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Review

Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells

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ABSTRACT

Significant correlations between obesity and incidence of various cancers have been reported. Obesity, considered a mild inflammatory process, is characterized by a high level of secretion of several cytokines from adipose tissue. These molecules have disparate effects, which could be relevant to cancer development. Among the inflammatory molecules, leptin, mainly produced by adipose tissue and overexpressed with its receptor (Ob-R) in cancer cells is the most studied adipokine. Mutations of leptin or Ob-R genes associated with obesity or cancer are rarely found. However, leptin is an anti-apoptotic molecule in many cell types, and its central roles in obesity-related cancers are based on its pro-angiogenic, pro-inflammatory and mitogenic actions. Notably, these leptin actions are commonly reinforced through entangled crosstalk with multiple oncogenes, cytokines and growth factors. Leptin-induced signals comprise several pathways commonly triggered by many cytokines (i.e., canonical: JAK2/STAT; MAPK/ERK1/2 and PI-3K/AKT1 and, non-canonical signaling pathways: PKC, JNK and p38 MAP kinase). Each of these leptin-induced signals is essential to its biological effects on food intake, energy balance, adiposity, immune and endocrine systems, as well as oncogenesis. This review is mainly focused on the current knowledge of the oncogenic role of leptin in breast cancer. Additionally, leptin pro-angiogenic molecular mechanisms and its potential role in breast cancer stem cells will be reviewed. Strict biunivocal binding-affinity and activation of leptin/Ob-R complex makes it a unique molecular target for prevention and treatment of breast cancer, particularly in obesity contexts.

Contents

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1. Introduction

Obesity and overweight conditions are prevalent in the world. The World Health Organization (WHO) reported that more than 400 million people are obese, with a predicted increase to possibly reach 700 million by 2015 worldwide [1]. In the United States, the current epidemic of obesity in adults is 30%–35%, posing a major public health challenge [2-5]. Obesity or overweight conditions are associated with a significantly increased risk of development of various diseases, particularly cardiovascular disease [6], type 2 diabetes [7], hypertension [8], dyslipidemia [9], liver disease [10], as well as cancer [11,12]. Compelling evidence indicates over 13 different cancers including breast, cervical, colon or rectal, esophageal, gall bladder, kidney, liver, ovarian, pancreatic, stomach, uterine cancer, as well as multiple myeloma, non-Hodgkin lymphoma are associated with obesity [11-14].

How obesity is connected to cancer incidence is still an unexplainable or unanswered question. However, accumulated evidence shows that these two conditions have intertwined inflammatory patterns. In obesity, deregulated secretion of pro-inflammatory cytokines, chemokines and adipokines such as TNF-α, plasminogen activator inhibitor-1 (PAI-1), IL-1, IL-6, adiponectin and leptin from the expanding adipose tissue and inflammatory cells could make a clinically relevant contribution to the onset and progression of cancer [15-17]. However, the individual contributions of these factors to obesity-related cancers are often contradictory and not well understood in diverse scenarios. Among the above mentioned molecules, leptin has been the most studied adipokine since this protein was first cloned in 1994 [18].

The identification of spontaneous mutations in the leptin (ob or LEP) and Ob-R (db or LEPR) genes in mice opened up a new field in obesity research. Although allelic frequencies of ob and db polymorphisms show ethnic variation, systematic search for mutations showed low penetration and scarce number of affected individuals. The data suggests the lack of association between the genes under study and obesity. The lack of association could be due to the complex pathogenesis of obesity, which involves a number of genetic and environmental factors [19]. High leptin levels in obesity and overweight individuals or populations are clearly correlated with body fat and adipocyte size. Under these conditions leptin is unable to regulate appetite/size of fat deposits leading to a "leptin resistance status", which could induce deregulated peripheral actions in many Ob-R expressing tissues. The molecular mechanisms underlying how obesity causes an increased risk of cancer are poorly understood, but compelling evidence shows that pandemic obesity and cancer incidence are connected [20]. A retrospective study on a large cohort of women (n = 495,477) in the US reported by Calle et al., shows a significant correlation between increasing risk and higher body-mass-index values and death from breast cancer in obese/overweight women [21]. Other studies have also found that women with a higher percentage of adipose tissue/leptin levels have higher incidence of breast cancer [11,22,23].

In light of the increasing reported role of leptin in several types of cancer [24-28], in this review we wish to focus on the role of leptin in breast cancer, highlighting the leptin-mediated signaling pathways and its potential as a drug target. Additionally, we will review and discuss recently identified molecular mechanisms of leptin in breast cancer, including its potential role in breast cancer stem cells (BCSC), tumor angiogenesis, as well as its crosstalk with other oncogenic signaling pathways.

2. Structure and function of leptin and leptin receptor

Leptin is a small 167-amino acid non-glycosylated protein with a molecular weight of 16 kDa, coded by the LEP gene, whose name is derived from the Greek word "leptos," which means "thin." The LEP gene is preserved in mammals providing a high sequence identity for leptin. Indeed, human leptin and mouse leptin share 84% sequence homology. The cDNA sequence encoding for leptin was identified on the mouse ob (obese) gene. A nonsense mutation in codon 105 (ob/ob) causes the lack of protein synthesis resulting in morbid obesity, hyperphagia, hypothermia, insulin resistance, and infertility [18]. The biological role of leptin in energy homeostasis was demonstrated by normalization of hyperphagy and obese phenotypes with recombinant leptin administration in rodents and humans [29,30]. In addition, leptin plays critical roles in the regulation of glucose homeostasis, reproduction, growth and the immune response [31-33]. It is currently believed that leptin binding to Ob-R induces the extracellular domains of Ob-R to form a homodimer which constitutes the functional unit responsible for leptin-mediated signals. Analysis of highly conserved regions in the leptin sequence and studies of a homology-based model of the leptin-Ob-R complex suggest that two helices of leptin (H1 and H3) contain the most important receptor binding sites [34]. The N-terminal region (94 amino acids) of leptin is essential for both the biological and the receptor binding activities [35].

The leptin receptor (Ob-R) belongs to a member of the class I cytokine receptor super-family, which includes the receptors of IL-1, IL-2, IL-6 and the growth hormone [36]. This super-family of receptors lacks autophosphorylation capabilities and needs auxiliary kinases for activation. Ob-R binding to leptin induces conformational changes that recruit JAKs (Janus kinases), which in turn phosphorylates Ob-R and activates STATs (signal transducers and activators of transcription). Six leptin receptor isoforms have been discovered so far, and are generated by mRNA alternative splicing [37]: the long isoform (OB-RL or OB-Rb) with full intracellular signaling capabilities and shorter isoforms with less biological activity (OB-RS) [36]. The