

Published in final edited form as:

Brain Res. 2012 June 26; 1462: 118–128. doi:10.1016/j.brainres.2012.01.047.

Progranulin: An emerging target for FTLD therapies

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Abstract

Frontotemporal lobar degeneration (FTLD), a neurodegenerative disease primarily affecting the frontal and temporal lobes, is one of the most common types of dementia. While the majority of FTLD cases are sporadic, approximately 10–40% of patients have an inherited form of FTLD. Mutations in the progranulin gene (*GRN*) have recently been identified as a major cause of FTLD with ubiquitin positive inclusions (FTLD-U). Because over 70 disease-linked *GRN* mutations cause abnormal deficiencies in the production of PGRN, a protein that plays a crucial role in embryogenesis, cell growth and survival, as well as wound repair and inflammation, researchers now aim to design therapies that would increase PGRN levels in affected individuals, thereby alleviating the symptoms associated with disease. Several compounds and genetic factors, as well as PGRN receptors, have recently been identified because of their ability to regulate PGRN levels. Strict quality control measures are needed given that extreme PGRN levels at either end of the spectrum – too low or too high – can lead to neurodegeneration or cancer, respectively. The aim of this review is to highlight what is known regarding PGRN biology; to improve understanding of the mechanisms involved in regulating PGRN levels and highlight studies that are laying the groundwork for the development of effective therapeutic modulators of PGRN.

Keywords

Progranulin; neurodegeneration; frontotemporal lobar degeneration; dementia; neurotrophic factors; sortilin

1. Introduction

New research shows that increasing levels of the protein progranulin (PGRN) may be beneficial to neurons and thereby prevent brain disorders such as frontotemporal lobar degeneration (FTLD). Mutations in the progranulin gene (*GRN*) are a major cause of frontotemporal lobar degeneration with ubiquitin positive inclusions (FTLD-U) (Baker et al., 2006; Cruts et al., 2006). Because these mutations have been linked to abnormal deficiencies in the production of PGRN, researchers currently aim to design therapies that would increase PGRN levels in affected individuals, thereby alleviating the symptoms associated with disease.

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FTLD is the second-most common form of presenile dementia after Alzheimer's disease (AD) accounting for 5–10% of all dementia patients (Graff-Radford and Woodruff, 2007). While the majority of FTLD cases are sporadic, approximately 10–40% of patients have a positive family history. The primary neuropathological hallmark of FTLD is degeneration of the brain's frontal and temporal lobes as well as accumulation of proteinaceous inclusions found within neurons and glial cells. FTLD subtypes have been established depending on the proteins found in these inclusions. The main subtypes include FTLD-tau for microtubule associated protein tau (MAPT) positive inclusions and FTLD-TDP for ubiquitin and transactive response DNA-binding protein 43 (TDP-43) (Mackenzie et al., 2006; Mackenzie, 2007; Sampathu et al., 2006). Symptoms of FTLD include behavioral/personality changes and language dysfunction. In some cases, FTLD patients display abnormal motor function commonly referred to as motor neuron disease (Lomen-Hoerth et al., 2002).

While a tipping point exists at which PGRN causes disease—increases have been reported in various cancers but decreased levels cause FTLD (Bateman and Bennett, 2009) – the recent discovery of PGRN receptors, genetic regulators and possible therapeutic compounds provide renewed hope that proper management of PGRN levels will be beneficial. This review will include an examination of such novel applications along with recent advances in PGRN research.

2. Mutations causing FTLD

2.1 Non-GRN mutations

Identification of FTLD-causing genetic mutations has been challenging due to the variety of genes involved and their diverse protein functions. In 1998, the first mutations causing FTLD were discovered in *MAPT*, located on chromosome 17 (FTLD-tau) (Hutton et al., 1998). *MAPT* mutations reduce the ability of tau to interact with microtubules leading to the accumulation of pathogenic tau aggregates (Spillantini et al., 1998). In the following years, two other genes were determined to be rare causes of FTLD: valosin-containing protein (*VCP*) (Watts et al., 2004) associated with Golgi assembly/disassembly and regulation of the ubiquitin–proteasome system as well as charged multivesicular body protein 2B (*CHMP2B*) (Skibinski et al., 2005) which is involved in endosomal sorting. Most recently, chromosome 9 open reading frame 72 (*C9ORF72*) mutations were determined to be the major cause of chromosome 9 linked FTLD and amyotrophic lateral sclerosis (ALS) (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Despite these discoveries, questions remained as to why many families showing strong genetic linkage to chromosome 17 remained negative for *MAPT* mutations. The reason: located only 1.7Mb away from *MAPT*, were genetic variants in *GRN*.

2.2 GRN mutations

Genetic analysis of chromosome 17q21 led to the identification of 70 pathogenic mutations within *GRN* that cause FTLD-U (Figure 1) (Baker et al., 2006; Cruts et al., 2006). The majority of pathogenic variants are characterized as nonsense, frameshift and splice site mutations causing a premature stop codon, however, other mechanisms have also been observed (Baker et al., 2006; Cruts and Van Broeckhoven, 2008; Gass et al., 2006). Various mutations (missense, silent and intronic) of unknown pathogenicity also occur. Functional studies of specific missense mutations (p.R432C, p.C139R, p.P248L, p.C521Y) point to possible changes in secretion and processing of PGRN, suggesting a partial loss of PGRN function (Shankaran et al., 2008; Wang et al., 2010a). Pathogenic *GRN* mutations typically lead to degradation of RNA through nonsense mediated decay, essentially resulting in a haploinsufficiency of the protein. Indeed, about a 75% reduction of PGRN in plasma were found in patients harboring *GRN* null mutations (Finch et al., 2009).

The frequency of *GRN* mutations is estimated to be in the range of 1 to 11.7% of the total FTLN population, and 3.4 to 25.6% of familial cases (Baker et al., 2006; Borroni et al., 2008; Bronner et al., 2007; Bruni et al., 2007; Cruts et al., 2006; Gass et al., 2006; Le Ber et al., 2007; Le Ber et al., 2008; Pickering-Brown et al., 2008). The wide range in familial cases may be due to the patient populations, as well as strong founder effects of the higher frequencies. The mean age of patients suffering from diseases caused by pathogenic mutations in *GRN* is 59±7 years (Gass et al., 2006). Fifty percent of *GRN* mutation carriers are affected by the age of 60 years, while 90% are affected by 70 years of age, according to liability curve data (Gass et al., 2006). In addition, disease duration in *GRN* mutation carriers is approximately 2.4 years shorter than *MAPT* mutation carriers, suggesting a more rapid disease progression in patients carrying *GRN* mutations (Cruts and Van Broeckhoven, 2008). Still other modifying factors – genetic or environmental – may potentially impact disease progression and severity and thereby account for the variable age at onset.

In rare circumstances, *GRN* mutations have been reported in clinically identified AD and Parkinson's disease (PD) patients (Brouwers et al., 2007; Kelley et al., 2010). Alternatively, PGRN is often increased in AD, ALS and PD, most likely due to microgliosis (Brouwers et al., 2007; Irwin et al., 2009; Pereson et al., 2009). Although *GRN* mutations are not a major cause of AD, ALS, PD, it is possible that certain genetic variants of *GRN* serve as risk factors.

3. Molecular biology of PGRN

GRN is composed of 13 exons, although exon 1 is non-coding (Figure 1). The PGRN protein is composed of a series of seven-and-a-half tandem repeats separated by interlinked spacer regions (Bhandari and Bateman, 1992). PGRN is a 68.5kDa protein, however, N-glycosylation of the protein at five potential sites, gives rise to secretion of a mature 88 kDa protein (Songsrirote et al., 2010). The distinctive structure allows for cleavage of PGRN into granulins, each composed of cysteine repeat motifs. Cleavage of PGRN occurs at the intra-linker spacer regions and it is achieved by several proteases; these include elastase (Zhu et al., 2002), proteinase 3 (Kessenbrock et al., 2008), matrix metalloproteinase-14 (Butler et al., 2008) and ADAM metalloproteinase with thrombospondin type 1 motif, 7 (Bai et al., 2009). Additionally, full length PGRN is preserved from cleavage by secretory leukocyte protease inhibitor (SLPI) (Zhu et al., 2002) and high-density lipoprotein (HDL)/Apolipoprotein A-I complex (Okura et al., 2010). SLPI binds to PGRN, as well as elastase to control the levels of PGRN and granulins as depicted in Figure 1.

Another interesting point is that FTLN-U patients harbor *GRN* mutations that contain TDP-43 positive inclusions (FTLN-TDP) (Mackenzie et al., 2006; Sampathu et al., 2006). Currently the relationship between *GRN* insufficiency and TDP-43 inclusions is not completely understood; however, ongoing research is starting to unveil a link between the two and disease. Briefly, TDP-43 is involved in RNA metabolism and recently has been shown to bind *GRN* RNA in mice (Polymenidou et al., 2011). In disease, TDP-43 may become hyperphosphorylated, cleaved into C-terminal fragments and translocated to the cytoplasm where it forms inclusions (Neumann et al., 2006; Zhang et al., 2007). These events would induce changes in the nuclear regulation of TDP-43 RNA targets, such as *GRN*. Tdp-43 downregulation in mice has been shown to increase *Grn* RNA levels (Polymenidou et al., 2011); however, details on how Tdp-43 regulates *Grn* and the consequences of this increase in *Grn* RNA requires further investigation. Changes in PGRN expression have been shown to alter TDP-43 biology *in vitro*. Briefly, modeling *GRN* insufficiency in cell culture models by treating cells with siRNA against *GRN* for 72 hours leads to caspase-dependent cleavage of TDP-43 into fragments similar to the 25 and 35 kDa species observed in humans (Zhang et al., 2007). However, downregulation of PGRN in

cells for shorter periods of time (48 hours) did not result in TDP-43 fragmentation (Dormann et al., 2009). Additional studies demonstrate that knock-down of PGRN in primary neuronal cultures promotes redistribution of TDP-43 into the cytosol (Guo et al., 2010). Although the relationship between PGRN and TDP-43 needs to be further evaluated, these data suggest that PGRN may be implicated not only in FTL, but also in other neurodegenerative diseases, such as ALS, that are also characterized by TDP-43 inclusions.

4. PGRN plays pivotal role in several biological functions

Progranulin and its orthologs are highly conserved proteins found in a variety of species ranging from eubacteria to mammals. PGRN was independently identified by various groups and is known by several synonymous names including granulin-epithelin precursor (GEP) (Xu et al., 1998), proepithelin (Plowman et al., 1992), PC cell derived growth factor (PCDGF) (Zhou et al., 1993) and acrogranin (Baba et al., 1993). As its many names suggest, PGRN play roles in multiple biological functions including embryogenesis (Daniel et al., 2003; Diaz-Cueto et al., 2000), cell growth and survival (Bateman et al., 1990; Plowman et al., 1992; Xu et al., 1998), transcriptional repression (Hoque et al., 2003; Hoque et al., 2010), and wound repair and inflammation (Bateman et al., 1990; He and Bateman, 1999; Kessenbrock et al., 2008; Yin et al., 2010; Zhu et al., 2002).

4.1 Neurotrophic functions of PGRN

Recently, PGRN's role in the central nervous system (CNS) has sparked interest. Experiments overexpressing PGRN in mouse cortical neurons have revealed that PGRN increases cell viability, suggesting PGRN can function as a neurotrophic growth factor (Ryan et al., 2009). Thorough evaluations of its neurotrophic properties revealed that when recombinant full-length PGRN and granulin E are added to cortical cultures, neurite outgrowth increases (Van Damme et al., 2008). Additionally, treatment with recombinant SLPI, which prevents cleavage, inhibits increased outgrowth produced by PGRN supplementation suggesting neurotrophic roles for granulins. In their recent publication, Tapia and colleagues determined when PGRN is knocked-down, via siRNA in rat primary hippocampal neurons, there is a decrease in neuronal arborization and length (Tapia et al., 2011). In addition to these decreases, they also observed reductions in synaptic densities that are believed to be compensated for increases in excitatory postsynaptic potentials of PGRN knockdown neurons. Such evidence demonstrates PGRN plays a crucial role in proper neuronal morphology and the connections between neurons.

4.2 Developmental functions and signaling pathways of PGRN

In terms of embryogenesis, *Grn* mRNA levels were measured in preimplantation mouse embryos, with the highest levels found in the blastocysts stage (Diaz-Cueto et al., 2000). Androgen treatment, or treatment with estrogen, increases PGRN levels within the neonatal rat hypothalamus, suggesting a possible regulatory role on sex differentiation (Suzuki et al., 2001; Suzuki and Nishihara, 2002). Moreover, in the developing brain, PGRN is widely expressed in the olfactory bulbs, retinal ganglia, forebrain and spinal cord (Daniel et al., 2003). As animals mature into adults this expression is localized to certain areas of the brain, including cerebellar Purkinje cells, pyramidal neurons of the cortex, and hippocampus, as well as activated microglia (Petkau et al., 2010).

PGRN interactions outside of the cell, as well as inside, reveal its ability to regulate several other cellular functions via signaling transduction pathways. *Wnt* signaling is involved in a variety of physiological processes. Interestingly, it is essential for neuronal development notably functioning in axon guidance (Lucas and Salinas, 1997) and neurite outgrowth (Lyuksyutova et al., 2003). According to recent studies, PGRN is involved in *Wnt* signaling,

suggesting disruption of this pathway due to decreased levels of PGRN may contribute to FTLD-TDP (Rosen et al., 2011). Additionally, PGRN can also activate various growth factor signaling pathways of the periphery involved in cell growth/survival including extracellular regulated kinase (ERK), phosphatidylinositol-3 (PI3K), protein kinase B/AKT and p70^{S6} (He et al., 2002; Kamrava et al., 2005; Monami et al., 2006; Zanocco-Marani et al., 1999). Interestingly, some of these signaling pathways are also activated in PGRN-induced neuronal outgrowth (Gao et al., 2010). Elevated levels of PGRN in various types of cancer are known to stimulate these pathways, which aid in tumorigenesis by increasing proliferation, migration and invasiveness.

4.3 Wound repair and inflammation

Cytokines, such as tumor necrosis factor alpha (TNF- α), help initiate the inflammation process via signaling through receptors. In wound repair, PGRN, but not granulins, inhibit TNF- α induced signal transduction in neutrophils (Zhu et al., 2002). Additionally, in a murine transcutaneous wound model, PGRN was found to increase accumulation of fibroblast, endothelial cells, macrophages, neutrophils and blood vessels after application to the wounded areas (He et al., 2003). Such data illustrate the function of PGRN in the early stages of wound healing. Thanks to the recent discovery of tumor necrosis factor receptors (TNFR) as possible receptors for PGRN, researchers will be able to pinpoint the role PGRN plays in inflammation.

5. PGRN deficient animal models mimic human disease

Many researchers have begun to study the effects of PGRN loss through the generation of *Grn* knockout animal models (*Grn*^{-/-}). Despite variations in the design, these models share many commonalities. For instance, murine *Grn*^{-/-} models have increased microglial and astroglial activation with age when compared to *Grn*^{+/+} and *Grn*^{+/-} mice (Ahmed et al., 2007; Yin et al., 2010). Furthermore, *Grn*^{-/-} mice have increased accumulation of ubiquitin staining that begins around 7 months. Unlike FTLD patients, the increased ubiquitin inclusions are not TDP-43 positive. Additional analyses determined that these aggregates were mainly composed of lipofuscin granules (Ahmed et al., 2007). Lipofuscin, alternatively known as “the aging pigment”, forms in response to normal aging but accelerates accumulation during mitochondrial stress and lysosomal injury, however, it has not been reported in FTLD patients. In a *Grn*^{-/-} mouse generated by Petkau et al, synaptic connectivity and plasticity were both altered (Petkau et al., 2011). Microphotographs of Golgi stained hippocampal neurons from these mice revealed decreased length and arborization of dendrites similar to experiments mentioned above using primary neurons.

Mice generated by Kayasuga and colleagues exhibit a phenotype that correlates with certain behavioral symptoms in FTLD (Kayasuga et al., 2007). Characterization of aged *Grn*^{-/-} mice using a resident-intruder test and Morris water maze determined that these mice display decreased social interaction and impaired learning and memory, which mimics behavior changes and advanced dementia problems observed in FTLD patients (Ghoshal et al., 2012). Another model developed by Yin et al., focused mainly on Pgrn's involvement in inflammation (Yin et al., 2010). Here they report that loss of Pgrn in *Grn*^{-/-} mice leads to an increase in the production of proinflammatory cytokines. Interestingly, these studies revealed that these mice also have behavioral abnormalities such as depression and impaired cognitive behaviors. Yin et al also report that ubiquitin positive inclusions contain TDP-43 (Yin et al., 2010), however, this finding is not observed in other models (Ahmed et al., 2007; Petkau et al., 2010).

PGRN deficiency models in zebrafish and the nematode *C. elegans* have been generated. Knockdown of zfPGRN-A, the ortholog of human PGRN, generated truncated

motorneurons and premature branching that was rescued by overexpression of zfPGRN-A (Chitramuthu et al., 2010). Loss of PGRN in a *C. elegans* model caused increased apoptotic clearance of dying cells, suggesting that cells are prematurely cleared before recovery can take place (Kao et al., 2011). In other words, stressed neurons would be removed leading to increased neurodegeneration. While many commonalities exist between these animal models and FTLN patients, differences exist. Still these models will be beneficial in therapy development and elucidating the functions of PGRN.

6. Potential therapeutic targets for PGRN

6.1 Regulators of PGRN

Several compounds and genetic factors have recently been identified because of their ability to regulate PGRN levels. Strict quality control measures to ensure PGRN levels are properly regulated are crucial, given PGRN's duality – its involvement in the progression of neurodegeneration and tumorigenesis – based on its concentrations throughout the body. Although PGRN levels are decreased in FTLN, its expression is upregulated in certain cancers and other neurodegenerative diseases.

6.1.1 Chemical Compounds—Researchers have begun to identify chemical compounds that can be used to manipulate PGRN levels. For example, Capell et al were able to pharmacologically stimulate the production of PGRN in *Grn*^{-/-} mice and patients with *GRN* mutations by the use of Bafilomycin A1 (BafA1) (Capell et al., 2011). BafA1, an inhibitor of vacuolar ATPase, was shown to increase PGRN levels independent of lysosomal degradation, autophagy, or endocytosis. The exact mechanism involved in BafA1 remains undetermined; however, it was suggested that translational upregulation of PGRN was initiated by increases in intracellular pH changes. Capell and colleagues also reported that other FDA-approved alkalizing compounds such as chloroquine, amiodarone and bepridil can increase PGRN levels. Additionally, suberoylanilide hydroxamic acid (SAHA) was found to increase *GRN* transcription leading to greater expression (Cenik et al., 2011). SAHA treatment led to increased *GRN* mRNA and protein levels in cultured Neuro-2a cells and lymphoblast cells from *GRN* mutational carriers. While these compounds would require testing before they could be used in FTLN patients, SAHA is currently approved to treat cutaneous T-cell lymphoma.

6.1.2 Genetic modifiers of PGRN levels—MicroRNAs (miRNA) are short RNA molecules that regulate gene expression by preventing mRNA from being translated. The single nucleotide polymorphism (SNP) rs5848, located in a predicted miRNA binding site for miR-659 in the 3' UTR of *GRN*, is shown to be a risk factor for FTLN-TDP (Rademakers et al., 2008). Thus, rs5848 is thought to cause a shift in the miRNA binding site when the risk T-allele of rs5848 is present, thereby decreasing *GRN* mRNA levels (Fenoglio et al., 2009; Rademakers et al., 2008). Nevertheless, one group has reported that they are unable to replicate these data (Rollinson et al., 2011). Additional groups have also shown that other miRNAs can regulate PGRN levels. Both miR-29b and miR-107 were determined to regulate PGRN expression (Jiao et al., 2010; Wang et al., 2010b). Increases in both miRNAs decreased PGRN levels.

The transmembrane protein 106B (*TMEM106B*) has been identified as a potential PGRN regulator, and thus, a possible drug target. In a collaborative study, researchers initially used a genome-wide association study that identified three SNPs in and around *TMEM106B* (Van Deerlin et al., 2010). These SNPs were shown to regulate *TMEM106B* expression, however, not much is known about its function. Independent follow up studies using *GRN* mutation carriers and controls report that the rare *TMEM106B* variants are protective, which was supported by data that these rare variants delay the age at onset of FTLN-TDP and

increase plasma PGRN levels (Cruchaga et al., 2011; Finch et al., 2011; van der Zee and Van Broeckhoven, 2011).

6.2 Receptors of PGRN

Designing potential therapies to reverse or combat PGRN loss in neurodegeneration, as well as other diseases, has been difficult. Recent identification of PGRN binding receptors is a critical step in understanding how PGRN functions and the development of new therapies. Increasing PGRN levels, for example to patients at risk of FTL-D-U, would reduce neuronal vulnerability to injury, inflammation or other insults that lead to increased risk of cell death and disease.

6.2.1 Sortilin—Sortilin 1 (SORT1) was identified as the first known receptor for PGRN (Hu et al., 2010). Independent of this finding, genome wide association studies also identified SORT1 as a regulator of PGRN levels (Carrasquillo et al., 2010). SORT1 belongs to a class of receptors known as vacuolar protein sorting 10 protein domain receptors (VSP10P) (Marcusson et al., 1994). This class of receptors is found in distinct areas of the CNS and peripheral nervous system suggesting roles in neuronal function. SORT1 is a sorting protein involved in endocytosis and transport to trans-golgi network (TGN) and endosomes (Petersen et al., 1997). SORT1 can form a complex with the low-affinity nerve growth factor receptor (P75^{NTR}) and proneurotrophin to activate cell death. On the other hand, P75^{NTR} forms complexes with tyrosine kinase receptors (Trk) to promote cell survival (Willnow et al., 2008). SORT1, however, does not associate with Trk receptors similar to P75^{NTR}; instead, it binds to Trk receptors to enhance their anterograde transport from the soma to nerve endings (Vaegter et al., 2011). While SORT is known to interact with several proteins, its interactions with PGRN remain relatively unspecified.

Association studies have identified that several VSP10P receptors are involved in neuronal diseases such as AD (SORLA and SORSC1) and bipolar disorder (SORCS2) (Grupe et al., 2006; Rogaeva et al., 2007). In a recent genome wide association study by Carrasquillo et al., *SORT1* variants were shown to regulate PGRN levels in human plasma (Carrasquillo et al., 2010). SNP rs646776 near *SORT1* is associated with increased levels of SORT1. However, rs646776 genotypes correlate only with PGRN levels specific for the liver and not within the CNS. Additional evaluations of SORT1 knockdown in HeLa cells showed increased levels of PGRN (Carrasquillo et al., 2010). Furthermore, overexpression of SORT1 resulted in decreased levels of PGRN suggesting that SORT1 regulates PGRN levels.

The identification of SORT1 as a major neuronal receptor for PGRN was a key development in PGRN biology. Using an alkaline phosphatase tagged PGRN binding assay, Hu et al discovered that SORT1 was the only high affinity binding partner of PGRN in neurons ($K_D \sim 15$) (Hu et al., 2010). Additional studies revealed that when PGRN binds to SORT1 it immediately gets endocytosed and delivered to the lysosome (Figure 2A). Uptake of PGRN via SORT1 dramatically decreases the extracellular levels of PGRN. Extensive experiments determined the C-terminal tail of PGRN (QLL) binds to the beta propeller region of SORT1 (Zheng et al., 2011). For future studies it will be important to know if SORT1 is able to act as a signaling receptor for PGRN as well as other functions. The use of this receptor for the identification of therapies will be of great use since SORT1 is known to regulate PGRN levels.

6.2.2 TNFR—Exciting new evidence of PGRN-related therapies decreasing inflammation in arthritis may also be beneficial to patients suffering from neurodegeneration, since inflammation is often associated with neurodegenerative diseases. The discovery that PGRN binds to TNFR suggests that PGRN acts as an antagonist for TNF α (Tang et al., 2011). Tang

and colleagues utilized a yeast two-hybrid system to identify tumor necrosis factor receptor 1 and 2 (TNFR1 and TNFR2) as major binding proteins of PGRN (Tang et al., 2011). Further experiments revealed that when PGRN binds to these receptors, downstream inflammatory signaling is blocked (Figure 2.b). Utilizing a collagen-induced arthritis (CIA) mouse model, they were able to show that loss of PGRN exacerbates inflammation and joint damage associated with arthritis. Interestingly, supplementation of recombinant PGRN in this model delayed symptoms of arthritis. The authors also determined that specific domains of PGRN bind to TNFRs, which they used to develop a peptide (Asttrin) that mimics PGRN binding. Experiments using Asttrin in the CIA mouse model showed a greater efficiency in preventing inflammation than PGRN, suggesting that development of specific compounds may be a key to treating these devastating diseases.

7. Conclusions

Although the specific functions of PGRN have not been fully characterized, it is becoming apparent that the expression and function of PGRN is an important determinant of successful aging. Mutations in *GRN* lead to reduced PGRN levels leading to FTLTDP, and may also increase risk of other neurodegenerative diseases. Recently identified PGRN binding receptors may aid in the development of therapeutics designed to regulate PGRN levels. By better understanding which receptors PGRN binds to, and by extension other proteins that act as PGRN antagonists, researchers may have greater success therapeutically modulating PGRN levels. Much remains unknown regarding the impact environmental insults have on the health of neurons, which also are sensitive to age-related stress accumulation. However given our increasing knowledge of PGRN function and its key regulators, researchers now aim to develop novel therapies in the hopes of improving patient care.

Acknowledgments

This work was supported by Mayo Clinic Foundation (LP), National Institutes of Health/National Institute on Aging [5R01AG026251-04(LP)], National Institutes of Health/National Institute of Neurological Disorders and Stroke [R01 NS 063964-01 (LP), R01 NS077402 (LP)], Amyotrophic Lateral Sclerosis Association (LP) and Department of Defense [W81XWH-10-1-0512-1 and W81XWH-09-1-0315AL093108 (LP)].

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Highlights

- We review PGRN's role in several biological functions
- We review how PGRN knockout animal models mimic human disease
- We review potential therapeutic targets for PGRN

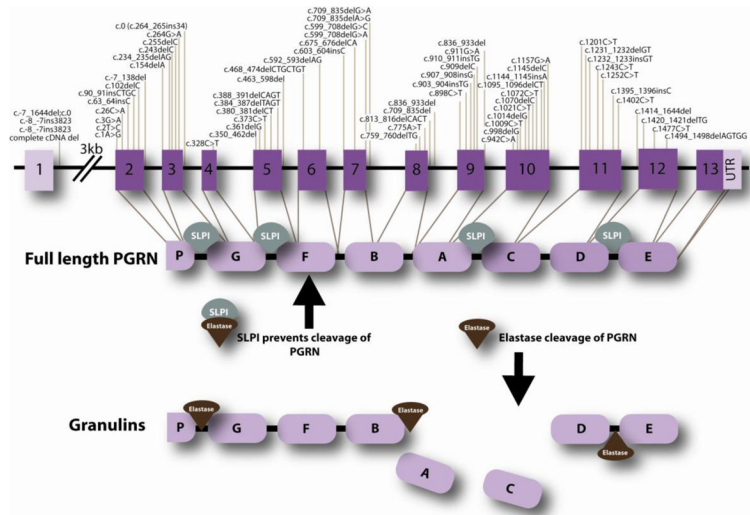


Figure 1. Seventy pathogenic *GRN* mutations have been identified in over 230 families. In the schematic diagram, mutations are numbered relative to the largest *GRN* transcript (GenBank accession number NM_002087.2). The gene encodes for a 593 amino acid protein composed of intra-linked granulin peptides that are cleaved by proteases into individual granulins. Secretory leukocyte protease inhibitor (SLPI) protects full-length PGRN by binding to both PGRN and elastase, therefore preventing cleavage into the 6 kDa granulin repeats.

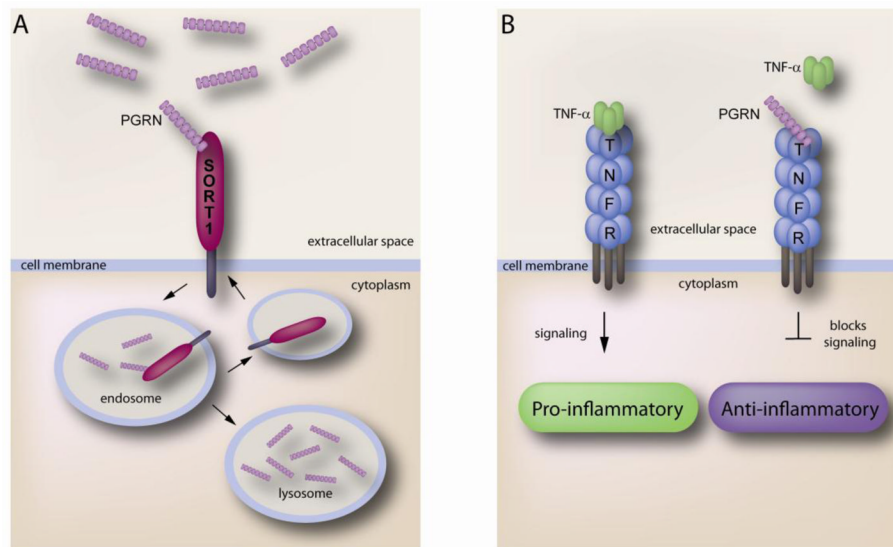


Figure 2. **A.** The C-terminal end of PGRN binds to the Beta-propeller region of SORT1. Upon binding, uptake of PGRN via SORT1 traffics PGRN to the lysosome. Endocytosed SORT1 is then recycled back to the cell membrane. **B.** PGRN binding to TNFR acts as an antagonist of TNF α . TNF α binding to TNFR activates pro-inflammatory signaling to induce inflammation. PGRN blocks this signaling pathway when bound to TNFR therefore inhibiting inflammation.