Cancer–Stromal Interactions in Scirrhous Gastric Carcinoma

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Abstract Fibroblasts play an important role in the progression, growth and spread of gastric cancers. Cancer–stroma interactions have been especially evident in the scirrhous type of gastric carcinoma. Fibroblasts are associated with the cancer progression at the primary and metastatic site. The proliferative and invasive ability of scirrhous gastric cancer cells are closely associated with the growth factors produced by organ-specific fibroblasts. Fibroblasts are therefore a key determinant in the malignant progression of gastric cancer and represent an important target for cancer therapies.

Keywords Scirrhous gastric cancer · Fibroblasts · Stromal cells · Interaction · Microenvironment · Growth factor

Introduction

Tumor growth is not only determined by malignant cancer cells themselves, but also by the tumor stroma. Recently, tumor progression has been recognized as the product of an evolving crosstalk between the cancer cells and its surrounding tissue or tumor stroma [1]. Fibroblasts origi-

nally maintain the homeostasis of adjacent epithelia through the secretion of growth factors and direct mesenchymal–epithelial cell interactions. In addition, fibroblasts are associated with tumor growth and progression in various carcinomas. Moreover, cancer cells themselves may alter their adjacent stroma to form a permissive and supportive environment for tumor progression.

Scirrhous gastric carcinoma (Fig. 1a), diffusely infiltrating carcinoma, or Borrmann type 4 also known as linitis plastica-type carcinoma is characterized by rapid cancer cell infiltration and proliferation accompanied by extensive stromal fibrosis [2] (Fig. 1b). Scirrhous carcinomas account for about 10% of all gastric carcinomas, and carry a worse prognosis than other types of gastric carcinoma, reflecting their rapid proliferation of cancer cells [3–5]. The common features of scirrhous gastric cancer include rapidly progressive invasion, and a high frequency of metastasis to the peritoneum [6]. Scirrhous gastric cancer cells proliferate with fibrosis when the cancer cells invade into the submucosa containing abundant stromal cells. These typical histological findings of rapid growth with fibrosis suggest that its development may be controlled by intercellular interactions between the scirrhous gastric cancer cells and the stromal fibroblasts. Do fibroblasts contribute to the tumor progression or suppression? This question still remains unclear [7], but data from co-cultures and in vivo experiments seem to indicate that fibroblasts have a stimulating-activity for cancer progression.

Tumor–Stroma Interactions at the Primary Site

In the early stage of carcinoma, carcinoma in situ, cancer cells are separated from stromal cells by the boundary of a basement membrane. After the tumor cells invade into

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Fig. 1 Scirrhus gastric cancer. **a** Macroscopic findings indicate that scirrhus gastric carcinoma diffusely infiltrates a broad region of the stomach without a prominent ulceration and elevation. **b** Microscopic views of scirrhus gastric carcinoma have the appearance of abundant fibrosis with the occasional presence of poorly differentiated cancer cells

the stroma, the surrounding stromal cells can affect cancer progression. Gastric cancer cells of varying differentiation have differential cancer–stroma interactions with fibroblasts.

Growth-Stimulating Interaction Between Gastric Cancer Cells and Orthotopic Fibroblasts

The interaction between gastric cancer cells and organ-specific fibroblasts is evident *in vivo* [8] and *in vitro* [6]. Co-inoculation of scirrhus gastric cancer cells with gastric fibroblasts into nude mice specifically increases tumorigenicity, in comparison to that of gastric cancer cells alone (Fig. 2a). The histological findings of the xenograft produced by co-inoculation with gastric fibroblasts show extensive stromal fibrosis with scirrhus gastric cancer cell proliferation, in comparison to that by inoculation by cancer cell alone (Fig. 2b). Furthermore, orthotopic implantation

of scirrhus gastric cancer cells in stomach shows extensive fibrosis with the occasional presence of poorly differentiated adenocarcinoma cells which resembled scirrhus gastric carcinoma (Fig. 3a, b and c). In contrast, the histological findings of subcutaneous xenografts of scirrhus gastric cancer cells showed medullary growth (Fig. 3d), thus suggesting that the histological findings of ectopic tumors show a difference in the histological type of original tumor from which cancer cells were derived. Conditioned medium from gastric fibroblasts stimulates the growth of gastric cancer cells. These findings suggest that the growth of scirrhus gastric cancer cells is effected by orthotopic fibroblasts. Gastric fibroblasts specifically stimulate the growth of scirrhus gastric cancer cells, but not that of well-differentiated cancer cells. Organ specificity may contribute to the histolo-pathological formation of gastric cancer, and the microenvironment inducing fibroblasts may be important for cancer development (Fig. 4).

Fig. 2 Interaction between gastric fibroblasts and scirrhus gastric cancer cells. **a** The tumor size achieved by the co-inoculation of scirrhus gastric cancer cells and gastric fibroblasts was much larger than that achieved by the inoculation of cancer cells alone. **b** The xenografts produced by the co-inoculation shows infiltrative growth with extensive fibrosis, while the xenografted tumor of scirrhus gastric cancer cells alone shows medullary growth with poor fibrosis

Fig. 3 Orthotopic implantation. **a** Macroscopic findings of the gastric tumor after orthotopic inoculation of gastric cancer cells showed scirrhous type carcinoma. **b** The orthotopic tumors showed extensive fibrosis with the presence of cancer cells which resemble human scirrhous gastric carcinoma. **c** Masson trichrome staining showed blue-colored multiple fibrosis in the orthotopic tumors. **d** In contrast, the histological findings of a subcutaneous tumor by scirrhous gastric carcinoma cells showed medullary growth with less fibrosis (**e**)

Fig. 4 Cancer–stroma interaction of scirrhous gastric carcinoma at primary sites. At early stage, tumor cells need to invade into submucosa beyond the mucularis mucosae. MMP-2 production from fibroblasts and loss of cell–cell adhesion by down-regulation of E-cadherin and Desmoglein-2 might be important for the invasion of scirrhous cancer cells. When the tumor cells invade into the submucosa, a close relationship between cancer cells and orthotopic fibroblasts was evident in the development of gastric scirrhous cancer. Fibroblast growth factor 7 (FGF-7); a ligand of FGFR-2, secreted from gastric fibroblasts is

likely to contribute in a paracrine manner to the remarkable cell proliferation seen in gastric cancer with *FGF-R2* amplification. TGF β or HGF produced from stromal fibroblasts stimulates the invasion ability of scirrhous gastric cancer cells. TGF β from gastric cancer cells stimulates the proliferation of fibroblasts. FGF-7, TGF β and HGF organ-specific fibroblasts and TGF β from gastric cancer cells could mutually increase each other's proliferation, thus resulting in the characteristic histology of scirrhous gastric carcinoma

FGF-7 Produced from Gastric Fibroblasts Stimulates Proliferation of Scirrhous Gastric Cancer Cells

Interactions between scirrhous gastric cancer cells and orthotopic fibroblasts suggest that the proliferation of scirrhous gastric carcinoma is related to growth factor production by gastric fibroblasts. Among the various growth factors which are produced from fibroblasts, one of growth-stimulating factors from gastric fibroblasts that affected scirrhous gastric cancer cells is fibroblast growth factor-7 (FGF-7) [9, 10]. FGF-7, a member of the FGF family [11] also known as keratinocyte growth factor (KGF), originally was isolated from human embryonic lung fibroblasts and is produced by mesenchymal cells in various tissues. FGF-7 exerts its effect in a paracrine manner limited to epithelial cells [10], while other FGF family members also stimulate the growth of cultured endothelial cells and fibroblasts. Four members of the FGF receptor (FGFR) family, FGFR-1 (Flg), FGFR-2 (K-sam), FGFR-3, and FGFR-4, have been identified [12]. FGFR-2 is identical to the *K-sam-II* gene which was initially identified in an extract from the scirrhous gastric cancer cell line KATO-III. FGFR-2 is preferentially expressed in scirrhous gastric cancer. *FGFR-2* mRNA is amplified from scirrhous gastric cancer cells, and the ligand FGF-7 is produced by gastric fibroblasts. FGF-7 affects the growth of scirrhous gastric cancer cells, but not that of well-differentiated adenocarcinoma cells. KGF secreted by gastric fibroblasts is important in the progression of scirrhous type of gastric cancer with *K-sam-II* amplification in a paracrine manner (Fig. 4).

TGF β from Gastric Cancer Cells Stimulates the Proliferation of Fibroblasts

Orthotopic implantation of scirrhous gastric cancer cells in the stomach shows extensive fibrosis with the occasional presence of poorly differentiated adenocarcinoma cells which resembles scirrhous gastric carcinoma [13]. Scirrhous gastric cancer cells increase the proliferation of fibroblasts, but not well-differentiated adenocarcinoma cells [14]. The tumor stroma comprises most of the tumor mass in many carcinomas [15]. Its volume and composition are partly regulated by the response of the fibroblasts to the growth factors that are released by cancer cells [16] such as, TGF β , platelet-derived growth factor (PDGF) and FGF2, all of which are key mediators of fibroblast activation and tissue fibrosis [17]. TGF β from scirrhous gastric cancer cells stimulates the proliferation of fibroblasts. Tumor cells in scirrhous carcinoma produce more TGF β that is key mediators of fibroblast activation, than non-scirrhous carcinoma [18, 19]. This different interaction between the two cell types and stromal cells is associated with the

different biologic behaviors between the diffuse-type and intestinal-type in gastric carcinoma. Most of intestinal-type carcinoma cells proliferate in a medullary pattern, while scirrhous gastric cancer cells proliferate diffusely with extensive fibrosis [2]. This histological difference in the volume of the stroma might be determined by the response of gastric cancer cells to gastric fibroblasts. The growth-promoting factors from gastric cancer cells and organ-specific fibroblasts might mutually increase each other's proliferation, thus resulting in the characteristic histology of gastric carcinoma (Fig. 4).

Migration-Stimulating Activity of Gastric Cancer Cells by Fibroblasts

Fibroblasts affect the invasiveness of gastric cancer cells [20–23]. TGF β produced from fibroblasts increases the invasiveness of scirrhous gastric cancer cells [24]. TGF β is detected in a latent form in the conditioned medium from fibroblasts and in an active form in the conditioned medium from gastric cancer cells [18, 24]. The latent TGF β is activated by proteases such as plasmin and cathepsin [25]. Most gastric cancer cells secrete urokinase-type plasminogen activator (u-PA) which converts latent TGF β to active TGF β [26, 27]. The latent TGF β from gastric fibroblasts and scirrhous gastric cancer cells may be activated by u-PA from scirrhous gastric cancer cells. TGF β produced from gastric fibroblasts and cancer cells themselves affect the invasiveness of scirrhous gastric cancer cells by inducing a morphologic change to a spindle shape known as the epithelial-to-mesenchymal transition (EMT) [28]. Cancer cells undergoing the EMT develop invasive and migratory abilities [29–31]. HGF is also produced by gastric fibroblasts, and affects the invasiveness of scirrhous gastric cancer cells. The *c-met* gene which encodes C-met as the HGF receptor is amplified more intensely in scirrhous gastric cancer than in non-scirrhous gastric cancer [5]. Since HGF is not detectable in the conditioned medium from gastric cancer cells, HGF affects the invasiveness of scirrhous gastric cancer cells in a paracrine fashion (Fig. 4). In addition to secreting growth factors that directly affect cell motility, matrix metalloproteinases (MMPs) from fibroblasts allow cancer cells to cross tissue boundaries [32, 33]. In early stage, tumor cells arise at the mucosa need to invade into submucosa beyond the mucularis mucosae. Extracellular matrix degradation and loss of cell–cell adhesion might facilitate the tumor invasion. MMP-2 produced from fibroblasts is activated by MT1-MMP expressed on gastric cancer cells [34]. MMP2 from the stromal cells may affect cancer progression in a paracrine manner, even though cancer cells are separated from stromal cells by the basement membrane. Moreover, down-regulation of E-cadherin frequently found in diffuse-

type gastric carcinoma by methylation and mutations may be involved in tumor invasion [35]. Also, loss of heterozygosity at chromosome 18q12, on which cell–cell adhesion molecule Desmoglein-2 exists, is frequent in diffuse-type gastric cancer [36, 37].

Cancer–Stromal Interactions at Peritoneal Metastatic Sites

Peritoneal metastasis is the most frequent type of metastasis in gastric cancer. The peritoneum is composed of a superficial monolayer of mesothelial cells and submesothelial stromal tissue. The peritoneal metastatic sites also offer cancer–stromal interactions [20]. Fibroblasts at peritoneal metastatic sites seem to be conducive to tumor progression.

Adhesion of Cancer Cells to the Peritoneum

The adhesion of cancer cells to the peritoneum during peritoneal metastatic spread is an important step for metastasis. Cancer cells initially adhere to the mesothelial cells, and then adhere to the submesothelial connective tissue after the exfoliation of the mesothelial cells. Since peritoneal mesothelial cells express hyaluronic acid on their cell surface, the adhesion molecule CD44 expressed on the cancer cells mediates the binding of cancer cells to hyaluronic acid on mesothelial cells [38] (Fig. 5). Stromal fibroblasts up-regulate the CD44 expression of gastric cancer cells via TGF β signaling, thus resulting in the stimulation of the adhesion ability of scirrhous gastric cancer cells to the mesothelium [39]. The adhesion of cancer cells to the submesothelial components is also an important process in peritoneal dissemination. The submesothelial matrix is mainly composed of laminin, fibronectin, type IV collagen and type I collagen. Among the family of integrins, $\alpha 2\beta 1$ - and $\alpha 3\beta 1$ -integrin on cancer cells are key molecules to adhere to these submesothelial components [12, 40] (Fig. 5). Gastric cancer cells leaving the primary tumor are exposed to low oxygen levels in the peritoneal cavity [41]. The binding ability of scirrhous gastric cancer cells is increased by hypoxic (1% O₂) conditions in comparison to normoxic (21% O₂) conditions. TGF β increases the adhesion ability and $\alpha 2$ -, $\alpha 3$ -, and $\alpha 5$ -integrin expression of gastric cancer cells under hypoxia. A hypoxic environment promotes adhesion of scirrhous gastric cancer cells to the peritoneum. The upregulation of $\alpha 2$ -, $\alpha 3$ -, and $\alpha 5$ -integrin by TGF β under hypoxic conditions may be one of the mechanisms responsible for the high metastatic potential of scirrhous gastric cancer cells. The adhesion polypeptides, Tyr-Ile-Gly-Ser-Arg (YIGSR) and Arg-Gly-Asp (RGD), are the cell binding domain of the extra-cellular matrix (ECM) [42, 43], and

these peptides interfere with cell binding by integrins [44]. The adhesion polypeptides, YIGSR and RGD inhibit the adhesion ability of $\beta 1$ -integrin on gastric cancer cells. The peritoneal injection of adhesion polypeptides may be useful for the prevention of peritoneal metastasis [45].

Cancer Cells Modulate Their Stromal Environment—“Seed and Soil”

Cancer cells usually generate a supportive microenvironment by producing stroma-modulating growth factors. These include the FGF family, vascular endothelial growth factor (VEGF) family, PDGF, epidermal growth factor receptor (EGFR) ligands, interleukins, TGF β . These factors activate surrounding stromal cell types, such as fibroblasts, leading to the secretion of additional growth factors and proteases. The scirrhous gastric cancer cells stimulate the proliferation of peritoneal fibroblasts probably by TGF β while, in contrast, well-differentiated adenocarcinoma cells do not [14]. The histological findings of peritoneums with carcinomatous peritonitis show extensive proliferation of fibroblasts [46]. Fibrosis of the peritoneum also is recognized in areas without cancer cell infiltration. Tumorigenicity following intraperitoneal inoculation of scirrhous gastric cancer cells is increased in mice with pre-existing peritoneal fibrosis [46]. The peritoneal fibrosis induced by factors from cancer cells stimulates the migratory capability of scirrhous gastric cancer cells into the peritoneum. In addition, peritoneal fibrosis decreases the anti-metastasis activity of the mesothelial cells [14]. Peritoneal fibroblasts might play an important role in peritoneal implantation of scirrhous gastric cancer cells, similar to the fibroblasts in the primary tumor. Clinical observations suggest that certain tumors consistently metastasize to particular organs. Paget has explained this phenomenon by the “seed and soil” theory [47, 48]; metastases occurs when some tumor cells “seed” only live and grow in a congenial environment “soil” [49]. Peritoneal fibrosis induced by cancer cells may create a congenial environment “soil” for peritoneal metastases of scirrhous gastric carcinoma (Fig. 5).

HGF and TGF β Affect Mesothelial Cell Morphology

Mesothelial cell monolayers prevent infiltration of cancer cells into the peritoneum. TGF β from gastric cancer cells causes morphological changes in mesothelial cells and may thus be closely associated with peritoneal dissemination [50]. Moreover, mesothelial cells become hemispherical and exfoliate from the peritoneum. Mesothelial cells exposed to fibroblasts proliferation become hemispherical and separated from each other, while unexposed mesothelium remains as a flat monolayer. Cultured-mesothelial cells round up or exhibit a fibroblast-like shape following the

Fig. 5 Cancer–stroma interactions in scirrhous gastric carcinoma at peritoneal metastatic sites. Cancer cells free in the abdominal cavity initially adhere to hyaluronic acid on the mesothelial cells mediated by CD44 on the cancer cells. Thereafter, cancer cells adhere to submesothelial matrix of laminin, fibronectin, and collagen by $\alpha 2\beta 1$ - and $\alpha 3\beta 1$ -integrin expressed on cancer cells. Gastric cancer cells leaving the primary tumor are exposed to low oxygen levels in

the peritoneal cavity. Hypoxia increases the expression of integrin by the cancer cells. Peritoneal fibroblasts are induced by cancer cells to morphologically change into mesothelial cells, and stimulate the migratory capability of cancer cells by TGF- β , HGF and MMPs. Peritoneal fibrosis induced by cancer cells prior to cancer metastases may create a congenial environmental “soil” for peritoneal metastases of scirrhous gastric carcinoma

addition of peritoneal fibroblasts. Morphological changes are stimulated in mesothelial cells not only by cancer cells, but also by host fibroblasts [46]. HGF produced by peritoneal fibroblasts affect the morphology of mesothelial cells in monolayers so that the resulting environment becomes compatible with the peritoneal dissemination of cancer cells [51]. Peritoneal fibroblasts may thus exert some effects on mesothelial cells that precede metastasis (Fig. 5).

Tumor-Activated Fibroblasts

Most of fibroblasts used in the above studies are derived from cancer tissues. Fibroblasts within the tumor stroma, known as carcinoma-associated fibroblasts (CAFs), may acquire a modified phenotype [52, 53]. A further link between growth factors and CAFs in tumor initiation is indicated by a series of studies comparing the effect of normal fibroblasts and of CAFs isolated from the primary tumor site [54]. In culture, the phenotypic features of CAFs can be induced by various growth factors such as TGF β , which mediates fibroblast activation. TGF β -induced chemotaxis of fibroblasts and their transdifferentiation into activated smooth-muscle reactive fibroblasts, termed myofibroblasts [55]. Fibroblasts could become activated and further modified when cultured in vitro. Therefore, the role of normal resident fibroblasts in cancer progression remains unclear. Additional studies are needed to determine whether

CAFs represent a unique fibroblast phenotype in comparison to normal host-fibroblasts. Furthermore, targeting CAFs as a therapeutic strategy against cancer is an intriguing concept that requires further study.

Therapies to Target the Cancer–Stromal Interactions

Recent advances in the understanding of tumor–stroma interactions have elucidated various molecules which are characteristic of the cancer environment. The elucidation of tumor–stroma molecular interactions could provide a new targeted cancer therapy. Since the mechanisms that regulate fibroblast activation and their accumulation in cancer are becoming to be clear, fibroblasts might serve as novel therapeutic targets in cancer. Such therapies can be given alone or in combination with chemotherapy, radiation or surgery. Scirrhous gastric carcinoma shows a poor 5-year survival rate from 10% to 15% [56]. Various types of therapy, including chemotherapy, hormonal therapy, hyperthermia, and immunotherapy, have been tested for effectiveness in scirrhous gastric carcinoma at advance stage, but none have been unsatisfactory [57]. Accordingly, new therapies based on the characteristic cancer–stromal interactions in scirrhous gastric cancer have been urgently sought.

Tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic acid), a drug used clinically for the treatment of excessive

proliferation of fibroblasts, decreases gastric carcinoma growth and induces cancer cell apoptosis through its effect in blocking the growth-interactions between fibroblasts and scirrhous gastric cancer cells [34]. Tranilast inhibits not only the proliferation of fibroblasts but also the release of growth-promoting factors from fibroblasts and cancer cells, and then down-regulates the growth-interactions between fibroblasts and cancer cells [58]. In addition, the combination treatment with Tranilast and cisplatin decreases the xenografted tumor size, fibrosis, and mitosis, and increases apoptosis [59]. Furthermore, Tranilast suppresses the invasion-stimulating ability of fibroblasts by inhibiting the production of MMP-2 and TGF β from fibroblasts [60]. Tranilast may be a promising new drug to inhibit the interaction of proliferation and invasion between fibroblasts and scirrhous gastric cancer cells [58].

Cyclooxygenase (COX), a molecular target of NSAIDs, has two isoforms, COX-1 and COX-2. While COX-1 is expressed constitutively at a constant rate, COX-2 expression is regulated by various factors. In particular, COX-2 is overexpressed in stromal cells such as macrophages [61] and fibroblasts [62, 63] in various tumors. COX-2 produced by stromal cells stimulates proliferation and invasion of human carcinoma by stimulating stromal production of various cytokines [64]. The overexpression of COX-2 has been linked to the development of various types of human cancers [65, 66]. Several reports have indicated that COX-2 affects the invasiveness of cancer cells [67–69]. Gastric fibroblasts stimulate the invasiveness of scirrhous gastric cancer cells, while a selective COX-2 inhibitor, JTE-522, decreases HGF production from gastric fibroblasts by suppression of PGE2 productions, thus resulting in decreased invasion ability of gastric cancer cells [62, 70]. Moreover, JTE-522 down-regulates FGF-7 production from gastric fibroblasts, thus resulting in the inhibition of paracrine epithelial–mesenchymal interactions of between scirrhous gastric cancer cells and gastric fibroblasts [71].

FGFR-2/K-samII, a tyrosine kinase growth factor receptor, is overexpressed on scirrhous gastric cancer cells [72–75]. The secretion of FGF-7; a ligand of FGFR-2, by gastric fibroblasts is likely to contribute in a paracrine manner to the remarkable cell proliferation seen in scirrhous gastric cancer with FGFR-2/K-samII amplification [9]. Tyrosine kinase inhibitors act on the cytosolic ATP-binding domain of such receptors by inhibiting autophosphorylation. A major downstream signaling route of the FGF-R family is via the MAPK pathway. Ki23057, a newly developed small molecule acting FGFR-2/K-samII inhibitor, is a kinase inhibitor that competes with ATP for the binding site in the kinase [76]. Ki23057 decreases the proliferation of scirrhous cancer cells by inhibiting the phosphorylation of FGFR-2/K-samII, thus resulting in an increase of apoptosis [77]. The oral administration of Ki23057 prolongs the

survival of mice with peritoneal metastasis of scirrhous cancer. The combined administration of S1 and Ki23057 decreases orthotopic tumors as well as LN metastasis more effectively than S1 alone [78, 79]. FGFR-2 phosphorylation inhibitor appears therapeutically promising in scirrhous gastric carcinoma with K-samII amplification.

TGF β is secreted by a range of tumor cells [7] and mediates the interaction of cancer cells with stromal fibroblasts [1]. The administration of TGF β receptor (TGF β -R) inhibitor, A-77, improves the prognosis of the mice with peritoneal dissemination [80]. A-77 administration reduces the fibrosis and causes the medullary formation of cancer cells in vivo. The invasiveness of scirrhous gastric cancer cells is significantly increased in a co-culture with fibroblasts, and A-77 significantly decreases the invasion ability of scirrhous gastric cancer cells. A-77 is therefore suggested to inhibit the invasion ability of cancer cells by suppressing the intercellular interaction between the scirrhous gastric cancer cells and surrounding fibroblasts. A-77 decreases the expression of α 2-, α 3- and α 5-integrin in gastric cancer cells. A-77 decreases the growth of fibroblast, and invasion-stimulating activity of fibroblasts on cancer cells. A-77 is thus considered to be useful for inhibiting the peritoneal dissemination of scirrhous gastric carcinoma. TGF β seems to stimulate tumor progression in the tumor–stroma interaction, while the specific role of TGF β in tumor progression is still controversial [81]. TGF β probably functions as a tumor suppressor before the initiation of cancer, and during the early stages of carcinogenesis. In contrast, during the advanced stages of cancer, TGF β signaling promotes cancer progression and metastasis [82]. Additional studies are needed to examine the clinical effect of TGF β -R inhibitor on the progression of gastric carcinoma at both the early and advanced stages.

In conclusion, stromal fibroblasts have been proven to play an important role in the progression of scirrhous gastric carcinomas. The tumor–stroma interaction might therefore be a promising target for cancer therapy in gastric cancer, especially in the scirrhous type of cancer.

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