Cytokine & Growth Factor Reviews 24 (2013) 503–513

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Role of adipokines and cytokines in obesity-associated breast cancer: Therapeutic targets

Sajid Khan, Samriddhi Shukla, Sonam Sinha, Syed Musthapa Meeran *

Division of Endocrinology, CSIR-Central Drug Research Institute, Lucknow, India

ARTICLE INFO

Article history:
Available online 21 October 2013

Keywords:
Obesity
Breast cancer
Leptin
Adiponectin
Cytokines

ABSTRACT

Obesity is the cause of a large proportion of breast cancer incidences and mortality in post-menopausal women. In obese people, elevated levels of various growth factors such as insulin and insulin-like growth factors (IGFs) are found. Elevated insulin level leads to increased secretion of estrogen by binding to the circulating sex hormone binding globulin (SHBG). The increased estrogen-mediated downstream signaling favors breast carcinogenesis. Obesity leads to altered expression profiles of various adipokines and cytokines including leptin, adiponectin, IL-6, TNF-α and IL-1β. The increased levels of leptin and decreased adiponectin secretion are directly associated with breast cancer development. Increased levels of pro-inflammatory cytokines within the tumor microenvironment promote tumor development. Efficacy of available breast cancer drugs against obesity-associated breast cancer is yet to be confirmed. In this review, we will discuss different adipokine- and cytokine-mediated molecular signaling pathways involved in obesity-associated breast cancer, available therapeutic strategies and potential therapeutic targets for obesity-associated breast cancer.

1. Introduction

Breast cancer is the most common type of cancer and also the leading cause of cancer-related deaths in women, worldwide. According to GLOBOCAN 2008, breast cancer accounted for 23% (1.38 million) of the total new cancer cases and 14% (458,000) of total cancer-related deaths in the year 2008 [1]. Several reproductive and lifestyle factors are associated with the development of breast cancer. Among the reproductive factors are long menstrual history, nulliparity, increased use of oral contraceptives, and giving birth to a child at later age [2]. Lifestyle factors including less physical activity, consumption of high calorie diets, cigarette smoking and alcohol consumption are strongly associated with increased risk of breast cancer development [3,4].

Obesity is an abnormal or excessive fat accumulation in adipose tissue which leads to impaired health [5]. According to World Health Organization (WHO), obesity is defined as having a body mass index (BMI) of equal to or higher than 30 kg/m^2. It is the major cause of onset of a number of diseases such as type-2 diabetes, cardiovascular diseases (CVDs), infertility, and several types of cancers [6]. It is estimated that 25–30% of cancers at numerous sites such as esophagus, pancreas, colorectum, endometrium, kidney and postmenopausal breast are caused by obesity and physical inactivity [7,8]. Obesity increases the risk of breast cancer by 30% in postmenopausal women and accounts for 21% of all breast cancer deaths, worldwide [9–11]. Obesity is also associated with worse prognosis and poor treatment outcome in cancer [12,13].

In postmenopausal women, estrogen is a major risk factor for breast cancer development. In general, estrogen is synthesized by

Abbreviations: IGFs, insulin-like growth factors; SHBG, sex hormone binding globulin; BMI, body mass index; IGFBPs, IGF binding proteins; IGF-1R, insulin-like growth factor-1 receptor; CLS, crown-like structure; NFκB, nuclear factor kappa-B; STAT3, signal transducer and activator of transcription-3; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-α; ILs, interleukins; IFNs, interferons; JNK, c-Jun N-terminal kinase; SOCS3, suppressor of cytokine signaling-3; JAK2, Janus kinase-2; MAPK, mitogen-activated protein kinase; VEGF, vascular endothelial growth factor; VEGF-R2, vascular endothelial growth factor receptor-2; ERα, estrogen receptor-α; ERK, extracellular signal-regulated kinase; HER-2, human epidermal growth factor receptor-2; hTERT, human telomerase reverse transcriptase; PARP, poly (ADP-ribose) polymerase; AMPK, AMP-activated protein kinase; LDL, low-density lipoprotein; PDGF-BB, platelet-derived growth factor subunit B homodimer; bFGF, basic fibroblast growth factor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; GSK-3β, glycogen synthase kinase-3β; HIF-1α, hypoxia-inducible factor-1α; C/EBPα, CCAAT/enhancer binding protein-α; PFS, progression-free survival; CDK, cyclin-dependent kinase; PEG-LPrA2, pegylated leptin peptide receptor antagonist 2; mTOR, mammalian target of rapamycin; EGCG, epigallocatechin-3-gallate; NSAIDs, non-steroidal anti-inflammatory drugs; PPARα, peroxisome proliferator-activated receptor-α.

* Corresponding author at: Division of Endocrinology, CSIR-Central Drug Research Institute (CSIR-CDRI), Jankipuram Extn., Sector-10, Sitapur Road, Lucknow 226 031, India. Tel.: +91 522 2612411x4491; fax: +91 522 2623938.
E-mail addresses: s.musthapa@cdri.res.in, syedmusthapa@gmail.com (S.M. Meeran).

1359-6101/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cytogfr.2013.10.001

sexual organs, whereas in obese postmenopausal women adipose tissue is the main source of estrogen synthesis [11]. Obesity leads to altered expression of hormones, growth factors, inflammatory cytokines and adipokines which promote cancer cell survival, metastasis, angiogenesis, and decreased cancer cell apoptosis. The detailed molecular mechanisms through which obesity promotes breast cancer development are discussed in the next section.

2. Factors involved in obesity-associated breast cancer and their mechanisms

2.1. Hormones and growth factors

Obesity is accompanied by increased estrogen synthesis from adipose-tissue associated stromal cells and elevated levels of insulin and insulin-like growth factors (IGFs) [14–16]. This rise in insulin level is found to be associated with the activation of IGF system and altered levels of IGF binding protein-1 (IGFBP1) and -2 (IGFBP2) which leads to increased bioavailability of IGFs. IGFBPs stabilize and prolong the half life of IGFs and prevent their binding to IGF receptors [17]. IGFBPs also influence the duration of signaling via the IGF receptor by slow release of IGF to its receptor. Further, IGFs lead to macrophage migration and invasion and increased production of pro-inflammatory cytokines by macrophages [18,19]. In chronic hyperinsulinemia, a decreased level of circulating sex-hormone binding globulin (SHBG) leads to increased bio-available estrogen levels which promote mammary tumorigenesis [14].

Insulin, IGFs and insulin like growth factor-1 receptor (IGF-1R) are over expressed in several subtypes of breast cancer [20]. The binding of these ligands to IGF-1R leads to activation of its tyrosine kinase activity [21]. Activation of IGF-1R can promote cell migration and redistribution of E-cadherin and, α- and β-catenins from adherens junctions into the cytoplasm and promote breast tumorigenesis [22]. In addition, IGF-1R leads to activation of PI3K/Akt and Ras-raf-MAPK signaling which alter the expression of genes involved in cellular proliferation and survival [23]. Overall, this altered hormonal and growth factor profile is associated with increased breast cancer risk.

2.2. Inflammation and inflammatory cytokines

Obesity causes subclinical inflammation in both visceral as well as subcutaneous adipose tissue. This inflammation is characterized by necrotic adipocytes surrounded by macrophages which are visualized as crown-like structures (CLS) under light microscope [24–26]. This subclinical inflammation might increases the risk of breast cancer.

The adipose tissue-derived factors activate key inflammatory molecules such as nuclear factor kappa-B (NFκB) and signal transducer and activator of transcription-3 (STAT3). Activation of *NFκB* in adipose tissue further induces the expression of several pro-inflammatory mediators like cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), which in turn induces aromatase expression and activity. Activation of these inflammatory mediators leads to altered expression of genes involved in breast carcinogenesis [27–29].

Cytokines, including TNF-α, interleukin-6 (IL-6) and interferons (IFNs) have been reported to be associated with breast cancer development as indicated by their presence within tumor microenvironment and in the tumor metastatic sites [30]. TNF-α regulates IL-6 synthesis and the expression of aromatase in adipose tissue [31]. Conditional media from preadipocyte-derived adipocytes was found to increase the proliferation of breast cancer cells, possibly due to the presence of IL-6 from adipocytes [32]. TNF-α treatment in adipocytes drastically decreases the adiponectin expression and secretion through insulin-like growth factor binding protein-3 (IGFBP-3) and c-Jun N-terminal kinase (JNK) cascades [33,34].

2.3. Adipokines

Adipokines are small peptide hormonal growth factors which are secreted mainly by adipocytes from white adipose tissue. These are the major contributing factors for obesity associated breast cancer [35]. The two most important adipokines which are associated with breast cancer development are leptin and adiponectin.

2.3.1. Leptin

Leptin, a multifunctional neuroendocrine peptide hormone, plays a key role in satiety, energy expenditure, food intake, and various reproductive processes [36,37]. Leptin is encoded by *obese (ob)* gene which is located on chromosome 7, in humans [38]. It consists of 167 amino acids and has a molecular weight of 16 kDa [39]. The molecular actions of leptin are mediated through the cell surface receptors which are members of cytokine family of receptors and are present in various tissues [40]. Six isoforms of leptin receptors ranging from Ob-Ra to Ob-Rf have been identified. Ob-Rb is a long isoform of leptin receptor as it contains a long intracellular domain, comprising of approximately 306 amino acids. The other isoforms (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf) are more abundant in peripheral tissues and contain a short intracellular domain consisting of 23 amino acids [41]. Ob-Re is a soluble leptin receptor, and has been shown to control circulating leptin levels [42].

Adipose tissue is the main source of leptin secretion. In addition, some amount of leptin is also secreted from normal and malignant breast tissue, placenta, stomach and skeletal muscle. The level of leptin increases in proportion to BMI. Serum leptin levels in obese individuals are higher due to its increased release from adipocytes [43]. Leptin could increase or decrease the risk of breast cancer depending on the menopausal status. Plasma leptin level increases the risk of breast cancer in postmenopausal women, whereas its level is inversely related to breast cancer risk in premenopausal women [44]. Leptin and its receptors are over expressed in breast tumors and are associated with distant metastasis [45,46]. Genetically obese leptin-deficient $Lep^{ob}Lep^{ob}$ and leptin receptor-deficient $Lepr^{db}Lepr^{db}$ female mice do not develop mammary tumors which provide supporting evidence that leptin and its receptor is involved in breast tumorigenesis [47,48].

The long form of leptin receptor which is mainly expressed in the hypothalamus acts through the activation of JAK2/STAT3 and MAPK pathways, whereas short isoforms activate mainly MAP kinases and appear to be responsible for mitogenic activity [49]. Through activation of JAK2/STAT3 pathway, leptin induces the expression of c-*MYC* and consequently leads to increased cell survival and proliferation [50]. Another downstream target of JAK/STAT signaling, cyclin D1 which promotes G1 to S-phase transition during cell cycle progression is found to be increased due to increased JAK/STAT signaling mediated by leptin [51]. Suppressor of cytokine signaling-3 (SOCS3) negatively regulates leptin-mediated activation of JAK2/STAT3 signaling by binding to phosphorylated JAK2 proteins [52,53]. Recently, SOCS3 has been reported to down regulate the expression of anti-apoptotic protein survivin through binding with long isoform of leptin receptor (Ob-Rb) and thus inhibiting leptin signaling through JAK/STAT pathway [54].

In a recent study, leptin has been shown to be involved in the regulation of endothelial cell proliferation and in the promotion of angiogenesis [55]. Leptin increases endothelial COX-2 expression