

REVIEW

The contribution of dynamic stromal remodeling during mammary development to breast carcinogenesis

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Abstract

Breast cancer is a heterogeneous disease whose prognosis varies depending upon the developmental stage of the breast tissue at diagnosis. Notably, breast cancers associated with pregnancy exhibit increased rates of metastasis and poorer long-term survival compared to those diagnosed after menopause. However, postmenopausal breast cancers associated with obesity exhibit a more aggressive behavior and confer decreased overall patient survival compared to those diagnosed in non-obese individuals. Since the mammary gland is a dynamic tissue that undergoes significant changes throughout a woman's lifetime, especially during pregnancy and following menopause, we present evidence to support the notion that changes occurring throughout development within the mammary stromal compartment may account for some of the biological differences in breast cancer subtypes and behaviors.

Introduction

Numerous factors are implicated in contributing to lifetime risk of developing breast cancer, including age, family history, age of menarche, age of menopause, and parity [1]. In addition to the multiple etiological factors that contribute to breast cancer risk, breast cancer is a disease with a wide spectrum of genetic alterations and phenotypic heterogeneity.

Breast cancers diagnosed in premenopausal women tend to be clinically unlike those diagnosed in the years following menopause. They are typically estrogen receptor negative (ER-), diagnosed at a higher stage, and

often metastasize [2-5]. Premenopausal breast cancers can be categorized into hereditary breast cancers, including those diagnosed in women with mutations in the *BRCA1* or *BRCA2* genes, or non-hereditary breast cancer [3]. Pregnancy-associated breast cancer (PABC) is a subclass of premenopausal breast cancer that is diagnosed during pregnancy or following pregnancy [6-9]. Currently there is no consensus on the time frame of PABC diagnosis. Some researchers and clinicians limit PABC to the diagnosis of cancer during pregnancy while others include cases diagnosed within 10 years following pregnancy. When compared to non-PABC cases, women diagnosed with PABC are typically diagnosed at a later stage, are commonly ER-, and also have a worse prognosis [8,10-13].

In contrast, breast cancers diagnosed following menopause are predominantly ER-positive (ER+), respond better to current therapies, and confer an overall better patient prognosis, except for breast cancers diagnosed in obese individuals [14,15]. In postmenopausal but not premenopausal women, obesity is linked with a further increased risk of developing breast cancer. These cancers are diagnosed at a later stage, are more aggressive tumors and exhibit a worse overall patient survival rate [16,17].

The molecular and cellular differences between premenopausal and postmenopausal breast cancers remain largely unknown. In principle, the cellular origins of premenopausal and postmenopausal cancers might differ. Alternatively, it could be that the inherent genetic or epigenetic alterations sustained within the same epithelial target population differ depending on the developmental stage or age of the breast epithelium. However, since there are substantial stromal and hormonal differences within premenopausal breast tissues compared to postmenopausal tissues, it is highly plausible that the influences of the microenvironment may also be equally important in the etiology of these different diseases. In this review, we will discuss the changes that occur throughout mammary gland development and focus on how differing stromal microenvironments might promote the formation of different subtypes of breast cancer.

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Premenopausal breast cancer: pregnancy-associated Overview

It is well established that one full term pregnancy reduces a woman's lifetime risk of developing breast cancer [18-21]. However, the extent of this protection is dependent upon age of the first pregnancy. Pregnancy before the age of 20 confers the greatest protection, but for each year that pregnancy is delayed, there is a 3.5% increase in breast cancer risk [22]. Furthermore, women who delay childbearing until after age 35 are not protected from breast cancer; rather, they are actually at an increased lifetime risk of developing breast cancer compared to nulliparous women [23,24]. The increasing trend to delay childbearing has resulted in an increase in the diagnosis of PABC cases [13]. Since the diagnosis of PABC is predicted to increase, we will focus our discussion of premenopausal breast cancers on PABC in this review.

Stroma of pregnancy and lactation

The breast mesenchyme is a complex connective tissue composed of heterogeneous cell types, including fibroblasts, adipocytes, immune cells, endothelial cells, pericytes, nerve cells and acellular matrix components, such as collagen I, III, IV, proteoglycans, and glycoproteins [25]. During pregnancy, there is significant remodeling of the breast stromal tissue to accommodate the needs of the expanding epithelium. This remodeling includes the generation of new blood vessels (angiogenesis), infiltration of immune and inflammatory cells, fibroblast reorganization and the loss of lipid droplets within adipocytes [26,27], all of which are necessary to supply nutrients and cues to the changing epithelial demands but may contribute to the development of breast cancer [28,29].

In addition to the extensive stromal remodeling occurring in the mammary gland during pregnancy, there are drastic increases in circulating hormones, production of localized growth factors, and substantial expansion of the epithelial tree. Since breast carcinoma cells that express ER proliferate faster in response to gestational hormones, one hypothesis to explain the transient increase in breast cancer risk following pregnancy is the effect of systemic hormones such as estrogen and progesterone, both of which are greatly elevated during pregnancy, on promoting the growth of initiated cancer cells. However, most PABCs lack appreciable expression of either the ER or progesterone receptor [30,31]. This important observation suggests that if hormones like estrogen or progesterone are involved in promoting breast cancer following pregnancy, they may not be doing so through direct binding to cognate receptors expressed by breast epithelial cells.

In fact, recent studies using a xenograft model of PABC, in which tumor cells lacked expression of ER and progesterone receptor, demonstrated that the stroma

played an active role in promoting ER- tumor growth in response to systemic hormones [32]. In response to treatment with exogenous estrogen, bone marrow derived macrophages, immune cells and fibroblasts, as well as non-bone marrow derived fibroblasts, adipocytes, pericytes and endothelial cells, were all recruited to the stroma at sites of angiogenesis and tumor growth, resulting in enhanced tumorigenesis. The authors concluded that estrogen enhanced growth of tumors by influencing the physiology of the host tissue rather than direct effects on the carcinoma cells.

Although abundant in the non-pregnant mammary gland, adipocytes begin to lose their lipid content and become less visible during late pregnancy and represent a small proportion of the overall gland by lactation. Despite this remarkable change in adipocyte content and proportion, the precise role of adipocytes in normal breast development remains unclear. The role of the adipocyte in premenopausal breast cancer is also understudied. As we will discuss below, obesity is a risk factor specifically for postmenopausal women [33], and as such, the majority of research conducted on adipocytes and cancer is in postmenopausal women. However, new evidence suggests that leptin, a cytokine secreted by adipocytes, can stimulate breast cancer growth in both estrogen-dependent (ER+) and estrogen-independent (ER-) cells [34] and may, therefore, also be important for the pathogenesis of premenopausal breast cancer.

Another cell type recruited to the mammary gland during pregnancy and lactation are macrophages. They are recruited from the bone marrow in response to the secretion of colony stimulating factor-1 (CSF-1) and associate with the elongating ducts during puberty and the lobulo-alveoli in pregnancy [35]. CSF-1 regulates the proliferation, survival and migration of macrophages [36]. Interestingly, mice lacking CSF-1 exhibit decreased numbers of recruited macrophages and display precocious development of lobulo-alveolar structures by mid-pregnancy, increasing further on day 18 of pregnancy (twice the normal size). Restoration of CSF-1 levels in these mice restored normal numbers of macrophages and normal tissue architecture, suggesting that macrophages alone are not sufficient for proper mammary gland development. CSF-1 may also contribute to the aggressive nature of ER-negative breast cancer cells. Use of blocking antibodies that specifically inhibit the receptor to CSF-1 in an animal model of aggressive breast cancer reduced tumor cell invasion *in vivo*, indicating that the paracrine interactions between host macrophages and breast cancer cells are involved in tumor cell invasion [37].

Given the extensive stromal remodeling occurring in the mammary gland during pregnancy, there are many possible factors that could fuel tumor growth. Further research will be necessary to fully understand the role

and recruitment of the different cell types that are involved during this stage of development. Further insight into the cellular and molecular factors that regulate stromal development might also provide a greater understanding of how these cells participate and promote cancer formation and progression.

Stroma of post-lactational involution

Upon weaning, considerable stromal remodeling is required for proper regression of the epithelium during post-lactational involution. This stage is characterized by recruitment of immune cells, regression of the expanded vasculature, degradation of extracellular matrix (ECM) and the re-appearance of lipid filled adipocytes [27,38]. The first stage of post-lactational involution is directed by loss of suckling, resulting in milk stasis, and is characterized by the apoptosis of epithelial cells. The accumulation of milk in the epithelial cells stimulates the release of both leukemia inhibitory factor (LIF) and transforming growth factor β 3 (TGF β 3) from the epithelium in the mammary gland. LIF expression levels peak in the mammary gland during the first phase of involution, resulting in a significant increase in epithelial cell apoptosis [39,40]. Epithelial cell apoptosis is also caused by the induction of TGF β 3 in response to milk stasis. Other cytokines are upregulated during post-lactational involution, such as FasL [41], IL-6 [42], and IL-10 [43]. Inhibition of any of these factors delays the onset of involution. Mice deficient in TGF β 3 also exhibit a delayed onset of apoptosis during post-lactational involution, suggesting it is a requisite factor for epithelial cell apoptosis in this phase of mammary gland development [44]. Indeed, the onset of post-lactational involution is accelerated by its premature expression. Additionally, the upregulation of a number of cell death pathways is also important for the first phase of post-lactational involution. p53, bax and bcl2 expression are all necessary components for the proper timing of the first phase of involution [45-47].

The second, irreversible phase of post-lactational involution is characterized by the collapse of glandular tissue structure and stromal remodeling changes that parallel the molecular and cellular changes associated with wound healing. For example, matrix metalloproteinase (MMP) expression becomes elevated in the mammary stroma around day 4 of involution, resulting in a multitude of cellular responses. MMPs degrade the basement membrane and the surrounding ECM, resulting in the breakdown of the matrix components as well as the release of ECM-embedded cytokines such as TGF β , IL1- β , and TNF α [48]. This destabilization of the epithelial cells may cause detachment-induced apoptosis (anoikis) and further regression of the expanded lobuloalveoli [49].

As epithelial cells are systematically removed from the mammary gland, adipocytes begin to refill with lipid and repopulate the stromal fat pad. Interestingly, MMP3, which is required for proper adipocyte maturation [50], is increased over 50-fold during post-lactational involution when compared to pregnant or lactating mammary glands. The precise cell type in the stroma that produces MMP3 has not been determined, nor has the precise role of MMP3 been fully elucidated. In fact, MMP3 knockout mice exhibit accelerated involution due, in part, to the rapid repopulation of adipocytes in the gland. Moreover, inhibition of MMP3 through overexpression of TIMP1 also accelerated the repopulation of adipocytes following involution. These mice contained approximately 40% more unilocular adipocytes when compared to control mice [50]. However, it is surprising that MMP3 transgenic mice also exhibit premature involution [51]. This latter observation could be reconciled by the fact that premature disruption of basement membrane integrity by any ECM-degrading enzyme could accelerate mammary epithelial cell death.

The elevated levels of MMP3 expression during post-lactational involution are also attendant with elevated entactin and platelet/endothelial cell adhesion molecule (PECAM) expression; entactin is enriched in the basement membrane of adipocytes, while PECAM is expressed by endothelial cells in capillaries and blood vessels. The synchronized expression of MMP3, entactin and PECAM indicates the orchestrated nature of stromal cell remodeling: mature adipocytes are repopulating the involuting mammary gland at the same time that new blood vessels are forming, allowing contact between endothelial cells and adipocytes.

Consistent with the notion that mammary gland involution mimics tissue remodeling associated with wound healing, it is not surprising that various types of immune and inflammatory cells infiltrate the mammary gland during involution. Immunohistochemistry of involuting murine mammary glands indicates that leukocytes, neutrophils, macrophages and plasma cells are abundant [52]. These cells are thought to play a role in the homeostasis of the normal mammary gland by actively suppressing inflammation but further research is necessary to confirm their role in involution.

The breast tissue microenvironment during post-lactational involution may also contribute to an increase in risk of PABC [53]. As discussed above, the mammary gland undergoes dramatic physical remodeling after lactation and many of the steps required for this process provide an ideal environment for breast cancer growth and progression. Co-injection of MDA-MB231 cancer cells with extracellular matrix derived from involuting mammary tissues resulted in a higher rate of metastasis to the lung, liver and kidney [53]. Tumors grown with the

involuting matrix exhibited increased angiogenesis and contained higher levels of vascular endothelial growth factor (VEGF). Additionally, ECM isolated from involuting mammary glands contained elevated levels of activated MMP2, 3, and 9 when compared to the matrix isolated from nulliparous glands [54], further explaining the increase in metastasis and elevated tumor VEGF levels.

The changes in extracellular matrix within the involuting mammary tissues are mediated, in part, by macrophages that are actively recruited to the gland. In breast cancer tissues, recruited macrophages correlate with early relapse and decreased patient prognosis [55]. These cells secrete pro-angiogenic cytokines such as VEGF, TNF α , IL6, and granulocyte colony stimulating factor, all of which have been suggested to promote angiogenesis [56]. In fact, macrophage infiltration preceded angiogenesis in a mouse model of human breast cancer and failure to recruit macrophages delayed the angiogenic switch and subsequent tumor progression [57]. Given the important role of macrophages in tumor formation and progression, the recruitment of macrophages during both pregnancy and involution of patients afflicted with PABC may enhance pre-neoplastic changes that have already taken place in the breast.

Postmenopausal breast cancer

Overview

Breast cancer incidence increases with age, but plateaus at a time that coincides with the onset of menopause [58]. When stratified for ER status, ER- breast cancer incidence plateaus following menopause while the incidence of ER+ tumors continues to rise [5]. Moreover, there is a further increased risk of developing ER+ breast cancers in postmenopausal women with a body mass index greater than 30 [59,60]. Indeed, postmenopausal breast cancers (obesity-associated or otherwise) are generally ER+ and respond to anti-hormone therapies [61,62]. This increased incidence of ER+ breast cancers has been attributed, in part, to the increased levels of estrogen produced in fat depots [63]. Androgens which are primarily of adrenal origin remain constant following menopause, but are metabolized to estrogen in peripheral adipose tissues by aromatase (reviewed in [64]). Thus, the increased levels of local estrogen [65] might lead to the overall increased risk of breast cancer. However, breast stromal tissue is a reservoir of subcutaneous fat. This adipose tissue has largely been ill-defined in the study of breast cancer, and in the background of the obese and post-menopausal state, the change in tissue constitution may have a profound effect on breast cancer development and progression. In addition, many other changes are taking place in the breast following menopause that could equally participate in promoting and accelerating tumor formation [66].

Stroma of lobular involution

In humans, menopause is characterized by the cessation of estrogen and progesterone production by the ovaries and the end of menstruation. These systemic endocrine changes coincide with an irreversible process that has been termed lobular involution in which the number and size of the lobules are reduced [67]. Furthermore, the number of ER-expressing breast epithelial cells increases dramatically: only approximately 10% of epithelial cells within lobules and ducts of premenopausal tissues express ER, while nearly 90% of cells within involuted postmenopausal breast tissues are ER+ [68]. In addition to epithelial attrition, the intralobular stroma of breast tissue is replaced with dense collagen connective tissue [69], and interlobular stroma is replaced with adipose tissue [70].

Mammographic density (MD) has routinely been used to measure the changes in tissue composition following menopause. Postmenopausal breast tissues are associated with lower MD, indicative of increased fatty tissue, while areas that have a higher density, representing the fibroblastic and epithelial portions of the breast, are greater in premenopausal breast tissues [71,72]. Breast tissue composition as measured by MD is an important risk factor for the development of breast cancer [73,74]. Involvement of 60% or more of the breast tissue with mammographically dense tissue confers a three- to five-fold increased relative risk for breast cancer, similar to the increase in risk conferred by having an inherited mutation in the breast cancer gene *BRCA1* [75,76].

Changes in the ECM composition in postmenopausal breast tissue may contribute to an increase in breast cancer risk as measured by an increase in MD. In a study of mostly postmenopausal women, patients with high MD had an increase in collagenous stroma [77] as well as an increase in the expression of lumican and decorin [78]. Fibrillar collagens are one of the most important ECM proteins in determining stromal architecture. Stromal integrity, including fibril spacing, is determined by lumican and decorin; therefore, an increase in MD similar to that seen in breast cancer patients may reflect changes in the composition of ECM proteins and mammary stroma. These changes may influence early events in tumorigenesis; however, further experiments are needed to determine possible mechanisms.

Several studies have been conducted to correlate genetic and environmental factors with breast MD. In particular, it has been suggested that the increased risk of breast cancer due to hormone replacement therapy in postmenopausal women is attributable, in part, to its role in increasing MD [79]. Consistent with this notion, recent experiments have demonstrated that systemic estrogen was sufficient to increase tissue stromalization, cellular density, and angiogenesis [32]. Moreover, women

treated with tamoxifen, a selective ER modulator, exhibit decreased MD [80]. Thus, decreasing circulating estrogens or inhibiting ER activation may have dual roles in inhibiting breast cancer progression by decreasing the proliferative potential of expanded ER+ breast epithelial cells, which would directly reduce the potential growth of premalignant or malignant cells, and by decreasing stromal cellularity and fibrous density, which may reduce the tumor-promoting effects of the surrounding micro-environment. However, additional clinical and experimental studies are needed to further understand the molecular and cellular connection between systemic hormones, MD and breast cancer.

Stroma associated with obesity

Age-related menopause is associated with increased visceral adiposity. Women who are obese are at a further increased risk of developing breast cancer [60,61]. Breast cancers associated with obesity are diagnosed at a later stage [81] and are more aggressive [82-84] when compared to breast cancer diagnosed in non-obese women. While the majority of breast cancers associated with obesity are ER+, some of them are ER-.

Adipose tissue in both the lean and obese state appears to have a significant impact on the development of breast cancer and its prognosis. Adipocytes are potent endocrine cells that produce a variety of hormones and growth factors that differ between the lean and obese state. It is now recognized that the infiltration and pro-inflammatory activation of immune cells in adipose tissue underlie obesity complications [85-87]. The obese state is accompanied by a dramatic influx of macrophages in the adipose tissue, resulting in an inflammatory state that is thought to promote local and systemic insulin resistance [86,88-90]. The influx of macrophages is thought to result, in part, from increased expression of monocyte-chemoattractant protein-1 (MCP-1) in obese adipose tissue, which is well known to recruit monocytes. Consistent with this notion, knockout of MCP-1 or its receptor, CCR2, in mice reduces macrophage infiltration, and protects against obesity-induced inflammation in adipose tissue [86,88,89,91].

Manifestations of the inflammatory state found in adipose tissue with obesity include increased expression of cytokines and factors such as TNF α , TGF β , IL1 β and hepatocyte growth factor [92,93]. Chronic inflammation itself is a potent tumor promoter of many cancers, including breast cancer [94], and both TGF β and hepatocyte growth factor have been implicated in the development of breast cancer [92,93,95].

The mechanisms by which inflammation occurs in adipose tissue remain unclear. However, it has been demonstrated that adipocytes release factors that can activate macrophages, resulting in the release of

Table 1. Clinical characteristics of developmental stage-specific breast cancers

Stage	Increased risk (tumor subtype)*	Clinical characteristics
Pregnancy	ER-	High stage diagnosis High grade Often metastatic
Postmenopause	ER+	Lower grade at diagnosis Respond to anti-hormone therapies
Postmenopause with obesity	ER-	High stage diagnosis Poor patient survival rate

*According to [5,10,30].

cytokines [96,97]. One obvious candidate for activating macrophages is fatty acids. Adipocytes release fatty acids as a byproduct of lipolysis. It has been demonstrated that saturated fatty acid and endotoxin can both bind and activate toll receptor 4 (TLR-4) on macrophages [98,99]. Palmitate is one of the major fatty acids that circulate in the body [100]; thus, release of palmitate in an obese state can bind and activate TLR-4, resulting in release of cytokines such as TNF α . The release of TNF α then acts in a paracrine and autocrine fashion on adipocytes to increase rates of lipolysis [101], resulting in further release of fatty acids and activation of macrophages. Thus, macrophages and adipocytes interact in adipose to promote a cycle of inflammation and lipolysis.

Leptin is another hormone that is predominantly produced by adipose tissue. Its expression levels correlate with body fat and its levels are particularly high in obese women [102]. Secretion of leptin creates a microenvironment that is favorable to an aggressive breast cancer. It stimulates tumor cell growth and invasion as well as angiogenesis [103]. High levels of circulating leptin, similar to those seen in obese women, cause an increase in breast cancer proliferation through the activation of the mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling pathways [104].

Adipocytes also secrete adiponectin (APN), whose levels have been inversely correlated with obesity [105] and breast cancer risk [106], suggesting that the increased risk of developing breast cancer in obese postmenopausal women may be due to a reduction in APN levels. Cytokines such as TNF α have been implicated in the obesity-associated reduction in adipocyte expression of APN and increased release of adipocyte fatty acids. In the obese state, there is a reduction of APN and increased release of fatty acids in the blood, which are thought to be critical in the development of obesity-associated insulin resistance, and insulin resistance itself is implicated in cancer development.

Table 2. Microenvironmental characteristics of developmental stage-specific breast cancers

Stage	Stromal changes	Growth factors/matrix
PABC	Macrophage recruitment, inflammation, angiogenesis, adipocyte remodeling	ECM degradation, MCP-1, CSF-1, IGF, HGF, TGF beta, systemic estrogen
Postmenopause	Aromatase, epithelial atrophy, stromal replacement, adipocyte remodeling	Local estrogen, lumican, decorin, collagen
Postmenopause with obesity	Macrophages, inflammation, angiogenesis, aromatase, reactive adipose	IGF, HGF, MCP-1, TGF beta, local and systemic estrogen

CSF-1, colony stimulating factor-1; ECM, extracellular matrix; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor 1; MCP-1, monocyte-chemoattractant protein-1; PABC, pregnancy-associated breast cancer; TGF, transforming growth factor.

Tumors generated in a mouse mammary tumor virus promoter-driven polyoma middle T oncogene (MMTV-PyMT) model in an APN^{-/-} background show reduced tumor growth only at the early stages of tumor development due to impaired tumor angiogenesis, consistent with the role of APN in blood vessel remodeling [98,107]. As the tumor progresses, tumor burden significantly increases in APN^{-/-} mice due to a mobilization of endothelial precursor cells and subsequent restoration of impeded angiogenesis [107].

Collagen VI is also abundantly produced within adipose tissue [108] and upregulated during the progression of mouse mammary tumors [109]. MMTV-PyMT mice in a collagen VI^{-/-} background have significantly reduced tumor burden and increased tumor latency compared to MMTV-PyMT collagen VI^{+/+} mice. The promotion of mammary tumor growth by adipocyte-derived collagen VI is mediated by Akt, β -catenin, and cyclin D1 signaling [110]. Since both APN and collagen VI null mice display delayed tumor development in an MMTV-PyMT background, these studies suggest that adipocyte-derived factors may influence the initiation and/or early progression of breast tumors. They also provide evidence that may explain the increase in risk of postmenopausal breast cancer in obese individuals.

Recent studies have also revealed that stromal stem cells isolated from fat depots in obese mice promote angiogenesis and tumor progression [111]. This suggests that in addition to the changes in cytokine production, the cellular constituents of adipose tissue are different from those of typical fat depots. However, it is unclear what molecular and epigenetic differences exist between stromal stem cells from obese and non-obese mice; thus, additional studies need to be designed to understand the role of these cells in postmenopausal associated obesity.

Conclusion

There are distinct differences in the composition of the stroma at different stages of breast development, which correlate with the biological characteristics of breast cancer subtypes and patient prognosis. PABCs have different characteristics from breast cancers diagnosed in non-obese postmenopausal women, which also are

somewhat different from those diagnosed in postmenopausal obese women (Table 1). For example, PABC and postmenopausal breast cancer associated with obesity are both diagnosed at a later stage, do not respond well to current therapies and confer an overall poorer patient prognosis. Analysis of the mammary microenvironment during pregnancy as well as the microenvironment of the adipose tissue associated with obesity reveals similarities that may account for these parallels (Table 2). Both involve the release of cytokines from adjacent stromal cells, thereby creating an inflammatory microenvironment that promotes angiogenesis, matrix remodeling and tumorigenesis. Macrophages are recruited into the mammary gland during remodeling associated with pregnancy as well as to the breast in postmenopausal obese women. Factors promoting angiogenesis are prevalent in both the involuting mammary gland as well as in the postmenopausal obese gland. The factors secreted by stromal cells that promote angiogenesis in the two stages, however, are not identical. For example, in the involuting mammary gland, recruited macrophages secrete pro-angiogenic factors such as VEGF and IL-6, while in the postmenopausal obese mammary gland, adipocytes secrete the pro-angiogenic hormone leptin and decrease the secretion of anti-angiogenic adiponectin. It is not surprising that stromal cells in different stages of development would secrete different factors, but it is interesting to suggest that in each case the stroma is responsible for promoting tumors with similar clinical and biological characteristics.

Current therapies target primarily the carcinoma cells; however, many women develop recurrent disease and/or distant metastases following treatment. Given the supportive and instructive role of the stroma in cancer progression, identifying therapeutics tailored to both the stroma and epithelium may have more clinical efficacy for prevention of local recurrence and prevention of metastases.

Abbreviations

APN = adiponectin; CSF = colony stimulating factor; ECM = extracellular matrix; ER = estrogen receptor; IL = interleukin; LIF = leukemia inhibitory factor; MD = mammographic density; MMP = matrix metalloproteinase; PABC = pregnancy-associated breast cancer; PECAM = platelet/endothelial cell adhesion molecule; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

Competing interests

The authors declare that they have no competing interests.

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