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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

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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).

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; Siegsmond 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; Daei 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 mitoxantrone (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 unstable (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 G₀/G₁ 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 are particularly 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, 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 chemo-resistance 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 Dishevelled, 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- κ B 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-X₃-C) depending on the composition of a conserved cysteine motif in the NH₂ 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 chemoattractant protein-1 or 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 (Dubrovskaya 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 cell 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-sincludng: $\alpha 2\beta 1$, $\alpha v\beta 3$, $\alpha 7\beta 1$, $\alpha 8\beta 1$, $\alpha 9\beta 1$, $\alpha 5\beta 3$, $\alpha 5\beta 6$ (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- κ B 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 greatly 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 α v β 1, α v β 3 and α v β 5 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 α v β 3 integrins promotes colon cancer cell survival through the AKT and NF- κ B pathway (Bao et al., 2004). In addition, periostin signaling through α 6 β 4 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.

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References

- Ablett MPOBC, Sims AH, Farnie G, Clarke RB. A differential role for CXCR4 in the regulation of normal versus malignant breast stem cell activity. *Oncotarget*. 2013 Epub.
- Adams DJ, Knick VC. P-glycoprotein mediated resistance to 5'-nor-anhydro-vinblastine (Navelbine). *Invest New Drugs*. 1995; 13(1):13–21. [PubMed: 7499103]
- Addadi Y, Moskovits N, Granot D, Lozano G, Carmi Y, Apte RN, Neeman M, Oren M. p53 status in stromal fibroblasts modulates tumor growth in an SDF1-dependent manner. *Cancer Res*. 2010; 70(23):9650–9658. [PubMed: 20952507]
- Aguirre-Ghiso JA, Ossowski L, Rosenbaum SK. Green fluorescent protein tagging of extracellular signal-regulated kinase and p38 pathways reveals novel dynamics of pathway activation during primary and metastatic growth. *Cancer Res*. 2004; 64(20):7336–7345. [PubMed: 15492254]
- Ahn S, Cho J, Sung J, Lee JE, Nam SJ, Kim KM, Cho EY. The prognostic significance of tumor-associated stroma in invasive breast carcinoma. *Tumour Biol*. 2012; 33(5):1573–1580. [PubMed: 22581521]
- Aishima S, Taguchi K, Terashi T, Matsuura S, Shimada M, Tsuneyoshi M. Tenascin expression at the invasive front is associated with poor prognosis in intrahepatic cholangiocarcinoma. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc*. 2003; 16(10):1019–1027.
- Allavena P, Germano G, Marchesi F, Mantovani A. Chemokines in cancer related inflammation. *Exp Cell Res*. 2011; 317(5):664–673. [PubMed: 21134366]
- Allinen M, Beroukhi R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. *Cancer Cell*. 2004; 6(1):17–32. [PubMed: 15261139]
- Amar S, Roy V, Perez EA. Treatment of metastatic breast cancer: looking towards the future. *Breast Cancer Res Treat*. 2009; 114(3):413–422. [PubMed: 18465221]
- Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. *Nat Rev Cancer*. 2013; 13(1):11–26. [PubMed: 23258168]
- Astsaturon I, Ratushny V, Sukhanova A, Einarson MB, Bagnyukova T, Zhou Y, Devarajan K, Silverman JS, Tikhmyanova N, Skobeleva N, Pecherskaya A, Nasto RE, Sharma C, Jablonski SA,

- Serebriiskii IG, Weiner LM, Golemis EA. Synthetic lethal screen of an EGFR-centered network to improve targeted therapies. *Sci Signal*. 2010; 3(140):ra67. [PubMed: 20858866]
- Ayala G, Tuxhorn JA, Wheeler TM, Frolov A, Scardino PT, Ohori M, Wheeler M, Spitler J, Rowley DR. Reactive stroma as a predictor of biochemical-free recurrence in prostate cancer. *Clin Cancer Res*. 2003; 9(13):4792–4801. [PubMed: 14581350]
- Balkwill FR. The chemokine system and cancer. *J Pathol*. 2012; 226(2):148–157. [PubMed: 21989643]
- Balkwill FR, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. *Semin Cancer Biol*. 2012; 22(1):33–40. [PubMed: 22210179]
- Bao L, Haque A, Jackson K, Hazari S, Moroz K, Jetly R, Dash S. Increased expression of P-glycoprotein is associated with doxorubicin chemoresistance in the metastatic 4T1 breast cancer model. *Am J Pathol*. 2011; 178(2):838–852. [PubMed: 21281816]
- Bao S, Ouyang G, Bai X, Huang Z, Ma C, Liu M, Shao R, Anderson RM, Rich JN, Wang XF. Periostin potently promotes metastatic growth of colon cancer by augmenting cell survival via the Akt/PKB pathway. *Cancer Cell*. 2004; 5(4):329–339. [PubMed: 15093540]
- Baril P, Gangeswaran R, Mahon PC, Caulee K, Kocher HM, Harada T, Zhu M, Kalthoff H, Crnogorac-Jurcevic T, Lemoine NR. Periostin promotes invasiveness and resistance of pancreatic cancer cells to hypoxia-induced cell death: role of the beta4 integrin and the PI3k pathway. *Oncogene*. 2007; 26(14):2082–2094. [PubMed: 17043657]
- Bielen H, Houart C. The Wnt Cries Many: Wnt regulation of neurogenesis through tissue patterning, proliferation and asymmetric cell division. *Dev Neurobiol*. 2014; 1002/dneu.22168
- Binaschi M, Supino R, Gambetta RA, Giaccone G, Prosperi E, Capranico G, Cataldo I, Zunino F. MRP gene overexpression in a human doxorubicin-resistant SCLC cell line: alterations in cellular pharmacokinetics and in pattern of cross-resistance. *Int J Cancer*. 1995; 62(1):84–89. [PubMed: 7601572]
- Brellier F, Chiquet-Ehrismann R. How do tenascins influence the birth and life of a malignant cell? *J Cell Mol Med*. 2012; 16(1):32–40. [PubMed: 21692981]
- Brewster AM, Hortobagyi GN, Broglio KR, Kau SW, Santa-Maria CA, Arun B, Buzdar AU, Booser DJ, Valero V, Bondy M, Esteva FJ. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst*. 2008; 100(16):1179–1183. [PubMed: 18695137]
- Brunner A, Mayerl C, Tzankov A, Verdorfer I, Tschörner I, Rogatsch H, Mikuz G. Prognostic significance of tenascin-C expression in superficial and invasive bladder cancer. *J Clin Pathol*. 2004; 57(9):927–931. [PubMed: 15333651]
- Buck MB, Pfizenmaier K, Knabbe C. Antiestrogens induce growth inhibition by sequential activation of p38 mitogen-activated protein kinase and transforming growth factor-beta pathways in human breast cancer cells. *Mol Endocrinol*. 2004; 18(7):1643–1657. [PubMed: 15056732]
- Burger JA, Kipps TJ. CXCR4: a key receptor in the crosstalk between tumor cells and their microenvironment. *Blood*. 2006; 107(5):1761–1767. [PubMed: 16269611]
- Busam KJ. Desmoplastic melanoma. *Clin Lab Med*. 2011; 31(2):321–330. [PubMed: 21549245]
- Buyukbayram H, Arslan A. Value of tenascin-C content and association with clinicopathological parameters in uterine cervical lesions. *Int J Cancer*. 2002; 100(6):719–722. [PubMed: 12209613]
- Camps JL, Chang SM, Hsu TC, Freeman MR, Hong SJ, Zhau HE, von Eschenbach AC, Chung LW. Fibroblast-mediated acceleration of human epithelial tumor growth *in vivo*. *Proc Natl Acad Sci USA*. 1990; 87(1):75–79. [PubMed: 2296606]
- Cecchi F, Rabe DC, Bottaro DP. Targeting the HGF/Met signalling pathway in cancer. *Eur J Cancer*. 2010; 46(7):1260–1270. [PubMed: 20303741]
- Chao C, Carmical JR, Ives KL, Wood TG, Aronson JF, Gomez GA, Djukom CD, Hellmich MR. CD133 + colon cancer cells are more interactive with the tumor microenvironment than CD133-cells. *Lab Invest*. 2012; 92(3):420–436. [PubMed: 22157717]
- Chen JT, Huang CY, Chiang YY, Chen WH, Chiou SH, Chen CY, Chow KC. HGF increases cisplatin resistance via down-regulation of AIF in lung cancer cells. *Am J Respir Cell Mol Biol*. 2008; 38(5):559–565. [PubMed: 18096875]

- Chen SS, Lee L. Prognostic significance of morphology of tumor and retroperitoneal lymph nodes in epithelial carcinoma of the ovary. II. Correlation with survival. *Gynecol Oncol.* 1984; 18(1):94–99. [PubMed: 6325309]
- Choi KU, Yun JS, Lee IH, Heo SC, Shin SH, Jeon ES, Choi YJ, Suh DS, Yoon MS, Kim JH. Lysophosphatidic acid-induced expression of periostin in stromal cells: Prognostic relevance of periostin expression in epithelial ovarian cancer. *Int J Cancer.* 2011; 128(2):332–342. [PubMed: 20309942]
- Cohen M, Marchand-Adam S, Lecon-Malas V, Marchal-Somme J, Boutten A, Durand G, Crestani B, Dehoux M. HGF synthesis in human lung fibroblasts is regulated by oncostatin M. *Am J Physiol Lung Cell Mol Physiol.* 2006; 290(6):L1097–L1103. [PubMed: 16684952]
- Cohen SJ, Alpaugh RK, Palazzo I, Meropol NJ, Rogatko A, Xu Z, Hoffman JP, Weiner LM, Cheng JD. Fibroblast activation protein and its relationship to clinical outcome in pancreatic adenocarcinoma. *Pancreas.* 2008; 37(2):154–158. [PubMed: 18665076]
- Conklin MW, Keely PJ. Why the stroma matters in breast cancer: insights into breast cancer patient outcomes through the examination of stromal biomarkers. *Cell Adhes Migr.* 2012; 6(3):249–260.
- Conti I, Rollins BJ. CCL2 (monocyte chemoattractant protein-1) and cancer. *Semin Cancer Biol.* 2004; 14(3):149–154. [PubMed: 15246049]
- Da evi M, Isakovi A, Podolski-Reni A, Isakovi AM, Stankovi T, Miloševi Z, Raki L, Ruždiji S, Peši M. Purine nucleoside analog—sulfinosine modulates diverse mechanisms of cancer progression in multi-drug resistant cancer cell lines. *PLoS ONE.* 2013; 8(1):e54044. [PubMed: 23326571]
- Daly AJ, McIlreavey L, Irwin CR. Regulation of HGF and SDF-1 expression by oral fibroblasts—implications for invasion of oral cancer. *Oral Oncol.* 2008; 44(7):646–651. [PubMed: 17996483]
- de Boer RA, van Veldhuisen DJ, Gansevoort RT, Muller Kobold AC, van Gilst WH, Hillege HL, Bakker SJ, van der Harst P. The fibrosis marker galectin-3 and outcome in the general population. *J Intern Med.* 2012; 272(1):55–64. [PubMed: 22026577]
- de Boussac H, Orbán TI, Várady G, Tihanyi B, Bacquet C, Brózik A, Váradi A, Sarkadi B, Arányi T. Stimulus-induced expression of the ABCG2 multidrug transporter in HepG2 hepatocarcinoma model cells involves the ERK1/2 cascade and alternative promoters. *Biochem Biophys Res Commun.* 2012; 426(2):172–176. [PubMed: 22922104]
- De Wever O, Nguyen QD, Van Hoorde L, Bracke M, Bruyneel E, Gespach C, Mareel M. Tenascin-C and SF/HGF produced by myofibroblasts in vitro provide convergent pro-invasive signals to human colon cancer cells through RhoA and Rac. *FASEB J.* 2004; 18(9):1016–1018. [PubMed: 15059978]
- Dean M. ABC transporters, drug resistance, and cancer stem cells. *J Mammary Gland Biol Neoplasia.* 2009; 14(1):3–9. [PubMed: 19224345]
- Deng B, Huang W, Tan QY, Fan XQ, Jiang YG, Lhi L, Zhong YY, Liang YG, Wang RW. Breast cancer anti-estrogen resistance protein 1 (BCAR1/p130cas) in pulmonary disease tissue and serum. *Mol Diagn Ther.* 2011; 15(1):31–40. [PubMed: 21469768]
- DeVita VT Jr, Chu E. A history of cancer chemotherapy. *Cancer Res.* 2008; 68(21):8643–8653. [PubMed: 18974103]
- Diah SK, Smitherman PK, Aldridge J, Vok EL, Schneider E, Townsend AJ, Morrow CS. Resistance to mitoxantrone in multidrug-resistant MCF7 breast cancer cells: evaluation of mitoxantrone transport and the role of multidrug resistance protein family proteins. *Cancer Res.* 2001; 61(14):5461–5467. [PubMed: 11454692]
- Diaz LA Jr, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, Bozic I, Reiter JG, Nowak MA, Kinzler KW, Oliner KS, Vogelstein B. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature.* 2012; 486(7404):537–540. [PubMed: 22722843]
- Domanska UM, Timmer-Bosscha H, Nagengast WB, Oude Munnink TH, Kruizinga RC, Ananias HJ, Kliphuis NM, Huls G, De Vries EG, de Jong IJ, Walenkamp AM. CXCR4 inhibition with AMD3100 sensitizes prostate cancer to docetaxel chemotherapy. *Neoplasia.* 2012; 14(8):709–718. [PubMed: 22952424]
- Dubrovskaya A, Elliott J, Salamone RJ, Telegeev GD, Stakhovsky AE, Schepotin IB, Yan F, Wang Y, Bouchez LC, Kularatne SA, Watson J, Trussell C, Reddy VA, Cho CY, Schultz PG. CXCR4

- expression in prostate cancer progenitor cells. PLoS ONE. 2012; 7(2):e31226. [PubMed: 22359577]
- Earp HS, Dawson TL, Li X, Yu H. Heterodimerization and functional interaction between EGF receptor family members: a new signaling paradigm with implications for breast cancer research. Breast Cancer Res Treat. 1995; 35(1):115–132. [PubMed: 7612898]
- Emoto K, Yamada Y, Sawada H, Fujimoto H, Ueno M, Takayama T, Kamada K, Naito A, Hirao S, Nakajima Y. Annexin II overexpression correlates with stromal tenascin-C overexpression: a prognostic marker in colorectal carcinoma. Cancer. 2001; 92(6):1419–1426. [PubMed: 11745218]
- Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma *in situ* of the breast a review. Breast Cancer Res Treat. 2006; 97(2):135–144. [PubMed: 16319971]
- Eyman D, Damodarasamy M, Plymate SR, Reed MJ. CCL5 secreted by senescent aged fibroblasts induces proliferation of prostate epithelial cells and expression of genes that modulate angiogenesis. J Cell Physiol. 2009; 220(2):376–381. [PubMed: 19360811]
- Fang WB, Jokar I, Zou A, Lambert D, Dendukuri P, Cheng N. CCL2/CCR2 chemokine signaling coordinates survival and motility of breast cancer cells through Smad3 protein- and p42/44 mitogen-activated protein kinase (MAPK)-dependent mechanisms. J Biol Chem. 2012; 287(43):36593–36608. [PubMed: 22927430]
- Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS, Connell CM, Roberts EW, Zhao Q, Caballero OL, Teichmann SA, Janowitz T, Jodrell DI, Tuveson DA, Fearon DT. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci USA. 2013; 110(50):20212–20217. [PubMed: 24277834]
- Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, O'Dwyer PJ, Lee RJ, Grippo JF, Nolop K, Chapman PB. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010; 363(9):809–819. [PubMed: 20818844]
- Fleming JM, Miller TC, Kidacki M, Ginsburg E, Stuelten CH, Stewart DA, Troester MA, Vonderhaar BK. Paracrine interactions between primary human macrophages and human fibroblasts enhance murine mammary gland humanization in vivo. Breast Cancer Res. 2012; 14(3):R97. [PubMed: 22731827]
- Foley J, Nickerson NK, Nam S, Allen KT, Gilmore JL, Nephew KP, Riese DJ 2nd. EGFR signaling in breast cancer: bad to the bone. Semin Cell Dev Biol. 2010; 21(9):951–960. [PubMed: 20813200]
- Fujimoto H, Sangai T, Ishii G, Ikehara A, Nagashima T, Miyazaki M, Ochiai A. Stromal MCP-1 in mammary tumors induces tumor-associated macrophage infiltration and contributes to tumor progression. Int J Cancer. 2009; 125(6):1276–1284. [PubMed: 19479998]
- Fukunaga-Kalabis M, Martinez G, Nguyen TK, Kim D, Santiago-Walker A, Roesch A, Herlyn M. Tenascin-C promotes melanoma progression by maintaining the ABCB5-positive side population. Oncogene. 2010; 29(46):6115–6124. [PubMed: 20729912]
- Gao CF, Vande Woude GF. HGF/SF-Met signaling in tumor progression. Cell Res. 2005; 15(1):49–51. [PubMed: 15686627]
- Gillan L, Matei D, Fishman DA, Gerbin CS, Karlan BY, Chang DD. Periostin secreted by epithelial ovarian carcinoma is a ligand for alpha(V)beta(3) and alpha(V)beta(5) integrins and promotes cell motility. Cancer Res. 2002; 62(18):5358–5364. [PubMed: 12235007]
- Goldberg RM. Intensive surveillance after stage II or III colorectal cancer is it worth it? J Clin Oncol. 2006; 24(3):330–331. [PubMed: 16365175]
- Gong XG, Lv YF, Li XQ, Xu FG, Ma QY. Gemcitabine resistance induced by interaction between alternatively spliced segment of tenascin-C and annexin A2 in pancreatic cancer cells. Biol Pharm Bull. 2010; 33(8):1261–1267. [PubMed: 20686216]
- Guirouilh J, Castroviejo M, Balabaud C, Desmouliere A, Rosenbaum J. Hepatocarcinoma cells stimulate hepatocyte growth factor secretion in human liver myofibroblasts. Int J Oncol. 2000; 17(4):777–781. [PubMed: 10995891]
- Gupta V, Bassi DE, Simons JD, Devarajan K, Al-Saleem T, Uzzo RG, Cukierman E. Elevated expression of stromal palladin predicts poor clinical outcome in renal cell carcinoma. PLoS ONE. 2011; 6(6):e21494. [PubMed: 21738681]

- Hasebe T, Mukai K, Tsuda H, Ochiai A. New prognostic histological parameter of invasive ductal carcinoma of the breast: clinicopathological significance of fibrotic focus. *Pathol Int.* 2000; 50(4): 263–272. [PubMed: 10849311]
- Heidelberger C, Chaudhuri NK, Danneberg P, Mooren D, Griesbach L, Duschinsky R, Schnitzer RJ, Plevin E, Scheiner J. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature.* 1957; 179(4561):663–666. [PubMed: 13418758]
- Hembruff SL, Jokar I, Yang L, Cheng N. 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.* 2010; 12(5):425–433. [PubMed: 20454514]
- Hermann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ, Heeschen C. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell.* 2007; 1(3):313–323. [PubMed: 18371365]
- 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. Cancer-associated fibroblast and M2 macrophage markers together predict outcome in colorectal cancer patients. *Cancer Sci.* 2013; 104(4):437–444. [PubMed: 23298232]
- Hidalgo M. Pancreatic cancer. *N Engl J Med.* 2010; 362(17):1605–1617. [PubMed: 20427809]
- Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. *Nat Rev Cancer.* 2013; 13 (10):714–726. [PubMed: 24060863]
- Hong LZ, Wei XW, Chen JF, Shi Y. Overexpression of periostin predicts poor prognosis in non-small cell lung cancer. *Oncol Lett.* 2013; 6(6):1595–1603. [PubMed: 24273600]
- Ibarra-Drendall C, Dietze EC, Seewaldt VL. Metabolic syndrome and breast cancer risk: Is mere a role for metformin? *Current Breast Cancer Rep.* 2011; 3(3):142–150.
- Ilmonen S, Jähkölä T, Turunen JP, Muhonen T, Asko-Seljavaara S. Tenascin-C in primary malignant melanoma of the skin. *Histopathology.* 2004; 45(4):405–411. [PubMed: 15469480]
- Jähkölä T, Toivonen T, Virtanen I, von Smitten K, Nordling S, von Boguslawski K, Haglund C, Nevanlinna H, Blomqvist C. Tenascin-C expression in invasion border of early breast cancer: a predictor of local and distant recurrence. *Br J Cancer.* 1998; 78(11):1507–1513. [PubMed: 9836485]
- Jin J, Huang M, Wei HL, Liu GT. Mechanism of 5-fluorouracil required resistance in human hepatocellular carcinoma cell line Bel (7402). *World J Gastroenterol.* 2002; 8(6):1029–1034. [PubMed: 12439919]
- Kahn N, Meister M, Eberhardt R, Muley T, Schnabel PA, Bender C, Johannes M, Keitel D, Sultmann H, Herth FJ, Kuner R. Early detection of lung cancer by molecular markers in endobronchial epithelial-lining fluid. *J Thoracic Oncol.* 2012; 7(6):1001–1008.
- Kalluri R, Zeisberg M. Fibroblasts in cancer. *Nat Rev Cancer.* 2006; 6 (5):392–401. [PubMed: 16572188]
- Kaseda K, Ishii G, Aokage K, Takahashi A, Kuwata T, Hishida T, Yoshida J, Kohno M, Nagai K, Ochiai A. Identification of intravascular tumor microenvironment features predicting die recurrence of pathological stage I lung adenocarcinoma. *Cancer Sci.* 2013; 104(9):1262–1269. [PubMed: 23786153]
- Kawashiri S, Tanaka A, Noguchi N, Hase T, Nakaya H, Ohara T, Kato K, Yamamoto E. Significance of stromal desmoplasia and myofibroblast appearance at the invasive front in squamous cell carcinoma of the oral cavity. *Head Neck.* 2009; 31(10):1346–1353. [PubMed: 19373786]
- Keizer HG, Schuunuis GJ, Broxterman HJ, Lankelma J, Schoonen WG, van Rijn J, Pinedo HM, Joenje H. Correlation of multidrug resistance with decreased drug accumulation, altered subcellular drug distribution, and increased P-glycoprotein expression in cultured SW-1573 human lung tumor cells. *Cancer Res.* 1989; 49(11):2988–2993. [PubMed: 2566376]
- Kemp LE, Mulloy B, Gherardi E. Signalling by HGF/SF and Met: the role of heparan sulphate co-receptors. *Biochem Soc Trans.* 2006; 34(Pt 3):414–417. [PubMed: 16709175]
- Khunamompong S, Lekawanvijit S, Settakom J, Sukpan K, Suprasert P, Siriaunkgul S. Prognostic model in patients with early-stage squamous cell carcinoma of the uterine cervix: a combination of

- invasive margin pathological characteristics and lymphovascular space invasion. *Asian Pac J Cancer Prev*. 2013; 14(11):6935–6940. [PubMed: 24377504]
- Kii I, Nishiyama T, Li M, Matsumoto K, Saito M, Amizuka N, Kudo A. Incorporation of tenascin-C into the extracellular matrix by periostin underlies an extracellular meshwork architecture. *J Biol Chem*. 2010; 285(3):2028–2039. [PubMed: 19887451]
- Kitano H, Kageyama S, Hewitt SM, Hayashi R, Doki Y, Ozaki Y, Fujino S, Takikita M, Kubo H, Fukuoka J. Podoplanin expression in cancerous stroma induces lymphangiogenesis and predicts lymphatic spread and patient survival. *Arch Pathol Lab Med*. 2010; 134(10):1520–1527. [PubMed: 20923309]
- Kojima M, Nakajima K, Ishii G, Saito N, Ochiai A. Peritoneal elastic laminal invasion of colorectal cancer: the diagnostic utility and clinicopathologic relationship. *Am J Surg Pathol*. 2010; 34(9):1351–1360. [PubMed: 20716999]
- Kreuzaler P, Watson CJ. Killing a cancer: what are the alternatives? *Nat Rev Cancer*. 2012; 12(6):411–424. [PubMed: 22576162]
- Kucia M, Jankowski K, Reza R, Wysoczynski M, Bandura L, Allendorf DJ, Zhang J, Ratajczak J, Ratajczak MZ. CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion. *J Mol Histol*. 2004; 35 (3):233–245. [PubMed: 15339043]
- Kwon Y, Smith BD, Zhou Y, Kaufman MD, Godwin AK. Effective inhibition of c-MET-mediated signaling, growth and migration of ovarian cancer cells is influenced by the ovarian tissue microenvironment. *Oncogene*. 2013
- Lari SA, Kuerer HM. Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review. *J Cancer*. 2011; 2:232–261. [PubMed: 21552384]
- Lee SH, Kim H, Hwang JH, Lee HS, Cho JY, Yoon YS, Han HS. Breast cancer resistance protein expression is associated with early recurrence and decreased survival in resectable pancreatic cancer patients. *Pathol Int*. 2012; 62(3):167–175. [PubMed: 22360504]
- Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010; 141(7):1117–1134. [PubMed: 20602996]
- Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature*. 1998; 396(6712):643–649. [PubMed: 9872311]
- Levina V, Marrangoni AM, DeMarco R, Gorelik E, Lokshin AE. Drug-selected human lung cancer stem cells: cytokine network, tumorigenic and metastatic properties. *PLoS ONE*. 2008; 3(8):e3077. [PubMed: 18728788]
- Lhomme C, Joly F, Walker JL, Lissoni AA, Nicoletto MO, Manikhas GM, Baekelandt MM, Gordon AN, Fracasso PM, Mietlowski WL, Jones GJ, Dugan MH. Phase III study of valspodar (PSC 833) combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone in patients with stage IV or suboptimally debulked stage III epithelial ovarian cancer or primary peritoneal cancer. *J Clin Oncol*. 2008; 26(16):2674–2682. [PubMed: 18509179]
- Li L, Dragulev B, Zigrino P, Mauch C, Fox JW. The invasive potential of human melanoma cell lines correlates with their ability to alter fibroblast gene expression *in vitro* and the stromal microenvironment *in vivo*. *Int J Cancer*. 2009; 125(8):1796–1804. [PubMed: 19569239]
- Li M, Li C, Li D, Xie Y, Shi J, Li G, Guan Y, Li M, Zhang P, Peng F, Xiao Z, Chen Z. Periostin, a stroma-associated protein, correlates with tumor invasiveness and progression in nasopharyngeal carcinoma. *Clin Exp Metastasis*. 2012; 29(8):865–877. [PubMed: 22706927]
- Liao D, Luo Y, Markowitz D, Xiang R, Reisfeld RA. Cancer associated fibroblasts promote tumor growth and metastasis by modulating the tumor immune microenvironment in a 4T1 murine breast cancer model. *PLoS ONE*. 2009; 4(11):e7965. [PubMed: 19956757]
- Lim KP, Cirillo N, Hassona Y, Wei W, Thurlow JK, Cheong SC, Pitiyage G, Parkinson EK, Prime SS. Fibroblast gene expression profile reflects the stage of tumour progression in oral squamous cell carcinoma. *J Pathol*. 2011; 223(4):459–469. [PubMed: 21294120]
- Liu R, Li J, Xie K, Zhang T, Lei Y, Chen Y, Zhang L, Huang K, Wang K, Wu H, Wu M, Nice EC, Huang C, Wei Y. FGFR4 promotes stroma-induced epithelial-to-mesenchymal transition in colorectal cancer. *Cancer Res*. 2013; 73(19):5926–5935. [PubMed: 23943801]
- Loebinger MR, Giangreco A, Groot KR, Prichard L, Allen K, Simpson C, Bazley L, Navani N, Tibrewal S, Davies D, Janes SM. Squamous cell cancers contain a side population of stem-like

- cells that are made chemosensitive by ABC transporter blockade. *Br J Cancer*. 2008; 98(2):380–387. [PubMed: 18219291]
- Lotti F, Jarrar AM, Pai RK, Hitomi M, Lathia J, Mace A, Gantt GA Jr, Sukhdeo K, DeVecchio J, Vasanji A, Leahy P, Hjelmeland AB, Kalady MF, Rich JN. Chemotherapy activates cancer-associated fibroblasts to maintain colorectal cancer-initiating cells by IL-17A. *J Exp Med*. 2013; 210(13):2851–2872. [PubMed: 24323355]
- Lu Y, Chen Q, Corey E, Xie W, Fan J, Mizokami A, Zhang J. Activation of MCP-1/CCR2 axis promotes prostate cancer growth in bone. *Clin Exp Metastasis*. 2009; 26(2):161–169. [PubMed: 19002595]
- Lu Y, Xiao G, Galson DL, Nishio Y, Mizokami A, Keller ET, Yao Z, Zhang J. PTHrP-induced MCP-1 production by human bone marrow endothelial cells and osteoblasts promotes osteoclast differentiation and prostate cancer cell proliferation and invasion *in vitro*. *Int J Cancer*. 2007; 121(4):724–733. [PubMed: 17390372]
- Lv Y, Wang W, Jia WD, Sun QK, Li JS, Ma JL, Liu WB, Zhou HC, Ge YS, Yu JH, Xia HH, Xu GL. High-level expression of periostin is closely related to metastatic potential and poor prognosis of hepatocellular carcinoma. *Med Oncol*. 2013; 30(1):385. [PubMed: 23275141]
- MacDonald BT, Tamai K, He X. Wnt/beta-eaten in signaling: components, mechanisms, and diseases. *Dev Cell*. 2009; 17(1):9–26. [PubMed: 19619488]
- Malanchi I, Santamaria-Martinez A, Susanto E, Peng H, Lehr HA, Delaloye JF, Huelsken J. Interactions between cancer stem cells and their niche govern metastatic colonization. *Nature*. 2012; 481 (7379):85–89. [PubMed: 22158103]
- Malofeeva EV, Domanitskaya N, Gudima M, Hopper-Borge EA. Modulation of the ATPase and transport activities of broad-acting multidrug resistance factor ABCC10 (MRP7). *Cancer Res*. 2012; 72 (24):6457–6467. [PubMed: 23087055]
- Marsh D, Suchak K, Moutasim KA, Vallath S, Hopper C, Jerjes W, Upile T, Kalavrezos N, Violette SM, Weinreb PH, Chester KA, Ghana JS, Marshall JF, Hart IR, Hackshaw AK, Piper K, Thomas GJ. Stromal features are predictive of disease mortality in oral cancer patients. *J Pathol*. 2011; 223(4):470–481. [PubMed: 21294121]
- Masuoka M, Shiraishi H, Ohta S, Suzuki S, Arima K, Aoki S, Toda S, Inagaki N, Kurihara Y, Hayashida S, Takeuchi S, Koike K, Ono J, Noshiro H, Fume M, Conway SJ, Narisawa Y, Izuhara K. Periostin promotes chronic allergic inflammation in response to Th2 cytokines. *J Clin Invest*. 2012; 122(7):2590–2600. [PubMed: 22684102]
- Mertens JC, Fingas CD, Christensen JD, Smoot RL, Bronk SF, Wemeburg NW, Gustafson MP, Dietz AB, Roberts LR, Sirica AE, Gores GJ. Therapeutic effects of deleting cancer-associated fibroblasts in cholangiocarcinoma. *Cancer Res*. 2013; 73(2):897–907. [PubMed: 23221385]
- Mhawech-Fauceglia P, Wang D, Samrao D, Kim G, Lawrenson K, Meneses T, Liu S, Yessaian A, Pejovic T. Clinical implications of marker expression of carcinoma-associated Fibroblasts (CAFs) in patients with epithelial ovarian carcinoma after treatment with neoadjuvant chemotherapy. *Cancer Microenviron*. 2013
- Millward MJ, Cantwell BM, Munro NC, Robinson A, Corns PA, Harris AL. Oral verapamil with chemotherapy for advanced non-small cell lung cancer: a randomised study. *Br J Cancer*. 1993; 67(5):1031–1035. [PubMed: 8388231]
- Mueller L, von Seggen L, Schumacher J, Goumas F, Wilms C, Braun F, Broering DC. TNF-alpha similarly induces DL-6 and MCP-1 in fibroblasts from colorectal liver metastases and normal liver fibroblasts. *Biochem Biophys Res Commun*. 2010; 397(3):586–591. [PubMed: 20617559]
- Naldini L, Weidner KM, Vigna E, Gaudino G, Bardelli A, Ponzetto C, Narsimhan RP, Hartmann G, Zarnegar R, Michalopoulos GK, et al. Scatter factor and hepatocyte growth factor are indistinguishable ligands for the MET receptor. *EMBO J*. 1991; 10(10):2867–2878. [PubMed: 1655405]
- Naumov GN, Townson JL, MacDonald IC, Wilson SM, Bramwell VH, Groom AC, Chambers AF. Ineffectiveness of doxorubicin treatment on solitary dormant mammary carcinoma cells or late-developing metastases. *Breast Cancer Res Treat*. 2003; 82(3):199–206. [PubMed: 14703067]

- Nicolo G, Sahvi S, Oliveri G, Borsi L, Castellani P, Zardi L. Expression of tenascin and of the ED-B containing oncofetal fibronectin isoform in human cancer. *Cell Differ Dev.* 1990; 32(3):401–408. [PubMed: 1711919]
- Nuzzo PV, Rubagotti A, Zinoli L, Ricci F, Salvi S, Boccardo S, Boccardo F. Prognostic value of stromal and epithelial periostin expression in human prostate cancer: correlation with clinical pathological features and the risk of biochemical relapse or death. *BMC Cancer.* 2012; 12(1):625. [PubMed: 23273263]
- O'Connell JT, Sugimoto H, Cooke VG, MacDonald BA, Mehta AI, LeBleu VS, Dewar R, Rocha RM, Brentani RR, Resnick MB, Neilson EG, Zeisberg M, Kalluri R. VEGF-A and Tenascin-C produced by S100A4+ stromal cells are important for metastatic colonization. *Proc Natl Acad Sci USA.* 2011; 108(38):16002–16007. [PubMed: 21911392]
- Oguri T, Ozasa H, Uemura T, Bessho Y, Miyazaki M, Maeno K, Maeda H, Sato S, Ueda R. MRP7/ABCC10 expression is a predictive biomarker for the resistance to paclitaxel in non-small cell lung cancer. *Mol Cancer Ther.* 2008; 7(5):1150–1155. [PubMed: 18445659]
- Ohira S, Sasaki M, Harada K, Sato Y, Zen Y, Isse K, Kozaka K, Ishikawa A, Oda K, Nimura Y, Nakanuma Y. Possible regulation of migration of intrahepatic cholangiocarcinoma cells by interaction of CXCR4 expressed in carcinoma cells with tumor necrosis factor- α and stromal-derived factor-1 released in stroma. *Am J Pathol.* 2006; 168(4):1155–1168. [PubMed: 16565491]
- Ohnishi T, Daikuhara Y. Hepatocyte growth factor/scatter factor in development, inflammation and carcinogenesis: its expression and role in oral tissues. *Arch Oral Biol.* 2003; 48(12):797–804. [PubMed: 14596869]
- Ohno Y, Izumi M, Yoshioka K, Ohori M, Yonou H, Tachibana M. Prognostic significance of tenascin-C expression in clear cell renal cell carcinoma. *Oncol Rep.* 2008; 20(3):511–516. [PubMed: 18695899]
- Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR. Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. *Cancer Res.* 1999; 59(19):5002–5011. [PubMed: 10519415]
- Orend G, Chiquet-Ehrismann R. Tenascin-C induced signaling in cancer. *Cancer Lett.* 2006; 244(2):143–163. [PubMed: 16632194]
- Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell.* 2005; 121(3):335–348. [PubMed: 15882617]
- Oskarsson T, Acharyya S, Zhang XH, Vanharanta S, Tavazoie SF, Morris PG, Downey RJ, Manova-Todorova K, Brogi E, Massagué J. Breast cancer cells produce tenascin C as a metastatic niche component to colonize the lungs. *Nat Med.* 2011; 17(7):867–874. [PubMed: 21706029]
- Ostman A, Augsten M. Cancer-associated fibroblasts and tumor growth—bystanders turning into key players. *Curr Opin Genet Dev.* 2009; 19(1):67–73. [PubMed: 19211240]
- Parr C, Jiang WG. Expression of hepatocyte growth factor/scatter factor, its activator, inhibitors and the c-Met receptor in human cancer cells. *Int J Oncol.* 2001; 19(4):857–863. [PubMed: 11562767]
- Paulsson J, Sjöblom T, Micke P, Pontén F, Landberg G, Heldin CH, Bergh J, Brennan DJ, Jirstrom K, Ostman A. Prognostic significance of stromal platelet-derived growth factor beta-receptor expression in human breast cancer. *Am J Pathol.* 2009; 175(1):334–341. [PubMed: 19498003]
- Peled A, Tavor S. Role of CXCR4 in the pathogenesis of acute myeloid leukemia. *Theranostics.* 2013; 3(1):34–39. [PubMed: 23382784]
- Pezzolo A, Parodi F, Marimpietri D, Raffaghello L, Cocco C, Pistorio A, Mosconi M, Gambini C, Cilli M, Deaglio S, Malavasi F, Pistoia V. Oct-4+/Tenascin C + neuroblastoma cells serve as progenitors of tumor-derived endothelial cells. *Cell Res.* 2011; 21(10):1470–1486. [PubMed: 21403679]
- Polanska UM, Orimo A. Carcinoma-associated fibroblasts: non-neoplastic tumour-promoting mesenchymal cells. *J Cell Physiol.* 2013; 228(8):1651–1657. [PubMed: 23460038]
- Polyak K, Kalhira R. The role of the microenvironment in mammary gland development and cancer. *Cold Spring Harb Perspect Biol.* 2010; 2(11):a003244. [PubMed: 20591988]

- Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, Kaiser EA, Snyder LA, Pollard JW. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature*. 2011; 475(7355):222–225. [PubMed: 21654748]
- Qian DZ, Rademacher BL, Pittsenger J, Huang CY, Myrthue A, Higano CS, Garzotto M, Nelson PS, Beer TM. CCL2 is induced by chemotherapy and protects prostate cancer cells from docetaxel-induced cytotoxicity. *Prostate*. 2010; 70(4):433–442. [PubMed: 19866475]
- Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene*. 2007; 26(22):3291–3310. [PubMed: 17496923]
- Roca H, Varsos Z, Pienta KJ. CCL2 protects prostate cancer PC3 cells from autophagic death via phosphatidylinositol 3-kinase/AKT-dependent survivin up-regulation. *J Biol Chem*. 2008; 283(36):25057–25073. [PubMed: 18611860]
- Roninson IB. Tumor cell senescence in cancer treatment. *Cancer Res*. 2003; 63(11):2705–2715. [PubMed: 12782571]
- Samaratunga H, Fairweather P, Purdie D. Significance of stromal reaction patterns in invasive urothelial carcinoma. *Am J Clin Pathol*. 2005; 123(6):851–857. [PubMed: 15899775]
- Sankala HM, Hait NC, Paugh SW, Shida D, Lépine S, Elmore LW, Dent P, Milstien S, Spiegel S. Involvement of sphingosine kinase 2 in p53-independent induction of p21 by the chemotherapeutic drug doxorubicin. *Cancer Res*. 2007; 67(21):10466–10474. [PubMed: 17974990]
- Schoppmann SF, Jesch B, Riegler MF, Maroske F, Schwameis K, Jomrich G, Bimer P. Podoplanin expressing cancer associated fibroblasts are associated with unfavourable prognosis in adenocarcinoma of the esophagus. *Clin Exp Metastasis*. 2013; 30(4):441–446. [PubMed: 23161183]
- Seslar SP, Nakamura T, Byers SW. Regulation of fibroblast hepatocyte growth factor/scatter factor expression by human breast carcinoma cell lines and peptide growth factors. *Cancer Res*. 1993; 53(6):1233–1238. [PubMed: 8443802]
- Shimao Y, Nabeshima K, Inoue T, Kono M. Role of fibroblasts in HGF/SF-induced cohort migration of human colorectal carcinoma cells: fibroblasts stimulate migration associated with increased fibronectin production via upregulated TGF- β 1. *Int J Cancer*. 1999; 82 (3):449–458. [PubMed: 10399964]
- Shinde AV, Frangogiannis NG. Fibroblasts in myocardial infarction: A role in inflammation and repair. *J Mol Cell Cardiol*. 2013; 1016/j.jmcc.2013.11.015
- Siegmund MJ, Kreukler C, Steidler A, Nebe T, Köhrmann KU, Alken P. Multidrug resistance in androgen-independent growing rat prostate carcinoma cells is mediated by P-glycoprotein. *Urol Res*. 1997; 25 (1):35–41. [PubMed: 9079744]
- Silzle T, Kreutz M, Dobler MA, Brockhoff G, Knuechel R, Kunz-Schughart LA. Tumor-associated fibroblasts recruit blood monocytes into tumor tissue. *Eur J Immunol*. 2003; 33(5):1311–1320. [PubMed: 12731056]
- Smith NZ. Treating metastatic breast cancer with systemic chemotherapies: current trends and future perspectives. *Clin J Oncol Nurs*. 2012; 16(2):E33–E43.
- Soon PS, Kim E, Pon CK, Gill AJ, Moore K, Spillane AJ, Benn DE, Baxter RC. Breast cancer-associated fibroblasts induce epithelial-to-mesenchymal transition in breast cancer cells. *Endocr Relat Cancer*. 2013; 20(1):1–12. [PubMed: 23111755]
- Stoker M, Gherardi E, Perryman M, Gray J. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. *Nature*. 1987; 327 (6119):239–242. [PubMed: 2952888]
- Stoker M, Perryman M. An epithelial scatter factor released by embryo fibroblasts. *J Cell Sci*. 1985; 77:209–223. [PubMed: 3841349]
- Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA, Golub TR. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature*. 2012; 487(7408):500–504. [PubMed: 22763439]
- Stupack DG, Cheresch DA. Get a ligand, get a life: integrins, signaling and cell survival. *J Cell Sci*. 2002; 115(Pt 19):3729–3738. [PubMed: 12235283]

- Sturm I, Bosanquet AG, Hermann S, Güner D, Dörken B, Daniel PT. Mutation of p53 and consecutive selective drug resistance in B-CLL occurs as a consequence of prior DNA-damaging chemotherapy. *Cell Death Differ.* 2003; 10(4):477–484. [PubMed: 12719725]
- Sun Y, Campisi J, Higano C, Beer TM, Porter P, Coleman I, True L, Nelson PS. Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B. *Nat Med.* 2012; 18(9):1359–1368. [PubMed: 22863786]
- Takeuchi K, Ito F. Receptor tyrosine kinases and targeted cancer therapeutics. *Biol Pharm Bull.* 2011; 34(12):1774–1780. [PubMed: 22130229]
- Taylor CW, Dalton WS, Parrish PR, Gleason MC, Bellamy WT, Thompson FH, Roe DJ, Trent JM. Different mechanisms of decreased drug accumulation in doxorubicin and mitoxantrone resistant variants of the MCF7 human breast cancer cell line. *Br J Cancer.* 1991; 63(6):923–929. [PubMed: 1676902]
- Tege B, Szállási Z, Haltrich I, Pénczváltó Z, Tóth Z, Likó I, Gyorffy B. Parallel evolution under chemotherapy pressure in 29 breast cancer cell lines results in dissimilar mechanisms of resistance. *PLoS ONE.* 2012; 7(2):e30804. [PubMed: 22319589]
- Thomas D, Vadas M, Lopez A. Regulation of haematopoiesis by growth factors- emerging insights and therapies. *Expert Opin Biol Ther.* 2004; 4(6):869–879. [PubMed: 15174969]
- Tjomsland V, Niklasson L, Sandström P, Borch K, Druid H, Bratth C II, Messmer D, Larsson M, Spångéus A. The desmoplastic stroma plays an essential role in the accumulation and modulation of infiltrated immune cells in pancreatic adenocarcinoma. *Clin Dev Immunol.* 2011; 2011:212810. [PubMed: 22190968]
- Torres S, Bartolomé RA, Mendes M, Barderas R, Fernandez-Aceñero MJ, Peláez-García A, Peña C, Lopez-Lucendo M, Villar-Vázquez R, de Herreros AG, Bonilla F, Casal JI. Proteome profiling of cancer-associated fibroblasts identifies novel proinflammatory signatures and prognostic markers for colorectal cancer. *Clin Cancer Res.* 2013; 19(21):6006–6019. [PubMed: 24025712]
- Tsujino T, Seshimo I, Yamamoto H, Ngan CY, Ezumi K, Takemasa I, Ikeda M, Sekimoto M, Matsuura N, Monden M. Stromal myofibroblasts predict disease recurrence for colorectal cancer. *Clin Cancer Res.* 2007; 13(7):2082–2090. [PubMed: 17404090]
- Tsuyada A, Chow A, Wu J, Somlo G, Chu P, Loera S, Luu T, Li AX, Wu X, Ye W, Chen S, Zhou W, Yu Y, Wang YZ, Ren X, Li H, Scherle P, Kuroki Y, Wang SE. CCL2 mediates cross-talk between cancer cells and stromal fibroblasts that regulates breast cancer stem cells. *Cancer Res.* 2012; 72(11):2768–2779. [PubMed: 22472119]
- Uchida D, Kawamata H, Omotehara F, Nakashiro Ki, Kimura-Yanagawa T, Hino S, Begum NM, Hoque MO, Yoshida H, Sato M, Fujimori T. Role of HGF/c-met system in invasion and metastasis of oral squamous cell carcinoma cells in vitro and its clinical significance. *Int J Cancer.* 2001; 93(4):489–496. [PubMed: 11477552]
- van Leenders GJ, Sookhlall R, Teubel WJ, de Ridder CM, Reneman S, Sacchetti A, Vissers KJ, van Weerden W, Jenster G. Activation of c-MET induces a stem-like phenotype in human prostate cancer. *PLoS ONE.* 2011; 6(11):e26753. [PubMed: 22110593]
- Vermeulen L, De Sousa E, Melo F, van der Heijden M, Cameron K, de Jong JH, Borovski T, Tuynman JB, Todaro M, Merz C, Rodermond H, Sprick MR, Kemper K, Richel DJ, Stassi G, Medema JP. Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. *Nat Cell Biol.* 2010; 12(5):468–476. [PubMed: 20418870]
- Wang B, Liu K, Lin HY, Bellam N, Ling S, Lin WC. 14-3-3Tau regulates ubiquitin-independent proteasomal degradation of p21, a novel mechanism of p21 downregulation in breast cancer. *Mol Cell Biol.* 2010; 30(6):1508–1527. [PubMed: 20086099]
- Wang P, Nishitani MA, Tanimoto S, Kishimoto T, Fukumori T, Takahashi M, Kanayama HO. Bladder cancer cell invasion is enhanced by cross-talk with fibroblasts through hepatocyte growth factor. *Urology.* 2007; 69(4):780–784. [PubMed: 17445681]
- Wang Q, Fiel MI, Blank S, Luan W, Kadri H, Kim KW, Manizate F, Rosenblatt AG, Labow DM, Schwartz ME, Hiotis SP. Impact of liver fibrosis on prognosis following liver resection for hepatitis B-associated hepatocellular carcinoma. *Br J Cancer.* 2013; 109(3):573–581. [PubMed: 23846171]

- Wang W, Li Q, Yamada T, Matsumoto K, Matsumoto I, Oda M, Watanabe G, Kayano Y, Nishioka Y, Sone S, Yano S. Crosstalk to stromal fibroblasts induces resistance of lung cancer to epidermal growth factor receptor tyrosine kinase inhibitors. *Clin Cancer Res.* 2009; 15(21):6630–6638. [PubMed: 19843665]
- Wartenberg M, Frey C, Diederhagen H, Ritgen J, Hescheler J, Sauer H. Development of an intrinsic P-glycoprotein-mediated doxorubicin resistance in quiescent cell layers of large, multicellular prostate tumor spheroids. *Int J Cancer.* 1998; 75(6):855–863. [PubMed: 9506530]
- White GE, Iqbal AJ, Greaves DR. CC chemokine receptors and chronic inflammation—therapeutic opportunities and pharmacological challenges. *Pharmacol Rev.* 2013; 65(1):47–89. [PubMed: 23300131]
- Wilson KJ, Mill C, Lambert S, Buchman J, Wilson TR, Hernandez-Gordillo V, Gallo RM, Ades LM, Settleman J, Riese DJ 2nd. EGFR ligands exhibit functional differences in models of paracrine and autocrine signaling. *Growth Factors.* 2012a; 30(2):107–116. [PubMed: 22260327]
- Wilson TR, Fridlyand J, Yan Y, Penuel E, Burton L, Chan E, Peng J, Lin E, Wang Y, Sosman J, Ribas A, Li J, Moffat J, Sutherlin DP, Koeppen H, Merchant M, Neve R, Settleman J. Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature.* 2012b; 487(7408):505–509. [PubMed: 22763448]
- Wishart GC, Bissett D, Paul J, Jodrell D, Harnett A, Habeshaw T, Kerr DJ, Macham MA, Soukop M, Leonard RC, et al. Quinidine as a resistance modulator of epirubicin in advanced breast cancer: mature results of a placebo-controlled randomized trial. *J Clin Oncol.* 1994; 12(9):1771–1777. [PubMed: 8083699]
- Wong MP, Cheung KN, Yuen ST, Fu KH, Chan AS, Leung SY, Chung LP. Monocyte chemoattractant protein-1 (MCP-1) expression in primary lymphoepithelioma-like carcinomas (LELCs) of the lung. *J Pathol.* 1998; 186(4):372–377. [PubMed: 10209485]
- Wu KJ. Direct activation of Bmi1 by Twist1: implications in cancer stemness, epithelial-mesenchymal transition, and clinical significance. *Chang Gung Med J.* 2011; 34(3):229–238. [PubMed: 21733352]
- Wu MH, Hong HC, Hong TM, Chiang WF, Jin YT, Chen YL. Targeting galectin-1 in carcinoma-associated fibroblasts inhibits oral squamous cell carcinoma metastasis by downregulating MCP-1/CCL2 expression. *Clin Cancer Res.* 2011; 17(6):1306–1316. [PubMed: 21385934]
- Xiong J, Balcioglu HE, Danen EH. Integrin signaling in control of tumor growth and progression. *Int J Biochem Cell Biol.* 2013; 45(5):1012–1015. [PubMed: 23428797]
- Xu D, Xu H, Ren Y, Liu C, Wang X, Zhang H, Lu P. Cancer stem cell-related gene periostin: a novel prognostic marker for breast cancer. *PLoS ONE.* 2012; 7(10):e46670. [PubMed: 23056395]
- Yamada T, Matsumoto K, Wang W, Li Q, Nishioka Y, Sekido Y, Sone S, Yano S. Hepatocyte growth factor reduces susceptibility to an irreversible epidermal growth factor receptor inhibitor in EGFR-T790M mutant lung cancer. *Clin Cancer Res.* 2010; 16(1):174–183. [PubMed: 20008840]
- Yasunaga M, Yamasaki F, Tokunaga O, Iwasaka T. Endometrial carcinomas with lymph node involvement novel histopathologic factors for predicting prognosis. *Int J Gynecol Pathol.* 2003; 22(4):341–346. [PubMed: 14501813]
- Yoshida S, Harada T, Iwabe T, Taniguchi F, Fujii A, Sakamoto Y, Yamauchi N, Shiota G, Terakawa N. Induction of hepatocyte growth factor in stromal cells by tumor-derived basic fibroblast growth factor enhances growth and invasion of endometrial cancer. *J Clin Endocrinol Metab.* 2002; 87(5):2376–2383. [PubMed: 11994390]
- Yu S, Xia S, Yang D, Wang K, Yeh S, Gao Z, Chang C. Androgen receptor in human prostate cancer-associated fibroblasts promotes prostate cancer epithelial cell growth and invasion. *Med Oncol.* 2013; 30 (3):674. [PubMed: 23925662]
- Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. *Nat Rev Cancer.* 2009; 9(1):28–39. [PubMed: 19104514]

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.

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 myofibroblasts, 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