Review Article

Leptin and cancer: Pathogenesis and therapeutic modulation

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ABSTRACT

Leptin, a product of Ob gene from adipocytes regulates appetite, energy expenditure and body mass composition by decreasing orexigenic and increasing anorexigenic neuropeptide release from hypothalamus. Research over the past few years have suggested leptin/leptin receptor dysregulation to have a role in the development of a large variety of malignancies like breast ca, thyroid ca, endometrial ca and gastrointestinal malignancies, predominantly through JAK/STAT pathway which modulates PI3K/AKT3 signaling, ERK1/2 signaling, expression of antiapoptotic proteins (like XIAP), systemic inflammation (TNF-α, IL6), angiogenic factors (VEGF) and hypoxia inducible factor-1a (HIF-1a) expression. In this review, the current understanding of leptin's role in carcinogenesis has been elaborated. Also a few agents modulating leptin signaling to inhibit cancer cell growth has been described.

Key words: Breast cancer, colorectal cancer, hepatocellular cancer, leptin, thyroid cancer

Introduction

Leptin is a 167-amino-acid peptide hormone produced predominantly by adipocytes and to a less extent by stomach, skeletal tissue and placenta, was discovered by Friedman *et al.* in 1994, the gene for which (Ob gene) is located on chromosome 7.[1] Derived from the Greek word leptos, meaning lean, leptin is the first discovered hormone secreted from adipocytes, with its primary role being in stimulating energy expenditure and decreasing appetite, through its action on the central nervous system.[1] Interestingly, *in vitro* studies have documented antiapoptotic and mitogenic effects of leptin on different cancer cell lines.[2,3] The aim of the article is to review the growing body of literature regarding the role of leptin in carcinogenesis and its modulation in cancer therapeutics.

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Pathophysiology

Leptin receptors are extensively distributed and are predominantly found in hypothalamus, islet cells, liver, kidney, lung, skeletal muscle and bone marrow.[4] Leptin secretion from adipocytes and its circulatory levels are mainly regulated by insulin, glucocorticoids and catecholamines.[5] Fasting, β-adrenergic agonists and thiazolidinediones are associated with decreased leptin expression.[6] Exogenous obesity leads to increased fat mass which in turn results in increased circulating levels of leptin, which, however, is not associated with the expected decrease in appetite and weight loss due to the associated central leptin insufficiency. Leptin in the central nervous system binds to hypothalamus resulting in decreased synthesis of orexins like neuropeptide-Y (NPY) and agouti-related peptide (AgRP), and increased synthesis of anorexins [α-melanocyte stimulating hormone (αMSH) and cocaine and amphetamine regulated transcript (CART)].[7]

Leptin acts predominantly by Ob-R receptor (encoded by db gene). It has several variants from Ob-Ra to Ob-Rf generated by alternative splicing, with Ob-Rb being the predominant isoform responsible for the biological actions

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of leptin, by activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which in turn stimulates phosphatidylinositol 3-kinase (PI3K) which promotes cellular growth, migration and invasion. Suppressor of cytokine signaling-3 (SOCS3) is a leptin-inducible inhibitor of leptin signaling which blocks Ob-R mediated signal transduction, and thus forming a negative feedback mechanism for leptin signaling.[8] Leptin induces production of inflammatory cytokines (TNF-α and IL-6) by macrophages[9] and shifts the T-helper (TH) balance toward a TH1 phenotype, especially in obese individuals. This low grade inflammation in individuals with metabolic syndrome in turn increases the risk of obesity related diseases and cancer.[10] Local leptin production through autocrine and paracrine pathways is a better predictor of carcinogenesis than circulating leptin levels.[11]

PI3K/AKT pathway has an important role in oncogenesis in various tumors like colorectal ca, hepatocellular ca and endometrial ca.[12] AKT has an important role in cancer cell survival by promoting glycolysis and maintaining mitochondrial membrane potential.[13] Leptin and leptin receptor in carcinogenesis has been elaborated in Figure 1. XIAP in a member of antiapoptotic proteins and is a physiological substrate of AKT.[14] Increased levels of XIAP are associated with increased tumor cell survival due to decreased apoptosis.[15]

Leptin and thyroid cancer

Serum leptin levels in papillary thyroid cancer (PTC) patients have been observed to be significantly higher than controls, irrespective of the BMI, which decreased after total thyroidectomy[16] Uddin *et al.* demonstrated Ob receptor protein expression in 80% of PTC tumor specimens. Increased Ob-R expression in PTC has also been documented in another study from Saudi Arabia.[17] This increased expression of Ob-R in PTC was associated with a more aggressive PTC phenotype (larger tumor size, extra-thyroid spread, lymph node metastasis, advanced stage, tall cell histology, poorer disease-free survival, disease persistence and recurrence. Functional leptin receptors have been demonstrated in PTC cell lines.[18] Treatment with leptin promoted cell growth, inhibited apoptosis and modulated migration of cancer cells. Increased XIAP expression (an antiapoptotic protein) secondary to increased leptin receptor expression has been documented in PTC.[19]

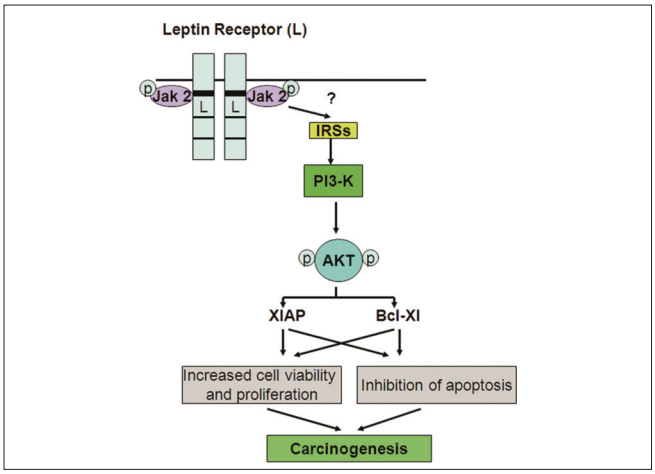

Figure 1: Leptin/Ob-Rb binding results in insulin receptor substrate (IRS) phosphorylation, which in turn activates PI3K/AKT pathway through the association of IRS with the regulatory subunit p85 of AKT. Activated AKT in turn phosphorylates XIAP (a member of antiapoptotic proteins) thus inhibiting its degradation, which leads to decreased caspase-3 activity and decreased apoptosis; PI3K: phosphoinositide-3-kinase; AKT: protein kinase B; XIAP: X-linked inhibitor of apoptosis protein; Bcl: base class library (adapted from Uddin S *et al.* Role of leptin and its receptor in the pathogenesis of thyroid cancer. Int J Clin Exp Pathol 2011;4:637-43)

Leptin and hepatocellular cancer

Leptin has an important role in the development of nonalcoholic fatty liver disease (NAFLD), through insulin resistance, steatosis, worsening hepatic inflammation and ultimately fibrosis.[20] Relation between leptin levels and liver fibrosis in humans is conflicting with some studies showing a significantly higher leptin levels in individuals with nonalcoholic steatohepatitis (NASH) as compared to controls with a positive correlation with liver fibrosis,[21,22] and others showing no relation.[23]

ObRb is expressed on Kupffer cells (KC) and sinusoidal cells, the expression of which is amplified during hepatic stellate cells (HSCs) activation due to various causes like chronic viral hepatitis, alcoholism, toxins and NAFLD.[24] Leptin through ObRb receptor increases the expression of TGFβ, type-I procollagen and tissue inhibitor of metallo-proteinase-1 (an inhibitor of collagen breakdown), thus promoting liver fibrosis.[25] Leptin induces vascular endothelial growth factor (VEGF) expression, through oxygen-independent activation of hypoxia inducible factor 1a (HIF1a).[26] Leptin has an important role in the development of hepatocellular carcinoma (HCC); however, whether the role is stimulatory or inhibitory remain controversial as of date, with some studies suggesting an important role of leptin in liver fibrosis and carcinogenesis,[27] while others suggesting an inhibitory role of exogenous leptin on tumor size in murine model of HCC.[28]

Leptin and colorectal cancer

Leptin in over expressed in colorectal cancer, and the expression increases gradually across the spectrum from normal mucosa, simple adenoma with low grade dysplasia, adenoma with high grade dysplasia to adenocarcinoma.[29,30] PPAR-γ expression also strongly correlates with leptin expression in colorectal ca. Interestingly, it has also been reported that increased leptin and PPAR-γ expression in

colorectal ca are both associated with favorable outcomes, more indolent course and longer disease-free survival.[31] PPAR-γ activation inhibits cytokine induced activation of JAK/STAT pathway; hence PPAR-γ agonists are functional antagonist of leptin signaling with respect to tumorogenesis.[32] PPAR-γ ligands and leptin compete with each other in modulating cytokine induced HSCs proliferation through downregulation/upregulation of ERK1/2 signaling, respectively.[33-35] However, the exact interaction between leptin and PPAR-γ in development of colorectal ca remains to be defined.

Leptin and breast cancer

Serum leptin has been documented to be higher in patients with ca breast as compared to controls.[36,37] Higher serum leptin, intratumoral leptin mRNA and intratumoral ObR isoforms mRNA level have been observed to be poor prognosis predictors in patients with ca breast.[38] Similar observations of increased leptin with leptin receptors expression, in both primary and metastatic breast cancer tissues, along with observations that expression of these proteins correlated with ER status, tumor size and higher tumor grade have been documented in several studies which was irrespective of the BMI of the patients.[39,40] Leptin plays an important role in breast carcinogenesis by modulating ER signaling and aromatase activity,[41,42] transactivating HER2 through both epidermal growth factor receptor and JAK2 activation[43] and upregulating expression of VEGF and VEGFR2[44] [Figure 2]. Obesity is a well known risk factor for breast cancer and obesity is associated with elevated serum leptin along with decreased adiponectin. Studies have shown that low levels of adiopnectin in the background of increased leptin increases the risk of breast cancer.[45,46] Hence a balance between leptin and adiponectin may have a more important role in breast carcinogenesis than either of them alone.[47]

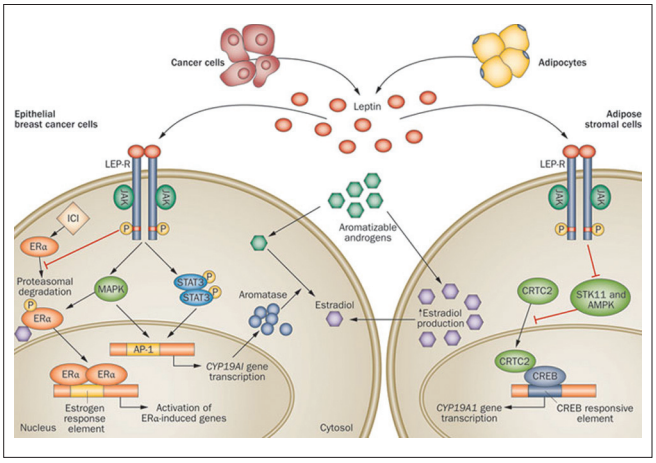

Figure 2: Leptin produced by cancer cells and adipocytes through ObRb activate JAK/STAT pathway and MAPK pathway which augments AP-1 expression which leads to increased CYP19A1 (aromatase) gene transcription leading to increased local estrogen production, thus augmenting estrogen signaling through ER-α. Leptin in addition blocks ER-α proteosomal degradation. This ultimately results in increased proliferation of breast cancer cells; JAK: janus kinase; STAT: transducer and activator of transcription; MAPK: mitogen-activated protein kinase; AP-1: activating protein-1; ER: estrogen receptor (adapted from Sebastiano Andò and Stefania Catalano. The multifactorial role of leptin in driving the breast cancer microenvironment Nature Reviews Endocrinology 2012;8:263-25)

Leptin and cachexia

Anorexia and cachexia is very common in patients with cancer and may account for up to 20% of the mortality.[48] Leptin levels are significantly decreased in patients with cancer cachexia, as compared to noncancer cachexia and healthy individuals.[49,50] However, the increase in appetite and hyperphagia seen in normal individuals secondary to decreased leptin is not seen in cancer cachexia, which may be the result of increased circulatory proinflammatory cytokines like IL-6, TNF-α and IL-1 which increases the expression of hypothalamic leptin receptor. However, anticytokine therapies like thalidomide and pentoxiphylline (TNF inhibitors) have not been found to improve cancer cachexia.[51,52]

Pharmacologic modulation of leptin signaling in cancer and disease

With mounting evidence of increased role of leptin in carcinogenesis, research on development of agents modulating leptin action has increased over the last few years. Metreleptin (recombinant methionyl human leptin), an analog of human leptin has been found to be useful in congenital leptin defieiency, lipodystrophy like Rabson Mendenhall syndrome and hypothalamic amenorrhea. Administered subcutaneously, it decreases hyperphagia, improves glucose-insulin metabolism and decreases fatty acid oxidation.[53] In addition, metreleptin-pramlintide combination has shown synergistic effects and elicited sustained reductions in food intake and body weight. Ob-R antagonist peptide (Allo-aca), a 9 amino acid peptide, analog of Ob-R binding site III of leptin, has shown efficacy in an experimental model of triple-negative breast cancer (ER negative, PR negative and HER2/neu negative).[54] Pegylated leptin peptide receptor antagonist 2 (PEG-LPrA2) reduced the expression of pro-angiogenic VEGF, VEGFR2, Ob-R, IL-1 receptor type I, and pro-proliferative molecules [proliferating cell nuclear antigen (PCNA) and cyclin D1] and overall growth in ER+breast tumors in experimental models.

Conclusions

Leptin, an adipocyte peptide hormone with a primary role in regulating appetite and body mass composition by regulating neurotransmitter release from hypothalamus has an important role in the development of a large variety

of malignancies, predominantly through JAK/STAT pathway which modulates PI3K/AKT3 signaling, ERK1/2 signaling, increasing expression of antiapoptotic proteins (like XIAP), increasing systemic inflammation (TNF-α, IL6), promoting angiogenic factors (VEGF) and increased hypoxia inducible factor-1a (HIF-1a) expression, which promotes cancer cell survival, proliferation and migration. Pharmacologic agents modulating leptin signaling are still in infancy with few encouraging reports of leptin receptor antagonists inhibiting the growth of breast cancer cells in experimental models. With further understanding of the role of lepin in carcinogenesis, development of a plethora of agents modulating leptin signaling as an anticancer therapy may be expected in the near future.

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