Chapter

Biodiversity of the Adipocyte-Derived Hormone, Leptin

Reji Manjunathan, Dharanibalan Kasiviswanathan and Jayaraman Selvaraj

Abstract

The adipocyte derived hormone leptin is known for its pivotal role in the regulation of a variety of physiological functions mainly associated with metabolism and energy homeostasis. One of the major functions of leptin is pertain with its angiogenic induction in support of organ development as well as under pathological conditions such as atherosclerosis and cancer. *Leptin is a well-known pro-angiogenic growth factor which exerts its role through* Ob-R receptor present on endothelial cells. The therapeutic application of leptin is based on its potential to maintain various functions at pathological conditions. In this book chapter, the multi-diversity potentials of leptin are discussed in detail.

Keywords: Leptin, obesity, angiogenesis, tumor progression, multi-signaling pathways

1. Introduction

Leptin is a 16 kDa non-glycosylated protein derived from adipose tissue, primarily by adipocytes. Leptin is a well-known mediator for food intake and weight loss [1]. Leptin mediates its functions mainly through the receptor located in the hypothalamus and activates signaling cascades associated with energy intake [2]. It circulates through the bloodstream, engages with normal metabolism, regulates energetic homeostasis, reproductive system, and influences the circadian cycle, lipid inflammation, and carbohydrate mechanisms. Leptin is well known for its pro-angiogenic potential and operates multiple signaling agencies through the receptor located in endothelial cells [3, 4]. Leptin is also secrets by other organs, such as the placenta, bone marrow, ovaries, stomach, and cellular structures, including mammary epithelial cells, P/D1 cells, and gastric chief cells [1]. Research has demonstrated that leptin plays a crucial role in maintaining the normal physiology of various vital systems such as the reproductive system and could balance cell proliferation (**Figure 1**). The pleiotropic hormone also could repair tissue damage and can prevent on-adipocyte lipotoxicity. Though leptin is highly acceptable for its protective mode of action, increased leptin level is often observed in several inflammatory conditions [5]. Hence, a therapeutic approach based on leptin and receptor has become the need of the hour to balance many inflammatory diseases in the human body. The particular book chapter provides an insight into the multi-diversity properties of the pleiotropic hormone leptin.

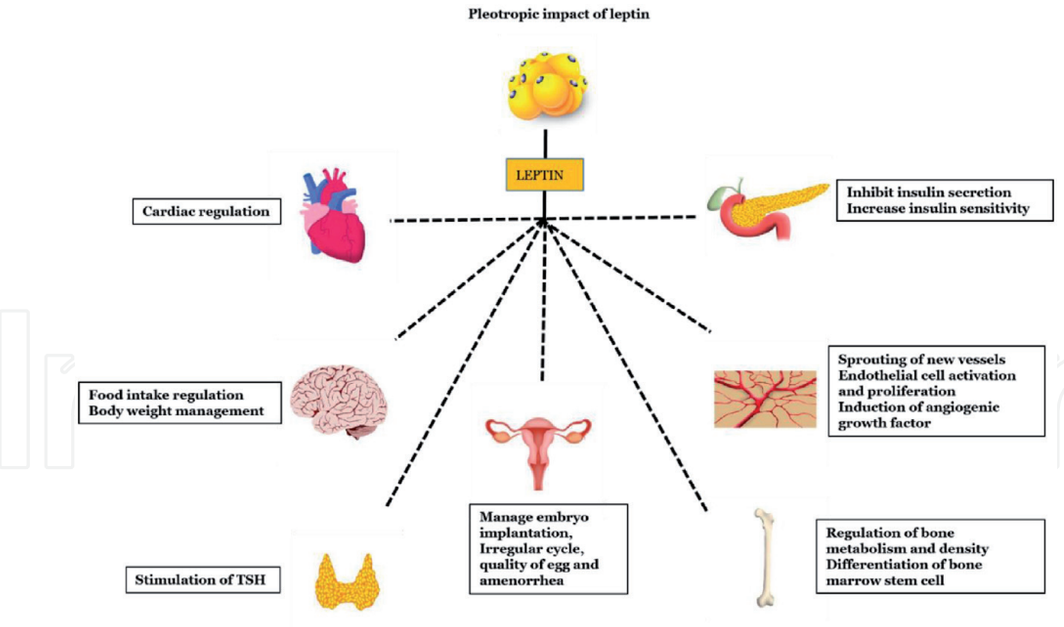

Figure 1.
Leptin exerts its pleiotropic impact on various organs. It maintains muscle tone and regulates cardiac function. Leptin regulates food intake and body weight management through binding with receptor located at brain. In the thyroid gland, leptin stimulates the secretion of TSH. In the female reproductive system, leptin manage menstrual cycle and supports in embryo implantation. Leptin inhibits insulin secretion and maintains blood-glucose level. Leptin induces sprouting of new vessels from existing ones and enhances ECs proliferation and migration and also it regulates bone metabolism and density.

2. Leptin synthesis and regulation

Leptin derives from adipose tissue's obese gene (OB) transcription product [6]. The OB gene function was first identified in the *ob/ob* obese mice model and is located on chromosome 7 (7q31.3) and has three exons and two introns (18 kb) [7, 8]. Leptin receptors are located on chromosome 1 (1p31) and are noted with 17 introns and 18 exons and encode two proteins of 166 and 1162 amino acids, respectively [9]. Leptin receptors are highly expressed in the hypothalamus, cerebellum, and other tissues associated with the vasculature, stomach, and placental organs [10]. Leptin receptors have five spliced isoforms, the longest form expressed in neuronal tissue and the short forms expressed almost in all tissue types [11]. Leptin receptors (OB-R) are structurally similar to the class I cytokine family receptors. Alternative splicing of leptin receptor RNA results in various isoforms, designated as OB-Ra, OB-Rb, OB-Rc, OB-Rd, OB-Re, and OB-Rf. They all have an extracellular domain of more than 800 amino acids, a transmembrane domain of 34 amino acids, and a variable intracellular domain. The pleiotropic biological effects of leptin are explained based on the wide distribution of leptin receptors in humans [5]. Leptin bind to its hypothalamic receptors (Ob-Rs) in the brain and activates appetite and satiety. The concentration of leptin in plasma depends on the person's dietary behavior, gender, and physical activities. The other hormonal constituents, such as insulin, estrogen, and glucocorticoids, can also influence the regulation mode and the level of leptin in the blood [12, 13]. On the other hand, low energy or fasting, thyroid hormones, androgens, inflammatory cytokines, and adrenergic agonists can inhibit leptin secretion [14].

3. Leptin signaling pathways

Leptin mediates its biological effects by binding to its various alternatively spliced isoforms receptor located at the brain and peripheral tissues. The binding of leptin to

its long-form of receptor activates various intracellular signaling pathways, including insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K), Janus kinase 2 (JAK2)/Signal transducer, and activator of transcription 3 (STAT3), SH2-containing protein tyrosine phosphatase 2 (SHP2)/Mitogen-activated protein kinase (MAPK), and 5′ adenosine monophosphate-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) [8]. The binding of leptin to its receptor activates JAK2, which in turn phosphorylates the Tyrosine amino acid residues in LepRb and is terminated by a suppressor of cytokine signaling 3 (SOC3) [15].

Leptin input a significant role in energy homeostasis and neuroendocrine function through JAK2/STAT3 signaling pathway. A selective deletion in LepRb or STAT3 in LepRb-expressing neurons ends with obesity and hyperphagia, which further supports the dominant role of the JAK2/STAT3 signaling pathway in the leptin-induced body weight regulation [16]. One interesting fact about leptin and insulin is that both have similar intracellular signaling pathways (PI3K/Akt) in neurons [17]. The ERK, a member of the MAPK family, acts downstream of LepRb and is mediated through SHP2 or by JAK2. Inhibition of ERK prevents leptin-based sympathetic function in brown adipose, which further supports SHP2/MAPK in leptin energy expenditure and food intake [18]. Leptin's suppressive mode of action on food intake initiates by inhibiting the effect of AMPK in the brain. The inhibition of AMPK regulates feeding through the mTOR (mammalian target of rapamycin)/s6Kinase pathway [19]. In skeletal muscle, leptin directly exists its effect through AMPK signaling and stimulates fatty acid oxidation and glucose uptake [20]. Leptin has a prominent role in the modulation of both innate and adaptive immunity. It stimulates neutrophil chemotaxis and promotes phagocytosis of macrophages through the receptor binding mechanism. It is also known to increase the production of IL-6 and TNF-alpha under pathological conditions [21]. Leptin protective action on neutrophils exerts through PI3K and MAPK depending on signaling and prevents apoptosis of neutrophils. Leptin via STAT3 activation promotes

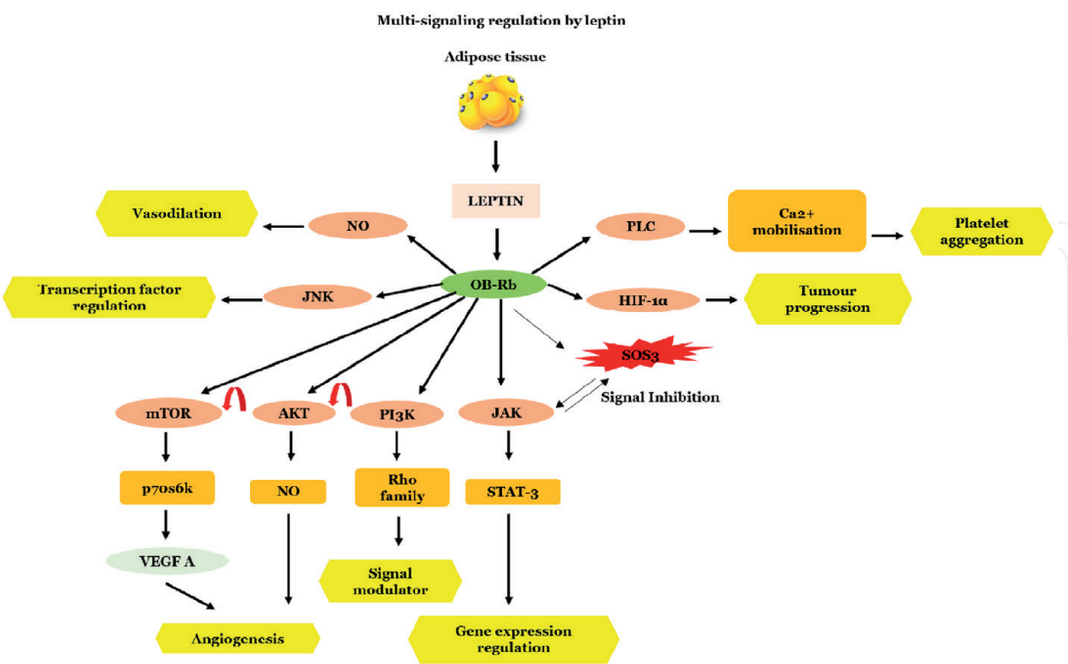

Figure 2.
Leptin regulates many signaling pathways through receptor (Ob-Rb) binding mechanism. It regulates gene expression through JAK/STAT3 pathway, modulates other signals through PI3K/rho family dependent pathway, induces vasodilation through NO-dependent pathway, and accelerates angiogenesis through PI3K/Akt/mTOR/s6 kinase/VEGF a and PI3/Akt/NO-dependent pathways. Promotes tumor progression through HIF-1 alpha pathway and enhances platelet aggregation through the PLC pathway. The SOS3 molecule function as a regulator of leptin induced signaling activations by negative feedback mechanism.

natural killer cell activation [22]. In the adaptive immune response, leptin promotes native T cells proliferation by increasing the expression of interferon-gamma and TNF-alpha in T cells [23].

Apart from the mentioned direct signaling pathways, leptin interacts with many signaling functions as a multifunctional cytokine. Leptin shows a potential functional relationship with Nitric Oxide (NO) and favors NO-mediated lipolysis and vascular tone [24]. The significant other functions of leptin are associated with its predominant role in angiogenesis. It is observed that Endothelial cells (ECs) express OB-R leptin receptors and the binding of leptin to OB-R enables the growth of small blood vessels [3]. Recently, it has been identified that leptin could induce PI3K/Akt/mTOR/s6Kinase signaling pathway and enhance VEGF mRNA's transcription level while inducing angiogenesis [4]. One of the intriguing possibilities of leptin is that it promotes neovascularization through paracrine mode concerning the volume of fat mass [25]. Leptin could promote proliferation in colonic epithelial cells in vitro conditions. Moreover, the presence of OB-R receptor in human colon cancer cell lines and human Colonia tissue thus supports the angiogenic role of leptin under cancer environment through PI3K/AKT, MAPK/ERK, and JAK2/STAT3 pathways [26, 27]. Leptin could induce apoptosis and regulate actin-myosin cytoskeleton associated with Rho family GTPases (**Figure 2**) [28].

4. Leptin as an energy balancer

Leptin acts in the brain and maintains energy homeostasis through a negative feedback mechanism [29]. The process is mediated through the receptors in the hypothalamic area named the paraventricular nucleus, ventromedial hypothalamic nucleus, lateral hypothalamic area (LHA), and arcuate nucleus (ARC). The ARC is the primary site for leptin to integrate peripheral energy balance signals [30]. Recently, it has been observed that leptin could play a significant role in the long-term regulation of energy balance and short-term management of body weight and food intake. The gastric leptin produced because of the actions of the intestinal peptide serves as a local stimulus and plays a vital role in food digestion and absorption [31]. The particular area requires more investigations to prove the role of gastric leptin in food digestion and absorption. Research supported the predominant role of leptin in neuroendocrine mediated starvation through changing sympathetic nervous system activity [32].

Overweight or obesity is characterized by increased fat mass and is proportional to circulating leptin levels in individuals [33]. The elevated levels of leptin in body fluid are explained based on leptin resistance. The hypothesis was proved using rodents fed with a high-fat diet and leptin sensitivity loss in ARC neurons [34]. At the cellular level, the inflammatory signals mediate the process of leptin resistance. The two significant characteristics of obesity connect with hyper-leptinemia and leptin resistance. At the molecular level, the leptin gene is over-expressed in overweight or obese individuals [35]. Apart from these functions, many researchers reported the genetic and epigenetic factors that control leptin action in energy homeostasis and food intake [36–38]. A better understanding of leptin-induced pathogenicity of obesity and obesity-related disorders and the regulation of energy homeostasis will provide an alternative solution in preventing obesity and obesity-related co-morbidities.

5. Leptin as an immune modulator

Despite nutritional regulation, leptin has gained more attention for its pivotal role in inflammation. The innate immune system plays a major role in the regulation

of leptin production. Leptin responds to immune cells and its receptors, expressed by most cells, and activates pro-inflammatory features in the host [39]. Leptin plays an essential role in T cell development, and leptin deficiency directly impacts the levels of circulating T cells [40]. Many studies supported the role of leptin in immunity modulation and mentioned the signaling pathways related to the notion [39, 41, 42]. Leptin could accelerate the proliferation process in native $CD4^{+}$T cells and favored by reducing the levels of IFN from T cells [43, 44]. During the wound healing process, leptin activates both inflammatory and proliferative phases in favor of tissue repair [45]. The increased plasma leptin level acts as an indicator of leptin-induced inflammatory response at the injury site. These exciting features of leptin gained attention as a pro-angiogenic molecule in ischemic tissues [46]. Leptin induces monocyte chemoattractant protein1 (MCP1) expression [47].

Leptin plays a vital role in producing GM-CSF and G-CSF and activating hematopoietic cells in humans [48]. In animal models, up-regulation of leptin has been found in acute inflammation states. But, experimental evidence from rodents does not match with human studies [49]. Leptin plays a significant role in basophils and eosinophils functions and acts as a chemoattractant [50]. Leptin is abnormally expressed in autoimmune diseases, particularly in skin disorders [51]. Obesity decorates skin normal physiology such as keratosis pilaris, tags, and striae diseases and increases the levels of pro-inflammatory cytokines and adipokines, including leptin [52, 53]. In the event of inflammation, leptin increases the release of Nitric Oxide and activates the macrophages and neutrophils, and increases natural killer cells' activity (NK) [54]. Leptin up-regulates the cytokines production and phagocytic function in obese conditions [55]. It balances monocytes and activations markers and directly involves in interleukin1 and cyclooxygenase expression [56]. One of the prominent roles of leptin pertains to maintaining the balance between the immune system and metabolism regulation. Under malnutrition state, leptin acts as an immunosuppressive factor [42].

6. Leptin as a pro-angiogenic factor

In 1998, Sierra-Hongmans reported that vascular endothelial cells express leptin receptors, especially the long-form. This discovery leads to an insight into the role of leptin in angiogenesis [57]. The angiogenic impact of leptin was conformed used on in vitro and in vivo models analysis [3, 58]. Jin et al. proved that leptin could induce angiogenesis in the cornea of the Zucker obese rat model through the activation of the Ob-R gene [59]. Leptin exerts a paracrine mode of action in tissues and activates various signaling during the promotion of angiogenesis. This endocrine hormone activates Akt signaling pathway and mediates NO-induced vasodilation [60]. In endothelial cell migration, leptin signals through the ERK pathway and activates the PI3k, Akt, and eNOS molecules. By stimulating the local neovascularization in adipose tissue, leptin promotes its release into the vascular system. This process enhances fatty acid oxidation and supports maintaining a proper balance between adipose tissue's fat deposits and blood supply [61]. Even though the vascular fenestration capacity of leptin is poorly understood, the effect is found similar to VEGF [62]. Leptin plays a crucial role in exchanging nutrients between the fetus and maternal circulation in the placenta via enhancing vascular permeability and could induce angiogenesis in the placenta [61].

7. Leptin and pathogenesis

Leptin does not only imply energy homeostasis but also extends its regulatory function at infectious conditions. But the contagious status regulation mode

of leptin is the least explored signaling mechanism. Latest research support that leptin could activate phagocytosis of macrophages and could secure the immune cells from pathogenic infections [63]. In *Klebsiella pneumonia* infection, exogenous administration of leptin shows CD11b dependent phagocytosis [64]. It protects lymphocyte deficient mice from various conditions [65]. Several studies have strongly highlighted the therapeutic application of the molecule to innervate infectious diseases, including AIDS [66].

8. Leptin resistance with disease

However, under certain conditions, like obesity, leptin levels decrease in association with leptin resistance. But it is still unclear how the leptin resistance mechanism is exerted throughout the tissue. So far, studies have suggested leptin resistance with metabolic process and revealed a defect in the Ob-R leptin receptor gene [67]. Up to date, the leptin resistance mechanism has been categorized as follows: gene mutation specific to the leptin structure, defect in the transport of leptin through the blood–brain barrier, and malfunctions of leptin receptors. Among these, mutations are rare in humans, occurring in substitution of guanine by adenine at the donor splice site of exon 16 of the leptin gene [68]. Second, the brain's blood vessels usually express leptin receptors and transport leptin into the cerebrospinal fluid. But excessive levels of leptin in the bloodstream decrease the permeability of BBB, thus develops leptin resistance [69]. Finally, the serum level of leptin significantly affects the transcriptional level of the OB (*ob*) gene and the equilibrium of leptin secretion in adipose tissue. In such cases, these dramatic changes promote leptin resistance until leptin level remains standard in the bloodstream. These changes have been widely observed in obesity [70].

Furthermore, several stimuli affect leptin resistance, including the circadian cycle. Interestingly, leptin also develops its leptin resistance, observed in diet-induced obesity [71]. This leptin resistance also provides an environment for the accumulation of immune response against pathogens, particularly high-fat diet-induced inflammation, which activates inflammatory cytokines [72]. But, in-depth leptin resistance mechanisms need much more attention.

9. Leptin role in disease conditions

9.1 Metabolic syndrome and obesity

Fat tissue is an energy storage tissue that functions as a negative feedback loop in energy homeostasis [73]. Homozygous mutation of leptin causes extreme obesity, diabetes and suppresses glucose metabolism in insulin-deficient diabetes [8]. The ob/ob mice model has relatively higher food intake and observed a larger volume of lipid accumulation in the liver than the control group [74]. It has been assumed that nearly 95% of individuals have resistance against leptin [75]. The type 2 diabetes condition is noted with an increased level of leptin and suggested using leptin as a biomarker to study the effect of obesity in diabetes-related morbidities [76]. Some studies also reported that higher leptin levels are associated with the risk of heart-related problems in obese individuals [76, 77]. In younger adults, elevated leptin levels are positively correlated with HOMA-IR and BMI index [78].

Development of severe early-onset obesity and hyperphagia are common in people with homozygous *LEP* mutation [79]. Replacement of leptin from a therapeutic viewpoint has improved insulin sensitivity and thus proved the role of leptin

in metabolic disorders, including T2DM. In humans, serum leptin level is positively correlated with the percentage of body fat, fat mass, size of adipocytes, and BMI [80]. Obesity connected with the enlargement of adipose cells enhances the serum leptin level, which further results in the progression of chronic hyperinsulinemia. The majority of obese patients are hyper leptinaemic which supports the development of hypertension, metabolic syndrome, and cardiovascular diseases [81]. Mutation in the leptin receptor located at the hypothalamus alters the transport of leptin across the blood–brain barrier. This incidence increases the level of serum leptin and hence diet-induced obesity. Obesity connected with the leptin receptor mutation is linked with insulin resistance and in the development of T2DM [82].

9.2 Cardiovascular diseases

The level of leptin could influence the function of the heart. It could lead to the progression of many heart-related problems such as coronary artery disease, stroke, chronic kidney disease (CKD), peripheral artery disease (DAP), carotid plaque instability [83]. It was observed that elevated level of serum leptin in obese patients contributes to the low-grade systemic inflammation in favor to develop cardiovascular disease. Moreover, a high level of leptin is used as a biomarker to measure the progression of heart failure in patients with dilated cardiomyopathy [84]. On the other hand, many studies using rodent, obese and diabetic models highlighted the beneficial impact of leptin on cardiac metabolism through glucose metabolism and fatty acid oxidation. This evidence suggested that leptin compensates for cardiac insults due to ischemia and heart failure [85]. Leptin signaling in the modulation of heart function is studied extensively using animal models. These studies demonstrated that impaired cardiac leptin signaling majorly reflects in metabolic inflexibility for glucose utilization, defects in cardiac contractibility, impaired recovery of cardiac function due to coronary artery ligation [86, 87]. Clinical data cemented that plasma leptin levels are associated with LV hypertrophy and increased myocardial wall thickening [88]. Leptin also increased the blood pressure level in obese individuals with a loss-of-function mutation in leptin or leptin receptor [89]. Thus, a leptin-mediated increase in blood pressure directly increases the heartbeat rate, developing into cardiac hypertrophy through the sympathetic nervous mechanism [90].

Leptin-mediated aldosterone synthesis impairs myocardial relaxation and contributes to cardiovascular diseases through a novel mechanism associated with endothelial dysfunctions [91]. Increased plasma leptin levels positively correlate with the number of stenotic coronary arteries in patients with coronary artery disease [92]. In vitro analysis using HUVEC cells demonstrated that leptin induces chronic oxidative stress in ECs and contributes to vascular pathology development [93]. Also, the cytokine hormone leptin could stimulate vascular smooth muscle cells proliferation and migration, thereby increasing calcification and vascular lesions [94]. Altogether, it was suggested that hypertension, obesity, and endothelial dysfunctions are more frequent in T2DM patients with elevated leptin levels [95].

9.3 Tumor progression

Cancer progression is a complex process that includes the interaction between ECs, fibroblast, insusceptible cells, and adipocytes [96]. Normal epithelial cells do not express leptin and leptin receptors but are overexpressed in a cancerous environment. Leptin enhances the survival rate of cancer cells through the activation of a downstream signaling molecule known as sirtuin-dependent NAD-dependent deacetylase 1 (SIRT 1) [97]. Leptin can activate many signaling pathways in cancer directly by activating TNF alpha, IL-6, ROS, VEGF, MMP2, and MMP9.

It can also support tumor growth by activating JAK/STAT, Akt, FGF2, and NO molecules through receptor (Ob-R) binding mechanisms in ECs [98, 99]. The appetite hormone can potentially interact with pre-neoplastic or cancerous breast epithelium in a breast cancer environment. Leptin secreted by the breast cancer surroundings inhibits inflammatory cytokines and thus blocks macrophages' production [100, 101]. The cytokine enhances neovascularization through VEGF in many cancerous conditions [102, 103].

Increased levels of serum leptin and insulin under obese conditions cause colorectal cancer [104]. Leptin supports the proliferation and invasiveness of colonic cells. Leptin receptors are found to express in human colon cell lines and are believed to initiate cancer angiogenesis. Hyperlipidemia and insulin resistance can cause low-grade systemic inflammation that promotes proliferation and angiogenesis and inhibits apoptotic rate in colon cancer [105]. Leptin and its receptors express in papillary thyroid tumors and enhance the pathogenicity through PI3K/Akt pathway [106].

Obesity enhances the concentration of leptin around the pancreatic carcinogenic environment. The enhanced concentration of leptin favors vascularization, migration, and invasiveness of pancreatic tumor cells [105]. Leptin has a crucial role in developing the non-alcoholic fatty liver disease (NAFLD) via insulin resistance. This imbalance ultimately worsens hepatic inflammation and results in the development of liver fibrosis [107]. The receptor Ob-R identified in Kupffer cells (KC), and binding of leptin with receptor enhances the expression of TGF beta, TIMP1 in liver fibrosis scenario [108]. However, the direct role of leptin in liver cancer is controversial, with some reports suggesting its role in liver cancer. In contrast, others offer its inhibitory potential on tumor size in hepatic cancer [109, 110]. The level of leptin was found to decrease in patients with cancer cachexia compared to non-cancer cachexia [111].

10. Leptin therapeutics past and future

The significant need for clinical implications of leptin is to regulate the regular physiological role of leptin in pathological conditions. There is a correlation between body weight loss and serum levels of leptin. As a result, several therapeutic approaches have been implemented for the use of leptin in obesity control. However, increased resistance to leptin is also a significant issue in the treatment of obesity. But, a combination of therapeutic approaches may be helpful to these problems [112, 113].

Among the adipocyte secreted hormones, leptin is the front that has been used for the treatment of hypoleptinemia status clinically. The most important therapeutic benefits of leptin are rely on providing a novel method for treating the conditions connected with mutation of leptin gene and lipodystrophy in humans [114]. Treatment with exogenous leptin in obese patients concluded that leptin can decrease the body weight and fat tissue of the subjects [115]. It was also noted that leptin excerpts a dose-dependent regulating potential as individuals energy intake and appetite [116, 117]. Development of leptin analogous with full biological effect, especially with the potential to cross the blood–brain barrier, can improve the results obtained from leptin therapy focusing on obesity management. The administration of leptin can accelerate wound healing in diabetic ob/ob and wild-type mice in a dose-dependent manner through leptin receptor mediation [118].

Exogenous administration of leptin can regulate fatty acid oxidation in muscles and control triglyceride synthesis in the liver [119, 120]. Even though the mechanisms in humans are not clear, administration of leptin and adiponectin was found to improve insulin resistance in type 2 diabetic conditions [121, 122]. The immunemodulatory impact of exogenous leptin administration in rodents highlighted that

the cytokine could activate encephalomyelitis [123]. Various in vitro assays also supported the immune stimulator action of leptin [124, 125]. Identifying high-affinity-binding molecules to control the level of circulating leptin is suggested as an advanced therapy for treating arthritis and inflammatory bowel disease. In addition, replacement with recombinant methionyl human leptin is a brilliant choice for treating pathological conditions associated with relative or absolute leptin deficiency and restoring immune functions [126]. One of the future therapeutic approaches of leptin relies on its use as a natural adjuvant in vaccinations since it can stimulate T helper I responses while down-modulating regulatory T cells [127].

Considering the cancerous conditions, ATLO-ACA, an Ob-R antagonist peptide, finds effective for treating triple-negative breast cancers in experimental models [128]. Also, therapy based on leptin/Ob R axis function inhibition was identified as adjunctive therapy for newly diagnosed and recurrent glioblastoma [129]. The modern therapeutic approaches of leptin are connected with molecular approaches at gene levels are 1) CRISPR-Cas 9 connected with floxed leptin-locus based approaches - to lower the leptin levels, 2) Cre-lox P- generation of one copy of Lep eliminates – to lower the leptin levels, glucose and insulin tolerance, c) administration of neutralizing leptin-specific antibodies –to reduce the circulating levels of leptin to reduce food intake and hepatic stenosis [130]. Administration of human recombinant leptin accelareated dose-dependent sprouting angiogenesis and hypothesized that the application of human recombinant leptin could improve the wound healing process through neovascularization [3]. So far, evidence gathered from previous studies highlights the role of leptin in therapeutic applications. But overcoming leptin resistance is a significant challenge in leptin-based therapy.

11. Conclusion

In conclusion, leptin is considered an essential pleiotropic adipokine with various effects on biological systems. However, leptin's structural and functional characteristics and its receptors are characterized by a unique signaling mechanism. Focusing on leptin could be a therapeutic approach to manage autoimmune inflammation associated with obesity, cancer, and metabolic diseases. But further research is needed to understand the relationship between leptin on biological systems, as it has complex signaling mechanisms.

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Authors Contribution

DK collected information and prepared the first draft, RM and JS critically evaluated and coordinated with final draft preparation.

Conflicts of interest

The authors declare no conflict of interest.

Author details

Reji Manjunathan[1,2,3]*, Dharanibalan Kasiviswanathan[2] and Jayaraman Selvaraj[4]*

1 Department of Genetics, Dr. Alagappa Mudaliyar Post Graduate Institute of Basic Medical Sciences, University of Madras, Tamil Nadu, India

2 Vascular Biology Lab, AU-KBC Research Centre, Anna University, Tamil Nadu, India

3 R CELL Diagnostic and Research Centre, Calicut, Kerala, India

4 Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Tamil Nadu, India

*Address all correspondence to: rejimanjunath@gmail.com and jselvaendo@gmail.com

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