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# Novel Insights Into the Role of Inflammation in Promoting Breast Cancer Development

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## 1. Introduction

In the past decades the major focus of cancer research has been the transformed tumor cells itself, while the role of cellular microenvironment in tumorigenesis has not been widely explored. Several studies have demonstrated the ability of stroma to regulate the growth and differentiation state of breast cancer cells, and the invasive behaviour, and polarity of normal mammary epithelial and breast carcinomas are influenced by tumor microenvironment, immune and stromal cells (Bissell, et al., 2002, Radisky & Radisky, 2007, Tlsty, 2001, Tlsty & Hein, 2001). In addition, genetic abnormalities, such as loss of heterozygosity, occur not only in cancer cells, but in stromal cells as well (Kurose, et al., 2002, Kurose, et al., 2001, Moinfar, et al., 2000).

It is believed that a better understanding of the tumor microenvironment could help render more accurate diagnostics or assist in predicting tumor aggressiveness (i.e., bad prognosis) thus facilitating the design of personalized treatments.

By the end of the nineteenth century, the English surgeon S. Paget suggested the idea that, in order for breast cancer to develop, a specific "seeding" process must occur and, for this primary onset to metastasize to a specific distant organ, particular stromal features would be required postulating his "seed and soil" hypothesis (Paget, 1889). His work greatly contributed to somewhat earlier observations by T. Langhans who first used the word stroma to describe the connective tissue, vessels and other components between tumors (Langhans, 1879) and to the theory postulated by R. Virchow suggesting a possible origin of cancer at sites of chronic inflammation (Balkwill& Mantovani, 2001). A century later, researchers such as B. Mintz and K. Illmensee in general, as well as M. Bisell, in breast cancer in particular, pointed to the tumor milieu as an essential component of neoplasias, not only for cancer evolution but also for cancer instigation (Mintz & Illmensee, 1975; Lochter & Bissell, 1995). Together these and additional findings had painted a broad picture of the complexity of tumor microenvironment, where diverse stromal cells interact with

each other and with the cancer cells playing important roles in tumorigenesis (Soto & Sonnenschein, 2004; Egeblad et al., 2010).

It is clear now that metastatic tumors represent the greatest threat to cancer patient mortality. Indeed, when breast cancer is diagnosed early and metastases are not present, 5-year survival is >88%; however, if metastases are also present, long-term survival is significantly diminished (~10%) (Jemal, et al., 2011). Thereby, the major cause of mortality of breast cancer and different types of cancer is due to metastasis to distant organs, such as lung, bone, liver and brain (Lu & Kang, 2007). A notable feature of this process is the variation in metastatic organ tropism displayed by different types of cancer (Chambers, et al., 2002, Fidler, 2002). A classic view has proposed that purely mechanical factors regulate the fate of blood-borne metastasis tumor cells (MacDonald, et al., 2002); however, this does not fully explain the non-random distribution and distinct pattern of metastasis in each tumor type (Lu & Kang, 2007). However, tumor microenvironment has also shown an important role in the regulation of this process (Valdivia-Silva, et al., 2009). A number of different molecules present in the microenvironment have been associated to the metastasis of breast cancer, among them, chemokines, which have been associated with regulation of cell migration and invasion of tumor cells into specific organs (Muller, et al., 2001, Zlotnik, 2006). Chemokines are a superfamily of chemotactic cytokines characterized by their ability to induce directed migration of leukocytes, during haematopoiesis, lymphoid organ development, and in disease (Sallusto, et al., 2000); their expression may be inducible, primarily by pro-inflammatory cytokines such as TNF-a and IL-1-b (Ben-Baruch, 2003). Chemokine receptor expression in many cancer cells have shown to be a non-random process (Shields, et al., 2007, Zlotnik, 2006) and to have a role in organ-specific metastasis: for example, CXCR4 expression and metastasis to lung, bone and lymph nodes (Muller, et al., 2001), CCR7 to lymph nodes (Shields, et al., 2007), CX3CR1 to brain (Mourad, et al., 2005), CCR9 to liver and small bowel (Amersi, et al., 2008, Letsch, et al., 2004), and CCR5 and CXCR2 to lung, liver, vessel endothelial cells and bone (Gross & Meier, 2009, Keeley, et al., 2010, Miller, et al., 1998).

Here, we will discuss the ability of the chemokines to affect tumor cell–microenvironment interactions, increasing the invasive behaviour and metastasis, confirming the importance of the host inflammatory response that may differ between tumor types, disease stages, and/or many other host factors; and the role of stromal contribution of the inflammatory microenvironment to cancer progression and metastasis.

## 2. Inflammatory mediators as regulator of breast cancer development and metastasis

The link between inflammation and cancer has been observed over 150 years ago when Rudolf Virchow noted that cancers tend to occur at sites of chronic inflammation. Indeed, epidemiological studies indicate that inflammatory and infectious diseases are often associated with an increased risk of cancer (Coussens & Werb, 2002). The microenvironment of tumors mimics that of tissues during the height of an inflammatory response to injury (Joyce & Pollard, 2009). However, unlike the organized morphology of normal tissue, and the ultimate resolution of the inflammation that occurs during healing, tumors exist in a state of chronic inflammation characterized by the presence of cancer cells, immune cells, aberrant vascular cells, and the persistence of inflammatory mediators, such as cytokines and chemokines.

The presence and significance of leukocyte infiltrates in developing neoplasms is now undisputed (Allen, et al., 2007, Moser & Loetscher, 2001, Moser & Willimann, 2004). It has been demonstrated that leukocyte infiltration in developing tumors is one of the host´s main immune mechanisms to eradicate malignant cells. However, while some leukocytes certainly have this potential, i.e., cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells (Luster, 1998), other leukocyte cell types, most notably innate immune cells, i.e., mast cells (MCs), immature myeloid cells, granulocytes, and macrophages, instead potentiate tumor progression (Baggiolini, et al., 1997, Chen, et al., 2006, Joyce & Pollard, 2009), and enhance neoplastic cell survival. Upon entry into the neoplastic microenvironment, infiltrating leukocytes become alternatively activated and manifest a pro-tumor phenotype as defined by activation of cellular programs involved in immune tolerance and tissue remodelling (Mishra, et al., 2011, Strieter, et al., 2006). During premalignant progression, a consequence of alternative activation of leukocytes is promotion and elaboration of a microenvironment rich in extracellular matrix (ECM) remodelling proteases, and increased presence of pro-survival, pro-growth and pro-angiogenic factors that further enhance proliferative and invasive capacities of neoplastic cells (Li, et al., 2007, Orimo, et al., 2005). Such pro-tumor inflammatory microenvironments promote not only malignant conversion and development of solid tumors, but also dissemination of neoplastic cells into blood vasculature by driving invasive capacity of malignant cells, expansion of angiogenic vasculature, and neoplastic cell entry into blood vessels (and lymphatics) (Keeley, et al., 2010).

Breast carcinomas are highly infiltrated by different types of host leukocytes, including primarily T cells, and monocytes that differentiate into tumor-associated macrophages (TAM) at the tumor site (Ben-Baruch, 2003, Crowther, et al., 2001). The presence of the cellular infiltrate in breast tumors was initially regarded as evidence for the potential activity of immune mechanisms against the growing neoplasm. As explained above, several studies suggest that T-cell antitumor responses are impaired in advanced stages of breast carcinoma, and there is no definite conclusion regarding the efficacy of T-cell-dependent immune mechanisms, or regarding the correlation between the type of T-cell infiltration and tumor progression in most subtypes of breast carcinoma (Hsiao, et al., 2010). The only exception is the relatively infrequent type of medullary carcinoma, in which favourable prognosis was correlated with intensive lymphoid infiltration (Hadden, 1999). In contrast to T lymphocytes, large evidence suggests that high levels of TAM are correlated with poor prognosis in breast carcinoma. Many studies have shown a positive relationship between high levels of TAM and lymph node metastases, and suggested that the density of TAM is associated with clinical aggressiveness (Crowther, et al., 2001, O'Sullivan & Lewis, 1994). Again, the potential contribution of TAM to tumor elimination, in view of several potential antimalignant activities that may be exerted by these cells, such as antigen presentation, cytotoxicity, or/and phagocytosis, was contradictory with the promalignant activities of TAM in breast carcinoma. These promalignant activities of TAM are the result of their ability to express numerous tumor-promoting mediators, such as growth factors for breast tumor cells, angiogenic molecules, ECM degrading enzymes, inflammatory cytokines, and chemokines (Balkwill & Mantovani, 2001, Colotta, et al., 2009). In addition, TAM might contribute to tumor progression by the release of reactive oxygen intermediates, which may induce mutagenic changes that could result in increased DNA damage and generation of new subtypes of cancer cells within the tumor (Colotta, et al., 2009). A major TAM-derived

inflammatory cytokine shown to be highly expressed in breast carcinomas is tumor necrosis factor alpha (TNF-a) (Leek, et al., 1998), which is a multifactorial cytokine. Tumor necrosis factor alpha was first isolated as an anti-cancer cytokines more than two decades ago (Aggarwal, 2003). However, these effects may depend on multiple factors, such as estrogen therapy and the expression of members of the epidermal growth factor receptor family. The fact that TNF-a activities vary under different physiological conditions and in a cell-type-dependent manner contributes to a sense of ambiguity regarding its antitumor effects (Kanoh, et al., 2001, Offersen, et al., 2002). A number of reports indicate that TNF-a induces cellular transformation, proliferation, and tumor promotion (Balkwill & Mantovani, 2001, Li, et al., 2007). A interesting study reported that human TNF-a is more effective than the chemical tumor promoters okadaic acid and 12-O-tetradecanoylphorbol-13-acetato in inducing cancer (Komori, et al., 1993).

The number of cells expressing TNF-a in inflammatory breast carcinoma has been correlated with increasing tumor grade and node involvement (Ben-Baruch, 2003, Leek, et al., 1998). Furthermore, patients with more progressed tumor phenotypes were shown to have significantly higher TNF-a and IL-2 serum concentration (Tesarová, et al., 2000). The tumor-promoting functions of TNF-a may be mediated by its ability to induce pro-angiogenic functions, to promote the expression of matrix metalloproteinases (MMP) and endothelial adhesion molecules, and to cause DNA damage via reactive oxygen, the overall effect of which is promotion of tumor-related processes (Garg & Aggarwal, 2002).

In addition, several inflammatory interleukins have been linked with carcinogenesis and tumor progression. Among these, IL-6 and IL-1 have been widely studied in breast carcinoma. In different types of cancer, IL-1 promotes growth and confers chemoresistance (Arlt, et al., 2002, Woodworth, et al., 1995). Furthermore, IL-1 secretion into the tumor milieu also induces several angiogenic factors from tumor and stromal cells that promotes tumor growth through hyperneovascularization (Zhou, et al., 2011). IL-6 may act as a paracrine growth factor for multiple myeloma, non-Hodgkin's lymphoma, bladder cancer, colorectal cancer, and renal carcinoma (Angelo, et al., 2002, Landi, et al., 2003, Okamoto, et al., 1995, Voorzanger, et al., 1996). However, contradictory studies suggested that elevated levels of IL-6 might contribute to breast cancer progression (Karczewska, et al., 2000, Kurebayashi, 2000). Initial analyses regarding IL-1b indicated that its levels were significantly higher in invasive carcinoma than in ductal carcinoma *in situ* or in benign lesions, implying that elevated levels of IL-1b are directly correlated with a more advanced disease (Jin, et al., 1997). Of interest is the fact that the two cytokines (IL-6 and IL-1b) and TNF-a are interrelated and may act in an additive manner, suggesting that these three cytokines form a network of related factors that may affect tumor cell progression in a cooperative manner.

Cyclooxygenase (COX)-2, an inducible enzyme with expression regulated by NF-kb, mediates tumorigenesis. COX-2, the inducible isoform of prostaglandin H synthase has been implicated in the growth and progression of a variety of human cancers, and its expression can be induced by various growth factors, cytokines, oncogenes, and other tumor factors. IL-1 has been reported to upregulate COX-2 expression in human colorectal cancer cells via multiple signalling pathways (Liu, et al., 2003). COX-2 is expressed at an intermediate or high level in epithelial cells of invasive breast cancers (Chang, et al., 2005, Half, et al., 2002). Expression of COX-2 in breast cancer correlates with poor prognosis, and COX-2 enzyme inhibitors reduce breast cancer incidence in humans. COX-2 overexpression has also been found in the mammary gland of transgenic mice induced mammary cancer (Kundu & Fulton, 2002).

Hypoxia is also an important cellular stressor that triggers a survival program by which cells attempt to adapt to the new environment. This primarily involves adaptation of metabolism and/or stimulation of oxygen delivery. These cell-rescuing mechanisms can be conducted rapidly by a transcription factor that reacts to hypoxic conditions, the hypoxia-inducible factor-1 (HIF-1a) (Semenza & Wang, 1992). HIF-1a stimulates processes such as angiogenesis, glycolysis, and erythropoiesis (Jiang, et al., 1996) by activating genes that are responsible for these processes. Cancer cells are able to survive and proliferate in extreme microenvironmental conditions and show changes in oncogenes and tumor suppressor genes. Hypoxia and HIF-1a have been implicated in carcinogenesis and in clinical behaviour of tumors. Upregulation of HIF-1a was noted during breast carcinogenesis (Bos, et al., 2001) especially in the poorly differentiated pathway. Hypoxia is related to poor response to therapy in various cancer types. In invasive breast cancer, high HIF-1a concentrations were associated with poor survival in lymph node-negative patients (Bos, et al., 2003). As prognosis in breast cancer is closely related to proliferation rate (van Diest & Baak, 1991) and poorly differentiated tumors usually exhibit high proliferation and HIF-1a overexpression, the prognostic value of HIF-1a might well be explained by a close association between HIF-1a and proliferation. Additionally, HIF-1a has shown to be a master regulator for surviving hypoxia interacting with cell cycle-related proteins. High concentrations of HIF-1a are associated with overexpression of p53 and markers of proliferation during the late SG2 phase of the cell cycle (Bos, et al., 2004).

## 3. Role of chemokines and their receptors in breast cancer progression and metastasis

While most evidence presented above suggests that proinflammatory cytokines and enzymes play an important role in mediating tumorigenesis, and tumor progression, the molecular mechanisms of metastasis and its relationship with the organotropism of cancer cell remain unclear. However, recent studies focused on the chemokines and their receptors, and the different interactions with inflammatory cytokines in the tumor microenvironment have provided additional information that might better explain the non-random patterns of organotropism during metastasis, including atypical metastasis to rare organs (Franco-Barraza, et al., 2010, Valdivia-Silva, et al., 2009).

Chemokine activities in different malignancy including breast cancer are mediated primarily by their ability to induce chemotaxis of leukocytes, endothelial cells, and/or the tumor cells. Chemokines induce migration of leukocyte subpopulations to tumor sites that may promote antitumor activities (such as Th1 cells or natural killer cells), while other chemokines are responsible for large quantities of deleterious tumor-associated macrophages (TAM) at tumor sites (Allavena, et al., 2008, Ben-Baruch, 2008, Soria & Ben-Baruch, 2008) as discussed above. Moreover, specific chemokines upregulate endothelial cell migration and proliferation, and promoting angiogenesis, whereas other chemokines have powerful angiostatic properties (Strieter, et al., 2006, Struyf, et al., 2011). Another very important activity of chemokines is induction of tumor cell invasion and migration, thereby playing key roles in dictating site-directed metastasis formation (Ben-Baruch, 2008, Zlotnik, 2006). Chemokines and their receptors can execute such multifaceted roles in malignancy because cells of the tumor microenvironment, and in many cases also by the tumor cells themselves express them. As such, they can affect through autocrine pathways the ability of

the cancer cells to express tumor-promoting functions, and can also act in paracrine manners on host cells, thereby influencing their roles in malignancy.

Breast cancer metastasis is the result of several sequential steps and represents a highly organized, non-random and organ selective process dependent on intricate stroma-stroma interactions at the target organ (Ben-Baruch, 2006, Lu & Kang, 2007), causing high mortality by invasion of vital organs, such as bone, lung, brain and liver. Important evidence suggests that chemokines have an important role in regulating trafficking and metastasis (Bagley, et al., 2010). Indeed, breast cancer cells express chemokine receptors in a non-random manner, and these observations pointed to several chemokine/ receptor pairs that control cell–cell migration (Zlotnik, 2008). Association of chemokine receptors with various cancers including breast carcinoma has been widely documented (Ali & Lazennec, 2007, Karnoub & Weinberg, 2006, Koizumi, et al., 2007, Ruffini, et al., 2007). Accumulative evidence, in particular from clinical retrospective studies, presents a compelling picture indicating that the experimental evidence derived from *in vitro* experiments and animal models pointing to a pivotal role of chemokine receptors in cancer metastasis. CXCR4 and CCR7 are the most widely expressed in many different cancers, and the expression of CXCL12 and CCL21, their specific ligands, respectively, are highest in lung, liver bone marrow for the first one and lymph nodes for both (Nevo, et al., 2004, Schimanski, et al., 2008). Additionally, the expression of CCR7 in patients with several types of cancer has an excellent correlation with the ability of the tumor to spread to the lymph nodes (Takanami, 2003, Wang, et al., 2005). Other chemokine receptors may participate in the regulation of metastasis of specific cancers and in tumor progression. CX3CR1 is involved in homing metastasis to brain for glioblastoma and breast cancer (Andre, et al., 2010, Lavergne, et al., 2003) and to bone and bone marrow endothelial cell for prostate cancer (Shulby, et al., 2004). CCR9/CCL25 axis was found in melanoma (Letsch, et al., 2004), ovarian cancer (Johnson-Holiday, et al., 2007), prostate cancer (Singh, et al., 2004), nasopharyngeal carcinoma (Ou, et al., 2006), acute lymphoblastic leukaemia (Annels, et al., 2004) and probably breast cancer (Johnson-Holiday, et al., 2011); most of the cases are related to metastatic lesions in the gastrointestinal tract included the liver. Additionally, elevated expression levels of CXCR2 and CCR5 and their ligands, CXCL8 and CCL5, respectively, in breast carcinoma and other neoplasias were significant associated with increased malignancy, advance disease, early relapse and poor prognosis (Ben-Baruch, 2006, Yaal-Hahoshen, et al., 2006). Moreover, it has been demonstrated that tumor cells can generate autocrine gradients of ligands of chemokine receptors (i.e., CCR7) that guide their migration in direction of a physiological level of interstitial flow towards functional lymphatics, even if lymphatic endothelial cells are absent; although the effect is greatly amplified when both flow and cells are present (Shields, et al., 2007). This data suggests that the chemokine–chemokine receptor interaction is of particular importance in the metastatic destination of many cancers.

However, a couple of questions are very important to make in this point: Is the chemokine receptor expression in cancer cells constant? Or might the tumor microenvironment or inflammation regulate the chemokine receptor expression in cancer cells? Interestingly, these questions, which are product of logic thinking on the tumor microenvironment, were not made until recently by our group (Valdivia-Silva, et al., 2009). Indeed, the chemokine receptor expression has not been thoroughly studied under inflammatory conditions.

Although there are reports demonstrating that tumor and leukocytes increase expression of chemokines and cytokines during disease progression, it is not clear what are the chemokine

receptors involved in regulation of metastasis. Most of the previously reported studies had focused in analysing chemokine receptors expressed in different neoplasias without evaluating their phenotypic changes and functionality during the progress of the disease (Ben-Baruch, 2008). However, it has not been clearly demonstrated any type of regulation of the microenvironment in these changes. Finally, the chemokine receptors expressed under non-stimulated conditions by cancer cells were considered biomarkers to specific homing to organs, but it does not explained atypical metastasis of cancer to rare organs (Charalabopoulos, et al., 2004, Johnson, 2010, Kilgore, et al., 2007, Saisho, et al., 2005).

Within the tumor microenvironment, chemokines and their receptors play different roles in modulating several functions as described above, and through these processes, help to define the progression of the cancer. Stromal, and immune cells, including leukocytes differentiating into tumor-associated macrophages (TAM) at the tumor site, express numerous promoting factors, such as growth factors, angiogenic mediators, extracellular matrix-degrading enzymes, inflammatory cytokines, and more chemokines (Polyak & Kalluri, 2010). Interestingly, pro-inflammatory cytokines like IL-1, IL-6, IFN-g and TNF-a, which are important modulators of chemokine receptors expression in different tissues, have demonstrated to regulate their expression in cancer cells in a non–random manner (Valdivia-Silva, et al., 2009). Similar to cytokines regulate for CXCR4 and CCR5 in astrocytes (Croitoru-Lamoury, et al., 2003), CXCR2 in human mesangial cells(Schwarz, et al., 2002), and CX3CR1 in smooth muscle cells (Chandrasekar, et al., 2003), synovium (Nanki, et al., 2002), and different epithelial cells (Fujimoto, et al., 2001, Matsumiya, et al., 2001); different doses and times of exposition allowed the expression of specific type of chemokine receptor in several breast cancer cell lines and the change of their phenotypes into more invasiveness ones (Franco-Barraza, et al., 2010).

We have analysed the human breast carcinoma MCF-7 cell line as a model of pre-invasive stage to demonstrate the regulation by an inflammatory microenvironment on chemokine receptor expression and functionality (Valdivia-Silva, et al., 2009). The comparison of the expression of CXCR4, CX3CR1, CXCR2, CCR9 and CCR5 at the transcriptional, protein, and functional levels under two different *in vitro* conditions (basal versus cytokine- stimulation) showed clearly the regulation of the specific cytokine over specific chemokine receptor, independently of the genetic background of MCF-7, which presents very low levels of these receptors under basal conditions. This was also observed in the highly metastatic MDA-MB-231, MDA-MB-361 and in the poorly metastatic T47D breast cancer cell lines; although the levels of expression observed after cytokine stimulation were different than those obtained in the MCF-7 cell line. A direct suggestion of these results, affirms that basal expression of a given chemokine receptor is not by itself a good marker of homing or aggressiveness and is subject to change by the microenvironment. Another important outcome in that work was the absence of correlation between the functionality of the receptor and their expression (gen or protein). For example, an increase in CXCR2 expression in MCF-7 cell line does not correlates with an increase in the migration index. In contrast, CX3CR, induced by TNF-a, had a small but significant increase at the protein level, which had an impact on their chemotactic activity. A considerable increase of chemokine receptors was found in non-migratory cancer cells indicating that that chemokine receptor expression does not necessarily result in migration response to a chemoattractant ligand. It also suggests that only a fraction of the cells have the potential to form metastases and capable to invade different organs. In fact, genetic analysis of the MDA-MB-231 breast cancer cell line subpopulations, obtained from *in vivo* experiments, identified a gene set whose expression

pattern is associated to metastasis to bone but not adrenal medulla (Kirschmann, et al., 1999, Xu, et al., 2010). Interestingly this signature is retained through repeated passage of the metastatic cell population both in vitro and in vivo. Therefore, breast cancer cells with a defined tissue-specific metastatic ability pre-exist in the parental tumor cell population and may have a distinctive metastasis gene expression signature. Thus, these data suggested that inflammatory stimulation in the tumor microenvironment might affect cancer cells migration by different mechanisms. Importantly, not all cancer cell population, including cell lines, had the same behaviour under the same cytokine stimulation. Finally, other important finding in this study suggested that cancer cells require constant inflammatory stimuli by the microenvironment to trigger their invasive and metastatic activity, because of after a short time without stimuli (hours to days), the cells diminished their specific-stimuli chemokine receptor expression.

Altogether, these data allowed us to propose that exist sub-populations expressing different levels of chemokine receptor expression, which under a particular stimuli in the host microenvironment, change their expression levels and thus their aggressiveness. Then, atypical metastasis of breast cancer to others organs, which are relatively rare, could fall under this scheme. The biological inflammatory global response in the tumor microenvironment might be triggering the expression of different chemokine receptors and determining a new homing for these cancer cells. More broadly, these observations strongly support the overall model where chemokines determine the metastatic destinations of cancer cells (Fig 1.)

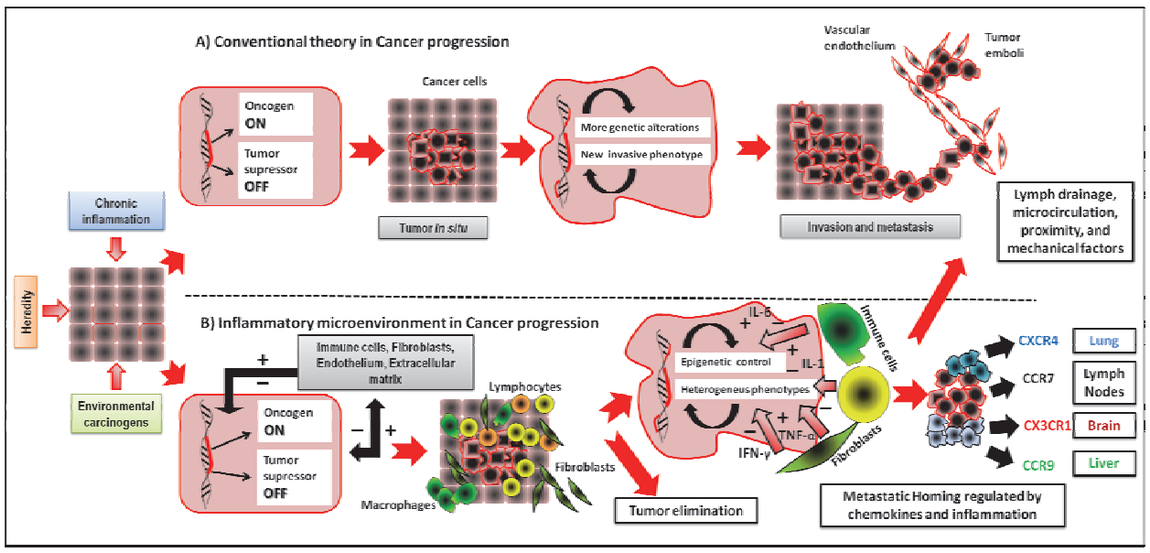


Fig. 1. Microenvironment and cancer progression.

Two theories have been proposed to explain this process, a conventional theory based on genetic alterations and a second view that involves participation of an inflammatory microenvironment. A) Initially, susceptible cells to different carcinogenic factors (e.g., genetic susceptibility obtained by inheritance) suffer specific DNA mutations that trigger tumorigenesis. The conventional theory is focused on the view that cancer progression is initially dependent on a sequence of genetic alterations and, finally, purely mechanical factors regulate the fate of blood-borne metastasis tumour cells (e.g. proximity,

microcirculation, direction of lymph or circulation drainage, etc.). B) A second view, based on the participation of an inflammatory microenvironment, takes into account constant interactions between tumor cells and surrounding cells during the different stages of cancer development. Therefore, the final response is the result of positive and negative effects and not only dependent on internal genetic changes in cancer cells but on interactions and epigenetic control of multiple inflammatory into molecules released into the tumor microenvironment. Therefore, the final metastatic homing, which is mediated by expression of chemokines and chemokine receptors, will be dependent on the deregulation of the host immune response

## 4. Targeting chemokines for breast cancer metastasis

As a consequence of studies focusing almost exclusively on cancer cells, nearly all of the currently used cancer therapeutic agents target the cancer cells that, due to their inherent genomic instability, frequently acquire therapeutic resistance (Rajagopalan, et al., 2003). In part due to frequent therapeutic failures during the course of treatment of advanced stage tumors, increasing emphasis has been placed on targeting various stromal cells, particularly endothelial cells, via therapeutic interventions. Since these cells are thought to be normal and genetically stable, they are less likely to develop acquired resistance to cancer therapy. Thus, isolating, and characterizing each cell type (epithelial, myoephitelial, and various stromal cells) comprising non-malignant and cancerous breast tissue would not only help us to understand the role these cells play in breast tumorigenesis, but would likely give us new molecular targets for cancer intervention and treatment.

There is now an abundant literature documenting the associations of chemokine receptors with various types of cancer (Zlotnik, 2006) and their importance to mediate the establishment or development of metastatic foci. In fact, some anticancer drugs currently in use -like Herceptin- may involve the downregulation of chemokine receptors as part of their mechanism of action (Li, et al., 2004). This would provide the ultimate validation of the hypothesis, and would also point to future opportunities for therapeutic intervention as we discussed below. Current therapies such as surgery, radiotherapy and chemotherapy are primarily concerned with destruction of cancer. Targeting chemokines and chemokine receptors will allow limiting angiogenesis or metastasis and may enable such therapies to act as chemotherapeutic agents alone or in synergism with conventional agents. The up-regulation of certain chemokine molecules in tumor as compared with normal cells offers a potential avenue—where cancer cells and their metastases can be specifically targeted. This selective destruction of cells is also pre-requisite of non-toxic treatment regimens.

Manipulation of the tumor microenvironment by treatment with chemokines can be used to recruit either immature dendritic cells for the initiation of anti-tumor responses or effector cells for cytotoxic responses. Intratumoral delivery of CCL21 using pox virus vaccine into established tumors derived from murine colon cancer line, CT26 results in enhanced infiltration of CD4 T cells which correlated with inhibition of tumor growth (Flanagan, et al., 2004). Non-immunogenic murine breast carcinoma is rejected after transducing cells with CCL19. The rejection of tumor was mediated by activated NK and CD4+ cells (Braun, et al., 2000). Adenoviral delivery of the CCL16 is able to inhibit growth of mammary tumors and prevent metastatic growth (Okada, et al., 2004). Importantly, in treatment involving delivery of chemokines to the tumor environment, there is a major problem of heterogeneity of the tumor cells. Chemokines may have dual effects, can be beneficial to one patient might be

harmful to another. However, this problem can be circumvented by chemokine typing every tumor prior to deciding on an appropriate therapy regime. They may be used as an adjunct to increase the efficacy of currently available therapies. Targeting specific chemokines can also modulate tumor infiltrating leukocytes or angiogenesis. High CXCL8 expression levels render tumor cells highly tumorigenic, angiogenic and invasive (Chavey, et al., 2007, Freund, et al., 2003, Freund, et al., 2004). In a murine model of breast cancer treatment with Met-CCL5, an antagonist of CCR1 and CCR5 led to a reduction in the total number of infiltrating inflammatory cells, in particular a decrease in macrophage infiltration and reduced growth of tumors (Liang, et al., 2004, Robinson, et al., 2003). The 7-transmembrane structure of chemokine receptors makes them attractive targets for small molecule inhibitors (Seaton, et al., 2009).

In summary, the exploration and manipulation of the chemokine network has just started and is likely to improve efficiency of current tumor therapies. However, since these chemotactic cytokines are also utilized in a plethora of normal interactions, caution is needed especially when extrapolating *in vitro* data into the clinical situation. Differences amongst tumor entities are obvious and the same chemokine/chemokine-receptor system seems to have divergent functions in different tumor entities. A more in-depth analysis of the real players in tumor immunosuppression, for example characterization of the subtypes of infiltrating immune cells and thorough analysis of the cytokine and chemokine milieu of primary tumors, will be necessary to pave the way for more efficient therapeutic interventions.

## 5. Tumor stroma: A permissive substrate for breast cancer development and progression

The stroma of carcinomas is an intricate ecosystem where heterogeneous cell populations coexist. This structural and functional connective tissue niche is inhabited by immune and inflammatory cells such as macrophages and monocytes, mesenchymal bone marrow-derived stem cells, endothelial and pericyte cells, lipocytes, additional smooth muscle cells and activated fibroblastic cells known as myofibroblasts, which are believed to be responsible for producing and maintaining the altered extracellular matrix (ECM) (Beacham & Cukierman, 2005; Li et al., 2007; Xouri & Christian, 2010). It is well accepted that the altered and excessive deposition of ECM, which is part of a process named desmoplasia, is directly associated with rapid progression and bad prognosis in carcinomas such as breast, pancreas, colon and prostate to name a few (Beacham & Cukierman, 2005; Arendt et al., 2010; Franco et al., 2010). In fact, we and others have suggested that stroma progression could be staged (analogously to classic tumor staging) into discrete stromagenic stages (Bissell et al., 2002; Mueller & Fusenig, 2002; Beacham & Cukierman, 2005; Quiros et al., 2008; Castello-Cros et al., 2009). Briefly, under normal (i.e., homeostatic) conditions, the breast stroma maintains the tissue architecture where a specialized ECM rich in collagen IV and laminin-1 known as basement membrane (BM) demarks a barrier between epithelium and the mesenchyme (Gudjonsson et al., 2002). A particular feature of the glandular epithelium in breast tissue is that both alveolar and ductal epithelial cells are not in direct contact with the BM. Instead, they are supported by a monolayer of myoepithelial cells that resides in between. Myoepithelial cells play an important role in supporting epithelial cell differentiation and controlling proliferation and cell polarity. These cells secrete the BM proteins and together with adjacent stromal fibroblasts maintain the integrity of this

specialized gland (Gudjonsson et al., 2002; Polyak & Kalluri, 2010). Under physiological conditions, a normal stroma preserves and drives regular breast tissue morphogenesis (Kuperwasser et al., 2004) and, at the same time, suppresses the transformation of epithelial cells thus preventing the development of breast carcinoma *in situ* (CIS) and inhibiting progression towards invasive cancer (Hu et al., 2008). Although not much information is available to describe the mechanistic events responsible for normal stroma prevention of carcinoma progression, recent data suggests that the tumor microenvironment lacks the regulatory mechanisms that are necessary to maintain a normal epithelial phenotype (Postovit et al., 2008). As shown by interesting work conducted by Mintz and Illmensee in 1975 where they observed that a normal embryo microenvironment is repressive of teratoma tumorigenesis (Mintz & Illmensee, 1975), more recent work by Postovit *et al* looking at specific human embryonic stem cells-secreted factors also concluded that embryonic microenvironments can control and sustain a normal behaviour of invasive tumor cells (Postovit et al., 2008). In summary, one could state that the normal stroma is a natural barrier or a non-permissive environment for tumor progression.

In an effort to understand premature events that occur during stroma progression (i.e., stromagenesis (Cukierman, 2009)), researchers have used animal models where they have shown stromal cells alterations at early stages of tumorigenesis. For example, prostate smooth muscle cells, known to support homeostasis and epithelium differentiation and considered to be analogous to normal myoepithelial cells in breast, have been shown to undergo alterations during early tumorigenesis (Wong & Tam, 2002). Similar to myoepithelial cells, smooth muscle cells are also lost in advanced stages of tumor progression, but prior to this they lower the expression levels of differentiation markers such as myosin, desmin, and laminin (Wong & Tam, 2002). This fact strongly suggests the advent of a discrete intermediate state between normal and activated stroma. To this end, the up-regulated expression of proteins, such as fibroblast activation protein, has been suggested as potential markers of this intermediate or primed stromal stage (Mathew et al., 1995; Huber et al., 2003; Santos et al., 2009). Another such molecule is tenascin-C, an ECM protein expressed in breast cancer at early stages of the tumorigenesis, which has been shown to have a diagnostic value (Adams et al., 2002; Guttery et al., 2010).

Once the stroma becomes activated, many histological features are evident. This stage is commonly described by pathologists as desmoplasia and is characterized by increased interstitial ECM-deposition. The desmoplastic ECM is believed to be produced by a highly proliferating fibroblastic and alpha-smooth muscle actin (α-SMA) expressing myofibroblastic cell population. It is common in many cancers including breast, and it can constitute up to 50% of the tumor mass (Kunz-Schughart & Knuechel, 2002a, b; Desmouliere et al., 2004). The altered architecture of the desmoplastic stroma reaction is characterized by the over expression of ECM proteins such as collagen I and differential spliced fibronectin isoforms such as EDA and EDB (Matsumoto et al., 1999; Desmouliere et al., 2004). The desmoplastic ECM is highly organized in a parallel fiber pattern, which is clearly oriented *in vivo* perpendicular to the tumor border (Provenzano et al., 2006). In fact, this particular feature of the tumor associated-ECM (TA-ECM) has been suggested to facilitate migration of breast cancer cells *in vitro*, in a β1-integrin dependent manner (Castello-Cros et al., 2009). Moreover, there is evidence to suggest that TA-ECM can induce a phenotypic switch upon naïve fibroblasts thus inducing a myofibroblastic (or activated) conformation (Amatangelo et al., 2005). To this end, in a xenograft model of human breast cancer, it was shown that

activated fibroblasts influence the local microenvironment to promote invasion (Orimo et al., 2005; Hu et al., 2008).

## 6. Tumor- or carcinoma-associated fibroblasts: A bad myofibroblastic influence

Fibroblasts are the main cellular component of the stroma and responsible for producing the mesenchymal (i.e., interstitial) ECM. These cells have been described as non-epithelial, non-inflammatory and non-vascular semi-differentiated connective tissue cells (Tarin & Croft, 1969). They are best known for their role in maintaining the tissue's integrity while they become quickly activated (e.g., myofibroblastic) and can modify the plasticity of the resident's tissue under conditions that alter the homeostatic equilibrium such as during wound healing, organogenesis, cancer and other pathological and inflammatory conditions (Kalluri & Zeisberg, 2006) . In fact, fibroblasts are known as tissue remodelers capable of renovating ECMs while, at the same time, facilitating access to ECM stored growth factors, such as transforming growth factor-beta (TGF-b), through a tightly regulated release and activation of matrix digestive enzymes such as matrix metalloproteinases (MMPs) (Jodele et al., 2006).

The fibroblastic cell population, known as carcinoma-associated fibroblasts (CAFs) or tumor-associated fibroblasts (Barsky et al., 1984), presents a myofibroblastic phenotype that is very similar to the one observed in activated fibroblasts during wound healing (Barsky et al., 1984). CAFs are the main stromal cell component of solid epithelial carcinomas (Shao et al., 2000). In addition to a characteristic, high proliferation rate and increased ECM deposition, the development of contractile cell features affects the physico-chemical characteristics of TA-ECM (Tomasek et al., 2002; Butcher et al., 2009; Cukierman & Bassi, 2010). Interestingly, CAFs are capable of establishing interactions with inflammatory, endothelial, and tumor cells by means of cytokines/chemokines secretions such as interleukin (IL)-1β, IL-6, CXCL-8, stromal derived factor-1 (SDF-1), also known as CXCL-12, and the monocyte chemotactic protein (MCPs/CCLs) among others (Silzle et al., 2004; Mishra et al., 2011). In an effort to find a discrete set of CAF specific markers, proteins such as γ- and α-SMA (Brouty-Boye et al., 1991; Kunz-Schughart & Knuechel, 2002b; Desmouliere et al., 2004; Xouri & Christian, 2010) specific isoforms of the actin binding protein palladin, (Ronty et al., 2006; Goicoechea et al., 2010; Gupta et al., 2011) as well as the intermediate filament proteins vimentin and desmin (Schmid et al., 1982) have been suggested. Furthermore, the specific breast cancer microenvironmental niche has been shown to contain increased levels of expression of ECM stabilizing (e.g., cross-linking) enzymes such as prolyl-4 hydroxylase (Orimo et al., 2005) and lysyl oxidase (Chang et al., 2005; Levental et al., 2009; Barry-Hamilton et al., 2010). Additional proteins have been shown to be specifically overexpressed at the tumor-associated stroma such as fibroblast activation protein (LeBeau et al., 2009; Lee, 2011), endosialin (Becker et al., 2008; Christian et al., 2008) S100A4 (Ambartsumian et al., 1996; Ryan et al., 2003; Katoh et al., 2010), and a plethora of MMPs, among others (Rasanen & Vaheri, 2010). In fact, some of these have already been proposed to serve as stromal monitoring or prognostic markers (Erkan et al., 2008; Gupta et al., 2011).

Nevertheless, this hardly consistent signature of myofibroblastic markers strongly suggests that the tumor stroma is a heterogeneous milieu (Sugimoto et al., 2006). The variety of

myofibroblastic phenotypes is also suggestive of the eliciting of different roles played by these cell populations at the tumor stroma. Interestingly, this heterogeneity could have been originated (i.e., differentiated) by the multiple cell lineages known to produce myofibroblastic CAFs. These are: local fibroblasts (Kalluri & Zeisberg, 2006), bone marrow recruited mesenchymal cells (Ishii et al., 2003; Goldstein et al., 2010), as well as endothelial and tumor (i.e., epithelial) cells (Petersen et al., 2003; Kalluri & Zeisberg, 2006; Zeisberg et al., 2007), among others. In all these cases, TGF-β has been closely associated with tumor-induced myofibroblastic activation or differentiation (Zeisberg et al., 2007; Hinz, 2010; Taylor et al., 2010). The myofibroblastic differentiation is a complex and not yet fully understood process that is believed to play a central role during breast tumorigenesis (Cukierman, 2004; McAllister & Weinberg, 2010). Even though a plethora of molecules has been implicated in regulating fibroblastic activation, the specific desmoplastic response in breast cancer is believed to be driven by four main groups of inducers; i) growth factors, ii) TA-ECM, iii) acute inflammation and iv) microenvironmental stress denoted by nutrient and oxygen depravation as well as low pH.

i. Specific growth factor presence at the tumor microenvironment may constitute the most studied aspect believed to trigger a myofibroblastic switch of the otherwise quiescent homeostatic fibroblasts. Determined mainly *in vitro* by an increment in proliferation rate, induction of α-SMA expression, and an up-regulation of ECM components, the growth factors most commonly implicated in this process are TGF-α, TGF-β, insulin-like growth factors I and II (TGF-I and TGF-II), the platelet-derived growth factor (PDGF), and the basic fibroblast growth factor (bFGF) (Beacham & Cukierman, 2005; Kalluri & Zeisberg, 2006; Rasanen & Vaheri, 2010; Xouri & Christian, 2010). Although many questions remain regarding specific triggers for breast cancer desmoplasia, work from Walker and Dearing implicated TGF-$\beta_1$, TGF-$\beta_2$ and TGF-β receptor as vital contributors of breast tumorigenesis associated with a stromal increment of fibronectin and tenascin in the tumor stroma (Walker & Dearing, 1992; Walker et al., 1994). Moreover, TGF-β known to induce myofibroblastic differentiation and to increase collagen I deposition during the wound healing process (Desmouliere et al., 2005), has also been implicated as a main factor in inducing breast cancer associated bone marrow-derived myofibroblasts differentiation (Goldstein et al., 2010). Similarly, PDGF has been shown to increase the breast myofibroblastic population by 30% while greatly increasing the amount of interstitial collagen I *in vivo* (Shao et al., 2000). In the context of epithelial to mesenchymal transition (EMT)-derived myofibroblasts, hepatocyte growth factor (HGF) and epidermal growth factor (EGF), in addition to the above-mentioned PDGF and TGF-β, have also been implicated (Mimeault & Batra, 2007; Kalluri & Weinberg, 2009).

ii. Breast TA-ECMs' features are known to become altered in both their molecular composition (Chen, S.T. et al., 2008; Levental et al., 2009; Ronnov-Jessen & Bissell, 2009) and their architectural characteristics (Provenzano et al., 2006). Together these two altered features can modulate tumorigenic behaviours of cancer cells and promote or delay the evolution of carcinomas in a permissive or restrictive manner (Ronnov-Jessen & Bissell, 2009; Cukierman & Bassi, 2010). In addition, it has been suggested that the physico-chemical characteristics of the ECM also affect the behaviour of mesenchymal cells (Discher et al., 2005). Fibroblasts are influenced by stromal stiffness, which exerts mechanical forces that modulate their cell behaviour. Thus, it has been demonstrated

that as the substrate stiffness increases, fibroblastic cells change exhibiting three discrete phenotypic switch stages: normal or naive fibroblasts, intermediate or proto-myofibroblastic and activated myofibroblastic (Hinz, 2010). The phenotype transition induced by the increased tension in the substratum is also accompanied by the maturation or elongation of focal adhesions, together with cytoskeletal changes known to build-up contractile stress fibers (Hinz, 2010). Interestingly, studies of normal breast revealed a relatively limp tissue composition (0.15 kPa, expressed in *E* values of a Young modulus) compared to the stiffer and highly desmoplastic ~4 kPa tissue that has been affected by breast cancer (Butcher et al., 2009). The altered (i.e., myofibroblastic) phenotype of fibroblasts is linked to the stiffer ECM during tumor progression as these cells are responsible for the production of the TA-ECM (Cukierman & Bassi, 2010). Indeed increments of mammographic density, suggesting excessive collagen deposition, have been associated with higher risk in breast cancer (Boyd et al., 1998). Moreover, increases in cross-linked collagen due to over expression of LOX together with patterned linearization of the TA-ECM and specific ECM receptor, integrin, clustering and enhanced phosphoinositide 3-kinase (PI3K) activity, have all been correlated with breast cancer progression (Levental et al., 2009). Additionally, it has been shown that the interstitial ECM can function as a reservoir for diffusible molecules, such as the above-mentioned TGF-β which is secreted by both stromal and tumor cells in its inactivated form (Wipff & Hinz, 2008), but can be both activated and released due to the intrinsic myofibroblastic forces that increase the tension of TA-ECM's fibrils (Wipff et al., 2007; Tenney & Discher, 2009).

iii. Recently, an inflammatory microenvironment has been suggested as the seventh hallmark of cancer (Colotta et al., 2009). This cancer hallmark is also believed to play an important role in desmoplasia as a fibroblast phenotypic-switch activator. To this end, it has been demonstrated that stromal inflammatory responses that result from wounding can trigger tumorigenesis (Arwert et al., 2010). The importance of an inflammatory component has also been suggested for the breast cancer stroma (Hu & Polyak, 2008), and its repercussion in inducing or promoting cancer aggressiveness and metastasis has been highlighted in numerous occasions (Pantschenko et al., 2003; Elaraj et al., 2006; Valdivia-Silva et al., 2009; Franco-Barraza et al., 2010; Goldberg & Schwertfeger, 2010). However, our current knowledge regarding fibroblastic responses to inflammatory cytokines in breast cancer remains relatively modest. Work conducted at the Polyak laboratory suggested that cytokines could participate in triggering a fibroblast phenotypic switch at the breast cancer microenvironment (Hu et al., 2009). This work and the work of others has opened up the possibility of targeting inflammatory cytokines for the treatment of neoplasias as in the case of COX-2 and arachidonic acid inhibitors (Chen, X. et al., 2006; Hu et al., 2009). In fact, in the kidney, it has been shown that collagen I regulates COX-2 expression in a pro-proliferative type of response (Alique et al., 2011). Interestingly, CAFs are known to promote inflammation in an NFκ-b dependent manner, suggesting a vicious cycle between inflammation and stromal activation during tumorigenesis (Erez et al., 2010). Moreover, it has been shown that CAFs effectively suppress anti-tumor inflammation while, at the same time, maintaining acute inflammatory (pro-tumor) conditions (Kraman et al., 2010).

As established before, the cytokine/growth factor TGF-β imparts a pleiotropic and decisive role in the promotion of the desmoplastic tumor microenvironment thus

supporting tumor progression (Yang et al., 2010). In addition, this same factor plays an additional important stromal role in inducing the expression of NADPH oxidase family protein, Nox4 (Bondi et al., 2010). Nox4 is a potent regulator of reactive oxygen species (ROS) (Barnes & Gorin, 2011) and has been shown to induce the accumulation of ROS in damaged tissues while transactivation of fibroblasts into myofibroblasts (Cucoranu et al., 2005; Rocic & Lucchesi, 2005). In breast cancer, the oxidative stress present at the tumor stroma is also considered to be an inductor for myofibroblastic differentiation, as recently shown in a JunD deficient mouse model, where the absence of this transcription factor allowed the accumulation of Ras-mediated production of ROS with the subsequent conversion of fibroblasts into myofibroblasts and shortening of the tumor free survival rate (Toullec et al., 2010).

iv. It is well known that as tumors progress increased regions of nutrient deprivation, low pH and low oxygen tension (hypoxia) are evident. Under these hypoxic stress conditions, breast cancer tissues are known to up-regulate the expression of hypoxia-inducible family (HIF) genes such as HIF-1α (Chen, C.L. et al., 2010). HIF proteins are known to participate in many cellular events such as angiogenesis, through the induction of vascular endothelium growth factor (VEGF), angiopoietin-2, PDFG and FGF (Allen & Louise Jones, 2011) which in turn can also activate stromal myofibroblastic differentiation in breast cancers (Shao et al., 2000). Finally, other molecules known to be induced by HIF-1α in carcinomas (and other fibrotic conditions) are the above mentioned ECM-cross-linkers (i.e., LOX) which have been associated with aggressive breast tumorigenesis (Chang et al., 2005; Levental et al., 2009; Barry-Hamilton et al., 2010).

## 7. Fibroblasts as moderators of signals at the tumor microenvironment

At the tumor microenvironment, intercellular communications resemble a social network emitting signals (either static or diffusible molecules) that in turn are collected, processed and emitted to additional cells. Using this analogy, it seems that CAFs play a decisive role during cancer progression acting as microenvironment signals moderators that sense extracellular signals and, after intracellular processing, emit new ones that in turn modulate both stromal and neoplastic neighbouring cells' behaviours (Bhowmick et al., 2004). In fact during cancer progression, CAFs constitute a very important source of the exogenous stimulants such as the above-mentioned TGF-β (Kalluri & Zeisberg, 2006). To this end, using an elegant humanized stromal reconstruction model of human breast cancer in mouse, Kuperwasser *et al* demonstrated that CAFs facilitate tumor development in a fibroblastic TGF-β- and HGF-dependent manner (Kuperwasser et al., 2004). Additionally, recent findings have demonstrated that epigenetic changes induced by mesenchymal cells on breast cancer cells that are regulated by the TGF-β/TGF- βR/Smad2 signalling axis provoke the silencing of critical epithelial genes resulting in the pro-tumorigenic EMT process (Papageorgis et al., 2010). To this end, in support of the above proposed vicious cycle effect, it is interesting to note that following quiescent fibroblasts transdifferentiation into CAFs, these cells support an invasive phenotype of mammary carcinomas where they secrete inflammatory cytokines (Powell et al., 1999; Buckley et al., 2001; Silzle et al., 2004) thus activating NF-κb and promoting EMT as well as promoting aggressiveness of breast cancer cells (Sullivan et al., 2009; Wu et al., 2009). An ever more complicated interplay between CAFs, cytokines and neoplastic cells has recently been proposed in breast cancers where,

due to the presence of an altered TA-ECM, an integrin-dependent activation of Src family kinases results in the increase of NF-κB activity which blocks the production of certain microRNAs such as Let-7. Under these conditions, IL-6 production is promoted resulting in the increased secretion of this pro-tumorigenic cytokine, which in turn induces or promotes a positive feedback in tumor cells (Iliopoulos et al., 2009). Moreover, activated myofibroblastic and cancer cells are known to remodel the stromal ECM by means of increased secretion of MMPs and urokinase-type plasminogen activator (uPA). These enzymes cleave the ECM molecules to release fragments that contain chemotactic properties called matrikines that activate leukocytes to also release inflammatory cytokines (Maquart et al., 2004; Silzle et al., 2004). For example, a special feature of MMP-2, -3 and -9 is that these proteases can increase the availability of IL-1b at the tumor microenvironment by cleavage of the pIL-1b (immature IL-1b) (Schonbeck et al., 1998). Also, analyses of co-cultures containing both breast cancer cells and CAFs have shown increases in stromal MMP-2 and MMP-9 expression (Singer et al., 2002). These observations concur with observations stemming from an immunohistochemical study where tissue arrays of breast cancer patients showed that intratumor stromal fibroblasts express MMP-2, -7, and -14, while fibroblast at the invasive front highly express MMP-9. What is more, this specific profile of stromal MMPs staining was found to be a predictor of future distant metastases occurrences (Del Casar et al., 2009). Another uncovered effect of released MMPs into the tumor stroma is the capacity of these molecules to promote a permissive environment that supports epithelial tumorigenic progression including the promotion of genomic alterations (Radisky, E.S. & Radisky, 2007). In the mammary glands of transgenic mice, the overexpression of MMP-3 has been shown to be sufficient to stimulate myofibroblastic presence, increased fibrosis, epithelial hyperplasia, and development of mammary carcinoma (Thomasset et al., 1998). What is more, mammary epithelial cells exposed to stromal MMP-3 showed activation of a genotoxic metabolic pathway, where the over expression of the spliced variant Rac1b produced DNA-damaging superoxide radicals and induced EMT (Radisky, D.C. et al., 2005). Interestingly, the epithelial genomic alterations induced by stromal MMPs *in vitro,* suggest a possible mechanism to understand the presence of areas with genomic imbalance patterns detected in histologically normal tissues adjacent to the tumor stroma (Ellsworth et al., 2004; Holliday et al., 2009).

## 8. Targeting fibroblasts as an anti-cancer therapy

Various aspects of the tumor microenvironment have been explored as putative therapeutic targets in the fight against cancer (Andre et al., 2010; Cukierman & Khan, 2010; Allen & Louise Jones, 2011). Since a desmoplastic reaction is an ECM component-rich substratum and some of the TA-ECM components are believed to be specific for discrete types of carcinomas, they constitute a promising basis for therapeutics (i.e., inhibitory functional antibodies). For example, in glioblastoma patients an iodine-131 radiolabeled anti-tenascin-C monoclonal antibody has produced encouraging results in phase II trials (Reardon et al., 2006). Similarly, the development of radioactive or bioactive molecules coupled to antibodies against TA-ECM specific EDB, the L-19 antibody, showed encouraging results when tested in various carcinomas (Kaspar et al., 2006). The TA-ECM has been considered as both a target as well as a means to attract anti-tumoral drugs. For example, as albumin binds efficiently to the TA-ECM protein osteonectin (also known as SPARC), known to be upregulated in a plethora of cancer stromas and often associated with bad prognosis (Tai &

Tang, 2008), paclitaxel delivered through nanoparticles conjugated to albumin (nab-paclitaxel) are being tested (Vishnu & Roy, 2010; Robert et al., 2011; Volk et al., 2011). Moreover inhibition of the serine protease activity of the CAF specific fibroblast activation protein has been suggested as a therapeutic target in a plethora of cancers including breast (Mersmann et al., 2001). In fact, antibodies against fibroblast activation protein induced a marked decrease in desmoplastic collagen I expression resulting in an increased (up to 70%) increment in chemotherapeutic drugs uptake (Loeffler et al., 2006). Therefore, it is not surprising that fibroblast activation protein has been suggested as a tumor targeting molecule for the delivery of peptide protoxins (amongst others) thus diminishing non-tumoral side effect toxicities (LeBeau et al., 2009).

Pro-inflammatory molecules have also been used as effective targets. For example TNF-α antagonists have been shown to have good results preventing disease acceleration in a considerable number of breast cancer patients (Madhusudan et al., 2004; Brown et al., 2008). The SDF-1α/CXCR4 chemokine axis has been proposed as a general target for anticancer strategies (Guleng et al., 2005), and recently a compound derived from marine organisms that blocks CXCR4 has been shown effective as well (He et al., 2008). Antibodies blocking the TGF-β signalling pathway have been developed and showed promising synergistic effects when added to known chemotherapeutics and, thus, have been regarded as anti angiogenesis-depending tumor stromal agents in breast cancer (Takahashi et al., 2001). Finally, it was recently shown that eliminating pro-tumorigenic macrophages in pancreas causes desmoplastic shrinkage and subsequent tumor stalling (Beatty et al., 2011). We believe that these types of treatments, together with similar novel ones, could provide increased hope in the common fight against breast cancers.

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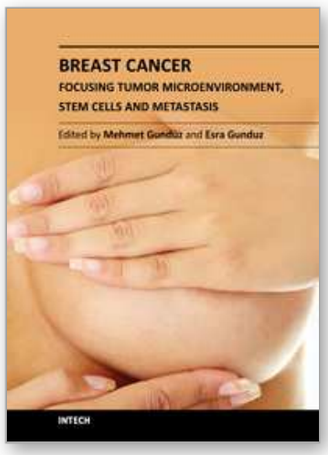


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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed characteristics of breast cancer cell, role of microenvironment, stem cells and metastasis for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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