Adipocyte is a non-trivial, dynamic partner of breast cancer cells

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ABSTRACT While the participation of adipocytes is well known in tissue architecture, energy supply and endocrine processes, their implication during natural cancer history is just beginning to unfold. An extensive review of the literature concerning the impact of resident adipocytes on breast cancer development/progression was performed. This review provides in vitro and in vivo evidence that adipocytes located close to invasive cancer cells, referred to as cancer-associated adipocytes (CAAs), are essential for breast tumor development/progression. Their deleterious function is dependent, at least partly, on their crosstalk with invasive cancer cells. Indeed, this event leads to dramatic phenotypic and/or functional modifications of both cell types. Adipocytes exhibit delipidation and acquire a fibroblast-like shape. In parallel, cancer cell aggressiveness is exacerbated through increased migratory and invasive properties. Moreover, obesity is currently a sign of poor prognosis in human carcinomas. In this context, a high number of “obese” resident adipocytes might be predicted to be detrimental. Accordingly, there are some similarities between the molecular alterations observed in hypertrophied adipocytes and in CAAs. How adipocytes function to favor tumorigenesis at the molecular level remains largely unknown. Nevertheless, progress has been made recently and molecular clues are starting to emerge. Deciphering the cellular and molecular mechanisms behind the adipocyte-cancer cell heterotypic crosstalk is of great interest since it might provide new targets for improving diagnosis/prognosis and for the design of innovative therapeutic strategies. They might also improve our understanding of the relationship between obesity/metabolic disorders and cancer risk and/or poor patient outcome.

KEY WORDS: adipocyte, breast cancer, metabolism, obesity, diabetes

Introduction

It is now well established that the tumor microenvironment actively participates in breast cancer progression (Basset et al., 1990; Jodelet et al., 2006; Kessenbrock et al., 2010). The connective tissue, also named stroma, is a complex structure composed of an extracellular matrix (ECM), and a variety of cell types including endothelial cells, inflammatory cells, fibroblasts, fibroblast-like cells and adipocytes. The present review is restricted to the latter cell type, and more precisely to the impact of mammary gland resident adipocytes on breast cancers. The first part focuses on cancer-associated adipocytes (CAAs) as local regulators of epithelial cancer cell growth, local invasion and/or metastases in carcinogenesis. Although the nature of interplay between adipocytes and cancer cells remains at present largely unknown, investigations in the field over the last 10 years indicate that the adipocyte occupies a central place in this disease. The morphological and functional alterations

Abbreviations used in this paper: Ad, adipocytes cultured alone; AdBCC, adipocytes cultured in the presence of breast cancer cells; BCC, breast cancer cells cultured alone; BCCAd, breast cancer cells cultured in the presence of adipocytes; CAA, cancer-associated adipocytes; CAF, cancer-associated fibroblasts; ECM, extracellular matrix; ER, estrogen receptors; MMP, matrix metalloproteinase.

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in order to better understand the particular place of the adipocyte in breast tissues. The fully differentiated breast (after the first gestation-lactation cycle) is composed of two cell compartments (Fig. 1). The epithelial compartment is constituted by the gland (strictly speaking) composed of branched ducts and lobuloalveolar differentiated units able to produce milk proteins when necessary. This gland is embedded in the connective tissue compartment commonly referred to as the mammary fat pad (Hovey and Aimo, 2010) since it mainly contains adipose tissues. In man, the mammary adipose depot is composed of fat lobules involving 100-1000 mature white adipocytes and stromal-vascular cells, blood vessels, lymph nodes and nerves.

In a general manner, each adipocyte is itself encapsulated by a basement membrane. Once cells are committed pre-adipocytes, the original ECM is remodeled. Indeed, adipogenesis is characterized by the conversion of a fibronectin-rich matrix to a basement membrane (Gregoire, 2001). During adipocyte differentiation, there is an increase in the secretion of basement membrane components such as type V and VI collagens (Nakajima et al., 2002) (Iyengar et al., 2005). Thus, in a general fashion, normal mature adipocytes are separated from epithelial cells by basement membranes, limiting therefore the possibilities of heterotypic cross-talk between the 2 cell types. In the normal breast, this equilibrium is dramatically disrupted during the postweaning mammary gland involution. At this time, there is an intense restructuration of the gland and cells of the 2 compartments are mixed together within the ECM, as observed in invasive primary tumors (Lefebvre et al., 1992).

Thus, fat tissue represents an important component of the normal breast. This obvious proximity of adipocytes and epithelial cells in the breast allows one to hypothesize that adipocytes might play a role during tumor progression.

**Histological evidence that adipocytes participate in breast cancer**

The role of adipocytes during cancer invasive processes has until recently been neglected. This lapse was mainly due to the fact that adipocytes disappear rapidly via the desmoplastic response of connective tissues during the early invasive steps. Thus, histological images of breast tumor biopsies contain very few adipocytes, or most often are totally devoid of adipocytes. However, from the breast anatomy (see above and Fig. 1), it might be expected that early local tumor invasion occurs in the immediate proximity of pre-adipocytes and/or adipocytes, allowing heterotypic cross-talk between invasive cancer cells and adipocytes, even if this event is ephemeral. In this context, histological sections of human breast carcinomas show that dynamic desmoplastic events involving adipocytes occur at the tumor invasive front located at the periphery of primary tumors (Fig. 2) (Andarawewa et al., 2005) (Dirat et al., 2011). Indeed, this area is devoid of fully constituted stroma and exhibits a high ratio...
of adipocytes to fibroblasts. Interestingly, a reduction in adipocyte size compared with those observed at a distance is observed. This size reduction of adipocytes implies lipolysis, modification of lipid droplets and modification of adipocyte-related basement membrane and the ECM. By contrast, at the tumor center, an extremely high fibroblast-like cell:adipocyte ratio is observed in the stroma surrounding cancer cells. Thus, one of the most obvious morphological changes that occur consecutively to cancer cell invasion concerns adipocytes, pointing-out the notion of CAAs. It is therefore clear that CAA-cancer cell heterotypic crosstalk occurs, at least in invasive primary tumors, when both cell types are physically close during the dynamic tumor progression processes. This event leads to a kind of “adipocyte dedifferentiation” and ultimately to an accumulation of fibroblast-like cells. Tumor progression may thus depend on the CAA “activation” induced by invading cancer cell stimuli. Moreover, these data strongly support the concept that cancer-associated fibroblasts (CAFs) might at least partly derive from CAAs (Andarawewa et al., 2005; Motrescu and Rio, 2008). Interestingly, numerous studies have shown that peritumor fibroblasts provide structural and biochemical support for cancer development (Ronnov-Jessen et al., 1995)(Kessenbrock et al., 2010).

Thus, the adipocyte is an excellent candidate to play a key role in inducing tumor behavior through heterotypic crosstalk with invasive cancer cells. In turn, signaling pathways critical for cancer cell survival, tumor growth and/or metastasis development may be inadvertently activated.

**In vivo evidence that adipocytes favor tumor progression**

Does CAA-cancer cell cross-talk have a pejorative impact on tumor progression? Numerous recent clinical studies have evaluated the prognosis value of local adipose tissue invasion by cancer cells at the tumor margin. Most of the data report a positive correlation with poor patient outcome. This is the case not only for breast cancers (Kimijima et al., 2000; Yamaguchi et al., 2008), but also for prostate, pancreas, kidney and colon cancers (Rio, 2011). Experimental data report a similar pejorative impact of adipocytes on cancer progression. It was shown that an adipocyte-rich environment facilitates SPI murine mammary carcinoma cell growth after subcutaneous injection in mice, and it was proposed that the adipose tissue exerts an estrogen-dependent positive regulatory effect on SPI (Elliott et al., 1992). The impact of the mammary fat pad in tumor development has also been extensively studied (Edwards, 2000). Moreover, adipose stromal cells have been shown to stimulate the migration and invasion of estrogen receptor (ER)-negative breast cancer cells in vitro and in vivo in a co-transplant xenograft mouse model. However, it should be noted that both the mammary fat pad and adipose stromal cells include both pre-adipocytes and/or adipocytes, as well as other cells like endothelial cells, that may interfere. An in vivo coinjection system using 3T3-L1 murine adipocytes and SUM159PT human breast cancer cells to recapitulate heterotypic crosstalk occurring in primary breast tumors has demonstrated that adipocytes favor tumorigenesis (Iyengar et al., 2003). Using a similar model, it has recently been shown that adipocytes also favor metastasis development. Indeed, tail vein injection of breast cancer cells previously co-cultured in the presence of adipocytes gives more lung metastases than breast cancer cells grown without adipocytes (Dirat et al., 2011).

Thus, clinical observations and in vivo experimental data strongly support a major function for mammary gland resident adipocytes in tumor progression.

**In vitro evidence that adipocytes favor cancer cell aggressiveness**

Because in vivo, several other local or systemic factors might interfere, in vitro cell models have been designed to uncover the intrinsic properties and functions of adipocytes in breast cancer. The relative influence of pre-adipocytes and mature adipocytes on various cancer cell lines have been studied by several laboratories. Mature adipocytes, but not pre-adipocytes, have been shown to promote the growth of breast cancer cells in collagen gel matrix cultures through cancer-stromal cell interactions (Manabe et al., 2003). More recently, a co-culture system in which adipocytes and breast cancer cells were separated by an insert to allow the diffusion of soluble factors, but not direct heterotypic cell-cell contact, was used to mimic the CAA-cancer cell crosstalk. The impact of this co-culture on both adipocytes and cancer cells was evaluated. As expected from previous histological studies (see above), dramatic morphological changes were observed in adipocytes co-cultured in the presence of breast cancer cells (Ad<sub>BCC</sub>) compared with those cultured alone (Ad). As observed at the invasive front of breast primary tumors, adipocytes became more elongated and exhibited a fibroblast-like phenotype with delipidation (Fig. 3). There was no obvious alteration in cancer cell morphology. However, adipocyte-primed cancer cells (BCC<sub>Ad</sub>) acquired new properties, notably an increased migration and invasive phenotype compared with cancer cells that had not “seen” adipocytes (BCC) (Fig. 4) (Dirat et al., 2011) (our unpublished results). Thus, this model satisfactorily recapitulates the invasive front of human breast tumors. These data indicate that soluble factors resulting from the adipocyte-cancer cell crosstalk impact both cell types. Indeed, adipocyte-derived secreted factors have been shown to promote breast cancer cell proliferation and
enzymes specialized in ECM remodeling. They have been shown to be involved at several steps of cancer development, and represent markers of poor prognosis in breast cancer (Basset et al., 1990; Jodele et al., 2006; Kessenbrock et al., 2010). MMPs are mainly paracrine factors which are expressed and secreted by connective tissue cells. Immunohistochemical analysis of the breast cancer invasive front shows that MMP11 (also named stromelysin-3) is expressed by CAAs at the proximity of invading cancer cells. In contrast, normal resting mature adipocytes are devoid of MMP11. Thus, cancer cells induce MMP11 expression in CAAs (Fig. 5). Interestingly, MMP11 has been shown to play a role in adipogenesis since it decreases pre-adipocyte differentiation. Moreover, in vitro addition of active MMP11 recombinant protein to the culture medium of mature adipocytes induces their “de-differentiation” (Andarawewa et al., 2005). Collectively, these data indicate that the negative regulatory function on adipogenesis of MMP11 is aberrantly restored during the early steps of local tumor invasion. MMP11 therefore participates in the accumulation of fibroblast-like cells that might in reality be pre-adipocytes or de-differentiated adipocytes, since these cells are morphologically indistinguishable from fibroblasts. Accordingly, at later points of invasive carcinoma development when the constituted stroma no longer contains adipocytes, MMP11 is restricted to a particular subpopulation of fibroblast-like cells that are not myofibroblasts (Fig. 5) (Andarawewa et al., 2005). Interestingly, the concept of “cancer cell-imprinted” fibroblasts which express MMP11 has been proposed in studies using CAFs and cancer cells isolated from human breast tumors (Wang and Tetu, 2002). Consistently, in the in vitro model described above, adipocytes co-cultured with cancer cells (Ad_{BCC}) exhibit an activated phenotype marked by MMP11 overexpression (Dirat et al., 2011 (our unpublished results). In addition to MMP11, MMP1 and MMP10 expression are also upregulated but by cancer cells (BCC_{Ad}) (Iyengar et al., 2003) (Kim et al., 2008). It cannot be excluded that some other MMPs might similarly be involved in adipocyte-cancer cell crosstalk as several MMPs contribute to adipogenesis as either positive or negative regulators (Andarawewa and Rio, 2008). Finally, the enzymatic plasminogen system is also involved, since the inhibitor of plasminogen activator (PAI1) is overexpressed in CAAs (Fig. 5) (Andarawewa et al., 2008). It was recently proposed that MMP11 inhibition may decrease the development of fibroblast-like cells that may be a new therapeutic target for breast cancer (Andarawewa et al., 2010).

Fig. 4. In vitro adipocyte-cancer cell crosstalk increases cancer cell aggressiveness. (A) Schemes of the coculture experiments. Breast cancer cells cultured in the presence (BCC_{Ad}) or in the absence (BCC) of adipocytes were further used to study their aggressive properties (migration, invasion, wound healing). (B) Photographs show cells penetrated through the membrane and present to its lower surface. BCC_{Ad} show increased cancer cell migration and invasion compared with BCC; wound healing is also higher for BCC_{Ad} than BCC. t = experiment timing in hours.

Molecular characterisation of the adipocyte-cancer cell crosstalk

To date, the molecular mechanisms responsible for the pejorative impact by in vivo/in vitro CAA/adipocyte-cancer cell heterotypic crosstalk have remained largely unknown. However, it might be hypothesized that they include paracrine pathways acting in both directions - from invasive cancer cells to adipocytes/CAAs, and from adipocytes/CAAs to cancer cells -. Moreover, adipocyte- or cancer cell-specific autocrine pathways might also be activated. The few results to date indicate that various biological processes are affected, including tissue remodeling, adipogenesis/energy metabolism, oncogenesis, inflammation and immune response.

ECM remodeling-related factors

There is some evidence that adipocyte ECM and ECM-related enzymes are modified, which is consistent with the dynamic modification in CAA morphology. Matrix metalloproteinase (MMPs) are enzymes specialized in ECM remodeling. They have been shown to be involved at several steps of cancer development, and represent markers of poor prognosis in breast cancer (Basset et al., 1990; Jodele et al., 2006; Kessenbrock et al., 2010). MMPs are mainly paracrine factors which are expressed and secreted by connective tissue cells. Immunohistochemical analysis of the breast cancer invasive front shows that MMP11 (also named stromelysin-3) is expressed by CAAs at the proximity of invading cancer cells. In contrast, normal resting mature adipocytes are devoid of MMP11. Thus, cancer cells induce MMP11 expression in CAAs (Fig. 5). Interestingly, MMP11 has been shown to play a role in adipogenesis since it decreases pre-adipocyte differentiation. Moreover, in vitro addition of active MMP11 recombinant protein to the culture medium of mature adipocytes induces their “de-differentiation” (Andarawewa et al., 2005). Collectively, these data indicate that the negative regulatory function on adipogenesis of MMP11 is aberrantly restored during the early steps of local tumor invasion. MMP11 therefore participates in the accumulation of fibroblast-like cells that might in reality be pre-adipocytes or de-differentiated adipocytes, since these cells are morphologically indistinguishable from fibroblasts. Accordingly, at later points of invasive carcinoma development when the constituted stroma no longer contains adipocytes, MMP11 is restricted to a particular subpopulation of fibroblast-like cells that are not myofibroblasts (Fig. 5) (Andarawewa et al., 2005). Interestingly, the concept of “cancer cell-imprinted” fibroblasts which express MMP11 has been proposed in studies using CAFs and cancer cells isolated from human breast tumors (Wang and Tetu, 2002). Consistently, in the in vitro model described above, adipocytes co-cultured with cancer cells (Ad_{BCC}) exhibit an activated phenotype marked by MMP11 overexpression (Dirat et al., 2011 (our unpublished results). In addition to MMP11, MMP1 and MMP10 expression are also upregulated but by cancer cells (BCC_{Ad}) (Iyengar et al., 2003) (Kim et al., 2008). It cannot be excluded that some other MMPs might similarly be involved in adipocyte-cancer cell crosstalk as several MMPs contribute to adipogenesis as either positive or negative regulators (Andarawewa and Rio, 2008). Finally, the enzymatic plasminogen system is also involved, since the inhibitor of plasminogen activator (PAI1) is overexpressed in adipocytes (Ad_{BCC}).

One of the ECM components that is altered is type VI collagen, a specific member of the soluble collagen family with predominant expression in the adipose tissue. Type VI collagen was shown to be up-regulated in adipocytes during tumorigenesis and to be critical for tumor progression due to effects of a alpha 3 chain C-terminal...
Tumor center

Invasion of estrogen receptor (ER)-negative breast cancer cells is especially interesting, it has been reported that the increase of migration and pro-inflammatory cytokines (IL-6, IL-1β) also overexpress by cancer cells following adipocyte-cancer cell crosstalk (Iyengar et al., 2008). Moreover, the in vitro recombinant MMP11-induced adipocyte “de-differentiation” is also associated with the downregulation at the transcriptional level of PPARγ and aP2 (Andarawewa et al., 2005). Moreover, CAAs have been shown to express abnormal levels of growth factors (IGF1, IGFβPs) and adipokines (leptin and adiponectin). There is increasing evidence that adiponectin and leptin, secreted by peritumor adipose tissues in several cancers including breast, are important (Miyoshi et al., 2006; Schaffler et al., 2007). Leptin appears to be a positive factor for tumor development and aggressiveness, while adiponectin protects against cancers.

Immune response and inflammation-related factors

A study profiling gene expression of breast cancer cells treated with adipocyte culture medium showed induction of several immune system-related genes (Kim et al., 2008). In vitro activated adipocytes co-cultured with cancer cells (AdCaco) also overexpress pro-inflammatory cytokines (IL-6, IL-1β) (Dirat et al., 2011). Interestingly, it has been reported that the increase of migration and invasion of estrogen receptor (ER)-negative breast cancer cells is dependent on adipocyte-secreted IL-6 (Walter et al., 2009).

Oncogenesis-related factors

Analysis of “adipocyte-primed” cancer cells (BCCAco) shows several modifications in gene expression patterns. The altered genes have been shown to be involved in various cellular functions but all are known to contribute to tumor development/progression.

Thus, cyclin D1, NFκB, cFos, ATF3, SOX9, A20 and IGF2 are overexpressed while E-cadherin is down-regulated (Iyengar et al., 2003) (Dirat et al., 2011). Thus, resident mammary gland adipocytes play an essential role during the first steps of the tumor desmoplastic response. Adipocyte/CAA-cancer cell crosstalk induces dramatic changes in the production of molecules able to potentially impact on cancer cell survival, proliferation and differentiation as well as invasive properties (Fig. 6).

Conclusion

Collectively, these data support the concept that crosstalk with adipocytes confers a selective advantage to invasive cancer cells. Adipocytes therefore participate in a kind of vicious tumor progression cycle initiated by the invasive cancer cells (Fig. 6) (Motrescu and Rio, 2008). Although some clues have started to emerge, most of the molecular mechanisms involved remain to be determined.

Do adipocyte/metabolic disorders impact on breast cancer development/progression?

Epidemiological evidence that obesity and insulin resistance/diabetes are detrimental for breast cancer patients

From the studies described above, an obvious concern is whether modifications in mammary resident adipocytes influence breast health. Normal adipocyte size heterogeneity is lost in obesity, and adipocyte hypertrophy (increase in cell size) often precedes hyperplasia (increase in cell number). Adipocyte hypertrophy results from excess triglyceride accumulation in existing adipocytes. Hyperplasia, referred to adipogenesis, results from the recruitment of new adipocytes from precursor cells in the adipose tissue, and involves the proliferation and differentiation of these pre-adipocytes (Greger, 2001). Several epidemiological studies have reported that large amounts of adipose tissues are closely associated with poor prognosis for breast cancer in obese post-menopausal women. It was proposed that elevated numbers of hypertrophied adipocytes might promote aggressive hormone-dependent breast cancers by increasing hormone synthesis (Manabe et al., 2003). Indeed, it is established that breast adipose tissue is an important site of estrogen production in post-menopausal women, and elevated estrogen biosynthesis from intratumor adipose tissue has been demonstrated (Kamat et al., 2002). This is dependent on aromatase, a key enzyme that is involved in peripheral estrogen aromatisation in the adipose tissue (Macedo et al., 2009). Moreover, several findings have indicated that mature human adipocytes possess estrogen receptors (ER), and that adipose tissue might itself be an estrogen-responsive tissue (Cooke and Naaz, 2004). However, more recent studies show that the poor prognosis for obese people with breast cancer is independent of menopause status, tumor stage, and tumor hormone status (Majed et al., 2008). Interestingly, emerging evidence suggest that host factors contribute to the occurrence of aggressive tumors in obese women, as defined by advanced stage, high grade and propensity to metastasize (Rose and Vona-Davis, 2009). In addition, it has been shown that hyperinsulinemia and type 2 diabetes are independent risk factors for poor prognosis in women with breast cancers (Duggan et al., 2010) (Gouveri et al., 2011).
Finally, weight gain in breast cancer survivors has been shown to be associated with adverse health consequences (Duggan et al., 2010). The pejorative effects of obesity are not restricted to breast cancer. Solid epidemiological data support the role of fat mass/distribution in the development of risk factors, morbidity and mortality in several types of cancers (Schaffler et al., 2007; Fair and Montgomery, 2009; Rio, 2011). A large American prospective analysis of the weight-cancer relationship has shown that excess body mass index (BMI) is the cause of approximately 14% of all cancer deaths in men and 20% in women aged 50 years or older (Calle et al., 2003). The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of a cancer-preventive effect for avoiding weight gain in several cancers (Vainio et al., 2002). A similar conclusion was drawn from a Shanghai Breast Cancer Study for breast cancer (Malin et al., 2005).

The main conclusions from epidemiological studies are that obesity as well as insulin resistance/diabetes influence cancer risk, tumor behavior and clinical outcome. Excess of fat tissues is detrimental for cancer patients regardless of organ. There is therefore great interest in understanding the mechanisms by which adipocytes contribute to carcinogenesis, since obesity/metabolic disorders are worldwide epidemic diseases.

“Obese” adipocytes and cancer cell-primed associated adipocytes (CAAs) show similar molecular modifications.

The clinical data call into question the potential molecular impact of excess of hypertrophied resident adipocytes on breast cancer development/progression. This topic is extremely difficult to explore, and very few data are available. Most concern circulating molecules. Indeed, in addition to their local function, it cannot be excluded that adipocytes/CAAs may also act systemically. In this context, it has been shown in vitro that several molecules expressed by CAAs following crosstalk with invasive cancer cells are secreted factors that might reach the circulation (see Fig. 6). Accordingly, breast cancer patients devoid of adipocyte/metabolic disorders exhibit molecular modifications in the blood, indicating that CAAs act via systemic route. In obese patients with breast cancer, we might expect obesity-dependent local and systemic effects to synergize with CAA effects. Indeed, the cellular homeostasis and the secretory profiles of hypertrophied adipocytes from cancer-free obese people are altered and increasingly dysregulated compared with normal adipocytes. Further, excess of adipose tissues located elsewhere in the body might also impact on tumor behavior via a systemic route. For example, obesity is associated with an altered cytokine profile, characterized by a reduction in the release of anti-inflammatory factors and an increase in the secretion of pro-inflammatory factors. Consequently, obesity is considered an important source of chronic inflammation (Hoene and Weigert, 2008). Moreover, in obesity, the adipose tissue is infiltrated with increased numbers of TNF-α and IL6-secreting macrophages (Weisberg et al., 2003). Leptin is also activated by obesity-related stimuli in adipocytes while adiponectin is decreased (Schaffler et al., 2007)(Kaur and Zhang, 2005). It is known that expanding adipose tissues require local active angiogenesis and neovascularization (Haussman and Richardson, 2004). Moreover, there are adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes (Guilherme et al., 2008)(Rabe et al., 2008). In addition, hyperinsulinemia promotes the synthesis and biological activity of...
Adipocytes as “fuel” for cancer cells

Although metabolic changes do not cause malignancy, they are necessary for tumor progression. Indeed, cancer cells need to proliferate rapidly and therefore use a high rate of energy-consuming processes to drive increased protein and DNA synthesis (Menendez and Lupu, 2007). There is also a need to maintain a constant supply of lipids and lipid precursors to fuel membrane production in the highly proliferating cancer cell population. The data reported above question the possible direct involvement of CAAs in these events. Interestingly, it has been reported that epithelial cells within the mouse mammary gland are able to utilize fatty acids sequestered from fat pad adipocytes (Hovey and Aimo, 2010). In this case, epithelial cells clearly induce lipolysis in adjacent adipocytes during lactation, presumably through the action of epithelial-derived lipoprotein lipase. In turn, these adipocyte-derived fatty acids can be utilized for de novo fatty acid synthesis by lactating mammary epithelial cells. It might therefore be hypothesized that this interaction could be aberrantly restored between invasive cancer cells and resident adipocytes. Delipidation in CAAs supports such a process. Moreover, in a mouse model, Raman microscopy revealed intracellular lipid accumulation in cancer cells. Lipid-rich cancer cells are linked to cancer metastases (Le et al., 2009). Free fatty acids (FFAs) might be used for the production of signalling lipids, converted to specific lipid species for incorporation into membranes or used for mitochondrial β-oxidation to produce ATP. Although it is thought that the bioenergetic needs of cancer are predominantly met through glycolysis, the oxidation of FFAs offers an interesting alternative. Indeed, it has been shown that an increase in intracellular FFAs enhances tumor progression potentially through β-oxidation (Nomura et al., 2010).

There is a clear link between deregulated energy processing and increased cancer aggressiveness. Emerging evidence suggests that the “transfer” of lipids between adipocytes and cancer cells might represent a key energetic source for cancer cells and as such stimulate cancer progression. In this context, having an excess of “obese” adipocytes could obviously provide more triglycerides and more available FFAs to the developing tumor than normal adipocytes.

Conclusion

Improving knowledge of adipocyte/CAA functions might help to decipher the relationship between high BMI, or type 2 diabetes, and increased cancer risk and poor clinical outcome. In this context, modulating the plasticity of adipocytes and elucidating their extracellular and intracellular signaling pathways are major challenges for future research in this field. Molecules linked to adipocyte biology might offer new therapeutic opportunities for treating cancer. These data justify work aimed at exploring the feasibility of current metabolic syndrome and associated disorder treatments for anti-cancer therapy (Gouveri et al., 2011). For example, recent studies provide clues that metformin, a drug usually given for the treatment of type 2 diabetes, is associated with reduced incidence and improved prognosis of various cancers including breast cancers (Ben Sahra et al., 2010).

General conclusion

The present review provides new insights into the function of resident adipocytes in tumors. As outlined above, adipocytes within mammary gland carcinomas are clearly dynamic cells that contribute to human breast cancer progression. Its deleterious function is initiated through crosstalk with cancer cells. This review strongly supports the more general concept that the loss of adipose tissue homeostasis favors tumor aggressive behavior. In this context, it provides insights into the relationship between obesity/diabetes and cancer. This is of particular interest since recent epidemiological studies have identified obesity as one of the major risk factors for cancer. Moreover, several important considerations arise from such data, notably concerning the possibility of promoting cancer recurrence by “activating” residual cancer cells in post-mastectomy reconstruction with autologous fat transfer, or dormant malignant cells or micrometastasis in breast augmentation.

The cellular and molecular processes underlying adipocyte function in cancer is just beginning to unfold. Many questions remain unanswered, and it is important to further study mechanisms and signaling pathways involved to understand how adipocytes promote tumor progression. One of the most important questions to be addressed concerns the possible role of resident adipocytes in the distant tissues colonized by metastatic cells. Indeed, phenomena similar to those observed at the primary tumor sites might be expected to exist at the secondary tumor sites. In this context, it should be noted that the microenvironment of preferential organs for metastasis development often contains adipocytes/lipids (Sicilari et al., 2006).

This research might lead in fine to the identification of adipocyte-related targets to improve diagnosis and prognosis, and/or to design innovative anticancer strategies.

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