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Review Article

Role of leptin and its receptors in the pathogenesis of thyroid cancer

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Abstract: Leptin is a multifunctional adipose-derived cytokines that play a critical role in bodyweight homeostasis and energy balance. Recently, leptin and leptin receptor dysreulation have been reported in variety of malignant cells including thyroid. Leptin modulates growth and proliferation of cancer cells via activation of various growth and survival signaling pathways including JAK/STAT, PI3-kinase/AKT and/or Map kinases. In this review, current understanding of leptin's role in the pathogenesis of thyroid cancer has been described.

Keywords: Leptin, leptin receptors, sinaling pathways, papillary thyroid carcinoma

Leptin and its receptors

Leptin, a product of the obese (o*b*) gene, is a 167-amino acid hormone [1, 2]. The *ob* gene is located on chromosome 7 [2]. Leptin acts through its receptor (Ob-R), which is encoded by the *db* gene [3]. Genetic deficiency of either leptin or Ob-R causes severe obesity and obesity-associated diabetes (Zhang et al 1994) [2]. Ob-R is a member of cytokine receptor family that including various interleukins, interferon-γ, erythropoietin, growth hormone and prolactin [3]. There are several leptin receptor variants (Ob-Ra through Ob-Rf) that are generated by alternative splicing. These variants share the same extracellular domain but have varied length of the transmembrane/cytoplasmic coding regions [4, 5]. The long Ob-Rb subtype (Ob-R_L) appears as the functional, signal-transducing isoform, responsible for the biological action of leptin (**Figure 1**). The biological function of the shorter Ob-R isoforms (Ob-R_S) remain to be characterized. Although leptin's precise sites of action are not known, its effect is thought largely mediated via hypothalamus. However, the wide expression of Ob-R_L suggests that leptin may also operate directly in other peripheral tissues [6]. There is now a significant amount of evidence implicating that leptin is active in the periphery [7].

Leptin mediated signaling

Leptin regulate multiple signaling pathways in various cancers. The major pathways that are regulated by leptin includes; JAK2/STAT3, erbB2, ERK, IRS and rho/rac pathways [8-13]. Binding of leptin with leptin receptors directly or indirectly activates these signaling pathways that involve kinase-induced phosphorylation of proteins. The leptin receptor is an external tyrosine kinase receptor; upon ligand binding each receptor can bind and activate the tyrosine kinase JAK2, which then cross-phosphorylates tyrosine residues in the other receptor in the dimmer [14]. There is an absolute requirement of the intracellular cytokine box 1 motif of the receptor for activation of JAK2. This sequence is present in all the transmembrane isoforms. Most studies, however, have focused on signaling mediated by Ob-Rb, the only isoform which has conserved intracellular tyrosine residues and which is capable of activating the transcription factor STAT3 [15, 16]. In addition, only Ob-Rb has a cytokine box 2, which does not seem to be required for JAK2 activation, and a sequence of 15 amino acids downstream of box 1 that are required for optimal JAK2 activation [17, 18].

Leptin/Ob-R mediates its signaling via another

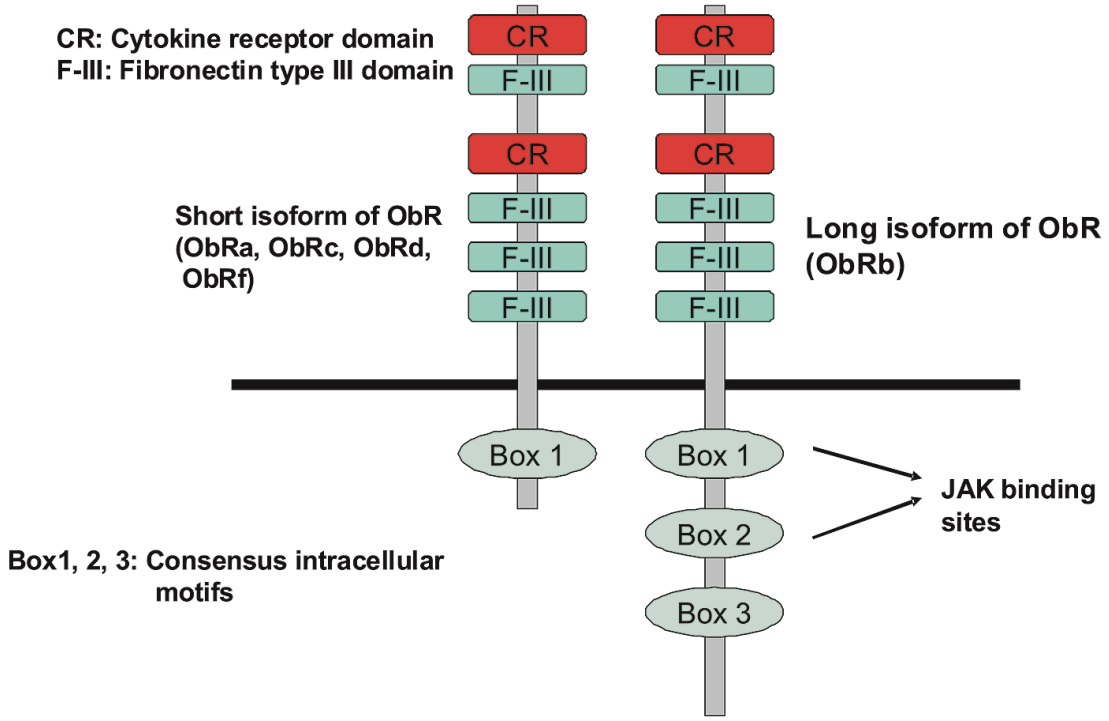

Figure 1. Schematic presentation of short and long form of leptin receptors.

major pathway, known as PI3K/AKT in oncogenesis in various tumor cells [19-23]. Leptin mediates Insulin receptor substrates (IRSs) phosphorylation by the intrinsic kinase activity of the receptor. Phosphorylation of IRSs increases the affinity by which they bind other signaling molecules, and initiates further steps on the pathway [24]. An important target of IRS molecules is phosphatidylinositol 3-kinase (PI 3-kinase) that generates inositoltrisphosphate (PIP3) [25]. IRSs exert PI 3-kinase activation through association with its regulatory subunit (p85), thus increasing the activity of the catalytic domain. Increased PIP3 levels lead to activation of PIP3-dependent serine/threonine kinases, such as PDK-1, 2, which can activate AKT, another serine/threonine kinase (**Figure 2**). AKT plays critical role in survival pathways by promoting glycolysis and maintaining a physiologic mitochondrial membrane potential [26]. In normal cells, growth factor and cytokines mediated signaling, recruits AKT through PH domain to the plasma membrane and activated by phosphorylation [27, 28]. Through its PH domain, AKT binds to PIP3, facilitating the activation of AKT by phosphoinositide-dependent kinase 1 and 2 (PDK1 and PDK2) by phosphorylation of threonine 308 and serine 473 [29]. Activated AKT has numerous targets that are important regulators of the cell cycle, the apoptotic pathway, and the translational and transcriptional machinery. AKT functions as an antiapoptotic factor through numerous mechanisms, including phosphorylation and inactivation of several proapoptotic factors such as Bad and caspase-9 [27]. Among these targets are the proapoptotic protein Bad, the cyclin-dependent kinase inhibitor $p27^{kip1}$, several forkhead family members, the mammalian target of rapamycin (mTOR), glycogen synthase kinase-3-β (GSK-3β), and the IκB kinases [30-34].

Recently we and others have shown that PTC cell lines expressed functional leptin receptors [35, 36]. Treatment of PTC cells with leptin enhances cell growth and prevented serum starved apoptosis [35]. Cheng SP et al [36] showed that leptin modulated the cell migration of thyroid cancer cell lines. These data suggests that oncogenic effect of leptin on PTC cells are due to a combination of cell proliferation and inhibition of apoptosis by leptin. In vitro experiments using PTC cell lines showed that leptin rapidly stimulates the PI3K pathway and induced the phosphorylation of AKT, thus activating of this key signal transduction pathway asso-

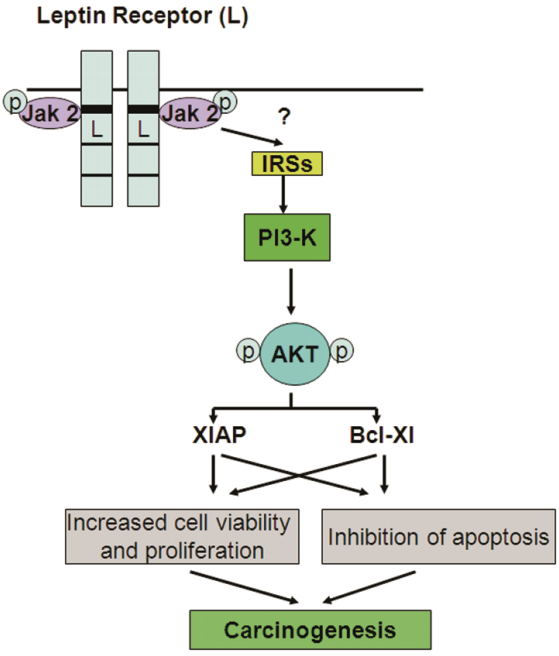

Figure 2: Schematic presentation showing leptin mediated signaling pathways. Upon leptin binding with extracellular domain of long isoform leptin receptor activates PI3-kinase/AKT pathway. The activated AKT in turn modulate the expression of antiapoptotic proteins XIAP and Bcl-xL leading to increased cell proliferation and inhibition of apoptosis resulting in initiation and progression of carcinogenesis.

ciated with cell growth. In addition, prevention of leptin-induced activation of PI3K with chemical inhibitors in turn significantly reduced the activation of AKT pathway. AKT provides a survival signal protecting cells from apoptosis induced by various stresses by multiple mechanisms such as phosphorylation of Bad, GSK3, FOXO transcription factors and caspase 9 [37, 38]. Phosphorylation of these proteins results in inactivation of their apoptotic functions. Leptin has been shown to activate AKT and its downstream targets such as GSK3, Foxo proteins in various tumor cells including prostate, colorectal and breast cancer cell lines [39-45]. Recently leptin has been shown to activate AKT and its downstream targets is a dose and time dependent manner in thyroid cancer cell lines BCPAP and TPC1 and inhibition of PI3K-kinase an upstream effector of AKT with LY294002 abolished leptin-mediated phosphorylation of AKT as well as cell proliferation. Thus we can hypothesize that leptin mediates its actions upstream of PI3K/AKT pathway. These data implicates that leptin mediated PTC carcinogenesis occurs through deregulation of PI3K/AKT signalling pathway.

Leptin and leptin receptors in thyroid pathogenesis

The relationship between serum leptin and cancer risk has not been documented well in thyroid cancer. Recently, Akinci et al [46] using 43 PTC patients and 30 healthy control group reported that Serum leptin levels of TPC patients were significantly higher than in control group subjects. The leptin levels was decreased after total thyroidectomy compared to prethyroidectomy levels in most patients. These findings link leptin as a possible etiologic factor in thyroid carcinogenesis. However, the decreased postthyroidectomy levels of leptin were still significantly higher than the control group levels of leptin, which may be related to hypothyroidism during the postoperative period for TSH stimulation. Leptin levels have been shown to increase with hypothyroidism [47]. Leptin is synthesised and secreted mainly by adipose cells, and its plasma levels in humans are strongly correlated with BMI [48]. However, Akinci et al (2009) study did not find significant difference in BMI in TPC and control groups. The leptin levels decreased postoperatively in all BMI subgroups in TPC patients.

Functional leptin receptors are expressed on diversed cancer cells derived from various solid tumors [49]. In these cancer cells, leptin able to mediates its growth and proliferative action via binding to its specific receptors [50]. Recently it has been shown that leptin receptors are expressed in PTC tumors. Using immunohistochemistry staining with Ob-R antibody on a large cohort of PTC tumor samples Ob-R protein expression was detected in 80% examined PTC [35]. Interestingly, Ob-R was significantly associated with older age, extra thyroid extension, larger tumor size, nodal metastasis, advanced stage and tall cell variant histologic subtype, thereby indicating that Ob-R overexpression identifies an aggressive phenotype of PTC. Furthermore patients with high Ob-R expressing tumors showed a significant poor disease free survival ($p<0.0235$) as compared with reduced Ob-R expression. Raef H et al [51] have reported a fairly high number of patients with differentiated thyroid cancer (DTC) in Saudi Arabia had locally advanced disease at presentation and/or persistent disease after standard treatment. These findings speculate that high Ob-R

expression levels seen in around 80% of the Saudi Arabian PTCs could be one of the putative factors for this disease persistence and or recurrence. These findings therefore suggest that Ob-R expression is indeed associated aggressive phenotype and might be used as a marker for recurrent or persistent diseases of Middle Eastern PTC. Activated AKT (pAKT) protein expression was seen in 55% of PTC samples examined. However, no correlation was observed with Ob-R expression and AKT activation by IHC staining suggesting that the presence of other upstream signaling pathways can also be involved in the activation of AKT. It has been reported that lepton activate PI3-kinase/AKT pathway via forming as complex between insulin receptor substrates and JAK2 by SH2-B, a Jak2 interacting protein [52].

Leptin expression was found in PTC cell lines and depletion of Ob-R expression by using Ob-R small interference RNA abrogated leptin mediated activation of AKT and its downstream signaling in PTC cell lines. Ob-R overexpression has been found to be significantly associated with PIK3CA 110 alpha protein expression ($p<0.0001$) in PTC tumors [35]. Leptin has been shown to mediate its action through the component of PI3-kinase/insulin signaling cascade [53]. XIAP is a member of anti apoptotic proteins, play a critical role in antiapoptotic function [54, 55]. XIAP is a physiological substrate of AKT. AKT interacts with XIAP and phosphorylates XIAP at serine 87. Phosphorylation of XIAP by AKT inhibits both its autoubiquitination and cisplatin-induced ubiquitination. These effects reduce XIAP degradation and the increased levels of XIAP are associated with decreased caspase 3 activity and programmed cell death [56]. Leptin receptor expression has been found to be significantly associated with XIAP expression in Saudi PTC tumors. In vitro studies small interference RNA of Ob-R in PTC cell lines downregulated XIAP transcript as well protein expression suggesting that leptin dysregulate PI3K/AKT signal transduction pathway leading to pathogenesis of PTC [35].

Conclusions

Evidence suggests that Leptin has multi effects in mediation of pathogenesis various malignant cells, including stimulation of tumor cell growth, migration and enhancement of angiogenesis. These actions of leptin play a role in tumor development and progression. In vitro studies have shown that malignant cell lines including PTC cells express receptors for leptin and respond in a dose-dependent way to the administration of leptin. Elevated serum leptin levels seem to be associated with a higher risk for many cancers. There is some evidence that the increased risk for PTC. In various cancers, epidemiological reports show that higher levels of leptin may be related to poor prognosis than to increased risk for developing the disease. Leptin increases IGF and has growth potential in many in vitro studies and its effect seems permissive that it may exert its role only in the range of very low to normal leptin levels, with no additional effect in the range of normal to high leptin levels. Leptin modulates a number of growth and survival signaling pathways in other tumors such as prostate, Breast, ovarian, however, these pathways were not investigated in PTC. Therefore, further studies with more robust epidemiologic design, preferably prospective cohort investigations, are needed to evaluate in a more specific way, hypotheses generated by laboratory data.

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Conflicts of Interest

No conflicts of interest exist. The authors declare that they have no competing financial interest.

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