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Extracellular Vesicles and Circulating Nucleic Acids

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Glucosylceramides trigger the shedding of alpha-synuclein laden ectosomes

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MAIN TEXT

Parkinson's disease (PD) is characterized by the progressive misfolding and spreading of alpha synuclein (αSyn), which aggregates into Lewy bodies and contributes to neuronal dysfunction and loss[1,2]. Although traditionally viewed as a movement disorder arising from dopaminergic degeneration in the substantia nigra, PD is now recognized as a multisystem disease with peripheral and central nervous system pathology. This perspective aligns with evidence that αSyn pathology propagates between interconnected neuronal and non-neuronal cells[3-6], suggesting that disease progression reflects both local vulnerability and intercellular spread.

Several routes for αSyn transfer have been identified including prion-like cell-to-cell[7] and vesicle-mediated transfer and direct propagation through tunneling nanotubes (TNTs) that enable direct cytoplasmic continuity between neighboring neurons[8] or neurons to glia[9]. TNTs contribute to the spread of αSyn fibrils and oligomers[10] but were mostly recognized as a means to deliver αSyn to glia for glia-mediated degradation[11-13]. In contrast to TNTs, extracellular vesicles (EVs) can transport αSyn cargo over longer distances and facilitate their uptake by recipient cells[14-16]. These complementary pathways promote the dissemination of αSyn pathology observed in PD. The stage or region-specific relative contribution is currently unknown.

Genetic and biochemical evidence further implicates lysosomal dysfunction as a critical amplifier of αSyn toxicity. Monoallelic mutations in GBA1, the gene encoding the lysosomal enzyme glucocerebrosidase (GCase), represent the most common genetic risk factor for PD[17-20]. Reduced GCase activity leads to the accumulation of its substrate glucosylceramide (GlcCer), which stabilizes soluble αSyn oligomers and promotes their aggregation[20-22]. Conversely, increasing the αSyn burden can impair GCase trafficking and function, creating a bidirectional pathogenic loop that accelerates neurodegeneration. Emerging data suggest that GlcCer may not only influence intracellular αSyn homeostasis but also trigger an innate immune response[23,24] and modulate the packaging of αSyn into EVs[25] [Figure 1].

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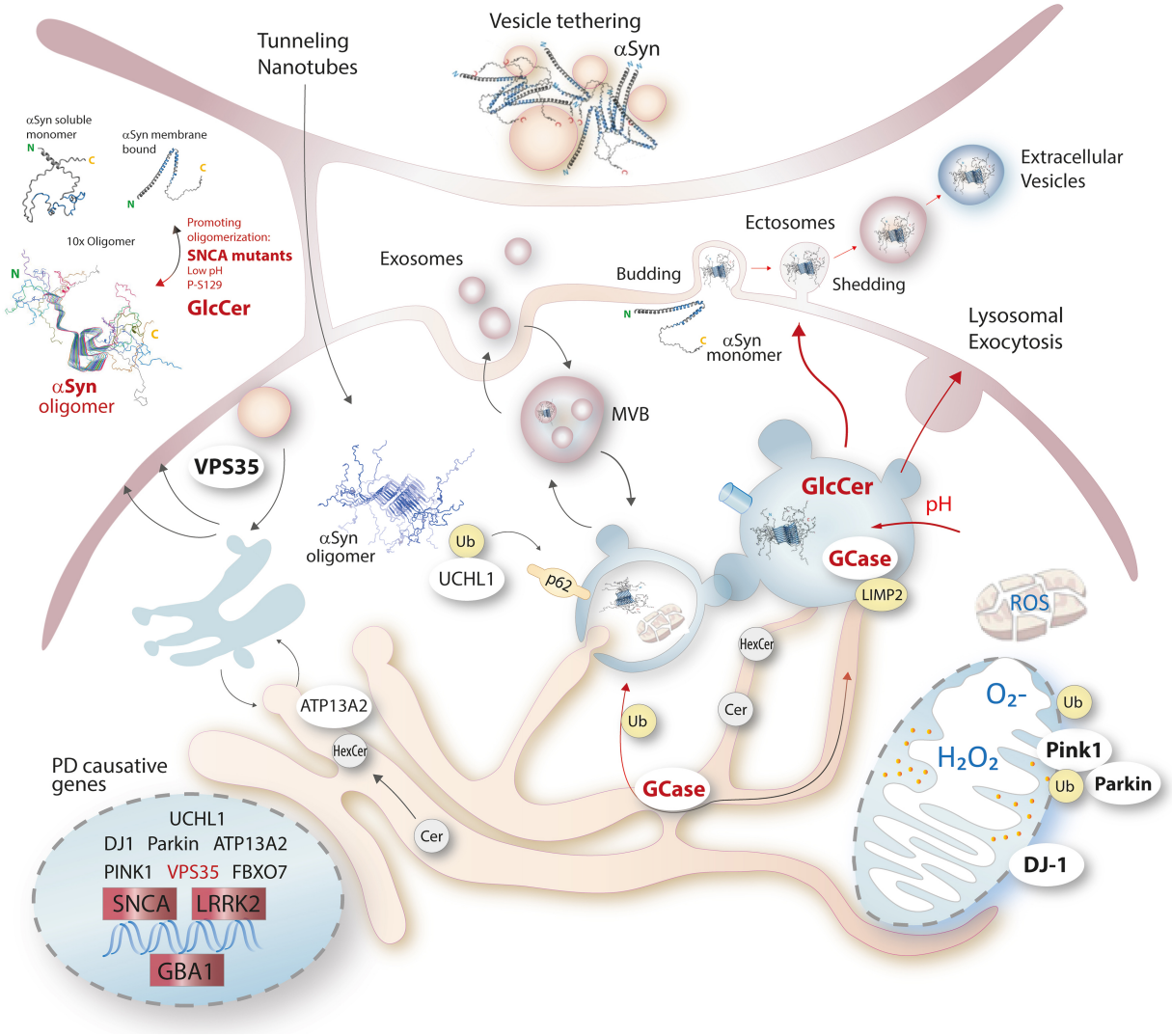

Figure 1. Illustration of PD genetics, the pathology of αSyn and glucosylceramides in the context of vesicle transport and release, autophagolysosomal degradation and mitochondrial damage. αSyn structure icons were obtained from PDB (micell bound monomer 1XQ8 | pdb_00001xq8[60]; 10x oligomer 2N0A | pdb_00002n0a)[61]. ATP13A2: Cation-transporting ATPase 13A2; FBXO7: F-box only protein 7; GBA1: gene encoding lysosomal glucocerebrosidase; GCase: glucocerebrosidase; LRRK2: leucine-rich repeat kinase 2; DJ-1/PARK7: protein/nucleic acid deglycase; PINK1: serine/threonine-protein kinase PINK1, mitochondrial; Parkin/Prkn: E3 ubiquitin-protein ligase parkin; p62/SQSTM1: Sequestosome-1; LIMP2/SCARB2: lysosome membrane protein 2; SNCA: alpha-synuclein; UCHL1: ubiquitin carboxyl-terminal hydrolase isozyme L1; VPS35: vacuolar protein sorting-associated protein 35; Cer: ceramides; HexCer: hexosylceramides; GlcCer: glucosylceramides; Ub: ubiquitin; MVB: multivesicular bodies; PD: Parkinson's disease; αSyn: alpha synuclein.

A major advance comes from the recent study demonstrating that GlcCer actively drives ectosome shedding thereby promoting αSyn propagation[25]. The authors show that increased GlcCer, as a consequence of reduced GCase activity, induces ectosome shedding from primary neurons and that these ectosomes are loaded with αSyn and lead to the transmission of αSyn pathology to neighboring neurons. Using live cell imaging, two-photon microscopy *in vivo*, and induced pluripotent stem cells (iPSC)-derived dopaminergic neurons from patients carrying GBA1 or leucine rich repeat kinase 2 (LRRK2) mutations, the study demonstrates that GlcCer directly stimulates the outward budding and fission of large plasma membrane-derived vesicles. These ectosomes contain cytosolic markers such as tubulin, are enriched in CD81, and display the characteristic sizes expected for microvesicle-type EVs.

The authors show in primary cortical neurons that both exogenous GlcCer and pharmacological GCase inhibition with conduritol-β-epoxide increase ectosome budding without inducing cell death, showing that the ectosome release is an active, regulated process that establishes a direct link between GlcCer accumulation and vesicle-mediated αSyn spread. *In vivo*, two-photon imaging in tdTomato labeled neurons revealed ectosome formation in the intact cortex following GlcCer injection. Histology further confirmed an increased number of detached tdTomato positive vesicles, which were taken up by neighboring neurons, providing direct evidence for intercellular transfer. The study further extended these findings to human iPSC-derived dopaminergic neurons carrying GBA1 or LRRK2 mutations. All PD-associated lines exhibited reduced GCase activity and a marked increase in ectosome shedding compared with their isogenic controls. Rescue experiments, either by pharmacological enhancement of GCase activity or by overexpressing wild-type GCase, normalized ectosome release. Restoring lysosomal acidification or LRRK2 kinase inhibition also reduced ectosome formation suggesting a causal relationship between lysosomal function, GlcCer accumulation and ectosome shedding.

Together, these experiments established ectosomes rather than exosomes as a major, previously underappreciated route for αSyn transmission in PD, which was further supported experimentally showing that pharmacologic inhibition of exosome formation with GW4869 did not prevent αSyn spreading. Ectosomes are likely more efficient at transferring pathogenic αSyn than exosomes because they are larger allowing package of fibrillar αSyn and they carry plasma-membrane proteins and lipids including externally exposed phosphatidylserine that mediate rapid capture and uptake[26-28] which impacts vesicle and hence, αSyn destiny[29,30]. Earlier studies reporting α-synuclein in EVs likely captured a mixed population of exosomes and ectosomes[14,16,31-34]. Given the now presented direct visualization of αSyn-laden ectosome budding[25], it is plausible that ectosomes contributed substantially to the pathogenic EV cargo previously attributed to exosomes. Mixed EV populations may also explain inconsistent findings of "exosomal" αSyn as biomarker of PD[32,35-37].

While the authors of[25] emphasize ectosomes as a mechanism of pathogenic propagation, the same biology can also be interpreted as a neuronal clearance strategy. Neurons have limited capacity for lysosomal degradation, especially under conditions of GCase deficiency. In this context, ectosome shedding may represent a compensatory mechanism to offload toxic cytosolic cargo. The exposure of phosphatidylserine on ectosomes[38,39] is a feature that flags the vesicles for phagocytosis or pinocytosis[40,41], accelerating the clearance from the extracellular space and reducing the half-life of toxic cargo[28,42-44]. Hence, once released, glial cells are integrated into the detoxification of αSyn. This is consistent with the broader concept that EV-mediated export is part of the neuron's stress response repertoire, analogous to lysosomal exocytosis or autophagic secretion[45,46]. In addition, αSyn containing EVs are detectable in peripheral body fluids[32,37,47-49], suggesting that vesicular export contributes to the systemic distribution and eventually, peripheral clearance of αSyn. From this perspective, GlcCer-induced ectosome release is not solely a pathological amplifier but a dynamic, context-dependent process balancing propagation and protection.

Ambroxol, a GCase chaperone currently under clinical investigation, exemplifies this duality. It is supposed to increase the activity of mutant GCase but primarily, it triggers lysosomal exocytosis[50-52]. Owing to its alkaline nature it is trapped in lysosomes, increases the lysosomal pH and triggers lysosomal exocytosis[50-52]. Although spilling out lysosomal αSyn content may facilitate αSyn spread by receptor-mediated internalization via e.g. FAM171[53] or LAG3[54,55], ambroxol nonetheless produces temporary symptomatic benefits and improves cellular proteostasis[52,56,57] suggesting that enhanced glial-mediated degradation outweighs the transient rise in extracellular αSyn, and that vesicle release may be protective when coupled with efficient downstream clearance.

The dual nature of ectosome biology opens intriguing therapeutic possibilities. If αSyn-laden EVs can be efficiently cleared in the periphery, then enhancing export from the brain, while simultaneously trapping or degrading vesicles outside the central nervous system (CNS), could shift the balance toward net detoxification. Several conceptual strategies emerge. Circulating αSyn EVs could be bound by engineered antibodies, nanobodies, or lipid binding polymers that selectively trap vesicles for hepatic or renal clearance or efflux through the blood-brain-barrier. Microglia and astrocytes are natural sinks for EVs. Enhancing their phagocytic capacity could accelerate the degradation of αSyn containing ectosomes before they propagate pathology. Importantly, EVs per se even without αSyn cargo or coat promote αSyn misfolding[14,32,58] owing to their ceramide and curvature-rich membrane lipid domains[59].

The discovery that GlcCer drives ectosome shedding provides a mechanistic bridge between lipid dysregulation, vesicle biology, and αSyn propagation. Yet, the same pathway may also serve as a neuronal survival mechanism, enabling the export of toxic cargo when intracellular degradation is compromised. Thus, the biological role of ectosomes is fundamentally dual, and their net effect depends on the balance between release and clearance.

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Authors' contributions

The author contributed solely to the article.

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Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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