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COMMENTARY

Commentary: Mammokine directs beige adipocytes to reserve energy for milk production in breast

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Beige/brown adipocytes play a crucial role in regulating the body's overall energy balance. The thermogenic function is under the influence of various tissues, including the brain, muscles, and liver. However, the breast tissue is not in the list. This issue has been addressed in a study recently published in *Nature*, which identified the paracrine function of breast epithelial cells for secreting "lipocalin 2" in the inhibition of thermogenesis of beige adipocytes to reserve mammary gland white adipose tissue (mgWAT)[1]. Within the female mammary gland, milk is produced by epithelial cells that form the glandular ducts and lobules in the adipose tissue and connective tissue within the breast[2]. The gland's structure is anatomically divided into four compartments: terminal ductal lobular units and branching epithelial cells in the lobules, primarily bilayered epithelium in the ducts, connective tissue rich in extracellular matrix, and adipose-rich areas[3]. While the exocrine function of epithelial cells is well-known in milk secretion, their paracrine/endocrine function was largely unexplored. The new study revealed that these epithelial cells have a paracrine function in secreting lipocalin 2, referred to as "mammokine".

There are three types of adipocytes: white, brown, and beige adipocytes[4]. White adipocytes are the major cell type in white adipose tissue (WAT) with functions in energy storage and adipokine secretion. WAT is predominantly found in various regions of the body, including the breast and subcutaneous[5]. In the breast, white adipocytes provide lipids supply to epithelial cells in production of the fatty acid portion of milk at about 3.5% by weight. In contrast, brown adipocytes are the major cell types in brown adipose tissue (BAT) with a primary function in thermogenesis, providing heat in the maintenance of body temperature[6]. This type of cells is characterized by abundant mitochondria and a high expression of uncoupling protein-1 (UCP-1). UCP-1 uncouples oxidative phosphorylation from ATP synthesis leading to the heat production for non-shivering thermogenesis[7]. Beige

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adipocytes distribute in subcutaneous WAT (scWAT) in mice, share similarities with brown adipocytes in thermogenesis. Beige function is induced by factors such as exercise, cold exposure, PPARγ activation, and β-adrenergic receptor agonists, which promote generation of beige cells from preadipocytes or mature adipocytes, known as WAT browning. Under conditions of warmth and high-fat diet feeding, beige cells are degenerated into white adipocytes, known as beige adipocyte whitening, decreasing the thermogenic activity of scWAT[8,9]. The WAT browning is considered a potential therapeutic approach for obesity and diabetes[10]. The impact of epithelial cells in beige adipocytes had not been previously explored in female breast.

The breasts contain a large portion of white adipose tissue to support milk production in the epithelial cells[11,12]. The adipocytes interact with the ductal epithelial cells, particularly during pregnancy, lactation, and involution[13,14]. The adipocytes also play a role in controlling ductal morphogenesis, cell differentiation, and function maturation of ductal epithelial cells through the interaction[13,15]. In breast cancer, the adipose tissue is reprogrammed by epithelial tumor cells to express more inflammatory cytokines supporting tumor growth as shown in a recent study using single-nuclear RNA sequencing (snRNA-seq) technology by our group[16]. The study indicates a crosstalk between adipocytes and epithelial cells in breast cancer, but the paracrine function of epithelial cells remains to be explored in breast.

In another recent study, Kumar et al. reported a comprehensive Human Breast Cell Atlas (HBCA) using multiple advanced technologies including single-cell RNA sequencing (scRNA-seq), snRNA-seq and spatial RNA sequencing technologies[17]. They identified 12 primary cell types and 58 cell states, revealing a high degree of diversity among luminal epithelial cells. There are three subtypes of epithelial cells, basal, luminal secretory (LumSec), and luminal hormone-responsive (LumHR), constitute the majority of breast ductal tissue. Additionally, they observed diversity in cellular states within these subsets. The basal epithelial cells were notably homogeneous, whereas the LumHR epithelial cells contained three different states, and LumSec epithelial cells displayed seven different states. They employed four different technologies to obtain spatial information of the subsets, providing valuable insights into breast biology and breast cancer. Notably, the subsets, including LumSec-basal, LumSec-HLA ductal basal colonization, LumSec-KIT, and LumSec-major basal lobular colonization, exhibited location-specific patterns. Unlike previous findings, LumHR and LumSec cells were not limited to alveoli and ducts as they presented in both ducts and lobular alveoli with varying abundance. The study identified a significant decrease in epithelial cell types in the breasts of postmenopausal women, with an increase in fibroblasts and myeloid cells in obese individuals[17]. They examined brown/beige adipocytes in the adipose tissue of breast. The conclusion is that the breast adipocytes were exclusively white adipocytes[17]. Despite the excellent work in construction of comprehensive and unbiased cellular map of breast tissue, the functional interactions between epithelial cells and adipocytes were not investigated in the study.

To this point, Patel et al.[1] investigated the interaction of epithelial cells and adipocytes in mice, and obtained similar patterns of cell subsets to those by Kumar et al.[17] They divided luminal cells into three subclusters, including luminal-hormone sensing (Luminal-HS), luminal-alveolar (Luminal-AV), luminal-hormone sensing alveolar (Luminal-HS-AV). Luminal-HS from Patel et al.'s studies and LumHR from Kumar et al.'s studies are hormone-sensing cells with high expression of hormone receptors, such as *Pgr*, *Esr1* and *Prlr*[18]. The Luminal-AV subsets specifically express luminal progenitor markers (*Cd14*) and milk biosynthesis-related genes (*Mfge8*). The Luminal−HS−AV subsets co-express hormone-sensing markers and alveolar progenitor markers, which is consistent with observations in other studies[18,19]. While the LumSec subsets express genes associated with milk production and secretory molecules with distinct expression of epithelial keratin[20−22].

More importantly, they identified a subtype of glandular luminal epithelium in female mice that secretes "mammokine" to regulate beige function of breast adipose tissue[1]. Using scRNA-seq technology, they analyzed cell types and cell subsets in the breast tissue. They demonstrated that mammary ducts could reduce UCP1 expression in breast adipocytes through secretion of mammokine, lipocalin 2 (LCN2). To confirm the activity, they employed *Lcn2* gene knockout mice and found that LCN2 inhibited the beige cell function in female-specific manner. In the female *Lcn2*-KO mice, the inhibition was removed by *Lcn* gene inactivation leading to elevation of energy expenditure, which was responsible for a significant decrease in body weight and subcutaneous fat under a cold environment. The effect was not observed in the wild-type controls and male *Lcn2*-KO mice. Expression of LCN2 was induced by cold stimulation and restricted to the luminal epithelium. The impact of the mammokine may extends beyond breast adipocytes to subcutaneous fat in other fat pads. Importantly, this effect was observed only in the female mice, suggesting that mammokine activity is sex-specific in regulation of adipose thermogenesis. The mammary-derived factor, secreted by ductal epithelial cells, preserves energy in the female body for breast development and milk production. In breast cancer, the interaction forces adipocytes to supply essential nutrients, energy, and growth factors to epithelial tumor cells to meet the metabolic demands of tumor[23].

The LCN2 activity remains controversial in adipocyte thermogenesis. There are several studies on LCN2 regulation of adipose thermogenesis[24−30]. One group of studies suggested that *Lcn2* was required for BAT thermogenesis and beiging activity of inguinal white adipose tissue (iWAT). They found that LCN2 deficiency significantly suppressed thermogenesis of adipose tissue in mice. In the mechanism of LCN2 activity, LCN2 was found to act *via* the COX2-PGs-mTOR pathway in adipocytes as LCN2 deficiency suppressed the mTOR signaling in control of thermogenic gene expression, lipogenesis, and lipolysis[24−26]. Furthermore, LCN2 was reported to regulate metabolic homeostasis of retinoids and retinoid-mediated thermogenesis in adipose tissue[27−30]. These studies demonstrated that LCN2 promotes thermogenesis of brown/beige adipocytes. However, another group of studies suggest that LCN2 represses the function of brown/beige adipocytes. Ishii et al. showed that the *Lcn2*-KO mice had enhanced non-shivering thermogenesis when exposed to 4 °C as indicated by higher body temperature and larger size of BATs, indicating that LCN2 inhibits function of BATs[31]. Lemecha et al.[32] observed that *Lcn2* gene deficiency significantly improved BAT function as indicated by body temperature in pancreatic ductal adenocarcinoma (PDAC)-bearing mice and increased expression of *Ucp1* and β3-adrenergic receptor in BAT. Park et al. found that LCN2 inhibited BAT function in dietary obese mice, and calorie restriction enhanced BAT function in the obese mice by suppression of LCN2 expression, which led to a reduction in inflammation, oxidative stress, and mitochondrial fission in BAT[33]. The two groups of reports suggest that LCN2 activity in adipocytes deserves more studies on thermogenesis.

The controversial may be explained by the sex-specific activity of LCN2. Previous studies of LCN2 *in vivo* were mainly conducted in male mice. In a study by Krishman et al.[34], LCN2 expression pattern and phenotypes were examined in both males and females in a panel of 100 inbred strains of mice (HMDP). They found that LCN2 overexpression in the adipose tissue induced metabolic disorders *via* an autocrine/paracrine manner through induction of inflammation and fibrosis in females, but not in males. While, LCN2 overexpression in the liver failed to generate the metabolic effect, suggesting a tissue-specific effect of LCN2. *Lcn2* gene transcription is regulated by estrogen through estrogen receptor Erα, which represses *Lcn2* gene expression by binding to the promoter DNA[35,36], suggesting a mechanism of sex-specific regulation of *Lcn2* gene. The study suggests that LCN2 level is lower in the female body as a result of suppressed transcription by the estrogen receptor. The conclusion by Krishman et al. is consistent with that of Patel et al. on the sex-specific activity of LCN-2 in the inhibition of thermogenic function of adipose tissue.

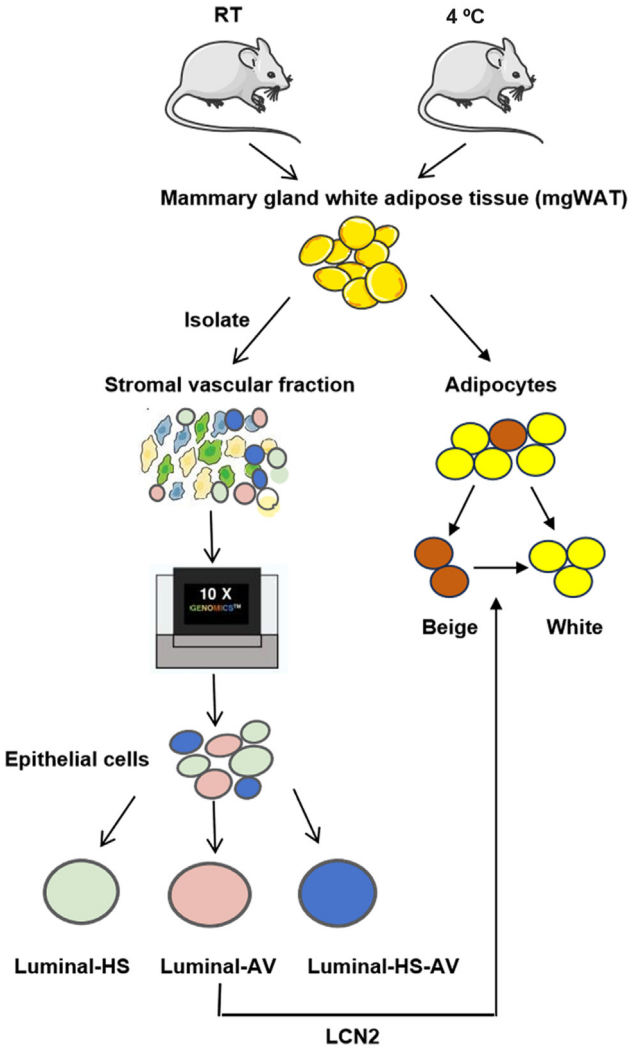

Figure 1 Cold-induced secretion of LCN2 from the luminal epithelial cells leads to beige cell whitening in the female breast. In the new study by Patel et al., the breast adipose tissues were collected from female mice treated with the room temperature (RT) or cold (4 °C) environment, respectively. The cell types and subsets of epithelial cells were investigated using single cell sequencing technology, which led to the finding that LCN2 expression was induced in the epithelial cells by the cold stimulation. The expression was restricted to the subset of luminal-alveolar (Lunimal-AV) of epithelial cells, but not the subset of luminal-hormone sensing (Luminal-HS) or luminal-hormone sensing alveolar (Luminal−HS−AV) epithelial cells. LCN2 was found to act on the beige adipocytes to reduce the thermogenesis activities leading to beige adipocyte whitening in the breast, which likely leads to reservation of energy for milk production in the breast.

There is a sex difference in beige function in fat pad-specific manner as reported in several studies[37−41]. It is generally believed that WAT browning occurs frequently in subcutaneous fat, instead of gonadal WAT (gWAT) depots as shown in most studies[42]. However, this feature may apply only to male mice, but not to female mice. In the female mice, WAT browning was more active in gWAT of female mice than that of male mice as reported in a study by Kim et al. in the model of β3-adrenergic stimulation[41]. Additionally, WAT browning was more active in gWAT than iWAT in the female mice[41]. These results are consistent with *in vitro* experiments conducted by Beukel et al.[43] using human perirenal tissues, suggesting that WAT browning has a gender difference and fat pad-specificity.

In addition to LCN2, other "mammokine" were identified in the luminal epithelial cells in the study[1]. Expression of those secreted factors was up-regulated in the epithelial cells by the cold treatments. Activities of those mammokine were not examined in the study, but their activities are indicated in other studies. For example, Angiopoietin-like 4 (ANGPTL4) increases circulating triglyceride levels and regulated lipid distribution across different tissues by inhibiting lipoprotein lipase activity. As such, ANGPTL4 has been considered as a potential therapeutic target[44,45]. Leucine-rich α-2 glycoprotein 1 (LRG1) is an adipokine secreted by mature adipocytes and LRG1 overexpression enhanced insulin sensitivity and suppressed inflammation[46]. Diacylglycerol acyltransferase 2 (DGAT2) regulates triacylglycerol (TG) synthesis of *de novo*-synthesized fatty acids and is the predominant enzyme for TG storage[47]. Adropin (*Enho*) modulates glucose and lipid metabolism[48]. Patel et al.[1] reported that the adropin and LRG1 secreted by luminal cells may not make an impact in adipose thermogenesis directly as they may change other metabolic functions of mgWAT. These data indicate that liminal epithelial cells regulate the function of breast adipose tissue by secreting multiple mammokines.

While this new study sheds light on the paracrine function of mammary epithelial cells for identification of mammokine LCN2 in the regulation of breast energy expenditure, which involves in beige adipocyte whitening[1] (Fig. 1). However, the precise molecular mechanism of LCN2 action remains to be investigated for the whitening[1].

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Author contributions

Lina Tang made the draft and revised the manuscript. Jianping Ye provided the idea and revised the manuscript in the original and revised submission.

Conflicts of interest

The authors declare no conflict of interest.

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