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Review

Adipocyte biology in breast cancer: From silent bystander to active facilitator

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ABSTRACT

Adipocytes account for the largest proportion among the cells that comprise breast tissue; therefore, they are considered to be a critical cell type in the tumor microenvironment of breast cancer. In breast cancer, adipocytes are not only found adjacent to cancer cells, but they also play an active role in the entire process of cancer development, progression, metastasis, and treatment response. Factors including the secretion of adipokines such as leptin and adiponectin, as well as autotaxin, interleukin 6, tumor necrosis factor alpha, and hepatic growth factor, metabolic remodeling that supports the growth of breast cancer by transfer of fatty acids to increase mitochondrial β-oxidation, extracellular matrix remodeling and endotrophin production from type IV collagen, and cancer-associated fibroblast phenotype changes have all been implicated in this comprehensive process. Moreover, adipocytes may act as obstacles to therapy, as they are involved in mechanisms of resistance against various breast cancer treatments. Adipose tissues may also be a reservoir for dormant tumor cells during postsurgical autologous fat grafting. Thus, adipocytes, and the processes and pathways in which they are involved, could be effective therapeutic targets for breast cancer. In this review, we focus on the current understanding of adipocyte biology as it affects breast cancer.

1. Introduction

Through drilling down into the complex mechanisms of cancer biology, the role of the interaction between cancer cells and stromal cells during the process of tumor initiation, progression, invasion, and metastasis is being increasingly recognized. Among these stromal cells, fibroblasts, also known as cancer-associated fibroblasts (CAFs), have been extensively studied in various tumor types [1–3]. Breast tissue is distinctive, in that it contains branched ducts, lobuloalveolar units, and fat-rich connective tissue comprising the mammary fat pad [4], which is a stromal part of breast tissue with cellular components such as adipocytes, fibroblasts, endothelial cells, inflammatory cells, and various types of extracellular matrix (ECM). Adipocytes constitute the major cellular component of the mammary fat pad, and it is reasonable to infer that adipocytes may have a role in the biology of breast cancer. In contrast to the previous perception of adipocytes as adjacent, static cells next to cancer cells, recent studies support the hypothesis that adipocytes have a dynamic interaction with cancer cells [5–7]. Epidemiological evidence support this idea, as previous studies showed a higher incidence of breast cancer in obese postmenopausal women [8] and correlations with the clinical prognosis of breast cancer [9,10].

In this review, we will comprehensively review literature focusing on the roles of adipocytes in tumor initiation, progression, invasion, and metastasis, and discuss the feasibility of this specific cellular component as a novel therapeutic target of breast cancer.

2. Adipocyte biology in breast tissue

Adipose tissue is distributed in various compartments of the human body. In the breast, it occupies 56% of the non-lactating breast tissue, as assessed radiographically [11], and 35% of lactating breast tissue [12]. Adipocytes that constitute breast tissue are white adipocytes (WAT),

Abbreviations: CAF, cancer-associated fibroblast; WAT, white adipose tissue; CLS, crown-like structure; CAA, cancer-associated adipocyte; ECM, extracellular matrix; IL, interleukin; ER, estrogen receptor; TNBC, triple-negative breast cancer; ATX, autotaxin; ENPP2, ectonucleotide pyrophosphatase/phosphhodesterase 2; LPC, lysophosphatidylchone; LPA, lysophosphatidate; IGF, Insulin-like growth factor; HGF, hepatocyte growth factor; HSL/ATGL, hormone sensitive lipase/adipose triglyceride lipase; MMP, matrix metalloproteinase; PAI, plasminogen activator inhibitor; EMT, epithelial-mesenchymal transition; ADF, adipocyte-derived fibroblast; FSP, fibroblast-specific protein; BMA, Bone marrow adipocyte; EGCG, epigallocatechin gallate; AIF, apoptosis-inducing factor; PEG-LPrA2, pegylated leptin peptide receptor antagonist 2; BITC, benzyl isothiocyanate; MCD, malonyl-CoA decarboxylase; FABP4, fatty acid binding protein 4; TME, tumor microenvironment

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90% of the cytoplasm of which is occupied by a large unilocular lipid droplet. There also exist adipocyte-precursor cells, preadipocytes, which have fibroblast-like morphology and high proliferative activity [13]. Although mammary adipose tissue may be considered as a mere component of subcutaneous adipose compartments, it has characteristics distinctive from those of subcutaneous adipose tissue in other body compartments; first, it undergoes cyclic structural changes in response to the female hormone cycle, and second, it is in permanent interaction with epithelial cells. During breast development, epithelial cells invade the mammary fat pad generating branching ducts and terminal buds that produce the fat-embedded glandular structure. The interaction between mammary fat pad and ductal epithelium seems to be an essential process in mammary ductal morphogenesis, as it was reported that total removal of breast fat resulted in the suppression of normal mammary gland development [14]. In female adults, mammary glandular epithelial cells differentiate to secretory and lactating alveoli, with simultaneous regression of mammary adipocytes, under hormonal influence during pregnancy or lactation, and the volume of glands and mammary adipocytes returns to original conditions on cessation of these events [4]. The tumorigenesis of breast tissue recapitulates this normal physiologic process, i.e. glandular epithelial cell proliferation, adipocyte differentiation, adipocyte dedifferentiation, and ECM remodeling, and reciprocal interactions between epithelial cell and adipocytes are also observed in the process of carcinogenesis in breast cancer.

3. Adipocyte biology in breast cancer

As mentioned above, an interaction between epithelial cells and adipocytes exists in normal breast tissue as well as breast cancer, and this close interaction occurs during the whole process of cancer: tumor initiation, tumor progression, invasion, and metastasis (Fig. 1).

3.1. Tumor initiation (tumorigenesis)

The process of tumorigenesis involves communication between tumor cells and adjacent normal cells, and it has been reported that the normal cells acquire traits that are essential for tumorigenesis during their interaction with premalignant and/or malignant cells [15,16]. A previous study on mice reported that inoculation or implant of normal epithelium, after irradiation [17] or treatment with chemical carcinogens such as N-nitro-methyl urea [18], to mammary fat pads generated tumors, suggesting the potential role of “activated adipocytes” in tumorigenesis. Adipocytes adjacent to breast cancer showed different gene expression profiles, functional characteristics, and higher browning activity, which may contribute to tumorigenesis [19]. Gene expression analysis of microdissected adipocyte tissue adjacent to and distant from invasive tumors and those adjacent to benign disease showed that adipocytes from invasive tumors regardless of the distance, had higher expression of anti-inflammatory genes such as MARCO and VISG4, and such increased immunotolerance may provide an appropriate microenvironment for tumorigenesis [20]. Furthermore, adipocytes in breast tumors showed higher levels of versican, CD44, and AdipoR1, and lower levels of adiponectin and perilipin; among these, versican is known to have a close relation with tumorigenic behavior [21]. Adipokines secreted from adipocytes increased the gene expression of NF-kappaB and cyclin D, inducing anti-apoptotic transcription and stabilizing pro-oncogenic factors such as beta-catenin and cyclin-dependent kinase 6, which may contribute to tumorigenesis [22]. Interleukin (IL)-6, a well-known adipokine secreted by adipocytes, induces the expression of aromatase in adipose tissue to promote the synthesis of estrogen; this may increase the risk of breast cancer in postmenopausal obese women [23,24].

One of the suggested mechanisms of tumorigenesis involving breast adipocytes is the formation of a crown-like structure (CLS). This is a histological feature of dead or dying adipocytes surrounded by macrophages that is a histologic hallmark of active pro-inflammatory

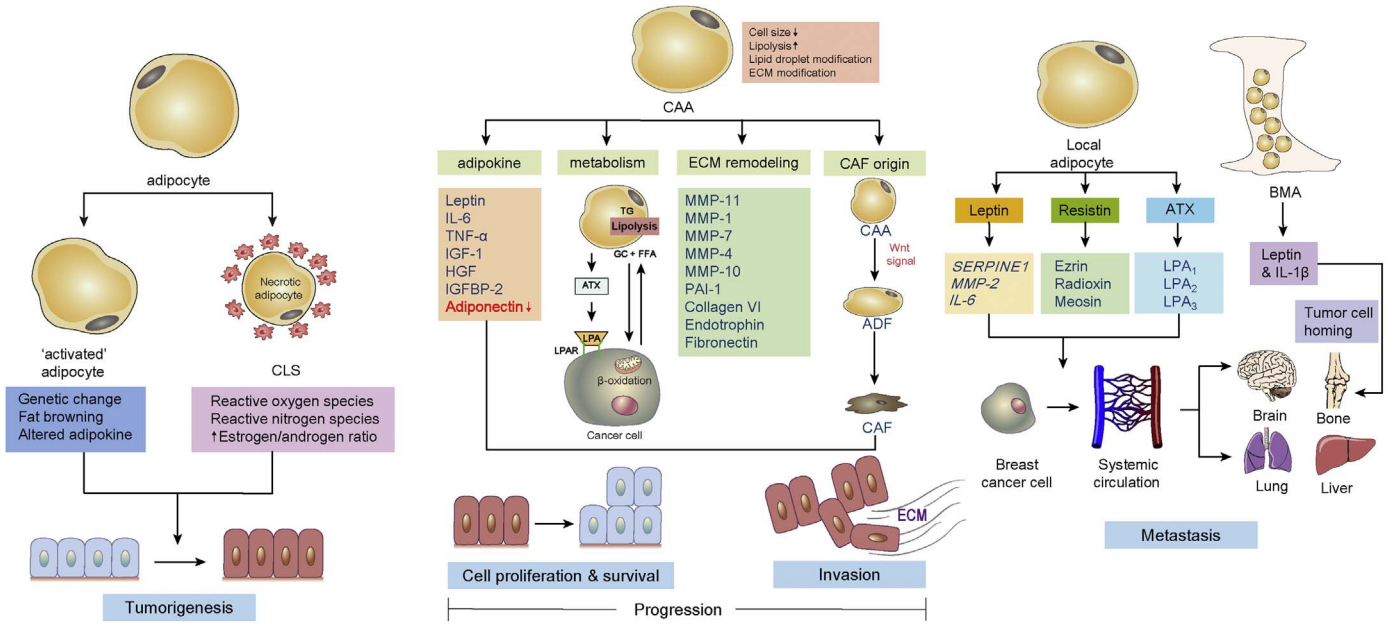

Fig. 1. Role of adipocyte as an active facilitator in breast cancer initiation, progression and metastasis. Adipocytes promote the tumorigenesis by stimulation of mammary duct cells through the activation such as changes in genetic signature and/or type of secreting adipokines and by forming CLS in which macrophages surround adipocytes, that generates possible mutagens like ROS and RNS from necrotic adipocytes. Adipocytes that affect in the progression of breast cancer are CAAs, characterized by their decreased size. Adipocytes affect the process of proliferation, survival and invasion of breast cancer through several functions of CAAs including (1) the secretion of various adipokines, (2) the metabolic remodeling that increases the β-oxidation by transferring free fatty acids that are generated in CAAs through increased lipolysis to cancer cells (3) ECM remodeling by the expression of MMPs, PAI-1, collagen VI, endotrophin, and fibronection, (4) the supply of CAFs through CAA-ADF-CAF process. Local adipocytes in breast secrete leptin, resistin and autotaxin and induce metastasis by the activation of metastasis-related molecules and BMAs in bone secreted leptin and IL-1β induce homing of breast cancer cells to the bone. CLS, crown like structure, ROS, reactive oxygen species, RNS, reactive nitrogen species, CAA, cancer-associated adipocyte, ATX, autotaxin, LPA, lysophosphatidate, LPAR, lysophosphatidate receptor, ECM, extracellular matrix, TG, triglyceride, GC, glycerol, FFA, free fatty acid, LSP, lysophospholipid, ADF, adipocyte-derived fibroblast, CAF, cancer-associated fibroblast, BMA, bone marrow adipocyte.