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The Role of Leptin in Cancer Pathogenesis

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ABSTRACT

Leptin is a hormone produced and secreted by adipose tissue. It is a member of adipokine family with a principal role in body weight regulation. It is reported that low brain leptin levels enhance the activity of hypothalamic orexigenic signals promoting feeding and suppressing energy expenditure and vice versa. Moreover, leptin via its three receptors participates in multiple neuroendocrine loops regulation. Serum leptin levels are positively associated with BMI (Body Mass Index) and whilst interact not only with other cytokines but also with serum insulin and cortisol levels. The aim of the present review is to study the role of leptin in carcinogenesis and its implications in cancer-related systemic inflammation.

Keywords: Leptin; Adipokines; Cancer; Systemic Inflammation

1. Introduction

Leptin was discovered in 1994, after the identification of the obese (*ob*) gene, which was first isolated in mutant *ob* mice. The product of the *ob* gene was subsequently named leptin, derived from the Greek word for thin, "leptos" [1].

Leptin is a 16 kDa multifunctional protein, produced predominantly by white adipose tissue, consisting of 167 amino acids. Additional tissues have been shown to express leptin mRNA, including the stomach, placenta, ovaries, liver, pituitary and skeletal muscles [2]. It is currently considered a member of adipokines, those are proteins exerting significant effects on metabolism, lipogenesis, as well as in regulation of human inflammatory responses [3].

The main role of leptin is to regulate energy homeostasis by controlling energy intake and energy expenditure, through its action on the arcuate nucleus of the hypothalamus. It has additional effects in the endocrine and immune systems, including reproduction, glucose homeostasis, bone formation, tissue remodelling, and inflammation [4]. Recent studies have shown that leptin also acts on peripheral cell types through interaction with other hormones, like insulin.

2. Main Part

2.1. Leptin Structure and Synthesis

The leptin receptor (LepR), distributed in the whole body [5], is a member of the class I cytokine-receptor family, having an extra-cellular ligand-binding domain, a transmembrane domain and a cytoplasmic signalling domain [6], there also exists a secreted form, which acts like a specific binding protein [7]. To date, some LepR isoforms have been identified (Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd and Ob-Re), resulting from alternative mRNA splicing and/or proteolytic processing: there are three classes identified: short, long and secreted isoform [8]. The long isoform OB-Rb is considered to play the main role, since it has been shown to be critical in mediating leptin's actions through activation of the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [9]. Ob-Rb isoform is normally expressed at high levels in hypothalamic neurons and in other cell types, including T cells, pancreatic β cells, colonic epithelial cells, vascular endothelial cells and others. Ob-Rb has been suggested to play a role in leptin transport into the CNS, transferring information regarding body fat mass and body weight regulation [10]. This is supported by the observation that leptin deficiency in both humans and mice may be treated by exogenous administration of leptin by injection; thus, leptin replacement was initially considered as a possible method of obesity treatment. Nevertheless, obesity in humans and in rodents is usually associated with high circulating leptin levels and leptin resistance; not in leptin deficiency [11,12]. Potential sites for leptin resistance include the blood-brain-barrier transport system through ObRa leptin receptor and the leptin

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signaling mechanism in leptin-responsive neurons in the hypothalamus [13].

The significance of the Ob-Ra isoform, which has a short cytoplasmic domain, is less clear. It is expressed in the choroid plexus and many other tissues, and it is postulated that it may function in the transport of leptin across the blood-brain barrier [14]. The s*Ob-R* isoform is the soluble fraction of *Ob-Re receptor*, that transports leptin through the blood stream regulating its clearance and half-life [15,16]. It represents the main binding plasmatic protein of leptin and is presented in two different N-glucosated isoforms, either dimeric or oligomeric [7, 17]. High blood sOB-R levels have been identified in anorectic and cachectic humans. Recent studied have shown that sOB-R overexpression may lead to leptin dysfunction in molecular level and play a role in leptin resistance on peripheral tissues [18,19].

2.2. Leptin Physiology

Leptin levels are not constant in the blood; instead they are considered to be pulsatile, with a frequency of about 1 pulse per 45 min. There is also a diurnal pattern to leptin secretion with concentrations peaking just after midnight [20,21]. In humans, the major factor influencing plasma leptin concentrations is adipose tissue mass. Circulating leptin levels exhibit a particularly strong positive correlation with total body fat, and to a lesser degree with BMI [22]. Circulating leptin concentrations are acutely modulated by nutritional state, with levels being markedly decreased in response to fasting or cold exposure [23]. After adequate food consumption, leptin blood levels are increased, acting as a feedback loop control, which maintains constancy of total body energy stores and a relative weight stability.

Serum leptin levels are significantly higher in women than in men, even after the adjustment for total body fat mass [3]. A possible explanation for this finding is that women have significantly greater subcutaneous adipose tissue mass relative to omental adipose mass, as well as the different synthesis and secretion sites between men and women. Additionally, this may be explained by the differential regulation of leptin expression by sex hormones, with estrogens reported to upregulate and testosterone observed to decrease leptin levels [3].

Circulating levels of leptin are influenced by a variety of metabolically active factors, like insulin and glucocorticoids [24]. Insulin stimulates leptin secretion *in vivo*, as well as cortisol increase leptin release *in vivo*. On the contrary, fasting, (cAMP) and β_3 adrenal agonists decrease the expression and the circulating levels of leptin [25]. Leptin levels increase after peak insulin levels following meals and decrease during insulin deficiency. Recent studies have demonstrated that insulin strongly influences leptin levels, by interacting with physiological factors associated with feeding behaviour and short-term meal-to-meal mechanisms [26].

Leptin affects the expression of many hypothalamic neuropeptides through mechanisms and pathways that are currently incompletely understood. It is shown that decreasing leptin concentrations in response to food deprivation are responsible for the starvation-induced suppression of the hypothalamic-pituitary-gonadal axes as well as the malfunction of several other neuroendocrine axes [27]. It seems that leptin may act as the critical link between adipose tissue, hypothalamic centers regulating energy homeostasis, and the reproductive system, indicating whether adequate energy reserves are present for normal reproductive function. Thus it has been shown *in vivo* that leptin administration corrects hypothalamic amenorrhoea [28].

These actions may, at least in part, be explained by the suppressive effect of leptin on neuropeptide Y (NPY) [29], that is produced and secreted by neurons in the arcuate nucleus. NPY is considered a strong stimulator of appetite [30], and is known to be involved in the regulation of various pituitary hormones: suppression of growth hormone (GH) through stimulation of somatostatin [31], suppression of gonadotropins [32], or stimulation of the pituitary-adrenal axis [33].

Leptin also acts directly on peripheral tissues. It has been shown that leptin reduces triglyceride synthesis and increases intracellular lipid oxidation upon direct addition to normal islets in short-term cultures [34]. It has also been suggested that leptin decreases insulin secretion by direct action in pancreatic b-cells. This finding, in comparison with the fact that insulin has been found to be capable of increasing leptin expression and levels, it might reveal a negative feedback loop between insulin and leptin. Lastly, it seems that leptin acts as a growth factor in hematopoiesis [34].

2.3. New Insights in Leptin Study

At least fifteen years after leptin identification, the exact function of the molecule has not been fully established. Recent studies have identified the possible role of leptin in the pathophysiology of obesity, chronic inflammation and cancer.

2.3.1. Leptin and Obesity

The mean serum leptin concentration in obese humans is approximately 40 ng/mL, as compared with 4 ng/mL in the normal-weight individuals [22]. An increase in plasma leptin suggests that obesity is the result of resistance to leptin. A low or normal plasma concentration of leptin in the context of obesity suggests decreased production of leptin. This interpretation is similar to that used in studies of insulin and the pathogenesis of type I and type II diabetes. This is shown by the fact that elevated leptin levels

presented in obese individuals do not act as a signal to control obesity through a negative feedback loop; on the contrary, circulating blood leptin levels are steadily increased with body fat gain [13]. The mechanism of leptin resistance in obesity is not yet identified. Data from studies of animals indicate that many factors may influence the activity of the neural circuit that regulates body weight. The entry of leptin into cerebrospinal fluid through the OB-Ra receptor may be limiting; morbid obesity could result when the plasma leptin levels exceed the capacity of the transport system. Factors that directly modulate energy expenditure or activate adipogenesis and lipogenesis could also result in apparent leptin resistance [35].

2.3.2. Leptin and Chronic Inflammation

The role of leptin in chronic inflammation is unclear. Studies have revealed elevated blood levels of leptin while in inflammatory response in septic patients [36,37]. Nevertheless, in diseases with a chronic inflammatory response combined with cachexia, leptin levels are low. This has been observed in patients with chronic obstructive pulmonary disease and pulmonary cachexia, although enhanced production of tumor necrosis factor-a (TNF-a) was present, plasma leptin levels were inversely low [38, 39].

2.3.3. Leptin and Cancer

Cancer is a systemic inflammation that is driven by proinflammatory cytokines, which exert their role on catabolism, gluconeogenesis and acute phase protein production. Besides systemic inflammation, advanced cancer mainly of the lung and gastrointestinal type are associated with weight loss. Based on this hypothesis, the potential role of leptin as a proinflammatory cytokine in cancer has been studied.

Aleman *et al*. examined leptin serum concentration in non small cell lung cancer (NSCLC) patients and found that it was lower than in healthy controls. However, serum leptin and nutritional status were inversely correlated with acute phase proteins and proinflammatory cytokines (CRP, ferritin, TNF-a, IL-6, and others) suggesting a stress-type malnutrition [40]. Same results in lung cancer have been published by Simons *et al.* [41], Brown *et al.* [42] and Karapanagiotou *et al.* [43]. The last study, nevertheless, did not correlate leptin levels with cachexia in advanced NSCLC patients, showing a dysregulation of adipose tissue hormones [43]. Same results were reported in gastrointestinal cancer patients, where leptin serum concentration was low in the cachectic group patients [44, 45]. Concluding, there might be a positive correlation between leptin blood levels and body fat mass.

According to epidemiological studies, excess weight is an important factor in death from cancer. The proportion of all deaths from cancer that is attributable to overweight and obesity in US adults 50 years of age or older may be as high as 14% in men and 20% in women [46]. Association has been consistently shown between adiposity and increased risk of cancers of the endometrium, kidney, gallbladder (in women), breast (in postmeno-pausal women), and colon (particularly in men) [47]. Although there is no strong support for an association between body-mass index and prostate cancer, some data suggest a slight increase in the risk of advanced prostate cancer or death among patients with a high body-mass index [46].

Leptin acts as a tissue growth factor under normal as well as under pathological conditions, while *in vitro* and *in vivo* studies support the relationship between leptin and cancer cell growth [48]. Leptin's role as an angiogenic factor has been reported since 1998 [49], when it was demonstrated that leptin stimulated angiogenesis in both *in vitro* and *in vivo* models. In addition, leptin enhances vascular endothelial cell proliferation *in vitro* with a potency similar to that of VEGF [50].

Angiogenesis, the process of new blood vessel formation, has physiological functions in embryonic implantation, the secretory phase of the menstrual cycle and wound healing [51]. In pathological conditions, it is involved in diabetic retinopathy [52], and solid tumor growth and metastasis [53].

The angiogenic process is complex, including endothelial cell proliferation, production of the matrix metalloproteinase (MMP) family of proteolytic enzymes, and cell migration. Successful completion of the process is dependent on a variety of growth factors, protein kinase C (PKC) activity and fatty acid derived eicosanoids [54], while studies confirmed the stimulatory effect of leptin on endothelial cell growth and migration [55].

Additionally, there was a complementary anti-apoptotic effect on vascular endothelial cells that required increased expression of the apoptosis inhibitor Bcl-2 [56]. It has been shown that leptin acts synergistically with VEGF and fibroblast growth factor 2 (FGF-2) to promote angiogenesis [57], with its action partially dependent on FGF-2 [58]. Moreover, leptin increases the expression of other genes involved in angiogenesis, for example, MMP-2 and MMP-9 gene products [55]. These belong to a complex system of proteolytic enzymes, the net activity of which is responsible for the digestion of matrix proteins as a preliminary step to cell migration [59].

3. Discussion

Regarding breast cancer, *Ob* gene is expressed in the normal and malignant human mammary epithelium [60, 61]. Estrogens, as well as other hormones and growth factors, some of which act as intermediaries or biological

proximate effectors for leptin's mitogenic activity, stimulate breast cancer [62]. Insulin is also a mitogenic agent for breast cancer cells, and its capacity to stimulate leptin release and elevate circulating leptin levels provides a potential interaction between insulin and the metastatic cascade as targets for leptin bioactivity. It has been hypothesized that the relationship between hyperinsulinism and a poor breast cancer prognosis is, at least in part, mediated by enhanced leptin production by adipose tissue, and elevated levels of the hormone in obese patients [63,64]. Insulin is also a mitogenic agent for breast cancer cells, and its capacity to stimulate leptin release and elevate circulating leptin levels provides a potential interaction between insulin and the metastatic cascade as targets for leptin bioactivity. There exicts the hypothesis that the relationship between hyperinsulinism and a poor breast cancer prognosis is, at least in part, mediated by enhanced leptin production by adipose tissue, and elevated levels of the hormone in obese patients [63]. Additionally, the leptin receptors huOb-Ra and huOb-Rb have been reported in breast cancer cells. The expression of ObR protein has also been demonstrated in cultured breast cancer cells with Ab against the common domain of ObR, or a specific ObRl region. In ERa-positive breast cancer cell lines, leptin stimulates DNA synthesis and cell growth acting through multiple signaling cascades, including the JAK/STAT, ERK1/2, and PKC-a pathways [65,66].

Angiogenesis is established as a biomarker of a poor prognosis in invasive breast cancer [67], as is the expression of vascular endothelial growth factor (VEGF) [68, 69]. A number of studies have associated mutations in p53, normally a regulator of the cell cycle and apoptosis, with a poor breast cancer prognosis, while such abnormalities were also correlated with increased VEGF expression [69]. The emerging relationship between p53, its mutated forms and angiogenesis, is of interest, as in experimental studies leptin was implicated in the development of mammary carcinomas in wild type p53-deficient mice [70]. In this model, caloric restriction was associated with a delaying of the appearance of tumor as well as a reduction in serum leptin and insulin-like growth factor I concentrations. However, further studies are necessary to determine the true significance of the association between delayed tumor development and a reduced serum leptin level [71].

In a study by Fain *et al*., leptin secretion by explants of human adipose tissue obtained from obese individuals was enhanced by both PGE2 and its metabolic precursor, arachidonic acid. Also, increased leptin production in the presence of arachidonic acid is reduced by selective pharmacologic inhibition of the cyclooxygenase 2 (COX-2) isoenzyme. It has been demonstrated in vitro that selective inhibition of COX-2 with rofecoxib reverses the proliferation of estrogen-responsive and estrogen receptor-positive human breast cancer cells with leptin administration [72].

Agents that reduce cancer cell proliferation in conjunction with high circulating levels of leptin should be evaluated for use in the prevention and treatment of cancer.

The drug ICI 182,780 (fulvestrant) is used for treatment of hormone receptor—positive metastatic breast cancer in post-menopausal women with disease progresssion following other hormonal therapy and acts by inducing estrogen receptor α degradation through ubiquitin-mediated mechanism. It has been shown that leptin interferes with the effects of ICI 182,780 on estrogen receptor alpha in breast cancer cells. Thus, high leptin levels in obese breast cancer patients might contribute to the development of antiestrogen resistance [73]. Vona-Davies and Rose summarises the contradictory results found in case-control studies (one of which was nested within a prospective study), with 3/10 showing positive correlations [74]. More recently, another prospective observational study demonstrated that BMI and leptin were significantly correlated with pathological tumour classification and TNM stage in postmenopausal breast cancer patients [75]. It seems that leptin may increase breast cancer risk in postmenopausal women specifically [75, 76], in which the only source of oestrogens is adipose tissue.

There is some evidence suggesting that leptin might play a role in the development of prostate cancer (CaP). Leptin mediates a proliferative response in human prostate cancer cells *in vitro*. It seems that the mechanism occurs via a suppression of apoptosis. There is also evidence that suggests a role for the Ob-Ra receptor isoform in response to leptin in prostate cancer cells [77].

Lagiou *et al*. evaluated the hypothesis that prostate cancer and/or benign prostatic hypertrophy (BPH) are associated with dysregulation of circulating levels of leptin [78]. It was found that leptin levels in elderly men with prostate cancer or BPH are not substantially or significantly different from matched healthy individuals. Chang *et al*. reported that men with higher plasma leptin concentrations, combined with higher plasma testosterone concentrations, may have a greater risk of diagnosis with higher tumor volume and/or extraprostatic disease. It was demonstrated that leptin's effect may be independent of testosterone level [79]. Statin *et al.* reported that leptin could be the nexus between the western life style (hypercaloric diets rich in fat and sedentarism) and the transition from a pre-neoplastic lession to a clinically detectable tumor [80]. Hsing *et al.* established that leptin could affect the risk of clinically detectable CaP by means of factors related to obesity. In short, leptin would affect CaP growth by factors such as testosterone, IGF-1,

VEFG, and could influence cell differentiation and prostate cancer progression [81]. Thus, the potential role for leptin in the pathogenesis of prostate cancer still remains inconclusive. Consistent to this observation, epidemiological studies found contradictory results associating leptin with prostate cancer. In the Physicians' Health Study, a 25-year prospective study, no associations were found between leptin and prostate cancer risk and mortality [82]. A recent genetic study demonstrated that the leptin polymorphism (−2548 G/A), leading to higher leptin levels, is associated with susceptibility to prostate cancer and risk of advanced disease [83]. It is suggested that, regardless of these contradictory data, leptin may be associated with more advanced, hormone-refractory prostate cancer [84].

Moreover, high-fat diets, increase serum leptin and colon carcinogenesis by stimulating colon cell proliferation [85,86]. Thus, it has been reported that some dietary fiber, that reduce colon carcinogenesis by mechanisms that lower colonocyte cell proliferation, also decreases serum leptin [87]. Conjugated linoleic acid has protective effects against colon cancer [88] and reduces body fat and serum leptin in rats [89]. The anti-obesity effect of physical exercise as well as its protective effect against colon carcinogenesis are also well known. It has been proposed that physical exercise causes a physiological change in the colon and reduces cell proliferation via a reduction in serum leptin [90]. The results suggest that colon carcinogenesis associated with a high-fat diet is in part mediated through a mechanism involving leptin.

Human colon cancer cell lines express leptin receptors and have mitogen-activated protein kinase activity [91]. Leptin levels are positively correlated with colorectal cancer in some prospective studies [92-94], but not in others [95,96]. It is questionable whether leptin is a cause or a mere bystander, since leptin is not as strongly associated with colorectal cancer in women, who have much higher leptin than men. In a study of Wallace *et al*., in gastrointestinal cancer patients with progressive weight loss, there were significantly lower leptin concentrations compared to healthy subjects with similar BMI, suggesting a possible role of leptin to cancer anorexia/cachexia [97]. Furthermore, a new role for leptin has been indicated, through linking the nutritional and body fat status to digestive cancer susceptibility by stimulating the invasive capacity of colonic epithelial cells at early stages of neoplasia. This finding may have potential clinical implications for colon cancer progression and management of obesity [91,98]. Paradoxically, some studies observed significantly lower serum leptin concentration in patients with colorectal cancer, independent of BMI and weight loss [99,100]. In less differentiated colorectal cancers, the leptin expression is decreased [101], and the expression level may be positively correlated with a better prognosis [102].

It has been found that *H. pylori* (HP) infection significantly increases gastric leptin expression. In addition, cure of *H. pylori* infection reduces gastric leptin expression, with a concomitant increase in BMI. In contrast, serum leptin levels did not change significantly after cure of *H. pylori* infection [103]. Since HP infection has been established as a risk factor for gastric cancer, further studies regarding the role of gastric leptin as an additional risk factor are warranted.

Additionally, in a recent study of patients with pancreatic cancer, lower leptin levels were recorded in patients as compared to healthy controls. In the same study, patients with chronic pancreatitis also had lower leptin, while patients with autoimmune pancreatitis had high leptin levels [104]. Furthermore, another case-control study showed that pancreatic adenocarcinoma was associated with low leptin levels, but the causality remained unclear [105]. Hypoleptinaemia may be just a consequence of weight loss, observed in many pancreatic cancer patients [42]. If in fact hypoleptinaemia increases the risk of pancreatic cancer, it could be explained by the increase in insulin resistance, which is another risk factor for the disease [106].

There are no data showing a relationship between serum leptin levels and esophageal cancer. In a case-control study, leptin was not associated with squamous cell carcinoma of the esophagus [107]. However, hyperleptinaemia has been shown to increase the risk of Barrett's oesophagus (BE), a precancerous lesion [108]. As in pancreatic cancer, hypoleptinaemia is observed in patients with weight loss and cachexia [109].

In a study by Petridou *et al.*, it was shown that leptin levels were correlated with the presence of endometrial cancer [110], nevertheless, it was not clarified, if leptin levels would be a bystander in obesity or the cause of endometrial cancer [58,111]. Furthermore, in a study of Lebrecht *et al.*, in patients with cervical cancer, serum leptin fell short of being a useful marker, since leptin was not associated with the pathophysiology of the disease [112].

Leptin receptors (ObRl and ObRs mRNAs) are also found to be expressed in leukemic cell lines [113]. Furthermore, leptin alone and in combination with other cytokines has stimulative effects on proliferation of leukemia blast cells, like in acute myeloid leukemia cells. Konopleva *et al*. studied the expression of the leptin receptor, OB-R, in human leukemia cell lines [114]. Results demonstrated the frequent expression of leptin receptor as well as proliferative effects and anti-apoptotic properties of leptin alone and in combination with other physiologic cytokines. Further studies are needed to clarify the exact role of leptin in hematopoietic stem cells and in the pathophysiology of leukemia.

4. Conclusion

Despite the important advances in our knowledge of leptin physiology and pathophysiology over the past 15 years, many questions remain to be answered. At a basic research level the mechanisms regulating leptin expression and secretion must be further analyzed. Additionally, the clinical implications and the underlying mechanisms responsible for leptin binding in the circulation, leptin transport across the BBB, as well as signal transduction through the leptin receptors must be clarified further. Both the neuroendocrine as well as the peripheral actions of leptin must be clearly established in humans. At the clinical level, even more questions are needed to be answered. Thus, it is hoped that ongoing research efforts will not only fully elucidate the pathophysiology of energy intake and homeostasis, but will also define the exact role of leptin in the pathophysiology of obesity, chronic inflammation and cancer.

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