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The peritumoural adipose tissue microenvironment and cancer. The roles of fatty acid binding protein 4 and fatty acid binding protein 5

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ABSTRACT

The adipose tissue microenvironment plays a key role in tumour initiation and progression because it provides fatty acids and adipokines to tumour cells. The fatty acid-binding protein (FABP) family is a group of small proteins that act as intracellular fatty acid transporters. Adipose-derived FABPs include FABP4 and FABP5. Both have an important role in lipid-related metabolic processes and overexpressed in many cancers, such as breast, prostate, colorectal and ovarian. Moreover, their expression in peritumoural adipose tissue is deregulated, and their circulating levels are upregulated in some tumours. In this review, we discuss the role of the peritumoural adipose tissue and the related adipokines FABP4 and FABP5 in cancer initiation and progression and the possible pathways implicated in these processes.

1. Introduction

Currently, the prevalence of obesity is growing dramatically, not only in adults but in children and adolescents as well. The World Health Organization stated that in 2014, more than 1.9 billion adults were overweight; of these, over 600 million were obese. That means that 39% of adults were overweight and 13% were obese. Furthermore, 41 million children under the age of 5 were overweight or obese (WHO, 2016). The estimations for the coming years are not much better. Just in the USA, if these trends continue, by 2030 86.3% adults will be overweight or obese (Finkelstein et al., 2012; Wang et al., 2008). Therefore, obesity has become a public health crisis worldwide, and it has been recognized as one of the major health problems because there is a link between this pathology and cardiovascular disease, type 2 diabetes and cancer (Calle and Kaaks, 2004; Prieto-Hontoria et al., 2011). In addition to obesity, several studies have indicated that patients with overweight, metabolic syndrome and type 2 diabetes have an increased risk of having cancer (Booth et al., 2015; Doyle et al., 2012; Khandekar et al., 2011; van Kruijsdijk et al., 2009; Nimptsch and Pischon, 2015; Parkin and Boyd, 2011; Renehan et al., 2008; Schmidt et al., 2015; Wang et al., 2016a). In fact, in men, body

Abbreviations: ADF, adipocyte-derived fibroblasts; BAT, brown adipose tissue; BMAT, bone marrow adipose tissue; BMI, body mass index; CAA, cancer-associated adipocytes; CAF, cancer-associated fibroblasts; CSC, cancer stem cell; CD36, cluster of differentiation 36; CK1, cytokeratin 1; ECM, extracellular matrix; EGFR/HER2, epidermal growth factor receptor/ receptor tyrosine-protein kinase erbB-2; EMT, epithelial to mesenchymal transition; FABP4, fatty acid binding protein 4; FABP5, fatty acid binding protein 5; FFA, free-fatty acid(s); FoxM1, forkhead box M1; Foxo3, forkhead box O3; IGFBP-2, insulin-like growth factor-binding protein 2; IL-6, interleukin-6; IL-8, interleukin-8; IL-11, interleukin-11; MAPK/ERK, mitogen-Activated Protein Kinase/extracellular-Regulated Kinase; MMP1, matrix metalloproteinase-1; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; NSCLC, non-small cell lung cancer; PAI-1, plasminogen activator inhibitor-1; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; PPARβ/δ, peroxisome proliferator-activated receptor β/δ; PPARγ, peroxisome proliferator-activated receptor γ; PTEN, phosphatase and tensin homolog; RBP4, retinol binding protein 4; ROS, reactive oxygen species; RXR, retinoid X receptor; SP-1, specificity protein 1; STAT3, signal transducer and activator of transcription 3; TAM, tumour-associated macrophages; TGF-β, transforming growth factor-β; TNBC, triple negative breast cancer; TNF-α, tumour necrosis factor-α; TNM, tumour size, nodal-status, and metastasis; UCP1, uncoupling Protein 1; VEGF, vascular endothelial growth factor; WAT, white adipose tissue.

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mass index (BMI) is associated with oesophageal adenocarcinoma, thyroid, colon, renal, and rectal cancers and malignant melanoma. In women, BMI is associated with endometrial, gallbladder, oesophageal adenocarcinoma, renal, postmenopausal breast, pancreatic, thyroid, and colon cancers. Finally, BMI is associated with leukaemia, multiple myeloma, and non-Hodgkin lymphoma in both sexes (Calle and Kaaks, 2004; Khandekar et al., 2011; Renehan et al., 2008).

Obesity is characterized by impaired adipose tissue function; this leads to adipocyte hypertrophy, inflammation, hypoxia, angiogenesis, extracellular matrix (ECM) remodelling, fibrosis and stress responses. Despite the fact that the epidemiological data are quite strong, the molecular mechanisms linking obesity with cancer are poorly known (Hefetz-Sela and Scherer, 2013). For this reason, obesity management is an opportunity for cancer prevention, and adipose tissue has been suggested as a target organ in the treatment of some cancers (Prieto-Hontoria et al., 2011).

Because BMI has been correlated with endometrial, breast and other cancers linked with hormones, the impact of increased circulating sex hormones in cancer initiation and progression has been described (De Pergola and Silvestris, 2013). In fact, endogenous sex hormones have an active role in tumour cell growth, mediating the effect of obesity on cancer (Brown and Simpson, 2010; De Pergola and Silvestris, 2013; Kaaks et al., 2005). Despite this association, other molecules provided by adipose tissue have been described as having a strong association with cancer initiation and progression. Actually, the positive association between obesity and cancer may be partly explained by insulin resistance, aberrant insulin growth factor (IGF) expression, obesity-induced hypoxia, hyperinsulinaemia, sustained hyperglycaemia, glucose intolerance, the above described sex hormone disorders, oxidative stress, altered lipid metabolism and chronic inflammation. Moreover, emerging research has also begun to focus on the role of circulating adipokines (i.e, adipocyte-secreted factors) in cancer (Booth et al., 2015; Nimptsch and Pischon, 2015; Prieto-Hontoria et al., 2011; Schmidt et al., 2015).

In fact, some recent data have suggested that paracrine and systemic factors secreted from adipose tissue can promote cancer development and progression. The local pro-tumourigenic effects due to adipocyte-derived factors are particularly interesting because adipocytes can represent an important part of the tumour microenvironment in some cancers. In this sense, it is crucial to describe which players are taking part in these processes (Hefetz-Sela and Scherer, 2013).

With all this evidence, it seems that the link between obesity and cancer involves metabolic and endocrine alterations from obesity. However, an active crosstalk can exist between tumour cells and “healthy” adipose tissue that can corrupt the surrounding adipocytes. There is a shift to dysfunctional adipose tissue mainly characterized by altered production of adipokines and hormones (Calle and Kaaks, 2004). Many studies are focused on the role of obesity in cancer, but what is the real role of “healthy” adipose tissue in cancer? Does this adipose tissue have any role in cancer progression? Can the tumour perturb the function of the adjacent adipose tissue to obtain lipids and other factors for its own benefit?(Hefetz-Sela and Scherer, 2013)

2. Cancer cells and the tumour microenvironment

Cancer cells can corrupt the non-transformed cells in the microenvironment. Interactions between malignant and non-transformed cells create the tumour microenvironment, and there is a constant crosstalk between cancer cells and other cells from the microenvironment. This constant communication occurs via a dynamic network of cytokines, chemokines, adipokines, growth factors, and inflammatory and matrix remodelling enzymes (Balkwill et al., 2012; Hefetz-Sela and Scherer, 2013; Prieto-Hontoria et al., 2011). Therefore, the microenvironment has a crucial role in cancer evolution and progression, undergoing many changes during this process. For this reason, the tumour microenvironment is under intense research to develop new tools for cancer prognosis and treatment (Muppalla et al., 2013). Apart from malignant cells, the tumour microenvironment contains cells of the immune system, the tumour vasculature and lymphatics, as well as fibroblasts, pericytes and adipocytes (Balkwill et al., 2012).

For many years, the focus on the investigation of the microenvironment concentrated mainly on fibroblasts. During cancer progression, there are substantial changes in fibroblasts, with the generation of cancer-associated fibroblasts (CAFs). These CAFs can secrete growth factors and cytokines that lead to an increase in angiogenesis, tumour growth and invasion. Moreover, all these changes lead to a modulation of cancer stem cell (CSC) phenotypes and an altered ECM. These modifications conclude with altered signalling in tumour cells (Allen and Louise Jones, 2011; Kalluri and Zeisberg, 2006).

Other important points of the study of microenvironment and cancer have been hypoxia and inflammation. In fact, there are substantial changes in tumour microenvironment that imply these two processes. Hypoxia and inflammation are mediated by secreted factors and signalling pathways. Hypoxia is an essential factor in cancer because it can promote tumour initiation, progression and resistance to therapy. During nutrient and oxygen deprivation, tumour cells undergo changes in metabolism and inflammation (Carnero and Lleonart, 2016; Huber et al., 2016). The main family of proteins implicated in these processes are the hypoxia-inducible factor (HIF) transcription factors. After oxygen deprivation, HIF proteins activate the transcription of genes that increase metabolism, angiogenesis, erythropoiesis, cell migration and invasion, cell proliferation, and inflammation (Simon, 2016). Hypoxia also impacts cell signalling pathways, including c-met and lysyl oxidase mediated pathways, which can promote tumour cell invasion (Allen and Louise Jones, 2011).

To understand the role of obesity in cancer, some studies have focused on local and systemic inflammation in cancer. In fact, there are many key events in cancer progression that can be regulated by the inflammation progress, such as proliferation, survival, angiogenesis, invasion and metastasis (Hanahan and Weinberg, 2011). Certain signalling pathways are implicated in the regulation of these events. The intracellular pathways involved in inflammation are signal transducer and activator of transcription 3 (STAT3) and nuclear factor-kB (NF-kB). STAT3 is involved in cell proliferation and survival, and NF-kB has a key role in proliferation, inflammation, and survival and negatively regulates cellular senescence. Moreover, both pathways are implicated in the epithelial to mesenchymal transition (EMT) and in DNA damage and repair (Donohoe et al., 2016).

Monocytes/macrophages have been studied to understand inflammation in tumour cells. Macrophages have been described in tumour tissue and, together with other cell types, form the tumour microenvironment (Komohara et al., 2014). In this sense, the infiltrated macrophages can modulate tumour progression (Allen and Louise Jones, 2011). In solid tumours, 5–40% of the tumour mass corresponds to tumour-associated macrophages (TAMs), and in many cancers this association reveals poor prognosis (Bingle et al., 2002; Pollard, 2008; Sousa et al., 2015). Moreover, macrophages can enhance tumour cell migration, invasion, angiogenesis and ECM remodelling through the secretion of chemotactic and chemokinetic factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and the regulation of collagen fibrillogenesis (Pollard, 2008).

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