Tumour-surrounding adipocytes are active players in breast cancer progression

Les adipocytes à proximité des cancers du sein sont des acteurs majeurs de la progression tumorale

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Abstract

Accumulating recent evidence highlights the tumour-surrounding adipose tissue as a key component of breast cancer progression. We have recently demonstrated that a bidirectional crosstalk is established with breast cancer cells and tumour-surrounding adipocytes. Tumour cell secretions are able to modify tumour-surrounding adipocytes to an activated state that we have named Cancer-Associated Adipocytes (CAAs). The role of CAAs in breast cancer progression, as well as the potential amplification of this negative effect in obesity conditions will be discussed.

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Résumé

De nombreuses études récentes ont souligné le rôle du tissu adipeux à proximité des cancers dans la progression tumorale. Nous avons montré qu’un dialogue bidirectionnel s’établit entre les cellules cancéreuses mammaires et les adipocytes péri-tumoraux. Les sécrétions tumorales sont en effet capables de modifier le phénotype des adipocytes en les « activant », adipocytes que nous avons nommé adipocytes-associés aux cancers (AAC). Le rôle de ces cellules dans la progression tumorale, ainsi que l’amplification de leur effet négatif dans des conditions d’obésité seront discutées.

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1. Introduction

In addition to epigenetic and genetic changes occurring in epithelial cells, it is now agreed that tumour progression is also the result of a bidirectional crosstalk between tumour cells and normal surrounding cells, the so-called tumour stroma or tumour microenvironment (for review [1]). Accordingly, tumours have been described as “wounds that never heals” as they surround themselves with a permissive microenvironment for malignant growth [1]. To date, most of the studies focused on cancer cell-mesenchymal cell interactions have emphasized the roles of fibroblasts, endothelial and inflammatory cells. Very little attention has been given to the adipocytes, although it is obvious that in numerous organs, such as breast, early local tumour invasion results in immediate proximity of cancer cells to both pre-adipocytes and fully differentiated adipocytes (for review [2,3]). This issue is clearly important in human medicine since obesity has been recently identified as a negative prognosis factor for certain cancers such as breast and prostate cancer [4]. In breast cancer, this poor prognosis seems to be independent of menopausal status, tumour stage, and tumour hormone binding characteristics. Interestingly, emerging evidences suggest that host factors contribute to the occurrence in obese women of tumours exhibiting aggressive biology defined by advanced stage and high grade and propensity for metastasis (for review [2,3]). This association is poorly understood but a paracrine role of adipocytes in stimulating tumour progression is an attractive hypothesis. In fact, aside from their energy-storing function, adipocytes are also active endocrine cells that secrete a large variety of molecules (termed adipokines), including hormones, growth factors, chemokines or pro-inflammatory molecules [5]. Adipocytes are therefore excellent candidates to influence tumour behaviour through heterotypic signalling processes and might prove to be critical for tumour survival, growth and metastasis. The crosstalk between the adipose and epithelial tumour components might be positively affected in obesity where the normal balance of these adipose tissue secretory...
proteins is perturbed [5]. According to these epidemiological findings, the main objective of our team is to study the paracrine role of mature adipocytes in tumour progression using mainly breast cancer as a model.

2. Contribution of mature adipocytes to breast cancer progression using in vitro and in vivo approaches

In order to investigate the role of tumour-surrounding adipocytes in breast cancer progression, a 2D coculture system in which adipocytes and breast cancer cells were separated by an insert, that allows the diffusion of soluble factors, was set up in our laboratory to mimic the adipocyte-cancer cell crosstalk at the tumour invasive front [6]. Using this original model, we extensively described tumour-induced changes in adipocytes that are reproducibly displayed by both mouse and human mammary adipocytes. Adipocytes cocultivated with various human and murine breast cancer cell lines generally exhibit a loss of lipid content, a decrease in late adipose markers expression, and over-expression of inflammatory cytokines (such as IL-6 and IL-1β) and proteases (such as MMP-11 and PAI-1). We named these tumour-surrounding adipocytes, “Cancer-Associated Adipocytes” (CAAs). Of equal importance, using immunohistochemistry and quantitative PCR, we confirmed the presence of these modified adipocytes in human breast tumours [6]. What are the effects of these CAAs on tumour progression? All murine and human tumour cells cocultivated with mature adipocytes exhibited increased invasive, but not proliferative, capacities in vitro and in vivo. In tumour cells, these increased invasive capacities were associated with incomplete epithelial to mesenchymal transition (EMT). In the case of IL-6, we further showed that it plays a key role in the acquired pro-invasive effect, and associated EMT, by tumour cells. Interestingly, the human breast tumours of larger size with/without lymph nodes involvement exhibit the highest levels of IL-6 in tumour-surrounding adipocytes [6]. Other teams have stressed the role of ECM (such as collagen VI) and ECM-remodelling enzymes in the paracrine effect of adipocytes on breast cancer (reviewed in [3]). Finally, it is important to note that Adipose-Derived Stem Cells (ADSCs) as well as pre-adipocytes also participate in breast cancer progression [3], emphasizing the involvement of all the major components of adipose tissue (AT) in this process. Using the 2D coculture system previously described as well as vivo approaches, our ongoing experiments expand the role of tumor-surrounding adipocytes in breast cancer progression. In fact, after modification by the tumour secrions, tumour-surrounding adipocytes appear to constitute a large part of the fibroblast-like cells that are present in the centre of the tumour (Bochet et al., submitted). We have also recently demonstrated that a metabolic crosstalk is established between breast cancer cells and tumour-surrounding adipocytes (Wang et al., in preparation). All these results, that will be presented in depth during the meeting, highlight the major role of adipocytes in cancer progression and pave the way for new pharmacological approaches for the treatment of breast cancer.

3. Perspectives for the role of obesity in breast cancer progression

Obesity is associated with elevated levels of pro-inflammatory cytokines in VAT and in the circulation, which generates a low-grade, chronic inflammatory state [5]. Interestingly, we have demonstrated that obesity and the defined profile of CAAs share inflammation as common traits [6]. Furthermore, in breast human tumours, the association of high levels of IL-6 in CAAs with high tumour size and enhanced local invasion reflect those traits present in obese patients [6]. Therefore, it is tempting to speculate that CAAs within an obese context should be more prone to amplifying the negative crosstalk with tumour cells. This assumption would suggest that such an inflammatory condition also exists in breast adipose tissue. In contrast to visceral adipose tissue, very little was known about mammary adipose tissue (MAT) and inflammation in obese subjects. Very interestingly, several recent publications have shown that a sub-inflammatory state is observed in the MAT of obese versus lean individuals (using both human and mouse models) and that in humans, the severity of breast inflammation was correlated with both BMI and breast adipocytes size (for review [3]). Therefore, these compelling recent results reinforce the hypothesis of an amplified paracrine negative crosstalk between adipose tissue and tumour cells to explain the poor prognosis observed in obese patients. Demonstrating this hypothesis and deciphering the molecular mechanisms involved would demand setting up adapted experimental approaches (including 3D coculture system with primary adipocytes obtained from lean and obese patients as well as breast cancer xenographs in immunocompetent obese and lean mice). The limiting steps in the implementation of these approaches and ways to overcome them will be discussed.

In conclusion, the AT has emerged these last five years as an integral and active component of breast cancer microenvironment. The role of the various cellular actors of AT begins to be addressed and it is important to underline that, to date, only the tumour-induced changes of mature adipocytes, the so-called CAAs, have been demonstrated in both in vitro studies, animal models and human tumours. Since population of obese people is constantly increasing, it is of fundamental and of clinical interest to further study the relationship existing between adipocytes and breast cancer cells in order to prevent and treat this subset of aggressive diseases.

Disclosure of interest

The author declares that she has no conflicts of interest concerning this article.

References