Inflammatory fibroblasts in cancer

Hyesol Lim & Aree Moon

Archives of Pharmacal Research

ISSN 0253-6269

Arch. Pharm. Res.
DOI 10.1007/s12272-016-0787-8

Springer

Arch. Pharm. Res.
DOI 10.1007/s12272-016-0787-8

REVIEW

Inflammatory fibroblasts in cancer

Hyesol Lim[1] · **Aree Moon**[1]

Received: 24 April 2016 / Accepted: 22 June 2016

Abstract The association between inflammation and cancer has been studied widely. Indeed, the tumor microenvironment is influenced by inflammatory cells and affects tumor progression, tumor growth, and the survival of cancer cells. Also, the tumor microenvironment is essential to invasion and metastasis of cancer. Fibroblasts, immune cells, the extracellular matrix and other various components all constitute the tumor stroma, ordinarily referred to as the 'reactive stroma'. Cancer-associated fibroblasts (CAFs), which are activated fibroblasts and one of the components of the tumor microenvironment, are associated with cancer progression, invasiveness and metastasis, and their functional contributions to these processes are beginning to emerge. CAFs mediate tumor-promoting inflammation through various signaling pathways. Epithelial–mesenchymal transition is a process for producing mesenchymal cells during invasion and metastasis of cancer cells. Fibroblasts have been identified as a key player in this mechanism. In the present review, we summarize the relationships between fibroblasts, inflammatory response, the tumor microenvironment and cancer progression. This review provides useful information for the development of cancer prevention and treatment therapies through controlling the inflammatory responses.

Keywords Fibroblasts · Cancer-associated fibroblasts (CAFs) · Tumor microenvironment · Epithelial–mesenchymal transition (EMT)

✉ Aree Moon
armoon@duksung.ac.kr

[1] Duksung Innovative Drug Center, College of Pharmacy, Duksung Women's University, Seoul 132-714, Korea

Introduction

Cancer cells do not exist alone; they exist in a tumor microenvironment that is composed of various types of non-cancer cells, such as fibroblasts, immune cells, mesenchymal stem cells and endothelial cells (Semenza and Ruvolo 2016). These tumor stromal components are crucial for supporting the malignant cancer cells (Yamaguchi and Sakai 2015). Many studies have identified that stromal cells in the tumor microenvironment contribute to cancer progression.

Cancer-associated fibroblasts (CAFs), one of the principal constituents of the tumor stroma, play powerful roles in the tumor microenvironment. CAFs release the signaling factors to promote cancer cell invasion in the tumor microenvironment and remodel the extracellular matrix (ECM) by secreting components and degrading enzymes (Karagiannis et al. 2012). In particular, recent studies have shown that breast cancer-associated fibroblasts induce breast cancer development including initiation, proliferation, invasion and metastasis (Buchsbaum and Oh 2016).

CAFs mediate cancer-related inflammation by expressing pro-inflammatory and tumor promoting factors (Sharon et al. 2015). Inflammation plays an important role in tumor growth, and some of the molecular mechanisms are well understood (Karin 2006). In addition, the role of inflammation in tumorigenesis is widely recognized (Mantovani et al. 2008).

CAFs act on motility of cancer cells through remodeling the ECM (Giannoni et al. 2011). CAFs are required for the malignancy of adjacent carcinoma epithelial cells by inducing EMT in tumor microenvironment (De Wever and Mareel 2003). The EMT refers to the loss of carcinoma epithelial phenotype and the acquisition and mesenchymal-associated features by inducing activation of a signaling

Published online: 06 July 2016

pathway. During EMT, epithelial cells acquire cell motility, increase matrix degradation, reorganize cytoskeletons, distribute adhesion molecules, change their polarity, and express mesenchymal markers (e.g., vimentin, Snail, α-SMA, fibronectin, and N-cadherin) (Radisky 2005; Gout and Huot 2008; Son and Moon 2010; Lee and Nelson 2012). Data from in vitro studies and experimental animal models now assist the role of EMT in cancer biology (Iwatsuki et al. 2010).

All of these roles of CAFs make tremendous contributions to cancer invasion and metastasis. Several experimental drugs targeting CAFs are in preclinical/clinical trials for various cancers. We believe that CAFs are a potential target for anti-cancer therapy and should be the focus of further studies. In this study, we summarize studies on tumor-enhancing inflammation mediated by CAFs in various cancers.

Inflammation and cancer

Inflammation plays a crucial role in tumor development, and this relationship has been recognized since the nineteenth century (Balkwill and Mantovani 2001). As such, researchers have supported the conclusion that chronic inflammation is a major risk factor in cancer etiology (Balkwill and Mantovani 2001). Chronic inflammation is caused by a variety of factors such as activated cytokines, chemokines, matrix-degrading enzymes and infiltrating leukocytes, and is highly correlated with diverse types of human cancers (Assenat et al. 2006; Allavena et al. 2008; Germano et al. 2008; Erez et al. 2010). Chronic inflammation is connected with cancer progression in several vital organs of body such as the breast, colon, stomach, and liver (Ames 1995; Platz and De Marzo 2004; Hojilla et al. 2008). Recent studies are aiming to more precisely define how inflammation is involved in cancer.

Well-known oncogenes such as *ras* and *myc* have been connected with tumor angiogenesis in diverse ways (Borrello et al. 2008). Oncogene-induced tumorigenesis is able to elicit an inflammatory response. In addition, cytokines are produced by activated innate immune cells that stimulate tumor growth and progression. For example, IL-6 is a potent pro-inflammatory cytokine that is considered a major growth-promoting and anti-apoptotic factor (Ishihara and Hirano 2002). A published study suggested that IL-6 gene polymorphism is a predisposing genetic factor that increases the probability of breast cancer prognosis (Berger 2004). Recently, IL-6 gene polymorphism has been associated with HBV-related hepatocellular carcinoma in a male Chinese Han population (Tang et al. 2014). Immune cells affect malignant cells through the production of cytokines, chemokines, growth factors, reactive oxygen and nitrogen species (Karin 2006). Several recent studies have implicated the activation of nuclear factor-κB (NF-κB) as a key modulator between inflammation and cancer (Pikarsky et al. 2004; Lu et al. 2006). Thus, the production of cytokines, such as TNF-α and IL-6, may activate NF-κB in cancer cells and induce chemokines that attract more inflammatory cells to the tumor (Zhou et al. 2003; Mantovani et al. 2008).

Additionally, immune cells were shown to be infiltrated into tumors of lung cancer patients (Johnson et al. 2000). Intratumoral infiltration by high levels of CD3+ and S100+ immune cells were associated with longer postoperative survival (Johnson et al. 2000). In patients with renal cell carcinoma, high amounts of immune cells expressing PD-1 and B7-H1 were observed in clinically aggressive forms of renal cell carcinoma (Thompson et al. 2007). Both PD-1 and B7-H1 lead to immune dysfunction and cancer progression (Thompson et al. 2007). All of these factors contribute to the complicated formation and progression of cancer.

Fibroblasts in the tumor microenvironment

Fibroblasts play major roles in human cancer progression. Cancer is a complex milieu of malignant cancer cells, fibroblasts, myeloid cells and all within a dynamic tumor stroma (Kessenbrock et al. 2010). Thus, the tumor microenvironment consists of a plethora of key modulators including stromal fibroblasts, infiltrating immune cells such as macrophages, blood vessels, components of the lymphatic vascular network, and the extracellular matrix (Joyce 2005; Qin et al. 2015).

The tumor microenvironment is shown to be controlled by various tumor-induced factors (Whiteside 2008). Interactions between tumor cells and inflammatory cells are regulated by cytokines and chemokines in breast carcinoma (Jin et al. 1997; Ben-Baruch 2003). In the tumor microenvironment, activation of released factors, such as CXCL14 and CXCL12, enhanced tumor progression (Fig. 1) (Allinen et al. 2004; Chiodoni et al. 2010). Matricellular proteins, which are secreted into the extracellular environment or matrix, but do not play a role in formation of structural elements (Bornstein 2009). Matricellular proteins regulate cell–matrix interactions, are produced by both tumor cells and surrounding stromal cells, such as fibroblasts and macrophages (Allinen et al. 2004; Chiodoni et al. 2010).

Fibroblasts are significant modifiers of cancer development in the tumor microenvironment. They are mostly established by their spindle-shaped morphology (den Braber et al. 1996). Fibroblasts have been identified in the tumor burden zone, the distal normal zone and the interface

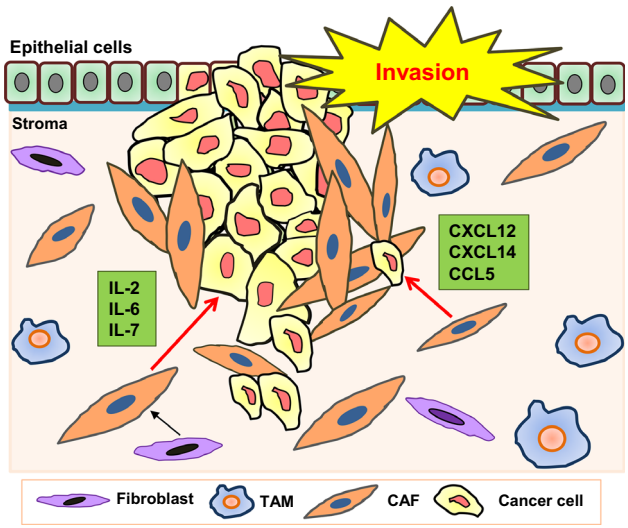

Fig. 1 CAFs lead to cancer cell invasion by releasing various cytokines

zone between normal tissue and tumor tissue in breast carcinomas; as such, these cells are referred to as CAFs, normal fibroblasts (NFs), and interface zone fibroblasts (INFs), respectively (Gao et al. 2012). When tissues are injured, fibroblasts differentiate into myofibroblasts (Balkwill et al. 2012). Differentiation of fibroblasts into myofibroblasts is regulated through various signaling cascades. Differentiation can also be triggered by transforming growth factor-beta (TGF-β) or SMAD signaling (Webber et al. 2010). In addition, differentiation is modulated by the cardiac glycoside ouabain by the fibroblast-induced cyclooxygenase-2 (COX-2) expression and protein kinase A (PKA) activation (La et al. 2016).

Activated fibroblasts are termed peritumoral fibroblasts, myofibroblasts and CAFs in tumor stroma (De Wever et al. 2008). In a non-cancerous environment, myofibroblasts play a key role in the reconstruction of connective tissue during wound healing and fibrosis development (Desmoulière et al. 2005). Myofibroblasts possess identifying markers such as α-smooth muscle actin (α-SMA), vimentin, collagen I, platelet derived growth factor receptor (PDGFR), neuron-glial antigen-2 (NG2) chondroitin sulfate proteoglycan and fibroblast-specific protein-1 (FSP1) (Ryan et al. 1974; Sugimoto et al. 2006). Specifically, α-SMA is one of the most significant markers of myofibroblast differentiation; it is the actin isoform that controls vascular smooth muscle actin and plays a crucial role in fibrogenesis (Yazhou et al. 2004; Yamashita et al. 2012). Contractile myofibroblasts that form *de novo* α-SMA-containing stress fibers in the tumor microenvironment are converted from fibroblasts (Hinz and Gabbiani 2003). In addition, fibroblast-activated protein (FAP) is an *N*-glycosylated, type II integral membrane protein that belongs to a family of plasma membrane-bound serine proteinases with gelatinase activity (Ariga et al. 2001). FAP silenced-SKOV3 cells significantly decreased the rate of tumor growth in xenograft mouse models and 4T1 murine breast carcinoma models (Lai et al. 2012; Cai et al. 2013).

Myofibroblasts modulate the surrounding environment through the secretion of matrix metalloproteases (MMPs), ECM components, cytokines, chemokines, and growth factors, as well as expression of their specific receptors (Powell et al. 2005; Hinz 2007). In addition to their effects on the tumor stroma, the fibroblasts play roles in the regulation of differentiation and homeostasis in adjacent epithelia (Mueller and Fusenig 2004). They are responsible for remodeling much of the ECM in tumor stroma (Bhowmick et al. 2004), and are also acknowledged as a source of growth factors that influence the growth of cancer cells (Bhowmick et al. 2004). Myofibroblast and fibroblast populations promoted the growth of bone marrow using a mouse model of pancreatic insulinoma (Direkze et al. 2004).

CAFs

CAFs are key determinants in the development, invasiveness and metastasis of diverse cancers. Activated fibroblasts that are found in association with cancer cells are called CAFs. CAFs are derived from multiple resident precursors, such as mesenchymal stem cells (MSCs), endothelial cells and myoepithelial cells (Tomasek et al. 2002; Spaeth et al. 2009).

Healthy fibroblasts are reprogrammed into CAFs via several microRNAs (miRNAs) (Tang et al. 2016). The miRNAs which are small noncoding RNA molecules involved in the post-transcriptional and translational regulation of gene expression (Hur 2015; Lee et al. 2016). Cancer cell invasion was promoted by stromal miR-200 s through CAFs activation and ECM remodeling in breast cancer (Tang et al. 2016). The miRNA-reprogrammed fibroblasts and CAFs enhance chemokine production, thereby activating their function. One of the most highly upregulated chemokines, CCL5, became a direct target of miR-214 in ovarian cancer (Fig. 1) (Mitra et al. 2012).

CAFs and tumor stromal components enhance tumor growth by stimulating angiogenesis, cancer cell proliferation, and invasion in human cancer (Choi et al. 2014; Jung et al. 2016). When A549, NCIH358 lung cancer cells, and CAFs were co-injected into the mice, significantly enhanced tumor formation was observed, compared with injection of both of these cancer cells without CAFs (Shintani et al. 2013). CAFs contributed to the invasion of cancer cells in ovary, breast and prostate cancers (Studebaker et al. 2008; Hwang et al. 2008; Zhang et al. 2011). In

rat model of colon carcinoma, CAFs induced tumor invasion of non-invasive epithelial tumor cells when CAFs were co-injected with colon tumor cells (Dimanche-Boitrel et al. 1994).

CAFs can be distinguished from normal fibroblasts by unique characteristics. In general, CAFs highly express α-SMA, p53, podoplanin, CD10, FAP, fibroblast specific protein 1 (FSP1), MMPs, tenascin-C and PDGFRα/β and lose expression of caveolin-1 (Cav-1) and cytokeratin (Garin-Chesa et al. 1990; Mao et al. 2013; Herrera et al. 2013; Luo et al. 2015; Shiga et al. 2015). Studies have demonstrated that increased expression of α-SMA in breast cancer stroma is associated with metastasis and poor overall survival rates (Yazhou et al. 2004; Yamashita et al. 2012).

CAFs play a role in rebuilding the ECM by expressing members of MMP family, which are well-known for their contribution to the degradation of ECM components when cancer cells invade and migrate (Kim et al. 2009). Recruitment of MMP-9 to the fibroblast cell surface leads to activation of TGF-β and fibroblasts (Dayer and Stamenkovic 2015). Extracellular matrix metalloproteinase inducer (EMMPRIN), which is involved in tumor progression, promotes expression of MMPs that enhance tumor invasiveness and metastasis in co-culture model with human malignant melanoma cells and dermal fibroblasts (Fig. 2) (Kanekura et al. 2002). In a recent study, curcumin inhibited CAF-induced invasion, EMT, expression of CXCR4, and expression of the IL-6 receptor in prostate cancer through a monoamine oxidase A (MAOA)/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α (HIF-1α) signaling pathway (Du et al. 2015).

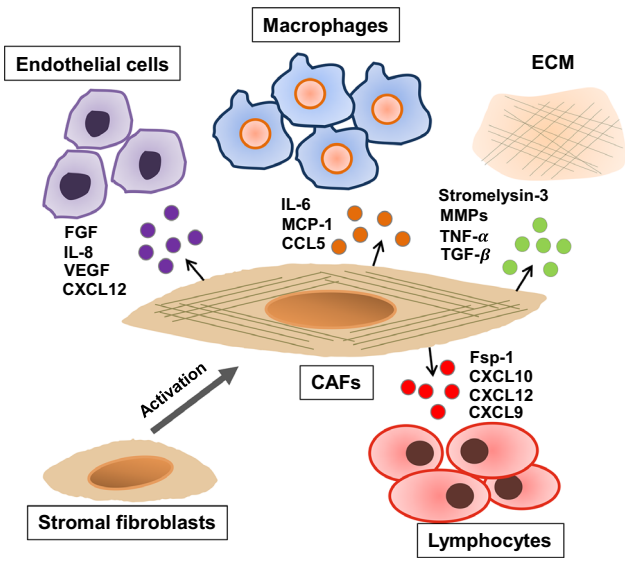

Fig. 2 CAFs affect tumor microenvironment consisting of endothelial cells, macrophages, ECM and lymphocytes by releasing various factors

CAFs and EMT

CAFs are key mediator of the EMT. The EMT plays a crucial role in the induction of invasion in breast cells (Cha et al. 2015; Koh et al. 2015) and is associated with various human cancer progression and metastasis (Thiery 2002; Polyak and Weinberg 2009).

CAFs and surrounding normal fibroblasts were able to induce EMT of breast cancer cells in a co-culture system (Soon et al. 2013). CAFs also stimulated prostate cancer cells to secrete MMPs and IL-6, resulting CAF-induced EMT (Giannoni et al. 2010; Doldi et al. 2015). Extracellular acidification by CAF-mediated carbonic anhydrase IX, which is a transmembrane enzyme and correlates with poor prognosis in various cancers, induced EMT, cell survival and stemness in prostate cancer (Fiaschi et al. 2013). In urinary bladder cancer, conditioned media (CM) of CAFs induced EMT through the TGFβ1-ZEB2NAT-ZEB2 axis (Zhuang et al. 2015). As a result, mRNA expression of TGFβ1 was positively associated with the ZEB2NAT transcript and ZEB2 protein levels in human bladder cancer (Zhuang et al. 2015).

Inflammatory CAFs in cancer

CAFs modulate tumor-promoting inflammation and alter the components of the inflammatory microenvironment that promote tumor initiation, progression, and metastasis (Servais and Erez 2013). Specifically, inflammatory CAFs facilitate tumor growth, invasion and metastasis by indirectly or directly stimulating tumor cells proliferation in various cancer.

CAFs released the inflammatory factors such as IL-6, COX-2 and CXCL1, leading to tumor cell invasion in in vivo breast cancer models (Erez et al. 2013). Liao et al. demonstrated that CAFs promoted tumor growth and metastasis by expressing high levels of IL-2 and IL-7 in a breast metastatic cancer model (Liao et al. 2009). In a recent study, CAFs enhanced cancer cell invasion by secreting IL-6 in colon cancer (Fig. 1) (Shiga et al. 2015).

The differentiation of macrophages toward tumor-associated macrophages (TAM, M2 macrophages) is promoted by CAFs via secretion of IL-6 and monocyte chemoattractant protein 1 (MCP-1) (Chiarugi 2013). The interplay between CAFs and M2 macrophages cooperated in increasing tumor cell motility, fostering cancer cell invasion (Chiarugi 2013). In contrast, it was reported that CAF·ERα(+) suppressed the migration and infiltration of

M2 macrophages, inhibiting neighboring pancreatic cancer cell invasion via CAF-secreted CCL5 (Yeh et al. 2016). CAFs also inhibited the invasion of pancreatic cancer cells into M2 macrophages by reducing IL-6 expression (Yeh et al. 2016). Elimination of the TGFβR2 in mammary CAFs secreted a high level of CCL2, promoting tumor growth and metastasis through the recruitment of M2 macrophages (Hembruff et al. 2010).

Lymphocytes including a subset of T helper cells (i.e., Th2, Th17 and T-regulatory cells) infiltrate tumor sites for cancer progression. The process stimulates CAFs to secrete the pro-inflammatory cytokines such as Fsp1, CXCL9, CXCL10 and CXCL12 (van de Veerdonk et al. 2009; De Monte et al. 2011; Wilke et al. 2011; Raz and Erez 2013; Servais and Erez 2013). CAFs-induced the pro-inflammatory cytokines facilitated the recruitment of lymphocytes, promoting tumor growth and metastasis (Fu et al. 2013; Raz and Erez 2013).

CAFs modulate the tumor immune microenvironment by inducing a shift from Th1- to Th2-type immunity in vivo models of metastatic breast cancer (Liao et al. 2009). Ablation of CAFs correlated with an increase in Th1 cytokine expression and noticeably inhibited the recruitment of CD8+ cytotoxic T lymphocytes in the tumor microenvironment (Liao et al. 2009).

CAFs secrete pro-angiogenic factors, such as IL-8, CXCL12, VEGF and FGF, into other stromal cell types including endothelial cells to promote tumor angiogenesis (De Veirman et al. 2014). These reactions lead to enhanced activity of endothelial cells and *de novo* angiogenesis, promoting tumor cell motility, metastatic tumor spread (Comito et al. 2014).

CAFs induce the production of pro-invasive proteases (e.g., stromelysin-3) that degrade the ECM (Basset et al. 1990; De Wever et al. 2008). CAF-secreted TGF-β as a competent ECM modulator leads to reduction of cancer cell adhesion (Van Bockstal et al. 2014). Cancer-derived stromal cells, including fibroblasts, in the tumor microenvironment provide an essential communication network between cancer cells and ECM components (Mbeunkui and Johann 2009). Increased secretion of TNF-α or TGF-β in mammary CAFs induces MMPs expression via PI3-kinase, *ras*, and SMAD signaling (Stuelten et al. 2005). CAFs contribute to tumor growth or suppression by releasing various factors in tumor microenvironment consisting of lymphocytes, macrophages, endothelial cells and ECM (Fig. 2).

CAFs in breast cancer

Breast cancer is the most common disease in women worldwide (Ham and Moon. 2013; Lee and Moon. 2016; Qiao et al. 2016). Metastasis of cancer cells is the primary cause of mortality in breast cancer patients (Chambers et al. 2002; Cha et al. 2012). Thus, breast cancer patients may have difficulty recovering completely if cancer cells have started to metastasize. Recently, the role of cell-stroma interactions is emphasized in the etiology of breast cancer (Rozenchan et al. 2015a, b).

Fibroblasts are prominent cellular components of connective tissue and play a crucial role in the tumor microenvironment. Specifically, CAFs are involved in various features of breast cancer, including tumorigenesis, carcinogenesis, tumor progression, invasion, metabolism, therapy resistance, and prognosis (Jung et al. 2016). Although many therapies are used to treat breast cancer, such as chemotherapy, immunotherapy, targeted therapy, radiation and surgery, it is not rare for the cancer to recur or metastasize (Mao et al. 2013) (Table 1).

CAFs influence the growth and differentiation of normal breast epithelial cells (i.e., MCF10A cells) and pre-cancerous breast cells (i.e., MCF10AT1-EIII8 cells) and support the estrogen response of MCF10AT1-EIII8 cells in a three-dimensional model (Shekhar et al. 2001). In contrast, CAFs inhibited the proliferation of MCF10A cells (Sadlonova et al. 2005). Expression of CAF-specific TGFβR2, a binding ligand of the TGF-β family, is related with enhanced recurrence-free survival. In addition, co-injection of TGFβR2 knockdown-CAFs and MCF7 cells caused an increase in tumor size in mouse xenograft models (Busch et al. 2015).

CAFs enhance invasion of breast cancer cells through expression of hepatocyte growth factor (HGF), which has been shown to promote with breast tumorigenesis compared to NFs isolated from the same patients and xenograft models (Tyan et al. 2011; Chen et al. 2012). HGF, in turn, improves the growth of ERα-positive breast cancer cells such as MCF7 and BT474 in xenograft mouse models (Studebaker et al. 2008). CAFs that display features of myofibroblasts play an important role in accelerating tumor progression through secretion of stromal cell-derived factor 1 (SDF-1) in invasive human breast cancer (Orimo et al. 2005). Also, CAFs express high levels of RhoA and Rac1, well-known adhesion molecules, compared to normal fibroblasts. CAFs promote the invasion of cancer cells into lymph nodes in breast cancer (Rozenchan et al. 2015).

Therapeutical approaches targeting CAFs

Herein, we discuss how CAFs are dominant components of stroma and how they play central roles in sustaining a tumor microenvironment that promotes carcinogenesis. We summarize the immunosuppressive mechanisms of CAFs and systematically investigate the alteration of cancer-associated immune responses by CAF-targeted therapies.

Table 1 Drugs that target CAFs in clinical trials

Target factor	Drug	Function	Clinical trials	References
FAP	Sibrotuzumab	Anti-FAP antibody	Phase I and II	Scott et al. (2003) Kloft et al. (2004) Cheng and Weiner (2003)
	DPP-IV	FAP inhibitor	Phase III	Van der Veken et al. (2007)
	Sc40-FasL	Inducing apoptosis of FAP^+ cells	Preclinical	Samel et al. (2003)
Activated fibroblasts	NK4	HGF inhibitor	Preclinical	Matsumoto and Nakamura (2003) Tomioka et al. (2001) Saga et al. (2001)
PDGF	Imatinib	PDGFR inhibitor	Phase II	Bauman et al. (2012)
	Sorafenib	PDGFR inhibitor	Phase III	Haas et al. (2016) Jiang et al. (2015)
	Sunitinib	PDGFR inhibitor	Phase III	Wiedmann and Mössner (2012)

There are several ways to target CAFs: (1) ablation of FAP which is fibroblast-activated protein by CAFs, (2) normalization of activated fibroblast, (3) inhibition of PDGF receptor (Kalluri and Zeisberg 2006). Depleting FAP-expressing CAFs causes the suppression of cancer cell growth in a mouse model of pancreatic ductal adenocarcinomas (Kraman et al. 2010). In vivo mouse models, vaccination of CAF-expressed FAP led to a reduction in tumor growth and the antitumor response was predominant against tumor cell-expressed antigens (Lee et al. 2005). Moreover, deletion of FAP inhibited proliferation of tumor cells, decreased the number of activated fibroblasts, and promoted accumulation of collagen in vivo mouse models (Santos et al. 2009). Also, in mouse models of colon cancer and K-Ras mutant lung cancer, genetic deletion of FAP hindered tumor growth (Santos et al. 2009). Growth of K-RasG12D-deriven lung cancer was inhibited by protease dipeptidyl peptidase IV (DPP-IV) (Santos et al. 2009). The prolyl peptidases related to DPP IV was suggested to have a therapeutic potential to inhibit FAP and thus treat various cancers as well (Van der Veken et al. 2007). Sibrotuzumab, an antibody to FAP, is now undergoing phase I and II clinical trials in patients with advanced colorectal carcinoma or non-small-cell lung cancer (Cheng and Weiner 2003; Scott et al. 2003; Kloft et al. 2004). Sc40-FasL as Anti-FAP fusion protein, which consists of the amino-terminus of FAP and the carboxyl-terminus of the extracellular domain of FasL, has also shown therapeutic potential in preclinical models (Samel et al. 2003). The FasL fusion protein induced apoptosis and inhibited FAP-positive tumor growth (Samel et al. 2003).

Recently, the process of normalization of activated fibroblasts has been suggested as another way to target CAFs (Kalluri and Zeisberg 2006). Several growth factors and hormones were used to inhibit normalization of activated fibroblasts in tissue fibrosis (Kalluri and Zeisberg 2006). Among these growth factors, HGF, which promotes cancer progression, inhibited activation of tissue fibrosis by liver myofibroblasts in animal models of chronic cirrhosis (Kim et al. 2005). The therapeutic potential of NK4, an antagonist of HGF, has been suggested to suppress tumor growth in vivo in pancreatic and ovarian cancers (Saga et al. 2001; Tomioka et al. 2001; Matsumoto and Nakamura 2003). The peptide hormone, relaxin, decreased the number of activated fibroblasts, and inhibits fibrosis (Heeg et al. 2005). Interestingly, increased concentration of serum relaxin correlated with a poor prognosis of breast cancer patients (Binder et al. 2004). The apparent discrepancy observed in the effect on diseases implicates that further detailed studies are required for therapeutic approaches of targeting CAFs.

The inhibition of PDGF receptor has been used for the way as a promising candidate for specifically targeting CAFs. Restoration of down-regulated PDGF receptors by TGF-β enhances activation of fibroblasts (Psarras et al. 1994). CAF derived PDGF-C has been shown to play a major role in stimulating VEGF production and antibodies targeted against PDGF-C were synergistic with anti-VEGF-A antibodies (Crawford et al. 2009). Currently, several PDGF receptor inhibitors are common in clinical use. Imatinib (brand name Gleevec), sorafenib (brand name Nexavar) and sunitinib (brand name Sutent) are used in the treatment of gastrointestinal stromal tumors, renal cell carcinoma, hepatocellular carcinoma and chronic myeloid leukemia (Escudier et al. 2007; Llovet et al. 2008; Gugliotta et al. 2016; Haas et al. 2016). The combination of sorafenib and DE605, which is a novel c-MET (epithelial–mesenchymal transition factor) inhibitor, caused meaningful tumor growth inhibition in vitro and in tumor xenograft models of hepatocellular carcinoma by inhibiting Raf, VEGF and PDGF receptors (Jiang et al. 2015). Sunitinib targets the tyrosine receptor kinase to reduce

tumor proliferation and angiogenesis; it has demonstrated progression-free survival and overall survival benefits in phase III pancreatic neuroendocrine tumors (Vinik and Raymond 2013). Notably, these ongoing studies are shedding light on the potential for CAFs to be pharmaceutical targets and can play pivotal roles in the development and optimization of anti-cancer therapies.

Conclusions

Inflammation can affect the progression and development of diverse tumors. Specifically, chronic inflammation is a risk factor for cancer metastasis after recurrence (Knupfer and Preiss 2007). In the tumor microenvironment, inflammatory fibroblasts are crucial contributors to cancer progression. In tumor growth, invasion and metastasis, they coordinate tumor-enhancing inflammation by performing functional roles and secreting essential factors. Franco et al. (2010) identified the tumor-promoting action of CAFs in the study that targeted them for anti-cancer therapy. Targeting CAFs as a therapeutic strategy against cancer is promising, but detailed functional mechanisms are needed through further understanding of their pathways and effects. In the present review, we highlight the importance of the interaction between stromal and malignant tumor cells, with a focus on the inflammatory CAFs and their therapeutic targets.

Acknowledgments The present study was supported by Priority Research Centers Program (No. 2016R1A6A1A03007648), and the Bio & Medical Technology Development Program (No. 2015M3A9 B6074045) of the NRF funded by the Korean government.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

Allavena P, Garlanda C, Borrello MG, Sica A, Mantovani A (2008) Pathways connecting inflammation and cancer. Curr Opin Genet Dev 18(1):3–10

Allinen M, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K (2004) Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell 6(1):17–32

Ames BN (1995) Understanding the causes of aging and cancer. Microbiologia 11(3):305–308

Ariga N, Sato E, Ohuchi N, Nagura H, Ohtani H (2001) Stromal expression of fibroblast activation protein/seprase, a cell membrane serine proteinase and gelatinase, is associated with longer survival in patients with invasive ductal carcinoma of breast. Int J Cancer 95(1):67–72

Assenat E, Gerbal-chaloin S, Maurel P, Vilarem MJ, Pascussi JM (2006) Is nuclear factor kappa-B the missing link between inflammation, cancer and alteration in hepatic drug metabolism in patients with cancer. Eur J Cancer 42(6):785–792

Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357:539–545

Balkwill FR, Capasso M, Hagemann T (2012) The tumor microenvironment at a glance. J Cell Sci 125(Pt 23):5591–5596

Basset P, Bellocq JP, Wolf C, Stoll I, Hutin P, Limacher JM, Podhajcer OL, Chenard MP, Rio MC, Chambon P (1990) A novel metalloproteinase gene specifically expressed in stromal cells of breast carcinomas. Nature 348(6303):699–704

Bauman JE, Eaton KD, Wallace SG, Carr LL, Lee SJ, Jones DV, Arias-Pulido H, Cerilli LA, Martins RG (2012) A Phase II study of pulse dose imatinib mesylate and weekly paclitaxel in patients aged 70 and over with advanced non-small cell lung cancer. BMC Cancer 12:449

Ben-Baruch A (2003) Host microenvironment in breast cancer development: inflammatory cells, cytokines and chemokines in breast cancer progression: reciprocal tumor-microenvironment interactions. Breast Cancer Res 5(1):31–36

Berger FG (2004) The interleukin-6 gene: a susceptibility factor that may contribute to racial and ethnic disparities in breast cancer mortality. Breast Cancer Res Treat 88(3):281–285

Bhowmick NA, Neilson EG, Moses HL (2004) Stromal fibroblasts in cancer initiation and progression. Nature 432(7015):332–337

Binder C, Simon A, Binder L, Hagemann T, Schulz M, Emons G, Trümper L, Einspanier A (2004) Elevated concentrations of serum relaxin are associated with metastatic disease in breast cancer patients. Breast Cancer Res Treat 87(2):157–166

Bornstein P (2009) Matricellular proteins: an overview. J Cell Commun Signal 3(3–4):163–165

Borrello MG, Degl'Innocenti D, Pierotti MA (2008) Inflammation and cancer: the oncogene-driven connection. Cancer Lett 267(2):262–270

Buchsbaum RJ, Oh SY (2016) Breast cancer-associated fibroblasts: where we are and where we need to go. Cancers (Basel) 8(2):19

Busch S, Acar A, Magnusson Y, Gregersson P, Rydén L, Landberg G (2015) TGF-beta receptor type-2 expression in cancer-associated fibroblasts regulates breast cancer cell growth and survival and is a prognostic marker in pre-menopausal breast cancer. Oncogene 34(1):27–38

Cai F, Li Z, Wang C, Xian S, Xu G, Peng F, Wei Y, Lu Y (2013) Short hairpin RNA targeting of fibroblast activation protein inhibits tumor growth and improves the tumor microenvironment in a mouse model. BMB Rep 46(5):252–257

Cha Y, Kang Y, Moon A (2012) HER2 induces expression of leptin in human breast epithelial cells. BMB Rep 45(12):719–723

Cha YH, Yook JI, Kim HS, Kim NH (2015) Catabolic metabolism during cancer EMT. Arch Pharm Res 38(3):313–320

Chambers AF, Groom AC, MacDonald IC (2002) Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2:563–572

Chen P, Mo Q, Wang B, Weng D, Wu P, Chen G (2012) Breast cancer associated fibroblasts promote MCF-7 invasion in vitro by secretion of HGF. J Huazhong Univ Sci Technol Med Sci 32(1):92–96

Cheng JD, Weiner LM (2003) Tumors and their microenvironments: tilling the soil. Clin Cancer Res 9(5):1590–1595

Chiarugi P (2013) Cancer-associated fibroblasts and macrophages: Friendly conspirators for malignancy. Oncoimmunology 2(9):e25563

Chiodoni C, Colombo MP, Sangaletti S (2010) Matricellular proteins: from homeostasis to inflammation, cancer, and metastasis. Cancer Metastasis Rev 29(2):295–307

Choi YP, Lee JH, Gao MQ, Kim BG, Kang S, Kim SH, Cho NH (2014) Cancer-associated fibroblast promote transmigration through endothelial brain cells in three-dimensional in vitro models. Int J Cancer 135(9):2024–2033

Comito G, Giannoni E, Segura CP, Barcellos-de-Souza P, Raspollini MR, Baroni G, Lanciotti M, Serni S, Chiarugi P (2014) Cancer-associated fibroblasts and M2-polarized macrophages synergize during prostate carcinoma progression. Oncog 33(19):2423–2431

Crawford Y, Kasman I, Yu L, Zhong C, Wu X, Modrusan Z, Kaminker J, Ferrara N (2009) PDGF-C mediates the angiogenic and tumorigenic properties of fibroblasts associated with tumors refractory to anti-VEGF treatment. Cancer Cell 15(1):21–34

Dayer C, Stamenkovic I (2015) Recruitment of matrix metalloproteinase-9 (MMP-9) to the fibroblast cell surface by lysyl hydroxylase 3 (LH3) triggers transforming growth factor-β (TGF-β) activation and fibroblast differentiation. J Biol Chem 290(22):13763–13778

De Monte L, Reni M, Tassi E, Clavenna D, Papa I, Recalde H, Braga M, Di Carlo V, Doglioni C, Protti MP (2011) Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. J Exp Med 208(3):469–478

De Veirman K, Rao L, De Bruyne E, Menu E, Van Valckenborgh E, Van Riet I, Frassanito MA, Di Marzo L, Vacca A, Vanderkerken K (2014) Cancer associated fibroblasts and tumor growth: focus on multiple myeloma. Cancers (Basel) 6(3):1363–1381

De Wever O, Mareel M (2003) Role of tissue stroma in cancer cell invasion. J Pathol 200(4):429–447

De Wever O, Demetter P, Mareel M, Bracke M (2008) Stromal myofibroblasts are drivers of invasive cancer growth. Int J Cancer 123(10):2229–2238

den Braber ET, de Ruijter JE, Ginsel LA, von Recum AF, Jansen JA (1996) Quantitative analysis of fibroblast morphology on Gicrogrooved surfaces with various groove atid ridge dimensions. Biomaterials 17(21):2037–2044

Desmoulière A, Chaponnier C, Gabbiani G (2005) Tissue repair, contraction, and the myofibroblast. Wound Repair Regen 13(1):7–12

Dimanche-Boitrel MT, Vakaet L Jr, Pujuguet P, Chauffert B, Martin MS, Hammann A, Van Roy F, Mareel M, Martin F (1994) In vivo and in vitro invasiveness of a rat colon-cancer cell line maintaining E-cadherin expression: an enhancing role of tumor-associated myofibroblasts. Int J Cancer 56(4):512–521

Direkze NC, Hodivala-Dilke K, Jeffery R, Hunt T, Poulsom R, Oukrif D, Alison MR, Wright NA (2004) Bone marrow contribution to tumor-associated myofibroblasts and fibroblasts. Cancer Res 64(23):8492–8495

Doldi V, Callari M, Giannoni E, D'Aiuto F, Maffezzini M, Valdagni R, Chiarugi P, Gandellini P, Zaffaroni N (2015) Integrated gene and miRNA expression analysis of prostate cancer associated fibroblasts supports a prominent role for interleukin-6 in fibroblast activation. Oncotarget 6(31):31441–31460

Du Y, Long Q, Zhang L, Shi Y, Liu X, Li X, Guan B, Tian Y, Wang X, Li L, He D (2015) Curcumin inhibits cancer-associated fibroblast-driven prostate cancer invasion through MAOA/mTOR/HIF-1α signaling. Int J Oncol 47(6):2064–2072

Erez N, Truitt M, Olson P, Arron ST, Hanahan D (2010) Cancer-associated fibroblasts are activated in incipient Neoplasia to orchestrate tumor-promoting inflammation in an NF-kappaB-Dependent manner. Cancer Cell 17(2):135–147

Erez N, Glanz S, Raz Y, Avivi C, Barshack I (2013) Cancer associated fibroblasts express pro-inflammatory factors in human breast and ovarian tumors. Biochem Biophys Res Commun 437(3):397–402

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM, TARGET Study Group (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356(2):125–134

Fiaschi T, Giannoni E, Taddei ML, Cirri P, Marini A, Pintus G, Nativi C, Richichi B, Scozzafava A, Carta F, Torre E, Supuran CT (2013) Chiarugi P (2013) Carbonic anhydrase IX from cancer-associated fibroblasts drives epithelial–mesenchymal transition in prostate carcinoma cells. Cell Cycle 12(11):1791–1801

Franco OE, Shaw AK, Strand DW, Hayward SW (2010) Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol 21(1):33–39

Fu Z, Zuo Y, Li D, Xu W, Li D, Chen H, Zheng S (2013) The crosstalk: tumor-infiltrating lymphocytes rich in regulatory T cells suppressed cancer-associated fibroblasts. Acta Oncol 52(8):1760–1770

Gao MQ, Kim BG, Kang S, Choi YP, Park H, Kang KS, Cho NH (2012) Stromal fibroblasts from the interface zone of human breast carcinomas induce an epithelial–mesenchymal transition-like state in breast cancer cells in vitro. J Cell Sci 123(Pt 20):3507–3514

Garin-Chesa P, Old LJ, Rettig WJ (1990) Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acad Sci USA 87(18):7235–7239

Germano G, Allavena P, Mantovani A (2008) Cytokines as a key component of cancer-related inflammation. Cytokine 43(3):374–379

Giannoni E, Bianchini F, Masieri L, Serni S, Torre E, Calorini L, Chiarugi P (2010) Reciprocal activation of prostate cancer cells and cancer-associated fibroblasts stimulates epithelial–mesenchymal transition and cancer stemness. Cancer Res 70(17):6945–6956

Giannoni E, Bianchini F, Calorini L, Chiarugi P (2011) Cancer associated fibroblasts exploit reactive oxygen species through a proinflammatory signature leading to epithelial mesenchymal transition and stemness. Antioxid Redox Signal 14(12):2361–2371

Gout S, Huot J (2008) Role of cancer microenvironment in metastasis: focus on colon cancer. Cancer Microenviron 1(1):69–83

Gugliotta G, Castagnetti F, Breccia M, Gozzini A, Usala E, Carella AM, Rege-Cambrin G, Martino B, Abruzzese E, Albano F, Stagno F, Luciano L, D'Adda M, Bocchia M, Cavazzini F, Tiribelli M, Lunghi M, Falcone AP, Musolino C, Levato L, Venturi C, Soverini S, Cavo M, Alimena G, Pane F, Martinelli G, Saglio G, Rosti G, Baccarani M, Working Party GIMEMACML (2016) Rotation of nilotinib and imatinib for first-line treatment of chronic phase chronic myeloid leukemia. Am J Hematol. doi:10.1002/ajh.24362

Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, Jewett M, Dutcher JP, Atkins MB, Pins M, Wilding G, Cella D, Wagner L, Matin S, Kuzel TM, Sexton WJ, Wong YN, Choueiri TK, Pili R, Puzanov I, Kohli M, Stadler W, Carducci M, Coomes R, DiPaola RS (2016) Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. doi:10.1016/S0140-6736(16)00559-6

Ham M, Moon A (2013) Inflammatory and microenvironmental factors involved in breast cancer progression. Arch Pharm Res 36(12):1419–1431

Heeg MH, Koziolek MJ, Vasko R, Schaefer L, Sharma K, Müller GA, Strutz F (2005) The antifibrotic effects of relaxin in human renal

fibroblasts are mediated in part by inhibition of the Smad2 pathway. Kidney Int 68(1):96–109
Hembruff SL, Jokar I, Yang L, Cheng N (2010) Loss of transforming growth factor-beta signaling in mammary fibroblasts enhances CCL2 secretion to promote mammary tumor progression through macrophage-dependent and -independent mechanisms. Neoplasia 12(5):425–433
Herrera M, Herrera A, Domínguez G, Silva J, García V, García JM, Gómez I, Soldevilla B, Muñoz C, Provencio M, Campos-Martin Y, García de Herreros A, Casal I, Bonilla F, Peña C (2013) Cancer-associated fibroblast and M2 macrophage markers together predict outcome in colorectal cancer patients. Cancer Sci 104(4):437–444
Hinz B (2007) Formation and function of the myofibroblast during tissue repair. J Invest Dermatol 127(3):526–537
Hinz B, Gabbiani G (2003) Mechanisms of force generation and transmission by myofibroblasts. Curr Opin Biotechnol 14(5):538–546
Hojilla CV, Wood GA, Khokha R (2008) Inflammation and breast cancer: metalloproteinases as common effectors of inflammation and extracellular matrix breakdown in breast cancer. Breast Cancer Res 10(2):205
Hur K (2015) MicroRNAs: promising biomarkers for diagnosis and therapeutic targets in human colorectal cancer metastasis. BMB Rep 48(4):217–222
Hwang RF, Moore T, Arumugam T, Ramachandran V, Amos KD, Rivera A, Ji B, Evans DB, Logsdon CD (2008) Cancer-associated stromal fibroblasts promote pancreatic tumor progression. Cancer Res 68(3):918–926
Ishihara K, Hirano T (2002) IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine Growth Factor Rev 13(4–5):357–368
Iwatsuki M, Mimori K, Yokobori T, Ishi H, Beppu T, Nakamori S, Baba H, Mori M (2010) Epithelial–mesenchymal transition in cancer development and its clinical significance. Cancer Sci 101(2):293–299
Jiang X, Feng K, Zhang Y, Li Z, Zhou F, Dou H, Wang T (2015) Sorafenib and DE605, a novel c-Met inhibitor, synergistically suppress hepatocellular carcinoma. Oncotarget 6(14):12340–12356
Jin L, Yuan RQ, Fuchs A, Yao Y, Joseph A, Schwall R, Schnitt SJ, Guida A, Hastings HM, Andres J, Turkel G, Polverini PJ, Goldberg ID, Rosen EM (1997) Expression of interleukin-1beta in human breast carcinoma. Cancer 80(3):421–434
Johnson SK, Kerr KM, Chapman AD, Kennedy MM, King G, Cockburn JS, Jeffrey RR (2000) Immune cell infiltrates and prognosis in primary carcinoma of the lung. Lung Cancer 27(1):27–35
Joyce JA (2005) Therapeutic targeting of the tumor microenvironment. Cancer Cell 7(6):513–520
Jung YY, Kim HM, Koo JS (2016) The role of cancer-associated fibroblasts in breast cancer pathobiology. Histol Histopathol 31(4):371–378
Kalluri R, Zeisberg M (2006) Fibroblasts in cancer. Nat Rev Cancer 6(5):392–401
Kanekura T, Chen X, Kanzaki T (2002) Basigin (CD147) is expressed on melanoma cells and induces tumor cell invasion by stimulating production of matrix metalloproteinases by fibroblasts. Int J Cancer 99(4):520–528
Karagiannis GS, Poutahidis T, Erdman SE, Kirsch R, Riddell RH, Diamandis EP (2012) Cancer-associated fibroblasts drive the progression of metastasis through both paracrine and mechanical pressure on cancer tissue. Mol Cancer Res 10(11):1403–1418
Karin M (2006) Nuclear factor-kappaB in cancer development and progression. Nature 441(7092):431–436
Kessenbrock K, Plaks V, Werb Z (2010) Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 141(1):52–67
Kim WH, Matsumoto K, Bessho K, Nakamura T (2005) Growth inhibition and apoptosis in liver myofibroblasts promoted by hepatocyte growth factor leads to resolution from liver cirrhosis. Am J Pathol 166(4):1017–1028
Kim IY, Yong HY, Kang KW, Moon A (2009) Overexpression of ErbB2 induces invasion of MCF10A human breast epithelial cells via MMP-9. Cancer Lett 275(2):227–233
Kloft C, Graefe EU, Tanswell P, Scott AM, Hofheinz R, Amelsberg A, Karlsson MO (2004) Population pharmacokinetics of sibrotuzumab, a novel therapeutic monoclonal antibody, in cancer patients. Invest New Drugs 22(1):39–52
Knupfer H, Preiss R (2007) Significance of interleukin-6 (IL-6) in breast cancer. Breast Cancer Res Treat 102:129–135
Koh M, Woo Y, Valiathan RR, Jung HY, Park SY, Kim YN, Kim HR, Fridman R, Moon A (2015) Discoidin domain receptor 1 is a novel transcriptional target of ZEB1 in breast epithelial cells undergoing H-Ras-induced epithelial to mesenchymal transition. Int J Cancer 136(6):E508–E520
Kraman M, Bambrough PJ, Arnold JN, Roberts EW, Magiera L, Jones JO, Gopinathan A, Tuveson DA, Fearon DT (2010) Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science 330(6005):827–830
La J, Reed EB, Koltsova SV, Akimova O, Hamanaka RB, Mutlu GM, Orlov SN, Dulin NO (2016) Regulation of myofibroblast differentiation by cardiac glycosides. Am J Physiol Lung Cell Mol Physiol. doi:10.1152/ajplung.00322.2015
Lai D, Ma L, Wang F (2012) Fibroblast activation protein regulates tumor-associated fibroblasts and epithelial ovarian cancer cells. Int J Oncol 41(2):541–550
Lee HM, Moon A (2016) Amygdalin regulates apoptosis and adhesion in Hs578T triple-negative breast cancer cells. Biomol Ther (Seoul) 24(1):62–66
Lee K, Nelson CM (2012) New insights into the regulation of epithelial–mesenchymal transition and tissue fibrosis. Int Rev Cell Mol Biol 294:171–221
Lee J, Fassnacht M, Nair S, Boczkowski D, Gilboa E (2005) Tumor immunotherapy targeting fibroblast activation protein, a product expressed in tumor-associated fibroblasts. Cancer Res 65(23):11156–11163
Lee J, Park EJ, Kiyono H (2016) MicroRNA-orchestrated pathophysiologic control in gut homeostasis and inflammation. BMB Rep 49(5):263–269
Liao D, Luo Y, Markowitz D, Xiang R, Reisfeld RA (2009) Cancer associated fibroblasts promote tumor growth and metastasis by modulating the tumor immune microenvironment in a 4T1 murine breast cancer model. PLoS One 4(11):e7965
Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J, SHARP Investigators Study Group (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4):378–390
Lu H, Ouyang W, Huang C (2006) Inflammation, a key event in cancer development. Mol Cancer Res 4(4):221–233
Luo H, Tu G, Liu Z, Liu M (2015) Cancer-associated fibroblasts: a multifaceted driver of breast cancer progression. Cancer Lett 361(2):155–163
Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454(7203):436–444
Mao Y, Keller ET, Garfield DH, Shen K, Wang J (2013) Stromal cells in tumor microenvironment and breast cancer. Cancer Metastasis Rev 32(1–2):303–315

Matsumoto K, Nakamura T (2003) NK4 (HGF-antagonist/angiogenesis inhibitor) in cancer biology and therapeutics. Cancer Sci 94(4):321–327

Mbeunkui F, Johann DJ Jr (2009) Cancer and the tumor microenvironment: a review of an essential relationship. Cancer Chemother Pharmacol 63(4):571–582

Mitra AK, Zillhardt M, Hua Y, Tiwari P, Murmann AE, Peter ME, Lengyel E (2012) MicroRNAs reprogram normal fibroblasts into cancer-associated fibroblasts in ovarian cancer. Cancer Discov 2(12):1100–1108

Mueller MM, Fusenig NE (2004) Friends or foes—bipolar effects of the tumour stroma in cancer. Nat Rev Cancer 4(11):839–849

Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA (2005) Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 121(3):335–348

Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, Gutkovich-Pyest E, Urieli-Shoval S, Galun E, Ben-Neriah Y (2004) NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature 431(7007):461–466

Polyak K, Weinberg RA (2009) Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. Nat Rev Cancer 9(4):265–273

Platz EA, De Marzo AM (2004) Epidemiology of inflammation and prostate cancer. J Urol 171(2 Pt 2):S36–S40

Powell DW, Adegboyega PA, Di Mari JF, Mifflin RC (2005) Epithelial cells and their neighbors I. Role of intestinal myofibroblasts in development, repair, and cancer. Am J Physiol Gastrointest Liver Physiol 289(1):G2–G7

Psarras S, Kletsas D, Stathakos D (1994) Restoration of down-regulated PDGF receptors by TGF-beta in human embryonic fibroblasts. Enhanced response during cellular in vitro aging. FEBS Lett 339(1–2):84–88

Qiao A, Gu F, Guo X, Zhang X, Fu L (2016) Breast cancer-associated fibroblasts: their roles in tumor initiation, progression and clinical applications. Front Med 10(1):33–40

Qin JF, Jin FJ, Li N, Guan HT, Lan L, Ni H, Wang Y (2015) Adrenergic receptor β2 activation by stress promotes breast cancer progression through macrophages M2 polarization in tumor microenvironment. BMB Rep 48(5):295–300

Radisky DC (2005) Epithelial–mesenchymal transition. J Cell Sci 118(Pt 19):4325–4326

Raz Y, Erez N (2013) An inflammatory vicious cycle: fibroblasts and immune cell recruitment in cancer. Exp Cell Res 319:1596–1603

Rozenchan PB, Pasini FS, Roela RA, Katayama ML, Mundim FG, Brentani H, Lyra EC, Brentani MM (2015) Specific upregulation of RHOA and RAC1 in cancer-associated fibroblasts found at primary tumor and lymph node metastatic sites in breast cancer. Tumour Biol 36(12):9589–9597

Ryan GB, Cliff WJ, Gabbiani G, Irlé C, Montandon D, Statkov PR, Majno G (1974) Myofibroblasts in human granulation tissue. Hum Pathol 5(1):55–67

Sadlonova A, Novak Z, Johnson MR, Bowe DB, Gault SR, Page GP, Thottassery JV, Welch DR, Frost AR (2005) Breast fibroblasts modulate epithelial cell proliferation in three-dimensional in vitro co-culture. Breast Cancer Res 7(1):R46–R59

Saga Y, Mizukami H, Suzuki M, Urabe M, Kume A, Nakamura T, Sato I, Ozawa K (2001) Expression of HGF/NK4 in ovarian cancer cells suppresses intraperitoneal dissemination and extends host survival. Gene Ther 8(19):1450–1455

Samel D, Muller D, Gerspach J, Assohou-Luty C, Sass G, Tiegs G, Pfizenmaier K, Wajant H (2003) Generation of a FasL-based proapoptotic fusion protein devoid of systemic toxicity due to cell-surface antigen-restricted Activation. J Biol Chem 278(34):32077–32082

Santos AM, Jung J, Aziz N, Kissil JL, Puré E (2009) Targeting fibroblast activation protein inhibits tumor stromagenesis and growth in mice. J Clin Invest 119(12):3613–3625

Scott AM, Wiseman G, Welt S, Adjei A, Lee FT, Hopkins W, Divgi CR, Hanson LH, Mitchell P, Gansen DN, Larson SM, Ingle JN, Hoffman EW, Tanswell P, Ritter G, Cohen LS, Bette P, Arvay L, Amelsberg A, Vlock D, Rettig WJ, Old LJ (2003) A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res 9(5):1639–1647

Semenza GL, Ruvolo PP (2016) Introduction to tumor microenvironment regulation of cancer cell survival, metastasis, inflammation, and immune surveillance. Biochim Biophys Acta 1863(3):379–381

Servais C, Erez N (2013) From sentinel cells to inflammatory culprits: cancer-associated fibroblasts in tumour-related inflammation. J. Pathol 229:198–207

Sharon Y, Raz Y, Cohen N, Ben-Shmuel A, Schwartz H, Geiger T, Erez N (2015) Tumor-derived osteopontin reprograms normal mammary fibroblasts to promote inflammation and tumor growth in breast cancer. Cancer Res 75(6):963–973

Shekhar MP, Werdell J, Santner SJ, Pauley RJ, Tait L (2001) Breast stroma plays a dominant regulatory role in breast epithelial growth and differentiation: implications for tumor development and progression. Cancer Res 61(4):1320–1326

Shiga K, Hara M, Nagasaki T, Sato T, Takahashi H, Takeyama H (2015) Cancer-associated fibroblasts: their characteristics and their roles in tumor growth. Cancers (Basel) 7(4):2443–2458

Shintani Y, Abulaiti A, Kimura T, Funaki S, Nakagiri T, Inoue M, Sawabata N, Minami M, Morii E, Okumura M (2013) Pulmonary fibroblasts induce epithelial mesenchymal transition and some characteristics of stem cells in non-small cell lung cancer. Ann Thorac Surg 96(2):425–433

Son H, Moon A (2010) Epithelial–mesenchymal transition and cell invasion. Toxicol Res 26(4):245–252

Soon PS, Kim E, Pon CK, Gill AJ, Moore K, Spillane AJ, Benn DE, Baxter RC (2013) Breast cancer-associated fibroblasts induce epithelial-to-mesenchymal transition in breast cancer cells. Endocr Relat Cancer 20(1):1–12

Spaeth EL, Dembinski JL, Sasser AK, Watson K, Klopp A, Hall B, Andreeff M, Marini F (2009) Mesenchymal stem cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression. PLoS One 4(4):e4992

Studebaker AW, Storci G, Werbeck JL, Sansone P, Sasser AK, Tavolari S, Huang T, Chan MW, Marini FC, Rosol TJ, Bonafé M, Hall BM (2008) Fibroblasts isolated from common sites of breast cancer metastasis enhance cancer cell growth rates and invasiveness in an interleukin-6-dependent manner. Cancer Res 68(21):9087–9095

Stuelten CH, DaCosta Byfield S, Arany PR, Karpova TS, Stetler-Stevenson WG, Roberts AB (2005) Breast cancer cells induce stromal fibroblasts to express MMP-9 via secretion of TNF-alpha and TGF-beta. J Cell Sci 118(Pt 10):2143–2153

Sugimoto H, Mundel TM, Kieran MW, Kalluri R (2006) Identification of fibroblast heterogeneity in the tumor microenvironment. Cancer Biol Ther 5(12):1640–1646

Tang S, Yuan Y, He Y, Pan D, Zhang Y, Liu Y, Liu Q, Zhang Z, Liu Z (2014) Genetic polymorphism of interleukin-6 influences susceptibility to HBV-related hepatocellular carcinoma in a male Chinese Han population. Hum Immunol 75(4):297–301

Tang X, Hou Y, Yang G, Wang X, Tang S, Du YE, Yang L, Yu T, Zhang H, Zhou M, Wen S, Xu L, Liu M (2016) Stromal miR-200s contribute to breast cancer cell invasion through CAF activation and ECM remodeling. Cell Death Differ 23(1):132–145

Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, Kwon ED (2007) PD-1 is expressed by tumor-

infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 13(6):1757–1761

Thiery JP (2002) Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2(6):442–454

Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA (2002) Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol 3(5):349–363

Tomioka D, Maehara N, Kuba K, Mizumoto K, Tanaka M, Matsumoto K, Nakamura T (2001) Inhibition of growth, invasion, and metastasis of human pancreatic carcinoma cells by NK4 in an orthotopic mouse model. Cancer Res 61(20):7518–7524

Tyan SW, Kuo WH, Huang CK, Pan CC, Shew JY, Chang KJ, Lee EY, Lee WH (2011) Breast cancer cells induce cancer-associated fibroblasts to secrete hepatocyte growth factor to enhance breast tumorigenesis. PLoS One 6(1):e15313

Van Bockstal M, Lambein K, Van Gele M, De Vlieghere E, Limame R, Braems G, Van den Broecke R, Cocquyt V, Denys H, Bracke M, Libbrecht L, De Wever O (2014) Differential regulation of extracellular matrix protein expression in carcinoma-associated fibroblasts by TGF-β1 regulates cancer cell spreading but not adhesion. Oncoscience 1(10):634–648

van de Veerdonk FL, Gresnigt MS, Kullberg BJ, van der Meer JW, Joosten LA, Netea MG (2009) BMB Rep 42(12):776–787

Van der Veken P, Haemers A, Augustyns K (2007) Prolyl peptidases related to dipeptidyl peptidase IV: potential of specific inhibitors in drug discovery. Curr Top Med Chem 7(6):621–635

Vinik AI, Raymond E (2013) Pancreatic neuroendocrine tumors: approach to treatment with focus on sunitinib. Ther Adv Gastroenterol 6(5):396–411

Webber J, Steadman R, Mason MD, Tabi Z, Clayton A (2010) Cancer exosomes trigger fibroblast to myofibroblast differentiation. Cancer Res 70(23):9621–9630

Whiteside TL (2008) The tumor microenvironment and its role in promoting tumor growth. Oncogene 27(45):5904–5912

Wiedmann MW, Mössner J (2012) Safety and efficacy of sunitinib in patients with unresectable pancreatic neuroendocrine tumors. Clin Med Insights Oncol 6:381–393

Wilke CM, Kryczek I, Wei S, Zhao E, Wu K, Wang G, Zou W (2011) Th17 cells in cancer: help or hindrance? Carcinogenesis 32:643–649

Yamaguchi H, Sakai R (2015) Direct interaction between carcinoma cells and cancer associated fibroblasts for the regulation of cancer invasion. Cancers (Basel) 7(4):2054–2062

Yamashita M, Ogawa T, Zhang X, Hanamura N, Kashikura Y, Takamura M, Yoneda M, Shiraishi T (2012) Role of stromal myofibroblasts in invasive breast cancer: stromal expres sion of alpha-smooth muscle actin correlates with worse clinical outcome. Breast Cancer 19(2):170–176

Yazhou C, Wenlv S, Weidong Z, Licun W (2004) Clinicopathological significance of stromal myofibroblasts in invasive ductal carcinoma of the breast. Tumour Biol 25(5–6):290–295

Yeh CR, Slavin S, Da J, Hsu I, Luo J, Xiao GQ, Ding J, Chou FJ, Yeh S (2016) Estrogen receptor α in cancer associated fibroblasts suppresses prostate cancer invasion via reducing CCL5, IL6 and macrophage infiltration in the tumor microenvironment. Mol Cancer 15(1):7

Zhou W, Jiang ZW, Tian J, Jiang J, Li N, Li JS (2003) Role of NF-kappaB and cytokine in experimental cancer cachexia. World J Gastroenterol 9(7):1567–1570

Zhang Y, Tang H, Cai J, Zhang T, Guo J, Feng D, Wang Z (2011) Ovarian cancer-associated fibroblasts contribute to epithelial ovarian carcinoma metastasis by promoting angiogenesis, lymphangiogenesis and tumor cell invasion. Cancer Lett 303(1):47–55

Zhuang J, Lu Q, Shen B, Huang X, Shen L, Zheng X, Huang R, Yan J, Guo H (2015) TGFβ1 secreted by cancer-associated fibroblasts induces epithelial–mesenchymal transition of bladder cancer cells through lncRNA-ZEB2NAT. Sci Rep 5:11924