Current status and prospects of GREM1 research in cancer (Review)

DANTONG ZHU[1*], DONG ZHAO[1*], NAIXUE WANG[2], FEI CAI[3], MINGZHE JIANG[1] and ZHENDONG ZHENG[1]

[1]Department of Medical Oncology, General Hospital of Northern Theater Command, Shenyang, Liaoning 110000; [2]Department of Oncology, General Hospital of Northern Theater Command, Jinzhou Medical University, Shenyang, Liaoning 121017; [3]Department of Oncology, General Hospital of Northern Theater Command, China Medical University, Shenyang, Liaoning 110000, P.R. China

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Abstract. GREM1 is a secreted protein that antagonizes bone morphogenetic proteins (BMPs) and participates in critical biological processes, including embryonic development, organogenesis and tissue differentiation. Gremlin 1 (GREM1) is also an inhibitor of TGF-β and a ligand for vascular endothelial growth factor receptor 2. In addition, GREM1 can induce cells, participate in the process of epithelial-mesenchymal transition, and then participate in tumor development. GREM1 has a variety of biological functions and can participate in the malignant progression of a variety of tumors through the BMP signaling pathway. GREM1 also can inhibit TGF-β in some tumors, thereby inhibiting tumors, and its involvement in tumor development varies in different types of cancer. The present review examines the role and function of GREM1 in tumors. GREM1 is expressed in a variety of tumor types. GREM1 expression can affect the epithelial-mesenchymal transformation of tumor cells. GREM1 has been studied in breast and colon cancer, and its potential role is to promote cancer. However, in pancreatic cancer, which was found to act differently from other cancer types, overexpression of GREM1 inhibits tumor metastasis. The present review suggests that GREM1 can be a diagnostic and prognostic indicator. In future studies, the study of GREM1 based on single-cell sequencing technology will further clarify its role and function in tumors.

Correspondence to: Professor Zhendong Zheng, Department of Medical Oncology, General Hospital of Northern Theater Command, 83 Wenhua Road, Building 3, Shenyang, Liaoning 110000, P.R. China
E-mail: gcp_zzd@sina.com

*Contributed equally

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Contents

1. Discovery and biological basis of GREM1

GREM1 was initially isolated from v-mos transfected rat fibroblasts by the BLAIR team in 1997 and named DRM (down-regulated in v-mos-transfected cells) (1). Drm contains an open reading frame (ORF) that encodes a 184-amino acid cysteine-rich protein with a calculated relative molecular weight of 20,682. In 2000, the team mapped the human homolog of DRM/Germlin, which maps to human chromosome 15. It screened a human cDNA library to obtain a protein size of 3.3 kb containing a 552 base region, and it is highly conserved during biological evolution (2,3). DRM is present on the outer surface of expressing cells and in the endoplasmic reticulum and Golgi apparatus (4). Like many growth factor proteins, it is a secreted protein (5). GREM1 antagonizes bone morphogenetic protein (BMP) signaling, regulates BMP during development, and controls limb and kidney formation (6,7). There is a single DRM-specific mRNA expressed in different human tissues, including the brain, ovary, intestine, and colon. GREM1 is expressed in normal cells and tissues, including normal neurons, astrocytes, and fibroblasts. GREM1 was earlier thought that expressed significantly in many organs of the human body during embryonic development, such as eyes, bones, lungs, kidneys, etc. With further research, GREM1 expression and distribution have also been found in many organs in mature animals and adults. GREM1 expression was detected in normal cells from several patients, but not in established tumor cell lines from the same patient. These data suggest that the downregulation of GREM1 is associated with tumor progression. GREM1 was detected both intracellularly and extracellularly, and it was demonstrated to be a weakly essential protein.

2. Biological function of GREM1

McMahon group identified GREM1, the human homolog of the rat developmental gene Drm/Gremlin, as a high

glucose-triggered gene in human mesangial cells (8). GREM1 is an antagonist of Bone morphogenetic proteins (BMPs) and belongs to the same family as Noggin, Chordin, and twisted gastrulation-1 (Twsg1). GREM1 is able to graft BMP binding to its cognate serine/threonine protein kinase receptor on lipid membranes (9). During BMP signaling, BMPs are processed by preprotein peptidases and then bind to type I and II BMP receptors to generate mature dimers. The binding of BMP homodimers to their cognate receptors results in the phosphorylation of the type I receptor by the type II receptor in the GS domain which is glycine and serine residue-rich region on the type I receptor. Activated BMP receptors then phosphorylate Smad1/5/8 protein, which dimerizes with Smad4 and accumulates in the nucleus, mediating changes in BMP-regulated gene expression. GREM1 plays an antagonistic role by regulating BMP dimer formation during this process (10,11). In addition, Gremlin overexpression may regulate both mesangial cell growth and transdifferentiation of cultured tubular epithelial cells to a more fibroblast-like phenotype (6). GREM1 can also induce mesenteric cell proliferation and extracellular matrix accumulation by enhancing the activation of the ERK1/2 pathway (12). GREM1 was highly expressed in proximal convoluted tubular epithelial cells (PTEC, HK-2) exposed to aristolochic acid and down-regulated BMP-7 and phosphorylated Smad1/5/8 levels, and restored BMP-7 signaling activity and attenuated aristolochic acid-induced EMT-related phenotypic changes after down-regulation of GREM1 (13). In mouse renal fibroblast cells, GREM1 was able to upregulate renal fibroblast and tubular epithelial cell fibrosis by activating TGF-β. Endogenous GREM1 silencing was also able to down-regulate TGF-β-mediated extracellular matrix protein (ECM) production and epithelial-mesenchymal transition (EMT) (14).

In addition to its antagonism with BMP, GREM1 has also shown other new effects in recent years. Grem1 binds to fibrin and binds to Sit proteins to regulate monocyte chemotaxis negatively. GREM1 can promote angiogenesis by attaching to vascular endothelial cytokine receptor (VEGFR2) as a regulatory factor that regulates and promotes angiogenesis (15). This is due to the binding of Grem1 to heparin and heparan sulfate proteoglycans on the surface of endothelial cells. Moreover, GREM1-mediated angiogenesis is also mediated by AVB3 integrin binding and AVB3/VEGFR2 complex. The identification of Grem1 as a new pro-angiogenic factor is of great significance in the field of highly vascularized tumors and endothelial cell biology. In the study of human umbilical cord blood hematopoietic cells, GREM1 also plays a certain regulatory role, participating in and regulating BMP2 and BMP4, which is related to the generation of atherosclerotic plaques. In $GREM1^{-/-}$ embryonic fibroblasts, the phosphorylation level of ERK is reduced compared with wild-type, and the activation of phosphorylated ERK1/2 is an effector downstream of GREM1.

3. Role of GREM1 in tumors

The discovery of GREM1 and cancer was first reported by Topol in 2000. It was found that the expression of GREM1 was higher in some normal cells but significantly lower in some cells after transfection of oncogenes, such as fibroblasts. In further gene sequencing studies, Topol showed that deletion of the GREM1 gene was associated with metastatic breast cancer and other metastatic tumors. Suzuki M, by measuring the mRNA expression of GREM1 found that GREM1 was expressed in some normal human cells, still expression of GREM1 mRNA in the corresponding cells was reduced or disappeared due to gene methylation after tumor occurrence. These studies suggest that early investigators believe that GREM1 is likely to inhibit tumor development and progression.

Hong Namkoong and others are against this view (16). The related research team found that the mRNA expression of GREM1 was significantly increased in many human malignant tumors compared with the corresponding normal non-tumor tissues. His initial research was on cervical cancer cells and later expanded to kidney, breast, and lung cancer, all with strikingly similar results (16). Subsequently, a larger and larger sample size study on the expression level of GREM1 mRNA in various tumors confirmed identical views. This study involved 774 samples of various solid tumors from human tissues, such as human lung cancer, colon cancer, bladder cancer, skin basal cell carcinoma, breast cancer, melanoma, uterine sarcoma, and 16 other kinds of tumors (17). GREM1 is widely expressed in the stroma of various tumors and can promote the proliferation of tumor cells. It is one of the key factors in tumorigenesis. Due to the different function of GREM1 in different tumors, its expression level is also different.

Recent studies have written that GREM1 plays a critical role in the occurrence and development of many tumors. As reported by Davis *et al* (17), GREM1 mutation is an essential cause of familial colon cancer, and its expression in colon cancer is significantly increased. Karagiannis found that GREM1 could regulate the progression of colorectal cancer (18). The possible mechanism is that GREM1 promotes EMT by activating TGFβ1/SMAD signaling pathway (19). Other studies have found that the expression of GREM1 is closely related to the metastasis of pancreatic cancer, which is one of the prognostic indicators of pancreatic cancer (20). It is believed that GREM1 is closely associated with angiogenesis. Its association with many other malignancies is also under further investigation.

Role of GREM1 in breast cancer. Breast cancer is a highly prevalent cancer in women worldwide, and the incidence of breast cancer in women has continued to rise slowly in recent years (0.5% per year). Breast cancer is also a common type in cancer-related deaths (21). Based on the results of multiple statistical analyses of breast cancer gene expression differences, GREM1 expression is elevated in breast cancer patients. This increase is associated with a decreased prognosis in breast cancer patients (22,23). In estrogen receptor (ER)-negative tumors, GREM1 knockout suppressed the proliferation of breast cancer cells and the growth of xenogeneic breast tumors, whereas overexpression enhanced the viability, growth, and invasiveness of the cells. Estrogen-associated receptor alpha (ERRα) is an orphan nuclear hormone receptor that increases GREM1 expression by interacting with the GREM1 promoter. GREM1 activates EGFR, the upstream regulator of ERRα, and also enhances the promoter of ESRRA encoding ERRα, thus forming a positive feedback loop (24). In breast cancer-associated fibroblasts (CAF), TGF-β and inflammatory cytokines can encourage the increase of CAF-derived GREM1, thereby inhibiting the BMP/SMAD pathway and

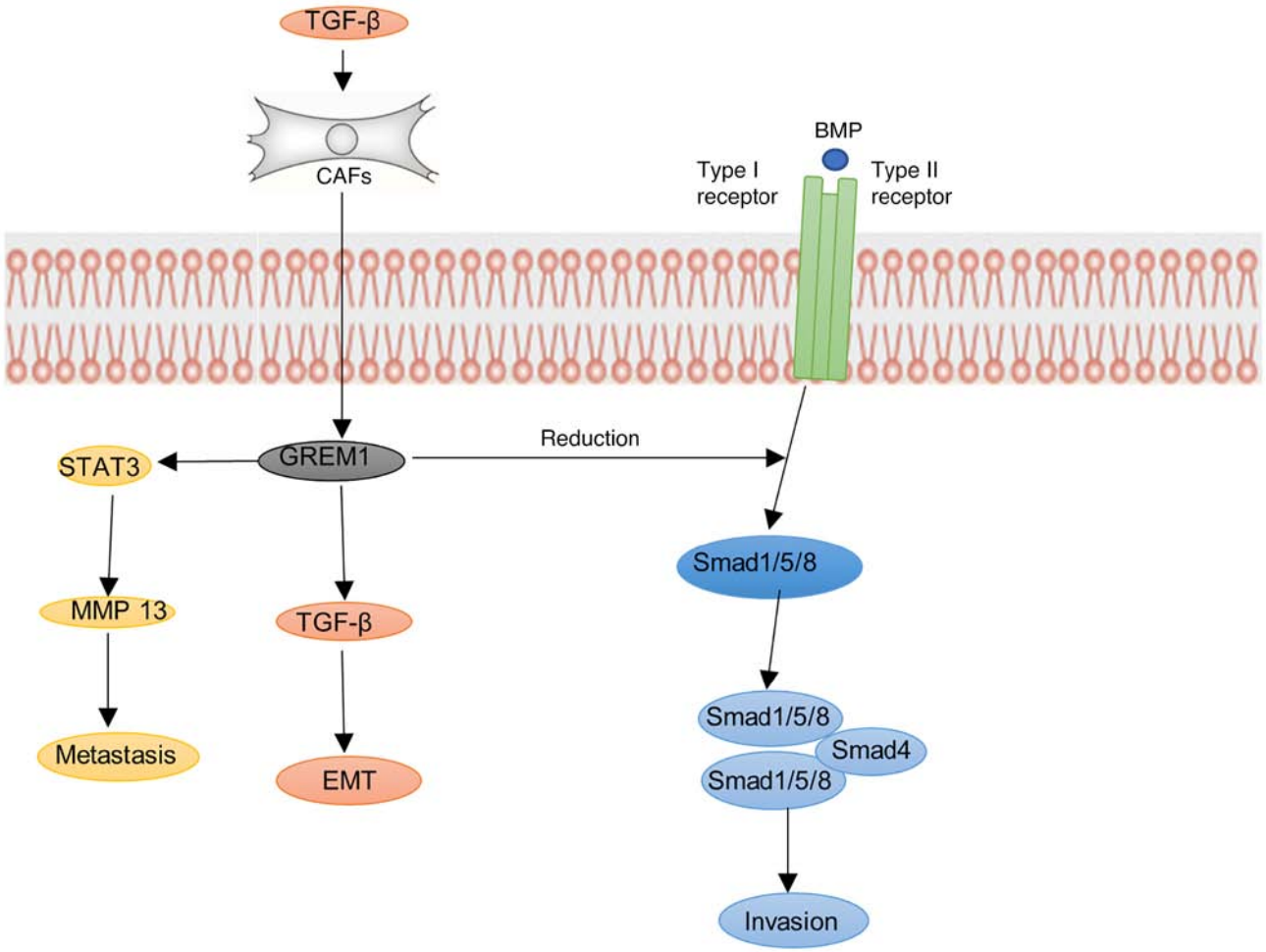

Figure 1. Mechanism diagram of GREM1 in breast cancer. In breast cancer, CAFs-derived GREM1 increases tumor aggressiveness by inhibiting the BMP/SMAD1/5/8 pathway by binding to BMP dimers, and GREM1 also increases stem and mesenchymal phenotypic transformation in breast cancer. BMP, bone morphogenetic protein; CAFs, cancer-associated fibroblasts; EMT, epithelial-mesenchymal transition; GREM1, gremlin 1.

increasing the mesenchymal phenotype, stemness and invasion of tumors, which strongly promotes the fibrosis of CAF to the internal and external exudation of breast cancer cells (25). In recent years, the role of the tumor immune microenvironment has emerged in breast cancer. It has been shown that GREM1 is highly expressed in the tumor-associated stroma of breast cancer (26). In molecular profiling of breast cancer spread and metastasis, GREM1 was shown to be localized in epithelial cells, and it is also a vital candidate gene associated with breast cancer invasion (22). During breast cancer metastasis, GREM1 promotes lung metastasis of breast cancer cells by increasing matrix metalloproteinase13 (MMP13) expression by activating signal transducer and activator of transcription3 (STAT3) (27). At present, the molecular characteristics of clinical diagnosis of breast cancer are mainly immunohistochemical markers such as ER, PR, and HER2, proliferation markers such as Ki-67, genomic markers such as PI3K, and immune markers such as PD-1 (28). Based on the study of GREM1 in breast cancer, it is likely to be a diagnostic marker for breast cancer (Fig. 1).

Function of GREM1 in colorectal cancer. Colorectal cancer is the second leading cause of cancer-related death. In recent years, through the development of surgery, radiotherapy and chemotherapy, the overall therapeutic effect of colorectal cancer has also made significant progress. In particular, the addition of fluorouracil and oxaliplatin to the treatment regimen also greatly improved the overall survival rate of patients with stage III colorectal cancer (29). Immune checkpoint inhibitor therapy, such as pembrolizumab, has been approved as the preferred regimen. There will also be many ICIs (approved or unapproved) immune checkpoint-related inhibitors supported by data in the future (30). Diabetes mellitus, and hyperglycemia impact the incidence, prognosis and metastasis of colorectal cancer (31). Increases in GREM1 are associated with the development of type II diabetes (32). In stage III colorectal cancer, GREM1 overexpression is associated with poor prognosis (33). BMP and TGF-β belong to the TGFR2 receptor-associated Smad pathway of the same family and are controlled by GREM1. GREM1 antagonism of BMP signaling can also regulate the development of intestinal cancer and the growth of liver metastases (34). GREM1 is an SNP (single nucleotide polymorphism) near the TGF-β gene (35). It has been shown that rs12915554, a low-frequency variant in the TGF-β-associated GREM1 3'UTR, increases GREM1 expression in a post-transcriptional manner mediated by disrupting the hsa-miR-185-3p binding site, which may be associated with a high incidence of colon cancer in

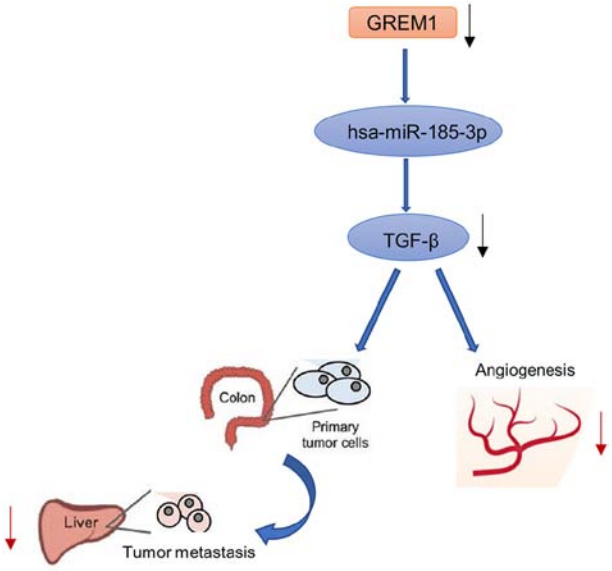

Figure 2. Mechanism diagram of GREM1 in colorectal cancer. GREM1 can regulate the TGF-β pathway by inhibiting has-miR-185-3p, ultimately reducing angiogenesis and liver metastasis in colorectal cancer. GREM1, gremlin 1; Lgr5, leucine rich repeat containing G protein-coupled receptor 5; miR, microRNA.

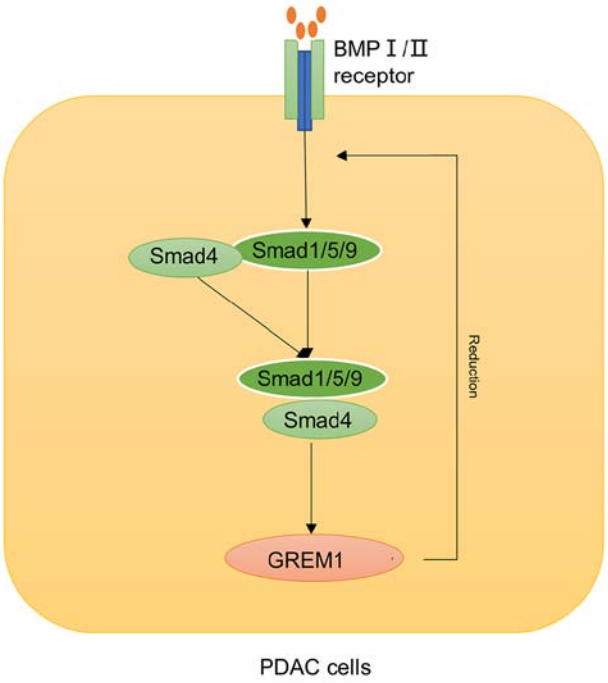

Figure 3. Mechanism diagram of GREM1 in pancreatic cancer. In pancreatic cancer, GREM1 forms a negative feedback loop with BMP via the BMP-SMAD1/5/9 pathway. BMP, bone morphogenetic protein; GREM1, gremlin 1; PDAC, pancreatic ductal adenocarcinoma.

the Chinese population (36). In hereditary mixed polyposis syndrome leading to colorectal cancer tumors, GREM1 is expressed in epithelial cells located in crypts. It is associated with the development of the disease, and GREM1 can enhance the increase in Lgr5-positive progenitor and stem cell characteristics and form ectopic crypts, proliferate, and trigger colorectal tumors (37). But in patients with long-standing ulcerative colitis, low GREM1 expression was associated with an increased risk of colitis-associated cancer (38) (Fig. 2).

Role of GREM1 in pancreatic cancer. Pancreatic cancer is highly malignant and its incidence is increasing worldwide (39). And in this era, when most tumors can prolong overall survival through various treatments, there is still no effective treatment for pancreatic cancer that can extend its overall survival, and patients are found late and inoperable. With the gradual deepening of researchers' research on GREM1, its application in pancreatic cancer has gradually increased. Lan *et al* (40), showed in a recent study that GREM1 is a critical regulator of heterogeneity in human and mouse pancreatic cancer cells, and loss of GREM1 is particularly significant for the transforming of pancreatic cancer epithelial cells into mesenchymal cells. Loss or presentation of GREM1 also plays an essential role in other earlier pancreatic cancer-related studies. The expression of GREM1 is positively correlated with high microvessel density in neuroendocrine tumors, and the increase of high microvessel density is associated with a good prognosis. At the same time, the loss of GREM1 is also associated with a poor prognosis in pancreatic neuroendocrine tumors (19). In terms of mechanism, it has been shown that deletion of GREM1 can increase the proliferation and migration of mouse embryonic fibroblasts by activating the phosphorylation of Smad1/5/8 and decreasing phosphorylated ERK by BMP4 (41). GREM1 silencing in many tumors is via promoter hypermethylation, which is also associated with increased Fuhrman grade and decreased overall survival in tumors and is associated with angiogenesis (42). In addition, GREM1 is also a soluble inhibitor of TGF-β, which also favors epithelial-mesenchymal transition and distal metastasis (43,44). Elevated GREM1, also increased the expression of $p21^{Cip1}$, and decreased the level of p42/44 MAPK, thus playing a role in inhibiting tumorigenesis (45). However, in studies of chronic pancreatitis and pancreatic ductal adenocarcinoma (PDAC), it has been shown that up-regulation of GREM1 in interstitial α-smooth muscle actin (SMA)-positive fibroblasts in chronic pancreatitis may promote the development of PDAC, and GREM1 may also play an important role in macrophage phenotype through its endogenous counter molecular macrophage migration inhibitory factor (MIF) (46). GREM1 is also generally overexpressed in cancer-associated stromal cells. In Sen Yang's study, elevated GREM1 in serum was also associate with worse patient prognosis, and loss of GREM1 increased metastasis in tissues (47). In pancreatic cancer, the expression level of GREM1 varies in different cell populations, so whether the treatment regimen can be more personalized for patients in clinical treatment provides a new idea for future GREM1 in this type of cancer research and clinical treatment (Fig. 3).

4. Discussion

GREM1 is an antagonist of BMP and can bind directly to BMP to inhibit BMP ligand binding to the corresponding receptor and participate in regulating embryonic kidney and other vital organ development (33). GREM1 showed various tumor-promoting or tumor-inhibiting effects in various cells, which were associated with different regulatory effects of GREM1 on BMP4 and other mitogen-driven cell proliferation.

In different cancers, the expression and role of GREM1 vary. In studies related to breast cancer and the immune microenvironment, GREM1 expression is elevated in the relevant stroma, and high GREM1 expression makes patients have a worse prognosis and are more likely to metastasize. Increased GREM1 expression is also associated with the development of type II diabetes, which is associated with poorer prognosis in colon cancer. However, in pancreatic cancer studies, the expression level of GREM1 is different from other cancers. Most studies have confirmed that GREM1 is lowly expressed in pancreatic cancer, especially in non-stromal cells. However, high expression of GREM1 has also been reported in mechanistic cells of pancreatic cancer, in addition to increased serum GREM1 in patients with pancreatic cancer. GREM1 is also an inhibitor of TGF-β, and loss of GREM1 relieves TGF-β regulation of tumors (34). Methylation of the CpG III region of the GREM1 promoter, which leads to GREM1 silencing, is associated with enhanced tumor malignancy and also increases active angiogenesis, which is associated with decreased overall survival in cancer patients (48). GREM1 binds VEGFR2 to initiate angiogenesis, whereas the knockdown of GREM1 in MEF cells reduced phospho-ERK and enhanced fibrocyte cell proliferation and migration by activating Smad1/5/8. GREM1 expression is generally elevated in different tumor microenvironments and the tumor stroma. However, among diverse marker cell populations and specific cancer types, loss of GREM1 is more likely to cause cancers with worse prognoses and more severe cancer metastasis. This suggests that GREM1 is essential for the plasticity of tumor cells, and even different ways to maintain its activity or related pathways activated can cause different final directions of tumors. In many studies, GREM1 has undoubtedly been considered by many researchers to be a target for the diagnosis and treatment of emerging tumors with important clinical translational significance. In the serum of patients with pancreatic cancer, the combined diagnosis of GREM1 and CA199 may play an important role in indicating the prognosis of patients with pancreatic cancer. In studies of pancreatic cancer single-cell populations, overexpression of GREM1 even reduced liver metastasis in pancreatic cancer tumors. In addition, specific antibodies to GREM1 have also progressed in mouse models of prostate cancer, which undoubtedly provides new ideas and strong hope for future GREM1-related research (48).

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Availability of data and materials

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Authors' contributions

DaZ was mainly responsible for writing this manuscript and collecting related documents. DoZ helped write the section on breast cancer. NW helped write and modify the colon cancer section. FC helped write the section on pancreatic cancer and modified the syntax, and was involved in template drawing. MJ helped revise the grammar and design of the article, and corrected the preprint manuscript. ZZ designed the overall structure of the paper, guided the revision of the paper and provided financial support. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Authors' information

ZZ: Director of Department of Medical Oncology, General Hospital of Northern Theater Command (Shenyang, China) and engaged in clinical tumor treatment for a long time. DaZ: Postdoctoral fellow of medical oncology, General Hospital of Northern Theater Command (Shenyang, China) and specializes in basic oncology research. DoZ: Postdoctoral fellow of medical oncology, General Hospital of Northern Theater Command (Shenyang, China) and specializes in basic oncology research. NW: Postgraduate medical oncology, General Hospital of Northern Theater Command, Jinzhou Medical University (Shenyang, China). FC: Postgraduate medical oncology, Department of Oncology, General Hospital of Northern Theater Command, China Medical University (Shenyang, China). MJ: Doctor of medical Oncology, General Hospital of Northern Theater Command (Shenyang, China).

Competing interests

The authors declare that they have no competing interests.

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