

Review Article

Biological functions of progranulin and research progress in neurodegenerative diseases

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Abstract: Progranulin (PGRN), a multifunctional glycoprotein, is widely expressed in the central nervous system, particularly in microglia. Dysregulation of PGRN is strongly linked to the pathogenesis of frontotemporal dementia (FTD), Alzheimer's disease (AD), and Parkinson's disease (PD), highlighting its essential role in brain homeostasis. While there are several mechanisms through which PGRN regulates lysosomal function, lipid metabolism, neuroinflammation, and microglial activation have been elucidated, its precise pathological network in neurodegenerative diseases remains incompletely understood. This review summarizes the biological functions of PGRN and recent research progress in neurodegenerative diseases, and discusses its potential as a biomarker and therapeutic target. In addition, we propose an integrative "cascade-amplifying pathological network" hypothesis - a self-reinforcing positive feedback loop involving lysosomal dysfunction, lipid accumulation, and microglial activation, with the strongest evidence in GRN-mutation FTD and emerging relevance to AD and PD. Moreover, we incorporate recent advances from 2024-2026, including updated clinical trial outcomes, novel insights into PGRN-mediated lipid metabolism regulation, and emerging evidence on cell-type-specific mechanisms of PGRN function.

Keywords: Progranulin, frontotemporal dementia, neurodegenerative diseases, neuroinflammation, lysosome, biomarker

Introduction

Progranulin (PGRN) is a secreted glycoprotein that contains 7.5 cysteine-rich repeats, called "granulin" peptides [1], and is widely expressed in many cell types, especially in microglia and macrophages [2]. PGRN can act via the secretory pathway or be trafficked to lysosomes where it is cleaved into individual granulin peptides [3]. PGRN haploinsufficiency has been established as a common cause of frontotemporal dementia (FTD) in carriers of *GRN* mutations [4, 5]. Recent studies have begun to elucidate PGRN functions and highlight its important roles in lysosomal homeostasis, lipid metabolism, neuroinflammation and myelination [6-8]. In addition, PGRN deficiency results in mitochondrial swelling, reduced respiratory function, and increased lipid droplets in animal

models, suggesting a close relationship with defects in mitochondrial and lipid functions [7]. Regarding neuroinflammation, PGRN deficiency leads to significantly increased inflammation-related proteins (glycoprotein nonmetastatic melanoma protein B (GPNMB) and galectin-3 (LGALS3)) in microglia and macrophages, triggering persistent neuroinflammatory responses [6-10]. Emerging evidence reveals that dysregulated PGRN expression is robustly associated with diseases of the central nervous system, and recent research has been progressing toward a mechanistic understanding of PGRN's role in CNS disease pathophysiology [11]. However, the relationship between full-length PGRN and its hydrolytic granulin products and how PGRN deficiency leads to neurodegeneration remain unclear and controversial, warranting further in-depth investigation.

Although these advances have been made, a systematic synthesis of PGRN's roles across the interconnected domains of lysosomal function, lipid metabolism, and microglial regulation, and how these domains collectively contribute to neurodegeneration remains lacking. In this narrative review, we summarize the biological functions of PGRN and recent research progress in major neurodegenerative diseases, including FTD, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). We also discuss the potential of PGRN as a biomarker and therapeutic target [5, 7, 12, 13]. Recent studies have demonstrated that PGRN has diverse roles as a cell signaling molecule that regulates lysosomal function, immune processes, and growth [11]. Building on the available evidence, we propose an integrative "cascade-amplifying pathological network" hypothesis, in which PGRN deficiency triggers a self-reinforcing positive feedback loop among lysosomal dysfunction, lipid accumulation, and sustained microglial activation [7, 14]. This model is best supported in *GRN*-mutation FTD [4, 5], with emerging relevance to AD and PD [7, 15, 16]. This review covers the structural characteristics, lysosomal functions, lipid metabolism, neuroinflammation, disease-specific pathology, biomarker potential, therapeutic strategies, and future perspectives.

Structural characteristics and intracellular processing of PGRN

Gene and protein structural features of PGRN

PGRN is coded by the *GRN* gene on human chromosome 17q21.31 [17]. The transcribed and translated product is a secreted glycoprotein of seven and a half complete granulin domains, with one half-granulin domain, containing a total of 7.5 conserved repeat units [18] that are able to fold into stable three-dimensional structures formed by disulfide bonds, which are the foundation for the broad biological activities of PGRN. Individual granulin peptides may thus have distinct or overlapping activities. Granulin-3 and granulin-5 reportedly have disordered structures in reducing conditions, and high affinities for copper ions, suggesting functions in metal homeostasis and oxidative-stress regulation [19]. Several mutations in the *GRN* gene, including nonsense

and frameshift mutations and splice-site mutations, are important causes of reduction or loss of function and PGRN expression, and therefore lead to neurodegenerative diseases such as FTD. The 5' untranslated region of the *GRN* contains upstream open reading frames that prevent translation; variations in this region (e.g. rs76783532) enhance downstream protein expression, indicating the complexity of gene regulation within genes [20]. *GRN* gene expression is then finely regulated by epigenetic mechanisms. Studies have shown that DNA hypermethylation in the promoter region of *GRN* is associated with reduced levels of PGRN mRNA. This non-hereditary gene silencing mechanism may contribute to the progression of sporadic FTD and other neurodegenerative diseases, expanding the horizon of understanding PGRN deficiency in non-mutation carriers [21, 22]. These structures and genetic variations together dictate the distribution and role of PGRN, the core of its involvement in physiological and pathological processes. *GRN* polymorphisms are also associated with increased risk for Alzheimer's disease and Parkinson's disease, and may influence cognitive aging. A common *GRN* polymorphism associated with the risk of AD and FTD modestly reduces progranulin levels, indicating that even a mild reduction in progranulin may increase the risk of neurodegenerative disease [23].

Lysosomal targeting and proteolytic processing of PGRN

Once secreted, PGRN can be trafficked to lysosomes through clathrin-dependent endocytosis or via sortilin as well as other receptors [19, 24]. Once inside the lysosome, PGRN is rapidly hydrolysed by a variety of proteases under acidic conditions to liberate individual granulin peptides [19]. Lysosomal processing of PGRN is critical to its function. Using cell type-specific lysosomal isolation proteomics in a recent study, it was shown that PGRN deletion leads to a cell type-specific alteration of the lysosomal proteome of astrocytes, neurons, and microglia, with respect to selected sphingolipid metabolism-related proteins and lysosome organization components suggesting that PGRN may fine-tune the lysosomal proteome post-translationally [25]. Human PGRN not only interacts with the lysosomal cargo receptor, but also with another lysosomal pro-

tein, prosaposin, in the ER lumen, promoting its efficient export from the ER via the Surf4 receptor for proper delivery to lysosomes [26]. These findings underscore the tight regulation that governs lysosomal targeting, hydrolysis, and feedback control of the lysosomal milieu by PGRN - a regulation that, when compromised, contributes to the pathogenesis of neurodegenerative diseases. Progranulin localizes to lysosomes and is necessary for maintaining lysosomal function, as people with mutations on both GRN alleles develop a lysosomal storage disorder, neuronal ceroid lipofuscinosis. Progranulin stimulates the activity of multiple lysosomal enzymes, including the protease cathepsin D and several sphingolipid-metabolizing enzymes [23].

Functional relationship between full-length PGRN and granulins

While it is commonly believed that full-length PGRN is the active form, recent work has suggested that specific granulin peptides have their own important independent actions in addition to those of the full-length protein. Studies in mouse models have demonstrated that in PGRN-deficient mice, independent expression of either of the granulin peptides GRN-2/F or GRN-4/A is sufficient to ameliorate dysregulated lysosomal proteins and lipids, microgliosis, and lipofuscin deposition [27]. Furthermore, functional studies have shown that overexpression of full-length PGRN inhibits autophagic flux and promotes the formation of pathological protein aggregates [28]. Moreover, Hofer and colleagues found that overexpressing C-terminally truncated PGRN (lacking the last two or four granulin domains) did not affect the colony formation ability of HepG2 hepatoma cells, whereas full-length PGRN promoted colony formation [29]. This raises the possibility that full-length PGRN and certain granulins have opposing functions, and that proteolytic processing might serve as an important regulatory switch for PGRN activity. Other studies suggest that the balance between full-length PGRN and granulins is important for normal cellular function [30, 31]. Ultimately, gradual understanding of the specific function of different forms of PGRN will be of paramount importance for the design of precision therapeutic strategies targeting PGRN-related diseases. The unique “progranulin-pep-

tide” structure of PGRN as well as its protease processing balance is the biological basis of its function, and when that balance breaks down due to the gene mutation or protease imbalance, it directly triggers lysosome dysfunction and lipid metabolism abnormality afterwards, giving rise to important insight for understanding its pathological role. Progranulin is constitutively secreted before trafficking to lysosomes, and may interact with several signaling receptors. There is evidence that progranulin may act either in lysosomes or through extracellular signaling to restrain inflammation and promote neuronal growth and survival [23].

Regulation of lysosomal function and lipid metabolism by PGRN

Interaction of PGRN with lysosomal membrane proteins

PGRN/Granulins exert their functions in the lysosomal microenvironment in part by depending on the fine interactions they establish with specific lysosomal membrane proteins. Work done at Cornell University established a direct interaction between granulin E and the lysosomal membrane protein cluster of differentiation 68 (CD68), with both progranulin and CD68 reciprocally regulating each other's protein homeostasis [32]. In the subfornical organ of SAP-D-deficient mice activated microglia highly express prosaposin (PSAP) and PGRN and the infiltration of microglia that are positive for the membrane protein CD68 is correlated with the accumulation of PSAP and PGRN. CD68 deletion selectively decreases granulin E levels without affecting the lysosomal localization of full-length PGRN or any other granulin peptide - revealing another mechanism by which PGRN/granulins exert regulatory functions in specific cell types through specific interaction partners [33]. Beyond CD68, another important risk modifier of frontotemporal lobar degeneration, in particular, is the lysosomal membrane protein transmembrane protein 106B (TMEM106B) [34, 35]. TMEM106B modulates lysosomal axonal transport and acidification [36]; in animal studies TMEM106B deletion exacerbates pathology in PGRN knockout mice [37]. TMEM106B was initially implicated in FTL with TDP-43 inclusions, and recent reviews have summarized advances in understanding PGRN and TMEM106B function within

the endolysosomal system. PGRN interacts with molecules like the ER protein endoplasmic reticulum protein 57 (ERp57) via its C-terminal granulin E domain and these interactions facilitate the protective role of PGRN in lysosomal storage disorders such as Gaucher disease [37]. Collectively these studies suggest that PGRN is not a standalone facilitator but rather a constituent that creates a dynamic interaction network with a series of lysosome-associated membrane proteins or auxiliary factors such as CD68, TMEM106B, and ERp57 and fine-tunes several aspects including lysosomal localization, transport, acidification, and substrate degradation, the imbalance of which is directly implicated in the pathologies of neurodegenerative diseases.

Regulation of sphingolipid metabolism by PGRN

PGRN plays a very important role in sphingolipid metabolism and maintenance of lysosomal lipid homeostasis. Boland et al. found that in PGRN-deficient human cells, mouse brains and frontal lobe tissues of FTD patients carrying GRN mutations, sialic acid containing glycosphingolipids such as gangliosides were significantly elevated, whilst levels of their degrading enzymes remained normal [37]. The key reason for this apparent paradox is that PGRN or perhaps even more importantly its derived granulins, are required to maintain lysosomal levels of bis(monoacylglycerol)phosphate (BMP), an endolysosomal phospholipid that is a pH-dependent interactor of PGRN and also a redox-sensitive enhancer of lysosomal proteolysis and lipolysis. Global BMP deficiency exists in *GRN* knockout mice [38]. Since BMP is a requisite cofactor for ganglioside degradation, PGRN deficiency is essentially a gangliosidosis [39]. This aberrant lipid loading is presumed to perturb lysosomal homeostasis and to trigger neuroinflammation and susceptibility to neurodegeneration. In line with this paradigm, loss of PGRN also leads to age-dependent marked accumulation of glucosylceramide and the glucosylsphingosine derivative, a lipid well characterized for its roles in neuroinflammation [38]. In Gaucher disease models, PGRN acts as an important cofactor for glucocerebrosidase and its deficiency exacerbates the glycosphingolipid accumulation and disease phenotype caused by *GBA1* mutations [40, 41]. As such, this main-

tenance of normal sphingolipid degradation by regulating BMP levels contributes to how the PGRN loss of function disorder serves as a bridge between lysosomal disorder and neurodegeneration. In essence, PGRN does not simply function in lysosome regulation, but acts as a coupling node between lysosomal homeostasis and lipid metabolism through its regulation of levels of key phospholipids such as BMP. This metabolic alteration not only directly damages neurons, but sends aberrant signaling to the brain immune cells from which they mount neuroinflammatory responses. Dysregulated lipid metabolism in microglia represents a hallmark of neuroinflammation and is often observed in a variety of neurodegenerative diseases. PGRN has recently been identified as a regulator of lipid droplet formation in microglia. Additionally, PGRN has been reported to interact with various molecules to modulate lysosomal lipid metabolism, including glycerolipids and sphingolipids in neurons. PGRN deficiency-mediated lipid dysregulation may be a significant contributing factor in neuroinflammation and the pathogenesis of related neurodegenerative diseases [7].

Regulation of neuroinflammation and microglial function by PGRN

PGRN is a lysosomal glycoprotein that is highly expressed in microglia. PGRN is required for normal homeostatic function and lipid metabolism in microglia; when PGRN is lost, distinct stages of microglial pathology ensue [42]. Yiyue Shi et al. demonstrate that loss of PGRN causes disruptions in microglial lipid metabolism, leading to accumulation of lipid droplets, which have been associated with neuroinflammation and various neurodegenerative diseases [7]. This impairment of lipid homeostasis, together with mitochondrial dysfunction and increased glycolysis, underlies the dysfunctional microgliopathy [7]. Such metabolic reprogramming consequently hinders the ability of microglia to migrate and phagocytose, whilst simultaneously ramping up the release of pro-inflammatory cytokines and reactive oxygen species [43-45]. In a remarkable series of observations, it has been demonstrated that microglia-derived PGRN itself is sufficient to rescue core pathological and behavioural phenotypes from systemic deficiency of the protein, implicating the immune cells as cellular

conduits of PGRN function, but also as effector cells of PGRN-mediated neuroprotective pathways. PGRN supports microglial homeostasis via programming of lysosomal function, lipid metabolism and autophagy; in the absence of this the integrity of neuroimmune signalling circuits falls apart leading to neuronal dysfunction. A resolution of neuroinflammation, for example, will depend on an understanding of how PGRN safeguards microglial homeostasis, and how the loss of this alters their rapid response. Microglial PGRN plays an important role in maintaining hypothalamic lysosomal function under healthy diet conditions, whereas increased cleavage of microglial PGRN in states of overnutrition disrupts hypothalamic lysosomal function, thereby fostering hypothalamic inflammation and obesity. Under normal diet conditions, microglial Grn depletion leads to increased lysosome mass, reduced lysosomal degradative capacity, and accumulation of lipofuscin and cytoplasmic TDP-43 in hypothalamic cells, indicative of lysosomal stress and dysfunction [46].

Pathological role of PGRN in major neurodegenerative diseases

PGRN and frontotemporal dementia with GRN gene mutations

PGRN is encoded by the *GRN* gene, which contains several types of mutations, including frameshift, nonsense, splice site mutations and segmental deletions that appear to create premature termination codons, which result in the degradation of *GRN* mRNA and PGRN haploinsufficiency. Besides that, missense variants that do not lead to mRNA degradation also lead to PGRN deficiency [47-49]. This haploinsufficiency reduces PGRN by approximately 50% and initiates a cascade of pathological events. First, PGRN deficiency leads to imbalance in the homeostasis of lysosomal β -glucocerebrosidase activity and BMP, leading to abnormal accumulation of glycosphingolipids [38]. Second, this lysosomal dysfunction triggers microglial activation and chronic neuroinflammation [42]. Third, these events promote TDP-43 protein aggregation, a pathological hallmark of FTD [14]. Heterozygous mutations in *GRN* gene lead to insufficient levels of the progranulin (PGRN) protein, resulting in frontotemporal dementia (FTD) with TAR DNA-

binding protein 43 (TDP-43) inclusions, classified pathologically as frontotemporal lobar degeneration (FTLD-TDP) [2]. Homozygous *GRN* mutations are exceedingly rare and cause neuronal ceroid lipofuscinosis 11, a lysosomal storage disease with onset in young adulthood, or an FTD syndrome with late-onset manifestations [2]. Regarding the role of microglia, current evidence suggests that microglial PGRN deficiency actively contributes to disease pathogenesis and that microglia act as primary drivers rather than merely downstream effectors [42]. Patients with FTD harboring *GRN* mutations have highly distinct clinical phenotypes. A large cohort study has estimated that the age at onset of motor symptoms in FTD patients with *GRN* mutations is later, and they are more likely to exhibit features such as apraxia, focal limb dystonia [50]. In the early stages of FTD, even before symptoms appear, the brains of FTD patients carrying *GRN* mutations undergo complex dynamic reorganization. Spatiotemporal chronnectome studies have found that in presymptomatic *GRN* mutation carriers, brain network connectivity is altered both spatially and temporally, characterized by a greater time spent in a spatial state with stronger activation of the insular and parietal cortices, and the duration of this state is significantly correlated with the expected years to symptom onset [51]. Currently, therapeutic strategies targeting PGRN haploinsufficiency are being actively developed, including adeno-associated virus-mediated gene therapy, stop-codon read-through compounds, sortilin 1 inhibitors, and antisense oligonucleotides, aiming to restore PGRN levels and slow disease progression [42]. *GRN* mutations were first identified in 2006 as a cause of frontotemporal dementia with TDP-43 inclusions. Six years later, they were identified to be also linked to neuronal ceroid lipofuscinosis 11 (CLN11), expanding the spectrum of *GRN*-related neurodegenerative disorders.

PGRN and Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder characterized by progressive cognitive decline; it has characteristic pathophysiological changes of extracellular senile plaques composed mainly of A β peptides and intracellular neurofibrillary tau accumulations [52, 53]. Genetic studies suggest that PGRN levels

are associated with the risk of AD, suggesting that PGRN may play an important role in AD pathophysiology. For example, studies have shown that the rs5848 single nucleotide polymorphism of the GRN gene is significantly associated with AD risk, and this variant may affect PGRN expression levels and function [51]. Furthermore, a study by Huashan Hospital affiliated with Fudan University on the FAM171A2 gene found that FAM171A2 regulates PGRN production, affecting PGRN levels, and is significantly associated with AD risk [15].

Neuroinflammation plays a key role in AD progression, and microglial activation is a central component [4, 5, 51]. A study involving the CABLE and ADNI cohorts found that cerebrospinal fluid (CSF) PGRN levels were significantly positively correlated with soluble Triggering Receptor Expressed on Myeloid cells-2 (sTREM2), and both may modulate A β deposition. Mediation analysis showed that PGRN indirectly increased CSF A β 1-42 levels by upregulating sTREM2 [54], suggesting that the PGRN-sTREM2 axis may modulate A β metabolism. This regulatory effect may be achieved through microglial metabolic reprogramming. PGRN may act as a regulator of immune homeostasis, maintaining stable TREM2 expression on the cell membrane and its proteolytic shedding by promoting microglial oxidative phosphorylation and energy supply, a process that may also involve signaling cascades mediated by cytokines such as IL-33. By optimizing the metabolic state of microglia, PGRN indirectly enhances their ability to monitor and clear amyloid pathology. These findings indicate a potential role for PGRN in modulating A β pathology, though direct causal evidence remains to be established. A recent two population-based study analyzing data from 905 participants in the CABLE cohort and 973 participants in ADNI found that CSF PGRN was associated with higher sTREM2 across the AD continuum and non-AD pathophysiology [55]. Bidirectional mediation was observed between PGRN (14.6% in CABLE, 15.6% in ADNI) and sTREM2 (29.7% in CABLE, 33.5% in ADNI) in modulating A β pathology ($P < 0.0001$). Proteomic analysis identified 1,539 CSF proteins simultaneously associated with PGRN, sTREM2, and A β 1-42, mainly enriched in immune processes and neural plasticity. These findings suggest that the interplay between lysosome function and microg-

lia-related neuroinflammation plays key roles in amyloid metabolism [55]. This indicates that PGRN participates in the regulation of A β pathology, and this regulation may be related to microglial metabolic status. However, direct causal evidence is still needed. Also, the expression of PGRN in Alzheimer's Disease (AD) is dynamic and follows a differential expression pattern across the disease spectrum. Within the A β continuum of AD, PGRN expression exhibits a distinct pattern of variation depending on the stage of the disease; in earlier stages of the continuum compensatory upregulation of PGRN may occur in response to early A β deposition and neuroinflammatory activation, followed by a failure of this compensatory mechanism in more moderate stages of disease where PGRN levels then decline. In late stages, persistent neuroinflammation and lysosomal failure may further lower PGRN expression [5]. This dynamic change reflects the complex role of PGRN in the AD pathological process.

PGRN and Parkinson's disease

Parkinson's disease is a common neurodegenerative disorder characterized primarily by motor dysfunction [52], and PGRN also plays an important role in PD. A meta-analysis found a significant association between the PGRN polymorphism rs5848 and PD risk [53]. However, findings from animal models should be interpreted with caution, as they do not directly demonstrate a definitive disease-modifying therapeutic role in human PD. A study by Kampen et al. using lentiviral vector-mediated PGRN gene delivery showed neuroprotective effects in an MPTP-induced mouse model of PD: PGRN overexpression enhanced resistance of nigral dopaminergic neurons to MPTP toxicity, preserved striatal dopamine levels, and prevented motor dysfunction, with mechanisms involving inhibition of neuroinflammation and reduction of apoptosis markers [56]. Similarly, intracerebroventricular administration of PGRN ameliorated tyrosine hydroxylase loss in MPTP-treated mice and improved motor deficits in a 6-hydroxydopamine model; in cellular models, PGRN promoted α -synuclein degradation via the autophagic-lysosomal pathway [57]. PGRN participates in α -Syn degradation via acceleration of the autophagy-lysosome pathway and is a potential therapeutic target for PD [58]. A

clinical study reported that plasma PGRN levels were significantly reduced in PD patients compared to healthy controls and negatively correlated with PD severity [59]. However, consensus is lacking due to limited studies. A case report described a GRN mutation carrier who exhibited a tremor-dominant PD phenotype with preserved cognition for 11 years, challenging the view that GRN mutations inevitably cause severe cognitive impairment and suggesting that genetic or environmental modifiers may influence phenotypic expression [60].

Regarding the association between PGRN levels and UPDRS-III scores, conflicting findings have been reported. One study found no correlation [61], whereas another reported a significant negative correlation [62]. This discrepancy may arise from multiple factors: sample type (plasma vs. CSF), disease stage, medication status (e.g., levodopa), motor subtype (tremor-dominant vs. akinetic-rigid), inflammatory comorbidities, assay methodology, and statistical adjustment for confounders. Longitudinal studies tracking PGRN levels over time in the same patients are needed to clarify these associations. Additionally, one study found that in PD patients with depression, lower PGRN levels in both CSF and plasma correlated with more severe depressive symptoms [63]. Whether reduced PGRN directly affects depression-related brain regions (e.g., prefrontal cortex, hippocampus, amygdala) remains inconclusive. Genetic evidence supports therapeutic modulation of progranulin levels in Alzheimer's Disease, with a genetically predicted two-fold increase in CSF PGRN levels potentially associated with approximately 35% lower odds of developing AD (OR = 0.65, P = 2.2×10^{-12}) [58].

PGRN and other neurodegenerative diseases

In recent years, PGRN has also been investigated in the field of multiple sclerosis. A recent clinical study demonstrated that PGRN is significantly overexpressed in brain tissue of MS patients, and higher PGRN levels in patients' CSF correlate with increased macrophage/microglial activation, especially in relapse and progressive phases of MS [62]. Furthermore, PGRN plays an important role in the pathogenesis of amyotrophic lateral sclerosis. Several studies have shown that aberrant expression of PGRN is closely associated with the patho-

genesis of ALS including neuroinflammation, oxidative stress, and TDP-43 proteinopathies [8]. In ALS animal models, loss of function of PGRN leads to microglial activation, lysosomal dysfunction and increased motor neuron death [63]. CSF levels of PGRN are found to be elevated in ALS patients and rising levels have been detected with progression of disease and may reflect an active neuroinflammatory state and macrophage/microglial activation, leading researchers to posit it as a biomarker reflecting axonal damage and disease progression [64]. Importantly, progranulin both boosts motor neuron survival and reduces inflammation in the ALS spinal cord, in part by regulating lysosomes, which remove harmful TDP-43 from the cell. However, a recent study found that PGRN deficiency leads to mild glial activation and behavioral deficits in TDP-43Q331K mice without inducing typical TDP-43 pathology, suggesting that the relationship between PGRN and TDP-43 proteinopathy may be more complex than previously appreciated [58]. PGRN is also associated with Huntington's disease and other tauopathies. In these diseases, PGRN may affect the onset and progression of the disease through mechanisms in common, such as modulating neuroinflammation, protein homeostasis and protective functions for neuronal health. The disease-specific roles of PGRN across neurodegenerative disorders are summarized in **Figure 1**.

Potential and challenges of PGRN as a biomarker for neurodegenerative diseases

PGRN is a promising biomarker for neurodegenerative diseases. Studies show that PGRN expression levels are closely tied to the pathology of many neurodegenerative diseases. In familial FTD, loss-of-function mutations in the GRN gene are a common genetic cause, resulting in reduced levels of the protein. Plasma PGRN concentration is a promising biomarker for identifying and diagnosing FTD patients with GRN mutations [65]. In AD, higher CSF PGRN levels have been shown to significantly mitigate the annual rate of cognitive decline and brain atrophy in key brain regions like the hippocampus by attenuating the neurotoxicity of aberrant tau proteins, indicating its potential as a biomarker for disease progression and prognostication [66]. However, the clinical application of PGRN as a potential biomarker for neurodegenerative diseases faces many

Progranulin in neurodegenerative diseases

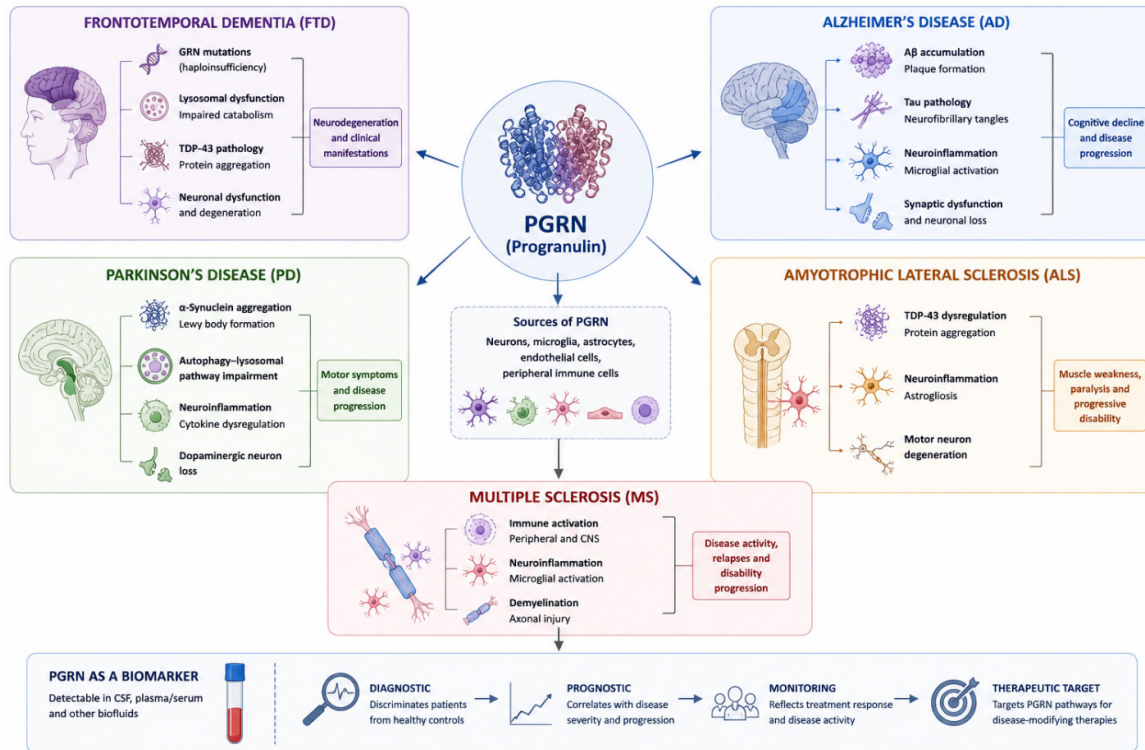


Figure 1. Disease-specific roles of progranulin (PGRN) in neurodegenerative disorders. The image summarizes PGRN's roles across neurodegenerative disorders: FTD (GRN mutations, lysosomal dysfunction, TDP-43), AD (A β , tau, microglial activation), PD (α -synuclein, autophagy), ALS (neuroinflammation, TDP-43), and MS (demyelination, immune activation). These findings support PGRN's potential as a diagnostic and therapeutic biomarker. Disease-specific patterns are summarized in **Table 1**.

challenges. The primary issue is its lack of disease specificity. As a multifunctional protein involved in inflammation, wound repair, and cell survival, PGRN levels are also abnormal in non-neurological conditions such as infections, autoimmune diseases, and tumors [67-70]. This broad reactivity greatly limits its value for differential diagnosis. Second, PGRN levels are influenced by various physiological and metabolic factors, including age, sex, and body mass index [66-68, 71, 72]. These confounding variables complicate the establishment of uniform diagnostic cut-off values. Furthermore, the direction of change in PGRN levels varies across different neurodegenerative diseases, further increasing the difficulty of interpreting results.

To address clinically relevant questions regarding PGRN as a biomarker:

First, plasma PGRN and CSF PGRN do not necessarily reflect identical pathological processes. Plasma PGRN primarily reflects peripheral sources (e.g., immune cells, liver), whereas CSF

PGRN more closely mirrors central nervous system (CNS) production, particularly from microglia. In GRN mutation carriers, reductions are seen in both compartments, but the correlation between plasma and CSF levels is moderate. Therefore, CSF PGRN is preferred for assessing CNS-specific pathology, while plasma PGRN may be useful for screening of GRN mutations [65, 66].

Second, PGRN has greater diagnostic value for identifying GRN mutation carriers than for sporadic neurodegenerative diseases. In FTD, reduced plasma PGRN (typically < 60 ng/mL) has high sensitivity and specificity for GRN mutations. In contrast, in sporadic AD and PD, PGRN levels are inconsistently altered and cannot reliably distinguish patients from controls. Thus, PGRN is best used as a genetic screening tool rather than a generalized biomarker for sporadic disease [65, 67].

Third, elevated PGRN levels do not necessarily confer clinical benefit. Although raising PGRN is

Table 1. Disease-specific alterations and biomarker potential of progranulin (PGRN) in major neurodegenerative disorders

Disease	Major PGRN Alteration	Principal Pathological Mechanisms	Biomarker Evidence	Therapeutic Implications
Frontotemporal Dementia (FTD)	Reduced PGRN due to GRN mutations	Lysosomal dysfunction, TDP-43 aggregation, impaired neuronal survival	Strong; plasma and CSF PGRN reliably identify GRN mutation carriers	PGRN replacement therapies, gene therapy, sortilin inhibition
Alzheimer's Disease (AD)	Altered PGRN expression; GRN variants associated with disease risk	Amyloid- β accumulation, tau pathology, neuroinflammation, microglial dysregulation	Moderate; altered CSF and plasma PGRN reported in several studies	Modulation of neuroinflammation and enhancement of lysosomal function
Parkinson's Disease (PD)	Reduced circulating PGRN levels in some cohorts	α -Synuclein aggregation, autophagy impairment, neuroinflammation	Emerging; potential association with disease progression and severity	Neuroprotective and anti-inflammatory therapeutic approaches
Amyotrophic Lateral Sclerosis (ALS)	Increased CSF PGRN observed in some studies	Neuroinflammation, TDP-43 dysregulation, motor neuron degeneration	Emerging; may reflect inflammatory activity and disease state	Regulation of neuroinflammatory pathways
Multiple Sclerosis (MS)	Elevated CSF PGRN levels during disease activity	Demyelination, microglial activation, immune-mediated inflammation	Emerging; may serve as an indicator of disease activity	Immunomodulatory and neuroprotective strategies

Abbreviation: PGRN, progranulin; CSF, cerebrospinal fluid; GRN, progranulin gene; TDP-43, TAR DNA-binding protein 43; A β , amyloid-beta; sTREM2, soluble Triggering Receptor Expressed on Myeloid cells-2.

a therapeutic goal in GRN haploinsufficiency, overexpression may be neurotoxic (see Section 7.3). Moreover, in some inflammatory conditions, elevated PGRN may reflect reactive gliosis instead of a protective response. Therefore, interpreting elevated PGRN levels requires context: the disease, the compartment (plasma vs. CSF), and the therapeutic intervention all influence whether higher PGRN is associated with benefit or harm [65, 71].

Therapeutic strategies targeting PGRN

Strategies to increase PGRN levels

For neurodegenerative diseases that involve a partial loss of PGRN function, methods are being explored to increase PGRN levels within the CNS. In the field of FTD, drug discovery efforts are also being focused on therapeutic strategies targeting *GRN* mutation carriers, especially monoclonal antibody therapies that aim to increase PGRN levels. For example, latozinemab is a humanized monoclonal antibody directed against the sortilin receptor. This antibody prevents PGRN sorting to lysosomes, leading to a 2- to 3-fold increase in circulating PGRN levels in plasma and CSF in non-human primates and in clinical trials in healthy volunteers [68, 70]. Latozinemab was granted U.S. Food and Drug Administration Breakthrough Therapy Designation for FTD-GRN in early 2024

[73]. However, the pivotal INFRONT-3 Phase 3 clinical trial of latozinemab did not meet its primary efficacy endpoint; researchers found that latozinemab succeeded in raising levels of plasma progranulin, but that didn't translate to tangible effects on disease progression. Topline data from this trial were anticipated by Q4 2025, and following the trial failure, Alector announced a workforce reduction of 49% [73]. Similarly, AL101 (GSK4527226) a monoclonal antibody against sortilin, was shown in preclinical studies, and Phase I in healthy subjects, to markedly increase PGRN levels in both plasma and CSF and thus has potential as a therapy for AD and other neurodegenerative diseases [50]. More recently, gene therapy approaches have made some headway in terms of the treatment of FTD due to *GRN* mutations whereby a normal copy of the *GRN* gene is delivered to cells of the central nervous system using viral vectors, thus allowing the cells to produce PGRN themselves continuously. A team led by Professor James M. Wilson at the University of Pennsylvania developed an in vivo gene therapy, PR006, which can cross the blood-brain barrier and act directly on the central nervous system to promote PGRN expression [74]. PR006 uses an adeno-associated virus serotype 9 (AAV9) vector, delivered directly into the central nervous system via intracisternal magna injection, bypassing the blood-brain barrier to achieve efficient neuronal transduction

and sustained PGRN expression for treating FTD patients carrying *GRN* mutations. Pre-clinical studies showed that PR006 effectively transduced induced pluripotent stem cell-derived neurons from FTD patients with *GRN* mutations and promoted PGRN expression, and also ameliorated lipofuscin deposition, lysosomal dysfunction, and neuroinflammatory pathology in *GRN* knockout mice. Subsequently, a Phase I/II open-label human trial showed that after a single intracisternal magna injection of PR006, all treated patients had elevated PGRN levels in CSF, and most patients also had transient elevations in blood PGRN levels [69]. The findings presented here provide important evidence and potential for gene therapy in neurodegenerative diseases. The advantages of gene therapy such as tissue-specific expression and long-term effects need longer follow-up and more studies to warrant its safety.

One option to deliver recombinant PGRN directly to patients is protein replacement therapy, giving PGRN protein as a therapy. The hardest part about this is delivery of such a large molecule across the blood-brain barrier, but Denali Therapeutics tackled this research and has developed a biologic, for FTD patients with *GRN* mutations, called PTV:PGRN. Their platform uses transferrin receptor-mediated transcytosis to bring PGRN across the blood-brain barrier (BBB) into the brain. In preclinical studies peripheral administration of the protein corrected BMP levels and glucosylsphingosine levels in the CNS of *GRN* knockout mice, ameliorating pathological phenotypes [38]. This drug is currently in Phase 1/2 for these FTD patients with *GRN* mutations, and the first patient data is expected in 2026.

Although the above strategies hold promise for enhancing PGRN levels, the biological effects of PGRN are bidirectional, underscoring the importance of finely tuning its levels to avoid unwanted side effects. Work from Tokyo Medical University indicated that transgenic mice with high levels of wild-type human PGRN showed a shorter lifespan, cerebellar phenotypes, cognitive defects, gliosis and lysosomal problems. This finding suggests that sustained, excessive upregulation of PGRN expression via viral vectors or genetic manipulation may cause potential neurotoxicity [71]. Therefore, future PGRN replacement therapies must achieve

precise dose control to maintain PGRN within an optimal physiological homeostatic window for different neuron types and specific brain regions [71]. Currently, several PGRN-targeting therapeutics have entered clinical trials. Their specific mechanisms of action, indications, and latest progress are summarized in **Table 2**.

Modulating downstream pathways and cell therapy

Intervening in specific downstream pathway defects caused by PGRN deficiency is another important strategy. PGRN is a key regulator of lysosomal function, and its deficiency leads to widespread lipid metabolic disturbances [7]. Additionally, PGRN deficiency impairs microglial metabolic homeostasis, leading to mitochondrial dysfunction, elevated glycolysis, and lipid droplet accumulation, thereby compromising their migration and phagocytic functions and increasing pro-inflammatory cytokine secretion [72]. Therefore, modulating sphingolipid metabolism, enhancing phagocytic function, or correcting microglial metabolic abnormalities represent potential therapeutic directions. Cyclic phosphatidic acid (cPA), a natural phospholipid mediator characterized by a unique cyclic phosphate ring, has been identified as a novel candidate therapeutic agent for a mouse model of frontotemporal dementia with progranulin deficiency [75]. In recent years, microglia-based cell therapy has been emerging. Since PGRN is highly expressed in microglia and reduction of PGRN in microglia alone is sufficient to trigger inflammation and lysosomal dysfunction in a cell-autonomous manner, targeting microglial dysfunction caused by PGRN deficiency represents a potential therapeutic strategy [41]. One cutting-edge approach is to replace dysfunctional microglia with peripheral macrophage precursors or induced pluripotent stem cell-derived microglia [16, 41, 76]. Another cutting-edge approach is to engineer microglia to target toxic protein aggregates or deliver therapeutic substances [14]. Studies have confirmed that PGRN plays an important role in regulating the microglial response to demyelination; its deficiency leads to sustained microglial activation and defective remyelination, and this effect is sex-dependent [8]. This indicates that microglia-targeted therapies need to consider sex differences. Furthermore, in a prion disease model, com-

Progranulin in neurodegenerative diseases

Table 2. Summary of major clinical trials targeting PGRN for the treatment of neurodegenerative diseases

Drug/Therapy	Mechanism of Action	Route of Administration	Indication	Clinical Trial Phase	Trial Identifier	Key Results/Conclusions
Latozinemab	Humanized monoclonal antibody targeting sortilin receptor; elevates PGRN by blocking sortilin-mediated lysosomal degradation	Intravenous (IV)	FTD-GRN	Phase I	NCT03636204	Significantly increased PGRN levels in plasma and CSF [68].
				Phase II	NCT03987295	Significantly elevated PGRN levels and slowed the rate of clinical progression by approximately 54% as measured by the Clinical Dementia Rating Scale Sum of Boxes (CDR [®] -SB) according to a company press release (Alector, 2022; not peer-reviewed).
				Phase III	NCT04374136	Did not meet the primary efficacy endpoint; failed to significantly delay disease progression.
AL101 (GSK4527226)	Binds to sortilin receptor, reduces cell surface sortilin levels, partially blocks PGRN-sortilin interaction, reducing lysosomal degradation of PGRN	Intravenous (IV)	AD	Phase I	NCT04111666	In healthy volunteers, single or multiple doses resulted in significant increases in PGRN levels in plasma and CSF [50].
VES001	Oral, brain-penetrant small molecule that selectively blocks sortilin-PGRN interaction via competitive binding	Oral	FTD-GRN	Phase II	NCT06079190	Results not yet available.
				Phase I	NCT05424783	Demonstrated excellent safety and tolerability in healthy volunteers; no serious adverse events. Oral administration resulted in significant, cumulative increases in PGRN levels in plasma and CNS.
PR006 (LY3884963)	AAV9 vector-mediated gene therapy delivering functional <i>GRN</i> gene to CNS	Intracisternal magna injection (direct CNS delivery)	FTD-GRN	Phase Ib/IIa	NCT06705192	In 6 asymptomatic <i>GRN</i> mutation carriers, daily oral dosing for 3 months led to a mean increase in CSF PGRN of over 95% from baseline, restoring levels to normal. Safety and tolerability were good.
				Phase I/II	NCT04408625	All treated patients showed elevated PGRN levels in CSF; most had transient elevations in blood PGRN-[69].
PBFT02	AAV1 vector-mediated gene therapy delivering functional <i>GRN</i> gene to CNS via intracisternal magna injection	Intracisternal magna injection (direct CNS delivery)	FTD-GRN	Phase I/II	NCT04747431	In the highest dose cohort, sustained, stable increases in CSF PGRN over 18 months. Annual rate of increase in plasma neurofilament light chain (NfL) was significantly lower compared to natural history data. Four out of 8 patients experienced serious adverse events.
AVB-101	AAV9 vector-mediated gene therapy delivering functional <i>GRN</i> gene to CNS via bilateral thalamic injection	Bilateral thalamic injection (direct CNS delivery)	FTD-GRN	Phase I/II	NCT06064890	Results not yet available.
AZP2006	Oral small molecule that enhances lysosomal function by stabilizing the PGRN-prosaposin complex	Oral	PSP	Phase I	NCT04008355	Nineteen mild adverse events resolved spontaneously; no serious adverse events.
				Phase IIa	(same)	Rapid absorption, long half-life. Demonstrated BBB penetration and target engagement, with stable PGRN levels. Well tolerated, with favorable trends in biomarkers and clinical outcomes.
PTV:PGRN	Utilizes Denali's protein transport vehicle technology; engineered Fc fragment binds to transferrin receptors on BBB, leveraging receptor mediated transcytosis	Intravenous (IV) with transferrin receptor-mediated transcytosis	FTD-GRN	Phase I/II	NCT05262023	Following a single IV dose, PGRN levels in CSF increased in a dose-dependent manner, confirming successful BBB penetration and central target engagement [38].

Abbreviations: PGRN, progranulin; FTD-GRN, frontotemporal dementia with *GRN* mutations; AD, Alzheimer's disease; NfL, neurofilament light chain; AAV, adeno-associated virus; PSP, progressive supranuclear palsy; BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; IV, intravenous; CDR, Clinical Dementia Rating Scale.

plete PGRN deficiency accelerated disease progression and enhanced early microglial activation, followed by excessive complement activation and insufficient clearance, suggesting that PGRN plays a key role in regulating prion-induced microglial activation [15].

Challenges and future directions of PGRN-targeted therapy

Although PGRN-targeted therapeutic strategies hold great promise, clinical translation also faces several challenges. The first issue to be addressed is how to balance central and peripheral effects. PGRN has pro-tumor and metabolic regulatory effects in peripheral tissues; therefore, globally upregulating PGRN could potentially bring adverse consequences to patients [15]. An optimal strategy here will be the development of tissue specific regulatory methods that engender central nervous system specific upregulation of PGRN in the absence of peripheral effects. Route of administration and control of dose also need to be accounted for. How to achieve efficient drug penetration across the blood-brain barrier and reach the optimal therapeutic window is the pressing issue. Regarding the potential neurotoxicity of excessive PGRN, the study by Kusakari et al. demonstrated that transgenic mice with high wild-type human PGRN expression developed a shorter lifespan, cerebellar phenotypes, cognitive defects, gliosis, and lysosomal abnormalities [71]. This indicates that PGRN levels must be maintained within a narrow therapeutic window - over-expression may be as harmful as deficiency. Therefore, future therapies should incorporate dose-finding studies that monitor both efficacy (e.g., CSF PGRN levels, lysosomal function) and safety (e.g., neurofilament light chain, cognitive assessments, brain imaging). Preclinical models should establish the maximum tolerated dose before clinical trials. Adaptive trial designs with sequential dose cohorts may help identify the optimal balance between benefit and toxicity [71, 77]. Novel delivery approaches (e.g. nanoparticles, exosome carriers) may enhance the brain delivery of PGRN or its inducers. Next steps the development of biomarkers and personalized therapies. Reliable biomarkers will be required for the stratification of patients as well as the monitoring of treatment responses, such as CSF PGRN levels, neuroinflammatory

imaging biomarkers and inflammatory cytokine profiles to flag those patients most likely to respond to PGRN-targeted therapy. Finally, by combining *GRN* genotype with PGRN levels and neuroinflammatory status, we will be able to precisely define which subpopulations of neurodegenerative diseases are most amenable to treatment. To give an example, for FTD: For those FTD patients with loss-of-function mutations in the *GRN* gene, whose disease is actually a direct result of PGRN haploinsufficiency, they are the most direct and likely population to benefit from PGRN-elevating therapies. For sporadic patients, whose impairment of the PGRN pathway may be due to something other than mutations in *GRN*, the effectiveness for a given patient to elevate PGRN may vary from individual to individual and should be screened for using biomarkers. Recent genetic studies using Mendelian randomization to mimic the CSF progranulin increases observed in Phase 1 clinical trials of PGRN-elevating antibodies that inhibit sortilin suggest that a two-fold increase in CSF PGRN may be associated with approximately 35% lower odds of developing AD [78].

The cascade-amplifying pathological network: definition, feedback loops, and evidence

The “cascade-amplifying pathological network” is a self-reinforcing positive feedback loop in which PGRN deficiency triggers lysosomal dysfunction, leading to lipid accumulation, which in turn activates sustained microglial responses; the resulting neuroinflammation further exacerbates lysosomal and lipid pathology. Three specific feedback loops are proposed: (1) Lysosomal dysfunction → impaired lipid degradation → accumulation of gangliosides and BMP reduction → further lysosomal impairment (direct evidence from *GRN* knockout models); (2) Lipid accumulation → microglial activation → release of pro-inflammatory cytokines → lysosomal stress → more lipid accumulation (supportive evidence from microglial studies); (3) Microglial activation → chronic neuroinflammation → neuronal dysfunction → additional microglial recruitment → amplification of inflammation (suggestive evidence from FTD and AD models [5, 14]). Recent reviews have characterized lipid droplet-accumulating microglia and alterations of myelin lipid content resulting from lysosomal dysfunction caused by

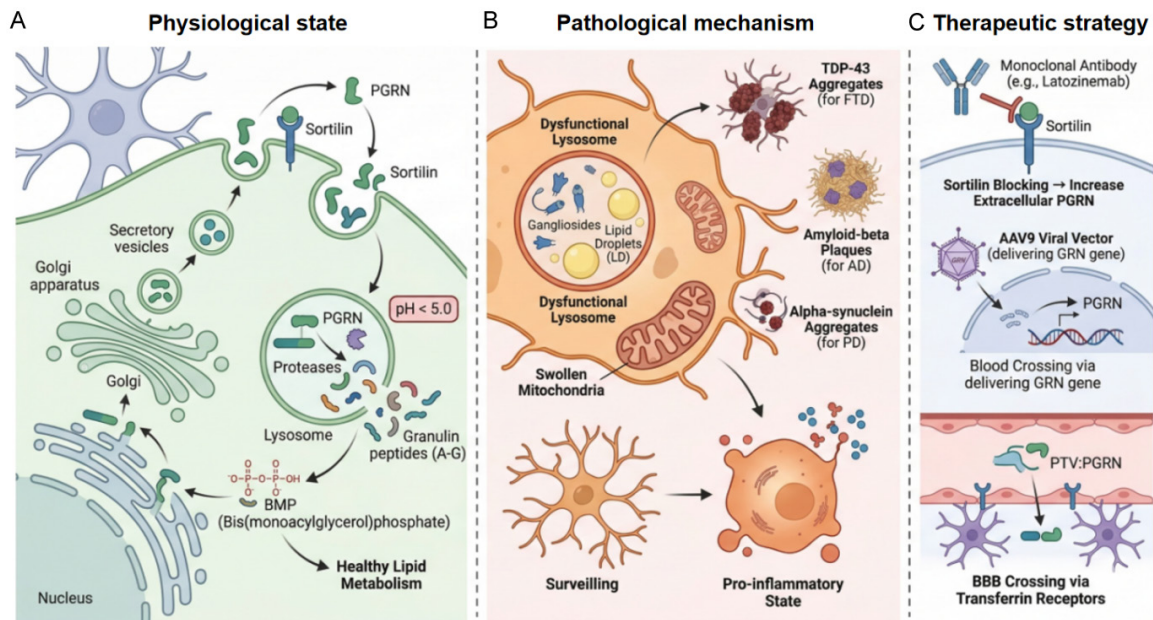


Figure 2. Physiological functions, pathological mechanisms, and therapeutic strategies of PGRN in neurodegenerative diseases. **A. Physiological state:** Under physiological conditions, secreted PGRN binds to sortilin receptor at the cell membrane, undergoes endocytosis, and is delivered to lysosomes. In the acidic lysosomal milieu ($\text{pH} < 5.0$), PGRN is cleaved into granulin peptides (A-G). PGRN and its granulins modulate bis(monoacylglycerol)phosphate (BMP) levels, promoting normal lipid metabolism and sphingolipid degradation. **B. Pathological mechanism (PGRN deficiency):** Loss of PGRN leads to lysosomal dysfunction, reduced BMP, and consequent accumulation of gangliosides, lipid droplets, and mitochondrial swelling. These changes drive microglia toward a pro-inflammatory phenotype, causing chronic neuroinflammation. This cascade ultimately promotes aggregation of toxic proteins: TDP-43 in frontotemporal dementia (FTD), amyloid- β ($\text{A}\beta$) in Alzheimer disease (AD), and α -synuclein (α -Syn) in Parkinson disease (PD). **C. Therapeutic strategies:** Three major approaches are under investigation: (1) Sortilin blockade using monoclonal antibodies (Latozinemab, AL101) or small molecules (VES001) to increase extracellular PGRN; (2) AAV9-mediated gene therapy delivered directly to the central nervous system (e.g., intracisternal magna injection) - *not via blood-brain barrier crossing* - (correction of inaccurate description); (3) Protein replacement (PTV:PGRN) using transferrin receptor-mediated transcytosis to cross the blood-brain barrier. Emerging microglia-based cell therapies are also being explored.

PGRN deficiency [2]. Dysregulated lipid metabolism in microglia represents a hallmark of neuroinflammation, and PGRN deficiency-mediated lipid dysregulation may represent a significant contributing factor to neuroinflammation and the pathogenesis of related neurodegenerative diseases. PGRN has recently been identified as a regulator of lipid droplet formation in microglia [7]. Evidence levels: Loops 1 and 2 are supported by direct experimental data; loop 3 is currently speculative and requires further validation. This model is best supported in GRN-mutation FTD, with emerging relevance to AD (based on microglial and lipid changes) and PD (based on α -synuclein and lysosomal links).

Summary and perspectives

PGRN is one of the core regulatory molecules for brain health, and its functional network is

intricately intertwined with the pathological mechanisms of neurodegeneration. The core physiological functions of PGRN in the nervous system, the cascade pathological network triggered by its deficiency, and current targeted therapeutic strategies are summarized in **Figure 2**. As detailed in Section 8, the cascade-amplifying network provides a mechanistic framework for understanding how PGRN deficiency leads to progressive pathology. Both full length PGRN and individual granulins are bioactive and the balance of these products in vivo can be crucial in functioning normally. This means that replacement therapies cannot only increase the total PGRN level but rather fine-tune the ratio between processing and product. Potentially combining our previously identified blood marker PGRN with a pharmacodynamic measure of disease activity such as ER proto-oncogene tyrosine kinase (MERTK) in CSF, we

may achieve near complete disease course management from risk prediction through efficacy monitoring. Recent studies have revealed that progranulin has diverse roles as a cell signaling molecule that regulates lysosomal function, immune processes, and growth. Understanding how PGRN regulates lipid metabolism is crucial for developing therapeutic strategies to restore lipid homeostasis in microglia and mitigate neuroinflammation.

Looking ahead, therapeutic development should adopt the principle of systemic intervention. PGRN/granulin replacement therapy is the basis of direct etiologic treatment, while modulation of its downstream pathways (large-scale lysosomal enhancement, lipid metabolism correction) can act as useful adjuncts. Perhaps the most exciting direction is durable microglia-based cell therapies that would sever the neuroinflammatory-neurodegenerative link through a fairly radical remodelling of brain immune homeostasis. Effective translation of these strategies depends on building a solid understanding of cell-type and circuit specificities for the function of PGRN. Only by dissecting its function at the level of specific cell types and fine circuits in the nervous system, will it be possible to design safe, efficacious interventions that translate basic research on this fascinating molecule into clinical reality for patients. The broad spectrum of clinical phenotypes associated with PGRN deficiency, including primary progressive aphasia and behavioral variants of frontotemporal dementia, highlights the need for cell-type-specific therapeutic approaches. Emerging evidence has revealed that PGRN deficiency is associated with cell cluster-specific, often conserved, genetic and molecular phenotypes in the central nervous system.

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Disclosure of conflict of interest

None.

Abbreviations

PGRN, progranulin; BMP, bis(monoacylglycerol) phosphate; CNS, central nervous system; BBB, blood-brain barrier; AAV9, adeno-associated virus serotype 9; FTD, frontotemporal dementia; AD, Alzheimer disease; PD, Parkinson disease; A β , amyloid-beta; α -Syn, alpha-synuclein.

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References

- [1] Bateman A and Bennett HP. The granulin gene family: from cancer to dementia. *Bioessays* 2009; 31: 1245-1254.
- [2] Gaweda-Walerych K, Aragona V, Lodato S, Sitek EJ, Narożańska E and Buratti E. Progranulin deficiency in the brain: the interplay between neuronal and non-neuronal cells. *Transl Neurodegener* 2025; 14: 18.
- [3] Santos MN, Paushter DH, Zhang T, Wu X, Feng T, Lou J, Du H, Becker SM, Fragoza R, Yu H and Hu F. Progranulin-derived granulin E and lysosome membrane protein CD68 interact to reciprocally regulate their protein homeostasis. *J Biol Chem* 2022; 298: 102348.
- [4] Bagyinszky E and An SSA. Targeting granulin haploinsufficiency in frontotemporal dementia: from genetic mechanisms to therapeutics. *Int J Mol Sci* 2025; 26: 9960.
- [5] Takahashi H and Strittmatter SM. The role of endolysosomal progranulin and TMEM106B in neurodegenerative diseases. *Mol Neurodegener* 2025; 20: 86.
- [6] Huang M, Modeste E, Dammer E, Merino P, Taylor G, Duong DM, Deng Q, Holler CJ, Gearing M, Dickson D, Seyfried NT and Kukar T. Network analysis of the progranulin-deficient mouse brain proteome reveals pathogenic mechanisms shared in human frontotemporal dementia caused by GRN mutations. *Acta Neuropathol Commun* 2020; 8: 163.
- [7] Shi Y, Hou W, Li B and Zhu C. PGRN as an emerging regulator of lipid metabolism in neurodegenerative diseases. *Commun Biol* 2025; 8: 844.
- [8] Zhang T, Feng T, Wu K, Guo J, Nana AL, Yang G, Seeley WW and Hu F. Progranulin deficiency results in sex-dependent alterations in microglia in response to demyelination. *Acta Neuropathol* 2023; 146: 97-119.
- [9] Ondaro J, Zúñiga-Elizari JL, Zufiría M, Garcian-dia-Arcelus M, Molleda ÁS, Zulaica M, Lafarga

- M, Riancho J, López de Munaín A, Moreno F, Gil-Bea FJ and Gerenu G. Mitochondria and lipid defects in hereditary progranulin-related frontotemporal dementia. *Cells* 2026; 15: 276.
- [10] Gillett DA, Neighbarger NK, Cole C, Wallings RL and Tansey MG. Investigating the role and regulation of GPNMB in progranulin-deficient macrophages. *Front Immunol* 2024; 15: 1417836.
- [11] Life BE and Leavitt BR. Progranulin function and regulation in the CNS. *Trends Neurosci* 2025; 48: 523-537.
- [12] Abella V, Pino J, Scotecce M, Conde J, Lago F, Gonzalez-Gay MA, Mera A, Gomez R, Mobasheri A and Gualillo O. Progranulin as a biomarker and potential therapeutic agent. *Drug Discov Today* 2017; 22: 1557-1564.
- [13] Cui Y, Hettinghouse A and Liu CJ. Progranulin: a conductor of receptors orchestra, a chaperone of lysosomal enzymes and a therapeutic target for multiple diseases. *Cytokine Growth Factor Rev* 2019; 45: 53-64.
- [14] Sung W, Noh MY, Nahm M, Kim YS, Ki CS, Kim YE, Kim HJ and Kim SH. Progranulin haploinsufficiency mediates cytoplasmic TDP-43 aggregation with lysosomal abnormalities in human microglia. *J Neuroinflammation* 2024; 21: 47.
- [15] Xu W, Han SD, Zhang C, Li JQ, Wang YJ, Tan CC, Li HQ, Dong Q, Mei C, Tan L and Yu JT. The FAM171A2 gene is a key regulator of progranulin expression and modifies the risk of multiple neurodegenerative diseases. *Sci Adv* 2020; 6: eabb3063.
- [16] He D, Xu H, Zhang H, Tang R, Lan Y, Xing R, Li S, Christian E, Hou Y, Lorello P, Caldarone B, Ding J, Nguyen L, Dionne D, Thakore P, Schnell A, Huh JR, Rozenblatt-Rosen O, Regev A and Kuchroo VK. Disruption of the IL-33-ST2-AKT signaling axis impairs neurodevelopment by inhibiting microglial metabolic adaptation and phagocytic function. *Immunity* 2022; 55: 159-173, e9.
- [17] Russillo MC, Sorrentino C, Scarpa A, Vinciguerra C, Cicarelli G, Cuoco S, Gagliardi M, Talarico M, Procopio R, Quattrone A, Barone P and Pellecchia MT. A novel phenotype in an Italian family with a rare progranulin mutation. *J Neurol* 2022; 269: 6170-6177.
- [18] Hembasat T, Chaityadet S, Ittiprasert W, Smout MJ, Young ND, Loukas A, Brindley PJ and Laha T. Peptide derived from progranulin of the carcinogenic liver fluke, *Opisthorchis viverrini* stimulates cell hyperproliferation and proinflammatory cytokine production. *Res Sq* 2023.
- [19] Bhopatkar AA and Rangachari V. Are granulins copper sequestering proteins? *Proteins* 2021; 89: 450-461.
- [20] Frydas A, Cacace R, van der Zee J, Van Broeckhoven C and Wauters E. Genetic variants in progranulin upstream open reading frames increase downstream protein expression. *Neurobiol Aging* 2022; 110: 113-121.
- [21] Banzhaf-Strathmann J, Claus R, Mücke O, Rentzsch K, van der Zee J, Engelborghs S, De Deyn PP, Cruts M, van Broeckhoven C, Plass C and Edbauer D. Promoter DNA methylation regulates progranulin expression and is altered in FTLD. *Acta Neuropathol Commun* 2013; 1: 16.
- [22] Galimberti D, D'Addario C, Dell'Osso B, Fenoglio C, Marcone A, Cerami C, Cappa SF, Palazzo MC, Arosio B, Mari D, Maccarrone M, Bresolin N, Altamura AC and Scarpini E. Progranulin gene (GRN) promoter methylation is increased in patients with sporadic frontotemporal lobar degeneration. *Neurol Sci* 2013; 34: 899-903.
- [23] Kaplelach AK, Hall JA, Nader WO, Davidson AG, Ireland MD, Janov L and Arrant AE. Delivering progranulin to astrocytic lysosomes promotes growth of co-cultured neurons. *J Neurochem* 2025; 169: e70284.
- [24] Miyakawa S, Sakuma H, Warude D, Asanuma S, Arimura N, Yoshihara T, Tavares D, Hata A, Ida K, Hori Y, Okuzono Y, Yamamoto S, Iida K, Shimizu H, Kondo S and Sato S. Anti-sortilin1 antibody up-regulates progranulin via sortilin1 down-regulation. *Front Neurosci* 2020; 14: 586107.
- [25] Werthmann GC and Herz J. Distinct lysosomal dysfunction patterns of GRN deficiency in the CNS implicate progranulin in cell type-specific protein sorting. *bioRxiv* 2025.
- [26] Devireddy S and Ferguson SM. Efficient progranulin exit from the ER requires its interaction with prosaposin, a Surf4 cargo. *J Cell Biol* 2021; 221: e202104044.
- [27] Root J, Mendsaikhan A, Taylor G, Merino P, Nandy S, Wang M, Araujo LT, Ryu D, Holler C, Thompson BM, Astarita G, Blain JF and Kukar T. Granulins rescue inflammation, lysosome dysfunction, lipofuscin, and neuropathology in a mouse model of progranulin deficiency. *Cell Rep* 2024; 43: 114985.
- [28] Tanaka Y, Kusumoto SY, Honma Y, Takeya K and Eto M. Overexpression of progranulin increases pathological protein accumulation by suppressing autophagic flux. *Biochem Biophys Res Commun* 2022; 611: 78-84.
- [29] Hofer AM, Tobler L, Ruepp MD and Mühlemann O. Analysing the effect of full-length and C-terminally truncated progranulin on proliferation, colony formation, and migration in HepG2 and U87 cells. *Sci Rep* 2025; 15: 42698.
- [30] Wang AL, Mambou EA and Kao AW. The progranulin cleavage product granulin 3 exerts a

- dominant negative effect on animal fitness. *Hum Mol Genet* 2024; 33: 245-253.
- [31] Park CB, Lee CH, Kang GM, Min SH and Kim MS. Microglial progranulin differently regulates hypothalamic lysosomal function in lean and obese conditions via cleavage-dependent mechanisms. *J Neuroinflammation* 2025; 22: 68.
- [32] Hisaki H, Susa T, Okudaira N, Akimoto M, Iizuka M, Matsuda J, Uchida S, Okinaga H, Okazaki T and Tamamori-Adachi M. Accumulation of prosaposin and progranulin around the subfornical organ induces polydipsia in SAP-D-deficient mice. *Biochem Biophys Rep* 2025; 45: 102388.
- [33] Werner G, Damme M, Schludi M, Gnörich J, Wind K, Fellerer K, Wefers B, Wurst W, Edbauer D, Brendel M, Haass C and Capell A. Loss of TMEM106B potentiates lysosomal and FTLD-like pathology in progranulin-deficient mice. *EMBO Rep* 2020; 21: e50241.
- [34] Perneel J, Manoochehri M, Huey ED, Rademakers R and Goldman J. Case report: TMEM106B haplotype alters penetrance of GRN mutation in frontotemporal dementia family. *Front Neurol* 2023; 14: 1160248.
- [35] Feng T, Lacrampe A and Hu F. Physiological and pathological functions of TMEM106B: a gene associated with brain aging and multiple brain disorders. *Acta Neuropathol* 2021; 141: 327-339.
- [36] Liu Y, Zhao X, Jian J, Hasan S and Liu C. Interaction with ERp57 is required for progranulin protection against type 2 Gaucher disease. *Biosci Trends* 2023; 17: 126-135.
- [37] Boland S, Swarup S, Ambaw YA, Malia PC, Richards RC, Fischer AW, Singh S, Aggarwal G, Spina S, Nana AL, Grinberg LT, Seeley WW, Surma MA, Klose C, Paulo JA, Nguyen AD, Harper JW, Walther TC and Farese RV Jr. Deficiency of the frontotemporal dementia gene GRN results in gangliosidosis. *Nat Commun* 2022; 13: 5924.
- [38] Logan T, Simon MJ, Rana A, Cherf GM, Srivastava A, Davis SS, Low RLY, Chiu CL, Fang M, Huang F, Bhalla A, Llapashtica C, Prorok R, Pizzo ME, Calvert MEK, Sun EW, Hsiao-Nakamoto J, Rajendra Y, Lexa KW, Srivastava DB, van Lengerich B, Wang J, Robles-Colmenares Y, Kim DJ, Duque J, Lenser M, Earr TK, Nguyen H, Chau R, Tsogtbaatar B, Ravi R, Skuja LL, Solanoy H, Rosen HJ, Boeve BF, Boxer AL, Heuer HW, Dennis MS, Kariolis MS, Monroe KM, Przybyla L, Sanchez PE, Meisner R, Diaz D, Henne KR, Watts RJ, Henry AG, Gunasekaran K, Astarita G, Suh JH, Lewcock JW, DeVos SL and Di Paolo G. Rescue of a lysosomal storage disorder caused by Grn loss of function with a brain penetrant progranulin biologic. *Cell* 2021; 184: 4651-4668, e25.
- [39] Zhao X, Lin Y, Liou B, Fu W, Jian J, Fannie V, Zhang W, Setchell KDR, Grabowski GA, Sun Y and Liu CJ. PGRN deficiency exacerbates, whereas a brain penetrant PGRN derivative protects, GBA1 mutation-associated pathologies and diseases. *Proc Natl Acad Sci U S A* 2023; 120: e2210442120.
- [40] Lin Y, Zhao X, Liou B, Fannie V, Zhang W, Setchell KDR, Wang X, Pan D, Grabowski GA, Liu CJ and Sun Y. Intrinsic link between PGRN and Gba1 D409V mutation dosage in potentiating Gaucher disease. *Hum Mol Genet* 2024; 33: 1771-1788.
- [41] Tan LX, Oertel FC, Cheng A, Cobigo Y, Keihani A, Bennett DJ, Abdelhak A, Montes SC, Chapman M, Chen RY, Cordano C, Ward ME, Casaletto K, Kramer JH, Rosen HJ, Boxer A, Miller BL, Green AJ, Elahi FM and Lakkaraju A. Targeting complement C3a receptor resolves mitochondrial hyperfusion and subretinal microglial activation in progranulin-deficient frontotemporal dementia. *bioRxiv* 2024.
- [42] De Houwer JFH, Dopfer EGP, Rajcic A, van Buuren R, Arcaro M, Galimberti D, Breedveld GJ, Wilke M, van Minkelen R, Jiskoot LC, van Swieten JC, Donker Kaat L and Seelaar H. Two novel variants in GRN: the relevance of CNV analysis and genetic screening in FTLD patients with a negative family history. *J Neurol* 2024; 272: 64.
- [43] Wauters E, Gossye H, Frydas A, Sieben A and Van Broeckhoven C. Rare exonic variant affects GRN splicing and contributes to frontotemporal lobar degeneration. *Neurobiol Aging* 2023; 130: 61-69.
- [44] Salzano S, Bertasini C, Tavakolian Haghighi S, Lundkvist J, Wahlberg LU, Chiamulera C, Vattemi GN, Gardoni F and Paolone G. Frontotemporal dementia as a consequence of GRN mutations: from disease cause to models to therapies. *Pharmacol Res* 2025; 221: 107957.
- [45] Yang C, Du H, Lee GB, Uematsu M, He W, Doré E, Yu W, Sanford EJ, Smolka MB, Boilard E, Baskin JM, Hao L and Hu F. sPLA2-IIA modifies progranulin deficiency phenotypes in mouse models. *Mol Neurodegener* 2025; 20: 72.
- [46] Park CB, Lee CH, Kang GM, Min SH and Kim MS. Microglial progranulin differently regulates hypothalamic lysosomal function in lean and obese conditions via cleavage-dependent mechanisms. *J Neuroinflammation* 2025; 22: 68.
- [47] Tipton PW, Deutschlaender AB, Savica R, Heckman MG, Brushaber DE, Dickerson BC, Gavrilo-va RH, Geschwind DH, Ghoshal N, Graff-Radford J, Graff-Radford NR, Grossman M, Hsiung GR, Huey ED, Irwin DJ, Jones DT, Knopman DS, McGinnis SM, Rademakers R, Ramos EM, Forsberg LK, Heuer HW, Onyike C, Tartaglia C,

- Domoto-Reilly K, Roberson ED, Mendez MF, Litvan I, Appleby BS, Grant I, Kaufer D, Boxer AL, Rosen HJ, Boeve BF and Wszolek ZK; ALLFTD Consortium. Differences in motor features of C9orf72, MAPT, or GRN variant carriers with familial frontotemporal lobar degeneration. *Neurology* 2022; 99: e1154-e1167.
- [48] Premi E, Giunta M, Iraj A, Rachakonda S, Calhoun VD, Gazzina S, Benussi A, Gasparotti R, Archetti S, Bocchetta M, Cash D, Todd E, Peakman G, Convery R, van Swieten JC, Jiskoot L, Sanchez-Valle R, Moreno F, Laforce R, Graff C, Synofzik M, Galimberti D, Rowe JB, Masellis M, Tartaglia C, Finger E, Vandenberghe R, de Mendonça A, Tagliavini F, Butler CR, Santana I, Gerhard A, Le Ber I, Pasquier F, Ducharme S, Levin J, Danek A, Sorbi S, Otto M, Rohrer JD and Borroni B; Genetic Frontotemporal dementia Initiative (GENFI). Dissemination in time and space in presymptomatic granulin mutation carriers: a GENFI spatial chronnectome study. *Neurobiol Aging* 2021; 108: 155-167.
- [49] Hein ZM, Karikalan B, Gopalakrishna PK, Dhevi K, Alkatiri A, Hussan F, Mohd Moklas MA, Jagadeesan S, Che Ramli MD, Che Mohd Nassir CMN and Vishnumukkala T. Toward a unified framework in molecular neurobiology of Alzheimer's disease: revisiting the pathophysiological hypotheses. *Mol Neurobiol* 2025; 63: 282.
- [50] Budda B, Mitra A, Park L, Long H, Kurnellas M, Bien-Ly N, Estacio W, Burgess B, Chao G, Schwabe T, Paul R, Kenkare-Mitra S and Rosenthal A. Development of AL101 (GSK-4527226), a progranulin-elevating monoclonal antibody, as a potential treatment for Alzheimer's disease. *Alzheimers Res Ther* 2025; 17: 174.
- [51] Sheng J, Su L, Xu Z and Chen G. Progranulin polymorphism rs5848 is associated with increased risk of Alzheimer's disease. *Gene* 2014; 542: 141-145.
- [52] Zhang J, Fan Y, Liang H and Zhang Y. Global, regional and national temporal trends in Parkinson's disease incidence, disability-adjusted life year rates in middle-aged and older adults: a cross-national inequality analysis and Bayesian age-period-cohort analysis based on the global burden of disease 2021. *Neurol Sci* 2025; 46: 1647-1660.
- [53] Chen Y, Li S, Su L, Sheng J, Lv W, Chen G and Xu Z. Association of progranulin polymorphism rs5848 with neurodegenerative diseases: a meta-analysis. *J Neurol* 2015; 262: 814-822.
- [54] Huang LY, Tan CC, Xu W and Tan L; Alzheimer's Disease Neuroimaging Initiative. Relationships of PGRN with sTREM2 in AD continuum and non-AD pathophysiology and their reciprocal roles in modulating amyloid pathology: two population-based study. *Transl Psychiatry* 2025; 15: 233.
- [55] Huang LY, Tan CC, Xu W and Tan L; Alzheimer's Disease Neuroimaging Initiative. Relationships of PGRN with sTREM2 in AD continuum and non-AD pathophysiology and their reciprocal roles in modulating amyloid pathology: two population-based study. *Transl Psychiatry* 2025; 15: 233.
- [56] Van Kampen JM, Baranowski D and Kay DG. Progranulin gene delivery protects dopaminergic neurons in a mouse model of Parkinson's disease. *PLoS One* 2014; 9: e97032.
- [57] Fujimori H, Ohba T, Nakamura S, Shimazawa M and Hara H. The involvement of progranulin for α -synuclein reduction through autolysosome formation. *Biol Pharm Bull* 2023; 46: 1032-1040.
- [58] Birnbaum E and Yue Z. The role of autophagy in synucleinopathy: clearance versus spread of α -synuclein. *Autophagy Rep* 2025; 4: 2577406.
- [59] Yao YN, Wang MD, Tang XC, Wu B and Sun HM. Reduced plasma progranulin levels are associated with the severity of Parkinson's disease. *Neurosci Lett* 2020; 725: 134873.
- [60] Makrygianni M, Beratis IN, Giagkou N, Papa-georgiou S, Stefanis L and Stamelou M. PGRN manifesting as Parkinson's disease: counseling and treatment implications. *Mov Disord Clin Pract* 2026; 13: 583-584.
- [61] Cosma C, Talli I, Pangrazzi E, Padoan A, Cerutti H, Zaninotto M, Gabelli C and Plebani M. Progranulin measurement with a new automated method: a step forward in the diagnostic approach to neurodegenerative disorders. *Clin Chem Lab Med* 2025; 63: 1118-1123.
- [62] Vercellino M, Grifoni S, Romagnolo A, Masera S, Mattioda A, Trebini C, Chiavazza C, Caligiana L, Capello E, Mancardi GL, Giobbe D, Mutani R, Giordana MT and Cavalla P. Progranulin expression in brain tissue and cerebrospinal fluid levels in multiple sclerosis. *Mult Scler* 2011; 17: 1194-1201.
- [63] Yang C, Feng T and Hu F. Progranulin deficiency does not exacerbate TDP-43 pathology in TDP-43 transgenic mouse models. *NPJ Dement* 2025; 1: 16.
- [64] Schreiber S, Debska-Vielhaber G, Abdulla S, Machts J, Schreiber F, Kropf S, Körtvelyessy P, Körner S, Kollewe K, Petri S, Dengler R, Kunz WS, Nestor PJ and Vielhaber S. Peripheral nerve atrophy together with higher cerebrospinal fluid progranulin indicate axonal damage in amyotrophic lateral sclerosis. *Muscle Nerve* 2018; 57: 273-278.
- [65] Swift IJ, Rademakers R, Finch N, Baker M, Ghidoni R, Benussi L, Binetti G, Rossi G, Synofzik M, Wilke C, Mengel D, Graff C, Takada LT, Sán-

- chez-Valle R, Antonell A, Galimberti D, Fenoglio C, Serpente M, Arcaro M, Schreiber S, Vielhaber S, Arndt P, Santana I, Almeida MR, Moreno F, Barandiaran M, Gabilondo A, Stubert J, Gómez-Tortosa E, Agüero P, Sainz MJ, Gohda T, Murakoshi M, Kamei N, Kittel-Schneider S, Reif A, Weigl J, Jian J, Liu C, Serrero G, Greither T, Theil G, Lohmann E, Gazzina S, Bagnoli S, Coppola G, Bruni A, Quante M, Kiess W, Hie-misch A, Jurkutat A, Block MS, Carlson AM, Bråthen G, Sando SB, Grøntvedt GR, Lauridsen C, Heslegrave A, Heller C, Abel E, Gómez-Núñez A, Puey R, Arighi A, Rotondo E, Jiskoot LC, Meeter LHH, Durães J, Lima M, Tábuas-Pereira M, Lemos J, Boeve B, Petersen RC, Dickson DW, Graff-Radford NR, LeBer I, Sellami L, Lamari F, Clot F, Borroni B, Cantoni V, Rivolta J, Lleó A, Fortea J, Alcolea D, Illán-Gala I, Andres-Cerezo L, Van Damme P, Clarimon J, Steinacker P, Feneberg E, Otto M, van der Ende EL, van Swieten JC, Seelaar H, Zetterberg H, Sogorb-Esteve A and Rohrer JD. A systematic review of progranulin concentrations in biofluids in over 7,000 people-assessing the pathogenicity of GRN mutations and other influencing factors. *Alzheimers Res Ther* 2024; 16: 66.
- [66] Wang F, Chen T, Sun L, Lv H, Li X, Shen J, Chen L, Chu Z and Hou M. Circulating PGRN levels are increased but not associated with insulin sensitivity or β -cell function in chinese obese children. *Dis Markers* 2018; 2018: 3729402.
- [67] Raffin J, Angioni D, Giudici KV, Valet P, Aggarwal G, Nguyen AD, Morley JE, Guyonnet S, Roland Y, Vellas B and de Souto Barreto P; MAPT/DSA Group. Physical activity, body mass index, and blood progranulin in older adults: cross-sectional associations in the MAPT study. *J Gerontol A Biol Sci Med Sci* 2022; 77: 1141-1149.
- [68] Kurnellas M, Mitra A, Schwabe T, Paul R, Arrant AE, Roberson ED, Ward M, Yeh F, Long H and Rosenthal A. Latozinemab, a novel progranulin-elevating therapy for frontotemporal dementia. *J Transl Med* 2023; 21: 387.
- [69] Sevigny J, Uspenskaya O, Heckman LD, Wong LC, Hatch DA, Tewari A, Vandenberghe R, Irwin DJ, Saracino D, Le Ber I, Ahmed R, Rohrer JD, Boxer AL, Boland S, Sheehan P, Brandes A, Burstein SR, Shykind BM, Kamalakaran S, Daniels CW, David Litwack E, Mahoney E, Velaga J, McNamara I, Sondergaard P, Sajjad SA, Kobayashi YM, Abeliovich A and Hefti F. Progranulin AAV gene therapy for frontotemporal dementia: translational studies and phase 1/2 trial interim results. *Nat Med* 2024; 30: 1406-1415.
- [70] Ward M, Carter LP, Huang JY, Maslyar D, Budda B, Paul R and Rosenthal A. Phase 1 study of latozinemab in progranulin-associated frontotemporal dementia. *Alzheimers Dement (N Y)* 2024; 10: e12452.
- [71] Kusakari S, Suzuki H, Nawa M, Sudo K, Yamazaki R, Miyagi T, Ohara T, Matsuoka M and Kanekura K. Excessive expression of progranulin leads to neurotoxicity rather than neuroprotection. *Neurobiol Dis* 2025; 209: 106895.
- [72] Afridi R, Lee WH and Suk K. Microglia gone awry: linking immunometabolism to neurodegeneration. *Front Cell Neurosci* 2020; 14: 246.
- [73] Carter L, Borroni B, Mummery C, Le Ber I, Boeve B, Boxer A, Smithey M, Chow T, Huang J, Guizzetti L, Salvatore G and Romano G. Baseline characteristics for INFRONT-3: a phase 3 double-blind, placebo-controlled 96-week study evaluating latozinemab in FTD-GRN. *Neurology* 2025; 104: 4085.
- [74] Hocquemiller M, Giersch L, Audrain M, Parker S and Cartier N. Adeno-associated virus-based gene therapy for CNS diseases. *Hum Gene Ther* 2016; 27: 478-496.
- [75] Yamamoto N, Takei R, Gotoh M, Miyamoto Y and Hashimoto K. Lysophosphatidic acid derivative is a novel candidate of therapeutic agents for a mouse model of frontotemporal dementia with progranulin deficiency. *Neurobiol Aging* 2026; 158: 39-51.
- [76] Xu R, Li X, Boreland AJ, Posyton A, Kwan K, Hart RP and Jiang P. Human iPSC-derived mature microglia retain their identity and functionally integrate in the chimeric mouse brain. *Nat Commun* 2020; 11: 1577.
- [77] Pallmann P, Bedding AW, Choodari-Oskoei B, Dimairo M, Flight L, Hampson LV, Holmes J, Mander AP, Odondi L, Sydes MR, Villar SS, Watson JMS, Weir CJ, Wheeler GM, Yap C and Jaki T. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018; 16: 29.
- [78] Robins C, Eicher JD, Liu J, Lo Y, Richardson TG, Western D, Davitte J, Cruchaga C and Kumar S; for the Alzheimer's Disease Neuroimaging Initiative. Genetic evidence supports therapeutic modulation of progranulin levels in Alzheimer's Disease. *Mol Neurodegener Adv* 2026; 2.