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REVIEW

Priming cancer cells for drug resistance: role of the fibroblast niche

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Abstract **Conventional and targeted chemotherapies remain integral strategies to treat solid tumors. Despite the large number of anti-cancer drugs available, chemotherapy does not completely eradicate disease. Disease recurrence and the growth of drug resistant tumors remain significant problems in anti-cancer treatment. To develop more effective treatment strategies, it is important to understand the underlying cellular and molecular mechanisms of drug resistance. It is generally accepted that cancer cells do not function alone, but evolve through interactions with the surrounding tumor microenvironment. As key cellular components of the tumor microenvironment, fibroblasts regulate the growth and progression of many solid tumors. Emerging studies demonstrate that fibroblasts secrete a multitude of factors that enable cancer cells to become drug resistant. This review will explore how fibroblast secretion of soluble factors act on cancer cells to enhance cancer cell survival and cancer stem cell renewal, contributing to the development of drug resistant cancer.**

Keywords fibroblasts, tumor recurrence, drug resistance, cell survival, stem cells, tumor dormancy

Introduction

For several decades, the use of cytotoxic agents has remained a key strategy to treat solid tumors. 5-Fluorouracil (5-FU), a nucleoside analog, was originally developed for the treatment of colorectal cancer in the 1950s (Heidelberger et al., 1957). Since then, the repertoire of chemotherapeutic agents has been expanded to include: topoisomerase inhibitors, anti-microtubule agents, antibiotics, DNA damaging alkylating agents and anti-metabolites (DeVita and Chu, 2008). Unfortunately, many of these agents are also toxic to normal tissues, causing adverse side effects in patients. In an effort to better target tumor tissues, agents have been developed to inhibit key oncogenic pathways in tumors (Zhang et al., 2009; Takeuchi and Ito, 2011). For example, clinically approved B-RAF inhibitors, such as Vemurafenib, inhibit tumor growth by targeting the B-RAF-MAPK pathway in melanomas (Flaherty et al., 2010). Both conventional and targeted therapies induce cancer cell death through apoptosis, necrosis and autophagy (Kreuzaler and Watson, 2012).

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While chemotherapeutic agents are initially effective at reducing tumor growth, disease recurrence is commonly observed in the treatment of solid tumors. Rates of recurrence vary widely among different cancer types. Colon cancer patients face a recurrence rate of 30%–40% within 5 years of primary treatment (Goldberg, 2006; Brewster et al., 2008). For breast cancer patients, 5%–20% of patients receiving standard surgery and radiation therapy experience disease relapse, and 1/2 to 2/3 of the cases are accompanied by invasive disease (Lari and Kuerer, 2011; Wu, 2011). Recurrent tumors are often characterized by resistance to multiple cytotoxic agents (Hidalgo, 2010). Without alternative treatments, non-invasive tumors that are drug resistant may progress to invasive disease, leading to decreased patient survival. To improve treatment effectiveness, it is important to examine the underlying cellular and molecular mechanisms governing the development of drug resistant tumors.

It is well known that overexpression of drug transport proteins in cancer cells confers resistance to a wide variety of cytotoxic drugs. These proteins are commonly referred to as ABC proteins due to a conserved ATP binding cassette domain. ABC transporters are ubiquitously expressed and are normally involved in transport of solutes, such as ions, across the cell membrane (Taylor et al., 1991; Bao et al., 2011). However, ABC proteins are actively exploited by cancer

cells. One member of the ABC family, ABCC1 (P-Glycoprotein) is known to promote drug resistance to doxorubicin in breast, prostate and lung cancer cells (Keizer et al., 1989; Binaschi et al., 1995; Siegsmund et al., 1997; Wartenberg et al., 1998). ABCC1 has also been implicated in resistance to 5-FU in lung and liver cancer (Jin et al., 2002; Dačević et al., 2013), and alkylating agents, such as Vinblastine, in breast, lung and ovarian cancer cells (Adams and Knick, 1995). Another member, ABCC10 (MRP7) confers resistance to taxanes, a class of anti-microtubule agents, in salivary gland carcinoma and kidney epithelial cells (Malofeeva et al., 2012). Overexpression of ABCC10 predicts resistance to the anti-microtubule agent, paclitaxel, in Small Cell Lung Cancer (Oguri et al., 2008). ABCG2 (BCRP) overexpression is associated with decreased drug efficacy and increased tumor recurrence in breast and pancreatic cancers (Lee et al., 2012). ABCG2 confers resistance to antibiotics such as mitoxantrane (Diah et al., 2001) and 5-FU (Binaschi et al., 1995; Jin et al., 2002). Despite the importance of ABC proteins in multi-drug resistance, drug transport inhibitors in clinical trials have not provided a significant benefit in the treatment of breast, lung or ovarian cancers (Millward et al., 1993; Wishart et al., 1994; Lhommé et al., 2008). These studies indicate that tumors acquire other drug resistance mechanisms, enabling survival and progression.

These alternative mechanisms are associated with a controversial paradigm. This paradigm suggests that chemotherapeutic drugs apply selective pressure to cancer cells, killing off the "weak" and "vulnerable" cells, while forcing "stronger" cancer cells to adapt to a more stressful environment. This model is supported by studies showing that cancer cells are genetically instable (Lengauer et al., 1998), and accumulate genetic mutations over the course of tumor progression, which provide a pro-survival advantage (Sturm et al., 2003; Diaz et al., 2012; Tegze et al., 2012). The inherent resistance associated with invasive cancers is directly related to lower patient survival (Amar et al., 2009; Smith, 2012; Holohan et al., 2013). In response to chemotherapeutic agents, cancer cells activate pro-survival pathways and downregulate apoptosis pathways, resulting in drug resistant cells (Holohan et al., 2013). Intriguingly, a subset of cancer cells enter G_0/G_1 resting phase, in a state known as cellular dormancy (Aguirre-Ghiso et al., 2004), which prevents induction of pro-death signals by cytotoxic drugs (Naumov et al., 2003; Buck et al., 2004; Sankala et al., 2007). Cell cycle activation of dormant cancer cells contribute to the recurrence of more aggressive disease (Levina et al., 2008). While dormant cells remain poorly understood, it is believed that cancer stem cells are one source of dormant cancer cells. Cancer stem cells are pre-dominantly quiescent (Roninson, 2003) and overexpress ABC proteins, which may contribute to their drug resistant nature (Levina et al., 2008; Loebinger et al., 2008; Dean, 2009; Astsaturov et al., 2010).

A prevailing question has been: how do cancer cells acquire these mechanisms of drug resistance? Part of the answer may lie with the surrounding tumor microenvironment.

Fibroblasts and cancer recurrence

Cancer cells do not function alone, but evolve through interactions with the surrounding tumor microenvironment (Balkwill and Mantovani, 2012; Conklin and Keely, 2012). As a major cell type in the tumor stroma, fibroblasts are normally found in the connective tissue, regulating tissue remodeling during wound healing and development (Polyak and Kalluri, 2010; Shinde and Frangogiannis, 2013). Increased fibroblast growth and activity have been observed in solid tumors. Desmoplasia is characterized by a dense collagenous stroma and accumulation of fibroblasts within the tumor. Activated fibroblasts are commonly identified by mesenchymal markers, including: fibroblast specific protein 1 (S10A4, FSP1), fibroblast activating protein (FAP), desmin, vimentin, paladin, urokinase-type plasminogen activator receptor associated protein (UPARAP), galectin-3, podoplanin, platelet derived growth factor receptor (PDGFR), or α smooth muscle actin (α-SMA). Myofibroblasts are a type of activated fibroblast characterized by an elongated, spindle cell morphology and expression of α-SMA (Polanska and Orimo, 2013). Studies demonstrate that the desmoplastic phenotype, presence of myofibroblasts or increased expression of fibroblastic markers correlate with poor patient prognosis (Table 1).

The importance of fibroblasts in cancer progression is well established through co-transplantation studies (Conklin and Keely, 2012; Ostman and Augsten, 2009; Polanska and Orimo, 2013). Carcinoma associated fibroblasts (CAFs) co-grafted with prostate, colon or breast carcinoma cells enhanced tumor formation in mice, compared to carcinoma cells grafted alone (Camps et al., 1990; Liao et al., 2009; Olumi et al., 1999). Recent studies show that CAFs areparticularly resistant to chemotherapy. Moreover, commonly used cytotoxic drugs, such as doxorubicin, increase fibroblast activity by increasing secretion of growth factors and cytokines, thus providing a survival advantage to prostate and colon cancers (Lotti et al., 2013; Sun et al., 2012). Molecular profiling studies have revealed significant molecular differences between CAFs and normal fibroblasts (Allinen et al., 2004; Lim et al., 2011; Torres et al., 2013). In particular, CAFs from various tumor types commonly express growth factors, chemokines and ECM related proteins, including: hepatocyte growth factor (HGF), chemokine (C-C) ligand 2 (CCL2), chemokine (C-X-C) ligand 12 (CXCL12), WNT16B, tenascin C and periostin. Increased protein expression of these soluble factors in primary tumors correlates with poor patient prognosis, indicating a clinical relevance for these factors (Table 2). In this review, we will further explore how these fibroblast derived factors regulate cancer cell survival and renewal of cancer stem cells,

Table 1 Histo-pathological features associating fibroblasts in the primary tumor with disease recurrence and decreased survival of patients with solid tumors

Tumor type	Increased recurrence	Decreased survival	Reference
Breast	Desmoplasia, increased expression of α-SMA and PDGFR	Desmoplasia, increased expression of α- SMA and PDGFR	Hasebe et al., 2000; Paulsson et al., 2009
Prostate	Increased numbers of myofibroblasts, increased vimentin and α-SMA expression, decreased expression of desmin	Increased numbers of myofibroblasts, increased vimentin expression, decreased desmin expression	Ayala et al., 2003
Lung	Increased expression of α-SMA and podoplanin	Increased podoplanin expression	Kitano et al., 2010; Kaseda et al., 2013; Schoppmann et al., 2013
Colon	Desmoplasia, increased numbers of myofibroblasts, increased α-SMA expression	Desmoplasia, increased numbers of myo-fibroblasts, increased expression of FSP1, α-SMA and FAP	Tsujino et al., 2007; Kojima et al., 2010; Herrera et al., 2013
Uterine/endometrial	Desmoplasia	Desmoplasia	Yasunaga et al., 2003; Khunamornpong et al., 2013
Urinary/ bladder	Desmoplasia	Desmoplasia	Samaratunga et al., 2005
Kidney	No data available	Increased expression of paladin, α-SMA, UPARAP, and galectin3	Gupta et al., 2011; de Boer et al., 2012
Melanoma	Desmoplasia	No significant association	Busam, 2011
Oral, head and neck	Increased expression of α- SMA, Vimentin and Desmin	NA	Kawashiri et al., 2009; Marsh et al., 2011
Liver	Desmoplasia	Desmoplasia	Wang et al., 2013
Pancreas	Increased FAP expression	Increased FAP expression	Cohen et al., 2008
Ovary	Increased FAP expression	Fewer fibroblasts	Chen and Lee, 1984; Mhawech-Fauceglia et al., 2013

Table 2 Carcinoma associated fibroblasts of solid tumors that express soluble factors associated with drug resistance

Soluble factor	Type of CAF	Reference
HGF	Breast, prostate, lung, colon, uterine, bladder, melanoma, liver, oral, pancreas, ovarian*	Seslar et al., 1993; Shimao et al., 1999; Guirouilh et al., 2000; Parr and Jiang, 2001; Uchida et al., 2001; Yoshida et al., 2002; Cohen et al., 2006; Wang et al., 2007; Chen et al., 2008; Kwon et al., 2013; Yu et al., 2013
CCL2	Breast, prostate, lung, colon, melanoma, liver, oral, pancreas	Wong et al., 1998; Silzle et al., 2003; Eyman et al., 2009; Li et al., 2009; Mueller et al., 2010; Tjomsland et al., 2011; Wu et al., 2011; Liu et al., 2013
CXCL12	Breast, prostate, lung, colon, liver, oral, pancreas, ovarian	Orimo et al., 2005; Ohira et al., 2006; Daly et al., 2008; Addadi et al., 2010; Ibarra-Drendall et al., 2011; Chao et al., 2012; Feig et al., 2013
WNT16B	Prostate	Ahn et al., 2012
Periostin	Breast, prostate, lung, oral, liver, ovarian	Choi et al., 2011; Li et al., 2012; Lv et al., 2013; Xu et al., 2012; Nuzzo et al., 2012; Hong et al., 2013
Tenascin C	Breast, lung, colon, uterine, bladder, kidney, melanoma, liver	Jahkola et al., 1998; Emoto et al., 2001; Buyukbayram and Arslan, 2002; Aishima et al., 2003; Brunner et al., 2004; Ilmonen et al., 2004; Ohno et al., 2008; JKahn et al., 2012

* Source of HGF comes from normal fibroblasts

providing a niche for the development of drug resistant tumors.

Growth factors: HGF and WNT16B

Growth factors commonly refer to a class of proteins that stimulate cell growth and differentiation, necessary in a wide range of biological events ranging from embryogenesis to cancer. Much of our knowledge from growth factor signaling stems from epidermal growth factor, one of the earliest growth factors identified (Earp et al., 1995; Foley et al., 2010). Similar to EGF, many growth factors signal through receptor tyrosine kinases (RTK). Activation of RTKs is characterized by receptor dimerization, trans- and auto-phosphorylation of tyrosines present on the receptor, and activation of signaling cascades. These signaling cascades modulate gene expression, cell growth and differentiation (Lemmon and Schlessinger, 2010). While growth factors are best known for their actions through RTKs, growth factors

also signal through other receptor classes including seven transmembrane spanning receptors, which activate guanosine nucleotide binding proteins (G-proteins) to transduce growth signals. Many of these growth factors are expressed by cancer cells to regulate tumor growth through autocrine mechanisms (Roberts and Der, 2007; Wilson et al., 2012a). Emerging studies show an important role for two different types of growth factors expressed by CAFs in modulating drug resistance: HGF and WNT16B.

Hepatocyte growth factor (HGF, scatter factor) is one of the most well studied growth factors in cancer. HGF was first identified as a soluble factor expressed by fibroblasts, which induced migration and scattering of Madin-Darby canine kidney cells (Stoker and Perryman, 1985; Stoker et al., 1987; Naldini et al., 1991). During normal physiological events, HGF regulates organ development, angiogenesis and hematopoiesis (Ohnishi and Daikuhara, 2003; Thomas et al., 2004; Cecchi et al., 2010). Overexpression of HGF in CAFs enhances tumor growth and metastasis (Gao and Vande Woude, 2005). These processes are regulated by HGF signaling through c-Met RTKs to stimulate tumor epithelial cell growth, survival and invasion (Gao and Vande Woude, 2005; Kemp et al., 2006). Our current understanding of HGF in the context of drug resistance is limited. Several studies have implicated HGF signaling in promoting chemoresistance to targeted therapies. HGF activates both MAPK and PI3K-AKT pathways in cancer cells to inhibit drug induced apoptosis (Straussman et al., 2012; Wilson et al., 2012b). Increased HGF protein levels in tumor tissues or plasma samples are associated with a reduced patient responsiveness to RAF inhibitors, which block MAPK activity (Straussman et al., 2012; Wilson et al., 2012b). In functional studies, coculture of HGF expressing fibroblasts with *BRAF* mutant melanoma cells enhances cancer cell resistance to RAF inhibitors (Straussman et al., 2012). This protective effect can be reversed by adding HGF neutralizing antibodies or HGF receptor inhibitors (Straussman et al., 2012; Wilson et al., 2012b). Moreover, modulating HGF-MET signaling activity reduces responsiveness of melanoma cells to RAF inhibitor in mouse xenograft models (Wilson et al., 2012b). Similarly, HGF derived from fibroblasts has also been reported to promote lung cancer resistance to EGFR tyrosine kinase inhibitors by activating PI3K-AKT pathway (Wang et al., 2009; Yamada et al., 2010). These studies demonstrate that HGF signaling confers resistance to targeted therapies through upregulation of MAPK and AKT pathways.

HGF may also contribute to drug resistant cancers through expansion of the cancer stem cell population. In one study, HGF derived from myofibroblasts, induced colon cancer cells to de-differentiate to a cancer stem cell state, which was characterized by increased expression of LRG5, a stem cell related gene. This cancer stem cell phenotype is associated with increased tumor growth when colon cancer cells are co-grafted with myofibroblasts (Vermeulen et al., 2010). In another study, HGF treatment of DU145 prostate cancer cells induced a molecular signature similar to stem cells. Notch signaling was increased, which was associated with increased expression of cancer stem cell markers, including: CD49b, CD49f, CD44 and Sox9. Implantation of DU145 cells in mice resulted in increased tumor growth, which was blocked by shRNA knockdown of c-Met (van Leenders et al., 2011). These works demonstrate that fibroblast specific HGF contributes to the expansion of the cancer stem cell population, which consequently enhances tumor progression. Given the drug resistant nature of cancer stem cells, it would be of further interest to determine the relationship of HGF modulation of cancer stem cell renewal to tumor recurrence.

WNT molecules belong to a family of secreted glycoproteins, which play an important role in embryonic development, regulating body axis patterning, cell fate specification, cell growth and migration (Anastas and Moon, 2013; Bielen and Houart, 2014). These processes are regulated by WNT ligand binding to G protein coupled Frizzled receptor, which bind to β catenin and downstream effector proteins, such as Disheveled, to modulate gene transcription and the actin cytoskeleton (Anastas and Moon, 2013; Bielen and Houart, 2014). Currently, 19 ligands have been identified. Mutations in the WNT pathway have been implicated in diabetes and cancer (MacDonald et al., 2009). While WNT autocrine signaling has been extensively studied in cancer cells (Bielen and Houart, 2014), recent studies have shown that a member of the WNT family, WNT16B, is secreted from CAFs to modulate prostate cancer drug resistance (Sun et al., 2012). In this study, treatment of prostate cancer patients, with Mitoxantrone and the anti-microtubule agent docetaxel, increased expression of WNT16B in prostate fibroblasts. The induction of WNT16B results from activation of NF-κB signaling due to DNA damage response, caused by these chemotherapeutic agents. These studies further demonstrate that WNT16B signaling to prostate cancer cells attenuate the cytotoxic effects caused by Mitoxantrone, and promote tumor growth in mice. These studies indicate that chemotherapy induced damage to cancer stroma enhance expression of soluble factors, which enhance cancer cell survival. As many chemotherapeutic drugs target cancer cells, it would be of interest to better understand the biologic effects of drug treatment on the surrounding stroma.

Chemokines: CCL2 and CXCL12

Chemokines are a large family of small soluble proteins (8–10 kDa), which regulate cell movement through generation of molecular gradients, a process important in recruitment of immune cells during infection, wound healing and inflammation (White et al., 2013). With over 40 ligands identified, the chemokine family has been subdivided into different families (C-C, C-X-C, C-X_3-C) depending on the composition of a

conserved cysteine motif in the NH_2 terminus(Balkwill, 2012). Aberrant expression of C-C and C-X-C chemokines has been reported in many types of cancers. Studies demonstrate an important role for chemokine signaling in enhancing tumor growth, survival and invasion through multiple mechanisms. These mechanisms include: recruitment of immune cells, stimulating tumor angiogenesis and directly signaling to cancer cells (Allavena et al., 2011; Balkwill, 2012). Emerging studies indicate that CCL2 and CXCL12 chemokines play important roles in cancer drug resistance.

CCL2 (also known as monocyte chemotactic protein-1or MCP-1), belongs to the C-C subfamily of chemokines and is an important regulator of macrophage recruitment during wound healing and cancer (Conti and Rollins, 2004). CCL2 is expressed in both epithelial cancer cells and in stromal cells, including fibroblasts (Lu et al., 2007; Fujimoto et al., 2009; Fang et al., 2012). In breast cancer, fibroblast derived CCL2 regulates breast cancer progression by the recruitment of macrophages (Hembruff et al., 2010; Qian et al., 2011). In addition, recent studies show that CCL2 can signal directly on cancer cells through CCR2 receptors to promote survival, migration and metastasis, with important implications on drug resistance. CCL2 protects LNCaP and LAPC4 prostate cancer cell lines from Docetaxel-induced cell death (Qian et al., 2010). CCL2 also inhibits autophagic cell death in PC-3 cells induced by the antibiotic, rapamycin (Roca et al., 2008). The protective effects in prostate cancer cells are mediated by PI3K-AKT pathways (Roca et al., 2008). In our laboratory, we have shown that CCL2 signaling through CCR2 confers breast cancer cell resistance to 5-FU through cooperation between MAPK and Smad3 pathways. We further demonstrate that CCL2 activates a secondary survival pathway mediated by MAPK signaling that is independent of Smad3 (Fang et al., 2012). These studies indicate that CCL2 promotes drug resistance by mediating multiple pathways to enhance cell survival.

Recent studies have implicated a role for fibroblast derived CCL2 in modulating cancer stem cell renewal (Tsuyada et al., 2012). In these studies, CCL2 secretion by CAFs promotes mammosphere formation in BT474 and MDA-MB-361 invasive breast cancer cells, which is blocked by neutralizing antibodies. CAF derived CCL2 also enhances the activity of aldehyde dehydrogenase, which is recognized as a cancer stem cell marker. Interestingly, CAF derived CCL2 does not significantly affect mammosphere formation of lowly invasive MCF-7 breast cancer cells. These studies indicate that CAF derived CCL2 is an important mediator of cancer stem cell renewal in a subset of breast cancer cell lines.

CXCL12 (also known as stromal derived factor 1 or SDF1), is a member of the C-X-C subfamily of chemokines that normally regulates the trafficking of lymphocytes and hematopoietic stem cells during inflammation. CXCL12 primarily functions through binding to CXCR4 expressing cells (Kucia et al., 2004). The role of CXCL12 in regulating tumor angiogenesis, growth and metastasis is well characterized (Burger and Kipps, 2006). The role of CXCL12 in drug resistance is best studied in leukemia (Peled and Tavor, 2013). Recent studies show that CXCL12 also promotes resistance of solid tumors to different forms of anti-cancer therapy. CAF derived CXCL12 enhances epithelial to mesenchymal transition and inhibits apoptosis of MCF-7 breast cancer cells induced by doxorubicin (Soon et al., 2013). Treatment of mice bearing PC-3 prostate tumors with the CXCR4 inhibitor, AMD300, enhances responsiveness to docetaxel, and inhibits tumor progression (Domanska et al., 2012). Interestingly, recent studies show that CXCL12 is a critical factor for resistance to alternative therapies such as immunotherapy, which involves T cell mediated killing of tumor cells (Feig et al., 2013). In mice bearing pancreatic tumors, $CD8^+$ T cells show reduced tumor suppressive activity, until FAP expressing CAFs are genetically depleted. CXCR4 inhibitors synergize with CAF depletion to further enhance T cell accumulation and inhibit tumor progression. These studies indicate that CXCL12 derived from fibroblasts play an important role in immune surveillance by blocking the proliferation and activity of tumor suppressive immune cells (Feig et al., 2013). These studies show an important role for CXCL12 derived from CAFs in modulating resistance to multiple forms of anti-cancer therapy.

There is increasing evidence that CXCL12 may regulate malignancy of drug resistant cells through increasing activity of the cancer stem cell niche. CXCL12 treatment of CD133 positive prostate cancer stem cells enhances transwell migration, indicating a potential role for CXCL12 induction of metastasis in cancer stem cells (Dubrovska et al., 2012). Similar effects of CXCL12 were observed in pancreatic stem cells (Hermann et al., 2007). In breast cancer, co-culture of MCF-7 cells with CAFs increased the number of mammospheres and number of $CD44^+/CD24^-$ cells, indicating increased number of cancer stem cells. Inhibition of CXCR4, with AMD3100, reduced the number of $CD44^+/CD24^-$ cells, indicating that CXCL12 derived from CAFs significantly increased the breast cancer stem cell population (Deng et al., 2011). Interestingly, Ablett et al. (2013) reported that CXCL12 affects primary breast cancer cells and transformed breast cancer cell lines differently in mammosphere formation assays. In primary breast cancer cells and T47D cells, treatment with CXCL12 increased mammosphere formation, but not in MCF7 or SKBR3 cell lines. These studies indicate that the role of CXCL12 in maintenance of cancer stem cells is specific to certain breast cancer cell lines and may also be dependent on other factors..

ECM proteins: tenascin/periostin complexes

Fibroblasts are integral in producing and maintaining the extracellular matrix (ECM) in tumors. The role of ECM in

cell survival is well known (Stupack and Cheresh, 2002; Xiong et al., 2013). ECM proteins bind to integrin receptors, heterodimeric transmembrane proteins, which convey signals through focal adhesion kinases (FAK), Src and Shc adaptor proteins. These adaptor proteins activate signaling cascades including MAPK and AKT pathways that enhance cell survival and inhibit anoikis, a form of apoptotic cell death that occurs in the absence of cell adhesion. As a dynamic structure, the ECM influences many different cells types within its proximity, including cancer cells and CSCs. Interestingly, two ECM proteins, tenascin C and periostin, have been reported to enhance cancer cell survival and cancer stem cell renewal, contributing to metastatic colonization.

Tenascin C is involved in tissue remodeling and formation during fetal development, and is naturally expressed in bone, cartilage and neural crest cells (Nicolo et al., 1990). Upregulation of tenascin C expression in CAFs enhances signaling to cancer cells through multiple integrin receptor-sincluding: α2β1, αvβ3, α7β1, α8β1, α9β1, α5β3, α5β6 (Orend and Chiquet-Ehrismann, 2006; Brellier and Chiquet-Ehrismann, 2012). Cellular adhesion to tenascin C enhances survival and drug resistance of various cancer cell types. Tenascin C inhibits cell cycle arrest and apoptosis of MCF-7 breast cancer cells induced by the antibiotic adriamycin (Wang et al., 2010). Tenascin C also confers resistance to the nucleoside analog, gemcitabine, in pancreatic cancer cells and enhances survival of human chondrosarcoma cells via AKT and NF-κB signaling (Gong et al., 2010). CAFs are an important source of tenascin C expression (De Wever et al., 2004). In a rat model of cholangiocarcinoma, depletion of CAFs with treatment of Navitoclax, a BH3 mimetic, resulted in decreased tenascin C expression associated with a reduction in tumor growth and increased animal survival (Mertens et al., 2013). FSP1 expressing CAFs in the lung support metastatic colonization of 4T1 mammary carcinoma cells through tenascin C expression (O'Connell et al., 2011). Interestingly, several recent works have noted that tenascin C expression is upregulated in several types of cancer stem cells (Fukunaga-Kalabis et al., 2010; Oskarsson et al., 2011; Pezzolo et al., 2011). Tenascin C expression induced cancer stem cell expansion mediated by increased WNT signaling and deletion of tenascin C great reduced lung metastasis (Oskarsson et al., 2011). These studies indicate a role for tenascin C in regulating the cancer stem niche through autocrine mechanisms. It is possible that CAF expression of tenascin C may regulate the cancer stem cell niche through dependent paracrine signaling mechanisms.

As an extracellular matrix associated protein, periostin is involved in the development of bone, tooth and heart valves (Erbas et al., 2006). Periostin functions as the ligand for αvβ1, αvβ3 and αvβ5 integrin receptors (Gillan et al., 2002; Masuoka et al., 2012). Evidence for periostin as a pro-survival protein comes from recent studies showing that periostin signaling through αvβ3 integrins promotes colon cancer cell survival through the AKT and NF-κB pathway (Bao et al., 2004). In addition, periostin signaling through α6β4 integrins enhances cell survival of pancreatic cancer cells through the FAK, PI-3 kinase and AKT signaling (Baril et al., 2007). Interestingly, periostin interacts with tenascin C, and could also promote cell survival through cooperation with tenascin C (Kii et al., 2010). Recent work has highlighted the novel function of periostin as a crucial fibroblast derived protein in promoting the cancer stem cell niche, contributing to metastasis (Malanchi et al., 2012). In these studies, mammary carcinoma cells and CD90/CD24 positive cancer stem cells, isolated from MMTV-PyVmT tumors, were injected into the tail vein of mice and only the CD90/CD24 positive cancer stem cells formed pulmonary metastasis. Periostin was found to be upregulated in fibroblasts of the metastatic lesions. Homozygous knockout of the periostin gene in MMTV-PyVmT mice inhibited lung metastasis. Cancer stem cells derived from periostin deficient tumors show reduced mammosphere formation, indicative of decreased breast cancer stem cell activity (Malanchi et al., 2012). These studies indicate that periostin expression in fibroblasts is crucial for metastatic colonization of cancer stem cells.

Concluding remarks/future directions

Current treatment strategies are focused on targeting the cancer cells, but ignore the tumor microenvironment. Fibroblasts provide an important niche for the development of drug resistant cancer cells, in part through paracrine signaling interactions with cancer cells and cancer stem cells (Fig. 1). Cancer associated fibroblasts are more genetically stable and proliferate more slowly than cancer cells. As such, fibroblasts or fibroblast secreted factors represent appealing drug targets (Kalluri and Zeisberg, 2006; Lu et al., 2009). Questions remain regarding the role of fibroblasts in drug resistance and tumor recurrence. Recent studies suggest that fibroblast secreted factors influence expression of drug transporter proteins in cancer cells. Liver cancer cells have been shown to induce HGF expression in CAFs, which in turn act on cancer cells to enhance expression of drug transporter proteins BCRP and MRP1 (de Boussac et al., 2012). These studies indicate that the fibroblast niche potentially regulates multi-drug resistance through drug efflux mechanisms; however, further studies must be performed to validate these mechanisms. Other studies show that CAFs interact with other stromal cell types including macrophages to regulate tumor progression (Balkwill and Mantovani, 2012; Fleming et al., 2012). It remains poorly understood how stromal cell: cell interactions contribute to drug resistance and tumor recurrence. Addressing these questions would help to define the fibroblast niche in drug resistant tumors, and support the advancement of therapies to more effectively prevent or treat drug resistant cancer.

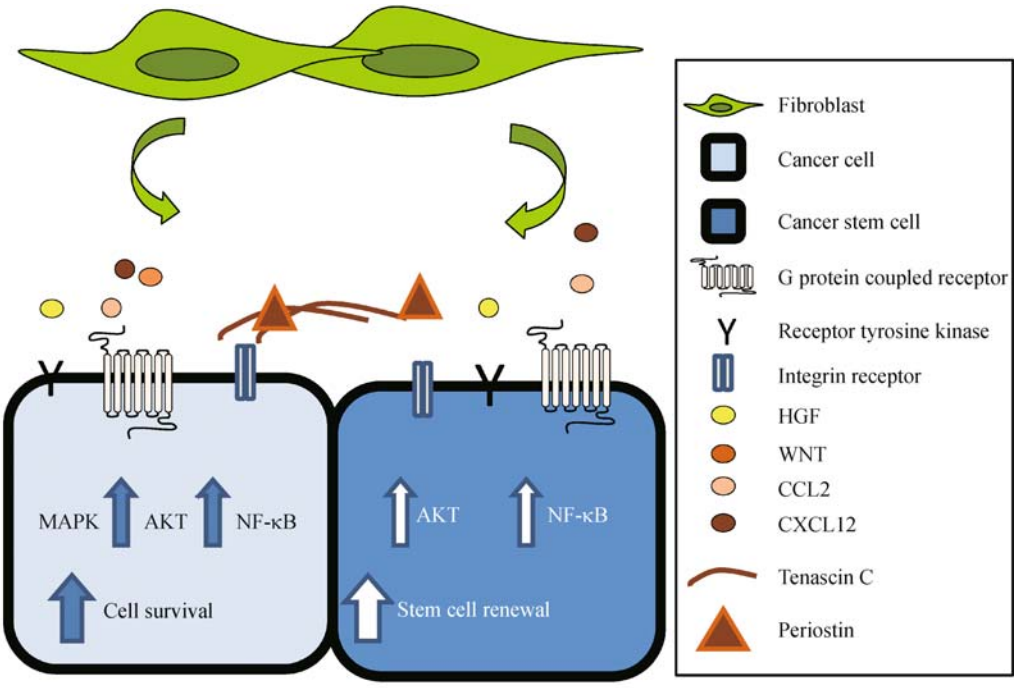

Figure 1 Role of fibroblast: cancer cell paracrine signaling interactions in the promotion of drug resistant tumors. An important function of the fibroblast niche is to communicate with cancer cells directly, to enhance cell survival and cancer stem cell renewal. Carcinoma associated fibroblasts secrete a combination of growth factors, cytokines, and extracellular matrix related proteins including: HGF, WNT16B, CCL2 and CXCL12, tenascin C and periostin. Activity of these factors are modulated through different classes of receptors. HGF activity is mediated through receptor tyrosine kinases, while WNT16, CCL2 and CXCL12 binds to G protein coupled receptors. Tenascin C/Periostin protein complexes signal through integrin receptors. These factors activate MAPK, NF-κB and AKT pathways in cancer cells to promote survival and inhibit cell death. These soluble factors also promote renewal of cancer stem cells through similar pathways. These cellular and molecular processes contribute to the development and progression of drug resistant tumors.

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Compliance with ethics guidelines

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