MINIREVIEWS

Adipocyte activation of cancer stem cell signaling in breast cancer

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Abstract

Signaling within the tumor microenvironment has a critical role in cancer initiation and progression. Adipocytes, one of the major components of the breast microenvironment, have been shown to provide pro-tumorigenic signals that promote cancer cell proliferation and invasiveness *in vitro* and tumorigenicity *in vivo*. Adipocyte secreted factors such as leptin and interleukin-6 (IL-6) have a paracrine effect on breast cancer cells. In adipocyte-adjacent breast cancer cells, the leptin and IL-6 signaling pathways activate janus kinase 2/signal transducer and activator of transcription 5, promoting the epithelial-mesenchymal transition, and upregulating stemness regulators such as Notch, Wnt and the Sex determining region Y-box 2/octamer binding transcription factor 4/Nanog signaling axis. In this review we will summarize the major signaling pathways that regulate cancer stem cells in breast cancer and describe the effects that adipocyte secreted IL-6 and leptin have on breast cancer stem cell signaling. Finally we will introduce a new potential treatment paradigm of inhibiting the adipocyte-breast cancer cell signaling *via* targeting the IL-6 or leptin pathways.

Core tip: We discuss the relationship between adipocytes in the microenvironment and breast cancer cells. We emphasize the role of adipocyte-secreted leptin and interleukin-6 in inducing breast cancer cell epithelial-mesenchymal transition and activating stemness pathways. Finally we summarize possible microenvironmental therapeutic targets and the potential role of non-coding RNAs in adipocyte-breast cancer interactions.

INTRODUCTION

Breast cancer occurs through the accumulation of genetic and epigenetic changes, activating oncogenes and silencing tumor suppressors in the mammary ductal or lobular tissues. Ductal carcinomas make up

approximately 85% of diagnosed breast cancers, and are the focus of this review[1]. Ductal tumors progress linearly beginning as atypical hyperplasia that grow into ductal carcinoma *in situ* (DCIS) lesions which later acquire malignant phenotypes and become invasive ductal carcinomas[2]. The final stage of breast cancer involves dissemination of primary tumor cells and colonization of distant tissues by metastatic tumor cells.

Gene expression profiling has been used to identify molecular subtypes of breast cancer with different prognosis and treatment responses. Luminal A and B both express estrogen (ER) and progesterone receptors (PR), differing primarily in their proliferation kinetics. Luminal subtype breast cancers comprise the majority of tumors and are among the best prognosis, in part due to availability of antiestrogen therapies. Human epidermal growth receptor breast cancers overexpress or amplify HER2 and respond to targeted anti-HER2 therapies. Basal-like breast cancers are frequently triple-negative (ER-/PR-/HER2-), often harbor *P53* mutations, and are aggressive with poor prognosis. A newly described molecular subtype, claudin-low breast cancers, also do not express ER and PR, but are identified through their characteristic lack of cell-cell adhesion molecules (claudins) and basal cytokeratins.

White adipose tissues account for approximately 80% of the volume of the adult breast, and are composed of a heterogeneous collection of cells including adipocytes, fibroblasts, capillaries, immune cells, and extracellular matrix. It was long believed the primary function of adipose tissue was energy storage; in fact stromal adipose is a complicated endocrine organ. Adipose tissues produce a wide variety of adipokines and signaling molecules that play numerous roles in breast tumor formation and progression[3]. This relationship is cemented by a well-established link between obesity and breast cancer. Obesity is a major risk factor for breast cancer development and patient survival, with a 33% increase of cancer mortality in obese patients[4]. The majority of the mammary microenvironment consists of adipocytes and adipocyte precursors. Mesenchymal stem cells differentiate into adipocytes through the two stages of adipogenesis, driven by transcription factors peroxisome proliferator-activated receptor γ and the C/EBP family. Initially mesenchymal stem cells commit to the adipocyte lineage forming preadipocytes, which become mature adipocytes through terminal differentiation[5]. Both preadipocytes[6] and mature adipocytes increase breast cancer growth, with marked effects on migration and the colony forming ability of breast cancer cells. Moreover, cancer associated adipocytes undergo phenotypic changes, forming a more supportive tumor niche[7]. Identifying the mechanisms of this relationship could lead to novel targets for prevention and treatment of breast cancer.

The standard of care for breast cancer is a combination of surgery, radiation and chemotherapy. Treatment success varies depending on molecular subtype of the tumor, and additional adjuvant and targeted therapies are available. While adjuvant hormonal therapies such as Tamoxifen are effective for ER+ patients, and targeted therapies such as the monoclonal antibody Trastuzumab are effective for HER2+ patients, there are no targeted treatments available for patients with basal-like or claudin-low breast cancer[8]. Additionally, drug resistance is a major factor in the treatment failure of all molecular subtypes. One suspected culprit of resistance is cancer stem cells. The cancer stem cell model describes an intratumoral subpopulation of cancer cells that have unregulated stem cell properties, primarily self-renewal and multipotent differentiation, which drive tumorigenesis and tumor heterogeneity[9]. First isolated from AML cell populations by using flow cytometry to sort cells based on the molecular markers CD34+ CD38-[10], cancer stem cells have been identified in breast cancer as the CD44+ CD24-/low ALDH1+ cell population[11,12]. Cancer stem cells are resistant to traditional cancer therapies due to their quiescence, DNA repair capabilities and overexpression of drug efflux pumps[13].

In part through the activation of cancer stem cell signaling, the tumor microenvironment plays a critical role in the development and progression of breast tumors. Targeting the microenvironment has the potential to inhibit cancer stem cells, preventing drug resistance and relapse across all molecular subtypes. This is an attractive therapeutic option due to the relative genetic stability and the reduced risk of resistance of the microenvironment[14]. Therapies targeting the microenvironment have been successful in multiple myeloma through targeting multiple myeloma cell-bone marrow interactions using bisphosphonates[15] and bortezomib[16]. Aromatase inhibitors, a recent success story in breast cancer, target post-menopausal estrogen produced by extragonadal aromatization in stromal cells as well as breast tissues and tumors[17].

In this review we will focus on the relationship between breast cancer cells and mature adipocytes, with emphasis on two of the best studied adipocyte secreted signaling molecules, leptin and interleukin-6 (IL-6). These molecules promote breast cancer progression through activation of the epithelial-mesenchymal transition and cancer stem cell signaling in breast cancer cells, and are potential novel microenvironmental targets.

BREAST CANCER STEM CELL SIGNALING

A number of signaling pathways that have fundamental roles in the regulation of self-renewal and differentiation of adult and embryonic stem cells have been linked to breast cancer stem cells. Adipocyte secreted leptin and IL-6 can activate many of these pathways, dysregulating self-renewal and differentiation within breast cancer cells. Targeting these signaling pathways within the microenvironment may be an important method of

targeting breast cancer stem cells. While numerous stemness pathways have been identified, we will focus on three of the best characterized: the Notch, Wnt and octamer binding transcription factor 4 (OCT-4)/ Sex determining region Y-box 2/Nanog pathways.

Notch

The Notch receptor is an important developmental mediator of self-renewal and regulator of cell fate decisions in many cell types, including within the mammary gland[18]. When ligand is bound, ADAM and γ-secretase proteases cleave the Notch receptor. The cleavage product is transported to the nucleus, where it activates gene transcription. In both basal like and ER$^+$/PR$^+$ breast cancer cell models Notch activates histone deacetylase SIRT2, which deacetylates and activates ALDH1A1, and increases mammosphere formation[19]. Inhibition of Notch signaling using a neutralizing antibody is sufficient to significantly reduce mammosphere formation of DCIS cells *in vitro*, indicating a crucial function in breast cancer stem cell signaling[20]. Constitutive Notch activation is a common feature of early stage breast cancer[20], and high levels of Notch are correlated with poor breast cancer prognosis[21].

Wnt

The Wnt signaling pathway is crucial for embryonic development, and is involved in cell fate determination, proliferation and cell migration. When Wnt ligand is present, it binds the Frizzled receptor, allowing β-catenin to be transported to the nucleus and activate gene transcription[22]. In the absence of Wnt, β-catenin is targeted for proteasomal degradation. Wnt pathway target genes such as LEF1 and AXIN2 are upregulated in breast cancer cells, especially in breast cancer stem cell populations[23]. Wnt signaling is important for breast cancer stem cell self renewal, when treated with Wnt inhibitor DKK1, ER$^+$ and ER$^-$ breast cancer cells had reduced mammosphere formation[23]. Unregulated activation of the Wnt pathway can occur *via* mutations in downstream Wnt target genes, β-catenin and over-expression of the Wnt ligand. Secretion of Wnt ligand from cells in the microenvironment has a paracrine effect on cells on the invasive edge of tumors, increasing their proliferative and invasive abilities[24].

Oct-4/SOX2/Nanog signaling axis

Oct-4 is a member of the POU transcription factor family, and is critical for self-renewal of undifferentiated cells. It is normally only expressed in embryonic stem and embryonic germ cells, and is used as a marker for undifferentiated cells. Oct-4 is necessary to maintain stem cells in a pluripotent state[25]. Through interaction with HMG domain protein SOX2, Oct-4 activates transcription of several genes in pluripotent cells, including *Fgf4*, *Utf1*, *Fbx15,* and the genes encoding themselves, *Sox2* and *Pou5f*. SOX2 and Oct-4 synergy also activates transcription of key pluripotent embryonic regulator Nanog[26], a homeodomain protein that maintains the primitive ectoderm in the embryo[27]. Nanog is expressed in cells that are able to form pluripotent stem cell lines, and plays a key role in inhibition of differentiation in these cells, as well as activation of self-renewal. Nanog also activates Oct-4 transcription, although it is not necessary for Oct-4 expression[28].

These key pluripotency transcription factors share numerous targets, and they are essential to the transcriptional pathways that regulate embryonic stem cell identity[29]. Therefore it is not surprising that all three are frequently activated in breast cancer stem cells[30-32]. Overexpression of Nanog enhances ER$^+$/PR$^+$ breast cancer cell ALDH1 expression and drug resistance[30], as well as invasiveness and mammosphere formation[33]. Nanog overexpression also increases tumor formation *in vivo*[33]. SOX2 is highly expressed in early stage breast tumors, and knockdown prevents mammosphere formation as well as delaying tumor formation *in vivo*[32]. OCT-4 overexpression in healthy primary breast tissue cultures generated cells capable of tumor initiation[34].

EPITHELIAL-MESENCHYMAL TRANSITION

Through the epithelial-mesenchymal transition (EMT), epithelial cells lose cell polarity, cell-cell adhesion and undergo cytoskeletal reorganization gaining a motile, invasive phenotype. In healthy cells, EMT plays a critical role in development, embryogenesis and wound healing through the reorganization of tissues and germ layers[35]. The classic markers for EMT are loss of E-cadherin, a protein necessary for cell adhesion, and increase in N-cadherin. Additional mesenchymal proteins include smooth-muscle actin, vimentin and fibronectin. Change in expression of these markers is used to characterize EMT *in vitro*[36].

The tumor microenvironment produces EMT signaling molecules, promoting the mesenchymal phenotype necessary for cancer progression and metastasis. Cells in the inflamed microenvironment secrete transforming growth factor-β (TGF-β), stimulating Snail and Slug which transcriptionally repress E-cadherin[37]. Hypoxia in the microenvironment activates HIF-1, stimulating transcription of EMT activating protein Twist. In ER$^+$ breast cancer cells, Twist is activated by locally produced IL-6 through signal transducer and activator of transcription 3 (STAT3) signaling[38]. EMT is also tightly regulated by microRNA signaling, most notably through repression of E-cadherin activators by the miR-200[39] and miR-34[40] families. miR-200 is significantly downregulated in breast cancer, a possible mechanism of EMT activation[41]. Loss of E-cadherin also increases the tumorigenicity of cancer cells, and is correlated with increased cancer grade[37].

Cancer stem cells and cells that have gone through EMT share many common characteristics. Breast cancer stem cells have protein expression consistent with EMT, decreased E-cadherin and increased N-cadherin and Slug expression[42]. Furthermore, non-tumorigenic immortalized

human mammary cells that have undergone EMT are enriched for cancer stem cell markers such as CD44^{+}/CD24^{-} and signaling proteins SOX2, Nanog and octamer binding transcription factor 4 (OCT4)[42]. When mammary epithelial cells transformed through HER2 overexpression undergo EMT *in vitro*, the proportion of cancer stem cells is significantly increased. Human mammary epithelial cells transformed with a V12H-Ras oncogene overexpressing EMT proteins Twist or Snail were able to form tumors *in vivo* from significantly fewer cells than control transformed cells[42]. EMT is an important process for cancer progression and metastasis, generating invasive cells with a cancer stem cell-like phenotype, however the exact relationship between EMT and cancer stem remains to be determined.

ADIPOSE SIGNALING

Adipose tissue is an amalgamation of adipocytes, fibroblasts, stromal precursors and immune cells. Adipose signaling regulates fatty acid metabolism, homeostasis, and insulin signaling *via* adipocyte-secreted factors such as adiponectin and leptin. Adipose tissue has significant immune and inflammatory signaling functions involving adipokines such as IL-6 and tumor necrosis factor-α (TNF-α). While IL-6 and TNF-α are classically produced by the non-adipocyte members of the adipose tissue, it has been demonstrated that cancer associated adipocytes secrete IL-6, one of the primary cytokines involved in adipocyte-tumor cell interaction.

The stromal microenvironment plays a critical role in breast cancer formation and progression, however the pro-tumorigenic abilities of mature adipocytes have only been recognized in the past 10 years[7]. In order to isolate the effects of cytokines from those of adipocyte produced estrogen, it is important to demonstrate the effects in both ER[+] and ER[-] model systems. Using conditioned media from adipocyte culture plates, both ER[+] and ER[-] breast cancer cells had significant increases in proliferation and survival[43]. Crosstalk between adipocytes and breast cancer cells leads to change in phenotype of the adipocyte cells in addition to the changes seen in breast cancer cells. Mature adipocytes co-cultured with breast cancer cells exhibit delipidation, loss of terminal differentiation markers and overexpression of inflammatory cytokines and adipokines. The expression of these signaling molecules plays a critical role in the tumor supporting functions of adipocytes[7] (Figure 1). Two of the best-characterized signaling molecules in the breast cancer-adipocyte relationship are leptin and IL-6.

Leptin in the tumor microenvironment

Leptin is a 16 kd protein encoded by the *ob* gene, first discovered in *ob/ob* mutant mice that exhibit an obese phenotype due to the lack of satiety. The classical function of leptin is appetite control. When fat stores reach a certain level, leptin is secreted, and activates leptin receptors (OB-R) in the brain to indicate satiety. While OB-R is found at highest concentrations in the hypothalamus, it has been identified in almost all tissues. Levels of circulating leptin directly correlate with total fat mass, as larger fat cells produce more. Leptin signaling is dysregulated in obese subjects, with up to seven times higher leptin secretion compared to lean[44].

Leptin receptor OB-R is a member of the class I cytokine receptor family. Different isoforms of the OB-R protein are able to activate several classical cytokine-signaling pathways, including the JAK/STAT, PI3K and MAPK pathways. Through these pathways leptin likely has significant, diverse effects on physiology and disease, many of which are not fully understood[45].

Leptin signaling is a significant factor in the adipocyte-tumor signaling relationship. OB-R mRNA expression is highly upregulated in patient tumors of all breast cancer subtypes, with little to no expression seen in normal epithelial tissue[46]. Leptin signaling enhances tumor formation, proliferation and invasion by activation of cancer stem cell signaling pathways Notch and Wnt, and by activating numerous oncogenic pathways, including HER2, AKT, STAT3 and NFkB. Both leptin and OB-R are significantly upregulated in breast cancer stem cells, which exhibit increased sensitivity to leptin signaling due to higher receptor expression[47]. In ER[+]/PR[+] breast cancer cells, STAT3 activation *via* leptin signaling also increases expression of chaperone binding protein Hsp90, resulting in upregulation of the HER2 oncogene. shRNA knockdown of STAT3 inhibited leptin induced HER2 upregulation[48].

Silencing of OB-R using shRNA in triple negative breast cancer cells inhibited expression of Nanog, SOX2 and OCT4. These cells had reduced cell proliferation and mammosphere formation, indicative of a reduction in self-renewal. Additionally, OB-R silenced cells went through mesenchymal to epithelial transition, with increased E-Cadherin and decreased vimentin expression[49].

Through the use of two mouse models, leptin-deficient *ob/ob* mice and OB-R deficient *db/db*, the role of leptin in tumorigenesis was confirmed *in vivo*. Both models form early onset obesity with nearly identical characteristics, however *ob/*ob mice have no circulating leptin, whereas *db/db* have high levels of leptin. Using tumors resected from MMTV-WNT-1 transgenic mice, a single cell suspension was injected into *db/db*, *ob/ob* or wild type mice. Tumor growth was detected earlier in *db/db* compared to wild type, and tumor volume was up to 8 times that of the WT tumors. *Ob/ob* mice formed tumors at a significantly lower rate, with volumes similar in size to the wild type tumors. Through the use of a limiting dilution assay, the authors demonstrated that injection tumor cells from wild type mice resulted in 100% secondary tumor growth formation, whereas the same number of cells from leptin deficient tumors were unable to form secondary tumors[50]. This provides *in vivo* evidence
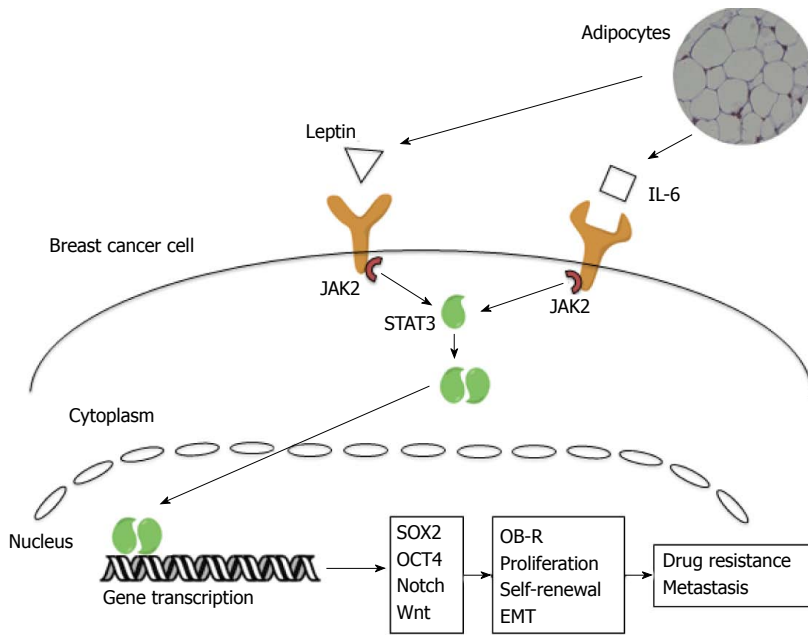
Figure 1 Adipocyte secreted leptin and interleukin-6 has a paracrine effect on nearby breast cancer cells. Through activation of the JAK2/STAT3 pathway, stemness factors SOX2 and OCT4 as well as EMT factors Notch and Wnt are transcribed. This leads to increased cancer cell proliferation and self-renewal entry into EMT and increased expression of leptin receptor OB-R. IL-6: Interleukin-6; OB-R: Leptin receptor; JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; SOX2: Sex determining region Y-box 2; OCT4: Octamer binding transcription factor 4; EMT: Epithelial mesenchymal transition.

of the necessity of leptin for breast cancer initiation and progression as well as implicating its role in breast cancer stem cell self-renewal. In triple-negative breast cancer cell cultures, OB-R activation increases levels of stem cell regulator Notch[21]. Inhibition of leptin signaling decrease expression of both Wnt and Notch in carcinogen induced mouse mammary tumors[51].

It is clear that leptin plays a significant role in activation of breast cancer stem cell signaling. Leptin activates several stemness pathways including the OCT-4/SOX2/Nanog axis, Notch signaling and Wnt/β-catenin signaling. Through these pathways leptin increases self-renewal, tumor initiation and ALDH1 expression, indicating an important role in adipocyte mediated pro-tumor signaling.

IL-6 in the tumor microenvironment

Adipose tissue is a significant source of IL-6, producing approximately one third of IL-6 found in the plasma. In healthy adipose tissue, non-adipocyte members produce the majority of adipose IL-6[44]. There are seven members of the IL-6 family; IL-6, oncostatin M (OSM), IL-11, leukemia inhibitory factor (LIF), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF) and cardiotrophin-1 (CT-1). There are 3 plasma membrane receptors, gp130, LIFR and OSMR, which activate the JAK/STAT, MAPK and PI3K pathways. Through these pathways IL-6 cytokines activate genes involved in inflammation, differentiation, survival, apoptosis and proliferation[52]. Within the adipose tissue, IL-6 stimulates glucose uptake, and activates glucose and fatty acid oxidation as well as insulin release[53].

Serum level of IL-6 is a negative prognostic marker in breast cancer patients[51,54]. While adipocyte secretion of IL-6 is low, proximity with tumor cells upregulates IL-6 expression. As mature adipocytes are the most common cells in tumor stroma, the combined amount of adipocyte IL-6 may have a significant impact on tumor cells[7]. IL-6 stimulates invasion in both ER+ and ER- breast cancer cells, similar to the phenotype observed in adipocyte/breast cancer cell co-culture[7]. When ER+/ER- breast cancer cells were treated with adipocyte-conditioned media, addition of an IL-6 blocking antibody significantly inhibited the pro-invasive effect[7]. However, depletion of IL-6 does not completely eliminate the invasive effects, supporting the model that multiple secreted molecules are important in the adipocyte-breast cancer cell interaction[55].

IL-6 activates transcription of OCT4 though the janus kinase 2 (JAK2)/STAT3 pathway, inducing EMT[38]. In triple negative breast cancer cells, there is higher IL-6/JAK2/STAT3 pathway activity in CD44+CD24- cancer stem cells compared to the differentiated CD44+CD24+ population[56]. Addition of IL-6 to culture media increased the proportion of cancer stem cells in triple negative breast cancer cell lines as well as in primary cells isolated from triple negative tumors[57]. Both breast cancer stem cells and mesenchymal breast cancer cells secrete up to 1000-fold more IL-6 than non-stem epithelial breast cancer cells, indicating the presence of an autocrine positive feedback loop[58].

FUTURE WORK AND THERAPEUTIC IMPLICATIONS

There is significant evidence that both adipocyte secreted IL-6 and leptin have pro-EMT activity, as well as promoting self-renewal and cancer stem cell signaling, however, these are just two of many signaling factors produced by adipocytes. Complete characterization of the adipocyte secretome in the breast cancer microenvironment is an important next step in the investigation of the adipocyte-breast cancer signaling relationship. Dirat *et al*[7] have demonstrated

the phenotypic plasticity of adipocytes in culture with breast cancer cells, further description of the exact mechanisms and consequences of cancer-associated adipocytes will contribute significantly to our knowledge of the tumor microenvironment. While the breast cancer microenvironment is heterogeneous, adipocytes are the primary constituent. Blocking adipocyte-cancer cell interactions has the potential to inhibit cancer stem cell activity and prevent tumor initiation/progression.

Conditioned media from adipocytes treated with Genistein and Sulforaphane has been shown to inhibit mammosphere formation of breast cancer cells[59,60]. Furthermore, there is already a clinically available anti-IL-6 antibody, Tocilizumab. Developed as a treatment for inflammatory rheumatic diseases, Tocilizumab may be useful for inhibiting adipocyte/breast cancer cell IL-6 signaling[61]. There also is significant interest in targeting leptin signaling for treatment of breast cancer. Leptin-signaling inhibition has anti-tumor effects in both ER$^+$, ER$^-$ and triple negative *in vitro* and *in vivo* models of breast cancer[62,63]. OB-R inhibitors, including leptin muteins[64], leptin peptide modulators[65], antibodies[66] and nanobodies[67] are under development, but have yet to enter clinical trials.

Future studies will reveal if other adipocyte-derived factors contribute to tumorigenesis. There are many adipocyte-secreted cytokines, with only a few currently investigated. It is likely that non-coding RNAs such as miRNAs and long non-coding RNAs (lncRNAs) are also involved in stromal-tumor cell signaling. Microvesicles such as exosomes mediate paracrine and endocrine transfer of miRNA and lncRNA, as well as proteins including TGF-β[68]. Targeting exosome mediated signaling may provide unique methods of inhibiting the adipocyte-breast cancer relationship.

miRNAs dysregulation is seen in almost all cancers[69] affecting nearly every hallmark of cancer[70]. Depending on the protein targeted, miRNAs act as either oncogenes or tumor suppressors, and miRNAs have a direct role in breast cancer stemness and progression[71,72]. Recently miRNAs with specific roles in adipogenesis and obesity have been identified[73]. There is differential miRNA expression in the adipocytes of obese mice compared to lean, including downregulation of miR-200 family microRNAs[74]. The miR-200 family inhibits epithelial mesenchymal transition through targeting of key EMT regulators such as ZEB1, SIP1[75] and SIRT1[41]. miR-200c expression is suppressed by IL-6, another potential mechanism for adipocyte-mediated increase in EMT signaling[76]. MiRNAs have important functions in both adipocytes and breast cancer cells, and may serve as signaling molecules or modify cancer cell interactions in the tumor microenvironment.

Current research on lncRNAs is rapidly changing the current paradigm of cell signaling. Initially found to have important regulatory roles during development and stem cell biology, lncRNAs may be involved in dysregulated signaling associated with transformation. lncRNA have diverse roles, and function during nearly all levels of gene expression. Differential lncRNAs expression may be used to predict patient outcomes or targeted to disrupt cell signaling[77]. Through profiling of preadipocyte and adipocyte transcriptomes, lncRNAs that control adipogenesis were identified[78]. Dissection of lncRNA's specific roles in adipocytes and breast cancer cells may provide new avenues of treatment.

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