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Progranulin and Its Biological Effects in Cancer

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Abstract

Cancer cells have defects in regulatory mechanisms that usually control cell proliferation and homeostasis. Different cancer cells share crucial alterations in cell physiology, which lead to malignant growth. Tumorigenesis or tumor growth requires a series of events that include constant cell proliferation, promotion of metastasis and invasion, stimulation of angiogenesis, evasion of tumor suppressor factors, as well as avoidance of cell death pathways. All these events in tumor progression may be regulated by growth factors produced by normal or malignant cells. The growth factor progranulin has significant biological effects in different types of cancer. This protein is a regulator of tumorigenesis because it stimulates cell proliferation, migration, invasion, angiogenesis, malignant transformation, resistance to anticancer drugs, and immune evasion. This review focuses on the biological effects of progranulin in several cancer models and provides evidence that this growth factor should be considered as a potential biomarker and target in cancer treatment.

Keywords

Progranulin; Cancer; Biomarker

Introduction

Progranulin (PGRN) is a protein also known as acrogranin, granulin/epithelin precursor (GEP), proepithelin (PEPI), PC cell-derived growth factor (PCDGF) and 88 kDa glycoprotein (GP88). These names were originated by the different groups that independently identified the parent glycoprotein or its derivative fragments in specific tissues or cells. PGRN is a 67–88 kDa glycoprotein identified in 1990 by Anakwe and Gerton in the sperm of the guinea-pig and, because it was present in the acrosome granule, they called it “acrogranin”. Later, they established its participation in the biogenesis of

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Conflict of interest

All authors declare that they do not have conflict of interest.

guinea-pig acrosome [1, 2]. Simultaneously, two other research groups isolated and characterized small cell growth-modulating proteins or peptides of approximately 6 kDa. The first group purified peptides from rat kidney, which they called “epithelins” [3]. The second research team utilized rat bone marrow and human peripheral leukocytes as sources, naming the peptides “granulins” [4]. Rat epithelins and rat and human granulins were subsequently recognized as homologous and derived from a common precursor named “proepithelin” [5] or PGRN [6], respectively, which were also homologous to acrogranin [2]. Another name for this autocrine growth factor, which is homologous to PGRN, is PCDGF since it was purified from PC cells derived from adipogenic teratoma cells (1246-3A cell line) [7].

The granulin precursor (*GRN)* gene encoding human PGRN, contains 13 exons and is located on the long arm of chromosome 17, specifically in the cytogenetic band 17q21.23, while the murine gene is found in a syntenic region on chromosome 11 [8, 9]. Human preprogranulin consists of 593 amino acids, of which about 15% of the residues correspond to cysteines; its sequence forms seven and a half repetitions in tandem of a highly conserved motif called the granulin domain [6, 9].

After secretion, PGRN may be proteolytically cleaved between the granulin domains to produce fragments or individual granulin peptides. Neutrophil secreted elastase, proteinase 3, matrix metalloproteinase 9 (MMP-9), MMP-12, and MMP-14, as well as a disintegrin-like and metalloproteinase domain 7 (ADAMTS-7), are proteases capable of processing PGRN [10–15]. Furthermore, a recent study demonstrated that cathepsin L (Cat L), a lysosomal protease, proteolytically processes and degrades intracellular PGRN in the lysosome [16]. In contrast, secretory leucocyte protease inhibitor protein (SLPI) and high-density lipoprotein/apolipoprotein A-I (HDL/Apo A-I) protect PGRN from proteolysis by two mechanisms: (1) binding to the inter-granulin linker regions to block accessibility to proteases and (2) inhibiting the converting protease directly [10, 17] (Figure 1).

Intact PGRN protein is a concatenation of 7 granulin domains (G-F-B-A-C-D-E) preceded by a half granulin domain, “paragranulin” (P) (Figure 1). The intact protein sequence (P-G-F-B-A-C-D-E) is encoded by 12 out of the 13 exons of the *GRN* gene. PGRN actions depend on the cellular target. As mentioned above, PGRN can be cleaved into bioactive fragments or individual granulin peptides. Generally, PGRN is considered anti-inflammatory; however, when PGRN is fragmented, the resulting granulin peptides take on new bioactivities. For example, some granulin peptides are pro-inflammatory. In other cases, granulin peptides are toxic; in the case of *Caenorhabditis elegans*, certain granulin peptides increase TDP-43 levels via a post-translational mechanism and exacerbate TDP-43 toxicity [18]. Rollinson et al. [19] expressed recombinant PGRN and each of the individual granulin peptides; they demonstrated that short-duration treatments with PGRN result in the down-regulation of several critical transcripts. Gene ontology analysis supports the regulation of biological processes such as the spliceosome and proteasome in response to PGRN treatment, as well as lysosomal pathway constituents. On the other hand, granulin peptide treatments alter the regulation of numerous non-coding RNAs.

PGRN and granulins produce significant biological effects, which are mediated through a cell-surface receptor. A unique PGRN-specific receptor has not yet been identified. Up to now, PGRN has been demonstrated to interact with different binding proteins depending on the cell type. PGRN is able to bind to the beta propeller region of sortilin through its C-terminal tail. This protein is a single-pass transmembrane protein in the vacuolar protein sorting/targeting protein 10 (VPS10) family, which regulates intracellular protein trafficking and acts as a cell surface receptor. In the brain, sortilin can regulate PGRN levels through endocytosis [20]. In castration-resistant prostate cancer cells, sortilin loss may contribute to prostate cancer enhancing PGRN effects. Therefore, extracellular PGRN levels depend on PGRN-sortilin interactions [21]. PGRN and granulin interactions with tumor necrosis factor receptor (TNFR) 1 and 2 has also been demonstrated. In these receptors, PGRN binds directly to the extracellular CRD2 and CRD3 domains. In mouse inflammatory models, binding of PGRN to TNF-receptors inhibits TNF-α binding and its biological effects, which may explain the anti-inflammatory properties of PGRN [22]. More recently, EphA2, a member of a large family of receptor tyrosine kinases (RTKs), was identified as a functional signal receptor for PGRN in a human urinary bladder cancer cell line. The interaction between EphA2 and PGRN provides the opportunity to understand the mechanisms through which PGRN activates tumorigenic signaling pathways [23].

In vitro and *in vivo* studies have demonstrated the important role of PGRN in diverse physiological processes. This protein participates in the growth stimulation of preimplantation mammalian embryo development [24], in early embryogenesis [25], in wound healing [26], inflammation [11, 27], angiogenesis [26, 28], and bone and cartilage development [29, 30]. It is also an adipokine implicated in obesity, insulin resistance, and rheumatic disease [31]. The role of PGRN in several neural pathologies led to an explosion of *GRN* genetic studies [32–35]. PGRN is a neurotropic and neuroprotective factor that shields neural tissue from inflammation and degeneration. Loss of function mutations in the *GRN* gene has been associated with neurological and neurodegenerative diseases as in frontotemporal dementia, Parkinson's disease, Creutzfeldt-Jakob disease, motor neuron disease, and Alzheimer's disease [36, 37].

PGRN overexpression has been observed in many different types of cancer as described in Figure 2. In these tissues, high expression of PGRN drives tumor progression since it promotes cellular responses such as cell proliferation, migration, invasion, angiogenesis, malignant transformation, resistance to anticancer drugs, and immune evasion (Figure 3). Numerous studies over the last two decades have pointed to the importance of PGRN in cancer, and this review focuses on the biological effects of PGRN in several cancer models. Furthermore, the uses of PGRN as a biomarker and as a target in cancer treatment are addressed.

Biological effects of progranulin in cancer

Cellular Proliferation

PGRN promotes proliferation of normal epithelial cells and several cancer cell lines. Cellular proliferation was first demonstrated by the PGRN-derivative epithelin 1 (granulin A) on BALB/MK mouse epidermal keratinocytes [3]. Later, a study in mouse embryos

revealed that exogenous PGRN added to cultures increases the number of trophectoderm cells compared to the controls, besides exhibiting other important effects on embryos [24, 38]. Moreover, to emphasize how important this protein is as a growth factor, PGRN purified from the culture medium of the PC cell line (highly tumorigenic cells) promotes proliferation of 3T3 mouse embryo fibroblast cells [7]. The 3T3 cells generally need two or more growth factors to proliferate *in vitro*; however, PGRN by itself can function as a mitogen in these cells. Furthermore, PGRN stimulates cell division in 3T3 cells lacking expression of insulin-like growth factor receptor 1 (IGF-1R), which is required for other growth factors [Insulin-like growth factor (IGF-1), epidermal growth factor (EGF) and platelet-derived growth factor (PDGF)] to promote proliferation [39, 40]. Additional evidence supporting PGRN proliferative effects comes from studies in which the inhibition of PGRN expression by transfection of a short hairpin RNA (shRNA) into the cell line derived from colorectal cancer SW1116 decreases Ki67, whereas overexpression of PGRN increases it [41].

Mitogenic effects of PGRN also have been observed in other cell lines such as the human epithelial adrenal carcinoma cell line SW-13, multiple myeloma ARP-1 and RPMI 8226 cells, lung carcinoma A549 cells, cervical cancer SiHa cells, prostate carcinoma DU145 cells, laryngeal carcinoma Hep-2 cells and breast cancer cell line SKBR3. Cell proliferation promoted by PGRN was through the activation of the signaling transduction pathways of MAPK/ERK 1/2 and PI3K/AKT/mTOR [42–48].

Molecular mechanisms by which PGRN induces proliferation are still poorly understood. However, studies in breast cancer cells have revealed that PGRN regulates the expression of cyclin D1 and B [49, 50]. Additionally, another study demonstrated a significant correlation between PGRN and cyclin D1 expression in cutaneous squamous cell carcinoma tissues compared with control samples [51]. Additional mechanisms that have been described include phosphorylation of c-myc in MCF-7 breast cancer cells that overexpress the human epidermal growth factor receptor 2 (HER2 receptor) [48], and inhibition of senescence in cervical cancer cell lines [46].

Migration and Invasion

Activation of the epithelium-mesenchymal transition (EMT) process, which can occur as tumorigenesis progresses, is important for cell migration and invasiveness. The EMT process allows cells to escape from the primary tumor after the epithelial cells acquire characteristics of mobile mesenchymal cells [52]. Several studies suggest that PGRN promotes migration and invasion in various cell lines such as breast cancer MCF-7 cells, colorectal cancer SW1116 cells, bladder cancer 5637 cells, prostate cancer LNCaP and DU145 cells, human epithelial adrenal carcinoma SW-13 cells, hepatocellular carcinoma Hep 3B cells, and ovarian carcinoma SW626 and A2780 cells [41, 42, 45, 49, 53–55].

PGRN-promoted migration and invasion of cancer cells can occur by multiple mechanisms. One is through the EMT process, since PGRN overexpression in ovarian cancer cell line A2780 increases mesenchymal marker expression, such as vimentin and twist, and decreases epithelial markers such as E-cadherin and cytokeratin, thereby increasing cell migration and invasiveness [56].

PGRN also increases the invasive capacity of ovarian and breast cancer cells through activation of MMP-2 and upregulation of MMP-9, respectively [49, 53]. In bladder cancer cells, PGRN activates focal adhesion kinase (FAK) through paxillin and ERK phosphorylation. Also, PGRN interacts with the F-actin protein drebrin and induces actin cytoskeleton remodeling. Both effects induce invasion and migration of malignant bladder cells [54]. In contrast to the effects of intact PGRN, the proteolysis-derived granulin A binds to α-enolase of human HepG-2 cancer cells to inhibit growth, glucose uptake, migration, and invasion [57].

Angiogenesis

The earliest relationship between PGRN and angiogenesis was established for wound healing, where PGRN induces human microvascular endothelial cell proliferation and promotes tube-like structures [26]. Subsequently, in the MCF-7 breast cancer cell line, elevated PGRN concentrations are associated with high endothelial growth factor (VEGF) expression [53]. Additionally, PGRN and its derivatives isolated from mesothelioma cells induce VEGF-independent angiogenesis [58]. Other studies have shown a correlation between high PGRN expression with elevated VEGF expression as well as high microvessel density in tissues from breast cancer tumors, esophageal squamous cell carcinoma, and colorectal tumors [41, 59, 60].

Downregulation or null PGRN expression by transfection of shRNA in the cell line SW1116 derived from colorectal carcinoma decreases expression of angiogenic factors such as VEGF-A, VEGF-C, and FGF-1 (fibroblast growth factor 1), and reduces secreted VEGF-A levels in the culture medium of the cells. Interestingly, PGRN overexpression increases the same angiogenic factors. VEGF-A expression induced by PGRN is mediated by tumor necrosis factor receptor 2 (TNFR2)/Akt and the ERK signal transduction pathways [41]. Another mechanism by which PGRN mediates angiogenesis is by promoting proliferation, migration and tubular structure formation by HUVEC cells (human umbilical vein endothelial cells). Interesting, all these events are mediated through the interaction between PGRN and midkine protein (MK), a heparin-binding growth factor [61].

Malignant Cell Transformation

Malignant transformation is the unsolved process by which cells acquire the properties of cancer. Efficient anchorage-independent growth, which is the ability of cells to grow independently of a solid surface, and tumor production in nude mice are commonly considered to indicate a highly transformed phenotype. The earliest study to demonstrate that PGRN can promote cell transformation was performed by He et al. [42], in which overexpression of this growth factor in non-transformed renal epithelial MDCK cells and human adrenal carcinoma SW-13 cells enhanced clonogenicity in semisolid agar. Also, in this study overproduction of PGRN in SW-13 cells markedly increases their tumorigenicity in nude mice. Later, another study with immortalized uterine smooth muscle cells transfected either with PGRN alone or in combination with human telomerase reverse transcriptase (hTERT) and Simian Virus 40 Early Region (SV40ER) genes, showed that PGRN transfection gene increases colony formation in soft agar; while co-expression of PGRN, hTERT, and SV40ER resulted in more extensive anchorage-independent growth and

tumor formation in nude mice. These results suggest that co-expression of these three genes is necessary and sufficient to transform uterine smooth muscle cells [62]. Similarly, transfection of PGRN gene into ovarian surface epithelial cells immortalized by co-transfection with the hTERT and Simian Virus 40 large T antigen (SV40LT) genes revealed that PGRN overexpression increases colonogenicity in soft agar and tumorigenicity in nude mice [63]. Moreover, in human cervical mucosa epithelial H8 cells, PGRN overexpression by gene transfection and cell culture treatment with human recombinant PGRN promotes malignant transformation *in vitro* and *in vivo* as illustrated by increases in cell proliferation and tumor formation in nude mice, respectively [64].

Progranulin and resistance to anticancer drugs

Resistance to anti-neoplastic drugs is a recurrent problem in the treatment of many types of cancers and is the major obstacle to survival in patients with metastatic chemoresistant cancer. The precise cause of this problem is unknown, but growth factor overexpression and their receptors are suspected to be involved. One study has reported that cancer cells that become resistant to anticancer drugs can influence the tumor microenvironment, since cells initially chemosensitive within a tumor, may become chemoresistant due to the secretion of soluble factors released by chemoresistant cells. PGRN is one of the factors identified in the conditioned medium of chemoresistant colorectal cancer cells, and it can influence the survival in otherwise chemosensitive tumor cells through the activation of growth and survival signaling pathways [65].

Tangkeangsirisin et al. [66] were one of the first groups to demonstrate that PGRN confers resistance to anticancer drugs. In their study, they observed that overexpression of PGRN in breast cancer cells MCF-7 prevents tamoxifen (anti-estrogen)-induced apoptosis, and promotes tumor growth and angiogenesis *in vivo*, even in the presence of tamoxifen. Subsequently, Wang and Serrero [67] revealed that PGRN overexpression in multiple myeloma cells leads to the development of resistance to dexamethasone, a conventional drug for treatment of patients with multiple myeloma. Furthermore, Kim and Serrero [68] showed that trastuzumab, a monoclonal antibody directed against HER2, does not have a significant growth-inhibitory effect on breast cancer cells overexpressing HER2 and PGRN. More recently, Abrhale et al. [69] described that PGRN overexpression in MCF-7 breast cancer cells confers resistance to letrozole, an aromatase inhibitor used in the treatment of estrogen receptor-positive (ER+) breast cancer, in a dose- and time-dependent manner. Conversely, PGRN silencing reduces cell viability and restores sensitivity to letrozole. Finally, chemoresistance to cisplatin has been shown in ovarian cancer cell lines overexpressing PGRN [70].

The mechanisms by which PGRN promotes drug-resistance in these types of cancer is unknown. Nevertheless, decreased expression of the anti-apoptotic Bcl-2 protein induced by letrozole and cisplatin does not occur in the presence of PGRN [69, 70]. Similarly, this same mechanism, where PGRN avoids down-regulation of Bcl-2, is involved in the development of resistance to tamoxifen and trastuzumab in breast cancer cells [50, 66, 68]. Another possible mechanism involved in progranulin-conferred chemoresistance includes the

inhibition of the poly (ADP-ribose) polymerase (PARP) cleavage induced by tamoxifen and dexamethasone, a hallmark of caspase-dependent apoptosis [66, 67].

Increased levels of PGRN have also been associated with chemoresistance to doxorubicin and cisplatin, and with a reduced survival time of patients with hepatocellular carcinoma. The mechanism of this association seems to be mediated by the expression of adenosine triphosphate-dependent binding cassette (ABC)B5 drug transporter in cells that also express the hepatic cancer stem cell markers CD133 and epithelial cell adhesion molecule (EpCAM) [71, 72].

In a more recent study with glioblastoma multiforme cells, PGRN overproduction induced resistance to temozolomide (alkylating agent) by upregulation of DNA repair genes PARP, serine/threonine kinase ATM, BRCA1, Rad51, and X-ray repair cross-complementing gene 1 (XRCC1) as well as enhanced expression of cancer stemness genes CD133, CD44 and ABCG2, through the activation of AP-1 transcription factor, specifically cFos/JunB [73].

Although it has been shown that PGRN confers resistance to anticancer drugs, more studies are warranted to further investigate other chemoresistance mechanisms in different types of cancer.

Progranulin and Immunoresponse

Immune evasion is a strategy used by tumors to escape the host immune response, enabling the tumor to continue growing. Cheung et al. [74] reported that PGRN renders hepatocellular carcinoma cells resistant to natural killer (NK) cell-mediated cytotoxicity. The resistance to NK cell lysis induced by PGRN seems to be due to downregulation of MHC class I chain-related molecule A (MICA), which is a ligand for NK stimulatory receptor NK group 2-member D (NKG2D), and upregulation of human leukocyte antigen-E (HLA-E), a ligand for NK inhibitory receptor CG94/NKG2A. Interestingly, inhibition of PGRN activity by neutralizing antibody in hepatocellular carcinoma cells enhanced sensitivity to NK cytotoxicity.

Progranulin as cancer biomarker

A cancer biomarker is a biomolecule such as DNA, RNA or protein that can be measured in tissues or body fluids and can assist in cancer diagnosis, design of treatment modalities, treatment effectiveness, or cancer recurrence detection. Therefore, based on their usage, cancer biomarkers can be diagnostic, predictive, and prognostic [75]. For its important role in carcinogenesis, PGRN has been considered to be a diagnostic, predictive, and prognostic biomarker for some types of cancer.

In epithelial ovarian cancer, PGRN levels in sera of patients with advanced stages of disease can predict who will have recurrence within 18 months of completion of chemotherapy and who will exhibit significantly shortened progression free-survival and overall survival [76]. Furthermore, a correlation between high expression of PGRN mRNA in tissues from malignant ovarian tumors and shorter patient overall survival was observed by Cuevas-Antonio et al. [77]. According to the previous studies, Carlson et al. [78] demonstrated that

PGRN serum concentrations are significantly elevated in patients with advanced stages (III and IV) of ovarian epithelial cancer but not in the earlier stages I and II. Also in this study, high PGRN concentrations were associated with decreased in overall patients' survival. Therefore, these studies demonstrate the promise in using PGRN as a biomarker of ovarian cancer.

Also, in breast cancer, PGRN levels in serum samples from patients with stage I–IV are significantly higher than in healthy women; nonetheless, no differences were observed between the diverse stages of this malignancy [79]. A cohort study of 697 newly diagnosed breast cancer patients who underwent curative surgery, evaluated the association between preoperative PGRN levels and breast cancer recurrence. This study revealed that preoperative serum PGRN levels are clinically significant for predicting recurrence in patients with hormone receptor-positive tumors; however, these data have several limitations that are important to consider when interpreting the study's results [80]. Serrero et al. [81] also analyzed PGRN expression by immunohistochemistry in paraffin-embedded breast tumor sections from patients with estrogen receptor-positive invasive ductal carcinoma. Their results showed that high PGRN expression was associated with a decrease in disease-free and overall survival as well as a 5.9-fold higher hazard of disease recurrence and a 2.5-higher mortality risk compared to patients with low PGRN expression in the tumor tissue. Taken together, all these data suggest that PGRN could be a predictive and prognostic marker in breast cancer. Nevertheless, more studies are required to determine whether PGRN could be a useful biomarker in other types of breast cancer that are receptor-positive or -negative for estrogen, HER2, and progesterone.

Tumor samples (n=210) surgically obtained from astrocytoma patients were analyzed to determine PGRN expression and its association with tumor grade and overall survival of the patients. PGRN expression is up-regulated in astrocytoma cells and tumor blood vessels as compared with normal brain and positively correlated with pathological grading. In grade II astrocytoma, strong vascular PGRN expression is closely related to tumor recurrence. Moreover, in glioblastoma patients, the increased PGRN expression correlates with decreased patient survival [82].

One study with tissue samples from patients with prostate cancer demonstrated that PGRN expression is detected in more than 50% of cells in all samples of high-grade prostatic intraepithelial neoplasia and invasive cancer. In normal prostate tissues, PGRN expression is low and less than 10% of cells express the protein [83]. Likewise, PGRN levels in malignant renal tissue detected by western blot analysis were significantly higher as compared to benign renal tissue. Also, in the same study, tissue samples from patients with renal cell carcinoma show higher levels of PGRN expression compared with low-grade renal cell carcinoma and normal tissue [84]. In patients with bladder cancer, urinary levels of PGRN are significantly increased relative to control samples; in addition, high PGRN levels correlate with the stage and pathological cancer grade [85]. Unfortunately, the small sample size of this study is a limitation; however, the results suggest that urine PGRN levels may serve as a simple test as part of a bladder cancer work-up. Other studies have reached the same conclusions but also with critical limitations; however, it is important to note that PGRN has been included in a panel of urinary diagnostic markers for non-invasive detection

of primary and recurrent urothelial urinary bladder carcinoma. So far, the analyses that have been performed are inconclusive and it is necessary to carry out larger or multicenter studies to substantiate the benefits of including PGRN in a diagnostic panel [86].

A cohort study of 131 patients with chronic lymphocytic leukemia demonstrated that PGRN concentrations measured in plasma are significantly increased compared to normal controls. Moreover, the high PGRN plasma levels are strongly associated with adverse risk factors including unmutated immunoglobulin heavy chain variable (*IGHV*) gene status, expression of CD38, and levels of ZAP-70. Therefore, PGRN, as well as the other risk factors, is a prognostic marker for establishing the time to first treatment and overall survival in these patients [87].

Edelman et al. [88] demonstrated the utility of PGRN as a biomarker for non-small cell lung carcinoma because the blood levels of patients with stages III and IV are higher in comparison with healthy patients and correlate with a low progression-free survival.

In a retrospective study of tissues from patients with advanced biliary tract cancer who received palliative chemotherapy, PGRN expression was evaluated by immunohistochemistry. A poorer response to chemotherapy in patients with PGRN-positive tumors is observed and also PGRN overexpression is significantly associated with poor progression-free survival [89]. In conclusion, PGRN could find application in predicting treatment outcomes.

Recently, a study of 254 patients with untreated malignant lymphoma showed that PGRN concentrations measured in sera of patients are significantly higher than levels found in the healthy control group [90]. In addition, the group of patients with high PGRN concentrations show a poor prognosis with respect to overall survival and progressive-free survival.

Collectively, the studies presented in this section show that PGRN concentrations in serum, urine or its expression in tissues can be useful for monitoring the clinical course of tumors and patient prognosis. Therefore, PGRN could be a worthy biomarker for some types of cancers.

Progranulin inhibition as treatment for cancer

Overexpression of PGRN in different types of cancer produces significant effects in carcinogenesis. Several studies have demonstrated that inhibition of PGRN expression with small interfering RNA (siRNA), short hairpin (shRNA), anti-sense cDNA, or specific neutralizing antibodies minimize its participation in tumorigenesis.

Strong inhibition of tumorigenicity *in vivo* was first documented using PC cells derived from adipogenic teratoma cells, where PGRN expression was inhibited by transfection of antisense PGRN cDNA [91]. The results of this study showed that tumors develop promptly when empty-vector control PC cells are injected into mice; while tumor growth is significantly inhibited if the PC cells are transfected with antisense PGRN cDNA prior to injection into mouse hosts.

Treatment of MDA-MB-468 breast cancer cells with anti-PGRN neutralizing antibody resulted in dose-dependent decrease of their proliferation [92]. Additionally, inhibition of PGRN expression by antisense PGRN cDNA transfection also reduces proliferation and colony formation; moreover, tumor formation *in vivo* is significantly inhibited. These results demonstrated that PGRN acts as an autocrine factor and is essential for the tumorigenicity of breast carcinomas.

In several ovarian cancer cell lines, inhibition of PGRN by antisense cDNA transfection decreases cell proliferation and invasion through downregulation of cyclin D and CDK4 and inactivation of MMP-2 [49]. Other studies using the ovarian cancer cell lines HEY-A8 and OVCAR-3 show that PGRN production and secretion can be regulated by endothelin 1 (ET-1), lysophosphatidic acid (LPA), and cAMP through the signal transduction pathway of cAMP-EPAC-ERK1/2. Treatment of these cells with neutralizing PGRN antibody inhibits basal as well as LPA, ET-1, and cAMP-induced proliferation. Moreover, apoptosis is induced by this treatment, as demonstrated by the presence of caspase-3 and PARP cleavage, DNA fragmentation, and nuclear condensation [93].

PGRN levels are significantly increased in gastric cancer tissue compared with healthy tissue. *Helicobacter pylori* infection is the primary cause of gastric cancer and is associated with an increased gastric epithelial cell proliferation and migration. A recent study demonstrated that infection of gastric epithelial cells by *H. pylori* significantly increase PGRN expression and induces cell proliferation and migration. Furthermore, downregulation of PGRN by specific siRNA reduces *H. pylori*-induced cell proliferation and migration in gastric epithelial cells [94].

Several studies using hepatocellular carcinoma cells and orthotopic liver tumor models demonstrated that PGRN neutralization by anti-PGRN antibody inhibited growth of hepatoma cells *in vitro* without significant effect on normal liver cells. In the nude mice model, neutralizing antibody therapy decreases PGRN serum levels, inhibits in a dose-dependent manner the growth of established tumors, and decreases tumor angiogenesis by reducing microvessel density and VEGF levels. It seems that these effects are at least partially mediated via p44/42 MAPK/Akt signal transduction pathway [95]. In another study, chemoresistant cells from hepatocellular carcinoma were generated by cisplatin and doxorubicin treatment [96]. These subpopulations express higher cancer stem cell markers such as CD133, PGRN and ABCB5 multidrug transporter as compared with the parental cell lines. Also, their ability to form colonies and spheroids is enhanced. Interestingly, incubation in the presence of anti-PGRN antibody sensitized these chemoresistant subpopulation and their parental cell lines to apoptosis induced by chemotherapy. The mechanism behind this enhanced chemotherapy response seems to be due to a decrease in ABCB5 expression, and cell survival signaling mediated via Akt and Bcl-2. In the same study, the combined effects of PGRN neutralizing antibody and cisplatin *in vivo* were evaluated in a orthotopic liver tumor model. Anti-PGRN treatment alone inhibited tumor growth, while combination with cisplatin eliminated the intrahepatic tumor in three weeks [96]. A recent study designed to identify effective and non-invasive diagnostic biomarkers for hepatocellular carcinoma by oncoproteogenomics technology (integration of proteomics, genomics, and transcriptomic

analyses) revealed a significantly higher co-amplification and co-expression of PGRN and S100A9 in tumor and urine samples from patients compared to the controls [97].

Finally, endogenous depletion of PGRN by shRNA in UMUC-3 urothelial cancer cells inhibits cell proliferation, migration, invasion, and anchorage-independent growth as well as reduced tumor cell growth *in vivo* in both xenograft and orthotopic tumor models. Furthermore, suppression of PGRN expression sensitized bladder cancer cells to cisplatin [98].

Collectively, the discussed evidence supports the hypothesis that PGRN neutralization may be an important target for cancer therapy. Thus, development of new anti-PGRN neutralizing antibodies for clinical use are warranted.

Conclusions

In the last two decades, the study of PGRN in cancer has advanced considerably. Research has been conducted to establish a role for PGRN in many forms of cancer, as well as to determine the mechanism of action for its biological effects. So far, several proteins have been proposed to act as the PGRN receptor. However, binding to these proteins does not fully explain PGRN growth factor or neuroprotective effects; therefore, it is thought that PGRN must have its own receptor. Signaling pathways activated by PGRN have already been described, and they are essential pathways in cancer development and progression. According to the data in the literature, it is clear that PGRN overexpression induces proliferation and migration in several cancer cells. Also, modulation of PGRN levels by RNA silencing or inhibition of PGRN by treatment with neutralizing antibodies counteracts these effects. All this evidence and the fact that PGRN is a unique secretory glycoprotein highlight its potential use as a biomarker or as a therapeutic target in cancer. The information that currently exists regarding PGRN is very exciting, but more clinical studies, with a larger patient base, are warranted to cement possible uses for this interesting growth factor in diagnosis and treatment.

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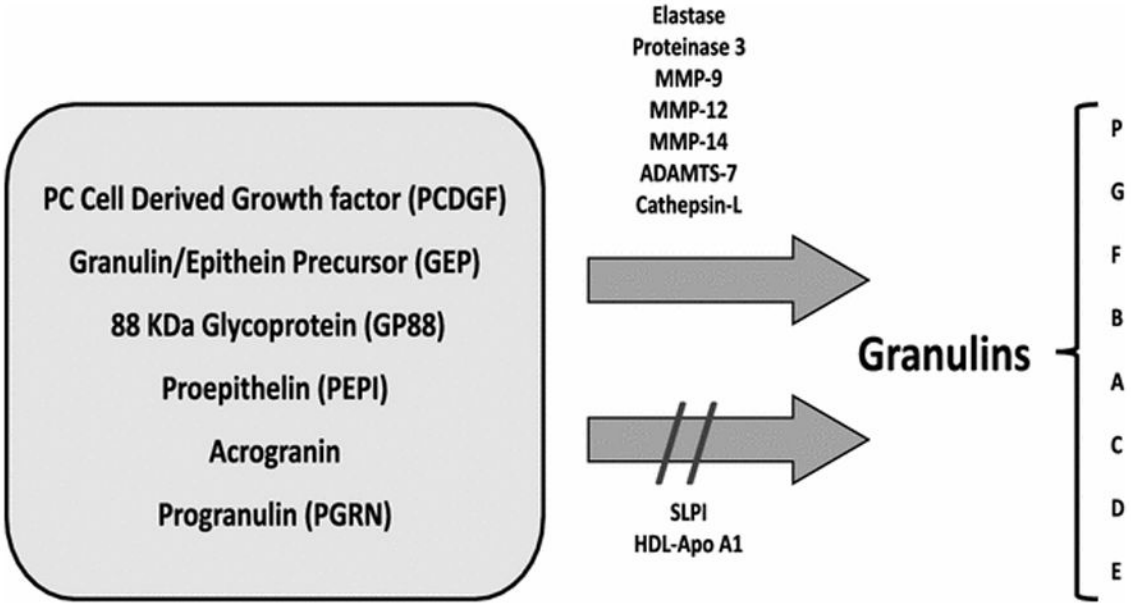

Figure 1.

Granulin Family. Granulins are small peptides derived from a larger precursor (PC cell-derived growth factor, granulin/epithein precursor, 88 kDa glycoprotein, proepithelin, acrogranin, or progranulin), which can be cleaved by several enzymes. PGRN cleavage releases seven full-length granulin domains (G, F, B, A, C, D, E) and one half-length paragranulin domain (P). Secretory leukocytes protease inhibitor (SLPI) or high-density lipoprotein/apolipoprotein A-1 (HDL-Apo A1) binding to the full-length PGRN prevents its proteolytic process.

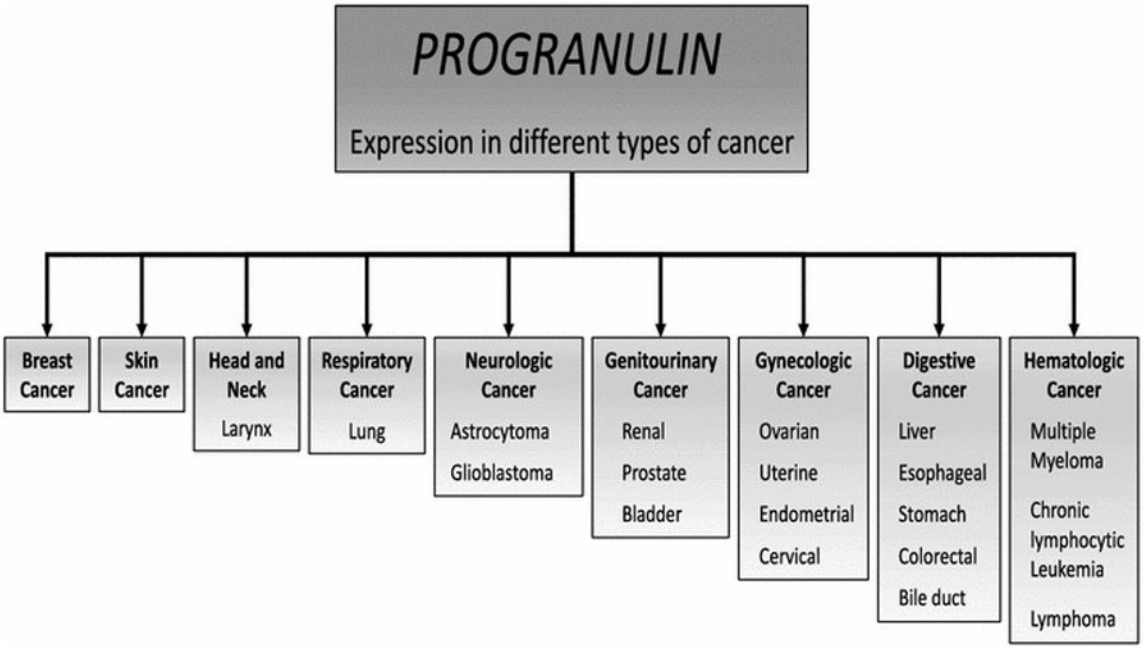

Figure 2.

Progranulin expression in cancer. Increased expression of PGRN has been detected in cancer tissue from different organs.

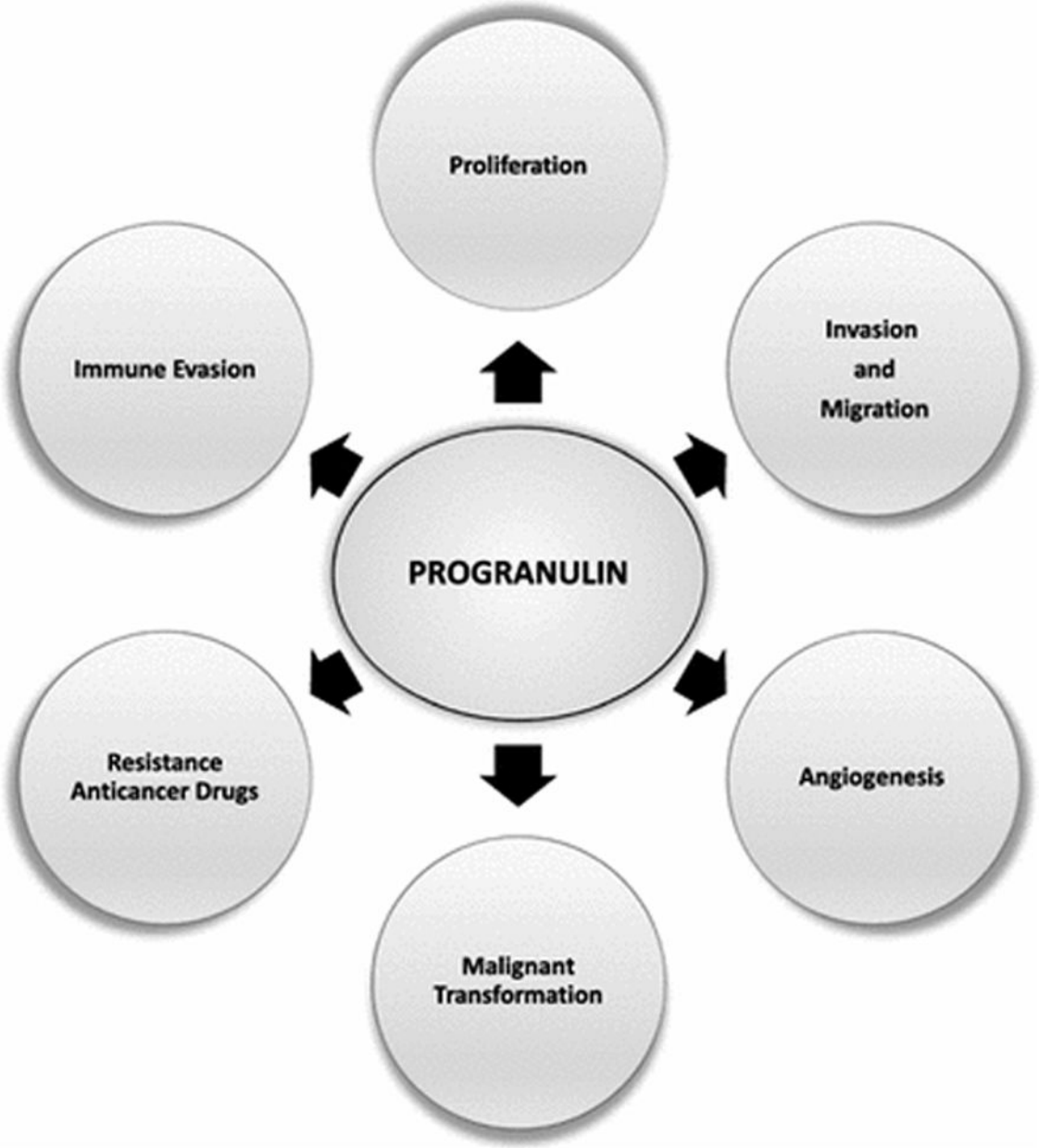

Figure 3.
Biological effects of PGRN. Increased expression of PGRN promotes different responses that can lead to the development of cancer.