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Progranulin as a biomarker and potential therapeutic agent

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Progranulin is a cysteine-rich secreted protein with diverse pleiotropic actions and participates in several processes, such as inflammation or tumorigenesis. Progranulin was first identified as a growth factor and, recently, it was characterised as an adipokine implicated in obesity, insulin resistance and rheumatic disease. At a central level, progranulin acts as a neurotropic and neuroprotective factor and protects from neural degeneration. In this review, we summarise the most recent research advances concerning the potential role of progranulin as a therapeutic target and biomarker in cancer, neurodegenerative and inflammatory diseases.

Introduction

Progranulin (PGRN) was first identified as an acrosomal glycoprotein in 1990, namely acrogranin, synthesised during spermatogenesis [1]. PGRN is also known as granulin-epithelin precursor (GEP) [2], proepithelin [3], GP88 [4] and PC-cell-derived growth factor (PCDGF) [5]. Owing to its pleiotropic nature, PGRN is secreted by a broad range of tissues and it is expressed by a wide variety of cell types, including epithelial cells, neurons, haematopoietic cells, skeletal muscle cells [6], macrophages [7], chondrocytes [8,9], adipocytes [10] and endothelial cells [11].

Since the discovery of this glycoprotein, the multifunctional properties of PGRN have been unravelled. It is implicated in multiple biological and pathological processes, such as cell growth, tumorigenesis [12], embryogenesis [13], wound healing [14], inflammation, immunity, infection [15], insulin resistance [10] or diabetes [16]; and lack of it is related to neurodegeneration [17]. PGRN overexpression was associated to the onset of different types of cancer [18–20] and PGRN downregulation was related to inflammatory diseases, like osteoarthritis (OA) [21] or rheumatoid arthritis (RA) [22]. Otherwise, null mutations within the gene that encodes PGRN cause frontotemporal lobar degeneration (FTLD) [23,24]. In the past few years, different studies have shed light on how PGRN performs its actions. In fact, the role of PGRN in

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inflammation has been studied in detail, with anti-inflammatory properties through interaction with tumour necrosis factor receptor (TNFR) [25]. Despite its anti-inflammatory role, it is possible that PGRN has multiple roles in inflammation. In 2012, PGRN was described as a key adipokine mediating high-fat diet-induced insulin-resistance by inducing upregulation of interleukin (IL)-6 expression in adipose tissue [10]. Thus, the pro- or anti-inflammatory function of PGRN might depend on the target tissue. In brief, PGRN can act either as a growth factor, an anti-inflammatory agent or an adipokine. As outlined above, PGRN is involved in multiple processes with diverse actions. Thus, the aim of the present review is to present the potential of PGRN as a therapeutic target in cancer, neurodegenerative and inflammatory diseases.

PGRN biology: structure and receptors

Human PGRN is encoded by the *GRN* gene, located on chromosome 17q21.32, which contains 12 protein-coding exons that result in three isoforms [26]. It is a protein consisting of 593 amino acids and a molecular weight of 68.5 kDa [27,28]. Owing to its highly glycosylated character, it commonly migrates around 88 kDa on a western blot. The mouse ortholog *Grn* is located on chromosome 11 and encodes a 589 amino acid protein, with 79% homology to the human PGRN protein [28].

PGRN has emerged as the prototypic member of a family of structurally unique proteins, evolutionarily conserved, related to growth factors [29]. Full-length PGRN consists of a secretory N-terminal signal peptide of 17 amino acids and seven and a half granulin domains [5]. These granulins are named, from the N terminus to the C terminus, granulins p (paragranulin domain), G, F, B, A, C, D and E. Granulin domains are composed of tandem repeats of a 12-cysteine motif [26]. The molecular structure of individual granulin domains consists of six parallel stacked beta-hairpins held together by six disulfide bonds [30]. After secretion, proteolytic cleavage of full-length protein can take place at linker regions between the granulin domains. Serine and threonine proteases, such us matrix metalloproteinase (MMP)-9 [31], MMP-12 [32], MMP-14 [33], a disintegrin and metalloproteinase with thrombospondin type I motif 7 (ADAMTS-7) [34], neutrophil-secreted elastase and proteinase 3 [35], can release individual granulin peptides of 6 kDa (Fig. 1). Incubation of full-length PGRN with these proteases does not always result in the release of individual 6 kDa fragments as would be expected if the precursor protein was completely processed to granulin domains. At least five intermediate products larger than 15 kDa seem to be present after digestion with all of these proteases [17,36]. Moreover, secretory leukocyte protease inhibitor (SLPI) binds directly to PGRN, blocking the proteolysis by elastase. Similarly, high-density lipoprotein (HDL) apolipoprotein AI can form a complex with PGRN suppressing granulin conversion [7].

Full-length PGRN and granulins are biologically active, although whether their effects are opposite or overlapping has not yet been clearly elucidated. For instance, PGRN plays an active

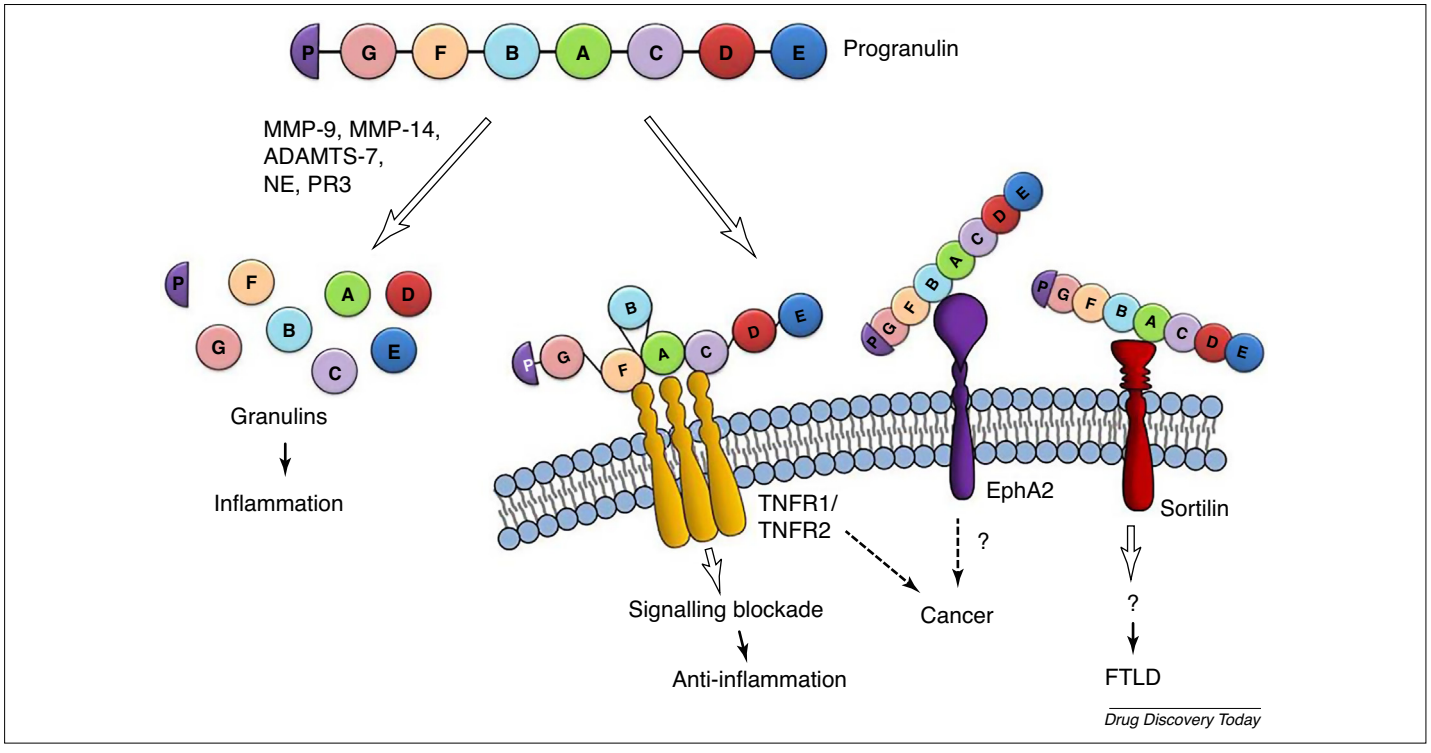

FIGURE 1

Schematic representation of progranulin (PGRN) and its receptors. Each circle represents granulin domains. PGRN can be subject to proteolytic cleavage by matrix metalloproteinase (MMP)-9, MMP-14, ADAMTS-7 (a disintegrin and metalloproteinase with thrombospondin type I motif 7), neutrophil-secreted elastase (NE) and proteinase (PR)3. Granulin individual peptides involve inflammatory effects. By contrast, full-length PGRN has an anti-inflammatory role by tumour necrosis factor receptor (TNFR) binding. Interactions between PGRN and sortilin have been implicated in frontotemporal lobar degeneration (FTLD) onset. Also, tumorigenic actions of PGRN are explained by TNFR2 or EphA2 binding.

part in resolution of inflammation, whereas granulins seem to be proinflammatory. Granulin B, but not PGRN, stimulates interleukin (IL)-8 expression in epithelial cells [36]. However, granulin E was reported to support neuronal cell survival similarly to PGRN [37].

It is not yet clear whether there is a unique receptor for PGRN, given the wide range of effects mediated either by PGRN or granulins in different cell types. The observation that PGRN is a secreted protein that is internalised through an endocytic mechanism suggests the existence of a PGRN cell-surface receptor. In fact, two cell-surface receptors for PGRN, but not for individual granulins, have been proposed: sortilin and TNFR1 and TNFR2 [38]. The first cell-surface protein shown to bind progranulin was sortilin, which mediates the uptake of extracellular PGRN and regulates its extracellular levels in the central nervous system (CNS) [39,40]. Sortilin was proposed as a neuronal receptor for PGRN, although the contribution of sortilin to PGRN function remains unclear [41,42]. Otherwise, binding to TNF receptors by PGRN has been demonstrated to have anti-inflammatory results [25] (Fig. 1). PGRN binding to TNFR1 and TNFR2 has been extensively studied. TNFR1 is expressed ubiquitously and promotes proinflammatory signalling pathways; by contrast, TNFR2 is mainly expressed by haematopoietic cells and is related to anabolic responses. PGRN demonstrated higher affinity for TNF receptors, especially TNFR2 when compared with TNF-α. In contrast to TNF-α, which demonstrated higher affinity for TNFR1 than TNFR2, PGRN exhibited comparable binding affinity for TNFR1 and TNFR2 [25]. To identify the domains of PGRN involved in TNF receptor interactions, there were recognised granulins F, A and C as well as the adjacent linker region. Recently, a minimal engineered molecule composed of half units of granulins F, A and C plus linker regions named atsttrin was developed (antagonist of TNF/TNFR signalling via targeting to TNF receptors) [25].

Recent work has shown that EphA2, a member of the large family of ephrin receptor tyrosine kinases, is a functional signalling receptor for PGRN. Activation of EphA2 by PGRN stimulated downstream mitogen-activated protein kinase and Akt, which could explain the role of this adipokine in cancer, although confirmation by independent laboratories is needed [43] (Fig. 1). Noteworthy, recent investigations have shown that PGRN-mediated regulation in several types of cancers depends on TNFR2 [44–46]. Despite these findings, a functional and specific PGRN receptor remains elusive.

PGRN as a therapeutic target

All previous research indicates that PGRN has emerged as an endogenous regulator of TNF receptor signalling [47]. Despite its anti-inflammatory actions, full-length PGRN could not be used directly as a therapeutic target owing to (i) its multifunctional properties, because it promotes tumorigenesis as growth factor [48], and (ii) its susceptibility to proteolytic cleavage into proinflammatory granulins [36]. The development of the abovementioned engineered protein atsttrin avoids these disadvantages. Moreover, it was found to be more effective in delaying the onset of inflammation than PGRN [49]. The discovery of atsttrin might suppose the next-generation therapeutic target for inflammatory diseases [22,50] (Fig. 2).

Rheumatoid arthritis

The development of atsttrin was made in the field of inflammatory arthritis, so its effects on the pathophysiology of RA have been extensively studied and reviewed [22,25,47,49,51,52]. In brief, atsttrin administration results in reduced disease severity in collagen-antibody-induced arthritis (CAIA) and in the collagen-induced arthritis (CIA) mouse model. Notably, atsttrin shows more-potent anti-inflammatory activity than PGRN, possibly as a result of the absence of a complete granulin domain with proinflammatory actions [25,47].

TNF-α is the main cytokine causing cartilage destruction in RA patients. Current biological therapies target proinflammatory cytokines like TNF-α. However, an alternative approach to block cytokine receptors has also emerged. Anakinra, which targets IL-1 receptor (IL1R), has shown clinical efficacy. Therefore, atsttrin was present as an 'anti-TNFR' approach, which is an alternative for patients whose anti-TNF-α therapies have failed [22]. In a mouse model of induced arthritis, atsttrin was more effective in reducing inflammation than etanercept, a fusion-soluble TNFR2 protein that inhibits TNF-α [25]. Atsttrin demonstrated high stability with a long half-life (~5 days) and was well absorbed via intraperitoneal administration, as shown in pharmacokinetic assays in mice [25].

Screening the associations of atsttrin with all members of the TNFR subfamily led to the discovery that, in addition to TNFR, PGRN–atsttrin directly bound to TNFR superfamily member 25 [TNFRSF25, also known as death receptor 3 (DR-3)] and inhibited the interaction between DR-3 and its TNF-like ligand 1A (TL1A). In addition, atsttrin inhibited TL1A activity over osteoclastogenesis *in vitro* [53,54]. Despite the promising data, thus far no clinical trials have been performed with atsttrin.

Osteoarthritis

PGRN has been reported to protect against OA through interacting with TNF-α and β-catenin signalling. Deficiency of PGRN leads to an OA-like phenotype in aged mice, and local injection of recombinant PGRN protein into a surgically-induced OA model attenuated cartilage degradation and exerted therapeutic effects [21]. Recently, our group demonstrated that PGRN could counteract IL-1-driven inflammation via TNFR1 in human OA chondrocytes [55]. The chondroprotective role of PGRN in OA was independently reproduced by PGRN-derived atsttrin. Intraarticular injection of MSC–atsttrin (genetically modified mesenchymal stem cells that expressed recombinant atsttrin) prevented the progression of degenerative changes and TNF-α-mediated upregulation of MMP-13 and ADAMTS-5 in a surgically induced OA mouse model [56]. This approach suggests that suppression of TNF-α signalling could be an effective strategy for OA treatment and that intraarticular injection of MSC–atsttrin could be a promising therapeutic intervention [56,57].

Bone regeneration

PGRN is also involved in bone metabolism and can induce osteoblastogenesis. Besides being induced by bone morphogenetic protein (BMP)2, PGRN is also required for BMP2-mediated ectopic bone formation. PGRN was shown to be a key downstream mediator of BMP2 signalling. High expression levels of proinflammatory TNF-α within bone can decelerate and impair bone regeneration through inhibition of BMP2 signalling [58]. Thus, PGRN

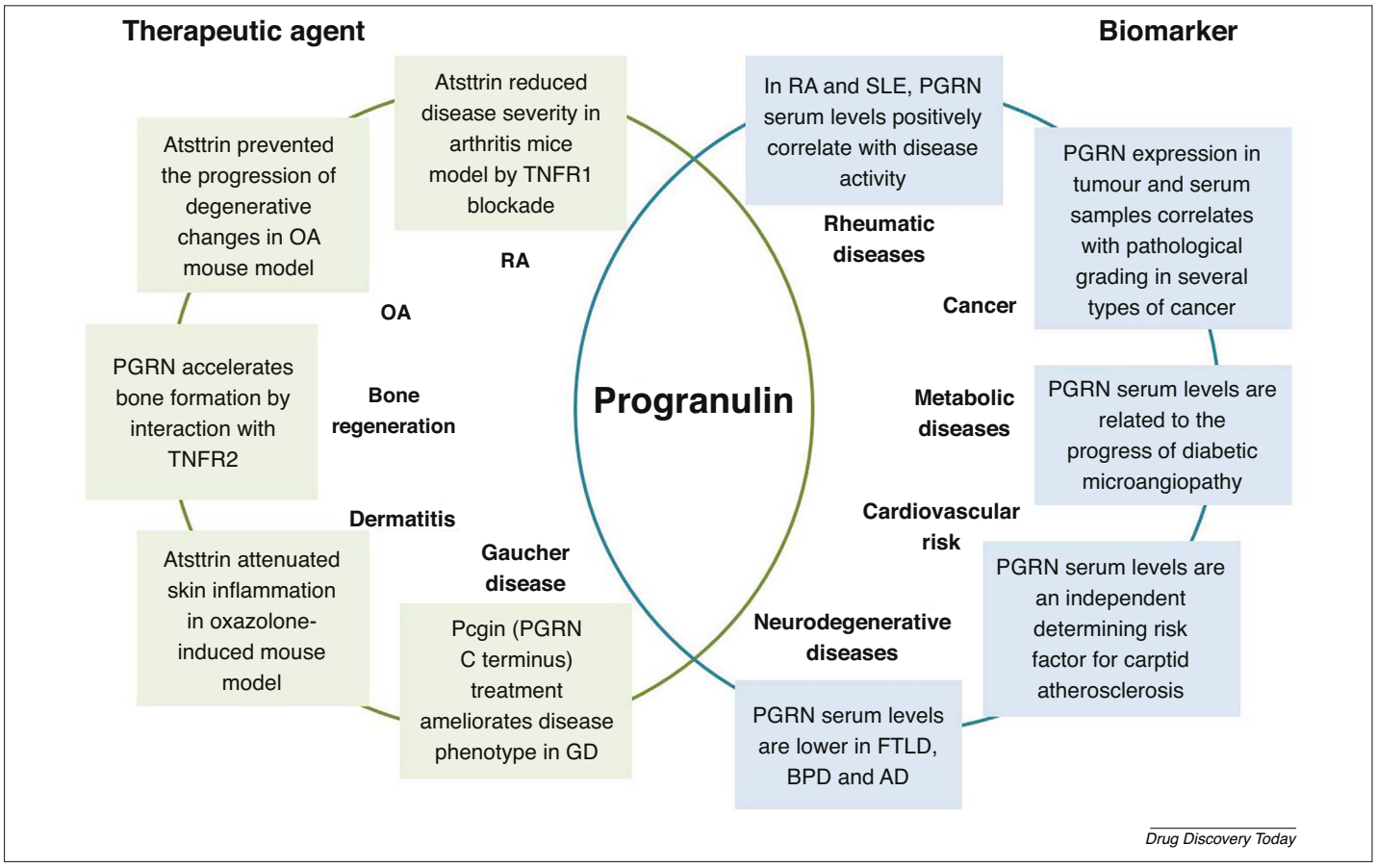

FIGURE 2

Progranulin (PGRN) as a therapeutic agent and biomarker. PGRN and, in particular, its derived peptide attstrin have been described as therapeutic agents in rheumatoid arthritis (RA), osteoarthritis (OA), bone regeneration, dermatitis and Gaucher disease. Moreover, it is proposed as a biomarker for RA and systemic lupus erythrematosus (SLE), several types of cancer, diabetic microangiopathy, cardiovascular risk and neurodegenerative diseases, such as frontotemporal lobar degeneration (FTLD), bipolar disorder (BPD) and Alzheimer's disease (AD).

interaction with TNFR1 has been found to prevent TNF-α-mediated osteoclastogenesis and PGRN interaction with TNFR2 to accelerate bone formation.

Recently, it was reported that atsttrin could stimulate bone regeneration through TNFR signalling inhibition. Actually, a decreased number of TNF-α-positive cells and the enhancement of bone regeneration processes have been observed in a mouse model of bone surgical damage by using 3D-printed alginate (Alg)–hydroxyapatite (nHAp) scaffolds with atsttrin incorporated inside. The anti-inflammatory and regenerative roles of atsttrin highlight the potential of this engineered protein as a promising therapeutic agent in bone repair [59].

Dermatitis

In addition to inflammatory disorders of the musculoskeletal system, PGRN–TNFR interactions have also been described in inflammatory diseases of the skin, such as dermatitis. PGRN expression was found upregulated in the skin of psoriasis patients and $PGRN^{-/-}$ mice show more-severe inflammation in an oxazolone-induced model of dermatitis [60]. Moreover, C-X-C motif chemokine ligand 9 (CXCL9) expression was strongly upregulated in PGRN knockout mice and its level correlates with severity of inflammation in a dermatitis model [61]. Treatment with PGRN derived atsttrin-attenuated skin inflammation in an oxazolone-induced mouse model. Hence, loss of PGRN enhanced, whereas atsttrin reduced, inflammation severity in dermatitis. The protective role of atsttrin was probably due to its ability to inhibit nuclear factor (NF)-κB signalling [60]. Altogether, atsttrin could represent a potential therapeutic agent for prevention and treatment of inflammatory skin diseases.

Gaucher disease

Very recently, a novel function of PGRN, as a co-chaperone with the heat shock protein (HSP)70 disaggregation system, was described. PGRN–HSP70 prevents the aggregation of lysosomal glucocerebrosidase (GCase) and lysosomal integral membrane protein (LIMP)2 in the cytoplasm. These findings have implications in Gaucher disease (GD), the most prevalent lysosomal storage disease that results from deficient GCase. In pathological conditions, GCase–LIMP2 complex aggregates in the cytoplasm. HSP70 is recruited to GCase–LIMP2 complex through PGRN as an indispensable co-chaperone, to unlock the disaggregation of GCase–LIMP2 [62,63].

Because PGRN has oncogenic properties, potential treatment of GD with this adipokine is limited. For this purpose, a 98-amino-acid peptide of C-terminal PGRN termed 'Pcgin' (PGRN C terminus

for GCase interaction) has been developed. Pcgin is a 15 kDa PGRN-derived protein that retains binding capacity to GCase and HSP70 without oncogenic activity. Pcgin treatment effectively ameliorates the disease phenotype in GD patient fibroblasts and animal models [63]. These findings provide evidence for potential therapeutic interventions using PGRN for lysosomal storage diseases.

Frontotemporal lobe degeneration

Mutations in the progranulin gene are a major cause of FTLD. 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 [64]. Nevertheless, given PGRN duality, with decreased levels in neurodegeneration and upregulated expression in cancer, increasing its levels could lead to tumorigenesis.

In recent years, several research groups have identified regulators of PGRN levels. Most notably, suberoylanilide hydroxamic acid was shown to increase GRN transcription while Bafilomycin A, a vacuolar ATPase inhibitor, increased PGRN levels in a post-translational manner [65,66]. In the study of Nicholson and colleagues, prosaposin (PSAP) was identified as a novel regulator of PGRN levels and PGRN oligomerisation [67]. However, no PGRN-modifying therapies are currently available to patients with neurodegenerative disorders.

The potential of PGRN as a biomarker

As a growth factor, PGRN has become increasingly relevant in recent years as a potential clinical biomarker in cancer. PGRN levels in biological fluids are generally low, being upregulated in the inflammatory state, which strongly indicates the potential of its use as a biomarker of disease onset and progression in several pathologies (Fig. 2).

Cancer

PGRN is a growth factor implicated in proliferation and tumorigenesis [12,68]. It was initially reported as PGRN overexpression in breast cancer tissues, and later in several human cancers, whereas normal tissues have been shown to express little or no PGRN. PGRN expression in breast cancer tumour samples was significantly correlated with tumour size, lymph node metastasis and angiogenesis [19,69]. Because PGRN is a secreted protein, an enzyme immunoassay to measure circulating levels of PGRN was recently developed. In a prospective longitudinal clinical study, it was found that serum PGRN levels in breast cancer patients were elevated to 40 ng/ml in early stages and over 100 ng/ml in later stages of breast cancer [70]. Moreover, serum PGRN levels were clinically significant for predicting recurrence in patients with hormone-receptor-positive breast cancer during adjuvant tamoxifen therapy [71]. Because PGRN can be measured in tumour tissue and in blood samples, this protein could be a valuable prognostic for breast cancer. Additionally, it was demonstrated that PGRN is expressed in non-small-cell lung cancer (NSCLC) but not in normal tissues or in small-cell lung cancer [72]. PGRN serum levels were elevated in stage IIIb/IV patients compared with controls and the association between PGRN serum levels and worse outcome disease was also reported. The lack of a serum-based biomarker for diagnosing or monitoring NSCLC during treatment and follow-up presents PGRN as a promising biomarker for disease prognosis as well as a potential therapeutic target in NSCLC [72].

PGRN has also been demonstrated to be a potent growth factor for epithelial ovarian cancer (EOC) [73]. In malignant ovarian tumours, PGRN was found overexpressed compared with benign and healthy ovarian tissues [74]. Some authors proposed PGRN as a predictive biomarker for EOC; these authors found that plasma levels of PGRN were independently associated with progression-free survival and overall survival concluding that PGRN levels might be useful as a potential screening tool for aggressive subtype EOC [75]. In another approach to identify early-stage disease markers for EOC, it has been reported that PGRN plasma levels were not significantly increased in patients with early-stage or late-stage EOC as a whole but they found association between increased PGRN levels and decreased overall survival in advanced EOC [76]. With regard to cervical cancer, PGRN was found to be upregulated in cervical cancer tissues [77,78]. In addition, PGRN contributes to cell proliferation, at least in part by inhibiting cell senescence [79], and promotes the malignant growth and transformation of cervical cells [77]. Although little is known about the role of PGRN in cervical cancer, it seems to be a likely candidate as a diagnostic biomarker.

PGRN expression is upregulated in astrocytoma sample tissues, the most frequent malignant primary brain tumour, and its expression positively correlates with pathological grading. PGRN serum levels from glioblastoma (astrocytoma grade IV) patients are also increased [80]. PGRN expression in biopsied glioblastoma tissue was found to be an independent prognostic factor for overall survival, suggesting that PGRN might be a potential prognostic biomarker for high-grade astrocytomas, like glioblastoma [80]. Furthermore, immunohistochemical (IHC) analysis of biliary tract carcinomas showed an association between PGRN overexpression and poor progression-free survival in advanced biliary tract cancer. This evidences that PGRN expression by IHC analysis might help predict treatment outcomes in a prognostic role [81].

Inflammatory and metabolic diseases

Recently, it was found that administration of PGRN caused glucose intolerance and insulin insensitivity through triggering autophagy via TNFR1 in the adipose tissue of mice, and ablation of PGRN prevented diet-induced insulin resistance [82]. Specifically, PGRN might mediate adipose insulin resistance, at least in part, by inducing autophagy via activated oxidative stress and endoplasmic reticulum stress [83]. To this regard, PGRN serum levels were closely related to the progress of diabetic microangiopathy, suggesting that PGRN could be considered as a marker for diabetic microangiopathy and its severity. Thus, PGRN levels in type 2 diabetes patients could be a potential therapeutic target for the management of diabetic microangiopathy [84].

Cardiovascular risk

Regarding cardiovascular diseases, different approaches to PGRN implications have been emerging in recent years. PGRN was found to be expressed in human carotid samples, exerting anti-inflammatory actions; however, its degradation into granulins enhanced inflammation in atherosclerotic plaque, contributing to atherosclerosis progression [85]. PGRN is likely to be implicated in the pathogenesis of atherosclerosis, given that PGRN deletion

exacerbates atherosclerosis in ApoE knockout mice [86], and PGRN treatment protects against inflammation state subjacent atherosclerosis [87]. Moreover, it was reported that serum PGRN level was an independent determining risk factor for carotid atherosclerosis in subjects without metabolic syndrome [88]. Very recently, PGRN was proposed as a serum biomarker that independently predicts all-cause mortality and adverse functional outcome in the short term in acute ischaemic stroke patients [89]. Besides this, PGRN was also proposed as a novel biomarker for cardiovascular risk in patients with polycystic ovary syndrome [90].

Neurodegenerative diseases

PGRN has been recognised as a useful diagnostic biomarker for FTLD owing to the discovery of null mutations in the *GRN* gene [91]. It has been reported that PGRN promotes neuronal survival and neurite outgrowth in cultured neurons [37], and a PGRN knockout mouse model reproduces some core features of FTLD [92]. FTLD is a heterogeneous disorder, characterised by cognitive impairment and behavioural dysfunction. The clinical overlapping with other dementias makes diagnosis even more awkward. Thus, the measurement of PGRN can identify patient carriers of *GRN* gene mutations, showing decreased levels of PGRN in blood and cerebrospinal fluid because of loss of functional PGRN or *GRN* haploinsufficiency [93–95]. This reduction in PGRN serum levels could distinguish not only between carriers and noncarriers of the mutation but also mutation carriers that remain unaffected by the disease could be identified with 100% sensitivity and specificity [93,95].

As described above, loss-of-function mutations in *GRN* are known to cause FTLD. However, PGRN mutations have also been reported to be present in Alzheimer's disease (AD) [96]. Several studies suggest that PGRN has a role in AD pathogenesis through different pathways [97]. PGRN levels were lower in AD brains compared with control brains from nondemented individuals [98]. Furthermore, molecular links between neurodegeneration and psychiatric phenotype have been reported. Because mutations in *GRN* cause FTLD, bipolar disorder (BPD) could share a common pathogenesis [99]. In fact, PGRN plasma levels were found to be significantly lower in BPD patients than in controls [100]. This finding was confirmed by other authors who suggested peripheral PGRN levels as a biomarker for BPD [101].

Rheumatic inflammatory and autoimmune diseases

Regarding the role of PGRN in the pathogenesis of RA [22], it has been shown that serum PGRN levels are upregulated in RA patients and related with disease activity. Moreover, serum PGRN positively correlated with disease activity score 28 (DAS28) and C-reactive protein (CRP) – two parameters employed for RA diagnosis [102]. Moreover, a prospective study showed changes in serum PGRN levels following initiation of TNF-antagonist therapy. Although pre-treatment serum PGRN levels might not predict clinical responsiveness to TNF-antagonist therapy, changes in serum PGRN levels also correlated with changes in disease metrics over time [103]. These results indicate a possible role for PGRN as a disease-activity biomarker.

Emerging evidence indicates that PGRN could also be associated with various autoimmune diseases, including systemic lupus erythematous (SLE), systemic sclerosis, multiple sclerosis and Sjogren's syndrome [104]. SLE is a systemic autoimmune rheumatic disease that leads to tissue inflammation and organ damage. Because PGRN presents anti-inflammatory properties, two approaches have addressed serum PGRN levels in SLE patients. In both studies, serum PGRN was significantly higher in SLE patients than healthy controls [105,106], even much higher than RA serum levels [105]. Moreover, PGRN levels correlated with disease activities. Thus, these authors proposed PGRN to be a useful biomarker for disease activity [105] and diagnosis [106].

Concluding remarks

The anti-inflammatory properties of PGRN highlight its potential for novel therapeutic approaches for inflammatory diseases. Evidence has emerged for a potential role of PGRN and its derived protein atsttrin as therapeutic agents in rheumatic diseases. All the studies described above highlight the involvement of PGRN in the three main processes: inflammation, tumorigenesis and neurodegeneration, highlighting the potential of this adipokine as a biomarker. Although advances are continually being made, much remains to be elucidated. Thus, additional research on the role of progranulin in cancer, neurodegenerative diseases and inflammation is crucial for developing novel pharmacological strategies for these diseases.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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