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Publication Date

2022-10-01

DOI

10.1016/j.conb.2022.102599

Peer reviewed

Published in final edited form as:

Curr Opin Neurobiol. 2022 October ; 76: 102599. doi:10.1016/j.conb.2022.102599.

Neuroimmune dysfunction in frontotemporal dementia: Insights from progranulin and C9orf72 deficiency

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Abstract

Neuroimmune dysfunction is a cardinal feature of neurodegenerative diseases. But how immune dysregulation in the brain and peripheral organs contribute to neurodegeneration remains unclear. Here, we discuss the recent advances highlighting neuroimmune dysfunction as a key disease-driving factor in frontotemporal dementia (FTD). We provide an overview of the clinical observations supporting a high prevalence of autoimmune diseases in FTD patients with mutations in *GRN* or *C9orf72*. We then focus on a myriad of evidence from human genetic studies, mouse models, in vitro assays, and multi-omics platform, which indicate that haploinsufficiency in *GRN* and *C9orf72* promotes neuroimmune dysfunction and contributes to neurodegeneration and premature death. These compelling data provide key insights to disease mechanisms, biomarker discovery, and therapeutic interventions for FTD (120 words).

Introduction

Age is a common denominator for neurodegenerative diseases. One hallmark of aging is the development of persistent proinflammatory responses that contribute to systemic diseases, including atherosclerosis, metabolic syndrome, cancer, and fragility. In a similar vein, dysfunction in the brain's innate immune system, characterized by the expansion of reactive microglia and astrocytes, has increasingly been recognized as a key factor that contributes to brain aging and neurodegeneration. Indeed, recent literature based on genome-wide association studies (GWAS), clinical studies, cell biology, animal models,

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Author contributions

Conceptualization: K.H. and E.J.H.; Review of literature and formal analysis: K.H. N.J., Z.A.M., and E.J.H.; Visualization and artwork: K.H.; Writing - original draft: K.H. and E.J.H.; Writing - review & editing: K.H., N.J., Z.A.M., and E.J.H.; Funding acquisition: K.H., N.J., Z.A.M., and E.J.H.

Conflict of interest statement

None declared.

and neuropathology indicate that perturbations in the expression of genes involved in the homeostasis of microglia and astrocytes may have critical role in the pathogenesis of late onset Alzheimer's disease (AD) [1]. In addition to the dysfunction in the brain's innate immune system in promoting neurodegeneration, there is compelling evidence that dysfunction in peripheral immunity can contribute to the pathophysiology of neurodegenerative diseases. This is supported by clinical and epidemiological studies that show elevated inflammatory markers increase the risk of developing AD [2].

This review focuses on the recent evidence supporting that dysfunction in the peripheral and brain's immune systems also have essential roles in the pathophysiology of frontotemporal dementia (FTD), the second most common neurodegenerative disease that affects patients younger than 65-years old [3]. We begin with an overview of the seminal clinical observations and genetic studies that suggest a role for peripheral immune dysfunction in FTD patients. We then summarize data from animal models that provide critical insights into how loss-of-function in two most common FTD genes leads to age-dependent dysregulation in the peripheral and central immune functions. Finally, we discuss several critical next-steps and opportunities for future research that will translate this knowledge into therapeutic interventions.

Clinical features, genetics, and neuropathology of FTD

The manifestations of FTD are characterized by progressive deficits in behaviors, executive functions, or language [3]. The underlying neuropathological features of FTD, collectively known as frontotemporal lobar degeneration (FTLD), involve severe atrophy in the frontal and temporal lobes and the accumulation of microtubule-associated protein tau and two RNA binding proteins, TDP-43 and FUS [4]. Among these, FTLD-TDP is the most common type of FTLD, representing > 50% of all FTD cases. Based on the distribution and the morphology of the misfolded TDP-43 inclusions and dystrophic neurites in the frontal cortex, FTLD-TDP can be further classified into 5 different subtypes (Figure 1a) [5].

Two major genetic mutations for FTLD-TDP provide key insights to uncovering disease mechanisms. The first is dominant mutations in the *Progranulin* (*GRN*) gene on chromosome 17q21.31, which activates nonsense-mediated decay of *GRN* mRNA and leads to significant reductions in Progranulin (PGRN) protein levels [6,7]. Another involves hexanucleotide $(GGGGCC)_n$ repeat expansion located between exons 1a and 1b of the gene on chromosome 9 open reading frame 72 (*C9orf72*) [8,9]. Subsequent large-scale GWAS confirm the central roles of *GRN* and *C9orf72* mutations in FTLD-TDP, each accounting for 13.9% and 25.5% of all cases [10]. Less frequent mutations in the gene encoding TANK-binding kinase 1 (*TBK1*) account for 1.5% of all FTLD-TDP patients. Other FTLD-TDP-associated mutations include *TARDBP, DCNT1, VCP, ATXN2, UBQLN2, MATR3, HNRNPA1/B2,* and *OPTN*. In addition, several genetic risk alleles for FTLD-TDP have been identified, including *HLA-DQA2, DPP6,* and *UNC13A* [10,11].

One intriguing clinical observation in FTLD-TDP patients is the co-occurrence of autoimmune diseases. Compared to AD patients and age-matched controls, FTLD-TDP cohorts, especially those with *GRN* and *C9orf72* mutation carriers show an increased

prevalence of non-thyroid autoimmune diseases, such as inflammatory arthritides, cutaneous disorders, and gastrointestinal conditions (Figure 1b) [12, 13]. Several lines of evidence support that dysfunction in the immunity in peripheral organs and central nervous system (CNS) may contribute to the pathogenesis of FTLD-TDP. First, GWAS studies identify polymorphisms in the 3' untranslated region (UTR) of *C9orf72* as one of the three risk alleles that influence whether patients with rheumatoid arthritis (RA) respond to anti-TNF treatment [14]. These results, reported years before *C9orf72* is identified as a disease gene for familial FTD and ALS, suggest that the gene product of *C9orf72* may modulate TNFα inflammatory pathway. Consistent with this idea, elevations in plasma TNFα were observed in FTD patients with *GRN* mutations [12]. Moreover, a recent study shows that patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) have a high propensity to carry intermediate GGGGCC expansion repeats (9–30) in *C9orf72* [15]. Several risk genes for FTLD-TDP identified via GWAS studies, including the *HLA* loci on chromosome 6, are well-known genes implicated in autoimmune disorders [11]. Finally, PET imaging using ligands for activated microglia and TDP-43 in FTD patients show positive correlation supporting the presence of microglial activation and TDP-43 accumulation [16,17].

Given the preponderance of new evidence supporting *GRN* and *C9orf72* as the gatekeepers of the neuroimmune systems, we believe that a timely review of these studies will provide an integrative and deeper understanding of the physiological functions of these genes. We define "neuroimmune" broadly to avoid compartmentalizing the CNS from peripheral immunity and to highlight the intricate interactions between these systems and their impact on the entire organism.

Neuroimmune dysfunction in PGRN deficiency

Initially isolated as a secreted glycoprotein, PGRN has been shown to promote neuronal survival and neurite outgrowth similar to neurotrophic factors [18]. The mechanism by which PGRN exerts its neurotrophic function remains unclear. However, PGRN can bind to sortilin, which facilitates PGRN endocytosis and its subsequent degradation in the lysosomes [19](Figure 2a). It is conceivable that PGRN may bind to other membrane-bound receptor(s) to activate signaling pathways to support survival and neurite outgrowth. In addition to its role as a secreted protein, PGRN can regulate the trafficking of intracellular vesicles and organelle dynamics. These functions are sortilin-independent and involve PGRN binding with prosaposin (PSAP) and subsequent delivery of the PGRN-PSAP complex to lysosomes through mannose 6-phosphate receptor (M6PR) and low-density lipoprotein (LDL) receptor-related protein 1 (LRP1). Interestingly, GWAS shows that single nucleotide polymorphisms in the human *PSAP* gene affect the PGRN levels in the plasma presumably through the role PSAP plays in regulating dimerization and secretion of PGRN [20]. Once in the lysosomes, PGRN can regulate cathepsin D activity, maintain the acidification of lysosomes, and exocytosis of lysosomes (or exophagy) upon treatment with aggregated LDL [21-24]. Finally, loss of PGRN inhibits lysosome fusion and induces autophagosome accumulation in microglia and macrophages, whereas in cortical neurons PGRN appears to have modest effects in regulating autophagic flux [25].

Several lines of evidence show that loss-of-function in PGRN leads to dysfunction in innate immunity and host defense in various organs, including spleen, liver, and brain. In peripheral immunity, *Grn*$^{-/-}$ macrophages produce more proinflammatory cytokines which can be aggravated by LPS treatment. Interestingly, *Grn*$^{-/-}$ mice exhibit increased sensitivity to *Listeria monocytogenes* infection due to reduced clearance of pathogens by macrophages [25,26]. The mechanism for reduced clearance of pathogens by *Grn*$^{-/-}$ macrophages is likely due to the role of PGRN in controlling macrophage-associated inflammatory responses and defects in lysosome-mediated degradation pathway. For instance, PGRN binds to and enhances toll-like receptor 9 (TLR9) signaling upon the treatment of CpG oligonucleotides in macrophage to promote the TNFα secretion [27]. Furthermore, in collagen-induced inflammatory arthritis model, PGRN attenuates TNFα-induced MAPK and NF-κB signaling for anti-inflammatory effects by binding to tumor necrosis factor receptors (TNFRs) and antagonizing TNFα [28], though the interaction between PGRN and TNFR is disputed by other studies [29,30].

Pertinent to the role of PGRN deficiency in neurodegeneration, several groups report that *Grn*$^{-/-}$ mice show an age-dependent expansion of microglia and heightened microglial responses in toxin-induced injury [26,31]. The microgliosis phenotype in *Grn*$^{-/-}$ mice preferentially affects the thalamocortical circuit and cerebellar white matter, leading to obsessive-compulsive disorder (OCD)-like behaviors, poor motor coordination, and gait imbalance [32,33]. The expansion of *Grn*$^{-/-}$ microglia is accompanied by progressive morphological and transcriptomic changes, suggesting that *Grn*$^{-/-}$ microglia undergo phenotypic transition into a proinflammatory state. Consistent with these results, *Grn*$^{-/-}$ microglia produce abundant complements, C1q and C3b, to promote synaptic pruning in the ventral thalamus, which leads to an imbalance in the excitation-inhibition input to the thalamocortical circuit and OCD-like grooming behaviors in *Grn*$^{-/-}$ mice [33]. Interestingly, pre-symptomatic *GRN* mutation carriers also show hyperconnectivity in the thalamocortical network [34]. While these results suggest that the thalamus could be a highly evolutionarily conserved neural circuit selectively affected by PGRN deficiency, it is noteworthy that microglial activation phenotypes can also be detected in the striatum in *Grn*$^{-/-}$ mice, leading to increased TNFα production and activation of the NFκB signaling [32]. Moreover, deletion of *C1q* or *Ikbkb* genes mitigates these behavioral phenotypes in *Grn*$^{-/-}$ mice.

The robust microglial phenotypes in *Grn*$^{-/-}$ mice raise the intriguing hypothesis that persistent microglial activation may contribute to neurodegeneration and TDP-43 protein aggregation (TDP-43 proteinopathy), two key neuropathological features in FTLD-GRN patients. Indeed, single nucleus RNA-sequencing (snRNA-seq) using microdissected thalamus from an aging cohort of *wild-type* (*Grn*$^{+/+}$) and *Grn*$^{-/-}$ mice shows that, among all the cell clusters in thalamus, microglia are the first to show transcriptomic changes as early as 7-months old, before the onset of behavioral phenotypes. As *Grn*$^{-/-}$ mice become older, *Grn*$^{-/-}$ microglia undergo further age-dependent transcriptomic changes indicating the transition of *Grn*$^{-/-}$ microglia from homeostatic state to disease state by downregulation of homeostasis-related genes and upregulation of genes related to lysosome functions, lipid metabolism, and trafficking [35,36]. Interestingly, snRNA-seq data show a selective loss of excitatory neurons in the thalamus of *Grn*$^{-/-}$ mice at 19-months old, which is preceded by the prominent accumulation of nuclear and cytoplasmic TDP-43 aggregation, nuclear pore

defects, and neuronal cell death [35]. Together, these results support the hypothesis that microglial toxicity and neuronal vulnerability contribute to neuronal degeneration in PGRN deficiency (Figure 2b).

In support of the critical role of PGRN deficiency in microglial activation, large-scale GWAS studies identify multiple SNPs in the *TMEM106B* gene as potential modifiers for neurodegeneration in FTLD-GRN patients [37-39]. These *TMEM106B* variants appear to modify PGRN expression level in FTLD-GRN patients. From the cell biology perspective, TMEM106B has partial functional overlaps with PGRN in regulating lysosomal trafficking. Consistent with this idea, upregulation of TMEM106B mitigates the lysosomal defects caused by the reduction of PGRN level. To characterize the *in vivo* functions of TMEM106B and PGRN, several groups generate $Grn^{-/-}$;$Tmem106b^{-/-}$ mice and show that the complete loss of TMEM106B and PGRN leads to more severe lysosomal abnormalities and neuroinflammation, characterized by early onset and drastic expansion of reactive microglia and astrocytes, and upregulation of many proinflammatory genes [40-42]. In addition, loss of TMEM106B and PGRN accelerates neuronal loss with prominent aggregation of ubiquitinated proteins and phospho-TDP-43 in the spinal cord leading to motor deficits [40,41]. Interestingly, partial loss of TMEM106B may provide some partial protection in lysosomal dysfunction caused by the loss of PGRN [43]. These findings provide critical insights into the dosage-dependent role of PGRN and TMEM106B in regulating lysosomal biogenesis and functions. They also underscore TMEM106B as a *bona fide* disease modifier for FTLD-GRN. Based on these studies, loss of TMEM106B appears to primarily affects the neuroinflammation. It remains unclear whether TMEM106B has any effect in the peripheral immunity.

Another prominent feature in the $Grn^{-/-}$ mouse brain and FTLD-GRN brain is the accumulation of lipofuscin, which consists of highly oxidized mixtures of proteins, lipids and carbohydrates [44-46]. Indeed, lipofuscin deposits in the retina have been proposed as an early manifestation of disease in *GRN* carriers [45]. Consistent with these results, lipidomic profiling using cortices in FTLD-GRN patients and aged $Grn^{-/-}$ mouse brain shows significant alteration of lipid composition, including glycolipids and phospholipids [47]. CRISPR-based genetic screening in BV2 cells identifies *GRN* as an important genetic modifier of lipid droplet accumulation that promotes pro-inflammatory states in microglia during brain aging [48]. Additional lipidomic profiling in aged $Grn^{-/-}$ mouse cortices shows lysosomal lipid dysregulation, including downregulation of bis-monoacylglycero-phosphate (BMP) and upregulation of glucosylsphingosine, which primarily affects $Grn^{-/-}$ microglia [49]. While these results strongly implicate PGRN as a key regulator of lipid metabolism, the exact mechanism remains unclear.

Neuroimmune dysfunction in *C9orf72* deficiency

The identification of hexanucleotide $(GGGGCC)_n$ repeat expansion in *C9orf72* gene represents a major milestone in FTD-amyotrophic lateral sclerosis (ALS) research [8,9]. Collectively, mutations in *C9orf72* account for ~26% of FTLD-TDP cases [10] and a majority of familial ALS patients. At least three distinct mechanisms have been postulated to promote neurodegeneration caused by *C9orf72* mutations, including the production of

dipeptide repeat (DPR) proteins repeat-associated non-ATG (RAN) translation via sense and antisense $(GGGGCC)_n$ RNA transcripts [50,51], the presence of RNA foci in neuronal nuclei, and haploinsufficiency in C9orf72 protein function. An indepth discussion on the first two mechanisms for C9orf72 mutations is beyond the scope of this article. Readers interested in these topics will find many exciting discoveries regarding the role of *C9orf72* mutations in nucleocytoplasmic transport [52-54], stress granule dynamics and heterochromatin organization [55,56], DNA damage repair [57], phase separation [58-60], mitochondrial functions [61], and in p53-mediated neuronal degeneration [62].

Aside from the gain-of-function properties associated with *C9orf72* mutations, C9orf72 has critical roles in the autophagy-lysosome pathway and mitochondrial energy metabolism (Figure 3a). Related to the autophagy pathway, C9orf72 forms multiprotein complex with SMCR8 and WPR41, which acts as a GDP-GTP exchange factor, and control Rab8a and Rab39b GTPases activity for the recruitment them to organelle membrane to regulate the membrane trafficking. Besides, C9orf72 regulates autophagy initiation through controlling ULK1 expression and activity [63-66]. Moreover, it has been also reported that coactivator-associated arginine methyltransferase 1 (CARM1)-related autophagy-lysosome pathway is supported by C9orf72 protein, showing that C9orf72 deficiency leads to dysregulated autophagic digestion which induces endoplasmic reticulum-derived lipid droplets accumulation and free fatty acid secretion under nutrient stress [67]. In addition to its role in the initiation of autophagy, C9orf72 has been shown to regulate Rab5-mediated recycling of glutamate receptors. iPSC-derived motor neurons from patients with *C9orf72* mutation show impaired lysosomal degradation of glutamate receptors, which render these neurons more vulnerable to excitotoxicity [68]. Finally, C9orf72 has a critical role in regulating oxidative phosphorylation and ATP production by the stabilizing translocase of inner mitochondrial membrane domain containing 1 (TIMMDC1)-associated mitochondrial complex I assembly [69].

Like $Grn^{-/-}$ mice, $C9orf72^{-/-}$ mice show shortened lifespan due in large part to autoimmune dysfunction (Figure 3b). In the cerebral cortex, *C9orf72* is most abundantly detected in microglia, followed by neurons [70]. Consistent with these results, RNA-seq analyses in $C9orf72^{-/-}$ brain show transcriptomic features indicative of activation in the interferon signaling and lysosomal dysfunction [70]. In addition to the neuroinflammatory phenotypes, $C9orf72^{-/-}$ mice show prominent autoimmune dysfunction with marked lymphadenopathy, splenomegaly, and glomerulonephritis [70-72]. Interestingly, deleting C9orf72 in myeloid cells using the *Cx3cr1-Cre* drive is sufficient to recapitulate the autoimmune dysfunction in the $C9orf72^{-/-}$ mice. The peripheral immune phenotypes are worse in $C9orf72^{-/-}$ mice that also express the hexanucleotide repeat expansion (HRE) transgene [73]. Furthermore, loss of C9orf72 activates the STING pathway-mediated interferon in the myeloid cells and increases neuroinflammation in the experimental allergic encephalitis model and increases antitumor immunity [74]. In addition, during brain aging, loss of C9orf72 activates STING-mediated interferon pathways in microglia and promotes microglia-mediated synaptic pruning via C1q activation [75]. In the 5XFAD model, loss of C9orf72 increases lysosomal accumulation in microglia, reduces dendritic arborization and synaptic density in cortical neurons, and impairs motor function [75]. Together, these results support the critical role of C9orf72 in maintaining microglia homeostasis during brain aging and the innate response

of microglia to amyloid deposits and amyloid-mediated toxicity. These results further underscore the similar roles of PGRN and C9orf72 in regulating microglial function during aging and in disease models.

Another critical manifestation of the systemic fatal autoimmune diseases in *C9orf72*$^{-/-}$ mice is the increased vulnerability to environment-associated gut bacteria microflora [76]. Specifically, increase in the abundance of bacterial species, such as *Helicobacter* spp and *Tritrichomonas muris*, is associated with severe immune defects and early lethality in *C9orf72*$^{-/-}$ mice. Conversely, therapeutic interventions, including antibiotic treatment and fecal transplantation, alter gut microflora abundance and drastically mitigate the production of proinflammatory cytokines, autoimmune dysfunction, and survival in *C9orf72*$^{-/-}$ mice [76]. Although it remains unclear how gut microflora aggravates the immune system in *C9orf72*$^{-/-}$ mice, there is evidence that changes in gut microflora can induce proliferation in the myeloid cells in the peripheral immune system and activate microgliosis in the spinal cord. Interestingly, the observation that gut microflora can impact the survival and disease progression in ALS are also detected in *SOD1*^{G93A} mice. However, the specific types of microflora and how they impact survival of *SOD1*^{G93A} mice are quite different from those in *C9orf72*$^{-/-}$ mice [77]. Unlike *C9orf72*$^{-/-}$ mice where gut microflora-induced inflammation appears to be a major pathogenic factor, the contribution of gut microflora to disease onset and progression in *SOD1*^{G93A} mice is due in part to the metabolites made by the bacteria, including the level of nicotinamide. Together, these results provide intriguing and contrasting mechanisms by which gut microflora use diverse mechanisms to promote disease onset and progression in ALS.

Conclusion and outlook

The discovery of *GRN* and *C9orf72* ushers in a new era of research that uncovers the disease mechanisms of FTD. It is now clear that PGRN and C9orf72 are not only required for maintaining the homeostasis of microglia during brain aging, but they can also regulate the intricate interaction between the innate and adaptive immunity in the peripheral organs. Collectively, these results provide new insights and bridge the gap between neuroinflammation and autoimmune dysfunction. There are, however, many unanswered questions as to how PGRN and C9orf72 regulate immune functions during the aging process. From cell biology perspectives, the current literature supports that loss of PGRN or C9orf72 leads to dysfunction in macrophages and other myeloid cells. Although it is well-established that PGRN regulates endolysosomal trafficking, it remains unclear how lysosomal defects caused by PGRN insufficiency activate microglia and/or other immune cell types, such as macrophages, lymphocytes, dendritic cells, or NK cells that ultimately contribute to neuroinflammation and autoimmune dysfunction. Interestingly, neuroinflammation similar to those in *Grn*$^{-/-}$ mouse brain has also been reported in several mouse models of lysosomal storage disease, including mucopolysaccharidosis (MPS), neuronal ceroid lipofuscinosis (NCL), and Niemann-Pick's disease (NPC) [78-81]. Future studies will be required to elucidate the mechanism(s) of lysosomal dysfunction in immune activation. The higher prevalence of autoimmune disorders in FTLD-TDP patients further raises the intriguing question as to whether the manifestations of peripheral immune dysfunction and neuroinflammation can serve as effective biomarkers that predict, capture,

and track the disease onset and progression in these patients. Finally, one major task for future studies is to determine how mutual interactions between the peripheral immune dysfunction and neuroinflammation might facilitate disease progression in FTLD-TDP patients. For FTLD caused by *C9orf72* mutations, it will be important to investigate the potential contributions of RNA foci and DPR to neuroinflammation and disease pathogenesis.

Since haploinsufficiency of PGRN and C9orf72 is a key disease-driving factor in FTLD and ALS, restoring PGRN and C9orf72 to their physiological levels is a plausible therapeutic strategy. As proof-of-concept approach, adeno-associated virus (AAV)-mediated delivery of PGRN can mitigate neuroinflammation and behavioral phenotypes in $Grn^{+/-}$ and $Grn^{-/-}$ mice [82,83]. However, similar AAV-mediated approaches to restore PGRN expression trigger a robust proliferation in T-lymphocytes [84]. Another non-viral PGRN replacement approach is to combine PGRN with a modified Fc domain that binds human transferrin receptor, which increases the efficiency for PGRN to cross the blood brain barrier (BBB). Results from this study shows that this BBB-penetrant PGRN can ameliorates microgliosis in $Grn^{-/-}$ mice and mitigate lysosomal phenotypes, such as depletion of BMP lipid and restoration of lysosomal pH and integrity in $Grn^{-/-}$ microglia *in vivo* [49]. In addition, there are ongoing clinical trials to suppress the toxic gain-of-function effects of *C9orf72* mutations with antisense oligonucleotides [85,86]. It is possible that combinatorial therapies that include C9orf72 replacement may have additional beneficial effects. Finally, given the implications of PGRN and C9orf72 in aging and AD [75,87-89], replacement therapy for PGRN and C9orf72 could have broader impacts in these conditions.

Acknowledgements

This work has been supported by the postdoctoral fellowship from the Japanese Society for the Promotion of Science (K.H.), NIH grants Blueprint for Neuroscience Diversity Supplement R01 AA027074-04S1 (N.J.), F99 NS124183-01A1 (N.J.), K23 AG048291 (Z.A.M.), Blueprint for Neuroscience R01 AA027074-04 (E.J.H.), R01 AG057462-05 (E.J.H.), R01 AG068290-02 (E.J.H.), Department of Veterans Affairs Merit Award I01 BX001108-09, and the Bluefield Project to Cure FTD (E.J.H.).

Abbreviations

FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
AD	Alzheimer’s disease
GWAS	Genome-wide association studies
TDP-43	TAR DNA binding protein 43
FUS	Fused in sarcoma
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
M6PR	Mannose 6-phosphate receptor

LRP1	Low-density lipoprotein receptor-related protein 1
TNF	Tumor necrosis factor
TNFR	Tumor necrosis factor receptor
SNP	Single nucleotide polymorphism
NCL	Neuronal ceroid lipofuscinosis
NPC	Niemann-Pick's disease
MPS	Mucopolysaccharidosis
BBB	Blood-brain barrier
ALS	Amyotrophic lateral sclerosis
GRN	*Progranulin*(gene)
PGRN	Progranulin (protein)
PSAP	Prosaposin (protein)
C9orf72	Chromosome 9 open reading frame 72
OCD	Obsessive-compulsive disorder

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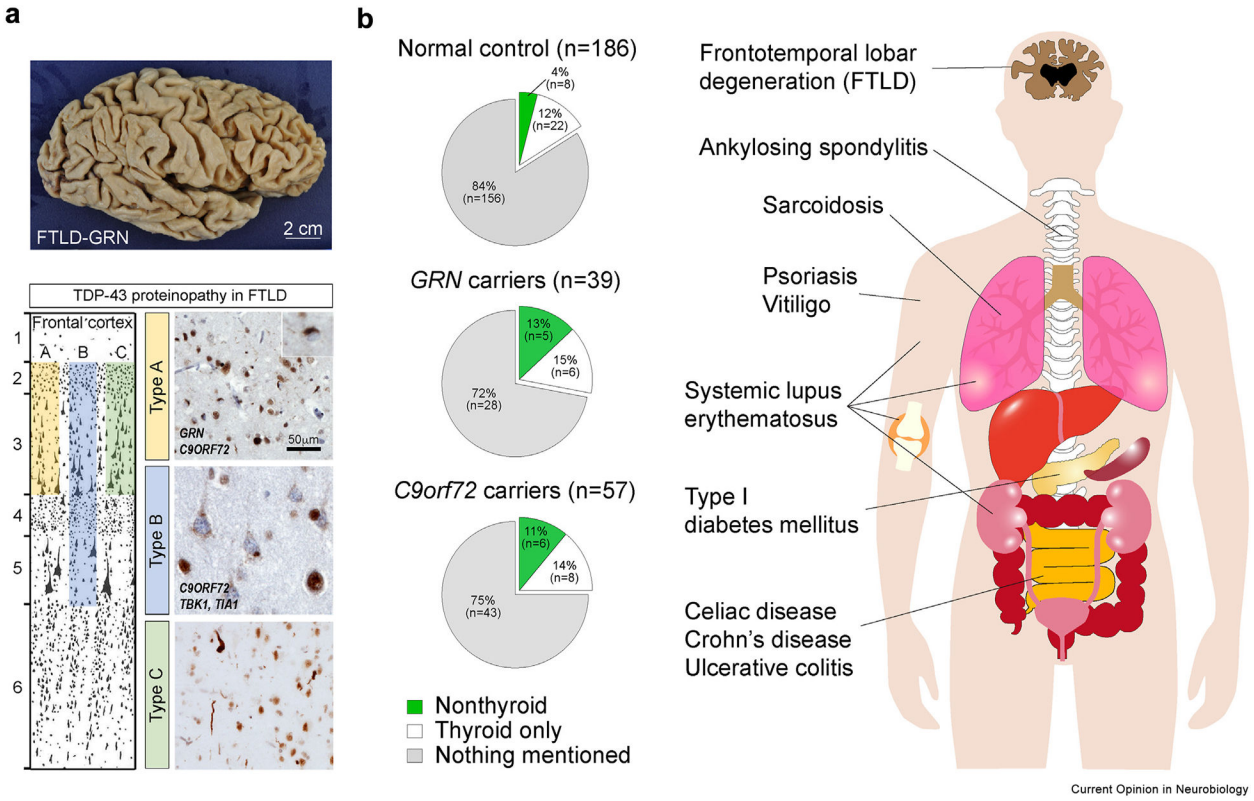

Figure 1. Neuropathology and autoimmune dysfunction in FTLD patients.

(a) Gross neuropathology of FTLD caused by GRN mutations (upper panel). Microscopic features of TDP-43 proteinopathy in FTLD that define type A, B and C. Although TDP-43 is located inside of nuclei in normal neurons, aggregates of TDP-43 are detected in the frontal cortex of FTLD-TDP patients. Based on the morphology of TDP-43 proteinopathy, FTLD-TDP can be classified into type A, which shows compact aggregation of TDP-43 in neuronal cytoplasm and TDP-43 thread-like inclusions in the neuropils or neurites in layers 2/3, type B, which shows diffuse cytoplasmic granular TDP-43 aggregates in layers 2–5, and type C, which contains long tortuous TDP-43-containing neurites and cytoplasmic TDP-43 aggregates in layer 2/3 in the frontal cortex **(b)** Case-control studies show a higher propensity for FTLD-TDP patients to have co-occurrence of systemic autoimmune diseases. Pie charts are modified based on the data previously published [12,13].

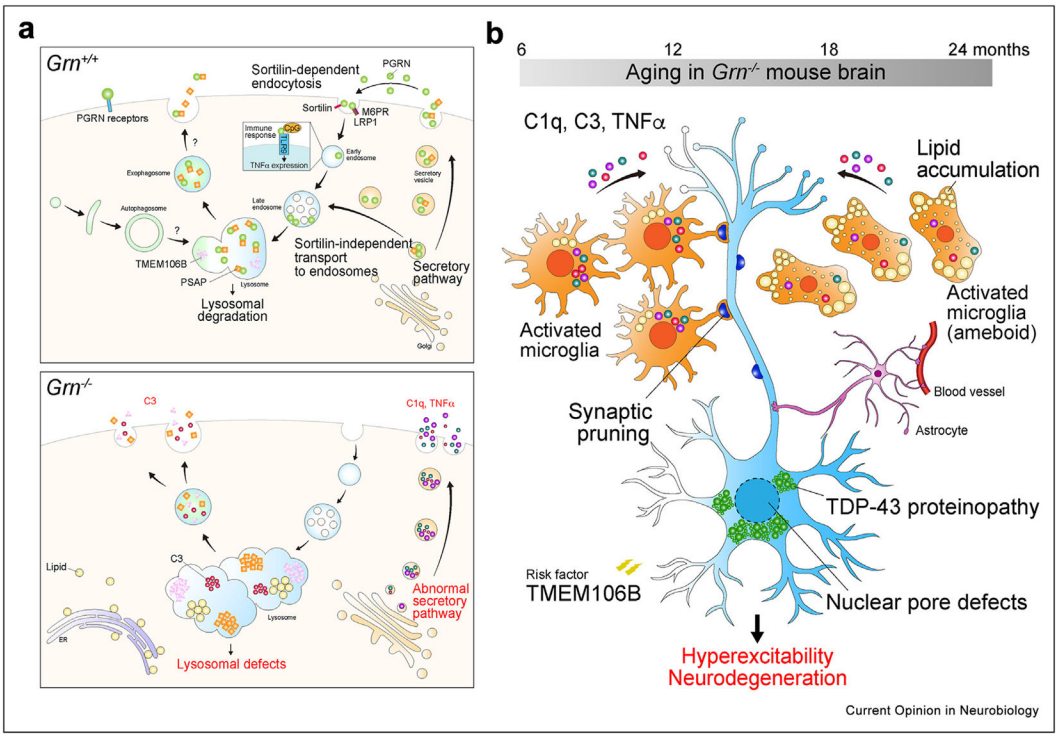

Figure 2. Cell biology of Progranulin (PGRN) deficiency in microglia.

(a) Secretion of PGRN can be mediated via the secretory and exophagy pathways. Once secreted, PGRN is endocytosed by binding with sortilin and M6PR and eventually reaches the lysosomes where it interacts with PSAP and regulates lysosomal acidification and degradation of cargoes. PGRN can interact with CpG and TLR9 to promote TNFα expression in innate immune response. In addition, PGRN can use sortilin-independent mechanism to transport from Golgi to late endosomes where it regulates vesicle trafficking from late endosomes to early lysosomes. In PGRN deficient microglia, there are increases in lysosomal storage materials, complement C3 and its cleavage product C3b, TMEM106B, PSAP and lipids. The excessive production of complement proteins, cytokines, and lipids in *Grn*$^{-/-}$ microglia **(b)** Transcriptomic analyses in *Grn*$^{-/-}$ thalamus show age-dependent microglial activation, characterized by overproduction of proinflammatory cytokines and complement proteins, C1q and C3b, from 7 to 12 months old. During this period, *Grn*$^{-/-}$ microglia promote synaptic pruning and cause hyperexcitability in the thalamocortical circuit. From 12 to 24 months old, *Grn*$^{-/-}$ microglia exhibit ameboid morphology and continue to produce excessive C1q, C3b, bioreactive lipids, and other unknown factors to accelerate neuronal cell death by compromising nuclear pore integrity and TDP-43 proteinopathy.

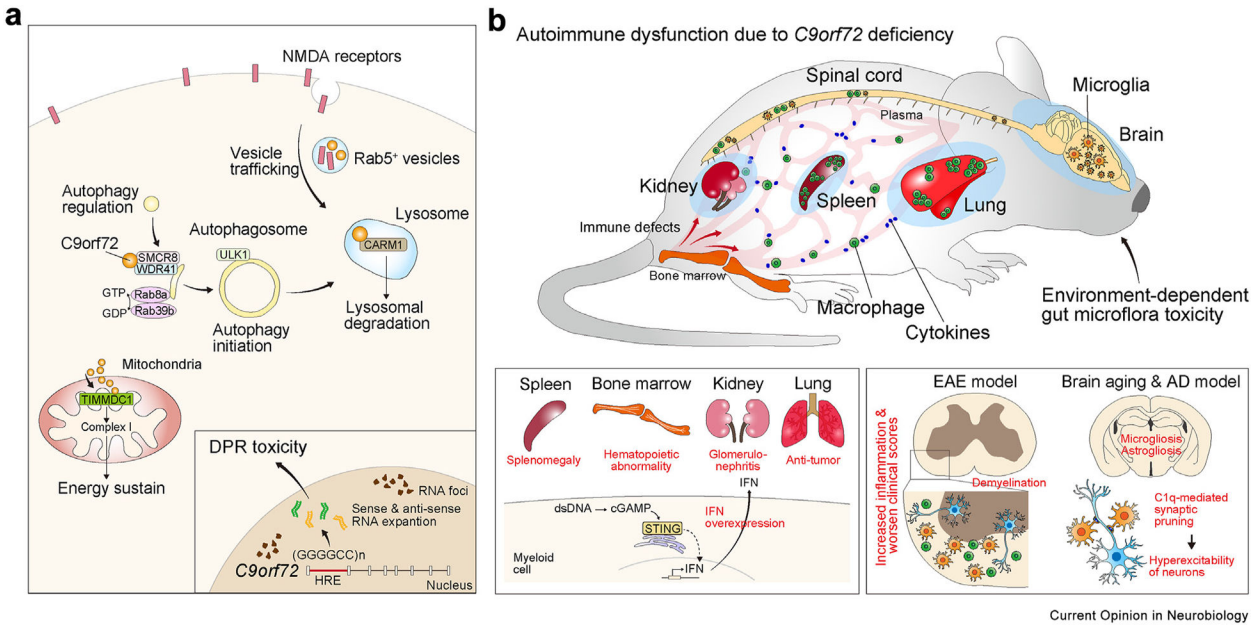

Figure 3. Cell biology of C9orf72 and its roles as a gatekeeper to peripheral immunity.

(a) Intracellular function of C9orf72 regulates the initiation of autophagy by forming protein complexes with SMCR8 and WDR41. In addition, C9orf72 regulates vesicle trafficking and autophagosome-lysosome fusion, and can interact with CARM1 to process lysosomal degradation. In addition, C9orf72 regulates energy homeostasis through mitochondrial complex I in oxidative phosphorylation. The (GGGGCC)n hexanucleotide repeat expansion (HRE) in *C9orf72* causes accumulation of RNA foci and production of dipeptide repeat (DPR) that can have neurotoxic properties. **(b)** Loss-of-function in C9orf72 causes autoimmune dysfunction in spleen, kidney, and lung. Transcriptomic and functional analyses show that C9orf72 deficiency leads to the overexpression of IFN in myeloid cells and microglia through the STING-cGAS pathway, thereby disrupting immune homeostasis. In the central nervous system, C9orf72 mutation also induces immune defects showing microgliosis during aging and in disease models for experimental allergic encephalitis and Alzheimer disease (AD). Abbreviations: DPR, dipeptide repeat; EAE, experimental allergic encephalitis; HRE, hexanucleotide repeat expansion; IFN, interferon.