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Review Article

Circulating progranulin as a biomarker for neurodegenerative diseases

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Abstract: Progranulin is a growth factor involved in the regulation of multiple processes including tumorigenesis, wound repair, development, and inflammation. The recent discovery that mutations in the gene encoding for progranulin (GRN) cause frontotemporal lobar degeneration (FTLD), and other neurodegenerative diseases leading to dementia, has brought renewed interest in progranulin and its functions in the central nervous system. GRN null mutations cause protein haploinsufficiency, leading to a significant decrease in progranulin levels that can be detected in plasma, serum and cerebrospinal fluid (CSF) of mutation carriers. The dosage of circulating progranulin sped up the identification of GRN mutations thus favoring genotype-phenotype correlation studies. Researchers demonstrated that, in GRN null mutation carriers, the shortage of progranulin invariably precedes clinical symptoms and thus mutation carriers are "captured" regardless of their disease status. GRN is a particularly appealing gene for drug targeting, in the way that boosting its expression may be beneficial for mutation carriers, preventing or delaying the onset of GRN-related neurodegenerative diseases. Physiological regulation of progranulin expression level is only partially known. Progranulin expression reflects mutation status and, intriguingly, its levels can be modulated by some additional factor (i.e. genetic background; drugs). Thus, factors increasing the production and secretion of progranulin from the normal gene are promising potential therapeutic avenues. In conclusion, peripheral progranulin is a nonintrusive highly accurate biomarker for early identification of mutation carriers and for monitoring future treatments that might boost the level of this protein.

Keywords: Progranulin, haploinsufficiency, cut-off, blood, CSF, expression, frontotemporal, dementia, GRN, modulator

Progranulin

Progranulin protein was discovered independently by several investigators and was given several different names including acrogranin, epithelin precursor, proepithelin and prostate cancer cell derived growth factor [1]. Previous work revealed that full length progranulin is proteolytically cleaved into mature 6-kDa granulins (granulins A to G and paragranulin) [2, 3]. Progranulin and granulins are secreted growth factors involved in multiple biological functions such as cell growth and survival, embryogenesis, wound repair, and inflammation [4-7]. The recent discovery that mutations in the gene encoding for progranulin (GRN) cause frontotemporal lobar degeneration (FTLD), and other neurodegenerative diseases leading to dementia, has brought renewed interest in progranulin and its functions in the central nervous system. Since progranulin is known to be a secreted protein, experiments have been conducted to determine the potential role of extracellular progranulin in neuronal development and survival [8-10]. Van Damme's group was the first to suggest a neurotrophic role for progranulin demonstrating that this protein promotes neuronal survival and enhances neurite outgrowth in cultured neurons [8]. In addition, under stress conditions it has been demonstrated that progranulin enhances neuronal survival [11]. The neuroprotective effects of PGRN might be due, at least in part, to the activation of cell signaling pathways involved in cell survival [9, 12-14]. In addition to its role in neuronal cell survival and development, progranulin has also been speculated to play a role in excitotoxicity and synaptic transmission [10, 15]. Taken together, progranulin seems to be a critical player in neuronal development and synaptic maintenance:

thus the loss of progranulin in patients carrying pathogenic GRN null mutations could result in an increased susceptibility to neuronal death.

Progranulin as genetic determinant in neurodegenerative diseases

The first mutations in the GRN gene were discovered in 2006 in the FTLD families linked to chromosome 17 in which mutations in MAPT, till then the only genetic cause of FTLD, had been excluded [16-19]. The discovery of mutations in GRN as a genetic determinant for FTLD resulted in the rapid identification of a large number of families carrying GRN mutations, inherited in an autosomal dominant pattern. At present seventy -seven different mutations in more than 240 unrelated families have been described, which account for 16% of families worldwide carrying a neurodegenerative disease causing mutation [www.molgen.ua.ac.be/FTDmutations, 20-27]. Mutation in the GRN gene is a common cause of FTLD: in subpopulations of patients with familial FTLD, the GRN mutation frequency can be up to 26% [21, 28-32]. Although there are a large number of distinct GRN mutations, several mutations are recurring in a number of independently ascertained families: the most common GRN mutations worldwide are the GRN p.Arg493X (c.1477C>T) [33], the Belgian GRN p.0 (c.138+1G>C) [17, 34], and the GRN p.Leu271LeufsX10 (c.813-816delCTCA), which is the most frequent mutation in Italy [29, 31, 35-37]. We provided evidences that the numerous cases with this specific GRN mutation in Lombardy can be traced to a single founder and we dated the origin of this mutation in the Middle Ages, at the turn of the first millennium [38]. Of note, the GRN p.Leu271LeufsX10 mutation was reported for the first time in homozygous state in a family from a village in Lombardy. A pleiotropic effects of GRN mutations in the heterozygous or homozygous state was suggested: while GRN p.Leu271LeufsX10 mutation cause late onset neurodegenerative disease in the heterozygous state, the homozygous mutation was found in two siblings who had neuronal ceroid lipofuscinosis, an early onset form of severe retinal disease with seizures, ataxia, and cognitive change [39]. Mutations are located throughout the entire GRN gene sequence - apart from the most 3' exon - and include different types of mutations: nonsense and splice-site mutations as well as small insertions and deletions, leading to a shift in the normal reading frame. Nonsense, splice-site and frameshift mutations cause haploinsufficiency due either to mRNA nonsense-mediated decay or to nuclear degradation of transcripts retaining the first intron of the GRN gene [16, 17]. Thus, it is believed that FTLD results from progranulin haploinsufficiency rather than the accumulation of mutant protein [40-43]. Loss of progranulin may also result from larger GRN deletions, including deletion of the complete GRN gene [44, 45]. In addition, missense GRN mutations were also observed in some sporadic FTLD patients [46, 47], in Alzheimer's disease patients (AD) [48] and in some patients with amyotrophic lateral sclerosis (ALS) [49-51]. However, few missense mutations were demonstrated to impair progranulin secretion/function [52-54], while the pathogenicity of other missense mutations is still unclear. Mutations in GRN have been associated with a broad spectrum of clinical phenotypic variability. FTLD comprises a clinically heterogeneous group of disorders, characterized by atrophy of the prefrontal and/or anterior temporal lobes. The main clinical subtypes of FTLD are behavioral frontotemporal dementia, in which social and executive dysfunction predominate, semantic dementia and progressive primary non fluent aphasia, with prominent early language disturbances [55-57]. FTLD is also clinically and pathologically related to motor neuron disease (FTD-MND), as well as to the parkinsonian syndromes, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) [58]. Different FTLD clinical subtypes as well as the related disorders FTD-MND, PSP and CBS may be present even among family members carrying the same GRN mutation [18, 23, 24, 59-62]. In addition, AD, Lewy body dementia (DBL), ALS and Parkinson disease (PD) have been reported in GRN positive families [23, 29, 45, 50, 63, 64]. Eventually, null mutation in the GRN gene has been detected in patients with a premorbid psychiatric history as well as in schizophrenic patients [36, 65]. Along with symptoms heterogeneity, a wide range in age at disease onset, ranging from 35 to 87 years, has been reported [www.molgen.ua.ac.be/FTDmutations, 20-27]. Since all GRN null mutations are expected to cause the disease through a common mechanism, the highly heterogeneous clinical presentations in patients carrying GRN mutations suggests that other genetic, epigenetic, and/or environmental factors might modify the phenotypic presentation of the disease. Monozygotic twins provide a unique opportunity to better under-

stand the manifestations of autosomal dominant inherited neurodegenerative diseases. An extensive clinical and neuropsychological examinations has been recently reported for a pair of monozygotic twins carrying a GRN null mutation [66]: as compared with the heterogeneity seen within families with GRN mutations, these twins showed stronger similarities in clinical symptoms and neuroimaging profiles, thus demonstrating the importance of shared genetic profiles beyond environmental influences in the symptomatic expression of the disease. Accordingly, we demonstrated that the GRN p.Leu271LeufsX10 mutation in patients bearing two different founder haplotypes is associated with dissimilar clinical phenotype at onset, further attesting the role played by genetic background in the profound phenotypic heterogeneity associated with GRN-related neurodegeneration [38].

Progranulin as a biomarker in neurodegenerative diseases

Is progranulin a useful diagnostic biomarker for neurodegenerative diseases? The answer is: yes. Recently dosage of circulating progranulin has been proposed as a useful tool for a quick and inexpensive large-scale screening of GRN mutations carriers [40-43]. All GRN mutations identified thus far cause disease through a uniform disease mechanism, i.e., the loss of functional progranulin or haploinsufficiency. Thus the shortage of progranulin is thought to underlie neuronal death. Earliest evidence came from cerebrospinal fluid (CSF) from FTLD patients: progranulin levels were significantly reduced in CSF of carriers of GRN mutations [8, 40]. Measurements performed on blood showed that a non-intrusive approach is suitable and that progranulin detectable in peripheral compartments is less than the 50% expected by haploinsufficiency mechanism. Two independent studies (i.e. Italian and American) established a very similar cutoff value for the detection of *GRN* mutation in human plasma using a commercially available ELISA kit. We initially reported that – in our Italian FTLD cohort – a progranulin cutoff level of 110.9 ng/ml was 92.8% specific and 100% sensitive to identify GRN mutations [40]; Finch and colleagues set this cutoff value at 112 ng/ml with 100% sensitivity and specificity [41]. Thus, plasma/serum screening sped up the identification of GRN null mutations [23, 24, 27, 37, 61, 67-69]. Successively, in order to refine the previously proposed cutoff and define the optimal plasma progranulin cutoff value for predicting null progranulin mutations in neurodegenerative diseases, we performed a retrospective evaluation of old and new data collected thus far in three different Northern Italian research clinical centers [43]. The cutoff values obtained using a large group of GRN mutated cases (n=72) and two different reference groups (n=309 cognitively healthy subjects; n=635 patients with incipient/overt progranulin-unrelated neurodegeneration) were very similar (61.6 and 61.55 ng/ml, respectively). We established a new plasma progranulin protein cutoff level of 61.55 ng/mL that identifies, with specificity of 99.6% and sensitivity of 95.8%, null mutation carriers among subjects attending to a memory clinic [43]. Of note, since progranulin dosage may vary slightly based on the experimental setting, it is important to include in the analysis mutation carriers as positive controls. Researchers examined progranulin protein levels in plasma/serum of both affected and unaffected GRN null mutation carriers and demonstrated that the shortage of progranulin invariably precedes clinical symptoms and thus mutation carriers are "captured" regardless of their disease status. Thus, circulating progranulin is a valid antecedent biomarker that will enable the prevention of GRN related neurodegeneration once a cure for this disease is available. Is there a relationship between levels of circulating progranulin and disease phenotype in GRN mutation carriers? Phenotypic variability is a common theme in progranulin-related neurodegeneration. The following are some key points: i) missense GRN mutations, whose pathogenic role is still unclear, seem to induce only a partial loss of progranulin protein expression; ii) in subjects carrying heterozygous null mutations circulating progranulin concentration is low regardless of the type of null mutations; usually these mutations cause FTLD and related disorders (CBS, PSP, FTD-MND); in these patients, a significant disease anticipation is associated with the lowest progranulin levels [43]; iii) in subjects carrying homozygous GRN null mutations, where circulating progranulin was undetectable, a strikingly different disease phenotype was observed since patients developed a rare early onset neurological disorder [39]. The normal progranulin values in FTLD patients, as well as in AD, MCI, ALS, PD and patients with multiple sclerosis [40, 41, 43, 67, 70-73] without GRN mutations, suggest that shortage of progranulin is restricted to neurodegeneration caused by GRN null mutations.

Progranulin regulators

Given that GRN mutations cause a loss of GRN in patients and even in pre-symptomatic individuals, GRN is a particularly appealing gene for drug targeting, in the way that boosting its expression may be beneficial for mutation carriers, preventing or delaying the onset of GRN-related neurodegenerative diseases. In carriers of GRN null mutations, the normal allele of GRN is still functional. Thus, factors increasing the production and secretion of progranulin from the normal gene are promising potential therapeutic avenues. However physiological regulation of progranulin expression level is only partially known. In a large multicenter study on cognitively healthy subjects and patients with incipient/overt neurodegeneration we demonstrated that plasma progranulin are not influenced by age, gender and body mass index [43]. The wide range in plasma GRN levels, in patients with progranulin-unrelated neurodegenerative diseases as well as in healthy controls, suggests that other genetic and environmental factors may play a role in regulating progranulin levels [41, 43]. Several genetic variants have been proposed to modulate progranulin protein levels. The first investigated gene was the GRN gene itself: a common genetic variant of GRN, rs5848, proposed as a genetic risk factor for FTLD, was demonstrated to regulate progranulin levels by modulating the microRNA (miRNA) miR -659 binding to the GRN 3'- untranslated region (UTR). Consistently, significantly reduced progranulin levels were observed in brain lysates of FTLD cases carrying the risk allele [73]. In an independent study, the rs5848 polymorphism was shown to significantly influence serum progranulin levels [74]. Two recent studies identified additional miRNA binding sites in the 3'-UTR of human GRN mRNA as potential regulators of GRN expression [75, 76]. A further level of control of the mRNA transcription is represented by the degree of promoter methylation. Of note, it has been recently demonstrated that GRN promoter methylation is significantly increased in patients with sporadic FTLD as compared with controls, likely leading to decreased expression of GRN [77]. A genome wide approach first implicated the SORT1 gene (encoding for sortilin protein) as an important regulator of GRN levels [78]. Interestingly, at the same time sortilin was identified as a progranulin receptor by Hu and collaborators. Authors also provided evidence that sortilin-mediated progranulin endocytosis and its targeting to lysosomes determines levels of progranulin protein *in vitro* and *in vivo* [79]. Recently, we demonstrated that genetic variants in the TMEM106B gene significantly reduce the disease penetrance in patients carrying GRN null mutations by modulating progranulin protein levels [80]. A following study on an independent large collection of GRN carriers showed an association of TMEM106B with age at disease onset, with the protective allele delaying the age at onset by 13 years [81]. Furthermore, it has been proposed that TMEM106B gene variants, modulating progranulin level, might influence the risk for sporadic FTLD [81-83]. A hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (C9ORF72) gene has recently been described as a cause of familial and sporadic FTLD; this expansion, along with GRN null mutations, represent a major genetic determinant in the disease [84, 85]. Despite the fact that both GRN mutations and C9ORF72 expansions show TDP-43 pathology, and thus probably share some disease mechanism, a recent study demonstrated that plasma progranulin levels are not modulated by the presence of C9ORF72 repeat expansion [86]. Along with human genetics, cellular studies were employed to identify progranulin regulators. Capell et al. screened for compounds capable of stimulating progranulin protein production and/or secretion and found several alkalizing reagents - including clinically used drugs - rescuing progranulin deficiency in primary cells derived from human patients with GRN null mutations [87]. A parallel study, by Cenik et al., performed a screening of chemical compounds able to enhance GRN expression, and identified suberoylanilide hydroxamic acid, a Food and Drug Administration-approved histone deacetylase inhibitor, increasing GRN mRNA and protein levels and thus restoring progranulin expression in GRN haploinsufficient cells [84]. Taken together, studies on progranulin modulators are of paramount importance since highlight possible targets/drugs as candidates for progranulin-related neurodegenerative diseases treatment. To ensure correct dosing of the drugs and to monitor their effects on progranulin, dosage in plasma and CSF will be essential.

Outlook

An immediate need to be addressed in order to provide a solid basis for the establishment of

risk-stratified cohorts and for upcoming multicentric diagnostic and therapeutic trials is the development of optimally informative biomarkers. Peripheral progranulin is a nonintrusive highly accurate biomarker that warrants screening in patients with cognitive and movement disorders, and people with mild cognitive impairment; the screening is foreseen specifically for, but not limited to, those that have a positive family history of neurodegenerative disease. Before it is included into diagnostic criteria for dementias, further standardization of the test and harmonization of its use are required. From a translational perspective, targeting mutation carriers could offer a unique model to test disease-modifying or preventing drugs in clinical trials. A better understanding of the regulation of GRN expression in the central nervous system will be crucial to gain insight in the disease pathogenesis of FTLD and related neurodegenerative disorders. Recent publications have now identified the receptors for progranulin, which will hopefully lead to additional therapeutic targets. In the last year, drug screens have been conducted to identify pharmacological regulators of circulating progranulin to be used as potential treatments for progranulin haploinsufficiency. Eventually, the level of circulating progranulin is a useful marker both for early identification of at risk asymptomatic subjects and for monitoring future treatments that might boost the level of this protein. Nevertheless, since it is still unclear how the levels of progranulin in the periphery correlate with levels in CSF or brain, monitoring the effectiveness of drugs based on progranulin in serum and plasma should be considered with caution.

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Conflict of interest

None to declare.

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