Journal of Cellular Physiology

Multifaceted Breast Cancer: The Molecular Connection With Obesity

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Obesity is characterized by a disruption in energy balance regulation that results in an excess accumulation of body fat. Its increasing prevalence poses a major public health concern because it is a risk factor for a host of additional chronic conditions, including type 2 diabetes, hypertension, and cardiovascular disease. Obesity is increasingly recognized as a growing cause of cancer risk. In particular excessive adipose expansion during obesity causes adipose dysfunction and inflammation that can regulate tumor growth. In obesity, dysregulated systemic metabolism and inflammation induce hyperinsulinemia, hyperglycemia, dyslipidemia, and enhance sex hormone production with increased secretion of proinflammatory adipokine that impact breast cancer development and progression. This review describes how adipose inflammation that characterizes obesity is responsible of microenvironment to promote cancer, and discuss how steroid hormones, that are essential for the maintenance of the normal development, growth and differentiation of the cells, influence the induction and progression of breast cancer.

J. Cell. Physiol. 232: 69–77, 2017.

Nowadays, it is clinically and epidemiologically demonstrated that obesity is correlated with a worse postmenopausal breast cancer prognosis and a higher risk of resistance to endocrine therapy. Several evidences demonstrate that obesity impacts negatively on prognosis for both pre- and post-menopausal patients. The most notable effects are in estrogen receptor alpha (ERα) positive post-menopausal patients (Wolters et al., 2012).

Clinical studies of obese patients under hormonal therapy for the treatment of breast cancer, indicate that obesity increases significantly the onset of relapse. As the primary site of estrogen expression in postmenopausal women is the fatty tissue, the abundance of this tissue produces higher levels of estradiol. This, therefore, may contribute to the increase in risk of breast cancer and worse outcome observed in this population (Hankinson et al., 1995; McTiernan et al., 2006).

The development of resistance to endocrine therapy may be mediated by different mechanisms. Often, hormone receptor signaling pathways are deregulated, in particular the insulin-like growth factor 1 receptor (IGF-1R) and the HER family of receptors, is responsible. These receptors can crosstalk with ERα, leading to increased activity of non-genomic pathways, ligand-independent activation of the ERα, and abnormal regulation of cell cycle and apoptotic signaling (Osborne and Schiff, 2011).

"About 70–80% of infiltrating breast carcinoma are estrogen receptor alpha (ER-α) positive, thus offering clinicians the opportunity of hormonal therapies (HTs) in adjuvant and/or metastatic situation. Modulation of estrogen signaling pathways using anti-estrogens, such as Tamoxifen, was indeed one of the first recognized targeted therapies and is currently the first-line treatment for ER-α positive tumors (Linares et al., 2011)."

"The effectiveness of HTs is directly linked to the expression and functionality of ER-α. Several retrospective studies and clinical trials have demonstrated that tumors expressing both ER-α and progesterone receptor (PR) respond significantly better to HTs than those with low receptor expression. Among patients who have a tumor expressing both ER-α and PR, a benefit from HTs is seen in about 60% of cases, but the initial response is often not durable, since tumors become resistant to hormonal manipulation, leading to an 'endocrine-resistant disease.' Moreover, patients with breast carcinoma

Conflicts of interest: All the authors declare no conflict of interest.

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Manuscript Received: 24 June 2016
Manuscript Accepted: 30 June 2016

Accepted manuscript online in Wiley Online Library (wileyonlinelibrary.com): 1 July 2016.
DOI: 10.1002/jcp.25475

lacking ER-α (ER-α negative) will not benefit from these therapies, as the expected efficiency of HTs in this situation is less than 10% (Linares et al., 2011)." Candidate molecular pathways "of intrinsic and acquired resistance to HTs emphasize the importance of signaling networks which control cell proliferation" or survival (Linares et al., 2011).

The adipose tissue associated with obesity display an altered adipokine secretion pattern that favor the establishment of chronic inflammation state that promote oncogenesis and tumor progression. It has been described that adipocytes produce growth factors and chemokines, which may directly affect breast cancer cell growth, motility, and invasion (D'Esposito et al., 2012, 2016). Recent reports link matrix metalloproteinases (MMPs) to the interplay between adipose tissue and subsequently to cancer transformations. In fact, MMPs mediate bidirectional crosstalk between invading cells and adjacent adipocyte/preadipocytes with a central role in tumor desmoplasia and represent a molecular link between obesity and cancer. It is known that several factors such as hormones and obesity are key drivers of cancer progression. In breast cancer miRNAs represent a link between steroid signaling and obesity. Several studies on differential miRNAs expression suggest the possibility to monitor breast cancer progression using their signature, likely with significant clinical impact. Such studies are essential to novel putative diagnostic/prognostic biomarkers and therapeutic targets to improve the treatment of breast cancer.

Estrogen receptors: "Genomic" and "non-genomic" actions in related to obesity breast cancer

Steroid hormones, such as 17β-estradiol (E2), play pivotal roles in the regulation of sexual development and fertility in both males and females (Couse and Korach, 1999; Nef and Parada, 2000). Estrogens also regulate metabolic processes in fat, liver, and bone tissues (de Cherney, 1993; Väänänen and Härkönen, 1996). In addition, estrogens, not only influence different disease states, for example, cancers (e.g., breast, uterine) causing hormone-dependent growth and proliferation (Prall et al., 1998), but also important physiological/pathological processes, such as inflammation, cellular differentiation, cardiovascular integrity, metabolism, and immunity. Estrogen elicits their actions through estrogen receptor (ER) proteins. ERs exist as two isoforms, ERα and ERβ, with different functions and tissue expressions, they are members of a conserved superfamily of nuclear receptors that have the same conservative structure (Migliaccio et al., 2000) (Fig. 1).

ERα, like the other nuclear receptors, contains two C4-type zinc fingers and binds as a dimer to palindromic sequences known as estrogen response elements (ERE), a ligand-binding domain (LBD) that is bound by estrogens and anti-estrogens and contains a ligand-activated transcription activation function, AF-2, as well as sequences required for ligand-dependent dimerization, and the N-terminal domain that contains transcription activation function AF-1 (Schwabe et al., 1993; Tanenbaum et al., 1998).

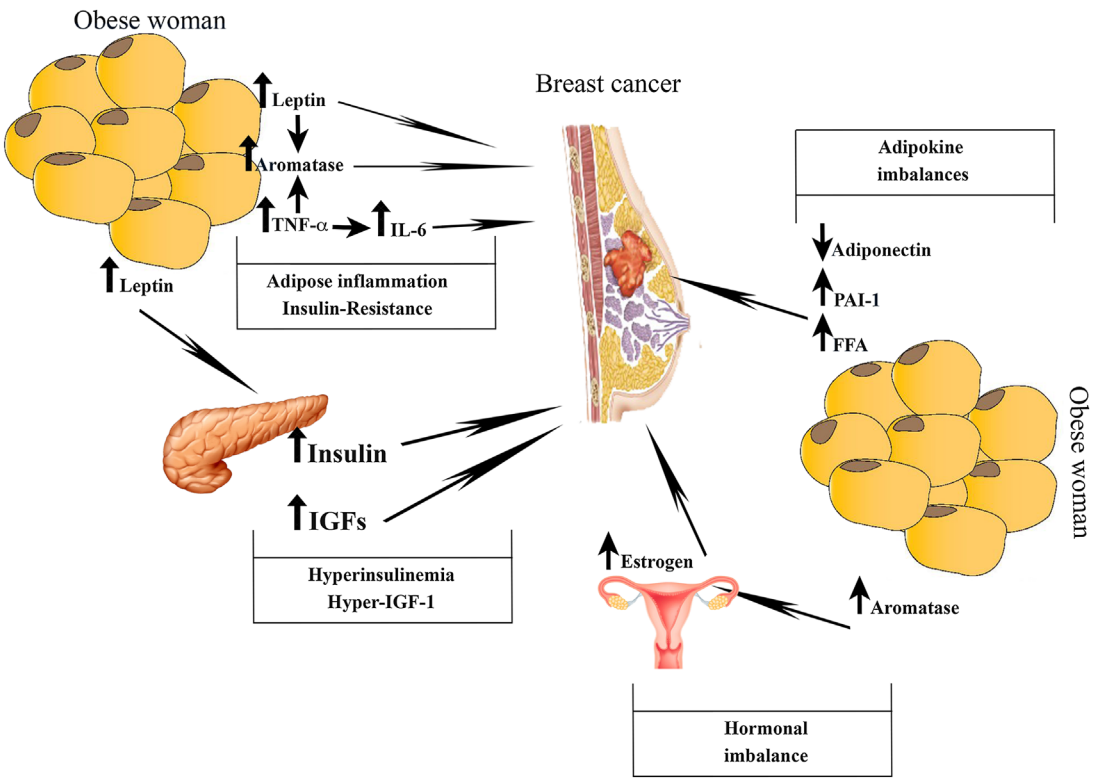

Fig. 1. Link between obesity and breast cancer. Adipose tissue of obese women produces higher levels of aromatase enzyme, so there is an increased production of estrogens. Moreover, obesity determines increasing circulating levels of insulin and insulin-like growth factor, which, by acting as mitogens for epithelial breast cells, stimulate their neoplastic degeneration. In addition, adipocytes can produce inflammatory cytokines, such as TNF- and IL-6, and leptin hormone that can influence aromatase activity and estrogen-dependent cell proliferation.

Extensive studies have shown that AF-1 and AF-2 can act both independently and synergistically in a promoter- and cell-specific manner (Tsai and O'Malley, 1994). A large number of studies have described the mechanisms underlying the inhibition of ERα activity by partial anti-estrogens such as tamoxifen and pure antagonists such as ICI 182, 780. These studies have shown that the activity of tamoxifen results in the inhibition of AF-2, whereas ICI 182, 780 prevents the activation both AF-1 and AF-2, increasing its turnover and causing the disruption of the estrogen receptor nucleo-cytoplasmic shuttling (Dauvois et al., 1992, 1993).

The "genomic" pathway of estrogen consists in the activation of estrogen receptors after hormone stimulation; ERs dissociate from nuclear chaperone proteins, dimerize, and bind to DNA at specific sequences known as estrogen response elements (EREs), modulating the estrogen-dependent transcription of responsive genes (Deroo and Korach, 2006). Estrogens, in addition to canonical genomic pathway, trigger a non-canonical pathway that active different transduction systems (Beato et al., 1989). One of the non-canonical pathway activate Adenylate Cyclase and the subsequent production of cAMP, which acts as a second messenger, propagating the estrogen signals to several cellular cytoplasmic and nuclear effectors (Aronica et al., 1994). There are evidences that demonstrate the involvement of PKA in ERα-mediated non-canonical effect of estrogen in many different processes, for example, in the induction of breast cancer cell proliferation (Hously and Kolch, 2000); in the transcription activation (Liu et al., 2009), while in the basal forebrain cholinergic neurons in vivo, PKA inhibitor reduces the estrogen-induced CREB phosphorylation (Szego et al., 2006).

In addition to the "genomic" pathway, it is recently described an alternative mechanism of action, "non-genomic," that is faster that the genomic one, and by which estrogen control the cell cycle progression, cell survival, and cell migration. Some of these effects are mediated by estrogen receptors, but most of them are dependent by the activation of cellular kinases, that are the proto-oncogenic tyrosine-kinase (Src), the phosphatidylinositol-3-kinase (PI3K), the mitogenic protein kinase (MAPK), the protein kinase A (PKA) and C (PKC) through G protein-coupled receptors (GPCRs), or ionic channel (Castoria et al., 2008). All these signaling pathways culminate, depending on the cell context, in differentiated effects of steroid hormones, such as proliferation, survival, migration, and differentiation, through the activation of several gene expression programs (Fig. 2).

Recently it is demonstrated that cells grown in obese patient sera supplemented media, "displayed both greater cell viability and growth" and "IGF-1R, Akt and ERK1/2 activation" compared "to control sera. Despite the lack of a significant difference in genomic ERα activity following growth in obese versus control patient sera, Bowers et al. (2013) observed a dramatic reduction in cell viability and growth after concurrent inhibition of the ERα and PI3K/Akt signaling pathways, and ERα inhibition attenuated obese serum-induced Akt and ERK1/2 activation." "Together, these data suggest that obesity promotes greater ERα positive breast cancer cell viability and growth through enhanced crosstalk between non-genomic ERα signaling and the PI3K/Akt and MAPK pathways (Bowers et al., 2013)."

Role of cAMP/PKA signaling pathway in controlling metabolism

The cyclic adenosine monophosphate (cAMP) is an important intracellular signaling molecule, which acting as second messengers between extracellular stimuli such as hormones, elicits intracellular response. While the specific function of a given signal varies according to the cell type and the extracellular environment, stimulus activating the signal, generally activates the cyclase enzyme with the formation of the cyclic nucleotide (cNT). This, in turn affects the activity of downstream effectors including kinases, ion channels, transcription factors, and scaffolding proteins. Among these, cAMP-dependent serine/threonine protein kinase A (PKA) play an important role in different cellular processes, for example, negative regulator of cAMP signaling, mediator of anti-apoptotic and pro-apoptotic cascades, etc. (Rehmann et al., 2007; Insel et al., 2012).

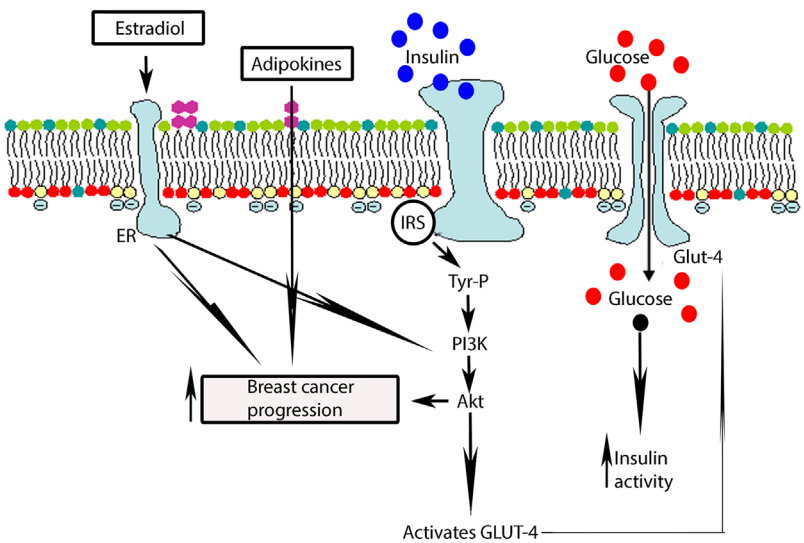

Fig. 2. The PI3K/Akt signaling pathway in the insulin sensitivity and breast cancer. In the fed state, insulin is secreted by the pancreas and binds the IR to active insulin signaling and to enhance the uptake of blood glucose by GLUT-4. The activavion of PI3K/Akt signaling pathway both by estrogen non-genomic signaling and insulin/IRS1 pathway contribuite to breast cancer progression.

The holoenzyme, PKA, is a tetramer consisting of two regulatory subunits (R) and two catalytic subunits (C): the formers contain two binding sites for cAMP, and upon its binding, the latters activate their substrates by phosphorylation (Gerits et al., 2008). The protein kinase inhibitor (PKI) is able to inhibit the catalytic activity of the C subunit, and to induce the nuclear export of the C subunit acting as a chaperone. PKA-anchoring proteins (AKAPs) act modulating the interaction of PKA with specific effectors and substrates in cAMP-dependent manner; the subcellular locations through the link to ACs for activation of PKA; the binding with PDEs in order to block the signaling with a negative feedback loops (Wong and Scott, 2004). PKA can activate through phosphorylation a large number of both cytosolic and nuclear proteins, including metabolic enzymes, glycogen synthase, and phosphorylase kinase (Tasken et al., 1997). PKA inhibits glycogen synthesis, promotes glycogen depletion, and inhibits lipid synthesis. PKA also regulates other signaling pathways, such as MAP kinases and in turn promotes phosphorylation and dissociation of an inhibitory tyrosine phosphatase (PTP); PKA phosphorylation inactivates phospholipase C (PLC) b2; also decreases the activities Raf and Rho and modulates ion channel permeability. In addition, PKA regulates the transcription by direct phosphorylation of the transcription factors cAMP-response element-binding protein (CREB), cAMP-responsive modulator (CREM), and ATF1 (Rehmann et al., 2007). This phosphorylation is a key event that allows these proteins to interact with the transcriptional coactivators at specific target genes (Mayr and Montminy, 2001). For negatively feeds back, the CREM gene encodes for the repressor ICER, which turn off the cAMP-induced transcription (Sassone-Corsi, 1995).

p85a/PI3K at the crossroads between obesity related-breast cancer and diabetes

Phosphatidylinositol (PI) 3-kinases are a class of enzyme that mediate the action of numerous growth factors phosphorylating the 3-position in the inositol ring of membrane phosphoinositides (Cantley, 2002). The family is classified into three different types: class I, class II and class III. The class IA is composed by three different regulatory subunits (p85a, p85b, and p55g) and also three catalytic subunits (p110a, p110b, and p110d), can be activated by nuclear receptors and GTP-bound Ras (Vanhaesebroeck and Waterfield, 1999; Stein and Waterfield, 2000). PI3-kinase is also activated by Src-family kinases through binding of the p85 subunit to the Src-SH3 domain (Pleiman et al., 1994). The biological effects of PI3-kinase activation are mediated by the PI3-kinase downstream targets (Stein and Waterfield, 2000). PI3-kinase regulates multiple biological functions through the activation of a downstream protein, protein kinase B (PKB), also called Akt, as well as gene expression, cell cycle, endocytosis and vesicular trafficking, survival, metabolic signals dependent by insulin, cell transformation, and oncogenesis (Coffer et al., 1998). Estradiol rapidly stimulates the p85PI3K/Akt pathway, increases expression of cyclin D1, so promoter the S-phase entry of cells through estradiol-induced Src activation. Moreover, estradiol treatment of MCF-7 cells induces the binding of ERa, with Src and p85 quickly. It is likely that hormonal induction of this association facilitates the estradiol activation of the two signalling members and their reciprocal communication. When estradiol enters the cells, it binds nuclear receptors, which dimerize and interact with DNA sequences to regulate gene transcription (Beato et al., 1989; Mangelsdorf et al., 1995; Parker and White, 1996). Alternatively, rather than interacting directly with DNA, ER bind DNA-associated transcription factors stimulating or repressing transcription (McKenna et al., 1999). The transcriptional activity of the ER can be modulated in the absence of ligand through receptor phosphorylation by kinases regulated by peptide hormones, such as EGF (Power et al., 1991; Pietras et al., 1995). Alternate oestrogen actions are very rapid and non-genomic (Revelli et al., 1998; McEwen and Alves, 1999). We have identified a novel non-genomic action of estradiol depending on the ability of the ERa or b to interact with Src and activate the Src/Shc/Ras/Erk pathway (Migliaccio et al., 1996, 2000). In addition to estradiol, also progestins (Migliaccio et al., 1998) and androgens (Migliaccio et al., 2000) activate the same pathway although with some remarkable differences in the initial steps leading to the hormonal Src activation. Interference with the pathway activation abolishes the hormone-dependent growth (Castoria et al., 2008). Estradiol activation of the same pathway protects osteoblasts from apoptotic stimuli (Kousteni et al., 2001), indicating that the Src/Ras/Erks stimulation has different effects, depending on the environmental conditions. and activates the PI3-kinase/AKT pathway in endothelial cells, leading to an increase of nitric oxide synthesis (Simoncini et al., 2000), in neuroprotection (Honda et al., 2000) and in cellular growth (Poser et al., 2000).

It was described by Ciullo et al. (2001) that cAMP–PKA influence Ras signaling, by selectively stimulating the Ras–PI3K complex. Moreover, p85aPI3K is an efficient PKA substrate in vitro (Ciullo et al., 2001). We have identified a serine (S83) in the Nterminal region of p85αPI3K that is phosphorylated in vivo and in vitro by PKA and is responsible for the the insulin dependent pathway (Cosentino et al., 2007; De Gregorio et al., 2007; Di Zazzo et al., 2014). We have recently determined the molecular mechanism linking PKA to insulin-mediated PI3K activation, using p85αPI3K mutated forms: one in which the S83 was substituted by alanine to prevent the phosphorylation (p85A); and an other one in which the S83 was substituted by aspartate to mimic the phosphorylated residue (p85D). Phosphorylation of p85αPI3K S83 modulates the formation of the p85αPI3K/IRS-1 complex and its subcellular localization influencing the kinetics of the insulin signaling both on MAPK-ERK and AKT pathways. Furthermore, the insulin-mediated p85αPI3K S83 phosphorylation plays a key role in the cell proliferation, growth, and motility in MCF-7 cells breast cancer model (Di Zazzo et al., 2014).

Matrix-metalloproteinases: A crucial link between obesity and breast cancer development

Matrix-metalloproteinases (MMPs) are a multifunctional family of zinc-dependent endopeptidases able to degrade basement membranes and extracellular matrix (ECM) components, which plays key roles in many biological processes. This family consists in 25 members and numerous homologues which are divided into five groups with respect to their preferential degradation matrix substrates: matrilysins, collagenases, gelatinases, stromelysins, and membrane MMPs (MT-MMPs) (Klein and Bischoff, 2011). Regarding the biological function, MMPs have been shown to be critically involved in numerous physiological processes, including organ development, wound healing, tissue remodeling, morphogenetic changes, etc., as well as in several pathological conditions, such as arthritis, nephritis, neurological diseases, skin ulceration and, in particular, in cancer development and progression, since their ability to create an environment that support the initiation and maintenance of growth of primary and metastatic tumors, and to regulate cytokines and chemokines activity by proteolytic processing (Sbardella et al., 2012).

In the last few years, among the wide range of pathologies in which MMPs have been shown to be implicated, metabolic disorders have obtained a strong interest. The role of MMPs in pathogenesis and in the development of clinical complications of dysmetabolic diseases, like obesity or type 2 diabetes, is supported by several in vivo and in vitro evidences, even if the physio-pathological mechanisms by which MMPs favor

metabolism alteration are still not completely understood (Hua and Nair, 2015). The deep implication of MMPs in cardiometabolic diseases has been prevalently explained by the strong association existing between metabolism and immunity. In fact, metabolic diseases and, in particular, obesity are generally characterized by a state of chronic low-grade inflammation with an abnormal release of pro-inflammatory mediators (cytokines, chemokines, adipokines, proteases, etc.) which can modulate immune response and alter metabolic homeostasis (Guarnerv and Rubio-Ruiz, 2015). Several studies, in fact, observed a strong increase of MMPs levels both in adipose tissue and in biological fluids of obese patients, compared to lean subjects, with a positive correlation to other inflammatory markers. Leitner et al. (2015a) observed a deep increase of MMP-9 levels in adipose tissue from obese donors, which improve Osteopontin (OPN) inflammatory and pro-diabetic effects on adipocytes. Dandona et al. (2014) also found high levels of MMP-9 in plasma from obese patients, with or without diabetes, directly associated with plasma nitric oxide metabolites levels positively related with responsivity to surgical therapy. Rouault et al. (2013) observed that blood neutrophils from obese subjects release high levels of MMP-9 and other pro-inflammatory mediators (IL-8, CCL2, MPO, etc.) which may improve the expression of inflammatory molecules by the visceral white adipocyte. Miksztowicz et al. (2012) shows that plasma activity of MMP-2 in overweight/obese women is associated with menopausal status and positively correlate to cardiovascular risk parameters (waist circumference, HOMA, lipidemia, etc.). On the contrary, in a prospective cross-sectional study on more than 70 obese young women, Kosmala et al. (2008) reported a decrease of MMP-2 and an increase of MMP-9 levels, positively related to cardiac function parameters. Many hypothesis also suggest a possible role of MMPs in regulation of adipocyte remodeling processes, which are necessary for fat mass development and which are pathologically accelerated in obese patients (Wronkowitz et al., 2014). Indeed, modulation of ECM components represents an essential step in adipocyte dysfunction, which favors the infiltration of immune cells into the adipose tissue causing the maintenance of low-grade inflammatory state (Catalán et al., 2012). Tokunaga et al. (2014), in fact, shown that focal MMP-dependent collagenolysis pattern is higher in visceral adipose tissue-derived vascular stromal cells compared to subcutaneous ones, with a differential expression of secreted collagenase like MMP-8 and MMP-13, suggesting a key role of these molecules in distinguishing patterns of ECM remodeling and adipose function in different fat depots. Moreover, a novel implication of MMPs has been underlined in hypoxia-dependent adipocyte dysfunction. Several observations, in fact, are consistent with the concept that adipose tissue mass expansion lead to tissue relative hypoxia, which favors the differential expression of some cytokines and growth factors involved in obesity-related adipocyte dysfunction In this context, Lolmède et al. (2003) observed that differentiated 3T3-F442A adipocytes undergone to hypoxia conditions show an upregulation of the expression of MMP-2, MMP-9, VEGF, and HIF-1alpha. On the other hand, MMPs have been demonstrated to be crucial during adipogenesis and their inhibition may lead to an impairment of adipose differentiation processes, giving rise to adipose tissue hypertrophy and/or hyperplasia (Chavey et al., 2003). Bauters et al. (2015), in fact, observed that murine embryonic fibroblasts derived from MMP-2 deficient mice and MMP-2 knockdown 3T3-F442A pre-adipocytes showed significantly impaired differentiation into mature adipocytes with 90% reduction of intracellular lipid content and expression of pro-adipogenic markers. In the same way, Shih and Ajuwon (2015) showed that MMP-13 knockdown 3T3-L1 cells display reduced differentiation and reduced expression of PPARγ.

Pathological events involved in obesity aethiology, such as inflammation and ECM modulation, also represents key steps in cancer development and progression (Barreto et al., 2015), so the hypothesis of a crucial implication of MMPs in obesity-related carcinogenesis has been largely underlined. In the past, MMPs were thought to have a role exclusively in invasion and metastasis processes, but recent studies demonstrated that they are also deeply involved in several steps of cancer formation and during the growth of tumor cells by releasing of cell membrane bound precursors of some growth factors, or the inhibition of apoptosis pathways. Indeed, a number of studies identified that MMPs levels are enhanced in the majority of solid tumors, both within neoplastic tissue and in body fluids, and are linkable with grade or stage and overall cancer-specific survival (Yadav et al., 2014). Specifically, in breast cancer there is a wide body of literature implicating MMPs in tumor progression in both clinical and preclinical investigation. Increasing levels of MMPs in the total population of breast cancer patient, in fact, have been associated with higher tumor grade and poor outcome. The increasing risk of breast cancer development has been observed in a high percentage of obese women, also in pre-menopausal state (Roy and Walsh, 2014). The relationship between breast cancer and metabolic dysfunction is almost complex. Among the wide range of risk factors, inflammation surely has a prominent role. Obesity-induced inflammation, with increased secretion of pro-inflammatory factors from the adipocytes and inflammatory cells, including matrix proteases, can promote the expansion of breast cancer cells resulting in an enhanced tumor mass growth and progression under obese condition (Roy and Walsh, 2014). Indeed, Soto-Guzman observed that free fatty acids, which are generally present in high concentration in obese subjects bloodstream (dyslipidemia), by a mechanisms involving PKC, Src, and EGFR, have been demonstrated to favor MMP-9 expression in breast cancer cell lines (MCF-7 and MDA-MB-231), which increases cell invasiveness potential (Soto-Guzman et al., 2010). Kim found that Visfatin, an adipokine which is highly produced in visceral fat of obese patients, can induce the expression of MMP-2 and MMP-9 and VEGF genes, with implication in metastasis and angiogenesis of breast cancer (Kim et al., 2010). Consistently, Strong underlined that another obesity-related adipokine called Leptin favors MMP-2 and MMP-9 secretion in HER2-MCF10A cells (Strong et al., 2015). Sinergically, MMPs and OPN have been observed, by Leitner et al. (2015b), to enhance Aromatase enzyme levels in MCF-7 cell line, which promote impaired estradiol production and, in this way, estrogen-dependent breast cancer development. In addition, studies on LM3 murine breast epithelial cells growth in 3T3-L1 adipocyte conditional medium, shown an enhancement of MMP-9 secretion able to influence normal and tumoral breast epithelial cell proliferation and migration (Creydt et al., 2010). Dirat et al. (2011) also confirmed the theory that peritumoral adipocytes exhibit a modified phenotype and specific biological features sufficient to be named cancer-associated adipocytes (CAA), with impaired cytokines and proteases expression, in particular of IL-6 and MMP-11, with an amplified risk of tumor progression in obese patients. Moreover, the ability of obese patients adipose-derived stem cells (ASCs) to paracrinally promote breast cancer tumorigenesis and metastasis have been associated, by Zhao et al. (2013) to a MMP-9 secretion. Besides, by tissue microarray of human clinical samples, Chukkapalli et al. (2014) identified that B-type Eph tyrosine kinase receptor, which is highly expressed in invasive and metastatic breast carcinomas, mediates pro-invasive function in breast cancer cells by involving MMP-2 and MMP-9 gelatinases and that this ability can be blocked by treatment with respective neutralizing antibodies.

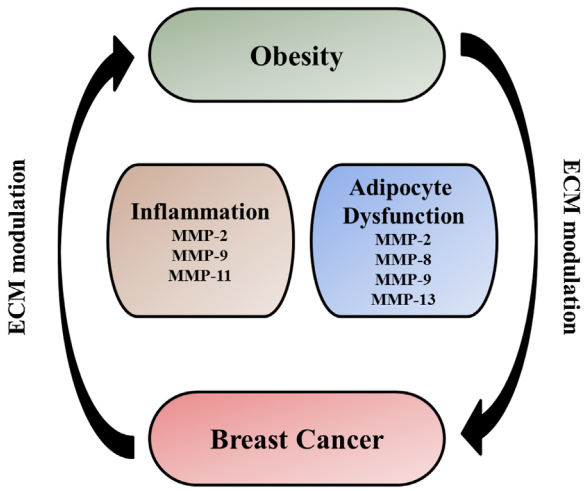

Fig. 3. Structure of matrix metalloproteinases. Matrix metalloproteinases (MMPs) are composed of different subdomains. All MMPs have the "minimal domain" in common, which contains three principal regions: a pre-peptide, a pre-domain, and catalytic domain containing a zinc-binding site. In addition to the minimal domain, most MMPs possess a hemopexin-like region, which is linked to the catalytic domain via a hinge region. MMPs are divided into secreted MMP and membrane-anchored proteinases (MT-MMPs). MMP-2 and MMP-9, also called gelatinases A and B, show gelatin-binding repeat that resemble the collagen-binding type II motif of fibronectin (FN). Figure adapted from Kessenbrock K, Plaks V, Werb Z. 2010. Matrix metalloproteinases: Regulators of the tumor microenvironment. Cell 141:52–67.

Based on these scientific evidences, not surprisingly MMPs have gained a potential of target in developing new therapeutic strategy useful to retard the progression and/or to prevent the recurrence of breast cancer, and intensive investigations are going on about how the use of dietary or pharmaceutical supplements may reduce the activity of inflammatory mediators ameliorating obesity-related breast tumor progression and prolong the life of patients (Fig. 3).

Role and implications of miRNAs in breast cancer

Over the last decades, extensive studies have demonstrated the gene profiling and signature as a tool to understand prognosis, therapy response, and resistance in breast cancer (Fig. 4).

Recently, revolutionary data of the Human Genome Project have given evidence that less than 2% of transcripts encode functional proteins and more than 93% of the genome DNA can be transcribed to RNA but most of the transcripts are non-coding RNAs (ncRNA) (International Human Genome Sequencing Consortium, 2004). Those ncRNAs include miRNAs (miRNA). miRNA genes represent approximately 1% of the genome and have length ranging from 18 to 24 nt which act mainly by negatively regulating gene expression through association with 30-UTRs of mRNA species (Zhang and Su, 2009). In fact, mature miRNAs constitute a class of singled-stranded small molecules, that regulate the stability or translational efficiency of targeted messenger RNAs. Interestingly, miRNA are reported to be involved in regulation of hundreds of different conserved or non-conserved targets, in temporal and tissue-specific fashion (Cui et al., 2006).

Currently obvious studies have identified critical roles for many pathogenesis such as cancer and obesity. In Iorio et al.

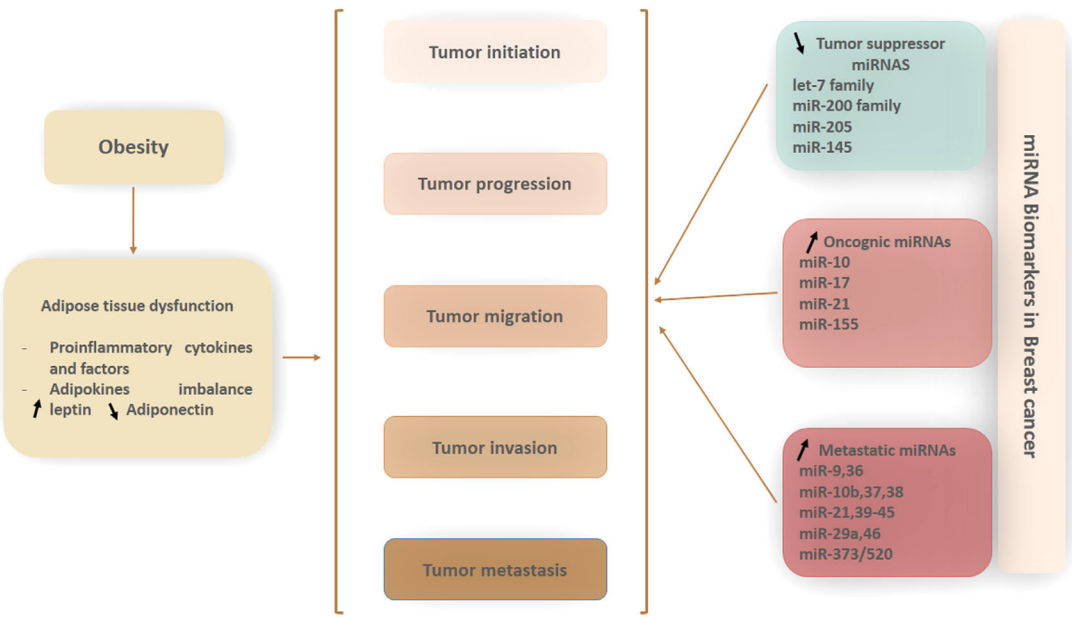

Fig. 4. The interplay between the role of obesity and MicroRNA signatures in breast cancer development. It is well established that obesity leads to altered expression profiles of various adipokines and cytokines including leptin and adiponectin, directly associated with breast cancer development. Recently, miRNA signature has been described to be aberrantly regulated in breast cancer associated obesity, and to strongly contribute to this pathogenesis. MiRNA play a pivotal role in tumor initiation and progression and control of epithelial-mesenchymal transition (EMT), as they can act as oncogenes or tumor suppressor genes. Consequently, miRNAs have been proposed as emerging biomarkers in the diagnosis, prognosis, and therapy of breast cancer.

(2005), breast cancer was the first solid tumors to be profiled for miRNAs expression. Further, a growing body of evidence implicates miRNAs in modulating human breast cancer behavior. Indeed, aberrantly expressed miRNAs is not only a random association with breast cancer, but also exerts a causal role in the tumorigenic process. Deregulation of miRNAs is emerging as a major aspect of cancer etiology and have been associated with breast cancer initiation and progression metastasis as well as epithelial to mesenchymal transition (EMT) (Iorio et al., 2008; Shi and Guo, 2009). It has been demonstrated that miRNAs can function either as oncogenes or as tumor suppressors, and more recently it has been demonstrated that a miRNAs can exploit both functions according to the cellular context of its target genes (Kwan et al., 2016).

Several large-scale microarray analysis demonstrate that number of miRNAs were expressed differently in breast cancer being either down-regulated or up-regulated (Andorfer et al., 2011). The exploitation of consequent results showed that miRNAs signature have considerable potential for use as biomarkers to differentiate between different molecular and cellular subtypes of breast cancer and to identify the tissue of origin of metastatic tumors (Iorio et al., 2011).

Furthermore, it has been indicated that specific miRNAs were considered to be associated and correlated with specific breast cancer clinic pathological factors, such as HER2, estrogen, and progesterone receptor level. Increasing data have identified distinct miRNA subsets distinguishing HER2-positive from HER2-negative and ER-positive from ER-negative breast cancers (Lowery et al., 2009).

Moreover, emerging evidence suggests that circulating miRNAs may be important in diagnosis and prognosis of breast cancer. Likewise, circulating miRNAs in blood of breast cancer patients demonstrate aberrantly expressed levels in breast cancer patients' serum even for early stage of the pathology. Interestingly, Zhao et al. (2016) have identified a direct quantification method for measuring plasma MiRNAs as potential biomarkers for detecting metastatic breast cancer.

One proposed mechanism to explain dysregulated miRNAs in breast cancer is that steroid hormones signaling directly or indirectly affect regulation of miRNAs biogenesis in in hormone related cancers. Functional in vitro studies performed in MCF7 breast cancer cells given evidence that steroid hormone receptors (SHRs) and miRNAs mutually regulate each other's activity through feedback loops, permitting a myriad of complex and subtle responses to stimuli (Fletcher et al., 2014). Several studies clearly indicate that estrogen is a key hormone that modulate the miRNA biogenesis at several steps of transcription, maturation, or auto-regulatory feedback loops (Fletcher et al., 2014; Jiang et al., 2016).

Nevertheless, further than hormonal deregulation, obesity is recognized as comorbidity of breast cancer. High-throughput assays have revealed the miRNAs expression profile were appreciably deregulated in obesity and obesity associated pathologies (Abente et al., 2016). In fact, miRNAs are aberrantly expressed in adipose tissue taken from obese subjects. Recent discoveries increasingly highlight how miRNAs influence shifts in metabolic pathways under various obesity-related disease settings. In fact, miRNAs play a crucial role in regulating metabolic pathways in liver disease such as Non-alcoholic fatty liver disease (NAFLD) and dyslipidemia (de Aguiar Vallim et al., 2013). Furthermore, miRNAs play mechanistic role in adipogenesis and insulin resistance. In addition, markedly deregulated miRNAs seems to function as inducers of pro-inflammatory secretion factors in obese adipose tissue (Peng et al., 2014).

Multiple research groups have studied on differential miRNAs expression in breast cancer and associated pathologies. Collectively, all these data suggest the ability to monitor breast cancer progression by determining miRNAs signature, likely with significant clinical impact. Such studies are vital in the identification of novel attractive putative diagnostic/prognostic biomarkers and therapeutic targets to improve clinical management and treatment of breast cancer. However, miRNAs act in complex biological networks, which are not fully understood. Indeed, several factors such as hormones or obesity are key drivers of cancer development. A more exhaustive understanding of the role of miRNAs in breast cancer should consider likewise the interplay between steroid signaling or obesity and miRNAs.

Conclusions

The "dramatic expansion of inflamed adipose tissue during obesity has several effects that impact cancer development," in particular breast cancer. "Inflamed adipose tissue is an important endocrine organ, producing adipokines, and other factors that promote tumor growth and metastasis while also inducing metabolic dysregulation. Adipose tissue is also a source of cells that can alter the tumor microenvironment that release" free fatty acids "and inflammatory cytokines and" adipose stem cells "that can contribute to the remodeling of the tumor microenvironment" in the breast tissue. In normal breast adipose tissue, little is known about the adipokine expression with obesity. In this review, we summarize the evidence "that adipose tissue inflammation is a key driver of estrogen production in obese postmenopausal" woman "and plays an important role in ER+ breast cancer (Deng et al., 2016)." Moreover, other adipokine such as leptin is a key regulator of breast tumor development and it is increased expression is associated with proliferation, angiogenesis, and tumor growth. Furthermore, leptin is responsible of increased production of several proangiogenic factors, including MMP-2 and MMP-9. In conclusion, "the obese population has significantly increased cancer risk due to obesity-associated adipose inflammation, which can increase adipose secretion of pro-inflammatory factors and alter the tumor microenvironment (Deng et al., 2016)." Then, a healthy diet, especially in childhood, associated with a correct prevention and a substantial weight loss reduces cancer risk, attenuating adipose-related inflammatory mechanisms than can regulate breast cancer development and progression. "Today, the main challenges in mammary cancer research are thus the development of more specific biomarkers to predict response or resistance to hormonal therapy and the development of new combined targeted therapies of hormone therapy-insensitive or therapy-resistant tumors (Linares et al., 2011)."

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