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Progranulin: A conductor of receptors orchestra, a chaperone of lysosomal enzymes and a therapeutic target for multiple diseases

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ABSTRACT

Progranulin (PGRN), a widely expressed glycoprotein with pleiotropic function, has been linked to a host of physiological processes and diverse pathological states. A series of contemporary preclinical disease models and clinical trials have evaluated various therapeutic strategies targeting PGRN, highlighting PGRN as a promising therapeutic target. Herein we summarize available knowledge of PGRN targeting in various kinds of diseases, including common neurological diseases, inflammatory autoimmune diseases, cancer, tissue repair, and rare lysosomal storage diseases, with a focus on the functional domain-oriented drug development strategies. In particular, we emphasize the role of extracellular PGRN as a non-conventional, extracellular matrix bound, growth factor-like conductor orchestrating multiple membrane receptors and intracellular PGRN as a chaperone/co-chaperone that mediates the folding and traffic of its various binding partners.

1. Introduction

Progranulin (PGRN), also known as granulin-epithelin precursor (GEP), proepithelin (PEPI), acrogranin, GP88 and PC-cell-derived growth factor (PCDGF), was first identified as a 593-aa secreted glycoprotein involved in the regulation of cancer progression and wound healing [1–5]. As a broadly expressed and functionally pleiotropic protein, PGRN has been considered a growth factor-like molecule implicated in additional biological and pathological processes including early embryogenesis [6], inflammation [7], host defense [8], cartilage development and degradation [9]. PGRN also functions as a neurotrophic factor [10,11], and the heterozygous and homozygous mutations of its encoding gene *Grn* are associated with frontotemporal dementia (FTD) and lysosomal storage diseases (LSDs) [12–18].

Currently, various PGRN-targeted approaches are emerging as attractive therapeutic interventions in a broad spectrum of diseases including cancer [11], inflammatory diseases [19–24], neurological disorders [25], injury [26], tissue regeneration [27–29], and some rare diseases such as lysosomal diseases [30]. Multiple PGRN targeting strategies including small molecule compounds that boost PGRN expression, viral vectors or mesenchymal stem cells (MSCs) delivering *Grn* genes, engineered full length proteins or domains, monoclonal neutralizing antibodies, and 3D-printed scaffold-incorporated recombinant proteins have been developed, and over 30 preclinical and clinical trials in this field have been undertaken (Table 1).

In this review, we will summarize PGRN-centered therapeutic approaches in all diseases and conditions reported, along with an illustration of its multifaceted roles in related pathological processes. It is noted that the role of PGRN and the underlying mechanisms in neurological diseases, cancer, inflammatory autoimmune diseases, and lysosomal storage diseases have been well reviewed, usually with a focus on a certain disease type [25,31–36]. Therefore, the present review specifically focuses on contemporary efforts to develop potential PGRN-targeting methods and evaluation of drug candidates in preclinical models or clinical trials for potential application in treatment of an array of common and rare diseases.

2. Domain-dependent interactions of PGRN with its partners

The functional pluripotency of PGRN lies in its domain or motif-dependent interactions with different partner proteins (Fig. 1). Full length PGRN contains 7½ tandem, non-identical repeats of a cysteine-rich motif (CX5-6CX5CCX8CCX6C CXDX2HCCPX4CX5-6C, X: any amino acid) separated by 7 linker regions (P1-P7) in the order P-G-F-B-A-C-D-E, where A-G are full repeats, and P is the 1/2 motif [2,37–39].

PGRN can be secreted, cytoplasmic, and is also abundant in

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Table 1
Targeting PGRN Strategies in Various Diseases.

Diseases	Subjects	Targeting strategy	Outcome	References
Frontotemporal dementia (FTD)	Lymphoblasts from patients; PGRN deficient SH-SY5Y neuroblastoma cells	Compound enhancing PGRN expression, SAHA	Inhibit the cytosolic TDP-43 accumulation	[56]
Frontotemporal dementia	Patients in a phase 2 clinical trial, (NCT02149160)	Compound enhancing PGRN expression, FRM-0334	Unavailable	[57]
Frontotemporal dementia	Patients in a phase 1 clinical trial, (NCT01835665)	Compound enhancing PGRN expression, nimodipine	Unavailable	[57]
Frontotemporal dementia	Patients in a pilot study	Compound enhancing PGRN expression, amiodarone	No effect	[59]
Frontotemporal dementia	Organotypic cortical slice cultures from *Grn* deficient mice; Primary cells derived from human patients	Compound enhancing PGRN expression, clinically used alkalizing drugs reagents (chloroquine, bepridil, and amiodarone)	Rescue *Grn* deficiency	[58]
Frontotemporal dementia	*Grn* +/- mice	Adeno-associated virus vector delivering *Grn* gene	Correct restored social behavior deficits and normalized lysosomal abnormalities	[60]
Frontotemporal dementia; Neuronal ceroid lipofuscinosis (NCL)	*Grn* +/- mice	Adeno-associated virus vector delivering *Grn* gene	Reduced lipofuscinosis, microgliosis, and improved lysosomal function	[61]
Parkinson's disease	MPTP induced mice model	Lentiviral delivery of the *Grn* gene	Reduced inflammation and apoptosis status; Preserved both dopamine content and locomotor function	[62]
Alzheimer's disease	Alzheimer's disease mice	Lentiviral delivery of the *Grn* gene	Lowered plaque load and prevent spatial memory deficits and hippocampal neuronal loss	[64]
Huntington's disease	Caenorhabditis elegans model	Plasmid expressing human PGRN	Reduced polyglutamine toxicity by TDP-43	[65]
Subarachnoid hemorrhage (SAH)	Experimental SAH in rats	rPGRN	Alleviates early brain injury after SAH	[66]
Traumatic brain injury (TBI)	Mice model of controlled cortical impact (CCI)	rPGRN	Intracerebroventricular administration prevented brain damage and neurological deficits	[23]
Stroke	Mice following middle cerebral artery occlusion (MCAo)	Lentiviral mediated *Grn* gene delivery	Decreased infarcted tissue damage and improved post-ischemic neurological functions	[67]
Stroke	MCAO (middle cerebral artery occlusion)	rPGRN	Intra-cerebroventricular administered reduced the infarct volume, decreased brain swelling, and improved neurological scores and survival rare	[68]
Stroke	Rat autologous thrombo- embolic model	rPGRN	Intravenously administered recombinant progranulin reduced cerebral infarct and oedema, suppressed haemorrhagic transformation, and improved motor outcomes.	[69]
Inflammatory arthritis	Collagen antibody-induced, collaben-induced arthritis and TNF-α transgenic mouse models	rPGRN; Attstrin	Both agents effectively inhibited the progression of inflammatory arthritis	[7]
Osteoarthritis	Surgically induced OA models	rPGRN	Significantly attenuated OA-like phenotypes and protected against its progression	[73]
Osteoarthritis	Non-surgically induced rat; surgically induced murine OA models	Atsttrin	Exhibited a preventative effect	[74]
Osteoarthritis	Surgically induced OA mouse model	Atsttrin-transduced mesenchymal stem cells (MSCs) articular treatment	Preventive effect on the progression of degenerative changes	[75]
Inflammatory bowel disease (IBD)	DSS and TNBS colitis models	rPGRN	Reduced the histological score, colonic hyperplasia and leukocyte infiltration	[76]
Myocarditis	coxsackievirus-B3-induced myocarditis in mice	rPGRN	Attenuated phenotypes by downregulating Th1 and Th17 cells, but no effect on Treg cells.	[77]
Allergic asthma	Antigen-challenged mouse allergic asthma	rPGRN	Intranasal pretreatments inhibited bronchial smooth muscle hyperresponsiveness	[78]
Dermatitis	oxazolone-induced mice model	Atsttrin	Effectively attenuated inflammation	[79]
Hyperhomocysteinemia (hHcys)	Uninephrectomy and folate-free diet induced hHcys mice model	Recombinant PGRN	Protected against cardiorenal dysfunction	[80]
Immune thrombocytopenia (ITP)	Anti-CD41 platelet antibody-induced mice ITP model; Antibody- and CD8 + T cell–mediated mice ITP model	Recombinant PGRN	Increased platelet count; Promoted Treg cells; Proliferation	[81]
Endo-toxic shock	Lipopolysaccharide induced model	rPGRN	Pretreatments ameliorated the survival and abnormalities	[82]
Lung injury	LPS-induced severe acute lung injury in mice.	rPGRN	Effectively reduced lung injury	[83]

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Table 1 (*continued*)

Diseases	Subjects	Targeting strategy	Outcome	References
Gaucher disease	OVA-challenged, PGRN-deficient animal models; D409V/- GD mice; Human fibroblasts from GD patients	rPGRN; Pcgin	Stabilized and increased the levels of GCase, reduced the pathological severity of GD models, and inhibited the accumulation of glycolipids, including β-GlcCer.	[25]
Tay-Sachs disease (TSD)	Aged or ovalbumin-challenged adult PGRN-deficient mice models with typical TSD phenotypes	rPGRN; Pcgin	Reduced GM2 accumulation and lysosomal storage	[18]
Hepatocellular carcinoma (HCC)	A nude mice model transplanted with human HCC	PGRN monoclonal antibody	Inhibited the growth of established tumors in a dose-dependent manner but without inhibitory effect on normal liver cells	[100]
Hepatocellular carcinoma (HCC)	A nude mice model transplanted with human HCC	PGRN monoclonal antibody	Sensitize chemotherapeutic agents-induced apoptosis	[102]
Bone defect	Segmental femoral bone defect model; Femoral drill-hole model; Nonunion segmental radial defect model; BMP-2-induced ectopic bone formation model	rPGRN	Enhanced bone regeneration	[104]
Inflammatory periodontal bone defect	Periodontal bone defects in periodontitis rats	rPGRN	Had significantly superior quantity and quality of newly formed bone, inhibited osteoclastogenesis and inflammation	[105]
Osteolysis	Titanium particles stimulated the mouse air pouch model; Two mouse osteoysis models	rPGRN	Inhibited inflammation and prevented the pathological progression	[106]
Bone defects	Mice calvarial bone defects model	3D-printed Atsttrin scaffold incorporated to alginate/hydroxyapatite	Enhanced the regeneration of bone defects	[24]

extracellular matrix (ECM). PGRN directly binds to some other ECM components such as cartilage oligomeric matrix protein (COMP) (with granulin A domain, involved in regulating PGRN-induced proliferation) [9], extracellular matrix protein 1 (ECM1) [40], perlecan (with granluin F and B, involved in the promotion of tumor growth [41]), and several ECM proteases ADAM metallopeptidase with thrombospondin type 1 motif 7 (ADAMTS7) and ADAM metallopeptidase with thrombospondin type 1 motif 12 (ADAMTS12) with each granulin unit [42–45]. PGRN can be subject to degradation into individual, approximately 6-kDa GRN fragments by these binding enzymes and other various proteinases, such as elastease and protease 3 [46]. Importantly, these degraded GRN fragments are also biologically active, but often demonstrate opposite actions to the full-length protein; for example, GRN fragments act as pro-inflammatory factors that can neutralize the intact PGRN's anti-inflammatory activities [4]. The secretory leucocyte protease inhibitor (SLPI) can bind at sequences between granulin modules to protect full length PGRN from proteolysis by elastase and other proteases [4].

Half units of granulins A, C, and F plus linkers P3, P4, and P5 are responsible for the interaction between PGRN and the cysteine rich domain 2 (CRD2) and CRD3 of tumor necrosis factor receptor 1 (TNFR1) and tumor necrosis factor receptor 2 (TNFR2) [7,47–49]. An engineered recombinant protein was created from this "minimal" FAC domain, referred to as Atsttrin (antagonist of TNF/TNFR signaling via targeting to TNF receptors), which exhibits higher binding affinity for TNFR2, but lower affinity for TNFR1 than TNF-α [7,47,49,50]. In addition to TNFR, through FAC domains, PGRN and Atsttrin also bind to death receptor 3 (DR3), the highest homolog of TNFR1, and effectively inhibit the interaction of DR3 to its only known ligand TNF-like ligand 1A (TL1A) [48,51]. Other domain-dependent PGRN binding membrane receptors include Toll-like receptor 9 (TLR9), interaction with granulin ACDE assists CpG binding to TLR9 [52], and sortilin, which associates with the last three amino acids QLL at C-terminal of PGRN to deliver PGRN to lysosome [53]. Notch receptors and EPH receptor A2 (EphA2) also demonstrated to be PGRN binding partners [54,55]; however, whether the interaction is direct or indirect and the binding domains involved remain to be determined.

PGRN has been shown to function as a chaperone of lysosomal enzymes together with heat-shock protein 70 (HSP 70), and its granulin G and E domains are required for the binding to lysosomal hydrolase glucocerebrosidase (GCase) [17,56], β-hexosaminidase A (HexA) [18], cathepsin D (CSTD) [57] and chaperone HSP70 [56]. Pcgin, a 98 amino acid engineered PGRN derivative, bears the PGRN C-terminal granulin E domain and is sufficient for effective binding to lysosomal enzymes and HSP70, but lacks PGRN's oncogenic activity [56].

Meanwhile, there are several domain-dependent interactions, such as HIV-1 Tat (trans-activator protein) with granulin BA or CDE, nuclear Cyclin T with granluin CDE [58–61]. Although these binding relationships haves been confirmed, the significance of the interactions is still unclear.

Although various PGRN-binding partners have been reported, the majority of PGRN associated proteins can be classed into three categories (Fig. 1): secreted and ECM molecules (e.g. COMP [9], ECM1 [40], perlecan [41], ADAMTS-7 [42], ADAMTS-12 [42] and matrix metalloproteinase 14 [MMP14] [62]), cell transmembrane receptors (e.g. TNFR1 [7,47–49,63], TNFR2 [7,47–49,63], DR3 [47–49], sortilin [53], Toll-like receptor 9 [TLR9] [52], Notch receptors [54], and EphA2 [55]), and intracellular chaperones (e.g. BiP [64], calreticulin [64], GRP94 [64], ERp57 [64], HSP70 [56]) and lysosomal hydrolases through which PGRN acts as a co-chaperone of HSP70 (e.g. lysosomal hydrolase GCase [17,56], HexA [18], CSTD [57]).

In terms of the interactions between PGRN and cell membrane receptors, a structural comparison of extracellular domains revealed that the extracellular domains of all of these reported PGRN-binding receptors contain at least one cysteine rich domain (CRD) or EGF-like domain or both, which are known PGRN-binding domains

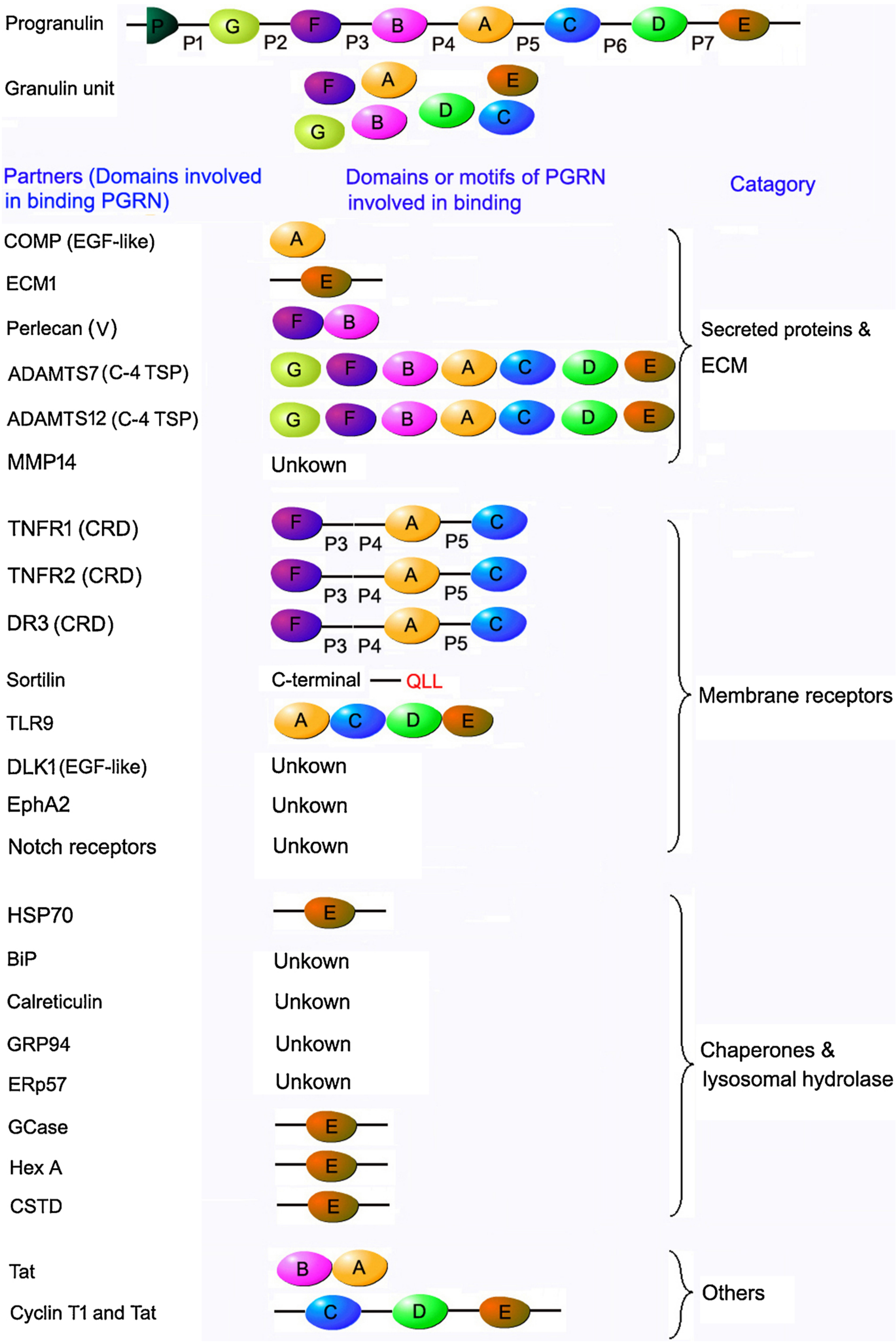

Fig. 1. Summary of the domains of PGRN known to be involved in the interactions of PGRN with its binding partners. PGRN possesses a high plasticity to bind to a wide spectrum of ECM proteins, membranous receptors and cytoplasmic chaperone and lysosomal hydrolases due to its unique beads-on-a-string structure and multiple binding domains. The domains known to be involved in PGRN and binding partner interactions are indicated. The cysteine rich domain (CRD) of TNFR and DR3 has been experimentally demonstrated to be required for interactions of these receptors with PGRN. Interestingly, a CRD is also present in the extracellular domains of Sortlin, EphA2, Notch receptors and TLR9. In addition, the extracellular domains of both Dlk1 and Notch receptors contain EGF-like domains, which is also known to bind to PGRN. It is expected that CRD and EGF-like domains are probably involved in the interactions of these aforementioned receptors with PGRN, although these associations need to be experimentally validated. "unknown" indicates that the binding domain(s) in PGRN remains to be determined.

[7,9,47,48,65]. Specifically, the extracellular domains of TNFR1, TNFR2, DR3, Sortlin, EphA2, TLR9 have CRD, the extracellular domain of Dlk1 has EGF-like domain, whereas Notch receptors posses both CRD and EGF-like domains. So far, only the CRDs of TNFR and DR3 have been confirmed to be required for interactions with PGRN [47–49]. We expect that the CRD in Sortlin, EphA2, TLR9 and Notch receptors and the EGF-like domain in Dlk1 and Notch receptors are likely also involved in their interactions with PGRN, although these associations need to be experimentally validated. In brief, the extracellular domains of currently reported PGRN receptors share domain/structure similarities, although these receptors are functionally different and belong to various receptors families.

3. PGRN targeting in neurological diseases

3.1. Neurodegenerative diseases

Decreased PGRN level due to heterozygous mutation of *GRN* gene mutations is the major cause of FTD-TDP, a subtype of FTD characterized by ubiquitinated and fragmented TDP-43 proteinopathy. Developing small molecule drug modifiers to restore the reduced expression of PGRN to its normal levels is becoming a promising avenue for the treatment of FTD-TDP [25,66]. Suberoylanilide hydroxamic acid (vorinostat, SAHA), a histone deacetylase (HDAC) inhibitor approved for use in cancer treatment, was identified as the first potent inducer of

PGRN expression in a screen of FDA-approved compounds [67]. SAHA enhanced PGRN levels at both mRNA and protein levels in haploinsufficient cells, and combined with ERK1/2 blocker selumetinib, SAHA could significantly inhibit cytosolic TDP-43 accumulation [67]. Currently, another HDAC inhibitor - FRM-0334, is in phase 2 clinical trials for amelioration of PGRN insufficiency resultant of *GRN* gene mutations [68]. Compared with SAHA, FRM-0334 can more easily cross the blood-brain barrier [68]. Except for HDAC inhibitors, channel blocker nimodipine, vacuolar ATPase inhibitors (bafilomycin A1, concanamycin A, archazolid B, and apicularen A), clinically used alkalizing drugs (chloroquine, bepridil, and amiodarone), and an mTOR-independent autophagy activator trehalose are also potential pharmacological stimulators of PGRN production [69]. Among them, nimodipine is in a phase 1 trial as a PGRN-elevating drug, however, a pilot study evaluating the effect of amiodarone on PGRN rescue in FTD-*Grn* patients failed to demonstrate a definite therapeutic result [70].

PGRN gene therapy is an alternate rational therapeutic strategy for neurodegenerative disorders due to *Grn* mutations. Arrant et al. observed that adeno-associated virus (AAV) vector delivery of *Grn* gene to the medial prefrontal cortex could correct social behavior deficits and normalize lysosomal abnormalities in *Grn* +/- mice [71]. They further extended the gene therapy approach into *Grn-/-* mice, which model aspects of neuronal ceroid lipofuscinosis (NCL) and FTD, and found that PGRN replacement specifically targeted neurons, reduced lipofuscinosis, microgliosis, and improved lysosomal function even at low doses [72].

As a potent regulator of neuro-inflammation and an autocrine neurotrophic factor, PGRN is also important for the long-term neuronal survival, and increased availability in the brain may have therapeutic benefits in neurodegenerative diseases other than FTD and NCL. Van Kampen et al. found that lentiviral delivery of the *Grn* gene could increase the PGRN expression level in nigrostriatal neurons accompanied by reduced inflammation and apoptosis in a 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced murine model of Parkinson’s disease [73]. Meanwhile, PGRN gene therapy also preserved both dopamine content and locomotor function [73]. *Grn* polymorphism may be associated with the late-onset Alzheimer's disease [74] and, functionally, PGRN inhibits amyloid β (Aβ) deposition and protects against Aβ toxicity [75]. Lentivirus-mediated PGRN overexpression lowered plaque load and prevented spatial memory deficits and hippocampal neuronal loss in Alzheimer's disease mice [75]. Therefore, these data supports the efficacy of PGRN-expressing gene therapy for neurodegenerative pathologies. A further study suggests that PGRN may have therapeutic benefits in a Caenorhabditis elegans model of Huntington’s disease by interacting with TDP-43 to regulate polyglutamine toxicity [76].

3.2. Nervous system injuries

In addition to neurodegenerative diseases, PGRN may also act as a treatment target for neurological injury. The PGRN level is significantly decreased in cerebrospinal fluid from subarachnoid hemorrhage (SAH) patients and cerebral cortex tissues after experimental SAH in rats. Recombinant PGRN (rPGRN) administration alleviated early brain injury in SAH rats, possibly by inhibiting neutrophil recruitment and the activity of inflammatory cytokines [77]. Another study indicated that intra-cerebroventricular administration of rPGRN could prevent traumatic injury induced brain damage and neurological deficits, partly due to its inhibitory effect on inflammatory factors such as TNF-α and iNOS [26]. The data from transgenic *Grn* mice or *Grn-/-* mice also support a protective benefit of PGRN on peripheral nerve regeneration and re-innervation [54]; however, the therapeutic effect of rPGRN strategies in peripheral nerve injury has not been reported.

3.3. Stroke

Several lines of evidences support therapeutic potential for PGRN in experimental acute ischemic stroke by multiple mechanisms including suppression of neuro-inflammation and neuro-protection, attenuation of ischemia-reperfusion and reduction of blood-brain barrier disruption. Several PGRN targeting strategies, including lentiviral mediated *Grn* gene delivery, intra-cerebroventricular and intravenously administered rPGRN protein with and without tissue plasminogen activator, have revealed the consistent and significant therapeutic effects of PGRN on infarcted tissue damage reduction and improvements in post-ischemic neurological functions [78–80].

4. PGRN targeting in autoimmune and inflammatory diseases

4.1. Inflammatory arthritis

Tang et al. demonstrated that rPGRN and Atsttrin, an engineered PGRN derivative containing the minimal TNFR binding motifs, significantly alleviated the disease severity in collagen antibody-induced, collagen-induced and TNF-α transgenic inflammatory arthritis mouse models [7,48,49,81]. Both agents effectively inhibited the progression of inflammatory arthritis, and inflammatory phenotypes returned following the cessation of Atsttrin treatment [7]. Additionally, PGRN and Atsttrin treatment also have decreased circulating levels of fragmentary COMP, a marker for cartilage destruction [7].

Generally, Atsttrin exhibits potent anti-inflammatory activity, which surpasses PGRN *in vivo* [7]. Compared to TNFα, Atsttrin exhibited a higher (10-fold) binding affinity for TNFR2, but lower (18-fold) affinity for TNFR1, and reversed the clinical scores of inflammatory arthritis mouse models to normal baseline level [7]. Pharmacokinetically, Atsttrin was well absorbed following intraperitoneal administration and demonstrated high stability with a significantly longer half-life (˜120 h) when compared to PGRN (˜40 h) [7]. More importantly, Atsttrin lacks other multiple functions of the source protein, particularly PGRN's oncogenic activity. Additionally, the composition of Atsttrin allows it to escape digestion into individual granulin units. No Atsttrin-related cytotoxic effects or lethality was observed even at exceedingly high dosages [7].

Compared with current TNF-α inhibitors, Atsttrin has a unique mechanism of action targeting TNFR, but not TNF-α [19,20]. Mechanistically, the anti-inflammatory effects of Atsttrin mostly depend on its direct activation of TNFR2 protective anti-inflammatory pathway, for example, through regulating the functions and differentiation of Treg cells in a TNFR2-dependent manner [82], therefore, the patients who fail to respond to current TNFα blockers may benefit from Atsttrin treatment. In several inflammatory arthritis mice models, Atsttrin also demonstrated more efficacious results than the current TNF-α inhibitors etanercept and adalimumab [7]. As mentioned, Atsttrin does not increase cancer incidence; moreover, Attstrin may act as a tumor suppressor and has potential for treating cancers that feature high PGRN expression [19].

4.2. Osteoarthritis (OA)

Osteoarthritis (OA) is the most common type of degenerative arthritis, and is also currently accepted as a chronic mild inflammatory joint disease [83–85]. It is believed that inflammatory cytokines, including TNF-α and IL-1β, play important roles in the pathogenesis of OA. PGRN has also been shown to be a potential target for the treatment of OA. Zhao et al. found that intra-articular injection of rPGRN protein significantly attenuated OA-like phenotypes and protected against its progression in surgically induced OA models [86]. This therapeutic effect is primarily reliant upon the stimulation of TNFR2-Akt-Erk1/2-dependent chondrocyte anabolism and inhibition of TNF-α/TNFR1-mediated inflammatory catabolism [86]. Wei et al. further extended the investigation to Atsttrin, revealing a preventative effect of the PGRN-derivative in OA in both non-surgically induced rat and surgically induced mouse OA models [87]. In addition, Xia et al. applied Atsttrin-transduced mesenchymal stem cells (MSCs) to deliver Atsttrin to the articular joint and demonstrated a similar preventive effect on the progression of degenerative changes in the surgically induced OA mouse model, providing an alternative cell-based delivery strategy to supply PGRN or Atsttrin into disease sites. [88].

4.3. Inflammatory bowel disease (IBD)

Wei et al. revealed that rPGRN ameliorated the pathology and reduced the histological score in both Dextran sulfate sodium (DSS)- and picrylsulfonic acid (TNBS)-induced colitis models [89]. Similar to results from models of inflammatory arthritis and OA, the PGRN-mediated protective action in IBD is also TNFR2-dependent and anti-inflammatory IL-10 signaling is required as well [89]. PGRN treatment significantly increased the IL-10 release in colonic explants from DSS colitis mice; colonic hyperplasia and leukocyte infiltration were also reduced [89].

4.4. Other inflammatory diseases

The therapeutic benefits of rPGRN and its derived Atsttrin were also reported in other inflammatory disease models. For example, rPGRN treatment attenuated coxsackievirus-B3-induced myocarditis in mice by downregulating Th1 and Th17 cells, but had no effect on Treg cells [90]. Intranasal pretreatments of rPGRN could inhibit bronchial smooth muscle hyper-responsiveness in antigen-challenged mouse allergic asthma [91]. Zhao et al. reported that Atsttrin effectively attenuated inflammation in a murine oxazolone-induced dermatitis model [92]. Fu et al. demonstrated that pretreatment with rPGRN protected against cardiorenal dysfunction in mice with hyperhomocysteinemia by negatively regulating Wnt/β-catenin signaling [93]. Yu et al. showed that administration of rPGRN increased platelet count in immune thrombocytopenia model mice by promoting Treg cell proliferation [94].

Not limited to chronic inflammatory diseases, acute inflammatory diseases may be also good candidates for PGRN treatment. Yu et al. reported that pretreatment with rPGRN significantly ameliorated the survival and abnormalities observed in mice subjected to endotoxic shock by lipopolysaccharide (LPS) [95]. Guo et al. also revealed that administration of rPGRN effectively reduced LPS-induced severe acute lung injury in mice [96].

5. PGRN targeting in lysosomal storage diseases

The therapeutic potential of PGRN for LSDs such as Gaucher disease (GD) mostly relies on its intracellular activity as a shared co-chaperone required for lysosomal delivery of lysosomal enzyme GCase, whose mutations cause GD [30]. Jian et al. found that rPGRN is therapeutic in various animal models of GD and human fibroblasts from GD patients, and more significantly, Pcgin, a 98 amino acid derivative of the PGRN C-terminal granulin E domain required for the binding to GCase and HSP70, can recapitulate this therapeutic effect [17,56]. In addition, another study also identified a PGRN downstream molecule chitinase-3-like Protein 1 (CHI3L1) as a novel biomarker for diagnosis and treatment efficacy surveillance of GD [97].

In addition to GCase, PGRN was shown to be therapeutic against aberrant accumulation of other lysosomal enzymes. Using fibroblasts from various LSDs patients, Chen et al. demonstrated that rPGRN was effective in reducing lysosomal storage in Tay-Sachs disease (TSD) cells [18]. Mechanistically, PGRN significantly increased the enzymatic activity and lysosomal delivery of TSD-associated enzyme Hex A, and PGRN directly bound to Hex A through granulins G and E [18]. Chen et al. also found that aged or ovalbumin-challenged adult PGRN-deficient mice showed typical TSD phenotypes including significant GM2 accumulation and the existence of typical TSD cells containing zebra bodies. Both rPGRN and PGRN derivative Pcgin significantly reduced GM2 accumulation and lysosomal storage in these animal models [18].

Actually, PGRN has a more universal function as a lysosomal protein chaperone, beyond its associations with GCase and Hex A. Beel et al. showed that cathepsin D (CSTD) is also a PGRN-binding lysosomal enzyme; their association is also mediated by PGRN's C-terminal granulin E domain [57]. Moreover, *Chen* et al. further observed that rPGRN also effectively reverted the altered lysosomes in fibroblasts from Farber's disease, mucolipidosis III, and mucopolysacharidosis III/VI [18].

6. PGRN targeting in cancers

PGRN is frequently overexpressed by many types of cancer and contributes to their progression [11,33,98–103]. It has been well-established that PGRN exerts complex and multifaceted actions on tumor development by regulating cancer cell proliferation, invasion, stem cell properties, and angiogenesis [3,103–106], and PGRN is also involved in stroma formation, resistance to anticancer drugs and immune evasion [107–112].

Currently, the most investigated and applicable PGRN-targeting strategy in cancer treatment is developing monoclonal neutralizing antibodies against PGRN. The feasibility of this strategy in the preclinical hepatocellular carcinoma (HCC) model has been demonstrated [113,114]. Ho et al. developed an anti-PGRN monoclonal antibody that significantly inhibited the growth of established tumors but not of normal liver cells in a dose-dependent manner [113]. The *in vivo* therapeutic effect of anti-PGRN monoclonal antibody was accompanied by decreased serum PGRN levels, suggesting its circulating level can be used to identify candidate HCC patients susceptible to anti-PGRN treatment and to monitor treatment response [113]. Wong et al. further showed that monoclonal antibodies against PGRN can sensitize chemotherapeutic agents-induced apoptosis in HCC cells and human HCC orthotopic xenograft models, indicating that blocking PGRN might be an alternative strategy to provoke cancer cell death [115].

Furthermore, Atsttrin was able to inhibit PGRN-stimulated cell proliferation of several cancer cell lines *in vitro* [7], suggesting Atsttrin may also be applicable for high PGRN activity cancers like breast cancer, ovarian carcinoma, and multiple myeloma, however further *in vivo* validation study is still needed.

Considering the utility of boosting PGRN strategies in neurological diseases, it is conceivable that small molecule compounds inhibiting PGRN expression or its activity (antagonists) should be an alternative approach to treat PGRN-associated cancers.

7. PGRN targeting in tissue repair and engineering

Considering the role of PGRN in stimulating chondrocyte differentiation and endochondral ossification [116], it is reasonable to speculate that PGRN would be also required for normal cartilage callus formation during bone regeneration. Indeed, Zhao et al. revealed that rPGRN enhanced bone regeneration in three surgically-induced bone defect models (segmental femoral bone defect model, femoral drill-hole model and nonunion segmental radial defect model) and one bone morphogenetic protein-2 (BMP-2)-induced ectopic bone formation model [117]. This effect remained in TNFR1 knockout mice but was lost in TNFR2 deficient mice, therefore, PGRN-stimulated bone regeneration primarily depends on TNFR2 [117]. Chen et al. demonstrated that local administration of rPGRN promotes regeneration of inflammatory periodontal bone defect in rats [118].

Bone-implant interface inflammatory osteolysis may result in aseptic loosening and subsequent failure in total joint arthroplasty. Zhao et al. revealed that rPGRN effectively inhibited inflammation in the titanium particle stimulated air pouch model, and prevented the pathological progression in two mouse osteoysis models through

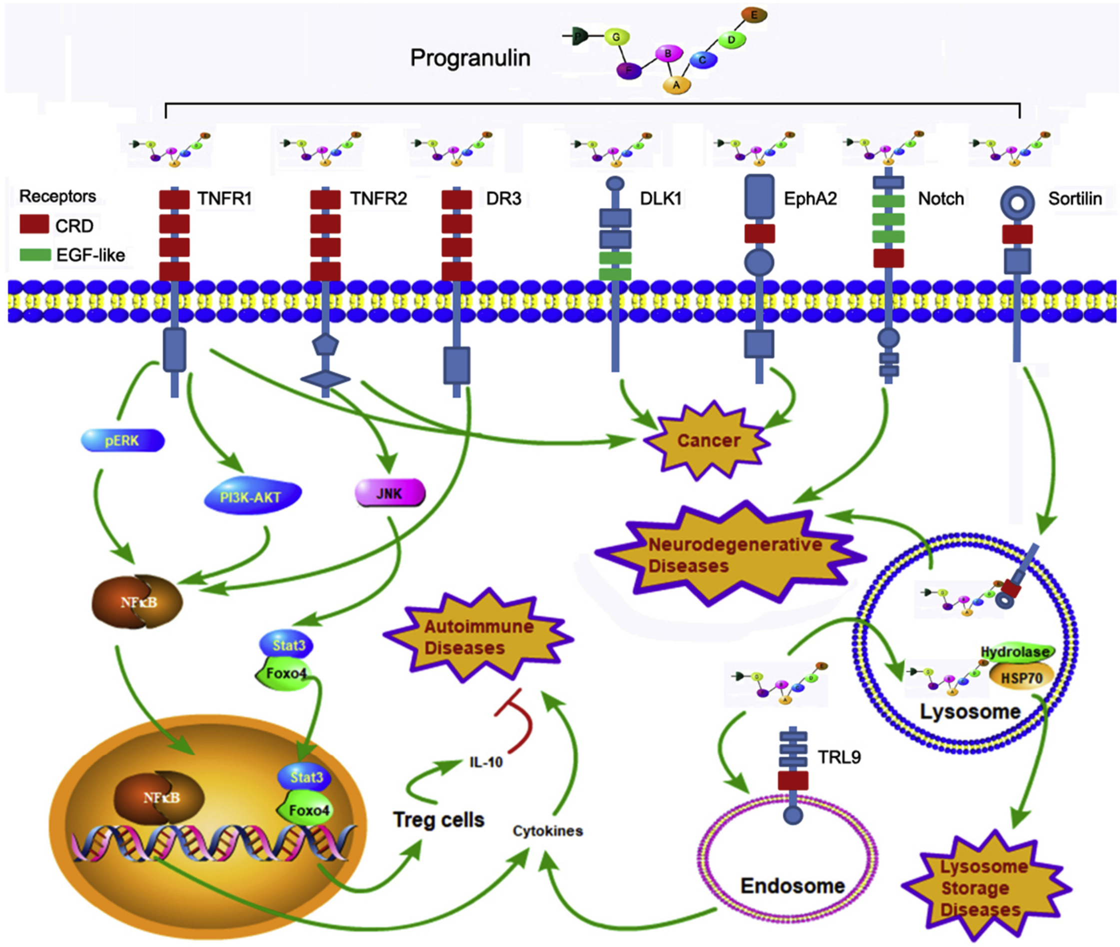

Fig. 2. Systematic illustration of PGRN-mediated signaling pathways. The functional pluripotency of PGRN and its associated targeting strategies lie on its motif-dependent activation of various signaling pathways. Associations with different membrane receptors from different families may account for PGRN's multiple functions under different pathophysiological conditions. For instance, in the course of inflammation, PGRN binds to TNFR1 and activates ERK and PI3K/AKT pathways, leading to the inhibition of TNF-α induced NF-κB inflammatory pathway, whereas PGRN also directly binds to TNFR2 with high affinity and promotes Treg cell differentiation by activating JNK-Stat3/Foxo4 signal cascade. PGRN binding to TLR9 in the endosome plays key roles in innate immunity against bacterial infection. Interactions with sortilin and Notch receptors play important roles in PGRN's protective role in neurons, particularly in preventing neuronal degeneration. EphA2 may be also involved in PGRN-mediated cell proliferation during carcinogenesis. In addition to functioning as a growth factor-like molecule extracellularly, PGRN also acts as a cytoplasmic co-chaperone intracellularly to assist lysosomal enzyme trafficking, and absence of this function leads to various lysosome storage diseases. The CRD and EGF-like domains in various receptors, which are probably involved in their interactions with PGRN, are indicated.

inhibiting TNF-α/NF-κB signaling pathway [119].

Wang et al. incorporated Atsttrin into alginate/hydroxyapatite to produce a 3D-printed scaffold that sustained Atsttrin release for at least 5 days with negligible cytotoxicity, and high cell adhesion ability and the 3D-printed Atsttrin scaffold significantly enhanced the regeneration of murine calvarial bone defects [27].

8. Targeting PGRN associated signaling mechanisms

The therapeutic effects of targeting PGRN in various diseases depend on PGRN’s mediation of various signaling pathways by associating with individual receptors or binding proteins (Fig. 2). PGRN binds to TNFR1 and activates ERK and PI3K/AKT pathways to competitively inhibit TNF-α activated NF-κB inflammatory pathway [7,47,49,116,120]. In contrast, the binding of PGRN to TNFR2 triggers the JNK-Stat3/Foxo4 protective signaling cascade and promotes the differentiation and function of regulatory T cells (Tregs) in inflammation [82,121]. In addition to cell transmembrane receptors, PGRN also binds to TLR9 in the endosome to assist the recruitment of CpG-ODNs in macrophages, leading to the enhancement of innate immunity against bacterial infection [52].

Other PGRN-binding receptors include sortilin, Notch receptors, and EphA2 [53–55,122,123]. Interaction between PGRN and sortilin was reported to be critical for their trafficking into lysosomes, particularly in neurons [122,124]. Altmann et al. suggested that PGRN may also bind to the extracellular domain of Notch receptors, and enhance the peripheral nerve regeneration and re-innervation [54]. Interaction between PGRN and EphA2 may be involved in the oncogenic role of PGRN [55]. The anti-proliferation effect on tumor cells of anti-PGNP monoclonal antibodies was dependent on its modulation on the p44/42 MAPK and Akt pathways, whereas the chemotherapeutic effect may result from the suppression of cancer stem cells and Akt/Bcl-2 signaling [115].

The major mechanism underlying PGRN-mediated therapeutic effects in lysosomal storage diseases lies in the interaction between the granulin E domain of PGRN with chaperone HSP70 to facilitate the folding and trafficking of mutated lysosomal enzymes, and rescue, at least in part, their activity, in turn alleviating the phenotypes of LSDs [18,30,56,72].

9. Perspectives

9.1. PGRN is a non-conventional, extracellular matrix bound, and multiple membrane receptors-associated growth factor-like molecule

PGRN has been long recognized as a growth factor for its binding to cell surface receptors. However, unlike conventional growth factors, which usually function at nanogram level, PGRN needs a relatively higher magnitude amount to activate the receptors, usually at microgram level. In addition, growth factors generally bind to cell membrane receptors as the specific cognate ligands. Increasing evidence indicate that PGRN binds to multiple receptors from several functionally different receptor families, and these associations are probably cell/tissue-specific and condition/disease-dependent. For example, the PGRN and sortilin interaction is more specific in neurological cells for delivering PGRN to lysosome. PGRN binding with TNFR has an important anti-inflammatory role in immune cells, particularly Tregs and macrophages. PGRN/EphA2 interaction is possibly involved in the proliferative influence of PGRN during carcinogenesis. Collectively, these emerging evidences support the conclusion that PGRN should be defined as an abundant, non-conventional, stress-induced, matrix-bound secreted growth factor-like molecule and cytoplasmic chaperone, that functions in a cellular and disease specific pattern.

Considering the unique structure of PGRN and the ability to bind to multiple membrane receptors, it is speculated that PGRN may form a ternary complexes through associating with multiple receptors (Fig. 3). In this aspect, PGRN may function as a "biological-glue" like conductor to mediate the signaling and activities of various receptors simultaneously and/or orchestrally. One or two receptors may play a major or dominant role and other receptors exert accompanist roles or are even not involved in a certain context, and vice versa in different conditions. This concept provides new insights into the understanding of the perplexing phenomena as well as the controversy and inconsistency in the fields of PGRN researches and its involvements in diverse conditions. It is conceivable that additional PGRN-associated receptors may be identified in different cell and animal models using various unbiased screen approaches. It is also likely that rPGRN derivatives targeting two or more disease-associated receptors simultaneously may further enhance the therapeutic potential over the current single-receptor targeting strategies.

ECM molecules are considered to act as "reservoirs" for certain growth factors and cytokines and regulate their signaling and activities through sequestering from or presenting to their cognate specific receptors. For instance, PGRN-interacting COMP is known to associate with numerous growth factors, including BMP2 [125] and TGFβ1 [126]. Therefore, it is speculated that PGRN's regulation of various signaling pathways may be also attributed to its associations with the ECM molecules, particularly COMP, leading to indirect activations or inhibitions of various growth factors/cytokines in diverse conditions (Fig. 3).

9.2. Diversity of PGRN levels in diseases and conditions

The levels of PGRN under different disease conditions are complicated. PGRN levels are usually elevated in multiple cancers [98–103], while decreased in most degenerative diseases such as FTD, NCL, and osteopenia [127–130]. As an anti-inflammatory factor, the expression of PGRN in most inflammatory models and patients was paradoxically up-regulated [131–135]. It is noted that the balance between PGRN and TNF-α is critical to the initiation and progression of autoimmune and inflammatory disorders (Fig. 4). PGRN and TNF-α reach a balance under physiological conditions at a low level, while inflammation may disturb the balance. Although the increase of PGRN has been frequently reported in inflammatory autoimmune diseases, probably due to the response of PGRN to inflammatory stress, its elevation is not sufficient to counteract elevated TNF-α under such conditions. When rPGRN and its derivatives are given, the imbalance would be restored and thus rPGRN and its derivatives demonstrate an anti-inflammatory effect in various inflammatory disease models. However, after PGRN supplementation, the level of TNF-α was reported to be unexpectedly increased, which suggests that a reciprocal feedback regulatory mechanism between PGRN and TNF-α may exist. Therefore, the regulatory pattern of PGRN expression in diseases is sophisticated and context-specific.

9.3. Consideration of side effects to targeting PGRN

The unique beads-on-a-string structure and sticky glycoprotein traits give PGRN high elasticity to bind to a wide spectrum of partners. PGRN, like other TNF blockers such as Humira (adalimumab) and Remicade (infliximab), exerts anti-inflammatory activities but has also been implicated in tumorigenesis, functioning as a double-edged sword. Long-term use of rPGRN is expected to cause excessive cell growth, thus increases the cancer risk; similar to the current clinically approved TNF-α blockers in treating TNF-associated autoimmune diseases. In addition to the cancer risk, direct use of rPGRN or boosting its expression using small compounds may have other side-effects due to its pluripotent features. Matsubara et al. indicated that administration of PGRN could induce insulin resistance [136]. Zhu et al. found that administration of rPGRN protein significantly promoted microglial activation in pilocarpine-induced status epilepticus [137]. Very recently, Amado et al. found that AAV delivering PGRN to the lateral ventricle or ependymal-

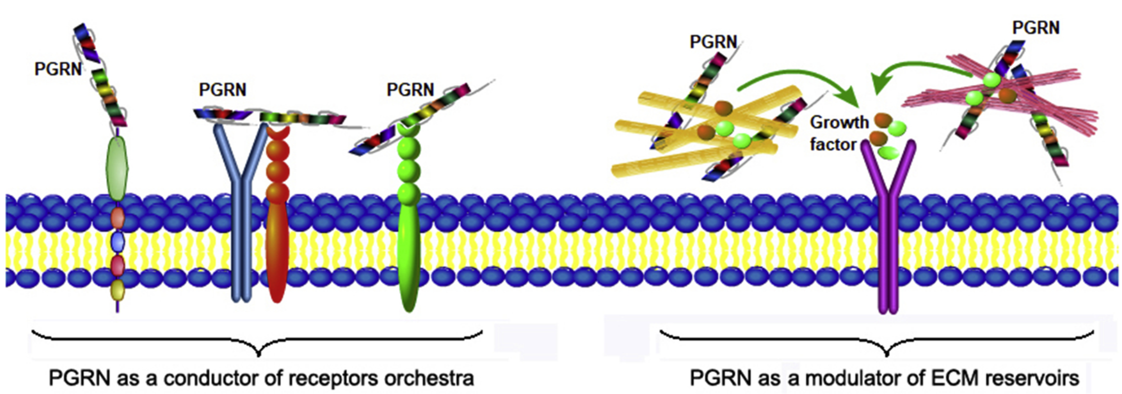

Fig. 3. A proposed model to explain how PGRN acts as a conductor of a receptors orchestra and how PGRN regulates growth factors/cytokines indirectly through associating with extracelluair matrix "reservoirs". PGRN may bind to multiple receptors and mediate the signaling and activities of various receptors simultaneously and/or synergistically. Except for direct binding to membrane receptors, PGRN regulates various signaling pathways through its associated ECM molecules, which leads to the indirect modulation of various growth factors and/or cytokines implicated in diverse conditions.

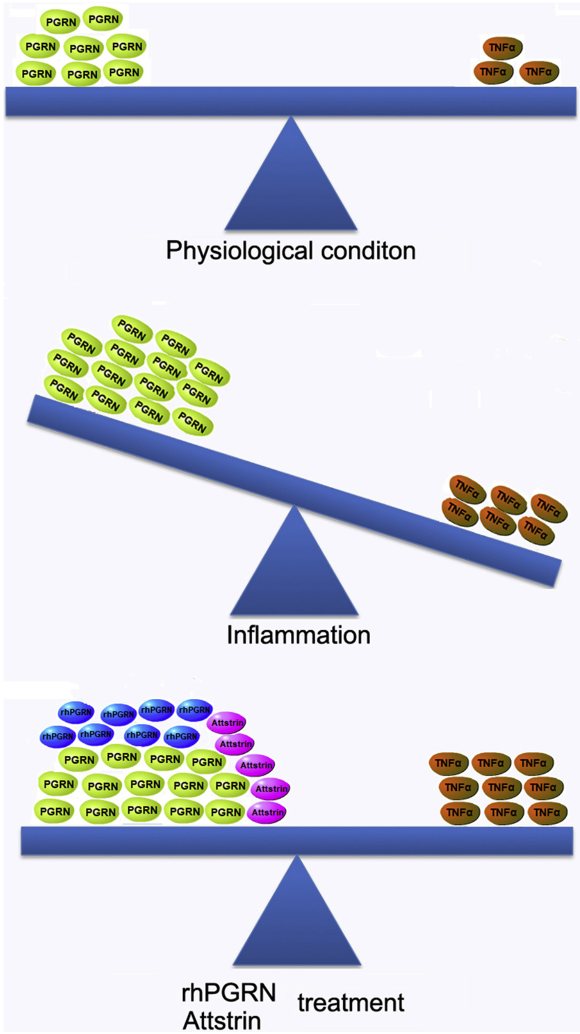

Fig. 4. Diagram to explain the balance between anti-inflammatory PGRN and pro-inflammatory TNF-α in regulating inflammation. The ratio of PGRN to TNF-α, but not their absolute concentrations, determines the trends of inflammation. Under physiological conditions, PGRN shows a higher baseline, and maintains an active balance of a pro-inflammation and anti-inflammation with TNF-α. In inflammatory autoimmune diseases, the level of PGRN is frequently found to be elevated, but increased PGRN is not sufficient to counteract the activity of simultaneously elevated TNF-α, leading to the disturbed balance between them and persistent inflammation. rPGRN and Attstrin exhibit therapeutic effects under such conditions, though, at least in part, restoring the balance between PGRN and TNF-α.

targeting caused T cell-mediated hippocampal toxicity or ependymal hypertrophy despite a significant increase in PGRN expression [138]. Therefore, the adverse and the off-target effects of application of rPGRN protein or the gene encoding PGRN would be comprehensive and unpredictable; similar concerns may be also true for small molecule drugs to stimulate the expression of PGRN. Generally, full-length PGRN protein increasing strategies may only be considered for acute diseases and short-term treatment circumstances such as acute inflammation and bone fracture healing. In terms of chronic diseases, the pharmacological utilization of PGRN must consider optimization of disease-specific targeting efficacy and minimization of off-target results. Success in preclinical models indicates that engineered, disease-specific PGRN-derivatives that maintain certain therapeutic effects of full length PGRN but possess minimal side effects, such as Attstrin and Pcgin, would lead to innovative therapeutics for various pathologies, in particular autoimmune diseases.

10. Conclusion

In summary, we present a timely update on the drug development efforts to target PGRN in multiple diseases, particularly in various preclinical disease models including neurological diseases, autoimmune diseases, lysosomal storage diseases, cancers and tissue repair and engineering. We emphasized that extracellular PGRN functions as a nonconventional, cellular and disease specific, matrix-bound, and multiple receptors-associated growth factor-like molecule, whereas intracellular PGRN acts as a co-chaperone involved in the folding and traffic of its associated proteins, particularly the lysosomal hydrolases. Associations of extracellular PGRN with cell membrane receptors mediate the uptake of PGRN and regulate the levels of intracellular PGRN (Jian and Liu, unpublished data); however, whether extracellular and intracellular PGRN mediated activities are functionally integrated or independent remains largely unknown. In addition, PGRN functional domain derivatives may provide innovative interventions to overcome the current bottlenecks in the efforts to develop PGRN targeting treatments.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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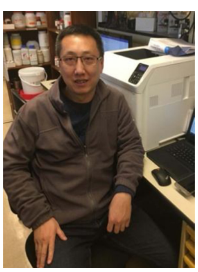

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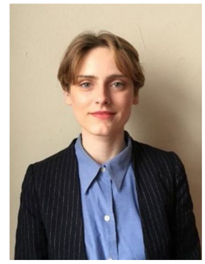

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