

## Role of Gremlin-1 in Cancer

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Gremlin-1 (GREM1) has been defined as an antagonist of bone morphogenetic proteins (BMPs), particularly during embryonic development and tissue differentiation. However, recent studies have shown that GREM1 has BMPs-dependent or -independent functions in diverse human diseases. GREM1 plays a key role in the process of organ fibrosis, including lungs, kidneys, and so on. The GREM1-induced fibrosis typically promotes the development of other diseases, such as pulmonary hypertension, renal inflammation, and diabetic nephropathy. More recently, considerable evidence has been reported showing that GREM1 is involved in the promotion and/or progression of tumors *in vitro* and *in vivo*. It also performs an oncogenic role in the maintenance of cancer stem cells. Although GREM1 is known to function in a variety of diseases, here we focus on the role of GREM1 in cancer, and suggest GREM1 as a potential therapeutic target in certain types of cancer.

**Key Words:** Gremlin-1, Epithelial-mesenchymal transition, Fibrosis, Cancer, Angiogenesis

### INTRODUCTION

Bone morphogenetic proteins (BMPs) are extracellular proteins that constitute the largest subfamily of the transforming growth factor- $\beta$  (TGF- $\beta$ ) (Bragdon et al., 2011). While BMPs were originally considered to play a role in bone formation, they have been known to perform diverse actions in biological processes including organogenesis and tissue differentiation. BMPs bind to BMP receptors, which are serine/threonine kinase receptors at the cell surface, to induce certain signaling pathways (Wang et al., 2014).

Importantly, the BMP-induced signaling pathways can be inhibited by a family of BMP antagonists: these bind directly to BMP ligands, then prevent interaction with the BMP

receptors and their ligands (Canalis et al., 2003; Ali and Brazil, 2014). Gremlin-1 (GREM1), a BMP antagonist, was first identified from its antagonism of BMPs during embryonic development (Canalis et al., 2003). Transgenic mice overexpressing *Grem1* exhibited bone fractures and reduced bone mineral density compared to controls (Gazzerro et al., 2005), whereas *Grem1*-conditional null mice displayed increased bone formation and mass (Gazzerro et al., 2007). GREM1 is also important for organ development. The targeted deletion or overexpression of GREM1 has been shown to cause lung (Cahill et al., 2012) or kidney (Church et al., 2017) abnormalities. In addition to its role in organogenesis, numerous studies have shown that GREM1 is a key molecule in the induction of tissue fibrosis (Myllarniemi et al., 2008; Heron et al., 2011).

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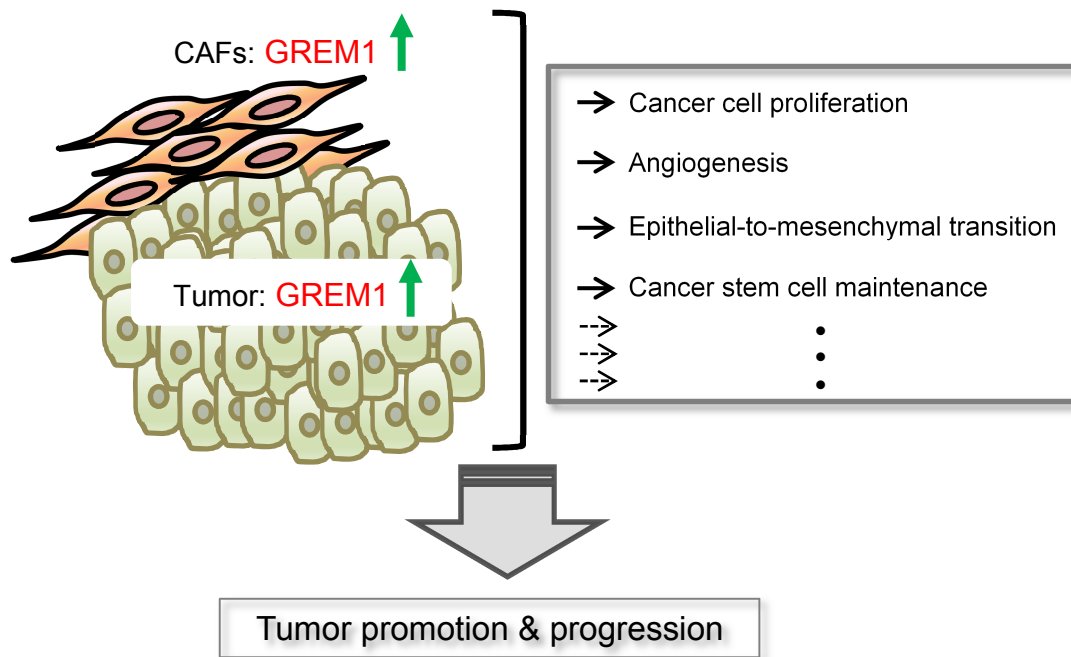
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**Fig. 1. The role of GREM1 in cancer.** The level of GREM1 is increased in several types of tumors and/or their surrounded stroma, particularly cancer-associated fibroblasts (CAFs). The overexpression of GREM1 in tumors and/or CAFs enhances the proliferation, angiogenesis, and epithelial-to-mesenchymal transition of cancer cells. In addition, it plays a role in cancer stem cell maintenance. Overall, GREM1 may eventually contribute to tumor promotion and progression.

Currently, GREM1 is known to be as a novel oncogenic or pro-angiogenic factor in cancer. The level of GREM1 has been shown to be overexpressed in multiple tumors and their stroma (Namkoong et al., 2006; Sneddon et al., 2006). GREM1 regulated the cancer cell growth (Kim et al., 2012; Wang et al., 2012) and cancer stem cell maintenance (Yan et al., 2014; Sato et al., 2016). In addition, GREM1 has been reported to mimic the effects of vascular endothelial growth factor (VEGF) on the VEGF receptor 2 (VEGFR2) in endothelial cells (Stabile et al., 2007), and to induce the epithelial-to-mesenchymal transition (EMT) in various cancer cells (Guan et al., 2017; Yin et al., 2017). Although there may be more roles of GREM1 in cancer, in this review, we particularly summarize some of the prominent functions of GREM1 (Fig. 1).

### Expression of GREM1 in tumors

Numerous studies have reported that the level of GREM1 is overexpressed in tumors compared to in surrounding normal tissues; this phenomenon has been observed in car-

cinomas of the colon (Galamb et al., 2012; Pelli et al., 2016; Li et al., 2017), lung (Mulvihill et al., 2012), gastric (Yamasaki et al., 2018), liver (Guimei et al., 2012), breast (Schuetz et al., 2006), and so on. The levels of mRNA and protein were both shown to be increased in the majority of human malignant mesothelioma tissues compared to control subjects (Wang et al., 2012). More recently, bioinformatic tools have been used to analyze the microRNAs and their target genes for the diagnosis of esophageal cancer, and GREM1 has been identified as one of those target genes. Subsequently, the expression of GREM1 was shown to be significantly increased in esophageal tumors compared to normal tissues (Cai et al., 2018). A common GREM1 polymorphism, rs16969681, has also been associated with colorectal cancer susceptibility and the higher *Grem1* mRNA levels increased the intestinal tumor burden in *Apc* (Min) mice (Lewis et al., 2014). In this context, a low-frequency variant rs12915554 in the 3' untranslated regions of GREM1 was also reported to be associated with colorectal cancer risk (Li et al., 2017).

Interestingly, GREM1 expression has been noticed not only in cancer cells but also in their surrounding stromal cells or cancer-associated fibroblasts. For example, GREM1 was widely overexpressed in the stroma of basal cell carcinoma of the skin, but not in the corresponding normal tissue counterparts (Sneddon et al., 2006). GREM1 expression was also particularly localized to activated myofibroblasts at the tumoral-stromal interface of basal cell carcinomas or scar tissues (Kim et al., 2017). In addition, GREM1-expressing fibroblasts are frequently observed in colorectal cancers, suggesting stromal GREM1 as a potential biomarker and possible candidate for the treatment of colorectal cancers (Jang et al., 2017).

### **GREM1 and tumor growth**

Increasing evidence suggests that high GREM1 expression affects the biological properties of cancer cells both *in vitro* and *in vivo*. Aberrant epithelial GREM1 expression has been shown to initiate colonic tumorigenesis in a synergistic fashion with Wnt signaling. Specifically, *Grem1* knockout markedly reduced Wnt-driven tumor progression *in vivo* (Davis et al., 2015). GREM1 knockdown using shRNA has also resulted in the inhibition of malignant mesothelioma cells (Wang et al., 2012). Likewise, treatment of recombinant GREM1 protein promoted the proliferation of basal cell carcinoma cells (Sneddon et al., 2006) and overexpression of GREM1 increased the growth of lung fibroblasts and epithelial cells (Mulvihill et al., 2012). Interestingly, GREM1 has been shown to directly interact with various types of cancer cells in a BMP-independent manner and it promoted proliferation, migration, and invasion of cancer cells (Kim et al., 2012).

Growing evidence has implicated that cancer stem cells play critical roles in tumor growth, recurrence, metastasis, and drug resistance (Chang, 2016). It has been shown that GREM1 promotes cancer stem cell maintenance, particularly in glioma and cervical cancer (Yan et al., 2014; Sato et al., 2016). The overexpression of GREM1 in non-glioma cancer stem cells decreased their endogenous BMP signaling to promote stem-like features and further increased the growth and tumor formation (Yan et al., 2014). In CaSki cervical cancer cells, the incubation with GREM1 has also been

shown to enhance the level of Nanog, one of the undifferentiated cell markers, and to increase their sphere-forming ability, thus maintaining their cancer stem cell-like properties (Sato et al., 2016).

### **GREM1 and angiogenesis**

Angiogenesis is an important process that promotes the aggressiveness of tumors. It has been reported that treatment of recombinant GREM1 stimulates the migration and invasion of endothelial cells. GREM1 has also been shown to be highly expressed in the endothelial cells of lung tumor vasculature, as compared to non-neoplastic lung (Stabile et al., 2007). The expression of GREM1 was correlated with microvessel density, suggesting its pro-angiogenic role in pancreatic neuroendocrine tumors (Chen et al., 2013). Moreover, GREM1 knockdown has been shown to reduce the proliferation, migration, and invasion of synoviocytes (Han et al., 2016). GREM1 promoted mesothelioma cell sprouting and invasion *in vitro* and it was overexpressed in tumors with a tendency to drive metastasis (Yin et al., 2017). Furthermore, GREM1 was overexpressed in desmoplastic invasion fronts in colorectal cancer (Karagiannis et al., 2014). Enrichment map profiling of the cancer invasion front suggested that GREM1 may trigger the motility of colorectal cancer cells (Karagiannis et al., 2013).

Remarkably, angiogenic VEGFR2 was bound by GREM1 in a BMP-independent manner, which activated VEGFR2-dependent angiogenic responses *in vitro* and *in vivo* (Mitola et al., 2010). Another study showed that the administration of recombinant GREM1 to murine kidneys induced sustained activation of VEGFR2 signaling (Lavoz et al., 2015). These findings suggest that the GREM1-VEGFR2 axis may be a promising target for multiple diseases including cancer (Erdmann et al., 2015).

### **GREM1 and EMT**

The EMT is a phenomenon in which epithelial cells loosen their cell-cell adhesion structures and become isolated and mobile (Savagner, 2010). EMT also plays a role in the genesis of fibroblasts during organ fibrosis or the transition of normal cells to transformed cell phenotypes during cancer progression (Kalluri and Neilson, 2003). It is well known that GREM1

is a key molecule in promoting pulmonary (Myllarniemi et al., 2008; Farkas et al., 2011) or renal fibrosis (Church et al., 2017). Importantly, the process of EMT is critically involved in GREM1-induced organ fibrosis (Allison, 2015).

In tubular epithelial cells, treatment of GREM1 has been shown to activate the TGF- $\beta$ 1/Smad signaling pathway which is a critical mechanism in the process of EMT or fibrosis (Rodrigues-Diez et al., 2014). Stimulation with recombinant GREM1 augmented EMT changes with the loss of epithelial markers and induction of mesenchymal markers in murine fibroblasts (Rodrigues-Diez et al., 2012) and in retinal pigment epithelial cells (Lee et al., 2007). According to another study, GREM1 also induced EMT by cadherin switching (loss of E-cadherin and upregulation of N-cadherin) and the overexpression of Snail, one of the major transcription factors involved in EMT regulation, in colon cancer cells (Karagiannis et al., 2015). The interaction between GREM1 and fibrillin microfibrils regulated malignant mesothelioma cell survival through the activation of another transcription factor Slug as well as mesenchymal proteins (Tamminen et al., 2013). GREM1 has been shown to promote carcinogenesis of glioma by regulating EMT. The knockdown of GREM1 abolished the TGF- $\beta$ 1-mediated activation of the Smad pathway, followed by the reduction of viability, migration, and invasion in glioma cells (Guan et al., 2017). More recently, the expression of GREM1 in mesenchymal stromal cells promoted EMT in human esophageal squamous cell carcinoma with an alteration in the expression levels of epithelial and mesenchymal markers (Hong et al., 2018).

## CONCLUSION

GREM1 is well known to be involved in the fibrosis of various organs including lungs (Myllarniemi et al., 2008) and kidneys (Church et al., 2017). In fact, GREM1 has been revealed to be one of the novel markers of liver fibrogenesis through the serial analysis of gene expression (Boers et al., 2006). In addition, GREM1 has been defined as a novel pro-fibrogenic factor in chronic pancreatitis (Staloch et al., 2015). In addition to organ fibrosis, increasing evidence has suggested that GREM1 plays an oncogenic role in multistep carcinogenesis. The level of GREM1 is increased in various

types of cancer cells both *in vitro* and *in vivo* (Schuetz et al., 2006; Mulvihill et al., 2012). Interestingly, GREM1 induces the proliferation, migration, and invasion of cancer cells (Kim et al., 2012; Yin et al., 2017). Apart from its role as an antagonist of BMP, GREM1 plays unique roles in a more complex pathological environment. GREM1 is widely expressed in cancer-associated stromal cells (Sneddon et al., 2006) and overexpressed in the cancer-associated myofibroblasts of basal cell carcinomas (Kim et al., 2017). These results also indicate that GREM1 can affect the promotion and progression of a tumor, not only in the tumor itself but also in the environment surrounding the tumor.

Although the involvement of GREM1 in metastasis has not been well-defined, GREM1 is one of the key regulators that can trigger the motility of cancer cells at the cancer invasion front (Karagiannis et al., 2013). GREM1-induced EMT may particularly affect the metastasis of cancer cells. BMP2/7 heterodimer has been shown to strongly inhibit the formation of bone metastasis, suggesting the role of BMP antagonists such as Coco, GREM1, etc., as an oncogenic driver of metastasis (Buijs et al., 2012). Moreover, Coco was reported to reactivate breast cancer cells at lung metastatic sites *in vivo* (Gao et al., 2012). Although the role of GREM1 in carcinogenesis has not yet been extensively investigated, we suggest here that GREM1 may be critically involved in tumor promotion and progression.

Previously, treatment with anti-GREM1 monoclonal antibody was shown to ameliorate chronic hypoxia/SU5416-induced pulmonary arterial hypertension in mice (Ciuculan et al., 2013). It has also been reported that microRNA-27b directly targeted GREM1 by binding to its 3'-UTR, reducing the GREM1 mRNA level in pulmonary cells (Graham et al., 2014). GREM1 may be a potential therapeutic target in a number of diseases including cancer, but there are still few reports of effective inhibitors for GREM1. In addition, future studies are necessary to determine the mechanism by which GREM1 expression is regulated as well as the mechanism by which it regulates other molecules.

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### CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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