Published in final edited form as:

Expert Rev Anticancer Ther. 2013 February ; 13(2): 111–113. doi:10.1586/era.12.164.

Endotrophin in the tumor stroma: a new therapeutic target for breast cancer?

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Keywords

Adipocyte; Breast cancer; Endotrophin; Microenvironment; Chemoresistance

Tumor stromal contribution of adipocyte towards cancer progression

The molecular mechanisms underlying how obesity causes an increased risk of cancer incidence and mortality are poorly understood although the epidemiological data is compelling [1]. Since we define obesity as an pathological expansion of adipose tissue, the adipocyte is a prime suspect as a contributor to the etiology of obesity-related cancers [2]. The adipocyte is an active endocrine cell secreting various factors, referred as adipokines, which signal to neighboring tissues through paracrine and endocrine interactions. The endocrine aspects of adipocytes have found widespread acceptance with respect to their role in maintaining whole body energy homeostasis [3]. During the pathogenesis of obesity, the adipokine profile changes significantly; these changes include differential expression of pro-inflammatory cytokines, mitogenic and pro-angiogenic factors, lipid metabolites and extracellular matrix molecules (ECM). While these changes may form the underlying mechanistic basis for the tight association between obesity and cancer, the impact of dysregulated adipocytes on tumor growth remain vastly underappreciated.

Nevertheless, the role of the adipocyte as a major constituent of the tumor stroma has been examined in the last few years, revealing its roles in cell proliferation, local anti-apoptotic action and invasive properties of cancer cells, mediated by adipocyte-derived factors, such as leptin, adiponectin, interleukin-6 (IL6) and interleukin-8 (IL-8). Beyond these paracrine interactions with cancer cells *per se*, there are additional metabolic changes originating in stromal adipocytes, creating a microenvironment more permissive for tumor progression. The altered microenvironment is further associated with chronic-inflammation, lipotoxicity, fibrosis and hypoxia. All of these changes are much more likely to occur when adipocytes

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

No writing assistance was utilized in the production of this manuscript.

become dysfunctional during the processes of hypertrophy and hyperplasia, phenomena characteristically seen in the context of obesity. Furthermore, metabolically active cancer cells consume vast amounts of energy to support rapid proliferation; hence, it has been speculated that tumor-associated adipocytes may constitute a critical fuel source for cancer cells. An elegant recent report showed that lipolysis in tumor-associated adipocytes is augmented, providing critically needed fatty acids to fuel cancer cells [4]. Combined, these findings emphasize the critical need for a better understanding of the tumor-associated adipocytes (TAAs), which shape the tumor microenvironment along with tumor-associated macrophages (TAMs). TAMs and TAAs are particularly relevant for the most prominent obesity-related cancers, such as breast, ovary, colon and pancreas. We need to appreciate though that it is clearly not adipose tissue *quantity* that is the most critical parameter in this context, rather it is the *quality* of the surrounding adipose tissue that is the most significant determinant of tumor progression and recurrence. Nevertheless, we still have very limited insights on which specific adipocyte-derived molecules and how their dysregulation leads to enhanced tumor progression and recurrence. We have recently identified the polypeptide endotrophin whose physiological functions are consistent with a factor that critically mediates obesity-associated changes with a more tumor-friendly environment.

Mechanistic basis for endotrophin action, a cleavage product of COL6, on cancer phenotype

The ECM and its key building blocks and modifying proteins, such as collagens, fibronectin, laminin, matrix metalloproteinases (MMPs) and their endogenous inhibitors (tissue inhibitor of MMPs, TIMP) assume crucial roles in organizing the tissue architecture. More importantly, ECM proteins are actively engaged in critical cellular properties, such as proliferation, differentiation, invasion and adhesion. Tumor cells achieve this through interactions with neighboring cells within the microenvironment. During adipose tissue expansion in obesity, adipocytes face a hypoxic environment due to insufficient angiogenesis; this in turn triggers the activation of multiple signaling pathways associated with pathological consequences of obesity, such as insulin resistance, chronic inflammation and ER stress. In the meantime, adipocytes actively reorganize the microenvironment by secreting ECM molecules to support their hypertrophic expansion of cells, ultimately triggering fibrosis. One of the major collagens secreted from adipocyte is collagen VI (COL6, encoded by COL6 α 1, - α 2, and - α 3 genes). COL6, particularly COL6 α 3 is increased upon onset of obesity and its levels are correlated with chronic inflammation and systemic insulin resistance with respect to metabolic aspects [5]. As the environmental stimulus of tumor dissemination is hypoxia, it is tempting to speculate that adipocyte-derived ECM, stimulated by prevailing hypoxia within the tumor microenvironment, actively influences tumor progression through increasing tissue rigidity and the fibrotic stress response. The adipocyte-derived ECM also functions through signaling molecules that critically affect cancer cells and other stromal components [2]. We have demonstrated that endotrophin, a soluble proteolytic fragment of the COL6 α 3 collagen chain, is highly enriched in the stroma of murine and human breast cancers. Endotrophin promotes tumor and metastatic growth in a mouse mammary tumor model (mammary tumor virus-polyoma middle T antigen, MMTV-PyMT); hence, endotrophin represents one of the potential molecular links between obesity and malignant tumor progression [6].

COL6 has been implicated as a tumor-promoting factor [7–8]. Lack of COL6 α 1 (through a functional knockout of holo-COL6 due to a failure of secretion of α 2 and α 3 without the α 1 subunit) in the PyMT model attenuates early onset of tumor progression. Nevertheless, the underlying molecular mechanism was unclear [7]. Our recent study in which we focus on endotrophin action indicates that this soluble fragment is acting as a signaling molecule, and for the most part, accounts for the tumor-promoting effects of COL6 on mammary tumors

through modulating a variety of effects in the tumor-stromal environment. These effects include an increase of the process of epithelial-mesenchymal transition (EMT) of cancer cells, as well as enhanced fibrosis, angiogenesis and immune cell infiltrations [6]. Ectopic expression of endotrophin in the mammary epithelium of MMTV-PyMT mice affects tumor progression, particularly the metastatic characteristics of cancer cells. Subsequent *in vivo* and *in vitro* studies suggested that endotrophin effects on EMT and fibrosis are critically relying on TGF β -dependent pathways which promote acquisition of invasive traits of cancer cells and stimulate fibrogenesis [9]. Thus, treatment with TGF β antagonizing antibodies efficiently suppresses the endotrophin-mediated increase of EMT and fibrosis in mammary tumor tissues. Other aspects of endotrophin action are however independent of TGF β signals. These include the prominent chemoattractant activities of endotrophin on endothelial cells and macrophages within the tumor stroma. This leads to enhanced angiogenesis and chronic inflammation, which supports tumor stroma expansion. Reconstitution of endotrophin into COL6 α 1^{-/-} mice crossed to PyMT mice showed that EMT, fibrosis and chemoattractant activities are tightly associated with the presence of endotrophin. Strikingly, neutralizing monoclonal antibodies against endotrophin attenuate the growth of tumors and metastasis *in vivo*. Histological analysis of tumor tissue treated with endotrophin neutralizing antibodies suggested that decreased levels of stromal cell infiltration prevail in mice receiving the endotrophin neutralizing antibodies, confirming that endotrophin acts at least partly through the manipulation of both the number and the nature of stromal cells interacting with tumor cells.

Clinical implications and concluding remarks

The source for endotrophin within the tumor microenvironment is heterogeneous; stromal adipocytes are a major source for endotrophin. However, a subset of cancer cells express COL6 α 3 (the precursor molecule of endotrophin) as an autocrine signal. Based on our current findings, endotrophin is expressed in multiple types of solid human cancers including breast, liver, colon and pancreas (our unpublished data). Therefore, endotrophin activities on various cancer models need to be further validated to see if their activities seen in mammary tumors [6] could be generalized to other types of cancers as well. In the clinical arena, characterizing the specific types and stages of tumors expressing high levels of endotrophin within the tumor stroma may lead to better treatment strategies; thus, combining endotrophin neutralization with an existing therapy regimen offers an interesting novel therapeutic aspect in tumors expressing endotrophin at high levels. We propose that targeting endotrophin for the treatment of breast cancer patients, especially those with a metabolically unfavorable microenvironment, would be beneficial, since unhealthy adipose tissue expansion in obesity causes an enrichment of endotrophin in the microenvironment through the adipocyte as a main local producer of endotrophin. More importantly, we have seen that diet-induced obese animal models receiving endotrophin neutralizing antibodies ameliorate the obesity-induced insulin resistance compared to those given a control IgG preparation (our unpublished data), suggesting that targeting endotrophin is a powerful approach for treating both systemic metabolism and tumor progression in obese breast cancer patients.

COL6 has been implicated in several fibrotic diseases, including hepatic steatosis [10–11], renal fibrosis [12] and pulmonary fibrosis [13]. Furthermore, COL6 α 1^{-/-} protects against fibrosis in myocardial infarction [14] and obesity-induced adipose tissue fibrosis [5]. Endotrophin-mediated effects influencing fibrogenesis are likely associated with the etiology of these fibrotic diseases as well. Therefore, our current efforts are directed toward further identifying the roles of endotrophin in various disease models, including metabolic disorders and fibrotic diseases and other types of cancers.

Acknowledgments

The authors were supported by NIH grants R01-DK55758, R01-CA112023, P01-DK088761 (PES). JP is supported in part by a fellowship from the Department of Defense (USAMRMC BC085909).

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