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Adipose Tissue and Desmoplastic Response in Breast Cancer

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1. Introduction

Breast tumors belong to a group of neoplastic lesions which, under the influence of tumoral cell products, originate a fibrous structure responsible for the dense and hard consistency of the tumoral mass. This trait also constitutes a factor that increases the relative risk of tumor recurrence (Hasabe et al., 1998). Myofibroblasts have been identified as major players in this phenomenon, acting either as producers of extracellular matrix (ECM) proteins and/or as functioning as elastic components of the tumor structure (Hinz B., 2007). Taken together, these pro-fibrotic processes are known as "tumoral desmoplastic reactions" (Shao et al., 2000).

The origin of the fibroblastic component in tumors is controversial. On one hand, it has been proposed that fibroblasts derive essentially from epithelia under an epithelial-to-mesenchymal transition (EMT) or, on the other, that the abundance of fibroblasts-like cells come from a dedifferentiation process by which mature adipose cells revert to fibroblastic -not lipid laden- cells (Taylor et al., 2010, Guerrero et al, 2010). In any case, the fibrotic outcome seems to be the result of a fluid cross-talk of signals among the predominant adipose stroma and epithelia. Epithelial control of mammary adipose cells is also observed under physiological conditions. During pregnancy and lactation, reproductive hormones induce the expansion and terminal differentiation of the mammary epithelium into secretory, milk-producing, lobular alveoli in a process that also includes the dedifferentiation of adipocytes into tiny preadipocytes (Wiseman and Werb, 2002). To further analyze the current hypothesis on the origin and possible fate or breast adipose tissue in the context of a tumoral breast, some aspects of breast adipose tissue need to be discussed in more detail.

2. Breast adipose tissue, obesity and cancer

Obesity, characterized by an excess of adipose tissue, has been linked in numerous epidemiological studies to an elevated risk of postmenopausal breast cancer (Petrelli et al., 2002, Calle et al., 2004, Pischon et al., 2008 and references therein). In general, the greater risk for several other cancers (such as colon, endometrium, kidney and esophagus) has been mechanistically linked to obesity via the metabolic and endocrine effects of the excess of adipose tissue, such as the alterations that it induces in the production of peptide and

steroid hormones, as well as inflammatory factors. In addition to this role of total body adipose tissue, the case of breast cancer is of particular interest, because an important part of breast tissue is composed of the adipose stroma, whose active and direct influence on cancer cells is becoming an important focus of attention.

It is well known that the microenvironment of breast cancer cells greatly influences the growth and progression of the tumor, due to several elements such as cell-cell contact, soluble secreted factors, and the insoluble extracellular matrix (Celis et al., 2005 and references therein). Cells present in the stromal fraction such as fibroblasts, endothelial and various inflammatory cells can influence the phenotypic behavior of malignant cells. At the same time, tumor cells –or factors produced by them- can influence the surrounding stroma to generate a compatible microoenvironment that favors tumor survival and progression.

Among the many different cell types present in mammary tissue, the most abundant that surround breast cancer cells are those that make up adipose tissue, mainly mature adipocytes and their precursor cells, preadipocytes. An important number of primary breast tumors are originated by the transformation of ductal or intraductal epithelial cells. In many cases, these lesions develop in close contact with adipocytes, and in this microenvironment a reciprocal functional interaction takes place (Celis et al., 2005). In spite of this, adipose tissue has not received the attention it deserves in the context of breast cancer research. A possible reason for this may be that up until recent decades, the adipocyte was viewed as a rather inert, fat-storing cell with no other relevant physiological roles or capabilities. More recently, though, it has become evident that adipose tissue is a highly active endocrine organ, capable of secreting a vast number of hormones and other factors ("adipokines") including growth factors, several proinflammatory substances, hormone-like molecules, and extracellular matrix proteins (Deng and Scherer 2010, Karastergiou and Mohamed-Ali 2010). Moreover, adipose tissue may be infiltrated with other cell types, such as proinflammatory environment-inducing macrophages, thus elevating the number of local factors that may influence tumor progression. In this scenario, breast adipose tissue can constitute an important possible player influencing breast cancer development and progress. Some of the possible mechanisms involved are described below.

2.1 Adipose secretory products

The versatile endocrine organ nature of adipose tissue creates a complex local environment in the mammary tissue, influenced not only by circulating levels of different factors and hormones, but also to a great extent by the local production of mammary fat. Given the observation that tumor cells are in close contact spreading through fat tissue in high risk breast cancer, Celis et al. searched for secretory factors produced by adipocytes that may help elucidate the phenomena derived from this close association (Celis et al., 2005). Using a proteomics approach, the authors identified over 350 proteins within mammary adipose tissue from cancer patients undergoing mastectomy. These proteins included signaling molecules, hormones, cytokines and growth factors, which could be linked to various biological processes such as signal transduction, cell communication, cell metabolism and growth, immune response and apoptosis, among others. Their observations suggest that breast tumor cells and adipocytes provide each other with growth support by secreting factors that are mutually beneficial. This proteomics-based study provides interesting information regarding the gene products expressed by adipose tissue that helps define the tumor microenvironment.

In support of the role of adipokines influencing breast tumor growth, work by Iyengar and colleagues (Iyengar et al., 2003) provide further evidence to define molecular interactions between adipocytes and malignant breast ductal epithelial cells. In experiments using adipose conditioned media, they observed that adipose secretory products have relevant effects of breast cancer cell survival and proliferation. They showed that many genes promoting such events were upregulated, whereas genes that suppress growth and induce apoptosis are downregulated. Additionally, they observed that adipokines can induce the expression of oncogenes and other tumor-supporting factors such as AP1, cFOS and cJUN in MCF-7 cells. The effect on endothelial cells showed that they are able to promote angiogenesis in breast tumors. Adipose secretory products were also shown to have an impact on the invasive/metastasic potential, as they were able to increase motility of breast cancer cells.

2.2 Estrogen and aromatase

Estrogen, especially 17β-estradiol, plays an important role in the development of hormone dependent breast cancer. In postmenopausal women, the biosynthesis of estrogens occurs mainly through aromatase-mediated metabolism of androgen precursors. Adipose tissue is a relevant site of this conversion, and its occurrence is directly proportional to the degree of adiposity. The concentration of 17β-estradiol in breast cancer tissues from postmenopausal women has been observed to be 10-fold greater than those in plasma, and increased presence of aromatase and/or estrogen biosynthesis has been associated with the development of postmenopausal breast cancer (Sasano et al., 1998). Moreover, it has been proposed that most of the relationship between obesity and breast cancer can be explained by the adiposity-related increase in endogenous estrogen levels (Calle et al., 2004).

Besides the direct influence that adipose-secreted factors have on the different aspects of tumor development and progression (Maccio et al., 2009 and references therein), there is a series of interactions between adipokines and estrogens. Such cross-talk becomes of great relevance in hormone-dependent breast cancer, and may influence the outcome of pharmacological treatment. Leptin, for example, can modulate the influence of estrogen on tumor cells at different levels; it can induce estrogen receptor expression, induce aromatase activity and interfere with the effect of anti-estrogen drugs (Catalano et al., 2004, Garofalo et al., 2004).

Interestingly, the tumor itself also influences local aromatase expression and thus estrogen production by the surrounding adipose tissue. In breast cancer, there is a switch in promoter utilization for the transcription of the aromatase gene, from the weaker adipose-specific I.4 promoter to the more potent ovary-specific PII, leading to elevated aromatase expression and subsequent estrogen production. One possible factor leading to this induction in PII aromatase expression is prostaglandin E2 produced by malignant breast epithelium and macrophages within the tumor (Simpson et al., 2002).

The above-mentioned factors may act independently or in concert to elevate the risk for the development or progression of breast tumors. Recently, Subbaramaiah and collaborators evaluated the connections between obesity, inflammation and aromatase through interactions between the different cell types present in adipose tissue; adipocytes, macrophages and epithelial cells. In mammary fat from mice models of obesity, they observed necrotic adipocytes surrounded by macrophages, forming the so-called “crown like structures” (CLS) that are well known in human obesity and its detrimental

consequences. The presence of CLS was associated with elevated levels of proinflammatory mediators as well as aromatase expression and activity in the mammary gland. Moreover, the proinflammatory mediators induced aromatase and estrogen-dependent gene expression in adipocytes. These authors thus have established important paracrine interactions between adipocytes and macrophages that may explain elevated local levels of aromatase.

2.3 Extracellular matrix

The extracellular matrix (ECM) is assembled by stromal cells within the mammary tissue. An altered ECM composition leads to tissue stiffness, which is characteristic of some solid tumors that develop desmoplastic reaction. Breast tumors are stiffer than the surrounding tissue. It has been proposed that this is the result of the recruitment and differentiation of tumoral myofibroblasts, cells that together with some elastic properties, provide the tumor environment with the capacity to generate a dense extracellular collagenous matrix scaffold (Egebland et al, 2005). In breast tumors, collagen is upregulated and densely crosslinked, and fibronectin –a molecule critical for collagen turnover- is also upregulated and associated with tumor malignancy (Chandler et al., 2011).

Adipocytes generate a basement membrane that promotes mammary tumor progression through collagen VI, and adipose-derived stem cells deposit an ECM rich in fibronectin. Collagen VI, which is abundantly expressed by adipocytes, seems to be an important factor contributing to the supportive role of adipose tissue in breast tumor survival. Iyengar and colleagues (Iyengar et al., 2005) showed in MCF-7 cells that adipocyte-derived collagen VI induces pro-mitogenic signals through the NG2/chondroitin sulfate proteoglycan receptor expressed on the surface of malignant ductal epithelial cells, to stabilize β-catenin and upregulate cyclin D1. The effects of collagen VI on breast cancer were also confirmed with *in vivo* experiments. Adipocytes thus play a vital role in defining the ECM environment for normal and tumor-derived ductal epithelial cells, and contribute significantly to tumor growth at early stages through secretion and processing of collagen VI. Immunohistochemistry studies of human mammary carcinoma tissue showed strong collagen VI staining around the tumors and the adipocytes whereas normal human mammary tissue showed low staining. This demonstration of collagen VI protein upregulation in human breast tumors, further suggests its relevance to human breast cancer.

Another mammary extracellular matrix component whose expression and assembly is modified by tumoral factors is fibronectin. The regulation of fibronectin matrix assembly and stiffness as a result of paracrine communication between breast cancer and adipose progenitor cells was recently assessed by Chandler and colleagues (Chandler et al., 2011). These authors evaluated the fibronectin assembled by 3T3-L1 preadipocytes that were treated with secretory products from MDA-MB231 breast cancer cells. Cultures exposed to the cancer cell-conditioned media produced a denser and more fibrilar fibronectin matrix, with increased fibronectin mRNA and protein levels. The results suggest that adipose-derived stem cells in the breast cancer microenvironment have enhanced fibronectin transcription and matrix assembly. In other experiments, they showed that adipose stromal cells enhanced fibronectin deposition and remodeling in the mammary tumor microenvironment, and that the factors derived from the tumor can alter the phenotype of the adipose cells, thus contributing to the changes. These data are yet another example of how paracrine signals from breast adipose tissue regulates mammary tumors, in this case by enhancing its rigidity.

3. TGF-β as a prototype of an epithelial factor that induces stromal reaction

It has been proposed that Transforming growth factor-beta (TGF-β), mainly produced by tumoral epithelial cells, plays a central role in the maintenance of a tumor-promoting stroma, acting as a key player in the stromal-epithelial dialogue (Derynck et al., 2001). In the advanced stages of the carcinogenic process, TGF-β acts either as a promoter of EMT or as an active stimulus in the fibroblastic activation to myofibroblasts (Stover et al., 2007). Because TGF-β is produced abundantly in malignant breast cancer cells as part of an autocrine repertoire, it is expected that this factor, in a paracrine manner, would exert a marked influence in the circumvent stroma and for that reason, would play a role in the mammary adipose structure (Guerrero et al, 2010). In the epithelial context, TGF-β is a multifunctional cytokine that displays a paradoxical behavior in carcinogenesis. During the premalignant phase, it inhibits epithelial cell proliferation and induces apoptosis. At more advanced steps of the process, this growth factor stimulates cancer progression in a manner strongly dependent of the tissue context, as it has been demonstrated in the bone metastasis model (Onishi et al 2010).

Our laboratory has provided evidence that at least part of the enhancement in tumor fibroblast abundance derives from a reversion process, in which mammary adipocytes lose their lipid load and become a typical elongated fibroblastic cell (Guerrero et al, 2010). We have proposed that this phenomenon is stimulated by soluble factors arising from epithelial tumoral cells among which TGF-β1 plays a relevant role. Human mammary adipose cells cultured in semi solid conditions in the presence of media conditioned by human tumoral mammary cell lines that secrete a different amount of TGF-β, showed an adipose reversion that is manifested in a high proportion of mammary fatty cells losing their lipid content and acquiring a fibroblast-like shape (Fig 1). The lipid loss also occurs when adipose cells are cultured in the presence of TGF-β1 and TNF-α that in these fatty cells are also able to inhibit the expression of the transcription factors C/EBPα and PPARγ, which are involved in the maintenance of the adipose phenotype. These data led us to propose that, in the tumoral microenvironment, TGF-β1 and TNF-α activate signaling routes that bring about the predominance of the fibroblastic over the adipocyte phenotype, which is concordant with the fibrotic response present in desmoplastic tumors. Moreover, the role of TGF-β1 on regulation of fibroblast/adipocyte ratio in mammary stroma was previously analyzed in studies that demonstrated that TGF-β1 strongly decreased adipogenesis, diminishing the cell-surface availability of TGF-β1 receptors (Choy, 2000).

In breast cancer models, it has been demonstrated that inflammatory mechanisms influence tumorigenesis and metastatic progression. This, despite that the etiology of breast cancer does not involve a pre-existing inflammation event (Grivennikov et al, 2010). Moreover, infiltration of inflammatory cells that include T cells, neutrophils and macrophages, among others, is a very common feature in breast cancer lesions. (Yang, 2010).

Current data allow us to suggest that in the tumoral environment, TGF-β1 not only regulates the abundance and activity of the fibroblastic compartment but also the relative amount and activity of the majority of infiltrated cells, such as immune cells, acting as an immunosuppressive cytokine. In this case, TGF-β1 suppresses the activity of cytotoxic T lymphocytes, through transcriptional repression of genes encoding key proteins engaged in the elimination of tumoral cells, counteracting in this manner the immunological surveillance against the tumor (Yang et al. 2010).

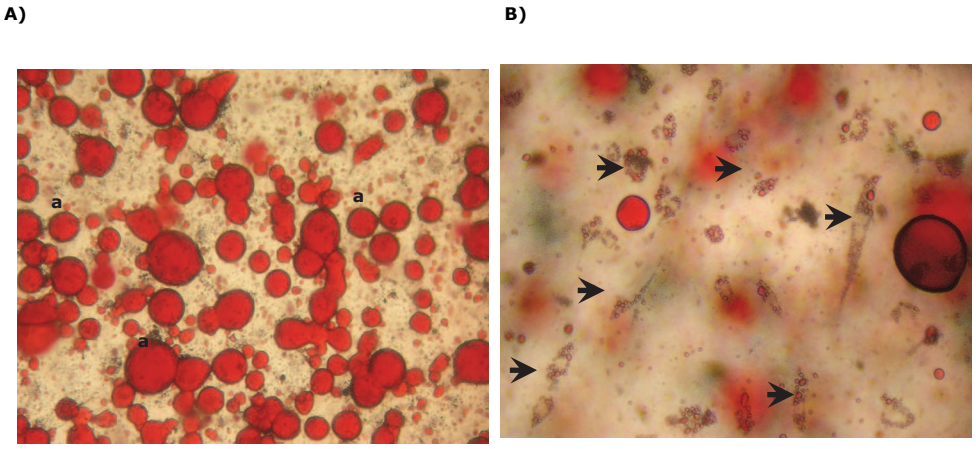

Fig. 1. Adipocyte reversion in three-dimensional collagen gel culture.
Human mature mammary adipocytes (10^5) were cultured in 1.5 ml semisolid collagen gel for 10 days in the absence (A) or presence (B) of 50% medium conditioned by human mammary MDA-MB-231 cells. Cells were stained with oil red O that identified lipid content in mature spherical adipocytes (a) and elongated cells with a fibroblast phenotype (b).

Macrophages frequently infiltrate tumors. In fact, a percentage of the tumoral mass is made up of the so-called tumor-associated macrophages (TAM) and their presence in the tumor environment correlate with poor prognosis (Flavell, 2010). However, depending on the type and specificities of tumoral microenvironments, TAMS may also have antitumor activity (Flavell, 2010). Besides active fibroblasts, these TAMs are among the main stromal components on desmoplastic breast tumors. Moreover, it has been proposed that tumor-associated fibroblasts are avid attractors for circulating monocytes (Silzle et al, 2003). It is plausible to suggest that macrophages play a relevant role in the mammary tumor-dependent fibrotic process. In adipose tissue, it has been demonstrated that soluble factors derived from macrophages promote a profibrotic phenotype which is the consequence of a significant overexpression of extracellular matrix (ECM) genes in inflammatory preadipocytes (Keophiphath et al, 2009).

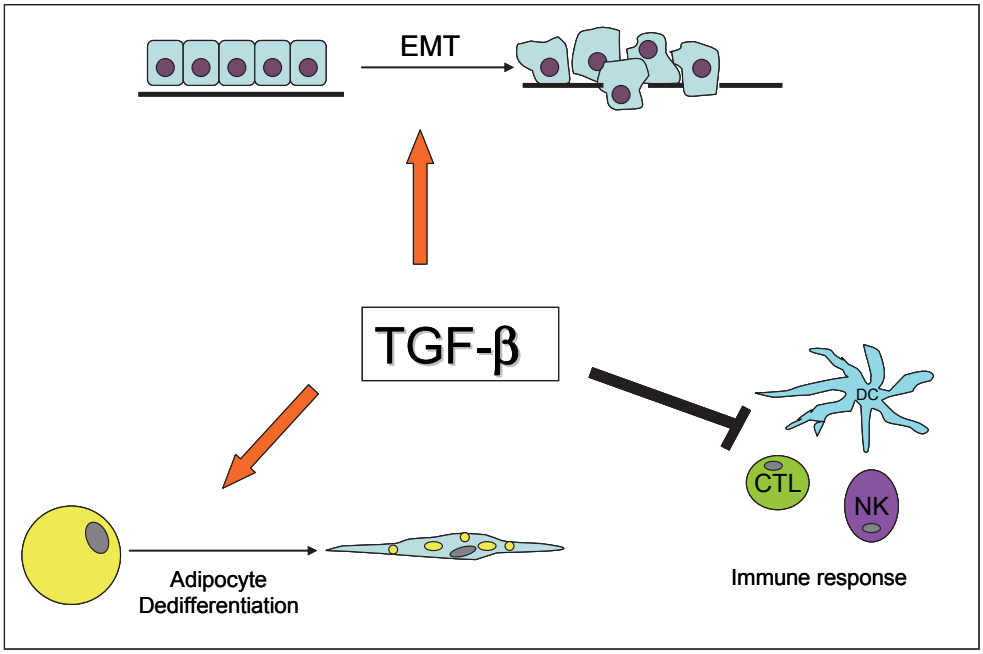

Fig. 2. TGF-β affects multiple components on tumoral environment.
TGF-β induces the reversion of adipose cells to a fibroblast-like phenotype, the epithelial-to-mesenchymal transition and the cytotoxic activity of immune cells. EMT: epithelial to mesenchymal transition; DC: dendritic cell; CTL: citotoxic T lymphocyte; NK: natural killer cell.

4. Concluding remarks

The desmoplastic reaction is one of the most common features of human breast cancer. Considering that mammary adipose cells are an important source of fibroblastic cells, which characterize desmoplastic tumors, it is relevant to take into account that some of the well-known physiological clues that regulate adipose tissue metabolism in other depots, can be also valid in the breast. Results from our laboratory propose that, in breast cancer, the fibrotic microenvironment that allows the expansion and progression of tumoral epithelia, has an original substratum in the adipose mammary tissue. We believe that different soluble

factors derived from epithelia, among which TGF- β1 is one of the most important, collaborate in different ways to constitute a fibrotic tumoral microenvironment. TGF-β1 is one of the more abundant factors released by tumoral cells, and a determinant factor in the epithelial-to-mesenchymal transition, the reversion of adipose to a fibroblastic phenotype and the inhibition of local tumoral immunosurveillance. In light of that, it is clear that TGF-β1, a well known antiadipogenic factor, constitutes a key player in the regulation and function of tumor microenvironment. This justifies the attention that has led to different clinical trials based in the inhibition of its signaling.

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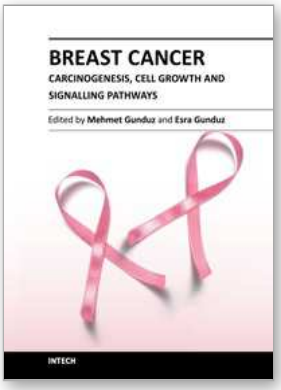

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various aspects of breast cancer carcinogenesis from clinics to its hormone-based as well as genetic-based etiologies 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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