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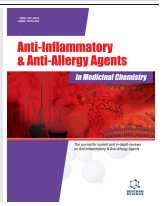

Progranulin Regulates Inflammation and Tumor

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Abstract: Progranulin (PGRN) mediates cell cycle progression and cell motility as a pleiotropic growth factor and acts as a universal regulator of cell growth, migration and transformation, cell cycle, wound healing, tumorigenesis, and cytotoxic drug resistance as a secreted glycoprotein. PGRN overexpression can induce the secretion of many inflammatory cytokines, such as IL-8, -6,-10, TNF-α. At the same time, this protein can promote tumor proliferation and the occurrence and development of many related diseases such as gastric cancer, breast cancer, cervical cancer, colorectal cancer, renal injury, neurodegeneration, neuroinflammatory, human atherosclerotic plaque, hepatocarcinoma**,** acute kidney injury, amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson's disease. In short, PGRN plays a very critical role in injury repair and tumorigenesis, it provides a new direction for succeeding research and serves as a target for clinical diagnosis and treatment, thus warranting further investigation. Here, we discuss the potential therapeutic utility and the effect of PGRN on the relationship between inflammation and cancer.

Keywords: Cell cycle, cell motility, inflammation, pleiotropic growth factor, progranulin, tumor.

1. INTRODUCTION

Progranulin (PGRN), also known as GEP (Granulin-epithelin precursor), Proepithelin, acroglanin, and GP88, is purified from conditioned tissue culture [1, 2] and is a growth factor composed of 593 amino acid residues mediated by signal peptides secreted by cells. PGRN is a functional precursor formed by connecting seven conservative granulin (A, B, C, D, F, G) units through a linking region (P1-7) and has an extremely wide range of physiological functions. The human PGRN gene is located on chromosome 17q21.32 and has a compact coding region with a total length of 4 *kB* and 12 exons (I-XII). The relative molecular weight of PGRN is 68,500. After glycosylation modification, its weight becomes 90×10³, which contains 7.5 repetitive motifs; each motif is a granulin (PGRN) domain linked by linkers (P1~7) that separates ~6kDA peptides, which are called granules (GRNA-G and paragranulin), and contains 12 cysteine residues that form six disulfide bonds [3-12]. On the spatial structure, the four β-folded "hairpin" structures are folded in ladder shape in turn [13]. PGRN can be digested by matrix metalloproteinases 9, 12, and 14, elastase, and other enzymes into GRN peptides with a size of approximately 6×10³.

Elastase can cleave PGRN into several GRNs (GRNA-F and para-GRN proteins) with various

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functions. In the wound-healing model, a secreted leukocyte protease inhibitor (SLPI) binds PGRN by inhibiting the enzymatic activity of elastase, thus isolating the protein from elastase and preventing the processing of PGRN [14, 15]. PGRN exists in the large majority of eukaryotes [16]. Interaction between three molecules produced by cells and/or epithelial cells: elastase, PEPI and SLPI are closely related to wound healing. PEPI was transformed into EPIs by elastase. Macrophages secrete SLPI and PEPI and can bind to each other. When SLPI is defective, recombinant PEPI can repair normal injured mice. Epithelial cells also produce PEPI to promote epithelial cell proliferation. Protein precursor and its processed fragment (epithelial protein) have biological and physiological functions. PEPI can considerably, and specifically block TNF signal transduction in neutrophils induced by TNF and promote the growth of epithelial cells. By contrast, EPI B inhibits the proliferation of epithelial cells and induces their secretion of IL-8 [15].

According to PGRN secretion, GRN localizes subcells together with the endoplasmic reticulum golgi apparatus, lysosomes, secretory granules, and vesicles [17]. After secretion, the full-length protein can be hydrolyzed and cleaved by metalloproteases, such as matrix metalloproteinase (MMP)-9 protein, MMP-14, disintegrate protein, and metalloprotease with thrombospondin type 1 motif 7, serine protease, and protease secreted by neutrophils 3 [18-20].

Many cascade reactions of growth factors and their related signals can regulate the development and repair of healthy tissues and even pathophysiological processes. Precursor protein is a family of growth factors that can inhibit inflammation and mucosal damage and has central clinical application value. PGRN is also highly expressed in rapidly growing tumor tissues, thus further aggravating the tumor. The role of PGRN in positive and negative relationships is mainly in growth, development (participating in early embryogenesis and angiogenesis), and regeneration, but it also plays a remarkable central role in tumor invasion, metastasis, proliferation, and regulation of immune responses. Here, we discuss the potential therapeutic utility and the effects of PGRN on the relationship between inflammation and carcinoma.

1.1. PGRN in Wound Healing

PGRN in injury repair is a controversial research topic and a complicated biological process. PGRN is highly expressed in inflammation and injury, and damage/wound repair is a coordinated process of cells involving cytokines and regulatory growth factors, such as platelet-derived growth factor and transfer growth factor epidermal growth factor (EGF), fibroblast growth factor, and insulin-like growth factor (IGF). Neutrophils secrete interleukin-1, TNF, vascular endothelial growth factor (VEGF), hepatocyte growth factor, and transforming growth factor-β. These growth factors can promote the healing of soft tissues and skin injuries and have good coordination with each other. BGF (repair factor) can activate CFOs by regulating the kinase (ERK) signaling pathway, thus effectively promoting the formation of new blood vessels. By binding to cell membrane surface receptors, G0 and G1 cells decrease their expression in the cell cycle but accelerate it in the S phase, thus resulting in the proliferation of repair cells and promotion of wound healing. EGF plays an important role in the later stage of wound healing and has a good clinical effect on skin wound healing [21]. The inhibition of chemokine expression by PGRN depends largely on tumor necrosis factor receptor 1 (TNFR1) [22]. High levels of PGRN mRNA appear in damaged skin and remain above the baseline level for at least 10 days. By contrast, PGRN mRNA is hardly expressed in undamaged skin and can rapidly and remarkably induce gene expression after skin damage. The administration of PGRN in skin wounds can prolong inflammatory infiltration, especially neutrophil infiltration, and increase the aggregation of fibroblasts and blood vessels in wounds. PGRN's role in inflammation comes from secretory leukocyte protease inhibitor factor (SLPI)'s role in the injury. SLPI is an inhibitor of protease, neutrophil elastase, and chymotrypsin, blocks the inflammatory reaction of macrophages and monocytes to microbial products, and protects PGRN from proteolysis in an inflammatory environment by directly inhibiting elastase activity, binding PGRN, and separating it from the enzyme [23]. PGRN knockout may enhance fibrosis through the TGF-β/Smad signaling pathway [14]. When lipopolysaccharide is increased due to mouse infection, PGRN overex-

pression can effectively prevent serious inflammation, lung injury and cell apoptosis caused by lipopolysaccharide-induced endotoxic shock [24].

1.2. PGRN in Gastritis

With the rapid economic development and fast pace of life, the younger age group of patients has increasingly being diagnosed with gastropathy. *Helicobacter pylori* is the main pathogen of gastrointestinal diseases and is related to the occurrence and development of superficial gastritis, atrophic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Our experimental results showed that the expression levels of PGRN mRNA and protein in normal gastric mucosa, superficial gastritis, and atrophic gastritis increased in clinical tissue specimens infected by *H. pylori* increase, and the expression increased with the passage of time. The same results were obtained by infecting gastric mucosal epithelial cells with various strains.

1.3. PGRN in Lung

PGRN is upregulated in influenza-virus-infected patients. More importantly, the concentration of PGRN in patients with severe clinical infection is higher than that in patients with mild infection. Lung injury, edema, and mortality of patients are decreased when PGRN is reduced, indicating that the increase in PGRN may be a potential predictor of influenza prognosis. In influenza and bacterial pneumonia, lack of PGRN will not affect the levels of TNF-α and IFN-γ in lung tissue [25].

1.4. PGRN in Viral Myocarditis

Viral myocarditis is mainly caused by coxsackie virus 3 (CVB3) infection and is the main cause of heart failure, sudden death of young people, and accidental death. After CVB3 infection, the level of PGRN in the serum and heart tissue remarkably increases, which was negatively correlated with the severity of the disease. However, the protective effect of PGRN on CVB3-induced myocarditis Treg was independent, and the survival rate and weight loss of mice lacking PGRN after Treg depletion were not affected. PGRN can prevent CVB3-induced myocarditis *in vivo* and *in vitro* by downregulating Th1 and Th17 cell responses and producing cytokines IL-17A, -21, and -B, IFN-r, and TNF-A. In other words, PGRN can prevent CVB3-induced myocarditis by regulating Th1 and Th17 cell responses. In addition, PGRN inhibited Th1 and Th17 cell differentiation in a dose-dependent manner through the JAK/STAT pathway. Notably, JAK2-activated STAT4 participates in Th1 differentiation. Similarly, GRN E and PGRN have dose-dependent effects on the cell proliferation of motor neurons and cortical neurons. By contrast, the development of Th17 cells depends on JAK 3 and STAT 3. More importantly, treatment with recombinant PGRN resulted in reduced mortality, weight loss, and heart inflammation in mice. Therefore, the application of recombinant PGRN can effectively improve fatal myocarditis induced by CVB3, and PGRN may be a new therapeutic target for viral myocarditis [3, 26].

1.5. PGRN in Scleroderma

Scleroderma is a connective tissue disease, which is an autoimmune disease of unknown etiology. Although not hereditary, this disease has certain relations with heredity, self-construction, and environment. Scleroderma can cause skin damage and seriously affect the internal organs of patients. This disease is divided into two types, systemic scleroderma (SSc) and localized scleroderma (LSc or scleroderma). In scleroderma, the expression of PGRN and TNF-α increases, but the increase of PGRN is regulated by the efficiency of transcription factor fragment virus insertion site 1 (Fli1), which is a potential susceptibility factor for SSc. The downregulation of Fli1 is caused by the activation of C-ABL/protein kinase C (PKC)-δ/ Fli1 pathway and participates in the induction of type I collagen expression. PGRN siRNA reverses the perception of TNF-α by LSc dermal fibroblasts. The composition activation of C-ABL/PKC-D/ Fli1 pathway is helpful to establish the embryonic phenotype of LSc dermal fibroblast protoplasts. In this pathway, activated C-ABL phosphorylates PKC-D and promotes its nuclear translocation. Nuclear PKC-D induces the phosphorylation of Fli1 on threonine 312, which in turn causes Fli1 lysine 380 to be acetylated by P300/CBP related factors. Subsequently, acetylated Fli1 loses its DNA binding ability and is rapidly degraded *via* the proteasome pathway. Therefore, the activation of C-ABL and PKC-D is helpful to induce the ex-

pression of PGRN in LSc skin fibroblasts. Excessive production of PGRN results in the inhibition of Fli1 in LSc dermal fibroblasts. When the expression of PGRN siRNA and Fli1 is normal, the decrease in Fli1 expression leads to the upregulation of PGRN. PGRN overproduction and Fli1 downregulation establish a feed-forward loop, thus greatly inhibiting the expression of Fli1. In addition, although TNF-α has an effective anti-tumor effect on skin fibroblasts, the increase of serum TNF-α level is related to LSc activity and the severity and high incidence of immune abnormalities. TNF-α has a dual mode of action in the development of LSc, stimulants, and inhibitors. In short, PGRN reduces the inhibitory effect of TNF-α on LSc pathology by blocking the antithrombotic effect of TNF-α on skin fibroblasts. PGRN defects become potential therapeutic targets for LSc through various mechanisms. Recently, Yang *et al*. found that PGRN can promote the development of skin fibrosis by up-regulating TβRI to activate TGF-β/Smad3 signals [27, 28].

1.6. PGRN in Neurons

Schwann cells are glial cells, which appear in the peripheral nervous system and have phagocytic ability. It can remove cell debris and provide space for neuron regeneration. Among the glial cells, Schwann cells have always been the focus of research due to their special position and their role in the composition of peripheral nerve structures. Their functions include promoting axonal regeneration (secretion of various neurotrophic factors), promoting myelination, repairing regenerated axons, and the interaction between cells and regenerated nerve fibers [29, 30].

Under normal circumstances, regenerating damaged central neurons is difficult. However, if the peripheral nerve graft or SC-containing extract is implanted into the reticular region, the regeneration of neurons in SC graft is efficient, which indicates that the cell surface provided by SC is very important compared with the empty graft. Combined administration with SLPI eliminated the neurotrophic effect of PGRN on motor neurons and cortical neurons. At the same time, PGRN hydrolyzed by protein can produce neurotrophic effect, that is, the single GRN formed by PGRN is blocked by SLPI, which directly binds PGRN, thus protecting PGRN from proteolytic cleavage. Combined administration of SLPI and PGRN almost completely eliminated the neurotrophic effect of PGRN. PGRN is secreted by stem cells *via* co-differentiation and is determined by the differentiation state of stem cells. With the passage of time, the level of PGRN mRNA also increases. PGRN and single GRN promote the nerve growth of MNS. SLPI prevents the promoting effect of axon growth in a dose-dependent manner. The enhanced MN activity in SC-MN cross well co-culture is mediated by the PGRN secreted by SCs. Dedifferentiated SCs induce PGRN expression *in vivo*. SCs provide necessary signals and cells to enhance MN survival and axonal growth. Therefore, PGRN is a neurotrophic factor that can enhance neuron survival and axon growth and has very important therapeutic potential for nerve regeneration disorders (frontotemporal dementia) [31-33].

FTLD is a family disease, accounting for 30%-40% of the cases. Mutation of granulin precursor is a common cause of FTLD. Loss of GRN gene function mutation is a common cause of neurodegenerative disease FTLD, and PGRN deficiency leads to neuronal atrophy and neurodegeneration. Interestingly, the mutation of GRN gene function loss leads to enhanced PGRN immunostaining in the activated microglia of FTLD patients [34]. Considering PGRN's neuroprotective effect, the physiological significance of PGRN's enhanced expression in microglia activated in neurodegenerative diseases has not been fully elucidated. Recombinant PGRN and single-particle protein (GRN C and GRN E) can both enhance neuronal survival and promote neuronal growth [4, 35-40]. The combination of PGRN and TNF-a to regulate WNT5A contributes to the treatment of FTLD-TDP associated with GRN mutation [41].

2. PGRN IN CANCER

In recent years, studies in PGRN have reported the potential of GC as a molecular biomarker of tumor state. Gastric cancer is a major disease affecting the quality of human life. Approximately one million people worldwide are diagnosed with gastric cancer every year. Research on the role of PGRN in gastric cancer is still limited. The ex-

pression level of PGRN in *H. pylori*-infected gastric cancer cells in human gastric cancer epithelial SGC 7901 and GES-1 cells increases [42]. PGRN infection can remarkably enhance the invasion and metastasis of gastric cancer cells. Interference with PGRN can remarkably reduce cell proliferation and migration caused by *H. pylori* infection. *H. pylori* infection can obviously improve the healing speed of scratch test, while the healing speed of *H. pylori* infection scratch test slowed down after PGRN was inhibited. This phenomenon indicates that the highest expression of PGRN caused by *H. pylori* infection is a strong promoter of gastric cancer. After *H. pylori* eradication, the incidence of gastric cancer decreased significantly. The overall survival rate (OS) and progression-free survival rate (PFS) of PGRN group were lower than those of the PGRN group.

The high expression of PGRN was closely related to lymph node metastasis, lymph node invasion, poor prognosis, and early clinical stage. Extracellular PGRN promoted the expression of intracellular PGRN in gastric cancer cell lines MKN-45 and MGC-803 through the Akt and ERK signaling pathways. Moreover, extracellular PGRN upregulated intracellular PGRN in a concentration-dependent manner. After administration of AKT inhibitor (U 0126) and ERK inhibitor (LY 294002), the upregulation of PGRN in rPGRN-induced cells was cancelled. The role of AKT and ERK also confirmed the positive feedback regulation mechanism of PGRN in gastric cancer cells. PGRN affects the proliferation and aging of gastric cancer cell BGC 823 through the aging pathway, indicating that PGRN is an important regulator in the aging process of BGC823 cells [43, 44]. Although eradicating *H. pylori* may be the main strategy to prevent GC occurrence, we should also consider the risks of the environment and other factors (smoking, alcohol, excessive salt intake, and vegetables and fruits), especially in high-risk groups such as Asia; hence, we should formulate appropriate control guidelines according to the numerous risks [45].

2.1. PGRN in Cervical Cancer

PGRN is overexpressed in cervical cancer cells and tissues, which indicates that PGRN contributes to cervical cancer cell proliferation. PGRN can also promote mTOR phosphorylation, and the expression of PGRN is positively correlated with mTOR phosphorylation. PGRN can also stimulate the phosphorylation of AKT, P706K, and GSK-3α/β (downstream factor of mTOR in C2C12 cells). Pretreatment with 500 ng/ml recombinant PGRN (rhPGRN) can remarkably enhance the mTOR phosphorylation of H8 cervical cells, and the same results were obtained in Siha and HeLa cells. However, when PGRN-siRNA and MEK/ERK inhibitor U0126 were applied, mTOR phosphorylation was reduced. In the catalytic subunit mTOR, The mTOR participated in two different complexes, rapamycin mTORC1 and mTORC2. PGRN promoted the activation of mTORC1 and mTORC2 in cervical cancer cells and played a role in cell proliferation, growth, survival, and differentiation. By using rapamycin and rhPGRN, results showed that rapamycin weakened the PGRN-activated mTORC1. Considering that mTORC1 controls the protein synthesis rate, the protein synthesis rate of HeLa cells decreased after PGRN-siRNA was applied. The application of rhPGRN enhanced the protein synthesis rate in HeLa cells but was cancelled by rapamycin pretreatment. PGRN in liver cancer cells causes IL-6 secretion through the mTOR signaling pathway, which leads to proliferation, migration, apoptosis, and infiltration of liver cancer cells. IL-6 increases the level of PGRN in hepatoma cells in a dose- and time-dependent manner. IL-6 partially drives the expression of PGRN through Erk/C/Ebpβ signal conduction [46].

TNFR is a potential binding receptor of PGRN [47] and is required for PGRN-mediated mTOR signal transduction by analyzing the binding of PGRN to TNFR 1 and TNFR 2 in HeLa cells. Notably, the decrease of TNFR 2 rather than TNFR 1 remarkably blocks the mTOR signaling stimulated by rhPGRN in HeLa cells. In cell transformation analysis, rhPGRN pretreatment enhanced the colony formation ability of H8 cells, while rapamycin pretreatment reduced the proliferation of PGRN-supported cells. RhPGRN pretreatment improved the survival rate of H8 cells in the low-serum culture. CCK-8 and cell count analysis confirmed that the pretreatment of mTOR signal inhibitor rapamycin inhibited PGRN from stimulating cervical cell proliferation. In comparison with PBS-

treated cervical cancer cells, PGRN-treated HeLa cells have enhanced DNA synthesis. Similarly, it was cancelled by rapamycin.

Single-layer wound test showed that rapamycin, an mTOR signal inhibitor, interfered with rhPGRN to promote H8 cell migration. Moreover, PGRN increased the expression of cyclin D1, but rapamycin had limited influence on it. In addition, the inhibition of mTOR signal can destroy PGRN's inhibition of apoptosis induced by HeLa cells. In animal experiments, rapamycin inhibited PGRN-stimulated tumorigenesis in nude mice. H8 and HeLa cells were injected into nude mice, rhPGRN was used to promote tumor growth, whereas rapamycin was used to inhibit tumor growth. Overall, the occurrence and development of cervical cancer caused by PGRN require mTOR signal. PGRN has little effect on the EMT of cervical cancer cells but can rearrange cytoskeleton. TNFR is the receptor of PGRN. PGRN activates the invasion of cervical cancer cells through the mTOR (mTOR-related protein) signal pathway of TNFR 2 and uses the mTOR inhibitor rapamycin to reduce the invasion and metastasis of cervical cancer cells. PGRN can activate FAK/Lick/Confil in the signaling pathway related to cytoskeleton rearrangement and promote the phosphorylation level of FAK. The PGRN activation of Rho small GTP enzyme depends on the mTOR signal pathway. PGRN-mediated cervical cancer cell migration, invasion and metastasis depend on FAK and Rho small GTP enzyme activities [48, 49].

After cisplatin treatment, the expression of PGRN in cervical cancer cells increases in a time- and concentration-dependent manner. Recombinant human PGRN can effectively alleviate the activity of cisplatin that kills cancer cells and remarkably resists cisplatin-induced cervical cancer cell death and DNA damage. This phenomenon occurred because PGRN promotes the outflow of cisplatin and reduces the accumulation of cisplatin *in vivo*. After inhibiting PGRN expression, the accumulation of cisplatin remarkably increased. When further detecting the mRNA of molecules related to cisplatin efflux, MRP 2 mRNA and protein levels were remarkably increased.PGRN guides the resistance of MPR 2 to cisplatin through NRF 2. In the detection of related molecules, rhPGRN can not only upregulate the expression of RAD51 mediated by homologous recombination repair but can also improve the level of DNA-PK protein mediated by error-prone repair. Therefore, PGRN may mediate the tolerance of cervical cancer cells to cisplatin through various mechanisms [50-52].

2.2. PGRN in Epithelial Ovarian Cancer and Colorectal Cancer

The downregulation of E-cadherin is a key step in EMT. RhoC promotes EMT and may participate in the downregulation of Notch receptor in cervical cancer. The stable expression of RhoC contributes to wound healing, invasion, and metastasis of cervical cancer cell lines Caski and Siha. The high expression of PGRN in cervical cancer can mediate the migration and invasion of ovarian cancer cells by enhancing the EMT program. RhPGRN can invade and transfer cervical cancer cells (HeLa, SiHa) [53]. In colorectal cancer (CRC), the expression of LncRNA H19 increased, the expression of miR-29b-3p decreased, the prognosis of CRC was poor, the overall survival rate (OS) decreased, the migration ability decreased, and the expression of PGRN increased. After miR-29b-3p inhibitor was used, the expression of e-cadherin increased, whereas the expression of c-myc, vimentin, and snail decreased. At the same time, the Lnc RNA H19 miR-29b-3 PGRN axis realized the epithelial-mesenchymal transformation of CRC through the Wnt signaling pathway [54, 55]. GP88 can inhibit apoptosis induced by the overexpression of anti-tumor drugs (Faslodex) through bacl-2 and bcl-xl [2, 56].

3. PGRN RECEPTORS AND SIGNAL TRANSDUCTION

TNFR 2 is the binding receptor of growth factor PGRN. The TNDR 2 explains the specific mechanism of PGRN's anti-TNFα-induced inflammatory response and provides a theoretical basis for the study of various biological effects and related molecular mechanisms of PGRN [57]. This conclusion is a milestone and unprecedented discovery. The interaction among PGRN, TNFRS, and TNFRSF RANK members was confirmed at the protein, cell, and animal levels. PGRN directly binds TNFR 1 and TNFR 2, especially TNFR 2,

and inhibits the function of TNF-α. Based on the analysis of PGRN/TNFR 2 binding fragments, PGRN-derived engineering proteins were constructed. Recombinant protein Atsttrin selectively binds TNFR 2 to inhibit TNF-TNFRS binding and TNF-α induced inflammatory response. PGRN also has a protective effect on inflammatory arthritis [58]. Atsttrin-alg/nhp scaffolds printed in 3D have anti-inflammatory properties and promote bone defect repair [59]. PGRN and RANK inhibit osteoclast differentiation and osteoporosis in mice, thus providing a new candidate protein for osteoporosis drug development [60].

PGRN plays an anti-inflammatory role in various inflammatory diseases, such as rheumatoid arthritis (RA) [61], systemic lupus erythematosus (SLE), Alzheimer's disease, atherosclerosis, septicemia, and bacterial pneumonia by interfering with TNF receptor signaling. However, the anti-inflammatory effect of proinflammatory factor PGRN may depend on the stage and tissue microenvironment.

The immunosuppressive job of PGRN is related to its effect on regulatory T (Treg) cells. Treg cells are naturally occurring, and their typical marker include $CD4^+$, $CD25^+$, $Foxp3^+$ (the most important molecular marker is transcription factor $Foxp3^+$). Lack of PGRN will not change the number and percentage of Treg cells in the thymus, spleen, and lymph nodes of normal mice. However, the lack of PGRN results in a remarkable decrease in Treg cells under inflammatory conditions, such as experimental dermatitis and collagen-induced inflammatory arthritis. PGRN also protects Treg cells from negative regulation by TNF. The complicated mechanism of PGRN regulating Treg cells under dissimilar inflammatory conditions needs to be discussed in forthcoming studies. PGRN can inhibit inflammation and treat inflammatory arthritis. PGRN-mediated amplification and activation of Treg cells and the production of IL-10 depend on JNK signals but not on known ERK and PI3K pathways [62]. In addition, microarray and chromatin immunoprecipitation sequencing screening led to the discovery of forkhead box protein O4 and signal transduction and transcription activator 3, which are transcription factors required by Treg cells to induce IL-10. PGRN can stimulate various intracellular pathways to promote cell proliferation, migration, and transformation, including ERK, PI3K and MAPK signal, p38, AKT *etc*. PGRN signal transduction depends on TNFR 2. Moreover, the blocking and deletion of TNFR 2 will damage Treg amplification and activation and eliminate the production of IL-10. In addition, whole- genome microarray analysis showed that transcription factors Foxo and Stat 3 bind to the conserved promoter region of IL-10 site in $CD4^+$ T cells and can control the production of IL-10 in these cells. Ultimately, PGRN can effectively improve chronic inflammatory diseases by producing Foxo4- and Stat3-dependent IL-10 in Treg cells. Th17/Treg imbalance may be related to the pathogenic reaction of rheumatoid arthritis. PGRN can reduce IL-6, which can explain the reduction of Th17 cells. Therefore, whether PGRN can offset Th17/Treg imbalance needs further research.

Akt is a key signaling pathway that manages endothelial nitric oxide synthase (eNOS) in endothelial cells [63]. ENOS is the key to order vascular function because it can not only produce nitric oxide to expand blood vessels but can also produce superoxide to contract blood vessels. Akt may participate in TSH's effect on eNOS expression and eNOS and PGRN expression in aortic endothelial cells of subclinical hypothyroidism rats. In endothelial cells cultured *in vitro*, TSH can increase eNOS expression through the AKT pathway, which is related to the increase of PGRN.

Autophagy was discovered in 1963 and has been a hot research topic up to now. However, the mechanism of PGRN and autophagy in diseases (inflammation and tumor) remains unclear. PGRN is an important regulator of glucose metabolism and insulin sensitivity. Circulating PGRN is remarkably related to insulin sensitivity and autophagy activity in adipose tissue. The new factor PGRN may induce autophagy through oxidative and ER stress and may induce defective autophagy through TNFR 1/NF-κb to mediate the pathogenic effect of liver insulin resistance. ER stress may be induced by PERK-eIF2alpha-dependent pathway [63-66]. The homozygous or heterozygous mutation of GRN gene and mutated PGRN leads to neuron-like red lipofuscin and frontotemporal de-

mentia (FTD), respectively. Trehalose, a new autophagy lysosomal regulator, can enhance the expression of PGRN and prevent PGRN defects in human fiber cells and neurons derived from induced pluripotent stem cells generated by GRN mutant vectors to treat various neurodegenerative diseases. Butler *et al*. [19] found that PGRN stimulates the maturation of lysosomal aspartyl protease cathepsin D *in vitro*. PGRN enhances the *in vitro* transformation of an inactive precursor to the mature state in a concentration-dependent manner, which will be helpful to improve the targeted treatment of neurodegenerative diseases.

Marc *et al*. evaluated the concentration of cerebrospinal fluid PGRN and neurofilament light chain in patients with radiological isolation syndrome as potential markers of early repair mechanism/inflammation and axonal loss among clinical patients.

In the hydrolysis product, GRN1-7, of PGRN, GRN has the background of FTD. Bhopatkar *et al*. studied the effect of oxidized and reduced GRN-3 on A β aggregation and found that GRN-3 (oxidation) and rGRN-3 (reduction) combines with monomer and oligomer A β 42 to promote fibril formation and reduce A β 42-induced apoptosis. In addition, the interaction of A β 42-GRN-3 can reduce the activation of caspase-3 and -7 in neuroblastoma cells and the apoptosis of neuroblastoma cells, which provides a new perspective for major events in AD. PGRN has a negative regulatory effect on the inflammatory response of keratinocytes induced by TNF α. PGRN also generates inflammatory factors through the Wnt/ β - catenin signaling pathway and actively mediates autophagy. Moreover, PGRN has a substantial negative correlation with the expression of beta-catenin in psoriatic skin. In tumor cells with defects in apoptosis, autophagy allows prolonged survival and thus is a new therapeutic target for PGRN-related diseases [67-78].

4. OTHERS

RPGRN greatly aggravates renal injury and can prevent renal chemical/ reperfusion injury [79]. PGRN can effectively resist bacterial infection, bacterial death, and endotoxin shock in mice after dissolution. It can improve the survival rate, alleviate the symptoms of lung injury and renal failure, reduce the production of proinflammatory mediators, and reduce the proliferation and apoptosis of proinflammatory cells in the lung, which can treat endotoxic shock [80, 81]. PGRN participates in the pathological process of rheumatoid arthritis (RA) and has an important value in the diagnosis of RA and the differential diagnosis between RA and OA. PGRN-abs may be a potential diagnostic marker in the serum of RA patients collected recently [82]. PGRN can promote the healing of gastritis inflammation, but it plays an anti-inflammatory role in inflammatory bowel disease and is realized through the TNFR and IL-10 signal pathway. Contrary to its anti-inflammatory effect, PGRN plays a pro-inflammatory role in obesity and insulin resistance diabetes [83]. Knocking down PGRN can effectively inhibit the growth of melanoma in C57BL/6J mice [84]. The increase in PGRN is related to the decrease in the cognitive ability of fragile X syndrome (FXS), indicating that PGRN Ko can improve FXS. GRN is also a new glucose adenosine inhibitor whose function is related to Gaucher's disease (GD). When GD occurs, the level of PGRN decreases markedly, whereas CHI3L1 increases substantially. Therefore, CHI3L1 is a downstream molecule of PGRN and a marker for inflammation and cancer. Studies based on human carotid endarterectomy specimens found that PGRN and GRN have opposite effects on IL-8 secretion. PGRN expression mainly reduces inflammatory reaction, but the degradation of GRN may lead to the development of atherosclerosis. PGRN is expressed in human mesothelioma cells. Mesothelioma-derived granulin precursor (PGRN) and granulin-like protein (GRN protein) induce VEGF-independent angiogenesis. Lectin (CLU) and PGRN can participate in the pathogenesis of TDI-induced occupational asthma (TDI-OA) by preventing TDI-induced oxidative stress. CLU/PGRN serum levels can be used as serum markers to identify the TDI-OA of workers exposed to TDI. PGRN is a necessary secretory cofactor to enhance the driving response of TLR 9 to CpG-ODNs. As a key soluble cofactor in TLR 9 signal transduction, PGRN is related to innate immunity [85-89].

Acute otitis media is mainly caused by *Streptococcus pneumoniae*. Wang *et al*. [49] established a C57BL/6 mouse model of acute otitis media and found that compared with the wild type, PGRN-/- mouse macrophage recruitment increased, and PGRN-/- mouse bacterial clearance rate decreased. This finding shows that PGRN has dual effects on macrophage activity. PGRN is related to the occurrence and development of many diseases. Therefore, exploring the regulation of PGRN gene transcription is important for screening drugs that target PGRN. Li *et al*. established a luciferase knock-in system in HEK 293 cells by integrating luciferase gene into the genome controlled by the endogenous PGRN promoter by using CRISPR/Cas9. They found that luciferase activity is directly related to the activity of the PGRN endogenous promoter. They also developed a high-sensitivity sandwich ELISA for PGRN to detect PGRN content in CSF that produces highly sensitive results compared with ordinary ELISA [90, 91].

5. DISCUSSION AND NEXT DIRECTIONS

The fine line between human health and disease can be driven by the interplay between host and microbial factors. This "metagenome" handles cancer initiation, progression, and repose to immune system. If gastric mucosa is infected with *H. pylori*, then a complete PGRN exists, and the kinetic energy increases its expression either during inflammation or gastric cancer. After *H. pylori* infects gastric mucosal epithelial cells, complete PGRN can play an anti-inflammatory role. However, the anti-inflammatory effect of PGRN when it enters the nucleus and after being decomposed by enzymes has not been analyzed. These research gaps are worthy of further investigation. PGRN is upregulated in most tumors, and the tumor and inflammatory mechanisms of PGRN have been widely studied. However, the relationship and mechanisms of PGRN in the prognosis of tumor treatment have not been clearly explained, and further research is needed for improved clinical service.

PGRN causes anti-inflammatory protection and pro-inflammatory injury in the inflammation system. GP88 exerts pro-inflammatory functions in high-fat-diet-induced insulin resistance and obesity [92, 93]. In foam cells and macrophages of atherosclerotic plaques [94], the knockout of PGRN leads to severe atherosclerotic lesions. MiR-34b-5p inhibits lung inflammation and the apoptosis mouse model of LPS-induced acute lung injury by targeting reduced protein precursor particles [95].

PGRN levels are also upregulated in other disease and cancer types. Serum PGRN is elevated and in sick person with RA and is related to disease activity. The serum PGRN level in patients with SLE is also remarkably higher than that in healthy controls, thus reflecting its disease activity. PGRN level also increases in individuals with clinical and experimental bacterial pneumonia and those with breast cancer, non-small cell lung cancer, epithelial ovarian cancer, cervical cancer and glioblastoma. These findings and our research results suggest that PGRN may be a new biomarker for the diagnosis and development of various diseases. Further research is needed to detect PGRN expression in the invalid with acute viral myocarditis and evaluate its diagnostic and prognostic value in human acute viral myocarditis.

PGRN is an endogenous protein with various signal pathways and IL-biological effects that facilitates the growth and repair of healthy tissues and plays an important anti-inflammatory role in injured tissues. PGRN is a potential inhibitor of TNF-α, because it can inhibit TNF-α- induced neutrophil activation and the release of oxides and proteases. This protein can also be used as a biomarker for predicting tumor recurrence and observing curative effect. PGRN can selectively bind to TNF receptors and inhibit the downstream inflammatory signaling pathways of various diseases such as arthritis. Owing to the intricate function of PGRN, its influence on TNFR molecular mechanism needs further study. Cancer is the main cause of high mortality in humans, and many cancer types are still incurable due to lack in effective treatment methods and unknown pathogenesis. Therefore, new cancer mechanisms and related treatments should be explored. The high PGRN expression is closely related to malignant tumor progression and high mortality. PGRN may become a new therapeutic target that provides a reliable basis and prospect for further diagnosis and clinical treatment of malignant tumors. Researchers might be inspired to explore PGRN in inflam-

mation and tumor healing. Therefore, the pathogenesis of PGRN (GP88) should be fully understood, and additional effective therapies should be developed.

CONCLUSION

PGRN stands out due to its anti-inflammatory and tumorigenesis functions; however, the related mechanism remains to be explored. For our further research on PGRN, the mechanism of molecule transformation between anti-inflammatory and tumorigenesis should be clarified. The role of PGRN is also different in different organizations, and we need specific analysis of specific problems to achieve symptomatic treatments. Finally, the physiological and pathological changes caused by GRN gene function loss mutation, such as the interaction with neurodegeneration, must be clarified. The role of autophagy in PGRN mediates the inflammation and tumor.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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