REVIEW

The effect of adipocyte–macrophage crosstalk in obesity-related breast cancer

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Abstract

Adipose tissue is the primary source of many pro-inflammatory cytokines in obesity. Macrophage numbers and pro-inflammatory gene expression are positively associated with adipocyte size. Free fatty acid and tumor necrosis factor-α involve in a vicious cycle between adipocytes and macrophages aggravating inflammatory changes. Thereby, M1 macrophages form a characteristic 'crown-like structure (CLS)' around necrotic adipocytes in obese adipose tissue. In obese women, CLSs of breast adipose tissue are responsible for both increase in local aromatase activity and aggressive behavior of breast cancer cells. Interlinked molecular mechanisms between adipocyte–macrophage–breast cancer cells in obesity involve seven consecutive processes: Excessive release of adipocyte- and macrophage-derived inflammatory cytokines, TSC1–TSC2 complex–mTOR crosstalk, insulin resistance, endoplasmic reticulum (ER) stress and excessive oxidative stress generation, uncoupled respiration and hypoxia, SIRT1 controversy, the increased levels of aromatase activity and estrogen production. Considering elevated risks of estrogen receptor (E2R)-positive postmenopausal breast cancer growth in obesity, adipocyte–macrophage crosstalk is important in the aforementioned issues. Increased mTORC1 signaling in obesity ensures the strong activation of oncogenic signaling in E2Rα-positive breast cancer cells. Since insulin and insulin-like growth factors have been identified as tumor promoters, hyperinsulinemia is an independent risk factor for poor prognosis in breast cancer despite peripheral insulin resistance. The unpredictable effects of adipocyte-derived leptin–estrogen–macrophage axis, and sirtuin 1 (SIRT1)–adipose-resident macrophage axis in obese postmenopausal patients with breast cancer are unresolved mechanistic gaps in the molecular links between the tumor growth and adipocytokines.

Key Words

- obesity
- breast cancer
- aromatase activity
- TSC1–TSC2 complex
- estrogen receptor

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Introduction

Obesity is mainly dependent on excessive fat accumulation in the regional adipose tissues. In obese individuals, more adipocytes release more adipocytokines. Large breast volume is proportional to the fat storage in the visceral and intermuscular depots in obese premenopausal women (Janiszewski *et al*. 2010). Postmenopausal patients with high visceral fat area have significantly shorter distant disease-free survival than premenopausal patients in breast cancer series (Iwase *et al*. 2016). Furthermore, peri-tumoral fat ratio significantly correlates with the

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positive axillary lymph nodes among obese patients with breast cancer (Obeid *et al.* 2017). In this context, the release of excessive inflammatory cytokines from hypertrophic adipocytes, and increase in inflammatory pathway activity due to increases in number of adipose tissue macrophages (ATMs) are important contributing factors to the pathogenesis of obesity-related diseases. Eventually, these biologically active polypeptides promote the inflammatory, endocrine, paracrine and autocrine pathways during the progression of breast cancer (Li & Han 2018). In fact, breast cancer results from interactions of various factors. Besides the genetic predisposition and obesity, aging is one of the important conditions that promotes the disease. According to the American Cancer Society, the most invasive breast cancer cases are reported among women aged 55 years or more (Minakshi *et al.* 2017). Therefore, the relationship between the prevalence of obesity and increased risk of invasive breast cancer should be considered, especially in postmenopausal women (Ng *et al.* 2014, Zhao *et al.* 2018). In postmenopausal women, the link between obesity and breast cancer is closely related to the hormonal imbalance and the release of growth factors and inflammatory cytokines by adipocytes (Lukanova *et al.* 2004). In a clinical study that involved a total of 16,608 women without hysterectomy, the patients were randomized for the estrogen-plus-progestin trial. In the estrogen-plus-progestin group, breast cancer incidence was higher, and the cases were more commonly lymph node positive (Chlebowski *et al.* 2010). However, obese, never users of hormone therapy have 1.7-fold to 2.3-fold elevated risks of ductal and E2R-positive–progesterone receptor (PR)-positive breast cancer, respectively, compared to thinner women (Li *et al.* 2006). In a large percentage of patients with invasive breast cancers, increasing central obesity is significantly associated with continuous elevation in risk of postmenopausal breast cancer. This relationship can be explained by the excessive endogenous estrogen production of breast adipose tissue adjacent to cancer cells observed in obesity (Guo *et al.* 2018). Thus, obese women have 35% higher concentrations of estrone and 130% higher concentrations of estradiol compared to normal weight women (McTiernan *et al.* 2003). There is abundance of data linking obesity-related breast cancer and E2R signaling. The comorbidities of obesity such as excessive local production of estrogens in adipose tissue, the influence of adipokines and inflammatory cytokines have been specified as independent risk factors for breast cancer in postmenopausal women (Boyd & McGuire 1990, McDonnell *et al.* 2014). Despite systemic estradiol declines in menopause, the incidence of E2Rα-positive breast cancer dramatically increases (Pfeilschifter *et al.* 2002, Sasser *et al.* 2007). In this regard, obesity-related breast inflammation is critical for the induction of aromatase activity. Aromatase also mediates the crosstalk of obesity-associated inflammation and hormone alterations in breast cancer (Subbaramaiah *et al.* 2012). However, aromatase inhibitors in breast cancer therapy are less efficient at suppressing estradiol serum levels in obese when compared with nonobese women (Pfeiler *et al.* 2013). Eventually, interlinked molecular mechanisms between adipocyte–macrophage–breast cancer cells in obesity involve seven consecutive processes: overexpression of adipocyte- and macrophage-derived inflammatory cytokines, tuberous sclerosis proteins 1 (hamartin)–2 (tuberin) (TSC1–TSC2) complex–mammalian target of rapamycin (mTOR) crosstalk, insulin resistance and hyperactivation of insulin-like growth factors (IGFs)-related pathways, the increased levels of aromatase activity, ER stress and excessive oxidative stress generation, uncoupled respiration and hypoxia, Sirtuin 1 (SIRT1) controversy (Simone *et al.* 2016). Regarding the continuous flow and accumulation of new macrophages/monocytes from circulation to adipose tissue in obesity, crosstalk between adipocytes and ATMs is an important process that initiates the chronic inflammation in obese adipose tissue (Bai & Sun 2015). In this review, unlike the previous studies, the effects of above-mentioned seven consecutive processes on the biological behavior of breast cancer have been reappraised by considering the crosstalk between adipocyte–macrophage–breast cancer cells in obesity.

Adipocyte–macrophage interaction

Adipose tissue is the primary source of many pro-inflammatory cytokines, but ATMs, which are important cellular components of adipose tissue, have key regulatory functions in inflammation, insulin resistance and adipocyte functions (Russo & Lumeng 2018). ATMs are responsible for almost all adipose tissue tumor necrosis factor-alpha (TNF-α) expression and significant amounts of nitric oxide and interleukin-6 (IL-6) expression. Indeed, macrophage-derived cytokines lead to a chronic low-grade inflammatory state that is crucial in the pathogenesis of obesity-related pathological conditions (Weisberg *et al.* 2003, Lee & Lam 2018). Furthermore, macrophage numbers and pro-inflammatory gene expression in adipose tissue are not only positively associated with adipocyte size, but also negatively associated with weight loss in

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obese individuals (Weisberg *et al.* 2003, Clément *et al.* 2004). Therefore, both body mass index (BMI) and average adipocyte size are significant predictors of macrophage accumulation in adipose tissue. In this context, the crosstalk between adipocytes and macrophages provokes the initiation of chronic inflammation in obese adipose tissue as well as exacerbating the inflammatory process (Wellen & Hotamisligil 2003). Approximately 10% of adipocytes are renewed annually by a continuous turnover. Low generation rates of adipocytes associate with adipose tissue hypertrophy (Spalding *et al.* 2008, Arner *et al.* 2010). Apoptotic old adipocytes are removed by macrophages (Duvall *et al.* 1985, Keuper *et al.* 2011). Necrosis of adipocytes driven by hypertrophy is a prominent phagocytic stimulus that regulates ATM infiltration which is gradually increased by obesity (Cinti *et al.* 2005). Apoptotic cells send an 'eat me' signal to macrophages, triggering their own engulfment (Krahling *et al.* 1999). Galectin-3 expression at sites of adipocyte necrosis and hypertrophic adipocyte-derived chemotactic 'monocyte chemoattractant protein-1 (MCP-1)/CC chemokine receptor 2 (CCR2)' pathway promotes macrophage accumulation into the obese adipose tissue (Cinti *et al.* 2005, Kanda *et al.* 2006). Infiltration of cytotoxic T cells into obese adipose tissue is thought to precede macrophage accumulation. T-cell-derived cytokines such as interferon-gamma (IFN-γ) promote the recruitment and activation of M1 macrophages, thereby adipose tissue inflammation is enhanced (Harford *et al.* 2011). While TNF-α induces inflammation in adipocytes as a major macrophage-derived mediator, adipocyte-derived free fatty acids (FFAs) induce inflammatory cytokines and chemokines expression in macrophages. Thus, pro-inflammatory adipokines of adipose tissue, such as MCP-1 and TNF-α, and saturated fatty acids released from adipocytes interact with toll-like receptor 4 (TLR4) complex, inducing nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) activation in resident macrophages. TLRs are the most well-characterized sensors that detect exogenous 'danger signals pattern-recognition receptor'. Saturated fatty acids that are released from hypertrophic adipocytes serve as a ligand for TLR4 (Fig. 1). Inflammatory process activation in obesity is initiated by 'adipocyte–macrophage–TLR4' pathway (Suganami *et al.* 2005, 2007, Wolowczuk *et al.* 2008). Thus, macrophages discriminate other molecular patterns from self-proteins through expression of pattern-

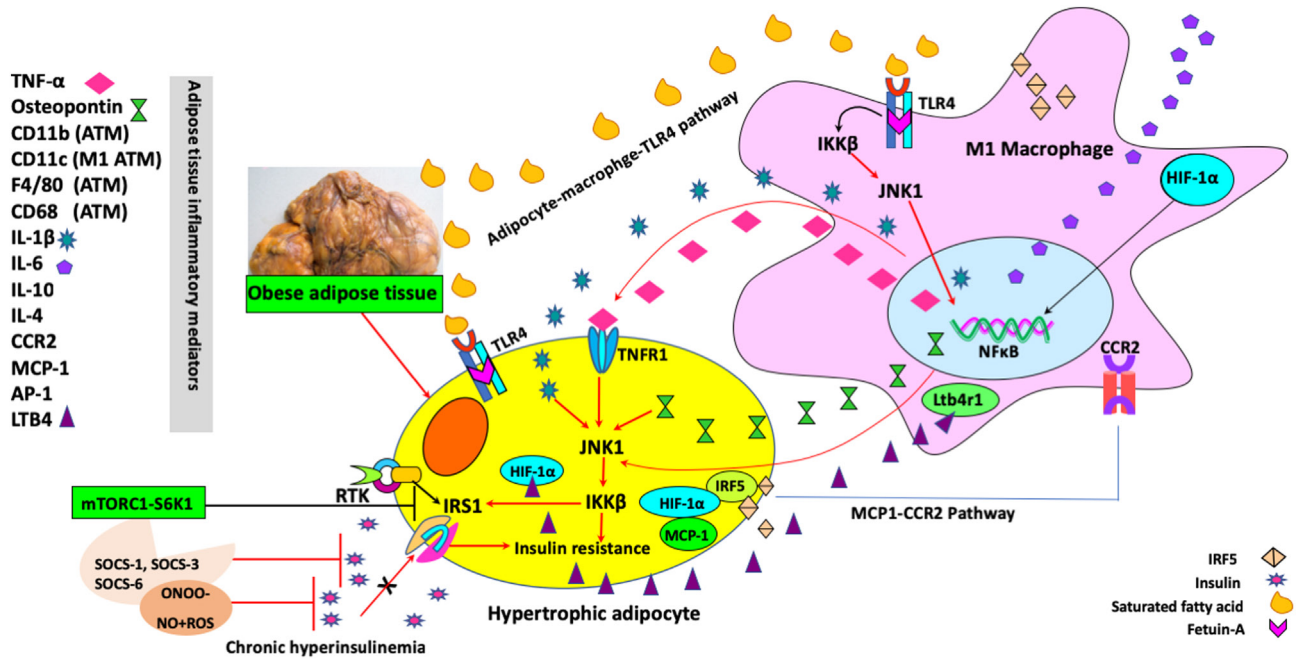


Figure 1
While TNF-α induces JNK1–IKKβ pathway in adipocytes as a major macrophage-derived mediator, hypertrophic adipocytes-derived saturated fatty acid serves as a ligand for TLR4 and induces inflammatory cytokines and chemokines expression in macrophages as well as adipocytes. AP-1, activating protein-1; CCL2, CCR2–chemokine (C–C motif) receptor ligand 2; HIF-1α, hypoxia-inducible factor-1α; IKKβ, inhibitor kappa B kinase-β; IL-1β, interleukin-1β; IRF5, interferon regulatory factor-5; IRS-1, insulin receptor substrate-1; JNK, c-Jun N-terminal kinase; LTB4, leukotriene B4; ltb4r1, leukotriene B4-G protein-coupled receptor; MCP-1, monocyte chemoattractant protein-1; mTORC1, mammalian target of rapamycin complex 1; NFκB, nuclear factor-kappa B; NO, nitric oxide; ONOO–, peroxynitrite; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; S6K, ribosomal protein S6 kinase-1; SOCS3, suppressor of cytokine signaling 3; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TNFR1, TNF receptor-1.

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recognition receptors, such as TLRs (Barton & Kagan 2009). Obesity-induced elevation in saturated FFAs induces insulin resistance by activating the TLR4-mediated signaling in both macrophages and adipocytes (Shi *et al.* 2006). However, FFAs do not directly bind to TLR4, fetuin-A is required as an endogenous ligand for TLR4 (Pal *et al.* 2012). Furthermore, macrophages can recognize the injured or damaged cell-derived 'danger-associated molecular patterns' and release pro-inflammatory cytokines. Members of the Nod-like receptor family, including NLRP3 and the adaptor apoptosis-associated speck-like protein containing CARD (ASC) are critical components of the inflammasome that link endogenous danger signals to caspase-1 activation leading to chronic inflammation (Franchi *et al.* 2009). Saturated fatty acids can trigger inflammation by activating inflammasomes (NLRP3) and induce macrophages (Wen *et al.* 2011). The NLRP3 senses lipotoxicity-associated danger signals that are increased in intracellular ceramide to induce caspase-1 cleavage in macrophages, and contributes to insulin resistance (Vandanmagsar *et al.* 2011). Macrophage-inducible C-type lectin (Mincle) is induced selectively in macrophages during the interaction between adipocytes and macrophages. Saturated fatty acid released from adipocytes induces Mincle mRNA expression in macrophages through the TLR4/NF-κB pathway. Macrophage-induced adipocyte lipolysis aggravates obesity-induced adipose tissue inflammation by this way (Ichioka *et al.* 2011). TLR-dependent polarization mediators of M1 macrophages include different transcription factors such as NF-κB, activator protein-1 (AP-1), transcription factor PU.1 (PU.1), CCAAT/enhancer-binding protein α (C/EBP-α), signal transducer and activator of transcription 1 (STAT1) as well as interferon regulatory factor-5 (IRF5) (Juhas *et al.* 2015). High expression of IRF5 is characteristic for M1 macrophages and it is negatively associated with insulin sensitivity in visceral adipose tissue (Krausgruber *et al.* 2011, Dalmas *et al.* 2015). Differentiation of M1 macrophages are dependent on the upregulation of IRF5 levels (Juhas *et al.* 2015). In fact, obesity is accompanied by a transformation in the polarized states of macrophages from an anti-inflammatory 'alternatively activated' M2 form, to a more pro-inflammatory 'classically activated' M1 form (Lumeng *et al.* 2007*a*, Kosteli *et al.* 2010). While the microenvironment in a lean adipose tissue is composed of a 4:1, M2:M1 ratio, obesity increases the number of M1 macrophages by 65-fold. Whereas the number of M2 macrophages per weight basis is also increased by six-fold. Thus, the ratio of M1-to-M2 macrophages is increased in obesity (Lumeng *et al.* 2008, Fujisaka *et al.* 2009).

Once infiltrated into the adipose tissue, macrophages become mature and interact with adipocytes. A paracrine loop involving FFAs and TNF-α between adipocytes and macrophages establishes a vicious cycle that aggravates inflammatory changes in the adipose tissue (Suganami *et al.* 2005). Because of this mutual relationship, macrophages form a characteristic crown-like structures (CLS) around necrotic adipocytes (Weisberg *et al.* 2003, Cinti *et al.* 2005, Murano *et al.* 2008, Olefsky & Glass 2010). CLS-associated macrophages intensely produce pro-inflammatory mediators (Kern *et al.* 2001, Xu *et al.* 2003, Olefsky & Glass 2010, Suganami & Ogawa 2010). Exposure of adipose tissue to Th2 cytokines, such as IL-4, IL-13 and granulocyte–macrophage colony-stimulating factor (GM-CSF), stimulates ATM proliferation, whereas Th1 cytokines, such as TNF-α, inhibit local ATM proliferation. CLSs exhibit a unique microenvironment for macrophage proliferation. Interestingly, locally proliferating macrophages are not classically activated (M1) type, but they have alternatively activated (M2) immune phenotype. IL-6 as a Th2 cytokine, stimulates M2 polarization and local ATM proliferation in obesity (Braune *et al.* 2017). There is a shift toward a M2 phenotype in non-CLS macrophages in adipose tissue from obese subjects compared with lean ones. Macrophages in CLS are predominantly M1, but most other macrophages, particularly those in fibrotic areas, are M2 (Spencer *et al.* 2010). CLSs in the white adipose tissue of the breast (CLS-B) in obese women with breast cancer are responsible for both increase in local aromatase activity, and enhanced invasiveness and metastasis capacity of breast cancer. As a matter of fact, the main mechanism that increases the risk of breast cancer in postmenopausal women is the excessive estrogen production of obese adipose tissue due to high aromatase activity of adipocytes (Rose & Vona-Davis 2014). Since ATMs are selectively localized to dead adipocytes, clearance of free lipid appears to be an important function of galectin-3 (MAC-2)-expressing macrophages (Cinti *et al.* 2005). Therefore, increased local extracellular lipid concentrations drive ATM infiltration to adipose tissue. A part of the FFAs released from necrotic adipocytes are transported to adjacent adipocytes, while the rest are taken by macrophages. Despite the presence of large quantities of lipid-filled macrophages in CLSs, increased flux of non-esterified fatty acids from apoptotic adipocytes indicate the lipid buffering capacity of ATMs is surpassed (Thompson *et al.* 2010, Shapiro *et al.* 2013, Boutens & Stienstra 2016). CLS-B in obese women with breast cancer indicates the relationship between inflammation and aromatase activity, and at the same

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time points to the increased breast cancer risk and poor prognosis (Morris *et al.* 2011). Breast inflammation defined by CLS-B is paralleled by increased NF-κB-binding activity and elevated levels of aromatase mRNA and aromatase activity. Besides the aromatase activity, cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) activities more strongly correlate with the CLS-B index (severity of breast inflammation) than with BMI (Morris *et al.* 2011). Additional important factors increasing breast cancer risks in obesity are adipocyte-related hyperleptinemia and obesity-related hyperinsulinemia (Rose & Vona-Davis 2014). Thus, leptin overexpression by the resident adipocytes in breast cancer tissue compared with adjacent healthy tissues is a serious factor promoting malignant growth in breast tissue (Liang *et al.* 2018). The crosstalk between leptin and aromatase increases estrogen levels. This effect of leptin is mediated through the mitogen-activated protein kinase (MAPK)/'extracellular signal-regulated kinase 1/2 (ERK1/2)'-STAT3 and phosphoinositide 3-kinase (PI3K) pathways (Masarwi *et al.* 2018). Consequently, adipocyte-derived leptin participates in cell growth and angiogenesis during breast cancer development by enhancing estrogen effects on malignant tissue via a paracrine pathway (Gonzalez *et al.* 2006, Schmidt *et al.* 2015). Since STAT proteins have an important role in the development of breast cancer, downregulation of STAT3 and STAT5a/b has been suggested as a mechanism for anti-proliferative effects of some anticancer agents in breast cancer cells. Methylsulfonylmethane (MSM), which is an organic sulfur-containing natural compound without any toxicity, suppresses the phosphorylation of STAT3 and STAT5b in E2Rα-positive breast cancer cells. Moreover, MSM decreases the DNA-binding activities of STAT5b and STAT3, to the target gene promoters (Lim *et al.* 2012). Synergy between the leptin/leptin receptor/STAT3 signaling pathway and the human epidermal growth factor receptor 2 (HER2) protects tamoxifen-treated HER2 overexpressing cells from the inhibitory effect of tamoxifen through differential regulation of apoptosis-related genes (Papanikolaou *et al.* 2015). Elevated serum levels of leptin maintain resistance to anti-estrogen drugs during hormonal therapy of breast cancer (Garofalo *et al.* 2004). On the other hand, leptin-mediated crosstalk between tumor-associated macrophages (M2 macrophages) and breast cancer cells shows that adipocytes provoke tumor growth and metastasis via stimulating IL-8 production of tumor-associated macrophages (TAMs). Eighty-three percent of breast cancer cases have leptin receptors. In accordance with this, distant metastasis is detected in 34% of all leptin receptor-positive tumors with leptin overexpression, but none of the patients with leptin receptor-negative and weak leptin expressing tumors are found to have distant metastasis (Ishikawa *et al.* 2004). Leptin–cytokine signaling pathways are also responsible for increasing the secretion of adipokines from both adipocytes and TAMs in obesity (Newman & Gonzalez-Perez 2014). It can be stated that, leptin is an important biomarker that could identify relapse and prognosis in breast cancer via adipocyte–macrophage interaction (Khabaz *et al.* 2017). Although, leptin receptor expression in primary breast cancer is positively correlated with estrogen receptor (E2R) expression, anti-estrogen therapy increases serum leptin levels in obese postmenopausal breast cancer patients due to stimulation of the synthesis and release of leptin in the adipocytes. Therefore, anti-proliferative efficacy of anti-estrogen drugs are attenuated. Thereby, obesity promotes therapeutic escape in breast cancer (Marttunen *et al.* 2000, Jardé *et al.* 2008, Bougaret *et al.* 2018).

TSC1–TSC2 complex–mTOR crosstalk

All these factors form an inflammatory microenvironment to regulate the biological function of transcription factors. Approximately 70–75% of breast cancers express the E2R, which indicates the estrogen dependency for tumor growth. When activated by 17β-estradiol, E2Rα plays an important role in the stimulation of cancer cell proliferation and prevention of apoptosis (Ali & Coombes 2000). The PI3K/protein kinase B (AKT)/mTOR pathway is a key intracellular signaling system that drives cellular growth and survival. Activation levels of this pathway determine the growth rate of E2R-positive breast cancer. Eventually, estrogen dependency of breast cancer cells also determines the prognosis of patients (Ciruelos Gil 2014). E2Rα-expressing tumors represent the largest group of breast cancer patients indicating that more women die from E2Rα-positive breast tumors than from other more malignant breast cancer subtypes (Molina *et al.* 2017).

In fact, mTOR is an atypical serine/threonine-protein kinase that belongs to the PI3K-related kinase family and interacts with several proteins to form two large protein complexes called mTOR complex 1 (mTORC1) and 2 (mTORC2) (Loewith *et al.* 2002) (Fig. 2). In adipocytes, mTOR-mediated phosphorylation at Ser501/503 changes the binding site of adaptor protein Growth factor receptor binding protein-10 (Grb10) from the insulin receptor to Raptor (Regulatory-associated protein of mTOR). The dissociation of Raptor from mTOR results in

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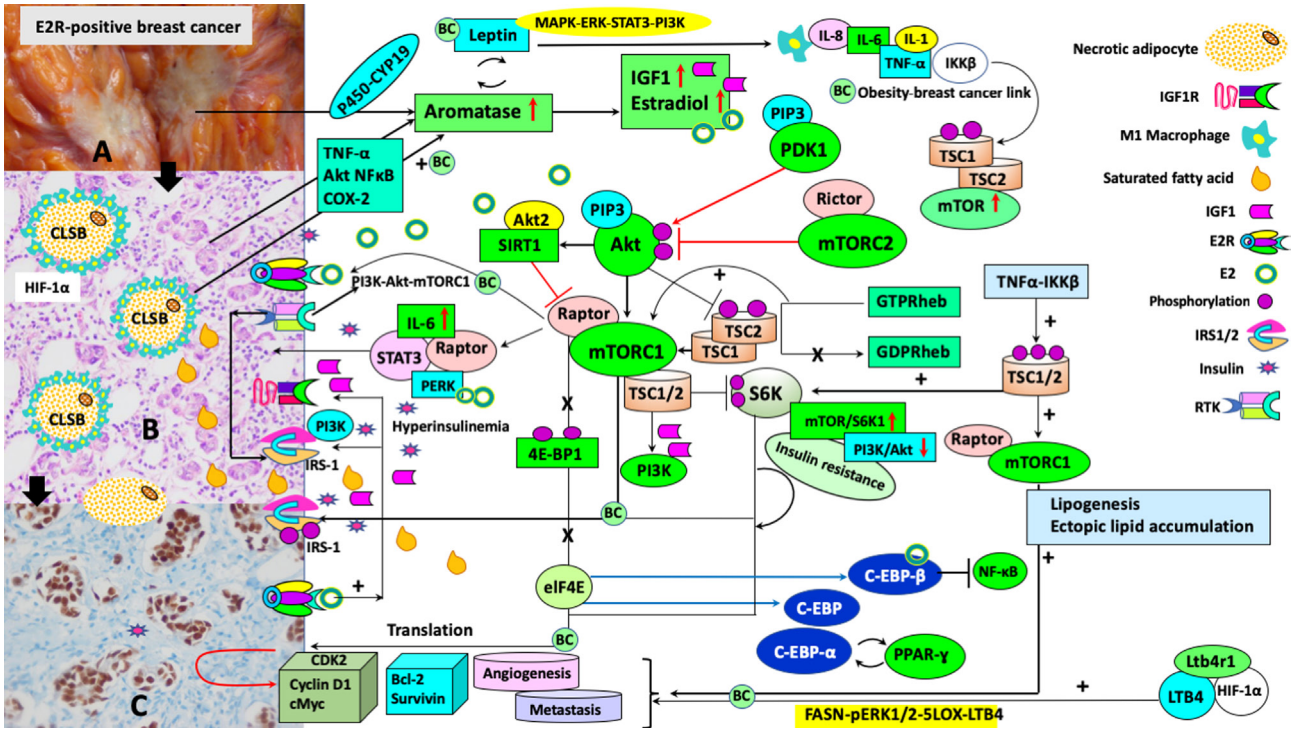


Figure 2

Connections between obesity and breast cancer. The extensive crosstalk between the E2R and PI3K/Akt/mTORC1 pathways is critical for invasiveness and metastasis capacity of E2R-positive breast cancer in obese patients. Estrogen activates PERK in response to the accumulation of unfolded proteins in the endoplasmic reticulum. PERK activates transcription factor STAT3, which increases apoptosis. CLSs-B in obese women with breast cancer are responsible for both increase in local aromatase activity, and enhanced invasiveness and metastasis capacity of cancer cells. Apoptotic hypertrophic fat cells send an 'eat me' signal to macrophages, triggering their own engulfment by ATM. Activated RTKs activate PI3K. PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to generate PIP3. Akt and PDK1 bind to PIP3 at the plasma membrane, and PDK1 phosphorylates the activation loop of Akt. RTK signaling also activates mTORC2 through a currently unknown mechanism, and mTORC2 phosphorylates Akt. Akt activates mTORC1 through multisite phosphorylation of TSC2 within the TSC1–TSC2 complex, and this blocks the ability of TSC2 to act as a GTPase-activating protein (GAP) for Rheb, thereby allowing Rheb-GTP to accumulate. Rheb-GTP activates mTORC1, which phosphorylates downstream targets such as 4E-BP1 and the hydrophobic site on the S6Ks. PDK1 phosphorylates the activation loop on the S6Ks in a reaction independent of PDK1 binding to PIP3. Both mTORC1 and S6K can phosphorylate serine residues on IRS1, which targets IRS1 for degradation, and this serves as a negative feedback mechanism to attenuate PI3K–Akt signaling (insulin resistance pathways). (A) E2R-positive breast cancer specimen; (B) invasive ductal breast cancer, H&EX400; (C) Diffuse strong nuclear estrogen receptor positivity in carcinoma cells. 4E-BP1, eIF4E-binding protein-1; Akt, serine/threonine kinase; ATM, adipose tissue macrophage; BC, breast carcinogenesis pathway; Bcl-2, B-cell lymphoma 2 protein; CDK2, cyclin-dependent kinase 2; C-EBP-α, CCAAT/enhancer-binding protein-α; CLS-B, crown-like structure in breast adipose tissue; c-Myc, Myc proto-oncogene protein; COX2, cyclooxygenase-2; E2R, estrogen receptor; ERK, extracellular signal-related kinase; FASN, fatty acid synthase; GTBRheb, GTPase-activating protein (GAP) for Ras-related small G protein; HIF-1α, hypoxia-inducible factor-1α; IGF1, insulin-like growth factor-1; IKKβ, inhibitor kappa B kinase-β; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; IRS-1, insulin receptor substrate-1; eIF4E, eukaryotic initiation factor 4E; LOX, lipoxygenases; LTB4, leukotriene B4; ltb4r1, leukotriene B4-G protein-coupled receptor; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; NFκB, nuclear factor-kappa B; p450-CYP19, aromatase cytochrome P450, product of the CYP19 gene; PDK1, phosphoinositide-dependent kinase-1; PERK, protein kinase RNA-like endoplasmic reticulum kinase; pERK1/2, phosphorylated ERK1–2; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PPAR-γ, peroxisome proliferator-activated receptor γ; RTK, receptor tyrosine kinase; S6K, ribosomal protein S6 kinase-1; SIRT1, silent information regulator-1; STAT3, signal transducer and activator transcription 3; TNF-α, tumor necrosis factor-α; TSC1, hamartin; TSC2, tuberin.

downregulation of mTORC1 signaling (Liu *et al.* 2014). Obesity-induced insulin resistance in breast cancer depends on chronic activation of mTORC1. However, inactivation of mTORC1 due to dissociation of Raptor causes elevated IL-6 production, activation of STAT3 and enhanced tumor growth rate (Umemura *et al.* 2014). The mRNA expression of Raptor is higher in tumors compared with normal tissues. Furthermore, the expression of Raptor is associated with a higher tumor grade (Wazir *et al.* 2013). Following the estrogen stimulation, E2Rα binds to Raptor and obliges it to translocate to the nucleus. Estrogen-regulated interaction between mTORC1 and E2Rα, besides the Raptor translocation into the nucleus, causes phosphorylation of E2Rα on S104/106. It is believed that the crosstalk between E2Rα and PI3K/Akt/mTORC1 signaling ensures the strong activation of oncogenic signaling in E2Rα-positive breast cancer cells (Alayev *et al.* 2016). Upstream regulators of mTORC1, TSC1 and

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TSC2 promotes PI3K signaling by suppressing ribosomal protein S6 kinase 1 (p70S6 kinase; S6K). These two tumor suppressor genes, TSC1 and TSC2, function as a guanosine triphosphatase (GTPase)-activating protein (GAP) for the Ras homolog enriched in brain (Rheb) GTPase. The GTP-bound form of Rheb directly interacts with mTORC1 and strongly stimulates its kinase activity (Laplante & Sabatini 2012). mTORC1 activation occurs on the surface of the lysosomal membrane in response to amino acid, whereas the 5′ adenosine monophosphate-activated protein kinase (AMPK)-dependent activation of TSC2 and phosphorylation of Raptor reduce mTORC1 signaling (Mihaylova & Shaw 2011, Bar-Peled *et al.* 2013). Increased mTORC1 signaling is implicated in obesity. Activation of mTORC1 is not only required for the differentiation of adipocytes, but also promotes carcinogenesis by inhibiting physiological protein turnover via autophagy (Bell *et al.* 2000, Nazio *et al.* 2013). Constitutive mTORC1 activation in myeloid cells inhibits developing high-fat diet-induced obesity by promoting macrophage polarization to M2. Additionally, TSC1 deletion increases M2 macrophage polarization together with the mRNA levels of fatty acid-binding protein 4 and PPARγ, in an mTORC1-dependent manner (Paschoal *et al.* 2018). Adipocyte-specific TSC1 deletion reduces visceral fat mass, as well as adipocyte number and diameter associated with increased lipolysis. Furthermore, mitochondrial oxidative activity, fatty acid oxidation and the expression of PPARγ coactivator (PGC)-1α and PPARα in both visceral and subcutaneous fat adipocyte are increased via TSC1 deletion (Paschoal *et al.* 2018). In human breast cancer, E2R induces the expression of IGF-1R, insulin receptor substrate 1 (IRS-1) and IRS-2. IGF-1R/insulin receptor kinase activity is required for feedback activation of PI3K/AKT during the inhibition of mTORC1. E2R-mediated nongenomic signaling via IGF-1R/insulin receptor drives PI3K/AKT activation in response to mTORC1 inhibition (Yang *et al.* 2018). In fact, oncogenic activation of mTOR signaling induces cancer cell growth. The deregulation of protein synthesis downstream of mTORC1 at the level of eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1)/eIF4E plays a central role in tumor formation. eiF4E may affect carcinogenesis by promoting the translation of specific mRNAs coding for pro-oncogenic proteins (Laplante & Sabatini 2012). Increase in de novo lipid synthesis is a hallmark of proliferating cancer cells. Crosstalk between cancer cells and fatty acid synthase (FASN), which is a key lipogenic enzyme catalyzing the terminal steps in the de novo biogenesis of fatty acids, indicates the oncogenic nature of FASN-driven lipogenesis (Menendez & Lupu 2007). mTORC1 controls the synthesis of lipids required for proliferating cancer cells to generate own membranes (Laplante & Sabatini 2009). PI3K signaling promotes the activation of the pro-lipogenic factor sterol regulatory element-binding transcription factor 1 (SREBP1), however, mTORC1 is necessary for oncogenic/growth factor signaling to SREBP1 (Düvel *et al.* 2010).

Both genomic and nongenomic actions of estrogen play pivotal roles in estrogen-induced cancer cell proliferation and survival (Alexaki *et al.* 2004). The biological actions of estrogen are mediated by both genomic transcriptional effects in the nucleus and nongenomic actions via E2Rα. The nongenomic effects of estrogen can lead to the rapid activation of six different groups of signaling molecules; (1) IGF-1R/insulin receptor complex, epidermal growth factor receptor (EGFR), Src, PI3K and mitogen-activated protein kinase kinase (MEK), (2) p21ras and Raf-1, (3) MAPK and Akt, (4) protein kinase C, (5) release of nitric oxide and stimulation of prolactin secretion and (6) alteration of calcium and Maxi-K channels (Yee & Lee 2000, Adams *et al.* 2004, Cheskis 2004). Thus, PI3K/Akt and MAPK/ERK1/2 signaling pathways are involved in IGF-1-induced VEGF-C upregulation, and they undertake important roles in lymphatic metastasis in breast cancer (Zhu *et al.* 2011). Interestingly, both IGF-1R and EGFR initiate activation of MAPK and Akt cascades downstream signaling pathways (Adams *et al.* 2004). Furthermore, E2R promotes the transcription of genes encoding growth factor receptor tyrosine kinases (RTKs), ligands and signaling adaptors, including IRS-1 and its activator, IGF-1R (Adams *et al.* 2004). Therefore, crosstalk between IGF- and E2R-signaling pathways results in synergistic growth. Estrogen enhances IGF signaling by inducing expression of three key IGF regulatory molecules, which include the IGF-1R and its downstream signaling molecules, IRS-1 and IRS-2. Estrogen induction of IGF-R1 and IRS expression results in enhanced tyrosine phosphorylation of IRS-1 after IGF-1 stimulation. This process is followed by augmented MAPK activation. IGF molecules are critical regulators of estrogen-mediated growth and breast cancer cells (Lee *et al.* 1999). Meanwhile, IRS-2 plays an important role in the crosstalk between progesterone and the IGFs in PR-positive breast cancer cells (Cui *et al.* 2003). Combination of PI3K/AKT/TORC1 inhibitors with RTK inhibitors provides an optimal suppression on breast cancer growth (Miller *et al.* 2011). Eventually, the extensive crosstalk between the E2R and PI3K/AKT/mTORC1 pathways provides rationale to target these pathways in E2Rα-positive breast cancer (Yang *et al.* 2018). TSC1/2 conducts several upstream

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signals that influence mTORC1 including IGF1. The effector kinases of these pathways, protein kinase B (Akt), ERK1/2 and ribosomal S6 kinase (RSK1), inactivate TSC1/TSC2 complex by phosphorylation and thus mTORC1 is activated (Ma *et al.* 2005, Laplante & Sabatini 2012). TSC2 is inactivated by Akt-dependent phosphorylation, which destabilizes TSC2 and disrupts its interaction with TSC1 (Inoki *et al.* 2002). However, in the state of lacking the TSC1–TSC2 complex, Akt signaling is inhibited due to constitutive activation of mTORC1, at large (Huang & Manning 2009). Aberrant phosphorylation and inhibition of the TSC1/TSC2 complex, and subsequent increased activity of mTOR and/or S6K1 contribute to tumorigenesis caused by mutations that activate the PI3K–Akt pathway. Upon activation of PI3K, TSC1 is phosphorylated on consensus recognition sites for PI3K-dependent serine/threonine kinases (Manning *et al.* 2002). ERK-dependent phosphorylation leads to TSC1–TSC2 dissociation and markedly impairs TSC2 ability to inhibit mTOR signaling, cell proliferation and oncogenic transformation (Ma *et al.* 2005).

mTOR plays a central role in the control of cell growth and proliferation through phosphorylation of its effector molecules, 4E-BP1 and S6K1. Activation of this pathway occurs in response to growth factors, amino acids and nutrients, leading to mRNA translation and ribosome biogenesis (Hay & Sonenberg 2004). When the TSC1/TSC2 complex genes are inhibited, excessive mTOR activity causes uncontrolled atypical cell proliferation and tumor formation. TSC1 in carriers is more sensitive to the low levels of circulating estrogens in postmenopausal women (Mehta *et al.* 2011). In premenopausal women, E2R binding to the TSC1 is unlimited due to higher estrogen circulating levels in comparison to postmenopausal women (Mehta *et al.* 2011). Considering the human breast cancer tissues, TSC1 genes are aberrantly expressed and their promoters are found in methylated form in breast tumor cells. Therefore, the expression of TSC1 shows poor prognosis in patients with breast cancer (Jiang *et al.* 2005). On the one hand, loss of the TSC1/TSC2 complex genes leads to activation of mTOR and downstream signaling elements. Increase in mTOR activity results in the breast tumor formation as well as severe insulin/IGF-1 resistance at the cellular level. On the other hand, loss of TSC1/TSC2 in human tumors causes endoplasmic reticulum (ER) stress and activates the unfolded protein response (UPR). Eventually, ER stress plays a significant role in the mTOR-mediated negative feedback inhibition of insulin action and increases the vulnerability to apoptosis (Ozcan *et al.* 2008).

As previously mentioned, TNF-α is one of the important factors that link obesity-derived chronic inflammation with insulin resistance. In this event, initial activation of mTOR signaling pathway suppresses insulin sensitivity through serine phosphorylation. Subsequently the inhibition of IRS-1 by mTOR and its downstream effector S6K1 contribute to the insulin resistance. TNFα-inhibitor of nuclear factor kappa-B (IKKβ)-mediated inactivation of TSC1 not only results in increased phosphorylation of IRS-1 at serine 307 and serine 636/639, but also impairs insulin-induced glucose uptake, tyrosine phosphorylation of IRS1 and the association between IRS-1 and PI3K p85 (Lee *et al.* 2008). TNFα, IL-1, IL-6 and IL-8 enhance cell proliferation, cell survival, cell migration and tumor angiogenesis, thereby promoting tumor development. The TNFα/IKKβ signaling pathway has been suggested to link inflammation to cancer pathogenesis and evasion of apoptosis (Greten *et al.* 2004, Karin & Greten 2005).

Furthermore, many cancer-promoting kinases have been identified as regulators of mTOR activity through phosphorylation and inactivation of the TSC1/TSC2 complex. TAMs-derived tumor-promoting factors are the important signaling molecules in tumor development. IKKβ activates the mTOR pathway and promotes tumor angiogenesis through inactivation of the TSC1/TSC2 complex by phosphorylating TSC1 (Lee & Hung 2007). Accordingly, the accumulation of M2 phenotype TAMs promotes tumor angiogenesis. The mTOR pathway is a critical element in the regulation of monocyte differentiation to TAMs. Rapamycin causes the monocytes to differentiate into M1 macrophages releasing more IL-12 and less IL-10, whereas TSC2 suppression causes the monocytes to differentiate into M2 macrophages releasing less IL-12 and more IL-10. The TSC2–mTOR pathway is a key determinant in the differentiation of monocytes into M2 phenotype (Chen *et al.* 2012). Although rapamycin does not affect the increase in body weight and adiposity, it exacerbates adipose tissue inflammation that is induced by high-fat diet. Increase in adipose tissue inflammation emerges with the increase in the adipose tissue M1 macrophages, activated cytotoxic T lymphocytes and mRNA levels of pro-inflammatory molecules. mTORC1 inhibition induces phosphorylation of NF-κB p65 and spontaneous polarization of macrophages to a pro-inflammatory M1 profile, while decreasing M2 polarization. These findings indicate that mTORC1 activity is an important determinant of adipose tissue inflammatory profile and macrophage polarization (Paschoal *et al.* 2017). Hence, mTORC1 is strongly activated in obesity. The disruption of mTORC1 signaling in macrophages

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protects against inflammation and insulin resistance by inhibiting high-fat diet-induced serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1α (IRE1α)/c-Jun N-terminal kinase (JNK)/NF-κB pathway. In this respect, macrophage mTORC1 regulates adipose tissue inflammation and insulin sensitivity (Jiang *et al.* 2014). In contrast, adipocyte-specific deletion of mTOR causes insulin resistance. Additionally, mTOR is required for adipocyte differentiation in vivo, however, activation of PPARγ may provide the differentiation of the mTOR-deficient adipocytes (Shan *et al.* 2016). Consequently, activation of the macrophage mTORC1 signaling pathway suppresses lipolysis, stimulates lipogenesis and promotes ectopic lipid accumulation in obesity (Chakrabarti *et al.* 2010). Whereas, inhibition of macrophage mTORC1 promotes triacylglycerol lipolysis and release of FFAs, blocks adipogenesis and reduces hypertrophic fat cells (Chakrabarti *et al.* 2010, Soliman 2011).

Insulin resistance

M2 macrophages sustain insulin sensitivity by secreting IL-4 and IL-10, while M1 macrophages induce insulin resistance through the secretion of pro-inflammatory cytokines, such as TNF-α, in obesity (Tateya *et al.* 2013). Progression of obesity increasingly induces a phenotypic switch from the M2 macrophages to the M1 macrophages. Hence pro-inflammatory CD11c+ M1 macrophage accumulation is a marker of insulin resistance in human obesity (Wentworth *et al.* 2010). Thus, the enhanced macrophage–adipocyte crosstalk in obesity disrupts insulin action in adipocytes. Macrophage-secreted factors block insulin action in adipocytes via downregulation of glucose transporter 4 (GLUT4) and IRS-1, leading to a decrease in Akt phosphorylation and impaired insulin-stimulated GLUT4 translocation to the plasma membrane (Lumeng *et al.* 2007*b*). Furthermore, macrophage-derived IL-1β significantly provokes the development of obesity-associated insulin resistance by inhibiting insulin signal transduction in adipocytes (Bing 2015). Adiposity-related leptin secretion promotes breast cancer growth directly not only by increasing estrogen secretion, but also by enhancing activity of insulin-signaling pathways (Schmidt *et al.* 2015). Compared with normal breast tissue, breast tumors express higher levels of insulin receptor and exhibit a greater sensitivity to insulin (Frittitta *et al.* 1993). In contrast to peripheral insulin resistance in obesity, obese breast adipose tissue may remain insulin sensitive (Vague *et al.* 1986, Widjaja *et al.* 1997, Schelbert 2009, Lumeng & Saltiel 2011). The activation of apoptosis-related proteins inhibits autophagy by degrading autophagy-related proteins (Song *et al.* 2017). In fact, overexpression of tumor suppressor phosphatase and tensin homolog (PTEN) (dual protein and phosphoinositide phosphatase), which hydrolyzes PtdIns(3,4)P2 and PtdIns(3,4,5)P3, stimulates autophagy. PTEN negatively controls the PI3K/Akt signaling pathway (Arico *et al.* 2001). In contrast, insulin promotes Akt signaling through 3-phosphoinositide-dependent protein kinase 1 (PDK1) by increasing PtdIns3K activity, and inhibits autophagy (Yang & Klionsky 2010). Activation of this pathway, by expressing an active form of PKB, or expressing a constitutively active form of PDK1, has an inhibitory effect on autophagy. The activation of PI3K-mTORC1 signaling in cancer cells strongly inhibits autophagy (Arico *et al.* 2001, Meijer & Codogno 2004).

Since chronic hyperinsulinemia changes insulin stimulation of IGF-1 production and suppression of insulin-like growth factor binding protein-1 (IGFBP-1) and IGFBP-2 production, free IGF-1 concentrations are higher in obese subjects than in normal controls. Despite the positive correlation between total IGF-1 and insulin, there is negative correlation between free IGF-1 and IGFBP-1 (Nam *et al.* 1997). Chronic hyperinsulinemia-associated decreased concentrations of IGFBP-1 and IGFBP-2 cause elevation of IGF-1 and provokes concomitant tumor formation (Renehan *et al.* 2006). Indeed, insulin, IGF-1 and IGF-2 have been identified as tumor promoters. IGF-2 induction of the aryl hydrocarbon receptor (AHR) promotes the expression of cyclin D1 and the proliferation of human E2Rα-positive breast cancer cells (Tomblin & Salisbury 2014). By contrast, AHR ligands inhibit the proliferative effects of IGF-2 in human E2Rα expressing breast cancer cells (Salisbury *et al.* 2013). Although there is a significant positive correlation between intratumoral AHR and aromatase status, AHR exerts contradictory effects on estrogen action in breast carcinoma cells (Saito *et al.* 2017). Higher expression of the AHR is significantly associated with increased overall survival and distant metastasis-free survival in E2Rα-positive breast cancers. Furthermore, raloxifene, which is a selective estrogen receptor modulator, is used for prevention of E2Rα-positive postmenopausal breast cancer, as an AHR activator (O'Donnell *et al.* 2014). Recently, PI3K/Akt/mTOR signaling pathway activation has frequently been observed in E2Rα-positive breast cancers. The activation of this pathway is associated with increased cell growth, and its overexpression indicates a poor prognosis (Sharma *et al.* 2017, Bahrami *et al.* 2018). Simultaneous, expression and activation of the Ras/Raf/MAPK pathway plays a key role in breast cancer cell growth and spreading of the

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tumor cells to distant organs (Chen *et al.* 2015, Adamczyk *et al.* 2017). However, some fundamental questions remain unresolved, including the relative importance or functions of the two major signal transduction pathways, PI3K/Akt/mTOR and Ras/Raf/MAPK, that are activated by the IGF-1/IGF-1R axis.

Tyrosine phosphorylation of IRSs and Shc (Src homology 2 (SH2)-domain-containing and collagen) protein initiate signaling via canonical PI3K/Akt and Ras/MAP kinase pathways. These metabolic pathways together mediate insulin and IGFs signal transduction (Siddle 2011). Activation of insulin receptor signaling due to elevated insulin levels in obesity increases protein synthesis as well as promotes differentiation and growth (Taniguchi *et al.* 2006). Hyperinsulinemia induces breast cancer progression by two different mechanisms. First, insulin-stimulated leptin expression is associated with increased activation of the leptin gene promoter. Second, hyperinsulinemia in combination with increased insulin receptor expression in tumor tissues results in stimulation of AKT/mTOR signaling and inactivation of AMPK, which leads to the acceleration of tumor growth (Bartella *et al.* 2008, Kim *et al.* 2015).

mTORC1-activated S6K1 directly phosphorylates the IRS-1, which promotes IRS-1 degradation and reduces the ability of growth factors to signal downstream of RTK (Harrington *et al.* 2004). TSC1 and TSC2 promote PI3K signaling and convey insulin signaling to PI3K by restraining the activity of S6K. Similarly, TSC1–2 promotes IGF signaling to PI3K by repressing a negative feedback from mTOR/S6K to the adaptor molecule IRS-1. When S6K is activated, IRS functions are inhibited, via repression of *IRS-1* gene expression and phosphorylation of IRS-1. Thereby, S6K-dependent inactivation of IRS-1 and IRS-2 is prevented (Harrington *et al.* 2004, Laplante & Sabatini 2012). Activation of mTOR/S6K1 signaling has been shown to contribute to the development of insulin resistance. Indeed, increased IRS-1 serine phosphorylation reduces the activity of IRS-1, thereby impairs PI3K/AKT signaling and increases insulin resistance (Draznin 2006). TSC2 seems to be the critical target of Akt in mediating growth signals for the insulin-signaling pathway (Potter *et al.* 2002). The serine/threonine-protein kinase, PKB, which is a key mediator of insulin signaling plays a major role in cancer progression by stimulating cell proliferation and inhibiting apoptosis (Lawlor & Alessi 2001). However, the absence of TSC1–2 complex function leads to failure in insulin's ability to activate PI3K. In the state of TSC1–2 dysfunction, IGFs cannot activate PI3K, because S6K inactivates the adaptor proteins IRS-1 and IRS-2 (Harrington *et al.* 2004).

In fact, the PI3K/mTOR pathway is natively activated as a checkpoint for nutrient/hormonal cell signaling. There is a strong positive association between the risk of breast cancer and fasting insulin levels in postmenopausal women. Breast cancer incidence rates are 2.4-fold greater among those with the highest fasting insulin level. The association between BMI and the risk of breast cancer is attenuated more by controlling the insulin level than by controlling the estradiol level (Gunter *et al.* 2009). The binding of insulin to the insulin receptor activates the MAPK and PI3K pathways, all leading to an increase in malignant cell proliferation (Antoine *et al.* 1998). These findings suggest that, breast cancer cells have functional insulin receptors that regulate cell proliferation. The effect of insulin is greater in breast cancer cells in comparison to nonmalignant breast cells. In these cells, insulin is active via both its own receptor and the IGF-1R (Milazzo *et al.* 1992). In this respect, type 2 diabetes accelerates the development of mammary gland carcinogenesis. The insulin receptor and/or the IGF-1R are major mediators of these effects (Novosyadlyy *et al.* 2010). Discoidin domain receptors (DDR1 and DDR2) are candidate molecular partners of insulin receptor. In breast cancer cells, IGF-1 stimulation induces tyrosine phosphorylation of DDR1, which is accompanied by increased association of the DDR1–IGF-1R receptor complex. DDR1–IGF-1R functional crosstalk may play a role in cancer progression (Malaguarnera *et al.* 2015). The crosstalk between the IGF-1 and DDR1 may have important implications in development and progression of cancer. In breast cancer cells, exposure to IGF-1 induces significant upregulation of DDR1 protein. DDR1 upregulation is dependent upon the activation of the PI3K/AKT pathway. The correlation between DDR1 and insulin receptor raises the possibility that insulin resistance and compensatory hyperinsulinemia may enhance DDR1 in malignant mammary tissue. In breast cancer cells, AKT/miR-199a-5p/DDR1 pathway plays an important role in modulating biological responses of IGFs (Matà *et al.* 2016).

Insulin and estradiol can act in concert to promote cell cycle progression in breast cancer cells. Estrogen significantly increases both mitogens c-Myc and cyclin D1 protein expressions, whereas insulin predominantly increases cyclin D1 levels. Eventually, ectopic expression of c-Myc or cyclin D1 in breast cancer tissue increases cell cycle progression (Mawson *et al.* 2005). Breast cancer becomes a lethal disease, when it metastasizes and proliferates at distant sites of the body. Enhanced IRS-2

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signaling is not only correlated with increased metastatic potential of breast cancer, but also with enhanced IGF-1-induced malignant cell proliferation in lymph nodes (Jackson *et al.* 2001). Signaling through the IGF-1R is an integral requirement for estrogen-dependent post-confluent proliferation and focus formation in human breast cancer (Bradley *et al.* 2008). Many recent studies showed that insulin plays an important role in breast carcinogenesis via the extensive crosstalk that occurs between the insulin–IGF and the estrogen-signaling pathways in breast tissue.

ER stress

Under conditions where more protein synthesis is required, such as during insulin and IGF signaling, early activation of type I transmembrane kinase protein kinase RNA-like ER kinase (PERK) can lead to interruption of protein synthesis and increase the activity of IRE1 kinase. Thereby, insulin receptor signaling can be blocked (Park *et al.* 2010). ER stress is an important factor accompanying obesity. In this regard, the amount of newly synthesized proteins entering the ER is under negative regulation of the PERK activity, which is ER stress-responsive eIF2α kinase. PERK is activated by unfolded protein stress in the ER lumen and inhibits new protein synthesis by the phosphorylation of translation initiation factor, eIF2α (Ron & Harding 2012). PERK/activating transcription factor 4 (ATF4)-, IRE1α-, ATF6- and Ca^{2+}-signaling pathways induced by ER stress may cause either the initiation of autophagy or apoptosis. However, there is a complex relationship between autophagy and apoptosis. Autophagy can not only block the induction of apoptosis by inhibiting the activation of apoptosis-associated caspase, but also can induce apoptosis (Song *et al.* 2017). Autophagy-defective cells accumulate protein aggregates, damaged mitochondria and reactive oxygen species, which are believed to promote DNA damage and tumorigenesis (Laplante & Sabatini 2012).

Nevertheless, PERK is critical to convey stress signals from the ER to the nucleus with multiple stress-responsive transcription factors (Fan *et al.* 2018). Estrogen significantly suppresses NF-κB activation in early phase. Thus, it completely blocks TNF-α-induced activation of NF-κB. However, PERK, as a stress sensor of UPR, plays an essential role in the late activation of NF-κB by estrogen. Inhibition of PERK activity completely blocks the DNA binding of both STAT3 and NF-κB, thereby prevents the induction of NF-κB-dependent genes and estrogen-induced apoptosis (Fan *et al.* 2018). The decline in estrogen levels during the postmenopausal period is associated with increased cytokine production and inflammation. In fact, estrogens exert anti-inflammatory effect by repressing TNF-α. This process reverses the ligand-independent activation by E2Rα and the stimulatory actions of c-jun-NF-κB-cAMP response element-binding protein (CREB)-binding protein (CBP) pathway (Cvoro *et al.* 2006). In the case of increased estrogen synthesis, estrogen enhances the expression of the adipogenic transcription factor, C/EBP-β, which is responsible for the suppression of NF-κB activation by estrogen (Fan *et al.* 2018). In postmenopausal period, TNF-α accumulates unliganded E2R along with heat shock protein 90 (Hsp90) to the TNF-α promoter. Thus, E2Rα acts as a TNF-α-activated coactivator and represents a unique transcriptional activity for E2R (Cvoro *et al.* 2006). Under ER stress, PERK can activate NF-κB-DNA binding through decreasing levels of inhibitor kappa-B-alpha (IκBα). In this manner, NF-KB activation correlates with decreased levels of the IκBα protein (Deng *et al.* 2004). Briefly, estrogen activates the sensors of the UPR, IRE1α and PERK in breast cancer cells. Estrogen also dramatically increases reactive oxygen species production and upregulates expression of heme oxygenase (HMOX1), an indicator of oxidative stress, along with the central energy sensor kinase AMPK (PRKAA2) (Fan *et al.* 2013).

Obesity-related ER stress simultaneously leads to suppression of insulin receptor signaling through hyperactivation of JNK and subsequent serine phosphorylation of IRS-1 (Ozcan *et al.* 2004). Obesity and insulin resistance indicate the failure of the ER's adaptive capacity. In this manner, activation of the UPR during the ER stress is associated with many different inflammatory and stress signaling pathways (Hotamisligil 2010). Indeed, one of the identified pathways leading to the development of ER stress in obesity is the mTOR pathway (Ozcan *et al.* 2008).

SIRT1–mTOR crosstalk

The high-fat diet decreases the expression of SIRT1 and elevates Akt2 and IL-6 expression (Liu *et al.* 2016). However, SIRT1 significantly decreases the levels of Raptor and inactivates mTORC1 signal by interacting with Akt2. SIRT1-mediated inhibition of mTORC1 enhances lipolysis. While FFAs increase in plasma, adipogenesis is inhibited (Liu *et al.* 2016). In high-fat diet-induced obesity, phosphorylation of Akt in macrophages could activate mTOR signal and then leads to inflammation and insulin resistance (Jiang *et al.* 2014). However, macrophage SIRT1 activators enhance systemic insulin

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sensitivity, by decreasing adipose tissue inflammation, and M1 macrophage accumulation (Yoshizaki *et al.* 2010). In parallel with macrophages, activation of SIRT1 in adipocyte can reduce TNF-α-induced insulin resistance and inflammation (Yoshizaki *et al.* 2009). Adipocyte SIRT1 controls systemic glucose homeostasis and insulin sensitivity via the crosstalk with adipose-resident macrophages (Hui *et al.* 2017). Consequently, it is evidenced that the interaction between SIRT1 and Akt2 is important in the mTOR/S6K1 pathway-mediated progression of adipose tissue inflammation in obesity (Liu *et al.* 2016).

The deleted breast cancer-1 (DBC1) is a nuclear protein, however it is absent in human breast cancer cells. DBC1 is employed as a native inhibitor of SIRT1 in human cells. DBC1-mediated repression of SIRT1 leads to increasing levels of p53 acetylation and upregulation of p53-mediated function (Zhao *et al.* 2008). Indeed, other SIRT1 inhibitors like DBC1 show anticancer activity through p53 acetylation in human breast cancer cells (Park *et al.* 2016). SIRT1 activity is positively regulated by the protein kinases, PKA and AMPK. However, AMPK-dependent PKA activation leads to the dissociation of SIRT1 from its endogenous inhibitor DBC1 and free SIRT1 increases. Thereby, SIRT1 is activated by cAMP/PKA/AMPK/DBC1-dependent pathway (Nin *et al.* 2012). Free DBC1 provokes NF-κB-induced pro-inflammatory activity in differentiated adipocytes of obese individuals (Park *et al.* 2013, Moreno-Navarrete *et al.* 2015). In high-fat diet, decreased SIRT1 activity and increased interaction with DBC1 is observed (Escande *et al.* 2010). Conversely, genetic deletion of DBC1 unexpectedly results in obesity-related insulin resistance. In addition, DBC1 depletion in adipocytes activates SIRT1-dependent function of stearoyl-coenzyme A desaturase 1 (Scd1), increasing plasma and tissue levels of unsaturated fatty acids (Qiang *et al.* 2015). Increased expression of SIRT1 in hormone receptor-positive breast cancer is significantly correlated with lower risks of axillary lymph node metastasis (LNM), whereas in estrogen-independent high-grade breast cancer excessive SIRT1 expression is more frequently observed in patients with LNM-positive (Chung *et al.* 2015). It is well-known that the enzymatic activity of aromatase is critical for the growth of estrogen-dependent breast cancers. However, SIRT1 inactivation suppresses E2Rα signaling, thereby inhibits estrogen/E2Rα-induced breast cancer growth by triggering apoptosis (Yao *et al.* 2010, Elangovan *et al.* 2011). Since SIRT1 is a positive regulator of aromatase mRNA levels, inhibitors of SIRT1 decrease the mRNA–protein levels of aromatase. Thus, SIRT1 controls aromatase expression by targeting nonhistone proteins or transcription factors that activates CYP19A1. SIRT1-specific inhibitors cause a reduction in aromatase levels (Holloway *et al.* 2013). In this context, transcriptional control of CYP19A1 by SIRT1 is achieved through PGC-1α, E2Rα and β-catenin (Rodgers *et al.* 2005, Holloway *et al.* 2010, Wilson *et al.* 2010). In fact, SIRT1 localizes to the PII/I.3 and PI.4 promoters in breast cancer cells and regulates E2Rα acetylation and protein levels. Therefore, SIRT1 is overexpressed by 2.6-fold in invasive ductal carcinoma cells in comparison to normal breast tissue (Holloway *et al.* 2013). In addition to reduction in aromatase activity, inhibition of SIRT1 causes the suppression of estrogen receptor signaling (Yao *et al.* 2010). In contrast, increased SIRT1 mRNA and protein levels ameliorate inflammation and improve insulin sensitivity, whereas SIRT1 deficiency intensifies adipose tissue inflammation and insulin resistance in obesity (Peng *et al.* 2017). There are two potential mechanisms by which E2R target genes are regulated by p53. First, protein–protein interaction between E2Rα and p53 can lead to alterations in E2R target gene expression (Liu *et al.* 1999). Second, E2Rα regulates some p53 target genes which contain estrogen response element (ERE) sites (Angeloni *et al.* 2004). SIRT1 promotes cell survival by deacetylating, and thereby negatively regulating the activity of important tumor suppressors such as p53. Therefore, the role of SIRT1 in breast cancer has been controversial in obesity (Han *et al.* 2013). SIRT1 expression induced by E2Rα activates antioxidant and pro-survival genes in the breast cancer cells. SIRT1 inactivation eliminates estrogen/E2Rα-induced cell growth and tumor development by triggering apoptosis (Elangovan *et al.* 2011). Unlike full length E2Rα and E2Rα46, E2Rα36 is localized in the cytoplasm and the plasma membrane, where it is thought to mediate nongenomic estrogen signaling. Overexpression of E2Rα36 is significantly associated with poorer disease-free survival and disease-specific survival in E2Rα66-positive patients. E2Rα66-positive tumors that also express high levels of E2Rα36 are less likely to benefit from tamoxifen treatment (Shi *et al.* 2009). Tamoxifen has not only been used for the treatment or prevention of recurrence in patients with E2R-positive breast cancers, but also for recurrent breast cancer (Zembutsu 2015). Overexpression of SIRT1 with FOXO1 increases multidrug resistance protein 2 expression, whereas the basal activity of SIRT1 is increased in tamoxifen-resistant breast cancer cells. However, SIRT1 inhibition reduces both the nuclear FOXO1 levels and multidrug resistance protein 2 expression, thereby cytotoxic effects of chemotherapeutics are enhanced in tamoxifen-resistant breast cancer cells (Choi *et al.* 2013).

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Since SIRT1 is a positive regulator of aromatase activity, aromatase inhibitors are superior to tamoxifen as adjuvant hormonal therapy for postmenopausal E2R-positive breast cancer (Rydén *et al.* 2016).

Uncoupled respiration and hypoxia

Decreasing mitochondrial coupling efficiency promotes uncoupled respiration of adipocytes in high-fat diet-induced obesity and increases energy expenditure as well as suppresses energy intake (Fu *et al.* 2013). In obesity, high level of saturated fatty acids induces adenine nucleotide translocase activity, which leads to the uncoupled respiration. Uncoupled respiration while increasing oxygen consumption causes relative adipocyte hypoxia. Consequently, relative cellular hypoxia due to increased adipocyte oxygen consumption triggers hypoxia-inducible factor-1α (HIF-1α) response (Lee *et al.* 2014). Adipocyte hypertrophy creates poorly oxygenated areas in the human obese adipose tissue (Murdoch *et al.* 2004). Decreased adipose tissue partial oxygen concentration is paralleled by an increase in the expression and secretion of the chemokine and markers of macrophage infiltration (Pasarica *et al.* 2009). HIF-1α stimulates production of the adipocyte-derived chemokines MCP-1 and leukotriene B4 (LTB4), which drive accumulation of pro-inflammatory ATMs (Lee *et al.* 2014). The LTB4/Ltb4r1 (G protein-coupled receptor) system is a major driver for the inflammation/insulin resistance syndrome in obesity. Thus, LTB4 promotes migration of monocytes into adipose tissue and directly stimulates macrophage Ltb4r1 to activate intracellular pro-inflammatory pathways (Li *et al.* 2015). A positive feedback loop containing fatty acid synthase (FASN)/phosphorylated ERK1–2 (p-ERK1–2)/lipoxygenases (5-LOX)/LTB4/FASN provides high proliferative capacity for breast cancer cells (Hu *et al.* 2011). While increased expression of HIF-1α by adipocytes is associated with the poor prognosis for breast cancer at early stage of obesity, at prolonged hypoxia HIF-2α expression is an indicator of reduced recurrence-free survival (Helczynska *et al.* 2008, Rausch *et al.* 2017). Indeed, in early stage of obesity, overexpression of adipocyte HIF-1α due to adipose tissue hypoxia mediates the production of reactive oxygen species that activate the NF-κB pathway, induces the expressions of several chemokines and increases the accumulation of ATMs in the adipose tissue (Halberg *et al.* 2009, Jiang *et al.* 2011, Lee *et al.* 2011, 2014). During the later stage of obesity, CLSs also create remarkably hypoxic areas in adipose tissues. Adipose tissue hypoxia induces inflammatory phenotype of M1 ATMs via HIF-1α-dependent mechanisms, partly (Fujisaka *et al.* 2013). Therefore, macrophage HIF-1α links hypoxia and inflammation through the CLSs of obese adipose tissue. Insulin resistance is the result of these sequential series of events in obesity (Takikawa *et al.* 2016). Conversely, overexpression of macrophage HIF-2α attenuates adipose tissue inflammation and improves insulin resistance in obese adipocytes (Choe *et al.* 2014). In this vicious circle, hyperinsulinemia induces HIF-1α expression, which upregulates oxidative stress in E2R-positive breast cancer cells (Wang *et al.* 2017). TAMs secrete pro-inflammatory cytokines and chemokines, including TNF-α, IL-1, IL-6 and IL-8, to enhance cell proliferation, cell survival and inflammation-mediated tumor angiogenesis and thereby promote tumor progression. TNF-α activates mTORC1 signaling, which is known to induce S6K1 activation and vascular endothelial growth factor (VEGF) production, through phosphorylation and inactivation of TSC1 by IKKβ in breast cancers. VEGF-regulated angiogenesis is a key factor for metastasis (Lee *et al.* 2007). Breast cancer is characterized by having a large population of TAMs. Hypoxia in the tumor microenvironment stimulates macrophages to further produce VEGF and suppresses the T-cell immune responses, thus enhancing the evasion of tumor cells and ultimately metastasis (Obeid *et al.* 2013). As mentioned above, it is thought that hypoxia due to increase in adipocyte diameter and decrease of adipose tissue capillary density are potential causes of the inflammatory changes occurring in obese adipose tissue (Fujisaka *et al.* 2013, Lee *et al.* 2014). In addition, the primary source of hypoxia-induced inflammatory cytokine is ATMs in obesity (O'Rourke *et al.* 2011). Consequently, enhanced macrophage pro-inflammatory cytokine production causes increased inflammatory response in adipocytes. In this respect, hypoxia is a potential factor to initiate pro-inflammatory adipocyte–macrophage crosstalk. Furthermore, activation of JNK signaling is critical for the enhancement of fatty acid-triggered inflammatory responses in hypoxia (Snodgrass *et al.* 2016). In fact, obesity is associated with the type-1 inflammatory responses, which is characterized by IFN-γ synthesis. IFN-γ expression shifts ATMs toward M1 phenotype (Wensveen *et al.* 2015). Hypoxic adipocyte-released exosomes contain 3- to 4-fold higher amounts of enzymes, which are related to de novo lipogenesis such as acetyl-CoA carboxylase and FASN. Exosomal proteins released from hypoxic adipocytes affect lipogenic activity in neighboring preadipocytes and adipocytes (Sano *et al.* 2014). IL-4–Akt–mTORC1 pathway acts as a nutrient sensor for the macrophages and control the enzyme,

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which is responsible for acetyl-CoA synthesis. Increase in acetyl-CoA levels changes the profile of M2 macrophages (Covarrubias *et al.* 2016). Hypoxia induces expression of regulated in development and DNA damage responses 1 (*REDD1*) gene, which promotes TSC1/2 complex and subsequently inhibits mTORC1 activity. Loss of either TSC1 or TSC2 blocks the effects of hypoxia on mTORC1 (Brugarolas *et al.* 2004). TNF-α–IL-10–mTORC1–STAT3 signaling pathway is induced by hypoxia in primary human macrophages and may modulate TNF responses during chronic inflammation (Huynh *et al.* 2016). In this respect, while STAT3 mRNA expression in adipose tissue is positively correlated with IL-10 and adiponectin expression, it is negatively correlated with triglycerides levels. Therefore, IL-10/JAK-STAT3 pathway activity is decreased due to obesity-related hypertriglyceridemia (Liu *et al.* 2018). PI3K/Akt contributes to hypoxic stress-induced TLR4 expression through the regulation of HIF-1 activation (Kim *et al.* 2012). Moreover, hypoxia increases the activation of JNK and p38 MAPK signaling in saturated fatty acid-treated macrophages. Hypoxia along with higher concentrations of FFAs exacerbates macrophage-mediated inflammation in obesity (Snodgrass *et al.* 2016).

Conclusion

Elevated estrogen concentrations in postmenopausal E2R-positive breast cancer patients are largely derived from obese adipose tissue aromatization. Moreover, hyperinsulinemia is an independent risk factor for poor prognosis in breast cancer, and is associated with high levels of leptin and shorter breast cancer-free survival in obesity. Collectively, as obese breast adipocyte is master regulator of tumor growth through leptin–aromatase–tumor-associated macrophage axis and SIRT1–adipose-resident macrophage axis, unresolved mechanistic gaps at molecular links of adipocyte–macrophages–tumor cell interactions in obesity-associated breast cancer create difficulties in patient's treatment.

Future perspectives

The role of SIRT1 in obese patients with breast cancer has been controversial. Inhibition of SIRT1 causes the suppression of estrogen receptor signaling, besides the reduction in aromatase activity. In contrast, increased expression of SIRT1 in E2Rα-positive breast cancer not only reduces TNF-α-induced insulin resistance, but also lowers risks of axillary LNM. Therefore, further investigation is necessary to clarify whether the levels of SIRT1 expression may provide an innovative strategy that may complement or synergize with existing therapies. In addition, the biological evaluations of sirtuin and PI3K/AKT/mTOR pathway inhibitors are still under investigation (Chen 2011, Villalba & Alcaín 2012, Brufsky 2014, Ciruelos Gil 2014).

A high-fat diet with estrogen deprivation leads to development of insulin resistance, which accelerates distant recurrence and death in patients with breast cancer. Hyperinsulinemia induces breast cancer progression through leptin-dependent mechanisms. Although most of the obese humans are characterized by leptin resistance, anti-estrogen therapy increases serum leptin levels and increases leptin resistance even more in obese postmenopausal breast cancer patients. Thus, excessive leptin correlates significantly with poor prognosis in overall and tamoxifen-treated breast cancer patients (Maffei *et al.* 1995). Since leptin also enhances aromatase expression in breast cancer cells, suppression of leptin effects may be a novel modality of circumventing resistance to anti-estrogen treatment. 'Anti-leptin receptor antibody treatment' seems to be a rational approach to resolve insulin resistance and anti-estrogen drug resistance in breast cancer (Rios Garcia *et al.* 2017).

Because of the activity of de novo fatty acid synthesis pathway, breast cancer cells are independent of the extracellular lipids. Acetyl-CoA carboxylase (ACC1) phosphorylation and inhibition are a necessary step in leptin-promoted epithelial–mesenchymal transition (EMT) in breast cancer. Therefore, inhibition of ACC1 increases the metastatic capacity of breast cancer cells. In tumor cells, which are treated with the EMT inducers, leptin and TGFβ, ACC1 phosphorylation increases. In this context, further investigation is necessary regarding the 'anti-leptin receptor antibody' treatment reducing the activity of leptin-ACC1 axis-dependent tumor invasiveness that may complement or synergize with existing therapies (Rios Garcia *et al.* 2017).

Taken together, evidences suggest that the leptin system and its second messengers might play an important role in breast cancer progression by enhancing estrogen effects via a paracrine pathway, and that might represent a novel target for therapeutic intervention in breast cancer. Although in breast cancer, benefit of anti-IGF/insulin-signaling agents in combination with hormone therapy has not yet been proven, and development of predictive biomarkers and optimal inhibitory strategies of the IGF/insulin pathway activity would yield better clinical outcomes (Yang & Yee 2012). Leptin resistance increases in SOCS3 expression. While leptin effect is mediated by

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MAPK/ERK1/2-STAT3, SOCS proteins potently regulate the intensity and extent of STAT signals. Therefore, downregulation of STAT3 and STAT5a/b has been suggested as a mechanism of anti-proliferative effects of some anticancer agents in breast cancer cells. Of these, MSM decreases the DNA-binding activities of STAT5b and STAT3 to the target gene promoters (Lim *et al.* 2012). Therefore, unclarified adipocyte–macrophage-tumor cell interactions in obesity-associated breast cancer create serious handicap, in planning breast cancer treatment modalities.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement

Immunological aspects of adipocyte–macrophage interactions were reviewed by A B Engin, breast cancer-related biochemical pathways in obesity were evaluated by A Engin and histopathological compliance was evaluated by I I Gonul.

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