key role in regulating various cellular physiological processes. For example, VPS35 is involved in the retrograde transport of the Wingless receptor protein from endosomes to the TGN, a process essential for proper Drosophila embryogenesis.[19] Additionally, VPS35 regulates the endosomal recycling of divalent metal transporter 1 (DMT1), which is critical for maintaining cellular iron homeostasis.[3] In addition to these roles, VPS35 significantly impacts mitochondrial functions. Studies have demonstrated that VPS35 participates in the transport of mitochondrial anchor protein ligase, influencing both mitochondrial morphology and function.[20] Moreover, VPS35 regulates the transport and degradation of mitochondrial E3 ubiquitin ligase 1 (MUL1), inhibiting MUL1-mediated degradation of mitochondrial fusion protein 2, which is essential for maintaining normal mitochondrial morphology and function.[21,22] These findings have been further supported by research into Parkinson's disease (PD), where VPS35 mutations lead to mitochondrial

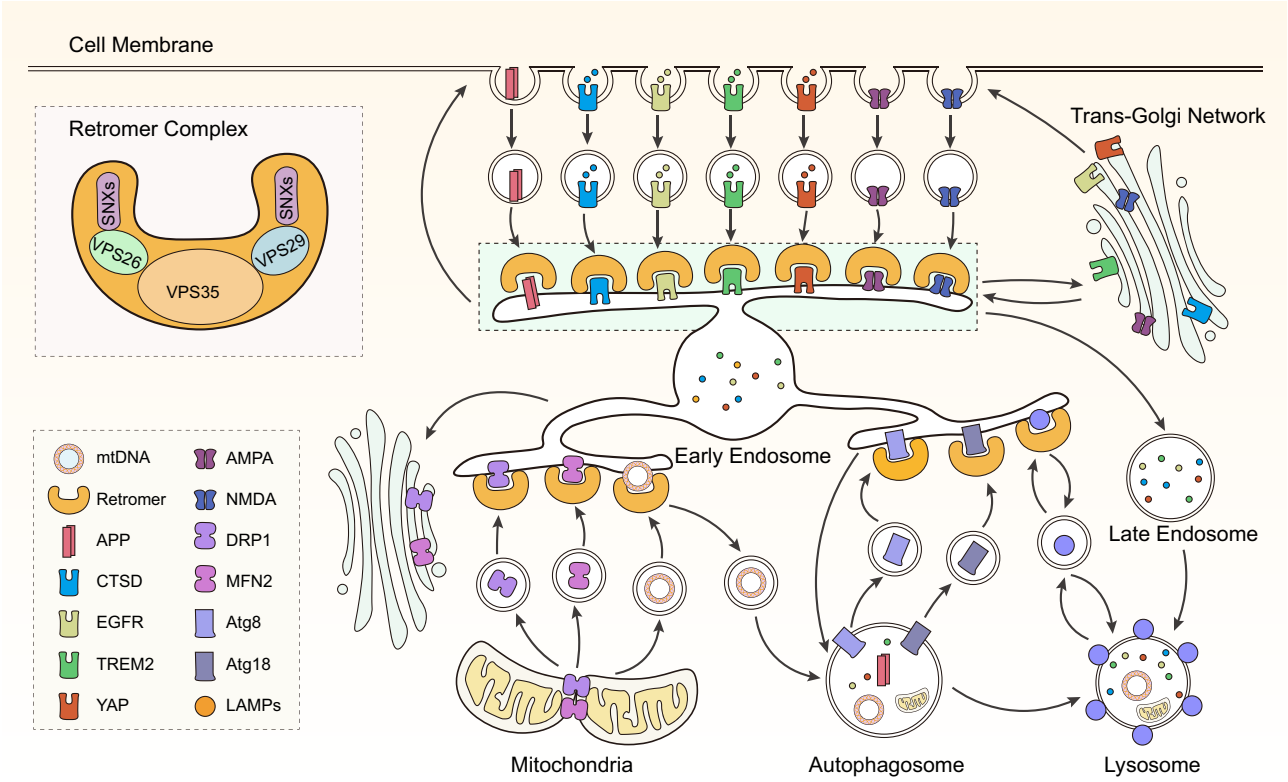

Figure 1 Cell biological functions of VPS35-retromer. The retromer complex is composed of three core components: VPS35, VPS26, and VPS29. The primary role of the retromer complex is to mediate the retrograde transport of cargos from endosomes to the trans-Golgi network (TGN) apparatus and plasma membrane, allowing these cargos to be reused within the cell and preventing their delivery to lysosomes for degradation. Specifically, membrane proteins can be directly retrogradely transported to the plasma membrane by the retromer or transported to the TGN for further processing before returning to the membrane. For mitochondrial and lysosomal proteins, they are transported from endosomes to the TGN, where they undergo processing before returning to the mitochondrial or lysosomal membranes. Additionally, the retromer can transport free mitochondrial DNA (mtDNA) into multivesicular body (MVB), preventing its accumulation.

fragmentation, disrupting normal cellular physiology.[23] Dysfunction of the Retromer complex's sorting function is closely linked to the onset of various diseases, including neurodegenerative disorders, cancer, infections, and immune deficiencies.[24]

In summary, as a core subunit of the Retromer complex, VPS35 plays an essential role in cargo recognition and transport, ensuring the stability and functionality of the complex. Beyond this, VPS35 is integral to several critical cellular processes, including embryogenesis, iron homeostasis, and the regulation of mitochondrial function and morphology. Thus, an in-depth investigation of the functions and regulatory mechanisms of VPS35 is essential for advancing our understanding of intracellular material cycling and the maintenance of cellular physiological functions.

Multiple Roles of VPS35-Retromer in Autophagy

As a core component of the Retromer complex, VPS35 is integral not only to protein sorting and transport but also to the regulation of intracellular degradation pathways. In cells with VPS35 silencing, there is an observed increase in autophagic flux coupled with impaired proteasomal activity.[25] Autophagy, a cellular process in which autophagosomes encapsulate substances for degradation and subsequently fuse with lysosomes, plays a vital role in maintaining intracellular homeostasis and responding to various stress conditions. The role of the VPS35-Retromer complex in autophagy is multifaceted, and its functions are critical to the efficient execution of this process.

During autophagy, cells must ensure the correct recycling of membrane proteins and receptors, which are essential at various stages of the pathway. VPS35, as a key component of the Retromer complex, mediates retrograde transport from endosomes to the Golgi apparatus, facilitating the recycling and reuse of important autophagy-related molecules, including LAMPs, Atg8, and Atg18.[13,16] This function is vital for the smooth progression of the autophagy pathway, and the absence of VPS35 results in the blockade of autophagy.[26] Studies have shown that impaired VPS35 function

https://doi.org/10.2147/JIR.S510768

disrupts the transport from endosomes to the Golgi, which in turn affects the recognition and processing of autophagic substrates.[27] The VPS35-Retromer complex plays a pivotal role in the selective recognition of autophagy substrates by identifying and binding to those containing specific retrograde transport signals. In Alzheimer's disease (AD) models, defects in Retromer function have been linked to increased β-amyloid (Aβ) production, suggesting that Retromer may influence autophagy substrate selection indirectly by affecting the transport and processing of Aβ precursors.[28]

Beyond its role in retrograde transport, VPS35 also regulates the formation and maturation of autophagosomes through interactions with other autophagy-related proteins. A key interaction occurs between VPS35 and the Wiskott-Aldrich Syndrome protein and scar homolog (WASH) complex, which plays an essential role in autophagosome formation. The WASH complex promotes actin polymerization during autophagosome formation, driving the creation of autophagosome precursors.[29] When VPS35 function is compromised, this interaction is disrupted, resulting in impaired autophagosome formation and reduced autophagic efficiency.[30]

The final step of autophagy involves the fusion of autophagosomes with lysosomes for the degradation of their contents. Although this fusion is primarily mediated by protein complexes such as soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) and the HOPS complex, VPS35 indirectly influences this process. By ensuring the proper distribution of key recognition molecules on the autophagosome membrane, VPS35 indirectly affects the efficiency of autophagosome-lysosome fusion.[31] Moreover, VPS35 plays a role in regulating lysosomal function and morphology, thereby impacting the degradation process within autophagosomes.[32] The acidic environment of lysosomes ensures normal fusion between autophagosomes and lysosomes.[33] Dysfunction in lysosomal acidification exacerbates the progression of neurodegenerative diseases.[34]

Given the critical role of VPS35 in autophagy, its dysfunction is closely associated with the onset and progression of various neurodegenerative diseases. A notable example is PD, where the D620N mutation in VPS35 has been extensively studied. This mutation impairs VPS35 function, thereby disrupting the normal flow of the autophagy pathway. The D620N mutation in VPS35 leads to a reduction in the number of autophagosomes, although partial restoration of autophagy function can be achieved by activating alternative autophagic pathways.[35] Individuals harboring the VPS35 D620N mutation exhibit progressive degeneration of dopaminergic neurons and synaptic dysfunction, which correlates with the key pathological features of PD.[18] Furthermore, VPS35 dysfunction may exacerbate neurodegenerative disease progression by disrupting other autophagy-related processes, such as mitophagy, which is essential for mitochondrial quality control.[36]

In summary, the VPS35-Retromer complex plays multiple vital roles in autophagy, including mediating the retrograde transport of autophagic substrates, regulating autophagosome formation and maturation, and indirectly influencing the fusion of autophagosomes with lysosomes. These functions collectively ensure the proper progression of the autophagy pathway, which is critical for maintaining cellular homeostasis and responding to cellular stress. Future research should further investigate the precise molecular mechanisms underlying VPS35's involvement in autophagy, as well as explore strategies to modulate VPS35 function to intervene in the development and progression of neurodegenerative diseases. Such studies could provide valuable theoretical and experimental insights for the development of novel therapeutic approaches.

Relationship Between VPS35-Retromer and Mitochondrial Function

The VPS35-Retromer complex plays a key role in cellular processes that extend beyond protein sorting and transport, significantly influencing mitochondrial function. Mitochondria, often described as the "energy factories" of the cell, are involved in ATP production as well as critical cellular functions such as calcium homeostasis, free radical production, and apoptosis. VPS35-Retromer impacts mitochondrial morphology, function, and homeostasis by regulating the transport of specific proteins that are essential for mitochondrial health. For example, the absence or mutation of VPS35 can lead to mitochondrial fragmentation, which impairs normal mitochondrial function.[18] VPS35 influences mitochondrial dynamics by regulating the sorting and transport of proteins that control mitochondrial fusion and fission, such as DRP1 and MFN2.[37] This mitochondrial dysfunction is commonly observed in various neurodegenerative diseases, including PD and AD, suggesting that VPS35-Retromer may contribute to the pathogenesis of these diseases by affecting mitochondrial integrity.[36]

Additionally, VPS35-Retromer is involved in the regulation of mitophagy, a process that ensures the removal of damaged mitochondria.[38] Dysfunction of VPS35 can impair mitophagy efficiency, leading to the accumulation of damaged mitochondria within the cell.[39] The membrane potential of damaged mitochondria decreases, leading to an

increase in ROS levels, which induces the enrichment of PINK1 on the outer mitochondrial membrane.[40] PINK1 initiates mitophagy by recruiting Parkin.[41] The VPS35 D620N mutant results in VPS35-dependent downregulation of PINK1, thereby inhibiting the recruitment of Parkin and causing impairments in PINK1/Parkin-dependent mitophagy.[39]

VPS35-Retromer also plays a direct role in the retrograde transport of certain mitochondrial proteins from endosomes to the Golgi apparatus or plasma membrane, thereby influencing their localization and function on mitochondria. For instance, the retrograde transport of ATP7B (Wilson's disease protein), a key protein involved in copper metabolism, depends on VPS35-Retromer. Dysfunction of this pathway can lead to copper metabolism disorders, which are associated with mitochondrial damage.[42] Moreover, VPS35-Retromer regulates apoptosis by modulating the transport of anti-apoptotic proteins, such as Bcl-xL, to the mitochondrial outer membrane.[43] In addition to these roles, recent studies have highlighted the involvement of VPS35-Retromer in mitochondrial quality control, particularly in the recycling and degradation of mitochondrial DNA (mtDNA). Free mtDNA enters early endosomes via secretory vesicles, where it is recognized by VPS35 and transported to multivesicular bodies for degradation. Downregulation of VPS35 results in the accumulation of mtDNA, leading to oxidative stress and pyroptosis, a form of inflammatory cell death.[44]

Other Cellular Biological Processes Involving VPS35-Retromer

In addition to its roles in protein transport, autophagy, and apoptosis, VPS35 is engaged in a range of cellular processes critical for maintaining cellular homeostasis and function. As a key component of the retromer complex, VPS35 participates in the recycling of neurotransmitter receptors, such as AMPA and NMDA receptors, from endosomes back to the cell membrane, a function essential for synaptic transmission and neuronal excitability.[45] By regulating the transport of proteins associated with synapse formation and plasticity, VPS35 influences synaptic structure and function. For instance, the loss of VPS35 can disrupt presynaptic vesicle release and recycling, thereby impairing neurotransmission.[46] VPS35 also contributes to the regulation of cellular signaling by retrogradely transporting specific signaling molecules, such as growth factors and cytokine receptors. Accurate sorting and transport of these molecules within endosomes are essential for proper cellular responses to external stimuli.[27] Furthermore, VPS35 plays a critical role in cell proliferation and differentiation. In gastric cancer cells, VPS35 promotes cell proliferation and tumor growth by regulating the recycling and downstream signaling pathways of the epidermal growth factor receptor (EGFR).[47] Additionally, VPS35 is involved in the differentiation of neural stem cells and adult neurogenesis.[48] VPS35 also significantly impacts immune responses and inflammatory processes. In a cerebral ischemia model, the absence of VPS35 results in abnormal microglial cell polarization, thereby impairing the inflammatory response and exacerbating neural damage.[49] In certain cancer cells, VPS35 modulates the metastatic potential by regulating the transport of proteins involved in cell migration and invasion, such as integrins and matrix metalloproteinases.[50] In summary, VPS35, as a multifunctional transport regulatory protein, is extensively involved in a variety of biological processes within cells, collectively contributing to the maintenance of cellular homeostasis and function.

The Role of VPS35-Retromer in Neurodegenerative Diseases

The Role of VPS35-Retromer in PD

PD is a neurodegenerative disorder with a high prevalence among the elderly and is closely linked to dysfunction in the Retromer complex. Its hallmark feature is the degeneration of dopamine-producing neurons in the substantia nigra, which leads to motor impairments.[51] The incidence of PD in individuals over 65 years old is approximately 1.7%. Pathologically, the most prominent changes observed in the brains of patients with PD include the degeneration and death of a large number of dopaminergic neurons in the ventral substantia nigra, along with the accumulation of Lewy bodies—abnormal protein aggregates primarily composed of α-synuclein (α-syn). The progressive loss of dopaminergic neurons and the deposition of Lewy bodies contribute to the characteristic extrapyramidal dysfunctions in PD, manifesting as bradykinesia, rigidity, resting tremor, and coordination disturbances.[52]

Studies have established a clear link between VPS35 mutations and PD pathogenesis (Figure 2A). Specifically, mutations in VPS35 caused by aspartic acid to asparagine substitution at position D620N (D620N) have been implicated in both familial and sporadic forms of PD.[53–55] α-Syn, a presynaptic protein predominantly expressed in the nervous system, is a major component of Lewy bodies. Mutations in the α-syn gene are strongly associated with autosomal

https://doi.org/10.2147/JIR.S510768

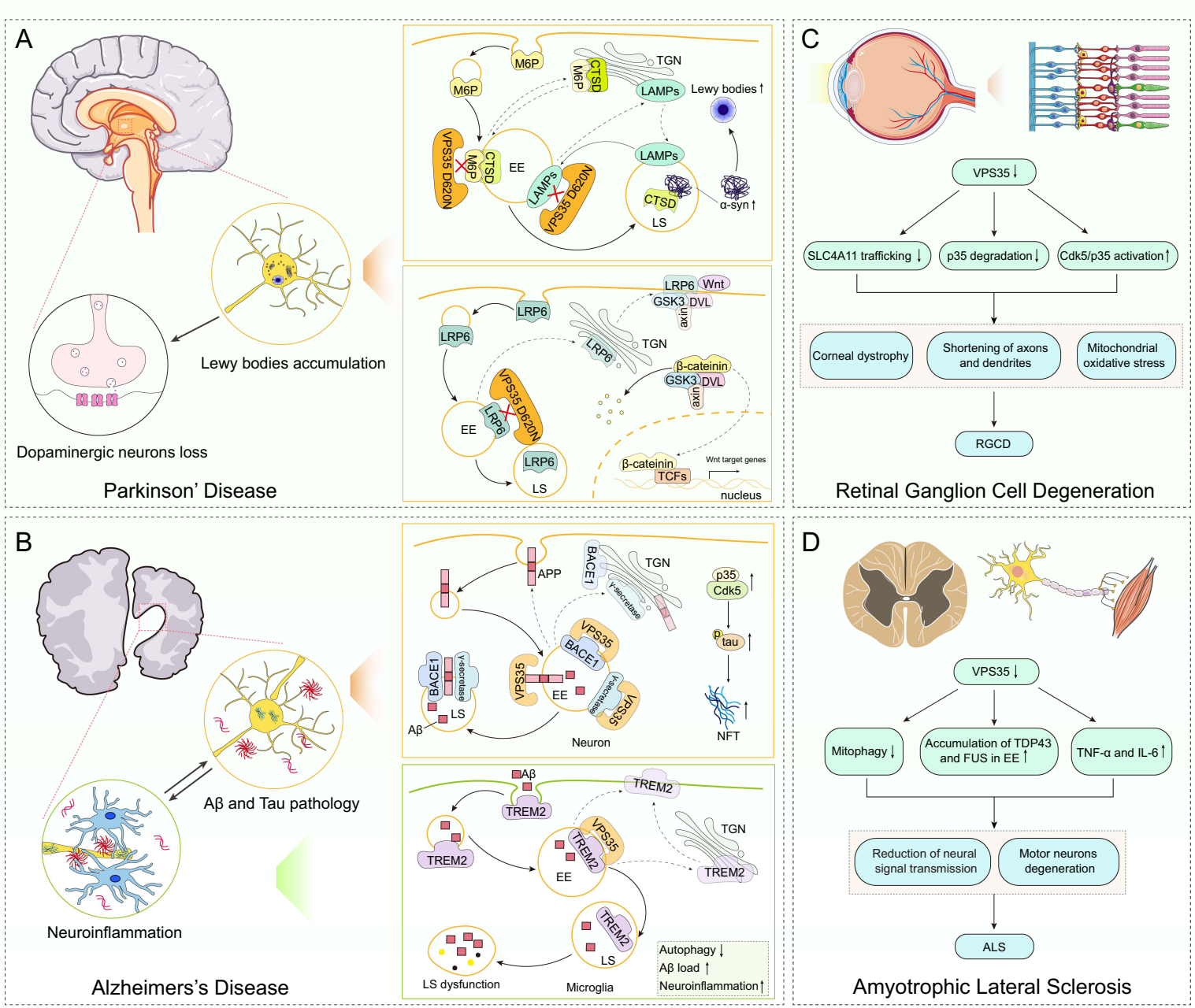

Figure 2 The Role of VPS35 in Neurodegenerative Diseases. (**A**) Mechanism of VPS35 D620N in PD. VPS35 D620N loses its ability to bind and transport M6P and LAMPs, leading to the accumulation of α-synuclein protein and the formation of Lewy bodies. Additionally, VPS35 D620N loses its capacity to bind and transport LRP6, resulting in the phosphorylation and degradation of β-catenin, which inhibits the Wnt/β-catenin signaling pathway and causes neuronal damage. (**B**) In AD, downregulation of VPS35 leads to the entry of APP into lysosomes in neurons, enhancing the production of Aβ. Simultaneously, it induces the phosphorylation and accumulation of Tau. In microglia, downregulation of VPS35 impairs TREM2-dependent endocytosis and autophagic flux of Aβ, causing further accumulation of Aβ and neuroinflammation. (**C** and **D**) Mechanisms of VPS35 in RGCD and ALS. Downregulation of VPS35 in both diseases results in neuronal dysfunction and degenerative changes.

Abbreviations: EE, early endosome; LS, lysosome.

dominant forms of inherited PD, and α-syn aggregates are also present in both sporadic PD cases and in individuals with α-syn gene mutations. In PD, α-syn is primarily degraded in lysosomes, but the D620N mutation in VPS35 disrupts the retrograde transport of ligands, such as the cation-independent mannose-6-phosphate receptor and cathepsin D, impairing the recycling of cathepsin D. This defect prevents efficient lysosomal degradation of α-syn, exacerbating its accumulation and thereby accelerating the progression of PD.[7,56]

Studies on PD have shown that mutations in VPS35 disrupt the Wnt/β-catenin signaling pathway,[57] which is essential for the development of midbrain dopaminergic neurons.[58] Impairments in this signaling cascade have been observed in various PD models, including the 6-hydroxydopamine rat model[59] and the MPTP-treated monkey model.[60] The proper function of the Wnt/β-catenin pathway is essential for protecting neurons, and any disruption in this signaling can contribute to the degeneration and death of dopaminergic neurons. Research has highlighted that VPS35, a key component of the Retromer complex, plays a vital role in maintaining Wnt/β-catenin signaling by mediating the retrograde transport of Wntless receptors from endosomes to the TGN. Mutations in VPS35 impair Retromer function, which disrupts this retrograde transport, leading to the extensive loss of dopaminergic neurons.[19,61] Additionally, VPS35 mutations in PD models have been shown to affect the endosomal recycling of DMT1, a key protein involved in iron homeostasis. Specifically, VPS35 mutations result in the mis-sorting of DMT1-II by the Retromer complex, leading to the upregulation of DMT1. This upregulation causes an accumulation of iron ions within cells, disrupting the intracellular "iron balance." This phenomenon correlates with observed iron accumulation in the substantia nigra of both patients with PD and animal models of PD.[52] Moreover, the dysregulation of iron transport by DMT1 can interact with α-synuclein, triggering microglial activation and elevating oxidative stress, which further accelerates the progression of PD.[4]

In summary, the VPS35-retromer complex is a key regulator of intracellular protein trafficking and plays a central role in the pathogenesis of PD. Understanding the interaction mechanisms between VPS35-retromer and PD-related proteins, as well as its specific functional pathways in the disease's progression, could provide new insights into PD diagnosis and treatment strategies. Future research should focus on elucidating the functional regulatory network of the VPS35-retromer complex and its dynamic alterations during PD onset and progression, thereby laying the groundwork for precision medicine approaches in PD therapy.

The Role of VPS35-Retromer in AD

AD is a neurodegenerative disorder characterized by a gradual and insidious onset, marked by the abnormal accumulation of β-amyloid plaques, neurofibrillary tangles resulting from the hyperphosphorylation of tau protein, and extensive neuronal and synaptic loss.[62] These pathological alterations lead to a progressive decline in cognitive abilities. Several studies have indicated that VPS35 expression is significantly reduced in the brains of patients with AD,[63] which may be linked to dysfunction of the retromer complex (Figure 2B), subsequently impacting critical pathological processes such as Aβ clearance and tau protein phosphorylation.[28]

The accumulation of Aβ is central to AD pathology. The VPS35-retromer complex plays a direct role in modulating the generation and clearance of Aβ by regulating the trafficking and processing of amyloid precursor protein (APP).[33] VPS35 facilitates the efficient release of APP from endosomes, thereby preventing its excessive degradation in lysosomes, which could otherwise lead to the overproduction of Aβ. A loss or dysfunction of VPS35 results in the aberrant accumulation of APP in endosomes, contributing to enhanced Aβ production.[13] Furthermore, VPS35 also regulates the transport and activity of Aβ-degrading enzymes, which in turn influences the efficiency of Aβ clearance.[64] Beta-Secretase 1 (BACE1), a key enzyme in Aβ formation, cleaves APP to generate Aβ. Studies have shown that silencing VPS35 leads to increased BACE1 activity in the hippocampal tissue of mice, resulting in elevated Aβ production and subsequent impairments in memory and synaptic function.[63] VPS35 is not only implicated in Aβ production but also regulates the phagocytic activity of microglia toward Aβ by modulating the recycling of the triggering receptor expressed on myeloid cells 2 (TREM2). This regulation further controls Aβ clearance.[65] Enhanced expression of VPS35 has been shown to restore the phagocytic function of plaque-associated microglia, thereby improving Aβ clearance.[66] Conversely, knockout of VPS35 in microglia results in the accumulation of Aβ plaques in the brains of 5XFAD mice, leading to further cognitive decline.[67]

Abnormal tau protein phosphorylation represents a critical pathological feature of AD. The VPS35-retromer complex plays a pivotal role in regulating tau phosphorylation by modulating the transport and activity of kinases and

phosphatases that are closely linked to tau phosphorylation. For example, VPS35 deficiency may impair the trafficking of the Cdk5/p35 complex, thereby promoting aberrant tau phosphorylation.[68] Additionally, VPS35 is involved in autophagy regulation, which influences the efficient clearance of tau protein aggregates.[26] Loss of synaptic function and neuronal death are central to cognitive decline in AD, and the VPS35-retromer complex contributes to the maintenance of synaptic transmission and neuronal survival by mediating the recycling and transport of neurotransmitter receptors and neurotrophic factors. Dysfunction of VPS35 can result in the improper distribution and functional impairment of these critical proteins at the postsynaptic site, further aggravating synaptic dysfunction and neuronal degeneration.[45] Moreover, VPS35 deficiency has been shown to promote the overexpression of inducible nitric oxide synthase (iNOS) and interleukin-6 (IL-6) production, exacerbating AD progression through increased neuroinflammation.[65]

In conclusion, the VPS35-retromer complex is a key regulator of intracellular protein trafficking and plays an indispensable role in the pathogenesis of AD. A deeper understanding of the interaction mechanisms between VPS35-retromer and AD-associated proteins, along with its specific pathways in disease progression, could provide novel insights into the diagnosis and treatment of AD. Future research should further investigate the functional regulatory network of the VPS35-retromer complex and its dynamic alterations during the onset and progression of AD, which will be instrumental in advancing precision medicine for AD.

The Role of VPS35-Retromer in Retinal Ganglion Cell Degeneration (RGCD)

The eye functions as the primary entry point for visual information in mammals, including humans. Anatomically, the retina is located at the posterior of the eye, with retinal ganglion cells (RGCs) positioned in the innermost cell layer, closest to the lens. These RGCs extend axons that converge to form the optic nerve, responsible for transmitting visual signals to the brain's visual centers.[69] Damage to RGCs can result in various visual impairments and blindness.[68] Factors such as optic nerve transection, intracranial hypertension, and glaucoma are known to damage RGC somata, often accompanied by excitotoxicity and retinal ischemia.[70]

RGCD is a key contributor to numerous blinding ocular diseases, including glaucoma and diabetic retinopathy. Studies indicate a strong association between glaucoma and irreversible vision loss, with an estimated 76 million patients with glaucoma globally in 2020, a number projected to rise to 112 million by 2040.[71] The underlying causes of RGC degeneration remain unclear, though two prominent hypotheses exist: (1) mechanical factors, such as elevated intraocular pressure, compress RGC axons, and (2) ischemia and hypoxia impair axonal transport, disrupting retrograde transport of neurotrophic factors, which in turn leads to RGC soma degeneration and the release of neurotoxic substances. This cascade results in secondary damage to adjacent RGCs, perpetuating a cycle of degeneration and exacerbating disease progression.[71,72] Once initiated, RGCD is irreversible, culminating in RGC death. As such, preventive measures are most effective when applied before significant degeneration occurs. VPS35, which is highly expressed in the layer of cells where RGCs reside, plays a critical role in RGC survival. Downregulation of VPS35 exacerbates RGCD (Figure 2C). In VPS35 knockout mice, RGCs display altered morphology, including significantly shortened axonal and dendritic protrusions. Additionally, VPS35 knockout leads to corneal dystrophy, characterized by reduced protrusions in corneal epithelial and endothelial cells, accompanied by corneal edema. Further investigations have shown that VPS35 knockout also disrupts the transport of Solute Carrier Family 4 Member 11 (SLC4A11), worsening the symptoms of corneal dystrophy.[73,74] Studies have also demonstrated that inhibiting VPS35 can increase Cdk5/p35 activity by impairing the lysosomal degradation of p35, thus contributing to RGC degeneration. Given its pivotal role, VPS35 represents a potential therapeutic target for both basic research and clinical treatment of RGC degeneration in various ocular diseases, including glaucoma.[68] Moreover, VPS35 dysfunction may also influence the pathogenesis of retinitis pigmentosa resulting from CRB1 gene mutations.[75] In models of optic nerve compression-induced RGC death, VPS35 has been shown to exert a protective effect by enhancing mitochondrial function, thereby slowing disease progression.[76]

Table 1 Regulatory Effects of VPS35 in Tumors

Tumors	Expression	Cargos	Function and Mechanism	References
Hepatocellular carcinoma	Upregulation	FGFR3	Induce PI3K/AKT signaling to trigger cell proliferation	[75,76]
		p27Kip1	Regulate the proportion of cells in the G1/S phase to promote cell proliferation	[77]
		Ccdc85c	Activate β-catenin signaling to promote cell proliferation	[78]
		FZD2 ROR1	Activate the Wnt/non-canonical planar cell polarity pathway to promoting cell metastasis	[45]
Breast Cancer	Upregulation	EGFR2	Inversely related to tumor cell apoptosis	[79]
		(-)*	Promote tumor cell proliferation, migration, invasion, and affect autophagy	[80]
Gastric Cancer	Upregulation	EGFR	Activate the ERK1/2 pathway and promote tumor cell growth	[42]
		ITGB3	Increase YAP nuclear translocation and promote tumor cell proliferation and metastasis	[81]
		SLC7A11	Promote the cancer progress	[82]
Melanoma	Upregulation	N-Ras	Increase Ras's GTP loading, and N-Ras-dependent tumor cell growth	[83,84]
Colorectal cancer	Frameshift mutation	(-)	Not mentioned	[85]

Notes: *VPS35 cargos are not mentioned in the references.

The Role of VPS35-Retromer in Cancer (Table 1)

VPS35 and Liver Cancer

Liver cancer is mainly categorized into primary and secondary types, with primary liver cancer further subdivided into hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, angiosarcoma, and hepatoblastoma, among others.[77] Of these, HCC is the predominant form, representing the leading cause of death among patients with liver cirrhosis and the most common type of liver cancer in adults. HCC ranks as the fourth leading cause of cancer-related mortality worldwide and is expected to become the third by 2030.[77] Risk factors such as chronic alcohol consumption, diabetes, and obesity significantly elevate the likelihood of HCC development. More critically, hepatitis B virus, hepatitis C virus, and non-alcoholic steatohepatitis are considered major etiological agents in the onset of HCC.[78] The progression of HCC typically begins with liver cell damage, followed by chronic inflammation that drives abnormal cell proliferation, fibrosis, and cirrhosis and ultimately leads to HCC.[86]

VPS35, a recently identified oncogene, has been shown to promote the proliferation and metastasis of liver cancer cells, exacerbating disease progression.[87] Increased expression of VPS35 has been detected in liver cancer cell lines such as HepG2 and Huh7.[88] During HCC development, activation of the Wnt/PCP signaling pathway, which governs cell differentiation and metastasis, and the PI3K/AKT signaling pathway, which regulates cell proliferation, has been observed.[88] Under normal physiological conditions, fibroblast growth factor receptor 3 (FGFR3) is internalized into endosomes or lysosomes for degradation, maintaining a balance between cell proliferation and apoptosis. However, in liver cancer cells, overexpression of VPS35 enhances the sorting and recycling of FGFR3 to the plasma membrane, thereby promoting AKT phosphorylation. This, in turn, activates the PI3K/AKT signaling pathway, driving hepatocellular proliferation and contributing to HCC progression.[87] Additionally, VPS35 influences the G1/S phase transition by inhibiting the expression of the cyclin-dependent kinase inhibitor p27Kip1, further facilitating liver cancer cell proliferation.[87] Krüppel-like factor 7, a known inducer of liver cancer metastasis, transcriptionally activates *VPS35* by binding to its promoter region. VPS35 interacts with Ccdc85c to activate the β-catenin signaling pathway, which enhances the proliferative capacity of liver cancer cells.[79]

Moreover, the upregulation of VPS35 plays a pivotal role in liver cancer cell metastasis. Overexpression of VPS35 leads to the upregulation of epithelial-mesenchymal transition (EMT) markers, which promote metastasis. VPS35 activates the Wnt/non-canonical planar cell polarity (PCP) pathway by regulating the sorting and trafficking of FZD2 and ROR1 in liver cancer cells, further contributing to metastatic potential.[50] Research by Tan et al has demonstrated that

VPS35 overexpression enhances the secretion of tumor-derived extracellular vesicles, thereby facilitating cancer cell dissemination and metastasis.[80] In summary, upregulation of VPS35 in liver cancer promotes tumor cell proliferation and metastasis. Despite extensive research supporting the critical role of VPS35 in liver cancer progression, no targeted therapies specifically targeting VPS35 have been reported to date. However, targeting VPS35 or other components of the retromer complex may hold promise in inhibiting tumor proliferation and metastasis. Further investigation into the molecular mechanisms underlying VPS35's role in liver cancer progression, as well as the development of targeted therapies, could provide new therapeutic strategies for the treatment of liver cancer.

VPS35 and Breast Cancer

Breast cancer is the most common malignant tumor among women worldwide, accounting for 24.5% of all new cancer cases in females.[89] Characterized by its poor prognosis and high recurrence rate, breast cancer remains a significant challenge in oncology.[90] The incidence and mortality of breast cancer exhibit considerable geographic variation. Developed countries typically report higher incidence rates but lower mortality rates, whereas in developing regions, including Southern Africa and South Asia, the incidence of breast cancer is lower, but the mortality rate is higher. Projections indicate that by 2050, breast cancer-related deaths in these areas will increase by 4.69% compared to 2019.[89] Breast cancer is classified into ductal carcinoma and lobular carcinoma, with triple-negative breast cancer (TNBC), a subtype of ductal carcinoma, associated with the poorest prognosis.[91]

In breast cancer cells, VPS35 is highly expressed, and its expression level has been found to positively correlate with tumor size, lymph node metastasis, estrogen receptor/progesterone receptor negativity, human EGFR2 positivity, and the triple-negative molecular subtype.[92] Knockdown of VPS35 induces apoptosis in breast ductal carcinoma cells, as demonstrated in mouse models, suggesting that VPS35 expression is inversely related to tumor cell apoptosis.[92] Research indicates that autophagy plays a critical role in the survival of disseminated dormant breast cancer cells, and VPS35, as an autophagy-related gene, contributes to the regulation of autophagy. Knockdown of VPS35 inhibits breast cancer cell proliferation, migration, and invasion, further implicating its role in modulating autophagy.[81] These findings suggest that VPS35 influences breast cancer initiation and progression through multiple cellular pathways. Although the mechanisms by which VPS35 regulates breast cancer initiation and metastasis are still under investigation, its role in liver cancer progression suggests that VPS35 may similarly affect breast cancer cell proliferation and metastasis. Further exploration of the mechanisms underlying VPS35 in breast cancer holds potential for the development of new therapeutic strategies, offering insights into improving the treatment and prognosis of breast cancer.

VPS35 and Gastric Cancer

Gastric cancer ranks as the third leading cause of cancer-related deaths globally, with higher incidence rates observed in East Asia, Eastern Europe, and certain regions of South America. According to the 2020 global cancer statistics from GLOBOCAN, approximately 1 million new cases of gastric cancer are diagnosed annually worldwide, with nearly 775,000 deaths attributed to the disease, representing 9.2% of all cancer-related fatalities.[89] Asia, particularly East Asian countries such as China, Japan, and Korea, accounts for over 50% of global gastric cancer cases. In contrast, the incidence is relatively low in North America and Western Europe.[82] Given the high burden of this disease, identifying novel therapeutic targets is essential for improving the management and prognosis of gastric cancer.

VPS35 has emerged as a potential gene associated with the poor prognosis of gastric cancer.[93] EGFR is recognized as a key oncogenic driver in gastric cancer,[94] and VPS35 upregulation enhances the recycling of EGFR to the cell membrane, thereby activating the ERK1/2 signaling pathway and promoting tumor cell proliferation.[47] Yes-associated protein (YAP), an oncoprotein that drives tumor cell proliferation and metastasis,[95] is also regulated by VPS35. The upregulation of VPS35 promotes the dephosphorylation of Mammalian Sterile 20-like kinase 1/2 and Large Tumor Suppressor Kinase 1, in addition to phosphorylating YAP at the Ser127 site—an indicator of YAP inactivation—thereby increasing YAP nuclear translocation.[96] Furthermore, VPS35 interacts with Integrin Subunit Beta 3 (ITGB3), a key player in cancer metastasis, and activates YAP, leading to the secretion of IL-6. IL-6, in turn, enhances STAT3 binding to the VPS35 promoter region, upregulating VPS35 expression and promoting tumor growth and metastasis through ITGB3-mediated activation of the FAK-SRC signaling pathway.[96] Knocking down VPS35 in gastric cancer cells reduces

their resistance to fluorouracil.[96] Additionally, elevated VPS35 expression is linked to increased levels of SLC7A11, a marker of advanced gastric cancer.[97] In conclusion, VPS35 plays a pivotal role in the progression of gastric cancer. Further investigation is required to elucidate the specific molecular mechanisms by which VPS35 regulates signaling pathways involved in gastric cancer development. Although targeted therapies aimed at VPS35 are still in the early stages of research, these studies offer potential avenues for drug development. Future research should explore the feasibility of targeting VPS35 for therapeutic intervention and investigate the development of specific drugs that modulate VPS35 activity or expression.

The Role of VPS35 in Other Diseases

VPS35 plays a pivotal role in the pathophysiology of both Amyotrophic Lateral Sclerosis (ALS) and Huntington's Disease (HD), two devastating neurodegenerative disorders. ALS primarily affects motor neurons, leading to progressive muscle weakness, atrophy, paralysis, and eventually death. The disease is more common in males than females, with recent studies implicating various genetic mutations, including VPS35, in its onset and progression.[22] Patients with ALS frequently display abnormal accumulation of TDP-43, a condition worsened by the functional loss of VPS35.[22] Increased stability of the retromer complex has been shown to support mitochondrial autophagy in ALS.[98] However, some studies suggest that mild inhibition of retromer function might have a protective effect, highlighting the complex and context-dependent role of the retromer in ALS[83] (Figure 2D).

HD, an inherited neurodegenerative disorder, is characterized by motor disturbances, cognitive decline, and psychiatric symptoms.[99] The disease is caused by a trinucleotide expansion in the HTT gene, resulting in the production of abnormal huntingtin protein that accumulates in neuronal cells.[100] Although VPS35 has been linked to multiple neurodegenerative diseases, its precise involvement in the pathology of HD remains poorly understood. Limited research suggests that VPS35 may indirectly contribute to the molecular mechanisms of HD.[25] While no direct therapeutic strategies targeting VPS35 currently exist for ALS or HD, its critical role in maintaining neuronal health presents a potential target for novel therapeutic interventions. Further studies are necessary to elucidate the full therapeutic potential of VPS35 in these disorders.

Iron is a vital cofactor for numerous biological processes, including oxygen transport, signal transduction, and DNA synthesis.[84] After binding to transferrin, iron interacts with the Transferrin Receptor (TfR) on the cell surface, entering cells via clathrin-mediated endocytosis. Research by Caiyong Chen et al has demonstrated that SNX3 plays a key role in recycling transferrin receptors, essential for maintaining iron homeostasis. Disruption of SNX3 function leads to mis-sorting of TfRs, impairing iron uptake and causing anemia and hemoglobin deficiencies in vertebrates. Additionally, SNX3, VPS35, and TfR interact to facilitate the sorting and transport of TfR to the plasma membrane.[85] Therefore, the Retromer complex, including VPS35, is crucial in regulating the recycling of TfR, maintaining iron homeostasis, and supporting erythropoiesis.

VPS35, an oncogene, plays a pivotal role in the pathogenesis of various malignancies, including melanoma, ovarian cancer, and colorectal cancer.[101,102] Melanoma, a skin cancer primarily originating from melanocytes, is influenced by a complex interplay of genetic mutations, environmental factors (such as ultraviolet radiation), immune responses, and cellular metabolic processes.[101] In 2020, approximately 32,500 new melanoma cases were diagnosed globally, resulting in 57,000 deaths. The disease predominantly affects Caucasians in Europe, with a notably higher incidence in males than in females.[82,103] VPS35 has been shown to bind to N-Ras in a farnesyl-dependent manner.[83] Depletion of VPS35 enhances the association between N-Ras and cytosolic vesicles, reduces Ras's GTP loading, and disrupts mitogen-activated protein kinase signaling, ultimately inhibiting N-Ras-driven melanoma cell proliferation.[104]

In recent years, increasing attention has been directed towards the gastrointestinal microbiota, as its dysbiosis can contribute to gastrointestinal inflammation and, in severe cases, the development of colorectal cancer.[22] Colorectal cancer exhibits higher incidence rates in Western countries, though in China, despite a lower global prevalence, its incidence has gradually increased due to the asymptomatic nature of the disease in its early stages. The primary clinical manifestations include rectal bleeding, which can progress to anemia in later stages. Current studies have identified frameshift mutations of VPS35 in colorectal cancer tissues.[105] However, the precise mechanisms through which VPS35 contributes to the development and progression of colorectal cancer remain to be fully elucidated.

Preclinical Therapeutic Targeting of VPS35

Given the pivotal role of VPS35 in a range of diseases, including AD, PD, RGCD, anemia, and even various cancers, the retromer complex has emerged as a promising therapeutic target. However, pharmacological targeting of VPS35 presents a significant challenge, as this core subunit does not possess intrinsic enzymatic activity but instead functions as a structural scaffold for retrograde transport. The presence of the D260N mutation in VPS35, particularly in PD, further complicates therapeutic development, leading to the hypothesis that stabilizing the retromer complex may offer a potential solution. In 2014, Mecozzi et al synthesized the compounds R55 and R33, which were shown to enhance the interaction between VPS35 and VPS29, thereby improving the stability of the retromer complex. These compounds have demonstrated neuroprotective effects in an iPSC-derived cell model of sporadic AD.[106] However, whether R55 and R33 can mitigate the dysfunction caused by the D260N mutation in VPS35 in PD remains to be fully explored. Recent advancements include the development of the macrocyclic peptide RT-L4 by Chen et al, which has shown promise as a more effective molecular chaperone for stabilizing the retromer complex.[107] While the therapeutic effects and precise mechanisms of these compounds in VPS35-related diseases remain unclear, their potential underscores the critical role of VPS35 in maintaining normal physiological processes and highlights its viability as a therapeutic target. Given its pivotal role, VPS35 represents a potential therapeutic target for both basic research and clinical treatment of RGC degeneration in various ocular diseases, including glaucoma.[68] Despite extensive research supporting the critical role of VPS35 in liver cancer progression, no targeted therapies specifically targeting VPS35 have been reported to date.

Ongoing research into VPS35 and the development of associated drugs could significantly advance our understanding of diseases linked to this protein, offering hope for new treatments for neurodegenerative diseases and cancers. Investigating whether these stabilizing drugs can elicit similar therapeutic benefits in a broader range of VPS35-related conditions may represent a crucial step toward providing effective treatment options for these challenging diseases.

Conclusion and Outlook

This review elaborates on the central regulatory role of VPS35 in various biological processes, including protein trafficking, regulation of autophagy and mitophagy, maintenance of mitochondrial function, and numerous physiological activities. The review not only unveils the complex structure and unique functions of VPS35 but also explores its potential therapeutic applications in the clinical field. In recent years, several groundbreaking studies have revealed the molecular mechanisms underlying "neuron-tumor microenvironment interactions".[108,109] This article integrates for the first time the dual regulatory roles of VPS35 in neurological disorders and tumors, providing not only new targets for deciphering the interactions between neurons and tumors but also suggesting potential therapeutic intervention strategies within the "brain-tumor axis".

Despite increasing understanding of VPS35's functions in recent years and its recognized positive therapeutic effects in various diseases, significant challenges remain in certain neurological disease areas. For instance, the role of VPS35 in HD and ALS has not been fully elucidated over the past five years. Furthermore, research on the functions of VPS35 in tumorigenesis and development remains fragmented. Although progress has been made in recent years in studying VPS35 and its associated structural proteins VPS26 and VPS29 in cancer, candidate drugs are still scarce. Therefore, a thorough understanding of the structure and function of VPS35, coupled with the exploration of the potential therapeutic effects of these drugs in VPS35-related diseases, undoubtedly brings hope for innovative treatment strategies in neurodegenerative diseases and cancer.

Abbreviations

α-syn, α-synuclein; Aβ, β-amyloid; AD, Alzheimer's disease; ALS, Amyotrophic Lateral Sclerosis; APP, amyloid precursor protein; BACE1, Beta-Secretase 1; DMT1, divalent metal transporter 1 DMT1; EGFR, epidermal growth factor receptor; FGFR3, fibroblast growth factor receptor 3; HD, Huntington's Disease; IL-6, interleukin 6; ITGB3, Integrin Subunit Beta 3; mtDNA, mitochondrial DNA; MUL1, mitochondrial E3 ubiquitin ligase 1; PD, Parkinson's disease; RGCD, retinal ganglion cell degeneration; RGCs, retinal ganglion cells; SNAREs, soluble N -ethylmaleimide-sensitive factor attachment protein receptors; SNX3, sorting nexin dimer 3 SNX3; TfR, Transferrin Receptor; TGN, trans-Golgi network TGN; VPS, vacuolar protein sorting VPS; WASH, Wiskott Aldrich Syndrome protein and scar homologue; YAP, Yes-associated protein.

Data Sharing Statement

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Acknowledgments

We thank Professor Xiaodong Han from Nanjing University for her suggestions on this work. We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China [grant number 32471229 and 82271914], the Postgraduate Research & Practice Innovation Program of Jiangsu Province [grant number KYCX24_3627] and Large Instruments Open Foundation of Nantong University.

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Sassone J, Reale C, Dati G, et al. The Role of VPS35 in the Pathobiology of Parkinson's Disease. *Cell mol Neurobiol*. 2021;41(2):199–227. doi:10.1007/s10571-020-00849-8
2. Rojas AL, Hierro A, Rojas R, et al. Functional architecture of the retromer cargo-recognition complex. *THE FASEB Journal*. 2009;23(S1). doi:10.1096/fasebj.23.1_supplement.698.3.
3. Tabuchi M, Yanatori I, Kawai Y, et al. Retromer-mediated direct sorting is required for proper endosomal recycling of the mammalian iron transporter DMT1. *J Cell Sci*. 2010;123(5):756–766. doi:10.1242/jcs.060574
4. Deng H, Gao K, Jankovic J. The VPS35 gene and Parkinson's disease. *Movement Disorders*. 2013;28(5):569–575. doi:10.1002/mds.25430
5. Gokool S, Tattersall D, Reddy J, et al. Identification of a conserved motif required for Vps35p/Vps26p interaction and assembly of the retromer complex. *Biochemical Journal*. 2007;408(2):287–295. doi:10.1042/BJ20070555
6. Lucas M, Gershlick DC, Vidaurrazaga A, et al. Structural Mechanism for Cargo Recognition by the Retromer Complex. *Cell*. 2016;167(6):1623. doi:10.1016/j.cell.2016.10.056
7. Wang SA, Bellen HJ. The retromer complex in development and disease. *Development*. 2015;142(14):2392–2396. doi:10.1242/dev.123737
8. Bonifacino JS, Hurley JH. Retromer. *Current Opinion in Cell Biology*. 2008;20(4):427–436. doi:10.1016/j.ceb.2008.03.009
9. Seaman MNJ, Michael Mccaffery J, Emr SD. A Membrane Coat Complex Essential for Endosome-to-Golgi Retrograde Transport in Yeast. *The Journal of Cell Biology*. 1998;142(3):665–681. doi:10.1083/jcb.142.3.665
10. Iwaki T, Hosomi A, Tokudomi S, et al. Vacuolar protein sorting receptor in Schizosaccharomyces pombe. *Microbiology*. 2006;152(5):1523–1532. doi:10.1099/mic.0.28627-0
11. Nakada-Tsukui K, Saito-Nakano Y, Ali V, et al. A retromerlike complex is a novel Rab7 effector that is involved in the transport of the virulence factor cysteine protease in the enteric protozoan parasite Entamoeba histolytica. *Molecular Biology of the Cell*. 2005;16(11):5294–5303. doi:10.1091/mbc.e05-04-0283
12. Li C, Shah SZA, Zhao D, et al. Role of the Retromer Complex in Neurodegenerative Diseases. *Frontiers in Aging Neuroscience*. 2016;8. doi:10.3389/fnagi.2016.00042
13. Ansell-Schultz A, Reyes JF, Samuelsson M, et al. Reduced retromer function results in the accumulation of amyloid-beta oligomers. *mol Cell Neurosci*. 2018;93:18–26. doi:10.1016/j.mcn.2018.09.003
14. Kovtun O, Leneva N, Bykov YS, et al. Structure of the membrane-assembled retromer coat determined by cryo-electron tomography. *Nature*. 2018;561(7724):561–564. doi:10.1038/s41586-018-0526-z
15. Brodin L, Shupliakov O. Retromer in Synaptic Function and Pathology. *Front Synaptic Neurosci*. 2018;10:37. doi:10.3389/fnsyn.2018.00037
16. Marquardt L, Taylor M, Kramer F, et al. Vacuole fragmentation depends on a novel Atg18-containing retromer-complex. *Autophagy*. 2023;19(1):278–295. doi:10.1080/15548627.2022.2072656
17. Seaman MNJ, Mukadam AS, Breusegem SY. Inhibition of TBC1D5 activates Rab7a and can enhance the function of the retromer cargo-selective complex. *J Cell Sci*. 2018;131(12). doi:10.1242/jcs.217398
18. Chen X, Kordich JK, Williams ET, et al. Parkinson's disease-linked D620N VPS35 knockin mice manifest tau neuropathology and dopaminergic neurodegeneration. *Proc Natl Acad Sci U S A*. 2019;116(12):5765–5774. doi:10.1073/pnas.1814909116
19. Port F, Kuster M, Herr P, et al. Wingless secretion promotes and requires retromer-dependent cycling of Wntless. *Nature Cell Biology*. 2008;10(2):178–U48. doi:10.1038/ncb1687

20. Neuspiel M, Schauss AC, Braschi E, et al. Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. *Current Biology*. 2008;18(2):102–108. doi:10.1016/j.cub.2007.12.038
21. Tang F-L, Erion JR, Tian Y, et al. VPS35 in Dopamine Neurons Is Required for Endosome-to-Golgi Retrieval of Lamp2a, a Receptor of Chaperone-Mediated Autophagy That Is Critical for -Synuclein Degradation and Prevention of Pathogenesis of Parkinson's Disease. *Journal of Neuroscience*. 2015;35(29):10613–10628. doi:10.1523/JNEUROSCI.0042-15.2015
22. Tang F-L, Liu W, Hu J-X, et al. VPS35 Deficiency or Mutation Causes Dopaminergic Neuronal Loss by Impairing Mitochondrial Fusion and Function. *Cell Reports*. 2015;12(10):1631–1643. doi:10.1016/j.celrep.2015.08.001
23. Wang WZ, Wang X, Fujioka H, et al. Parkinson's disease–associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. *Nature Medicine*. 2016;22(1):54. doi:10.1038/nm.3983
24. Perez-Victoria FJ, Mardones GA, Bonifacino JS, Gruenberg J. Requirement of the human GARP complex for mannose 6-phosphate-receptor-dependent sorting of cathepsin D to lysosomes. *Molecular Biology of the Cell*. 2008;19(6):2350–2362. doi:10.1091/mbc.e07-11-1189
25. Filippone A, Li J-G, Pratico D, Mecocci P. VPS35 Downregulation Alters Degradation Pathways in Neuronal Cells. *J Alzheimers Dis*. 2021;84 (3):1079–1089. doi:10.3233/JAD-210701
26. Carosi JM, Hein LK, van den Hurk M, et al. Retromer regulates the lysosomal clearance of MAPT/tau. *Autophagy*. 2021;17(9):2217–2237. doi:10.1080/15548627.2020.1821545
27. Cataldi S, Follett J, Fox JD, et al. Altered dopamine release and monoamine transporters in Vps35 p.D620N knock-in mice. *NPJ Parkinsons Dis*. 2018;4(1):27. doi:10.1038/s41531-018-0063-3
28. Curtis ME, Yu D, Pratico D. Dysregulation of the Retromer Complex System in Down Syndrome. *Ann Neurol*. 2020;88(1):137–147. doi:10.1002/ana.25752
29. Williams ET, Glauser L, Tsika E, et al. Parkin mediates the ubiquitination of VPS35 and modulates retromer-dependent endosomal sorting. *Hum mol Genet*. 2018;27(18):3189–3205. doi:10.1093/hmg/ddy224
30. Mir R, Tonelli F, Lis P, et al. The Parkinson's disease VPS35[D620N] mutation enhances LRRK2-mediated Rab protein phosphorylation in mouse and human. *Biochem J*. 2018;475(11):1861–1883. doi:10.1042/BCJ20180248
31. Baba T, Toth DJ, Sengupta N, et al. Phosphatidylinositol 4,5-bisphosphate controls Rab7 and PLEKHM 1 membrane cycling during autophagosome–lysosome fusion. *EMBO J*. 2019;38(8):e100312. doi:10.15252/embj.2018100312
32. Cui Y, Carosi JM, Yang Z, et al. Retromer has a selective function in cargo sorting via endosome transport carriers. *J Cell Biol*. 2019;218 (2):615–631. doi:10.1083/jcb.201806153
33. Hu Y-B, Dammer EB, Ren R-J, et al. The endosomal-lysosomal system: from acidification and cargo sorting to neurodegeneration. *Transl Neurodegener*. 2015;4(1):18. doi:10.1186/s40035-015-0041-1
34. Lo CH, Zeng J. Defective lysosomal acidification: a new prognostic marker and therapeutic target for neurodegenerative diseases. *Transl Neurodegener*. 2023;12(1):29. doi:10.1186/s40035-023-00362-0
35. Shiraishi T, Bono K, Hiraki H, et al. The impact of VPS35 D620N mutation on alternative autophagy and its reversal by estrogen in Parkinson's disease. *Cell mol Life Sci*. 2024;81(1):103. doi:10.1007/s00018-024-05123-4
36. Eleuteri S, Albanese A. VPS35-Based Approach: a Potential Innovative Treatment in Parkinson's Disease. *Front Neurol*. 2019;10:1272. doi:10.3389/fneur.2019.01272
37. Cutillo G, Simon DK, Eleuteri S. VPS35 and the mitochondria: connecting the dots in Parkinson's disease pathophysiology. *Neurobiol Dis*. 2020;145:105056. doi:10.1016/j.nbd.2020.105056
38. Sen A, Boix J, Pla-Martin D. Endosomal-dependent mitophagy coordinates mitochondrial nucleoid and mtDNA elimination. *Autophagy*. 2023;19(9):2609–2610. doi:10.1080/15548627.2023.2170959
39. Ma KY, Fokkens MR, Reggiori F, et al. Parkinson's disease–associated VPS35 mutant reduces mitochondrial membrane potential and impairs PINK1/Parkin-mediated mitophagy. *Transl Neurodegener*. 2021;10(1):19. doi:10.1186/s40035-021-00243-4
40. Song SB, Jang S-Y, Kang HT, et al. Modulation of Mitochondrial Membrane Potential and ROS Generation by Nicotinamide in a Manner Independent of SIRT1 and Mitophagy. *mol Cells*. 2017;40(7):503–514. doi:10.14348/molcells.2017.0081
41. Strappazzon F, Nazio F, Corrado M, et al. AMBRA1 is able to induce mitophagy via LC3 binding, regardless of PARKIN and p62/SQSTM1. *Cell Death Differ*. 2015;22(3):419–432. doi:10.1038/cdd.2014.139
42. Das S, Maji S, et al. Retromer retrieves the Wilson disease protein ATP7B from endolysosomes in a copper-dependent manner. *J Cell Sci*. 2020;133(24):6819. doi:10.1242/jcs.246819.
43. Farmer T, O'Neill KL, Naslavsky N, et al. Retromer facilitates the localization of Bcl-xL to the mitochondrial outer membrane. *mol Biol Cell*. 2019;30(10):1138–1146. doi:10.1091/mbc.E19-01-0044
44. Sen A, Kallabis S, Gaedke F, et al. Mitochondrial membrane proteins and VPS35 orchestrate selective removal of mtDNA. *Nat Commun*. 2022;13(1):6704. doi:10.1038/s41467-022-34205-9
45. Kadgien CA, Kamesh A, Milnerwood AJ. Endosomal traffic and glutamate synapse activity are increased in VPS35 D620N mutant knock-in mouse neurons, and resistant to LRRK2 kinase inhibition. *mol Brain*. 2021;14(1):143. doi:10.1186/s13041-021-00848-w
46. Vazquez-Sanchez S, Bobeldijk S, Dekker MP, et al. VPS35 depletion does not impair presynaptic structure and function. *Sci Rep*. 2018;8 (1):2996. doi:10.1038/s41598-018-20448-4
47. Yu J, Feng H, Sang Q, et al. VPS35 promotes cell proliferation via EGFR recycling and enhances EGFR inhibitors response in gastric cancer. *EBioMedicine*. 2023;89:104451. doi:10.1016/j.ebiom.2023.104451
48. Appel JR, Ye S, Tang F, et al. Increased Microglial Activity, Impaired Adult Hippocampal Neurogenesis, and Depressive-like Behavior in Microglial VPS35-Depleted Mice. *J Neurosci*. 2018;38(26):5949–5968. doi:10.1523/JNEUROSCI.3621-17.2018
49. Ye S-Y, Apple JE, Ren X, et al. Microglial VPS35 deficiency regulates microglial polarization and decreases ischemic stroke-induced damage in the cortex. *J Neuroinflammation*. 2019;16(1):235. doi:10.1186/s12974-019-1633-y
50. Liu Y, Deng H, Liang L, et al. Depletion of VPS35 attenuates metastasis of hepatocellular carcinoma by restraining the Wnt/PCP signaling pathway. *Genes Dis*. 2021;8(2):232–240. doi:10.1016/j.gendis.2020.07.009
51. Elbaz A, Carcaillon L, Kab S, et al. Epidemiology of Parkinson's disease. *Revue Neurologique*. 2016;172(1):14–26. doi:10.1016/j.neurol.2015.09.012

52. Jankovic J. Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008;79(4):368–376. doi:10.1136/jnnp.2007.131045
53. Vilariño-Güell C, Wider C, Ross O, et al. VPS35 Mutations in Parkinson Disease. *The American Journal of Human Genetics*. 2011;89(1):162–167. doi:10.1016/j.ajhg.2011.06.001
54. Verstraeten A, Wauters E, Crosiers D, et al. Contribution of VPS35 genetic variability to LBD in the Flanders-Belgian population. *Neurobiology of Aging*. 2012;33(8):1844.e11–1844.e13. doi:10.1016/j.neurobiolaging.2012.01.006
55. Zimprich A, Benet-Pagès A, Struhal W, et al. A Mutation in VPS35, Encoding a Subunit of the Retromer Complex, Causes Late-Onset Parkinson Disease. *The American Journal of Human Genetics*. 2011;89(1):168–175. doi:10.1016/j.ajhg.2011.06.008
56. Norwood SJ, Shaw DJ, Cowieson NP, et al. Assembly and Solution Structure of the Core Retromer Protein Complex. *Traffic*. 2011;12(1):56–71. doi:10.1111/j.1600-0854.2010.01124.x
57. Rodriguez-Oroz MC, Jahanshahi M, Krack P, et al. Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms. *The Lancet Neurology*. 2009;8(12):1128–1139. doi:10.1016/S1474-4422(09)70293-5
58. Castelo-Branco G, Wagner J, Rodriguez FJ, et al. Differential regulation of midbrain dopaminergic neuron development by Wnt-1, Wnt-3a, and Wnt-5a. *Proceedings of the National Academy of Sciences*. 2003;100(22):12747–12752. doi:10.1073/pnas.1534900100
59. Scali C, Caraci F, Gianfriddo M, et al. Inhibition of Wnt signaling, modulation of Tau phosphorylation and induction of neuronal cell death by DKK1. *Neurobiology of Disease*. 2006;24(2):254–265. doi:10.1016/j.nbd.2006.06.016
60. L'Episcopo F, Tirolo C, Testa N, et al. Reactive astrocytes and Wnt/β-catenin signaling link nigrostriatal injury to repair in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *Neurobiology of Disease*. 2011;41(2):508–527. doi:10.1016/j.nbd.2010.10.023
61. Franch-Marro X, Wendler F, Guidato S, et al. Wingless secretion requires endosome-to-Golgi retrieval of Wntless/Evi/Sprinter by the retromer complex. *Nature Cell Biology*. 2008;10(2):170–U40. doi:10.1038/ncb1678
62. Liang X, Slifer M, Martin ER, et al. Genomic convergence to identify candidate genes for Alzheimer Disease on chromosome 10. *Human Mutation*. 2009;30(3):463–471. doi:10.1002/humu.20953
63. Wen L, Tang F-L, Hong Y, et al. VPS35 haploinsufficiency increases Alzheimer's disease neuropathology. *J Cell Biol*. 2011;195(5):765–779. doi:10.1083/jcb.201105109
64. Simoes S, et al. Tau and other proteins found in Alzheimer's disease spinal fluid are linked to retromer-mediated endosomal traffic in mice and humans. *Sci Transl Med*. 2020;12(571):6334.
65. Yin J, Liu X, He Q, et al. Vps35-dependent recycling of Trem2 regulates microglial function. *Traffic*. 2016;17(12):1286–1296. doi:10.1111/tra.12451
66. Wang X, Xie Y, Fan X, et al. Intermittent hypoxia training enhances Aβ endocytosis by plaque associated microglia via VPS35-dependent TREM2 recycling in murine Alzheimer's disease. *Alzheimers Res Ther*. 2024;16(1):121. doi:10.1186/s13195-024-01489-6
67. Ren X, Yao L, Wang Y, et al. Microglial VPS35 deficiency impairs Aβ phagocytosis and Aβ-induced disease-associated microglia, and enhances Aβ associated pathology. *Journal of Neuroinflammation*. 2022;19(1):61. doi:10.1186/s12974-022-02422-0
68. Gao L, Xiao H, Ai L-Q-Y, et al. Vps35 Deficiency Impairs Cdk5/p35 Degradation and Promotes the Hyperphosphorylation of Tau Protein in Retinal Ganglion Cells. *Invest Ophthalmol Vis Sci*. 2020;61(1):1. doi:10.1167/iovs.61.1.1
69. Yang Y, Sun X. Retinal Ganglion Cell Death in Glaucoma: advances and Caveats. *Curr Eye Res*. 2023;48(1):1–10. doi:10.1080/02713683.2022.2068182
70. Dhande OS, et al. Contributions of Retinal Ganglion Cells to Subcortical Visual Processing and Behaviors. In: *Annual Review of Vision Science*. Movshon JA, Wandell BA. editors. 2015;1:291–328
71. Guo XZ, Zhou J, Starr C, et al. Preservation of vision after CaMKII-mediated protection of retinal ganglion cells. *Cell*. 2021;184(16):4299. doi:10.1016/j.cell.2021.06.031
72. Levin LA, Gordon LK. Retinal ganglion cell disorders: types and treatments. *Progress in Retinal and Eye Research*. 2002;21(5):465–484. doi:10.1016/s1350-9462(02)00012-5
73. Liu W, et al. Vps35-deficiency impairs SLC4A11 trafficking and promotes corneal dystrophy. *PLoS One*. 2017;12(9):e0184906.
74. Liu W, Tang F-L, Erion J, et al. Vps35 haploinsufficiency results in degenerative-like deficit in mouse retinal ganglion neurons and impairment of optic nerve injury-induced gliosis. *Molecular Brain*. 2014;7. doi:10.1186/1756-6606-7-10
75. Buck TM, Quinn PMJ, Pellissier LP, et al. CRB1 is required for recycling by RAB11A+ vesicles in human retinal organoids. *Stem Cell Reports*. 2023;18(9):1793–1810. doi:10.1016/j.stemcr.2023.07.001
76. Shin H-A, Park M, Lee HJ, et al. Unveiling Neuroprotection and Regeneration Mechanisms in Optic Nerve Injury: insight from Neural Progenitor Cell Therapy with Focus on Vps35 and Syntaxin12. *Cells*. 2023;12(19):2412. doi:10.3390/cells12192412
77. Zhang M, Zhang S, Guo W, et al. Novel molecular hepatocellular carcinoma subtypes and RiskScore utilizing apoptosis-related genes. *Sci Rep*. 2024;14(1):3913. doi:10.1038/s41598-024-54673-x
78. Fracanzani AL, et al. Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non–iron-related chronic liver disease. *Hepatology*. 2001;33(3):647–651. doi:10.1053/jhep.2001.22506
79. Guo Y, Chai B, Jia J, et al. KLF7/VPS35 axis contributes to hepatocellular carcinoma progression through CCDC85C-activated β-catenin pathway. *Cell Biosci*. 2021;11(1):73. doi:10.1186/s13578-021-00585-6
80. Tan W, Zhang J, Liu L, et al. Hsp90 Inhibitor STA9090 induced VPS35 related extracellular vesicle release and metastasis in hepatocellular carcinoma. *Transl Oncol*. 2022;26:101502. doi:10.1016/j.tranon.2022.101502
81. Li X, Cao Y, Yu X, et al. A novel autophagy-related genes prognostic risk model and validation of autophagy-related oncogene VPS35 in breast cancer. *Cancer Cell Int*. 2021;21(1):265. doi:10.1186/s12935-021-01970-4
82. Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer. *Lancet*. 2020;396(10251):635–648. doi:10.1016/S0140-6736(20)31288-5
83. Pérez-Torres EJ. Retromer dysfunction in amyotrophic lateral sclerosis. *Proceedings of the National Academy of Sciences of the United States of America*. 2022;119(26):e2118755119.
84. De Domenico I, McVey Ward D, Kaplan J. Regulation of iron acquisition and storage: consequences for iron-linked disorders. *Nat Rev mol Cell Biol*. 2008;9(1):72–81. doi:10.1038/nrm2295
85. Chen C, Garcia-Santos D, Ishikawa Y, et al. Snx3 regulates recycling of the transferrin receptor and iron assimilation. *Cell Metab*. 2013;17(3):343–352. doi:10.1016/j.cmet.2013.01.013

86. Vogelstein B, Kinzler KW. The multistep nature of cancer. *Trends Genet*. 1993;9(4):138–141. doi:10.1016/0168-9525(93)90209-Z
87. Zhang GJ, Tang X, Liang L, et al. DNA and RNA sequencing identified a novel oncogene VPS35 in liver hepatocellular carcinoma. *Oncogene*. 2020;39(16):3229–3244. doi:10.1038/s41388-020-1215-6
88. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2016;2:16018. doi:10.1038/nrdp.2016.18
89. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
90. Xu Y, Gong M, Wang Y, et al. Global trends and forecasts of breast cancer incidence and deaths. *Scientific Data*. 2023;10(1):334. doi:10.1038/s41597-023-02253-5
91. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med*. 2010;363(20):1938–1948. doi:10.1056/NEJMra1001389
92. Stanton SE, Gad E, Ramos E, et al. Tumor-associated autoantibodies from mouse breast cancer models are found in serum of breast cancer patients. *NPJ Breast Cancer*. 2021;7(1):50. doi:10.1038/s41523-021-00257-1
93. Li F, Li J, Yu J, et al. Identification of ARGLU1 as a potential therapeutic target for gastric cancer based on genome-wide functional screening data. *EBioMedicine*. 2021;69:103436. doi:10.1016/j.ebiom.2021.103436
94. Maron SB, Alpert L, Kwak HA, et al. Targeted Therapies for Targeted Populations: anti-EGFR Treatment for EGFR -Amplified Gastroesophageal Adenocarcinoma. *Cancer Discov*. 2018;8(6):696–713. doi:10.1158/2159-8290.CD-17-1260
95. Zender L, Spector MS, Xue W, et al. Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell*. 2006;125(7):1253–1267. doi:10.1016/j.cell.2006.05.030
96. Zhou Q, Qi F, Zhou C, et al. VPS35 promotes gastric cancer progression through integrin/FAK/SRC signalling-mediated IL-6/STAT3 pathway activation in a YAP-dependent manner. *Oncogene*. 2024;43(2):106–122. doi:10.1038/s41388-023-02885-2
97. Wang C, Chen Y, Zhou R, et al. Systematic Analysis of Tumor Stem Cell-related Gene Characteristics to Predict the PD-L1 Immunotherapy and Prognosis of Gastric Cancer. *Curr Med Chem*. 2024;31(17):2467–2482. doi:10.2174/0109298673278775231101064235
98. Muzio L, Sirtori R, Gornati D, et al. Retromer stabilization results in neuroprotection in a model of Amyotrophic Lateral Sclerosis. *Nature Communications*. 2020;11(1). doi:10.1038/s41467-020-17524-7.
99. Walker FO. Huntington's disease. *Lancet*. 2007;369(9557):218–228. doi:10.1016/S0140-6736(07)60111-1
100. MACDONALD M. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell*. 1993;72(6):971–983. doi:10.1016/0092-8674(93)90585-E
101. Miller AJ, Mihm Jr MC. Melanoma. *N Engl J Med*. 2006;355(1):51–65. doi:10.1056/NEJMra052166
102. Park J, Jeong GH, Song M, et al. The global, regional, and national burden of inflammatory bowel diseases, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Dig Liver Dis*. 2023;55(10):1352–1359. doi:10.1016/j.dld.2023.04.003
103. Whiteman DC, Green AC, Olsen CM. The Growing Burden of Invasive Melanoma: projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. *J Invest Dermatol*. 2016;136(6):1161–1171. doi:10.1016/j.jid.2016.01.035
104. Zhou M, Wiener H, Su W, et al. VPS35 binds farnesylated N-Ras in the cytosol to regulate N-Ras trafficking. *J Cell Biol*. 2016;214(4):445–458. doi:10.1083/jcb.201604061
105. An CH, Kim YR, Kim HS, et al. Frameshift mutations of vacuolar protein sorting genes in gastric and colorectal cancers with microsatellite instability. *Hum Pathol*. 2012;43(1):40–47. doi:10.1016/j.humpath.2010.03.015
106. Mecozzi VJ, Berman DE, Simoes S, et al. Pharmacological chaperones stabilize retromer to limit APP processing. *Nature Chemical Biology*. 2014;10(6):443–449. doi:10.1038/nchembio.1508
107. Chen K-E, Guo Q, Hill TA, et al. De novo macrocyclic peptides for inhibiting, stabilizing, and probing the function of the retromer endosomal trafficking complex. *Science Advances*. 2021;7(49). doi:10.1126/sciadv.abg4007.
108. Balood M, Ahmadi M, Eichwald T, et al. Nociceptor neurons affect cancer immunosurveillance. *Nature*. 2022;611(7935):405–412. doi:10.1038/s41586-022-05374-w
109. Sattler A, Korzun T, Gupta K, et al. Sympathetic nerve signaling rewires the tumor microenvironment: a shift in "microenvironmental-ity". *Cancer Metastasis Rev*. 2025;44(1):25. doi:10.1007/s10555-025-10241-x