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Potential Mechanisms of Progranulin-deficient FTLD

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Abstract

Frontotemporal lobar dementia (FTLD) is the most common cause of dementia in patients younger than 60 years of age, and causes progressive neurodegeneration of the frontal and temporal lobes usually accompanied by devastating changes in language or behavior in affected individuals. Mutations in the progranulin (*GRN*) gene account for a significant fraction of familial FTLD, and in the vast majority of cases, these mutations lead to reduced expression of progranulin via nonsense-mediated mRNA decay. Progranulin is a secreted glycoprotein that regulates a diverse range of cellular functions including cell proliferation, cell migration, and inflammation. Recent fundamental discoveries about progranulin biology, including the findings that sortilin and tumor necrosis factor receptor (TNFR) are high affinity progranulin receptors, are beginning to shed light on the mechanism(s) by which progranulin deficiency causes FTLD. This review will explore how alterations in basic cellular functions due to PGRN deficiency, both intrinsic and extrinsic to neurons, might lead to the development of FTLD.

Keywords

Progranulin; Frontotemporal lobar dementia; Sortilin; Tumor necrosis factor receptor; TDP-43; Neuroinflammation

Overview

Frontotemporal lobar dementia (FTLD) causes a progressive neurodegenerative condition associated with selective degeneration of frontotemporal cortex. Patients with FTLD present with variable clinical syndromes that include behavioral disturbance, progressive aphasia and Parkinsonism (Roberson 2006). Accompanying these clinical changes is prominent atrophy of the frontal and temporal lobes, which is microscopically characterized by microgliosis, astrogliosis, neuronal loss and abnormal cytoplasmic accumulations of the proteins tau, TDP-43, or FUS (Arnold et al. 2000; Ahmed et al. 2007). Though most cases of FTLD are sporadic, mutations in the gene encoding progranulin (*GRN*), a secreted glycoprotein, cause inherited FTLD in a significant number (5%) of cases (Baker et al. 2006; Pickering-Brown and Hutton 2008; Cruts et al. 2006). Many mutations in *GRN* cause nonsense-mediated mRNA decay and lead to a corresponding reduction in PGRN protein levels (usually 30–40% of normal levels) (Baker et al. 2006). The mechanism by which reduced levels of PGRN lead to neuronal loss and FTLD is poorly understood. PGRN plays important roles in a host of cellular functions including malignancy, cell migration, and inflammation, and its function has been the subject of a number of excellent reviews (Ahmed et al. 2007; Bateman and Bennett 2009; Neumann et al. 2009; Alberici et al. 2011).

This past year has yielded fundamental discoveries about basic PGRN biology, including the long-awaited identification of PGRN receptors (Hu et al. 2010; Tang et al. 2011). With this new information in hand, scientists are now tantalizingly close to unraveling how PGRN is involved in FTLN.

Clinical Spectrum of FTLN due *GRN* Mutations

The time lag between the discovery of tau (*MAPT*) and *GRN* mutations was 8 years and the close location between progranulin and tau on chromosome 17 was a factor in this delay. Yet, there are key distinctions between families with *MAPT* versus *GRN* mutations. Patients with *MAPT* mutations tend to present earlier in life with a mean age of onset early in the sixth decade, while those with *GRN* mutations are typically diagnosed during the seventh decade. Importantly, *MAPT* mutations are nearly always penetrant, while approximately 10% of individuals with *GRN* mutations are clinically well after the age of 70 (Rademakers et al. 2007). The new finding of a TMEM106 variant that delays the age of onset of FTD suggests that genetic factors play a major, if not the only role, in age of onset (Finch et al. 2011).

In the UCSF patient cohort, we have seen a wide variety of clinical syndromes in *GRN* mutation carriers. These clinical disorders have ranged from later-life sociopathy, marital infidelity, accusations of pedophilia, poor judgment, disinhibition, apathy and repetitive compulsive behaviors to progressive aphasia and asymmetric Parkinsonism (Roberson 2006). Exciting work from Rohrer et al. in London suggests that while tau mutations lead to fairly symmetrical degeneration of the frontotemporal and basal ganglia regions, *GRN* mutations tend to cause a highly asymmetric neurodegenerative syndrome that spreads along one hemisphere (Rohrer et al. 2010). These clinical distinctions may suggest that distinctive (but as of yet unidentified) mechanisms underlie neurodegeneration with these differing mutations.

The *GRN* gene is on chromosome 17, and >70 different mutations in *GRN* have been discovered, all of which are associated with the development of FTLN in a highly penetrant autosomal-dominant inheritance pattern (Ahmed et al. 2007; Seeley 2008). In the vast majority of cases, these are null mutations leading to nonsense-mediated decay of the mutant mRNAs (Baker et al. 2006). This in turn leads to *GRN* haploinsufficiency via decreased *GRN* expression, and PGRN levels measured in either the serum or CSF of patients with *GRN* mutations are ~30–50% of normal (Van Damme et al. 2008). The mechanism by which a reduction in PGRN levels leads to neurodegeneration is a matter of intense debate, and will be the subject of the remainder of the review.

Molecular Characteristics and Processing of PGRN

Full-length PGRN is a ~90-kDa glycoprotein of 7.5 tandem, cysteine-rich modules termed granulins (GRNs), each of which is separated by a linker sequence (Bateman and Bennett 2009). GRNs are evolutionarily conserved, and, remarkably, are present in animals ranging from worms to humans. Each GRN is composed of a 12-residue cysteine motif that takes the form of a parallel stack of beta-hairpins arranged in a left-handed helical structure (Hrabal et al. 1996; Belcourt et al. 1993). The linker sequences between GRN domains can be cleaved by extracellular proteases expressed by neutrophils (e.g., proteinase-3 and neutrophil elastase) to generate individual GRN peptides (Zhu et al. 2002; Kessenbrock et al. 2008).

Full-length PGRN and individual GRNs are biologically active, though how these different species might be involved in FTLN pathogenesis is unclear. Much of what we know about the differences in function between PGRN and GRNs comes from investigations into their effects on inflammation, and this work suggests that full-length PGRN and GRNs have

opposing functions. For example, full-length PGRN abrogates neutrophil activation and promotes the secretion of IL-10 (an anti-inflammatory cytokine) in macrophages (Zhu et al. 2002; Yin et al. 2010b). Some individual GRNs appear to exert proinflammatory effects on neutrophils and possibly macrophages (Zhu et al. 2002; Okura et al. 2010). It is unclear whether the anti-inflammatory properties of “full-length” PGRN are due to intact PGRN per se or to smaller (partially cleaved) species generated after the addition of PGRN to these cells, as the treated neutrophils also secrete proteases that cleave PGRN (Kessenbrock et al. 2008). In fact, it was recently demonstrated that an artificially synthesized peptide made of multiple GRN domains displayed biologic, anti-inflammatory activity (Tang et al. 2011). Immunomodulatory functions of the majority of individual GRNs have not been determined, and the particular types of GRNs present in the brain are unknown.

PGRN processing is highly regulated. Secreted leukocyte protease inhibitor (SLPI) is a ~12-kDa protein secreted by neutrophils and macrophages, whereupon it inhibits extracellular serine proteases such as neutrophil elastase (Jin et al. 1997; Grobmyer et al. 2000). SLPI also binds to PGRN, and in doing so prevents its conversion into GRNs by blocking interGRN linker cleavage (Zhu et al. 2002). When coincubated with PGRN, SLPI augments the anti-inflammatory effects of PGRN on neutrophils, possibly by preventing its processing to proinflammatory GRNs (Zhu et al. 2002). Furthermore, higher levels of full-length PGRN are observed in the wounds of SLPI-deficient mice, suggesting that SLPI protects PGRN from cleavage in vivo in settings of cellular repair or inflammation (Zhu et al. 2002). Intriguingly, it appears that HDL/apolipoprotein A-I can also bind PGRN, and like SLPI, prevents its processing by macrophages into proinflammatory GRNs (Okura et al. 2010). It is unknown if PGRN processing is regulated in a similar manner in the brain.

Human Pathology Observed in Patients with GRN Mutations

PGRN deficiency leads to unique neuropathological features that were first emphasized by Mackenzie in British Columbia. Prior to the discovery of the protein TDP43, Mackenzie observed unique intranuclear inclusions in patients with familial FTD who were tau negative. Soon, it was discovered that these families had *GRN* mutations and that TDP43 aggregation occurred with this subtype of FTD both in the nuclear and cytoplasmic inclusions (Mackenzie 2007). The hippocampus is often the nidus for neuronal inclusions in patients dying from *GRN* mutations (Mackenzie et al. 2006). While many other forms of FTD are highly symmetrical, *GRN* mutations can lead to highly asymmetric pathology affecting one hemisphere. Similarly, *GRN* is associated with neurodegeneration in the posterior parietal cortex. Extensive microgliosis and astrogliosis are apparent in all affected areas of the brain (Ahmed et al. 2007).

A Mouse Model of PGRN-deficient FTLT

Abnormalities in social interactions are defining clinical features of behavioral variant frontotemporal lobar dementia (bvFTLD). Recently, it was found that mice deficient in PGRN (*Grn*^{-/-}) also exhibited abnormal social behaviors. To demonstrate this, Yin et al. (2010a, b) placed a test mouse in the center chamber of a threechambered plexiglass box. One of the side chambers contained an empty cup and the other side contained an unfamiliar mouse. The time that the test mouse spent exploring the two chambers was then recorded. Whereas wild-type mice spent more time exploring the chamber containing the novel mouse, PGRN-deficient mice spent an equivalent amount of time in both chambers, an observation that is consistent with apathy. PGRN-deficient mice also displayed significantly more depressionlike behaviors (such as increased immobility in a forced swimming test) and cognitive deficits (the latter of which was only observed late in the course of the disease, as is seen in humans with FTLT).

In healthy mice, PGRN is expressed primarily by neurons and is found at high levels in the hippocampus (especially in the dentate gyrus), cortex (especially cingulate gyrus), amygdala, thalamus, and hypothalamus (Ahmed et al. 2010; Matsuwaki et al. 2010). In contrast, in the setting of injury or disease, PGRN expression increases dramatically in microglia (Ahmed et al. 2007; Moisse et al. 2009b; Philips et al. 2010). Such enhanced expression of PGRN in microglia is also found in patients with FTLN due to *GRN* mutations, despite the overall lower levels of *GRN* expression in the brains of these patients (Baker et al. 2006). In addition, the brains of aging *Grn*^{-/-} mice accumulate large numbers of activated microglia and astrocytes (Ahmed et al. 2010; Yin et al. 2010a). Interestingly, the degree of microgliosis seems to be especially pronounced in the hippocampus, thalamus, and cortex—the same regions that display high levels of neuronally expressed PGRN in wild-type animals. Abnormal microgliosis and astrogliosis can be detected as early as 7 months of age in *Grn*^{-/-} mice, which intriguingly is the same age at which social behavior abnormalities are first observable. Also by this time, *Grn*^{-/-} neurons begin to accumulate abnormal intracellular accumulations of ubiquitinated autofluorescent lipid-protein aggregates called lipofuscin, which are by-products of failed proteolysis (Brunk and Terman 2002a). Older *Grn*^{-/-} mice exhibit lipofuscin deposits not only within neurons, but also within microglia, suggesting ongoing phagocytosis of dead or dying neurons in aging *Grn*^{-/-} mice.

Grn^{-/-} mice do not exhibit any appreciable neuronal loss at the ages when they display abnormal social behaviors (7 months of age) (Ahmed et al. 2010; Yin et al. 2010a). Modest neurodegeneration may be apparent late in life, occurring primarily in the hippocampus (Ahmed et al. 2010). Though it is possible that subtle (and thus difficult to quantify) neuronal loss occurs in *Grn*^{-/-} mice that underlies the behavioral phenotype, an alternative possibility would be that *Grn*^{-/-} mice exhibit abnormalities in neuronal electrophysiological properties or functionally important changes in subcellular structures such as dendritic spines. In addition, *Grn*^{-/-} mice do not develop significant cytoplasmic accumulations of TDP-43, a pathological hallmark of FTLN in humans with PGRN mutations (see below for further discussion of this point). Finally, despite the fact that humans with *GRN* haploinsufficiency develop FTD, mice heterozygous for *Grn* do not seem to develop the same pathological abnormalities that PGRN-deficient humans or *Grn*^{-/-} mice have (Ahmed et al. 2010). It is unknown if heterozygous (*Grn*^{+/-}) mice develop a behavioral phenotype. In summary, it appears that certain aspects PGRN-deficient FTLN can be modeled in the mouse, which will provide an essential platform for understanding the pathophysiology of FTLN and basic biology of PGRN in the brain. It is worth noting, however, that significant pathological and biochemical differences exist between the mouse model and what is observed in patients with PGRN-deficient FTLN.

Discovery of a Neuron-Specific PGRN Receptor

Despite the discovery of GRN peptides nearly 20 years ago, the identification of PGRN receptors has proved difficult (Bateman et al. 1990). However, groundbreaking studies published this year identified two separate transmembrane receptors for PGRN. The first PGRN receptor to be discovered was sortilin (Hu et al. 2010), a previously characterized transmembrane receptor involved in the trafficking of hydrolases to the lysosome and in binding neurotrophin (Ni et al. 2006; Al-Shawi et al. 2007). In the brain, sortilin is expressed primarily by neurons, and has minimal (if any) expression in microglia. PGRN has a high affinity for sortilin (*K_d* 11 nM), and upon binding to sortilin, PGRN rapidly undergoes endocytosis and shuttling to lysosomes. This correlates with the lysosomal pattern of PGRN staining observed in frontal cortex neurons, indicating that much of the PGRN detectable in the cortex by immunostaining is actually intracellular (Hu et al. 2010). Consistent with the observed function of sortilin in mediating PGRN endocytosis, sortilin knockout mice have

5-fold higher levels of PGRN in the brain. These data suggest that sortilin may be involved in regulating the levels of extracellular PGRN by acting as a scavenger receptor, and additionally, that sortilin may be a viable drug target for increasing PGRN levels in FTLN patients.

Sortilin as a Mediator of Cell Survival

PGRN has been reported to promote neuronal survival in culture (Van Damme et al. 2008), though the degree of this effect is controversial (Hu et al. 2010). Conversely, PGRN-deficient neurons display reduced survival (but only in stressful conditions, e.g. following H₂O₂ administration (Guo et al. 2010). Studies utilizing nonneuronal cells suggest that PGRN can influence apoptosis (Zanocco-Marani et al. 1999; Kamrava et al. 2005; Guerra et al. 2007; Guo et al. 2010). Pronerve growth factor (proNGF), the precursor of nerve growth factor, causes neuronal apoptosis via simultaneous binding to sortilin and the transmembrane receptor p75^{NTR}, and cells lacking sortilin are immune to proNGF-induced apoptosis (Nykjaer et al. 2004). Given the high affinity of PGRN for sortilin, it is tempting to hypothesize that PGRN mediates neuronal survival through influencing proNGF-/sortilin-induced apoptosis. However, proNGF and PGRN appear to have distinct sortilin binding sites, and PGRN does not display increased affinity to the p75^{NTR}/sortilin complex compared to sortilin alone (Hu et al. 2010). It is unknown if PGRN/sortilin binding indirectly affects proNGF/sortilin/p75^{NTR} signaling (e.g. through sortilin endocytosis or altered sortilin/p75^{NTR} interactions).

Potential Contribution of Impaired Proteolysis to PGRN-deficient FTLN

Whether PGRN directly regulates neuronal function via sortilin binding is unclear. A rare progranulin mutation (A9D) in the secretion peptide of progranulin causes FTLN (Mukherjee et al. 2008). Patients with this mutation have near-normal levels of intracellular PGRN, but exhibit a ~ 50% reduction in extracellular PGRN due to dysfunctional PGRN secretion. These data suggest that PGRN must be secreted to become biologically active, but leave open the possibility that endocytosed (receptor-bound) intracellular PGRN regulates normal neuronal function. Sortilin is involved in mannose-6 phosphate-independent trafficking of multiple soluble proteins to the lysosome. In fact, some lysosomal hydrolases either partially or entirely depend on sortilin for proper trafficking (Ni et al. 2006). Mutations in one such protease, cathepsin D, cause the pediatric neurodegenerative disease neuronal ceroid lipofuscinosis (NCL), which as the name suggests is characterized by abnormal deposition of intracellular lipofuscin in neurons due to impaired proteolysis (Szweda et al. 2003). Abnormal lipofuscin accumulation is also a prominent phenotype of neurons in *Gm1*^{-/-} mice (Ahmed et al. 2010). It is possible that the PGRN/sortilin complex may be necessary for the proper trafficking of hydrolases to the lysosome. Mistrafficking of hydrolases as a result of PGRN deficiency could result in impaired lysosomal function and lipofuscin formation, eventually causing cellular dysfunction. Additional support for the hypothesis that impaired proteolysis plays a role in the pathophysiology of FTLN comes from other inherited forms of the disease. Mutations in a protein involved in autophagy valosin-containing protein (VCP), can cause an inherited form of FTLN often associated with myopathy and Paget's disease (Watts et al. 2004; Ju et al. 2009). Interestingly, neuronal lipofuscin deposits are also found in patients with FTLN caused by VCP mutations, and colocalize with VCP itself (Schroder et al. 2005). Alternatively, intralysosomal PGRN might regulate lysosomal function independent of hydrolase trafficking.

Despite its discovery over 100 years ago, the role of lipofuscin in the pathophysiology of neurodegenerative diseases remains unclear. Lipofuscin is a heterogeneous intracellular aggregate made up of heavily oxidized, undigestible lipids, proteins, and metals. Deposition

of lipofuscin occurs gradually during “normal aging,” and preferentially accumulates in long-lived, nondividing division (Gray and Woulfe 2005). Prominent lipofuscin accumulations can be found in a number of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease (Ulfing 1989; Braak and Braak 1992; Dawson et al. 1992, 1995). Lipofuscin is also abundant in Von Economo neurons, which may be essential for the social behavior of high-order mammals and appear to be selectively vulnerable in FTD (Braak 1979; Seeley et al. 2006). Though it is unknown if lipofuscin accumulations occur in patients with PGRN-deficient FTLD, striking lipofuscin deposits within hippocampal neurons have been observed in patients with FTLD/ALS (Nakano 2000). Lipofuscin may contribute to neurotoxicity through the generation of reactive oxygen species (ROS), inhibition of mitochondria turnover, and/or impaired proteolysis (Brunk and Terman 2002a; Szweda et al. 2003; Brunk and Terman 2002b). Alternatively, lipofuscin aggregates may serve a cell protection role by sequestering toxic species, as has been suggested for huntingtin protein, or may simply be an inert by-product of cellular metabolism (Arrasate et al. 2004).

Making the Link between PGRN and TDP-43

One of the pathologic hallmarks of PGRN-deficient FTLD is exclusion of TDP-43 from the nucleus, and the accumulation of this protein within the cytoplasm of diseased neurons (Seeley et al. 2007). Mutations in TDP-43 have been identified in patients with familial amyotrophic lateral sclerosis (ALS), a neurodegenerative disease that primarily affects motor neurons, as well as in patients with familial FTLD-ALS, characterized by loss of both motor and cortical neurons (Kabashi et al. 2008). The normal function of TDP-43 in the brain is unclear, but it actively regulates the expression of numerous genes involved in neuronal development and functioning, and regulates alternative splicing of several premRNA transcripts (Polymenidou et al. 2011; Tollervey et al. 2011). Null mutations in TDP-43 are lethal in embryogenesis (Sephton et al. 2010; Wu et al. 2010), and the conditional knockout or overexpression of TDP-43 in adult animals results in cell death and toxicity (Chiang et al. 2010; Voigt et al. 2010; Miguel et al. 2011), confirming the fundamental importance of this protein for cellular survival. When overexpressed in cultured cortical neurons, TDP-43 results in neuron death that is often preceded by abnormal translocation of TDP-43 from the nucleus to the cytoplasm (Barmada et al. 2010). When mutated TDP-43 (A315T; a cause of familial ALS) is overexpressed at modest levels in neurons, even higher rate of neuronal death as well as an increase in cytoplasmic localization of TDP-43 is observed, compared to wild-type TDP-43 overexpression (Barmada et al. 2010). Although it is unknown whether neuronal death is caused by loss of the normal function of nuclear TDP-43 or gain of function of cytoplasmic TDP-43, these data strongly suggest that mislocalization of TDP-43 is a mechanism of neuronal death in cellular models of neurodegeneration. In newly axotomized motor neurons, TDP-43 is dramatically upregulated and translocates from the nucleus to the cytoplasm, then returns to its normal localization in the nucleus once axon repair has been completed (Moisse et al. 2009a). Interestingly, in these same neurons PGRN expression decreases as TDP-43 redistributes to the cytoplasm. These data hint that PGRN may be involved in the regulation of TDP-43 localization during normal neuronal repair processes, and suggest a possible mechanism for pathologic TDP-43 accumulation in patients with FTLD secondary to chronically reduced expression of progranulin. Likewise, studies performed in HeLa cells show that PGRN knockdown is associated with the caspase-dependent redistribution of TDP-43 to the cytoplasm (Zhang et al. 2007). Furthermore, knockdown of PGRN in primary cortical neurons caused an increased cytoplasmic/nuclear ratio of TDP-43, which could be rescued by coexpressing siRNA-resistant human PGRN. Though the authors did not study whether these neurons containing cytoplasmic TDP-43 had a lower rate of survival, the

above-described findings of cytoplasmic TDP-43 toxicity by Barmada et al. (2010) suggest that they might.

One problematic aspect of modeling the FTLTLD-relevant relationship between PGRN and TDP-43 in mice, however, is that PGRN-deficient mice do not appear to develop some cardinal pathologic features of humans with FTLTLD due to PGRN mutations. In particular, the nuclear exclusion and cytoplasmic accumulation of TDP-43 in neurons are absent in these animals (Ahmed et al. 2010). Although this finding indicates that not all aspects of human PGRN biology are recapitulated in the current mouse model, it also suggests that loss of PGRN may have neurotoxic effects independent of TDP-43, as PGRN-deficient mice develop other behavioral and pathological abnormalities consistent with FTLTLD despite a lack of TDP-43 pathology. Nevertheless, it is not entirely surprising that TDP-43 is not required for some of the pathology observed in FTLTLD: mice overexpressing TDP-43 develop a different pathological phenotype than PGRN-deficient mice that resembles ALS more than FTLTLD (Wegorzewska et al. 2009; Wils et al. 2010). Furthermore, the majority of TDP-43 mutations that have been discovered cause FTLTLD only with concomitant ALS, and not FTLTLD alone. Finally, recent studies in humans suggest that pathologic TDP-43 accumulations can occur in a significant fraction of patients with end-stage Alzheimer's disease (Amador-Ortiz et al. 2007; Kadokura et al. 2009). Taken together, these data suggest that TDP-43 may not be absolutely essential for the early the stages of PGRN-deficient FTLTLD, and that perhaps abnormalities in TDP-43 function may be a more widespread phenomenon in a variety of end-stage dementias than initially appreciated. The precise mechanism by which loss of PGRN leads to cytoplasmic TDP-43 accumulation and how TDP-43 influences FTLTLD pathogenesis remains unclear.

Inflammation as an Indirect Cause of Neurotoxicity in PGRN-deficient FTLTLD

Dysregulation of the immune system is a common observation in many neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and ALS (Lucin and Wyss-Coray 2009). Microglia are central mediators of the immune response in the CNS, can have either neurotrophic or neurotoxic effects, and are morphologically activated in neurodegenerative diseases (Streit et al. 2008; Tambuyzer et al. 2008). Though it is currently unknown if PGRN-deficient microglia are proinflammatory or neurotoxic, *Grn*^{-/-} macrophages exhibit a proinflammatory phenotype (Yin et al. 2010b). Also, *Grn*^{-/-} macrophages are neurotoxic in a brain slice model, and display accelerated clearance of dying cells (Yin et al. 2010b; Kao et al. 2011). Despite the fact that microglia express very low levels of sortilin, they have a robust signaling response to PGRN and are able to migrate toward a PGRN source in vitro and in vivo (Pickford et al. 2011). Together, these data suggest that PGRN might have indirect effects on neuronal survival via a receptor (other than sortilin) expressed by myeloid cells. One such receptor was recently identified as TNFR in a landmark study conducted by Tang et al. (2011).

PGRN binds both TNFR1 (which is broadly expressed) and TNFR2 (which is primarily expressed by leukocytes) in a dose-dependent manner (Tang et al. 2011). Surprisingly, PGRN has a higher affinity for TNFR than TNF (K_d= 1.77 nM versus 7.94 nM, respectively), indicating that PGRN can out-compete TNF for TNFR. Consistent with this observation, binding of PGRN to TNFR blocked the association of TNFR with its native ligand, TNF. These results explain prior observations that PGRN inhibits TNF-induced neutrophil activation (Zhu et al. 2002). In addition, Tang et al. (2011) found that PGRN blocked TNF-mediated signaling in human regulatory T cells, and downregulated interferon (IFN) gamma secretion in effector T cells. It is unclear if PGRN directly regulates cell signaling in leukocytes via its interaction with TNFR. These results suggest that PGRN

can directly regulate intracellular signaling by directly binding to TNFR and by inhibiting TNF α -mediated pathways.

Whereas the C-terminus of PGRN (specifically GRN E), is sufficient to bind sortilin, PGRN interacts with TNFR via multiple granulin-linker domains (specifically, F-P3, P4-A, and P5-C) (Tang et al. 2011). These observations suggest that extracellular processing of PGRN could significantly influence PGRN-mediated signaling—cleavage of GRN E could increase the half-life of PGRN by inhibiting sortilin-mediated endocytosis, and at the same time free the remaining PGRN fragment to associate with TNFR. Conversely, cleavage between GRN F and C should reduce the affinity of PGRN for TNFR, in turn increasing the amount of PGRN available for sortilin binding. At present, it is unknown whether such regulated proteolytic processing of PGRN occurs.

Though PGRN binds TNFR with high affinity, it is unclear if TNFR is the only PGRN receptor on leukocytes. TNFR-blocking antibodies prevent PGRN-induced signaling in effector T cells, suggesting that TNFR is the only functional PGRN receptor in these cells (Tang et al. 2011). However, other TNFR family members (such as RANK, NGFR, and FAS) also bind PGRN (albeit with a significantly lower affinity than TNFR). In addition, though sortilin expression in resting leukocytes is minimal, it is possible that sortilin is upregulated in the setting of inflammation or neurodegeneration (as is the case with PGRN). It will be interesting to determine whether PGRN is able to bind to and mediate signaling in leukocytes lacking TNFR.

Double knockout of TNFR1 and TNFR2 results in a neuroprotective effect in an animal model of Parkinson's disease, accompanied by a simultaneous decrease in the level of microglial activation (Sriram et al. 2006). PGRN-mediated inhibition of TNF α -induced TNFR activation might have similar effects. On the other hand, recent data indicate that activation of TNFR2 by inflammatory stimuli in microglia actually causes an anti-inflammatory (M2) response (Veroni et al. 2010). Also, it is important to note that both TNFR1 and TNFR2 are expressed by neurons. Although the functions of TNF α receptors in neurons are not as well-characterized as they are in leukocytes, these receptors appear to have the ability to directly influence neuronal survival (Marchetti et al. 2004; Alvarez et al. 2011). Additional experiments will be needed to determine how the binding of PGRN to TNFR regulates macrophages/microglia and neurons, and what the effects of this interaction on the function of these cells may be.

The identification of TNFR as a PGRN receptor may also explain why *Grn*^{+/-} mice fail to develop pathological changes associated with FTLN in humans. Systemic inflammatory conditions (such as infections) can precipitate or accelerate neurodegenerative diseases, both in animal models of neurodegeneration and in humans (Cunningham et al. 2005; Whitton 2007; Lee et al. 2008; Ehlenbach et al. 2010). Since TNF α is normally secreted by cells in these settings, it is tempting to speculate that loss of PGRN disinhibits TNF α -mediated signaling through TNFR, thereby lowering the threshold at which myeloid cells become activated. In patients with PGRN haploinsufficiency, it is possible that normally benign illnesses (such as mild infections) initiate a positive feedback loop (mediated by unbalanced autocrine or paracrine TNF α signaling) that leads to an aberrant and persistent proinflammatory state. Over the lifetime of a PGRN-deficient organism, the accumulation of these systemic insults could ultimately lead to neurotoxicity and neurodegeneration. In *Grn*^{+/-} mice housed in pathogen-free conditions, PGRN may be expressed at sufficient levels to prevent such a proinflammatory feedback loop. Exposure of *Grn*^{+/-} mice to pathogens might be necessary to precipitate neurodegenerative disease.

Concluding Remarks

The relationship between *GRN* haploinsufficiency and FTLT remains poorly understood, in part because PGRN appears to be involved in such a wide variety of cellular processes. As we have described, PGRN deficiency could cause neuronal dysfunction and/or neurodegeneration via impaired lysosomal function, dysregulated apoptosis, mislocalization of TDP-43, and/or neuroinflammation. The recent characterization of a mouse model of PGRN-deficient FTLT and the discoveries that sortilin and TNFR act as PGRN receptors are important milestones in FTLT research and should aid in determining the FTLT-relevant functions of PGRN. Such knowledge will hopefully lead to the rational design of new therapeutics for FTLT and other neurodegenerative diseases in the short term.

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