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REVIEW

Deciphering the molecular and physiological connections between obesity and breast cancer

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Abstract **Obesity is associated with the higher risk of breast cancer in postmenopausal women. The leptin signaling pathway is recognized to primarily regulate energy balance and associated with breast cancer. Furthermore, the estrogen signaling pathway plays a critical role in breast carcinogenesis. In this review, we discuss how obesity is linked to breast cancer via cross-talk of leptin and estrogen pathways.**

Introduction

Obesity refers to excessive fat storage in the body that has an adverse effect on health. It has continued to be prevalent globally in the past decade. It is also one of the leading preventable causes of death worldwide, and the most serious public health problem in the 21st century (Barness et al., 2007). Moreover, it increases the frequency of several complication diseases, such as type-II diabetes, inflammation, dysfunctional reproduction and breast cancer. Several signaling pathways are involved in the regulation of energy balance and obesity development. Leptin, a hormone secreted by adipose tissue, is recognized as the primary signal that mediates food intake and energy expenditure (Zhang et al., 1994).

Breast cancer is the most common cancer in women. Every year, breast cancer causes the deaths of about half a million people all over the world (World Health Organization, 2006). Breast cancer is mostly derived from milk ducts or the lobules of breast tissue. Several risk factors enhance the frequency of breast carcinogenesis. Currently, estrogen signaling pathway is thought to play an important role in the breast tumorigenesis (Kurzer, 2002). Several clinical studies have shown that an elevated estrogen level increases the risk of breast cancer in postmenopausal women.

Many epidemiological risk factors which increase the frequency of breast cancer have been identified in recent years. Substantial data have shown that obesity is one of the risk factors, which increases the risk of breast tumorigenesis in women (Pischon et al., 2008; Percik and Stumvoll, 2009). Several reports also showed that breast cancer occurs at a higher frequency in postmenopausal than in premenopausal women (Asseryanis et al., 2004). Obese patients have higher levels of serum adipokines than normal or lean individuals. The excess adipokines, particularly leptin, bring about many complicating diseases, such as hypertension, breast cancer, and type-II diabetes (Saxena et al., 2008). However, little is known about the molecular mechanism of cross-talk between obesity and breast cancer. Herein we review the connections between the leptin and the estrogen signaling pathways.

Leptin signaling pathway and breast cancer

As an endocrine organ, adipose tissue produces several hormones or cytokines to mediate various physiological processes. Leptin is recognized as the primary factor which regulates energy balance. Leptin receptors are expressed in several tissues, such as ovary, brain, heart and bone, suggesting that the leptin signaling pathway plays widespread roles in different physiological processes. Through blood system transportation, circulating leptin binds to the leptin receptor to perform various functions in different tissues or organs by activating downstream signaling pathways. In rodents, the deficiency of leptin or the leptin receptor generates not only the obese phenotype and type-II diabetes mellitus but also abnormal reproductive function (Barash et al., 1996; Chehab et al., 1996; Mounzih et al., 1997; Malik et al., 2001; Qiu et al., 2001).

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Epidemiological investigation has also shown a strong relationship between breast cancer and obesity (Maccio et al., 2010). Obesity increases the risk of breast cancer and advanced tumor stage in postmenopausal women (Maccio et al., 2010). Leptin, which is elevated in obese people, has been associated with breast carcinogenesis, tumor migration and invasion, enhancement of angiogenesis, and increased aromatase activity (Liu et al., 2007). The expression of leptin and leptin receptor has been detected in human breast cancer cell lines and in human primary breast carcinoma (Revillion et al., 2006; Jarde et al., 2008). Compared with normal individuals, breast cancer patients always exhibit higher levels of serum leptin, leptin mRNA and leptin receptor mRNA in breast cancer cells (Tessitore et al., 2004; Han et al., 2005; Miyoshi et al., 2006; Revillion et al., 2006; Snoussi et al., 2006). In some reports, serum leptin levels positively correlated with the frequency of ER-positive breast cancer in women (Liu et al., 2007). Leptin promotes the carcinogenesis and metastasis of breast cancer in an autocrine manner (Ishikawa et al., 2004). In breast cancer survivors, serum leptin level and bodyweight are significantly reduced compared to pre-treatment (Jen et al., 2004). In another report, breast cancer patients without leptin receptor expression have a significantly higher survival rate (Kim, 2009). Mechanistically, leptin has been found to be associated with breast cancer by promoting the activity of aromatase and increasing the expression of estrogen and estrogen receptor alpha (Magoffin et al., 1999; Tessitore et al., 2004; Geisler et al., 2007). After treatment with different drugs, the leptin level in patients using tamoxifen is significantly higher than that in patients without using tamoxifen (Marttunen et al., 2000; Ozet et al., 2001).

In the hypothalamus, leptin activates downstream STAT3 and ERK signals to regulate food intake and energy expenditure. The expression level of leptin and downstream signals are associated with mammary tumorigenesis (Dogan et al., 2007). Moreover, the deficiency of leptin signaling in rodents leads to not only an obese phenotype, but also the suppression of oncogene-induced mammary carcinogenesis (Cleary et al., 2003). Deletion of the leptin receptor also attenuates oncogene-induced mammary carcinogenesis (Cleary et al., 2004b).

In breast cancer cells *in vitro*, leptin functions as a mitogen to induce breast cancer cell proliferation, survival and invasion through activating JAK/STAT3, ERK1/2, IRS and PI3K pathways, and mediate angiogenesis by inducing VEGF expression (Dieudonne et al., 2002; Garofalo et al., 2004; Gonzalez et al., 2006). Leptin induces the survival of breast cancer cells by activating Akt and plays an anti-apoptotic effect by inhibiting the expression of apoptotic proteins (Koda et al., 2007). Leptin regulates breast cancer cell growth and survival by activating ERK and STAT3 pathways (Jiang et al., 2008; Saxena et al., 2007; Yin et al., 2004). It also regulates cell cycle-related genes to enhance the proliferation of cancer cells (Catalano et al., 2004; Okumura et al., 2002; Perera et al., 2008). In MCF-7 cells, leptin activates JNK to promote metastasis of breast cancer (McMurtry et al., 2009). Leptin mediates breast carcinogenesis by regulating estrogen receptor alpha expression (Ray et al., 2007), and leptin-induced STAT3 activation is enhanced by the overexpression of ERα in MCF-7 cells (Binai et al., 2010). In ER positive breast cancer cells, leptin increases estrogen levels by stimulating the expression of aromatase. In another study, leptin interferes with the effect of tamoxifen by the ERα pathway in breast cancer cells (Garofalo et al., 2004). Interestingly, adiponectin has the opposite effect of leptin on proliferation of breast cancer cells (Grossmann et al., 2008; Nkhata et al., 2009b). Together, these studies indicate leptin involvement in breast tumorigenesis.

Estrogen signaling pathway and obesity

Obese development is a chronic process in humans. Generally, young men are prone to form central obesity—"apple shaped" —while young women are liable to show lower obesity— "pear shaped". After menopause, pear-shaped women often change to apple-shaped. Epidemiological data have suggested that apple-shaped obesity is more prone to produce type-II diabetes, hypertension and cancer than pear-shaped (Farag et al., 2004; Donato et al., 2006). These results indicate that sex hormones, especially estrogen, play an important role in the development of obesity (Tchernof et al., 2000). Circulating estrogen, particularly the bioactive estradiol, elevates the risk of breast tumorigenesis in women in addition to functioning as a sex hormone. Estrogen mainly binds to ERα, a nuclear receptor, to increase breast cell proliferation by activating downstream signal pathways. However, in animal experiments, silenced or deficient ERα in the hypothalamus generates the obese phenotype and metabolic syndrome (Musatov et al., 2007). Estrogen also mimics the leptin action to regulate downstream STAT3 action for energy balance in the hypothalamus (Gao et al., 2007). The deficiency or deletion of aromatase or ERα induces the obese phenotype by increasing fat tissue due to reduced energy expenditure (Heine et al., 2000; Ohlsson et al., 2000; Cooke et al., 2001). Ovariectomization in rodents could establish the status for lack of estrogen. These estrogen-deficient animals show an obese phenotype. Furthermore, estrogen deficiency-induced obesity can be reversed by administration of estradiol-17β, which reduces accumulation of adipose tissue and food intake (Cave et al., 2007; Geisler et al., 2002; Liang et al., 2002). Meanwhile, activation of ERα by estrogen reduces food intake and increases energy expenditure (Cave et al., 2007). Interestingly, ERβ signaling pathway plays an opposite role of ERα in obese development through the anorectic action of estrogen in the central nervous system (Liang et al., 2002; Naaz et al., 2002). These studies indicate that the estrogen signaling pathway not only regulates breast carcinogenesis but also engages in food

intake and energy balance.

More importantly, in postmenopausal obese women, the level of ERα expression is associated with the BMI, used to evaluate obesity (Meza-Munoz et al., 2006), and estrogen receptor polymorphisms are also associated with fat tissue distribution and obesity (Okura et al., 2003). Mutations of ERα are linked with obesity development by reducing oxygen uptake and caloric expenditure (Goulart et al., 2009; Gu et al., 2009). The reduction of ERα expression in human is likely involved in the control of bodyweight (Nilsson et al., 2007). However, in the Chinese population, ERα polymorphisms are not associated with obesity (Jian et al., 2005). In aggregate, these studies suggest that estrogen signaling defect is involved in obesity development. However, the molecular mechanism of estrogen-mediated obesity development is not fully understood.

In vitro experiments on cell lines have shown estrogen involvement in adipogenesis and osteogenesis (Dang and Löwik, 2004). In human adipocytes, estradiol-17β upregulates the expression of ERα and ERβ mRNAs to mediate adipose tissue development and metabolism (Dieudonné et al., 2004). In bone marrow stromal cell lines, estrogen inhibited adipocyte differentiation and promoted osteogenesis (Picó et al., 1998; Okazaki et al., 2002). Estrogen activates the ERK and Akt pathways to increase the expression of leptin in placental cells (Gambino et al., 2010). Estrogen plays an anti-obesity role by inhibiting 11β-HSD1 and induces the expression of PPARγ *in vitro* (Tagawa et al., 2009; Ueki et al., 2009). However, ERβ inhibits adipogenesis by suppressing the activity of PPARγ transcription (Foryst-Ludwig et al., 2008). These findings have also been replicated in human studies (Dieudonné et al., 2004).

Notably, ERα and ERβ have common and distinct expression patterns in various tissues and organs. ERβ is mainly expressed in brain, epithelial cells, bone, heart, kidney, lung and intestinal mucosa (Couse et al., 1997), while ERα is primarily found in breast cells, hypothalamus, ovarian stroma cells and endometrium cells (Couse et al., 1997). More importantly, the two receptors often exhibit opposing action on some physiological or pathological processes. Accumulating data so far suggest a critical role of ERα in ERα-positive breast cancer and obesity develop-

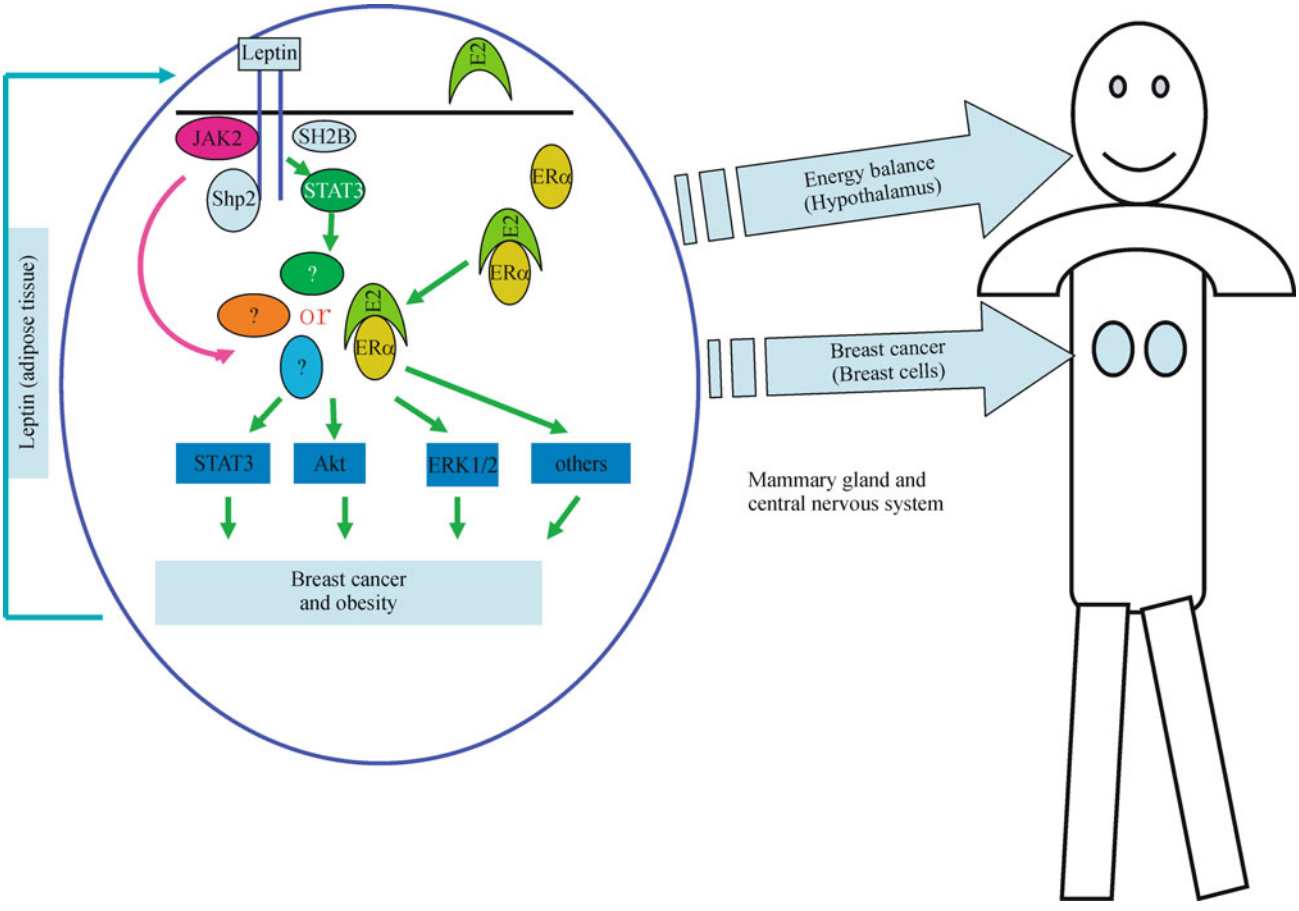

Figure 1 The model of molecular link between breast cancer and obesity. We propose that one or more signaling components acting downstream of leptin receptor may interact with ERα, thereby mediating the direct cross-talk of leptin and estrogen signaling pathways. Identification of these components and elucidation of the biochemical basis will lead to the better understanding of how obesity is associated with breast carcinogenesis.

ment. It is less clear whether ERβ is associated with the breast carcinogenesis or in cross-talk with the leptin signaling. The deletion of ERβ did not cause a severe phenotype (Antal et al., 2008; Dupont et al., 2000). Accordingly, the discussion in this article is more focused on ERα in obesity and breast cancer.

Perspectives

Based on clinical studies and animal model experiments, both estrogen and leptin signals are involved in obesity development and breast carcinogenesis and mediate overlapping and intertwining pathways, which are yet to be fully elucidated.

Some studies have shown that leptin is upstream of the estrogen signaling pathway. Leptin increases the activation of estrogen receptor and inhibits the effect of tamoxifen on breast cancer cell proliferation in human (Ozet et al., 2001; Garofalo et al., 2004). Leptin upregulates the expression of ERα, while suppressing ERβ expression in human breast cancer cells (Yu et al., 2010). Moreover, the deficiency of estrogen receptor prevents leptin-mediated mammary tumorigenesis in an animal model (Cleary et al., 2004a). However, the deletion of lepin receptor attenuates oncogene-induced mammary tumor. Lack of estrogen production by ovariectomization cannot inhibit ER-positive breast tumorigenesis (Nkhata et al., 2009a). These results challenge the notion that leptin signal is upstream of the estrogen signaling pathway.

Alternatively, ERα is required for both leptin and estrogen signal transduction, which can explain all current results. ERα-mediated leptin signaling is likely associated with either leptin receptor binding proteins (JAK2, SHP2 and STAT3) or adaptor/transducer proteins (SH2B, SOCS3, SOS, PTP1B and PI3K) of leptin signaling pathway. ERα is a critical component in both leptin and estrogen signaling pathways. Several reports have shown that leptin and estrogen stimulate some common downstream signaling pathways. Estrogen induces the phosphorylation of ERK, STAT3, IRS and PI3K pathways in breast cancer cell lines, just as leptin does, indicating that ERα is downstream of leptin and upstream of these signaling molecules. One recent study showed that leptin receptor and ERα have a bidirectional communication in breast cancer cells (Fusco et al., 2010). Overexpression of ERα increases the leptin-induced STAT3 activity. Leptin directly regulates the activation of ERα in breast cancer cells (Catalano et al., 2004). Therefore, ERα possibly mediates both leptin and estrogen signals by associating with elements downstream of leptin receptor (Fig. 1). Evidently, more experiments are required to elucidate the molecular mechanism of connections between leptin and estrogen signaling pathways.

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