



A narrative review of multiple mechanisms of progranulin in cancer: a potential target for anti-cancer therapy

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Abstract: Progranulin (PGRN) is an autocrine growth factor and has important effects on regulation of cell growth, motility, tissue repair and embryonic development. Recent years, several researches found the expression of PGRN was at higher levels in a number of cancer cells and its high levels are associated with poor outcome of patients. More and more studies investigated the role of PGRN in cancer and found PGRN exerted various biological functions in cancer cells, such as promoting proliferation, inhibiting apoptosis, inducing migration and invasion of cells, accelerating angiogenesis and enhancing the effectiveness of chemoresistance and radiation. Now the effects of PGRN have been demonstrated in several cancers, including breast cancer, lung cancer, and bladder cancer. In addition, several signaling pathways and molecules are involved in the effects of PGRN on cancer cells, including Akt, mitogen-activated protein kinase (MAPK), vascular endothelial growth factor (VEGF) and cyclin D1. Therefore, PGRN is probably a significant diagnostic and prognostic biomarker for cancer and may be a potential target for anti-cancer therapy. Here, we reviewed the advancing field of PGRN in cancer as well as several signaling pathways activated by PGRN and confirmed PGRN is a key role in cancer. Moreover, future studies are still necessary to elucidate the biological functions and signaling pathways of PGRN in cancer.

Keywords: Cancer; molecular targets; progranulin (PGRN)

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Introduction

Progranulin (PGRN), also known as proepithelin, granulin-epithelin precursor, or acrogranin, is a growth factor that is ubiquitously expressed throughout the body (1,2). PGRN has various biological functions such as regulation of cell growth and motility, tissue repair, and embryonic development (3,4). The effects of PGRN include wound healing, brain injury, and cancer progression (2,5). Studies

have shown that PGRN plays a role in multiple cancers including leukemia, breast cancer, ovarian cancer, and glioblastoma. PGRN is expressed at elevated levels in tumors (compared to normal controls), and increased PGRN level is associated with increased tumorigenicity and drug resistance, and a poor prognosis (6,7). PGRN exerts multiple effects on cancer progression including promoting proliferation, stimulating migration and invasion, and

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Table 1 Functions and molecular targets of PGRN in cancer

| Cancer | Functions | Molecular targets |
|--------------------------|--|------------------------------------|
| Leukemia | Induces an inflammatory response | TNF- α |
| Lung cancer | Induces invasion and migration; induces chemotherapy resistance | VEGF |
| Hepatocellular carcinoma | Induces angiogenesis; promotes proliferation, invasion, and migration; reduces chemosensitivity | VEGF, Akt, MAPK, mTOR |
| Breast cancer | Promotes proliferation, invasion, and migration; induces angiogenesis; induces chemotherapy resistance and resistance to endocrine therapy | VEGF, estrogen receptor, cyclin D1 |
| Colorectal cancer | Induces cancer growth, migration, and invasion; promotes angiogenesis and activation of fibroblasts | TNFR2/Akt, ERK, Wnt |
| Ovarian cancer (8) | Promotes proliferation and motility of cancer cells; inhibits apoptosis; induces migration and invasion | PKC, CDK4, cyclin D, MAPK, MMP-2 |
| Bladder cancer (9) | Stimulates migration and invasion; promotes proliferation and motility of cancer cells; reduces chemosensitivity | MAPK, Akt |
| Prostate cancer | Promotes proliferation; promotes invasion and migration | Akt, ERK1/2 |
| Glioma | Induces chemotherapy resistance; inhibits apoptosis | AP-1, PI3K/Akt, ERK1/2, CDK4/6/pRb |
| Cervical cancer | Induces proliferation; inhibits senescence | PI3K/Akt/mTOR |
| Endometrial cancer | Promotes proliferation, invasion, and metastasis; induces angiogenesis | VEGF |
| Gastric cancer | Promotes proliferation and migration | Akt, MAPK, MEK1/2 |
| Pancreatic cancer | Supports metastasis; stimulates proliferation | – |
| Esophageal cancer | Promotes angiogenesis | VEGF |
| Mesothelioma | Induces angiogenesis and tube formation | – |
| Skin cancer | Promotes invasion and migration | Cyclin D |
| Myeloma | Promotes cell growth; induces resistance of dexamethasone | MAPK, PI3K |
| Laryngeal carcinoma | Promotes proliferation | – |

CDK4, cyclin dependent kinase 4; ERK, extracellular regulated protein kinases; MAPK, mitogen-activated protein kinase; MEK1/2, mitogen-activated protein kinase kinases 1 and 2; MMP-2, matrix metalloproteinase 2; mTOR, mammalian target of rapamycin; PGRN, TNF- α , tumor necrosis factor- α ; PI3K, phosphatidylinositol-3-kinase.; PKC, protein kinase C; TNFR2, tumor necrosis factor receptor 2; VEGF, vascular endothelial growth factor.

mediating angiogenesis and resistance to apoptosis. In this review, we describe the latest progress of PGRN in cancer study (*Table 1*) (8,9). We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/tcr-20-2972>).

Effects of PGRN on cancer progression

Promotes proliferation of cancer cells

The rapid proliferation of cancer cells is a main characteristic of cancer progression and can promote migration and invasion (10,11). Cancer cell proliferation is regulated by

growth factors and several signaling pathways such as Akt and mitogen-activated protein kinase (MAPK) (12,13). The processes of cancer cell proliferation and migration and invasion depend on rearrangement of the actin cytoskeleton (14), which is associated with the formation of new integrin substratum contacts and the release of pre-existing cell matrix contacts (15). The effect of PGRN on the proliferation of cancer cells has been explored, and PGRN has emerged as a critical regulator of proliferation in several cancer types include prostate, colorectal, cervical, and ovarian cancers (7,8,16). PGRN defines a cancer stem cell subpopulation and can enhance the colony-forming capability of tumor cells (17). In addition, several signaling

pathways such as tumor necrosis factor receptor 2 (TNFR2)/Akt, protein kinase C, and MAPK are involved in the PGRN-mediated regulation of cancer cell proliferation (7,18). Yang *et al.* (7) found that PGRN overexpression increased the expression of vascular endothelial growth factor A (VEGF-A) and promoted the growth of colorectal cancer cells. This regulation by PGRN was mediated by TNFR2/Akt and extracellular signal-regulated kinase (ERK) signaling pathways in both colorectal cancer and human umbilical vein endothelial cells (HUVECs). In addition, a previous study demonstrated that knockdown of PGRN caused a decrease in the growth of glioma cells (19). Therefore, because PGRN plays a clear role in promoting cancer cell proliferation, inhibiting PGRN may have anti-proliferative effects (20).

Resistance to apoptosis

Apoptosis is the process of programmed cell death and comprises several events such as chromosomal DNA fragmentation, nuclear fragmentation, cellular blebbing, and ultimately cell death (21-23). Apoptosis occurs in many tissues and organs and takes place in a regulated process, conferring advantage during an organism's life cycle (24,25). Therefore, accelerating apoptosis in tumor cells can diminish tumor burden (26,27). The role of PGRN in apoptosis in cancer has been demonstrated (28). In cholangiocarcinoma, PGRN inhibits apoptosis, and knockdown of PGRN promotes apoptosis by increasing the ratio of B-cell lymphoma 2 (Bcl-2) to Bcl-2-associated X protein (29). Studies have showed that anti-PGRN antibody can induce ovarian cancer cell apoptosis by regulating cleaved caspase-3, DNA fragmentation, nuclear condensation, and poly (ADP ribose) polymerase cleavage (30).

Induces migration and invasion

Migration and invasion are two important properties of cancer (31,32), and are the most pivotal factors leading to cancer-associated mortality (33). Malignant cancer cells cross the basement membrane, escape from the primary tumor, and attach to the surrounding extracellular matrix (ECM) (34). Then cancer cells metastasize and invade the surrounding tissue. They break away from the original location and migrate to other organs and tissues of the body by direct extension or through the circulatory and lymphatic systems (35). Matrix metalloproteinases (MMPs) play an essential role in the migration and invasion of cancer

cells (36). Swerlick *et al.* (37) found four membrane-type MMPs that were highly expressed in PGRN-stimulated cancer and PGRN treatment could elevate the transcription of specific matrix-degrading enzymes. In addition to MMPs, PGRN can activate ERK1/2 and form a paxillin/focal adhesion kinase/ERK complex to promote migration and invasion in bladder cancer (9). In addition, Blood *et al.* (38) reported that PGRN is a key target for microRNA-588, leading to the suppression of migration and invasion in lung cancer. Thus, inhibiting PGRN may be valuable in preventing the migration and invasion of cancer cells.

Mediates angiogenesis

Angiogenesis is a process by which new vasculature is formed (37). Angiogenesis in physical condition is just transient (39), and sustained angiogenesis is observed during tumorigenesis (38). Tumor angiogenesis is essential for tumor progression and is always associated with an adverse prognosis (40). VEGF is a key angiogenic factor and is considered a pivotal target of tumor treatment (41). Anti-VEGF antibodies, such as bevacizumab, have been used as anti-angiogenic therapy for the treatment of several cancers and the therapeutic benefits are approved (42). The relationship between PGRN and angiogenesis has been established, and the effect of PGRN on promoting angiogenesis has been confirmed in various cancers. In addition, the high expression of PGRN is associated with elevated VEGF concentrations in tissue from breast cancer, colorectal cancer, and esophageal squamous cell carcinoma (43,44). Previous studies found that recombinant PGRN not only increased the expression of VEGF in HUVECs but also directly activated the angiogenic characteristic of HUVECs, suggesting the direct and indirect effects of PGRN on tumor angiogenesis. The overexpression of VEGF induced by PGRN is through the TNFR2/Akt and ERK signaling pathways (7). In addition to targeting VEGF, the midkine protein/PGRN complex stimulates angiogenesis by another mechanism and the co-stimulatory effect is significantly increased. This complex promotes migration, proliferation, and tubular structure formation to mediate tumor angiogenesis (39). Therefore, therapies to neutralize the effect of PGRN are available as an anti-angiogenic treatment strategy for cancers.

Promote chemoresistance and radiation

Chemotherapy is important for patients with cancer and is

widely used for the treatment of unresectable cancer (45,46). However, many types of cancer cells are resistant to anti-cancer drugs, which is a huge obstacle to chemotherapy (47). Chemoresistance observably affects the survival of patients with cancer, but the precise mechanism is still unknown. Several studies have indicated that growth factors may be involved in the mechanism of chemoresistance. PGRN, as a growth factor, is associated with chemoresistance in several cancer cells (48). In breast cancer, PGRN overexpression and cross-talk with the estrogen receptor are considered factors that cause chemoresistance (49,50). PGRN also confers letrozole resistance by preventing the downregulation of Bcl-2 expression by letrozole in breast cancer (51). In addition, PGRN plays a crucial role in promoting glioblastoma chemoresistance by orchestrating DNA repair (19). In addition, PGRN has effects on radiation. Granulin (GRN) was upregulated in response to ionizing radiation in PC-3 prostate cancer cells. On the other hand, miRNA-107 enhances radiosensitivity by suppressing GRN in these cells (52).

Molecular targets of PGRN in cancer

Akt

Akt is a key factor for the proliferation, progression, and metastasis of tumors, and its function has been demonstrated in several cancers such as breast cancer, colorectal cancer, and cholangiocarcinoma (53,54). Akt-mediated Girdin phosphorylation in cancer-associated fibroblasts is closely related to the development of tumors, and inhibiting this function of Akt can cause a decrease in tumor progression (55). Radiotherapy (RT) is a powerful therapeutic method for cancer treatment, and inhibition of the Akt/cyclin D1 pathway can result in radiosensitization of both surviving tumor cells and cancer stem cells (56). The effects of PGRN on regulating Akt have been confirmed in several cancer types including colorectal, bladder, gastric, and cervical cancers (57-59). PGRN can stimulate the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway in cancer tissues and contributes to the carcinogenesis of cancer (58). In colorectal cancer, PGRN can promote proliferation and angiogenesis via the TNFR2/Akt/ERK pathway (7). PGRN-dependent activation of Akt is related to the invasion, motility, and anchorage-dependent growth of cancer (60).

MAPK

The effects of MAPK on proliferation, survival, differentiation, and migration have been reported in a number of cancers (61,62). In addition, MAPK plays an important role in several cancers including mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress (63-65). MAPK is critical for PGRN biological responses in cancer (66). PGRN contributes to the activation of MAPK by regulating drebrin and then induces F-actin remodeling, thereby regulating growth, motility, and invasion of urothelial cancer cells. PGRN downregulation inhibits bladder cancer cell growth and sensitizes cancer cells to cisplatin, and MAPK plays a critical role in this process (67). Anti-PGRN monoclonal antibody can reduce tumor cell proliferation and tumor angiogenesis through suppression of p44/42 MAPK in hepatocellular carcinoma (HCC) (68).

VEGF

The VEGF family comprises a number of members, among which VEGF-A is the most potent angiogenic factor and vascular endothelial growth factor receptor 2 (VEGFR-2) is the most crucial receptor in cancer (69). High VEGF levels have been reported in several cancers (70). As an angiogenic growth factor, the prominent role of VEGF in cancer, specifically in stimulating angiogenesis, has been highlighted by many studies (71). A previous study confirmed that suppressing the expression of VEGF can promote cancer cell apoptosis and inhibit angiogenesis (72). Bevacizumab, an anti-VEGF targeting monoclonal antibody, can reduce vasculature density, and inhibit cancer progression and activation of several interrelated signaling pathways (73). PGRN reportedly has effects on promoting angiogenesis and metastasis through the regulation of VEGF in several cancers (74). In colorectal cancer cell lines, PGRN upregulation can promote the expression of Ki67 and VEGF-A as well as cancer growth rate, whereas PGRN downregulation has the opposite effects (7). In esophageal cancer, PGRN plays a significant role in promoting lymphangiogenesis by activating VEGF (75).

Cyclin D1

Cyclin D1 plays a pivotal role in cancer. Cyclin D1

participates in promoting cell cycle progression in the G1 phase and has various biological activities in the process of tumorigenesis including promoting proliferation, enhancing DNA damage repair, and stimulating migration (76,77). Meanwhile, suppression of cyclin D1 can inhibit the proliferation, invasion, and metastasis of cancer cells (78-80) and enhance chemosensitivity and radiosensitivity (81,82). In addition, it has been demonstrated that cancer patients with high cyclin D1 levels have a worse prognosis and increased risk of mortality than those with low levels (83,84). Several studies have demonstrated the effects of PGRN on the regulation of cyclin D1 levels in cancer. PGRN takes part in promoting the invasion and metastasis of squamous cell carcinoma through elevating the expression of cyclin D1 (85). Moreover, PGRN reportedly mediates mitogenic effects by stimulating cyclin D1 in cancer cells (86). PGRN short hairpin RNA, which can reduce cancer cell proliferation through cell cycle arrest at the G2/M stage and expression of cyclin D1, would be an effective approach for treating HCC (87). In ovarian cancer, the antisense PGRN vector inhibits the proliferation and invasion of highly malignant cancer cells, and partially reverses the malignant phenotype, which is related to downregulation of cyclin D1 and cyclin-dependent kinase 4 (88,89).

PGRN as a biomarker of cancer and a target for anti-cancer therapy

Studies have reported that PGRN is overexpressed in a number of cancers such as ovarian, bladder, breast, lung, and cervical cancers (90-92); however, little PGRN expression has been detected in normal tissue (93). In addition, high levels of PGRN are associated with the higher malignancy of cancer and poor outcomes of cancer patients (18,74,94). In non-small cell lung cancer, the serum expression of PGRN in stage IIIB/IV patients is much higher than that in stage lower patients (95). It also has been demonstrated that PGRN upregulation is closely correlated with the worse progression-free survival of patients with glioblastoma (96). Moreover, PGRN levels are important for predicting recurrence in cancer patients (97). Recurrence probability is much higher in breast cancer patients with higher PGRN serum levels (98). Therefore, PGRN is probably a significant diagnostic and prognostic biomarker for cancer. In addition, PGRN may be a potential target for cancer treatment because of its effects on the proliferation, angiogenesis, migration, and invasion of cancer. It has been confirmed that the downregulation of PGRN minimizes its

effects on tumorigenesis (99). PGRN is a key factor for the tumorigenicity of breast cancer, as reducing PGRN levels can decrease proliferation and colony formation (100). In gastric cancer, inhibition of PGRN expression with small interfering RNA inhibits cancer cell migration (101). Inhibiting PGRN by antisense cDNA transfection can reduce proliferation and invasion in ovarian cancer (102). Suppression of PGRN expression by neutralizing antibody inhibits angiogenesis by decreasing VEGF expression and microvessel density (39). Furthermore, anti-PGRN antibody can sensitize the chemoresistant subpopulation generated by antineoplastic drugs and their parental cells to apoptosis (67,103). Therefore, PGRN is not only a diagnostic and prognostic biomarker but also a potential target for cancer therapy.

Future prospects of PGRN

Cancer progression is a complex procedure involving many biological characteristics including proliferation, apoptosis, invasion, angiogenesis, and autophagy. Although the roles of PGRN in proliferation, apoptosis, invasion, and angiogenesis have been widely reported, the effect of PGRN on autophagy in cancer remains unclear. However, autophagy plays a significant role in cancer progression (104,105). Autophagy induces the invasion and migration of cancer cells (106), and is a key factor in RT; thus, suppression of autophagy could decrease the clonogenic survival of cancer cells following irradiation (107,108). In addition, there is a tight connection between apoptosis and autophagy, and the relationship is a hot point in cancer research. Autophagy is double-edged sword in different types of cancer cells, as it both induces and inhibits apoptosis (109,110). Therefore, clarifying the effects and mechanisms of PGRN on autophagy in cancer is very essential for cancer treatment. In addition, RT is a powerful tool for the treatment of cancer and is widely used in cancer patients (111-113). However, radioresistance is a big problem (114,115). Thus, effective measures to overcome radioresistance are urgently needed for cancer treatment. As there are no studies showing that PGRN has effects on RT, expounding the role of PGRN in RT is necessary.

Conclusions

An increasing number of studies have shown that PGRN is a key factor in cancer. In this review, we presented some of the important biological effects of PGRN in cancer as

well as several molecular targets of PGRN involved in cancer progression. This evidence confirms that PGRN is a potential prognostic biomarker for cancer and an attractive therapeutic target for anti-cancer therapy. Current information regarding the role of PGRN in cancer is exciting, but future studies are warranted to elucidate the functions and signaling pathways of PGRN in cancer.

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Footnote

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