Chapter

Leptin and Its Role in Oxidative Stress and Apoptosis: An Overview

Volkan Gelen, Abdulsamed Kükürt, Emin Şengül and Hacı Ahmet Devecı

Abstract

Adipose tissue (AT) in the body plays a very important role in the regulation of energy metabolism. AT regulates energy metabolism by secreting adipokines. Some of the adipokines released are vaspin, resistin, adiponectin, visfatin and omentin, and leptin. In addition to regulating energy metabolism, leptin plays a role in the regulation of many physiological functions of the body such as regulation of blood pressure, inflammation, nutrition, appetite, insulin and glucose metabolism, lipid metabolism, coagulation, and apoptosis. Among all these physiological functions, the relationship between leptin, oxidative stress, and apoptosis has gained great importance recently due to its therapeutic effect in various types of cancer. For this reason, in this study, the release of leptin, its cellular effects and its effect on oxidative stress, and apoptosis are discussed in line with current information.

Keywords: Apoptosis, leptin, obesity, oxidative stress

1. Introduction

Obesity is defined as a chronic disease that results in an increase in adipose tissue (AT) in the body as a result of the energy intake being more than the energy spent. Today, it has become a common and important health problem in both developed and developing countries due to various reasons such as changes in eating habits and inactivity [1, 2]. Obesity directly or indirectly affects national economies. Obesity causes an increase in the rates of noncommunicable diseases, damage to various organs, shortens the life span, and negatively affects the quality of life [3–5]. In the case of obesity, which is so important, the level of leptin increases. Leptin is an adipokine secreted in fat cells [6]. After leptin is released from the fat cell, it reaches the central nervous system via the blood, binds to its receptor, and reduces food intake through this receptor [7, 8]. Leptin is produced by the obese *(ob)* gene in adipose cells by encoding it into mRNA [9, 10]. As the number of fat cells in the body increases, the plasma leptin level also increases. While leptin decreases plasma glucose and insulin levels, it increases metabolic rate and physical activity, resulting in a decrease in body fat [11]. It has been determined that leptin, which has such important effects on fat cells and hunger, is effective on cancer cells. In line with this information, this study aimed to explain leptin synthesis, its receptor, factors affecting its release, and the relationship between leptin, oxidative stress, and apoptosis.

2. Leptin

Leptin (a fat tissue hormone), the *ob* gene product, was the first adipokine discovered. Its discovery is based on work done in the 1950s. It begins with the researchers' discovery of two genes, called diabetic *(db/db)* and obese *(ob/ob)*, in two separate strains of mice [12, 13]. In a study conducted in these mice, which have the same phenotypic characteristics (such as insulin resistance, morbid obesity, lethargy, and infertility), blood leptin level was found to be deficient in the *ob/ob* gene product, while the *db/db* gene product was found to have a deficient leptin receptor. In addition, in the study where *db* and *ob* genes were examined in detail, *db/db* and *ob/ob* mice were both three times heavier than controls, and both groups of animals had five times more fat than the control [14]. About 40 years after the first studies, the *ob* or *Lep* gene encoding leptin was discovered and given this name because of its weak meaning [15]. About a year later, the isolation of the leptin receptor gene was reported [16].

The mouse leptin gene size is 4.5 kilobases long containing 167 amino acids [15]. Regulation of the leptin gene initiator that controls leptin production, is mediated by glucocorticoid response elements, CCAAT/enhancers, cyclic adenosine monophosphate (cAMP), and specificity protein 1 (SP1) binding sites [17]. Studies have shown that human leptin is 84% similar to mouse leptin and 83% to rat leptin [18]. Besides, a positive correlation was found between plasma leptin concentrations and AT leptin mRNA levels. Therefore, as leptin mRNA increases, plasma leptin concentrations also increase [19].

Human leptin is produced from a gene on chromosome 7. The structure of human leptin, a 16 kilodalton protein, is in the form of a 4 α helical bundle coil, like class-I helical cytokines [20]. The most highly conserved amino acid extension is the GLDFIP sequence [21, 22]. Leptin, synthesized by adipocytes, is a hormone that notifies the brain of energy reserves and affects metabolism, reproduction, growth, and development processes [16, 22]. Circulating leptin levels act at the hypothalamic central level to increase energy expenditure and reduce food intake when the body is well nourished [23]. It induces the storage of triglycerides in AT and has an effect on appetite [7]. When plasma leptin levels increase, it sends a signal of satiety to the brain in the short term, while it sends information about the energy status in the long term [24]. It also influences hypothalamic neuropeptide signaling [25]. The main physiological role of leptin during periods of hunger is to regulate the neuroendocrine system. With regard to obesity, leptin levels rise with increasing adiposity [26]. Circulating leptin levels are high in obese, pointing to the importance of leptin resistance in the obese [24]. Leptin-deficient mice have been found to show neuroendocrine abnormalities similar to starving mice. Leptin supplementation causes neuroendocrine normalization and reduced food intake in leptin-deficient obese rodents and humans, thereby reversing obesity [10]. Mutations of the *ob* gene result in leptin resistance and extreme obesity in mice [15]. *Ob/ob* mice have neuroendocrine abnormalities and they are generally classified as hyperphagic, hypothermic, morbidly obese [27].

It has been reported that leptin plays a proinflammatory role by increasing the inflammatory immune response, and this is associated with the pathogenesis of many complications of obesity [28]. It is noted that leptin can affect both adaptive and innate immunity by inducing proinflammatory response and thus playing a key role in regulating the pathogenesis of various autoimmune/inflammatory diseases [29]. It has been shown that as the degree of obesity increases in adults, the levels of plasminogen activator inhibitor-1 (PAI-1) and leptin, which is a proinflammatory marker, increase. It has been reported that it is responsible for the proinflammatory process, which is associated with an increased level of obesity [30]. Leptin regulates

the functions of immune cells, such as natural killer cells, dendritic cells, neutrophils, eosinophils, macrophages, and basophils [23].

3. Leptin synthesis

Effector systems that control energy intake and energy expenditure, hypothalamic control centers where leptin signals from different sources are received, and the size of AT mass are the regulatory steps of leptin synthesis [31]. The major sites of leptin mRNA expression are in the stomach, liver, and AT [32]. Leptin mRNA is also expressed at minor levels in the fetal tissue, placenta, heart, brain, and pituitary gland [18]. Leptin synthesized is generally related to the degree of adiposity. Larger adipocytes express more leptin genes than smaller adipocytes [33]. Mechanical stretching of the fat cell, determined by the amount of stored triglycerides, can generate signals to increase leptin synthesis [24]. In addition, in humans, uridine diphosphate N-acetylglucosamine (UDPGlcNAc) and hexosamine act as potential links between cell size and leptin content. Body mass index is positively correlated with the amount of UDPGlcNAc in subcutaneous AT [34].

The composition of the food, not the amount, affects leptin production [35]. The composition of a meal affects leptin levels; for example, low-fat and high-carb food causes increased leptin levels [36]. Compared to high-carbohydrate meals, high-fat meals lower circulating plasma leptin levels 24 hours after a meal [37]. It has been reported that meals rich in ω-6 polyunsaturated fatty acids (PUFA) increase leptin production [35]. It has been reported that the protein composition of a meal does not affect leptin production [38].

Gender differences have an effect on leptin production. Although there is no difference in leptin levels between girls and boys in the prepubertal period, leptin levels increase in girls and decrease in boys with puberty development [39, 40]. This is explained by the fact that with puberty, the amount of body fat in girls increases more than in boys, and testosterone suppresses leptin levels in boys [41]. In addition, the fact that the subcutaneous AT mass is significantly larger than the omental fat mass of women is also among the factors [39]. Reproductive hormones greatly affect leptin production. Androgenic hormones inhibit leptin synthesis, while estrogens stimulate leptin synthesis [42]. In one study, it was thought that increased estrogen concentrations caused an increase in leptin concentration, which may have been caused by leptin stimulating gonadotrophin releasing hormone (GnRH) synthesis and thus increasing estrogen synthesis [43]. In addition, chronic insomnia and an increase in melatonin concentrations have been reported to decrease plasma leptin concentrations [44].

4. Leptin release factors

The immune system has a role in regulating energy expenditure and AT lipolysis [45]. White adipose tissue (WAT) is the primary energy store; brown adipose tissue (BAT) is associated with heat production. Sympathetic activity in WAT is increased in conditions associated with decreased leptin synthesis/secretion, such as cold exposure and starvation. By the way, catecholamine and β-adrenoceptor agonists inhibit leptin production; this suppressive effect is mediated by β3-adrenoceptor agonists, which actively reduce leptin levels [46]. Leptin also causes sympathetic nervous system activation, resulting in regulatory feedback inhibition [47]. Intracerebroventricular injections of leptin have been noted to increase metabolic rates through increased norepinephrine release from sympathetic nerve terminals innervating BAT [48].

After a meal, plasma insulin and amino acid levels initiate the mammalian target of rapamycin (mTOR) pathway, which stimulates leptin biosynthesis via mechanisms involving the 5′/3′ untranslated region (UTR) [49]. Cyclic AMP activates cyclic AMP-activated exchange proteins (EPACs). Deletion of *EPAC1* genes causes an increase in leptin sensitivity in the hypothalamus. *EPAC1* is also involved in leptin secretion and expression in WAT [50].

Leptin antagonizes orexigenic pathways and stimulates anorexigenic pathways. Leptin exerts its general effects on the nervous system through these pathways [7]. Orexigenic neuropeptides that are down-regulated by leptin are orexins, agouti-related peptides, neuropeptide Y, and melanin-concentrating hormone. By the way, the anorexigenic neuropeptides upregulated by leptin are alpha-melanocyte-stimulating hormone, which acts on corticotropin-releasing hormone, cocaine and amphetamine-regulated transcript, and melanocortin-4 receptor (**Figure 1**) [31].

Glucocorticoids are long-term regulators of leptin expression [52, 53]. They increase leptin mRNA levels by acting on adipocytes; *in vitro* incubation of a synthetic glucocorticoid in rats, adipocytes have been found to increase leptin secretion [54]. Oral glucocorticoids doubled serum leptin levels and leptin mRNA 24–48 hours after absorption. Furthermore, cell cultures incubated with a glucocorticoid and insulin combination synergistically increased leptin mRNA levels [55].

Lactates and hexoses also increase leptin secretion [56]. Because leptin secretion requires ATP, suppressing glucose uptake suppresses leptin secretion. When the energy supply is low, food is needed to increase it. Glucose, the cellular sensor of energy stock, stimulates leptin gene expression and secretion in both muscle and AT via hexosamine biosynthetic [57]. Insulin lowers blood sugar when glucose levels rise above normal and also increases leptin promoter activity [58]. No increase in leptin mRNA levels was observed after adipocytes were incubated with insulin for 1–2 hours, but an increase in leptin release was observed [54].

Regulation of tumor necrosis factor-alpha(TNFα) and leptin may be interdependent and similar as they have comparable functions such as suppressing

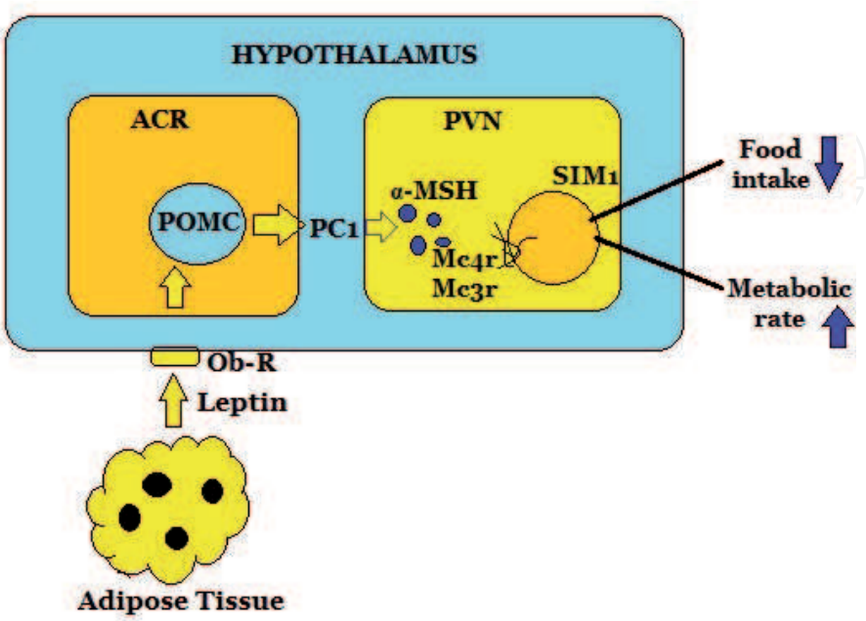

Figure 1.
The leptin/Melanocortin pathway. ARC; the arcuate nucleus of the hypothalamus, POMC; proopiomelanocortin, Ob-R; leptin receptor, PVN; paraventricular nucleus, MSH; melanocyte-stimulating hormone (α-MSH,β-MSH,γ-MSH), MC4R; melanocortin-4 receptor, SIM1; single-minded 1 [51].

lipid synthesis, reducing food intake, and stimulating lipolysis [59]. Leptin limits AT mass. TNFα has the role of stimulating leptin secretion from mature human adipocytes. TNFα therapy has been shown to cause increased leptin levels in humans [60].

5. Leptin receptor and leptin resistance

Leptin receptors are in the family of cytokine receptors. There are six isoforms encoded by the *LepR* gene. The *OB-Rb* receptor is the dominant longest form. Its mutations cause obesity because it cannot bind to the receptor [16]. Obese people have high leptin levels. Circulating leptin levels are correlated with body mass index [61]. On the other hand, in diet-related exogenous obesity, studies in fat mice and humans without leptin deficiency, it has been shown that external leptin treatment does not provide a significant reduction in body weight and food intake [62]. In obese people, leptin levels increase, but hyperglycemia-correcting or appetite-reducing effects are not observed [63]. Despite the increased leptin levels in obese patients, the absence of the functions of leptin, an appetite-reducing hormone, suggests leptin resistance [64]. It has been suggested that leptin resistance plays a role in the pathogenesis of obesity triggered by overeating [65]. However, the molecular mechanisms underlying leptin resistance have not yet been clearly elucidated. The inability of leptin to cross the blood–brain barrier, inhibition of the intracellular leptin signaling pathway in neurons, and/or downregulation of leptin receptors are thought to be the underlying mechanisms of leptin resistance. It has been reported that a high-fat diet causes an increase in fat mass, leading to hyperleptinemia and triggering leptin resistance [66]. In high-fat rats *(fa/fa)*, substitutions in *OB-Rb* result in reduced signaling capacity, leptin binding affinity, and cell surface expression [67]. Obese *fa/fa* rats have leptin resistance and are not sensitive to the effects of leptin. Although obese people may have high plasma leptin concentrations due to leptin resistance, they do not experience the effects of leptin [19].

In gastric chief cells (also known as zymogenic cell or peptic cell), leptin is released upon sensing gastrin and secretin and it is actively inhibited by cholecystokinin [68]. The binding of leptin to its receptor activates the Janus kinase (JAK) signal transducer and activator of the transcription 3 (STAT3) signal transduction pathway, inducing cellular anti-apoptotic events, angiogenesis, and proliferation [69, 70]. The gene product also interacts with IL-1 and Notch cascade, which are involved in promoting tumor growth. Some other pathways activated are mitogen-activated protein kinases/extracellular signal-regulated kinases pathway (MAPK/ERK), phosphatidylinositol 3 kinase (PI3K), 5′AMP activated protein kinase (AMPK), and mTOR [71].

6. Leptin-related cellular pathways

After leptin binds to its receptor on the cell membrane, it acts by stimulating the following signaling pathways in the cell.

6.1 JAK2/ STAT3 signaling pathway

In the activation of this signaling pathway, leptin is activated by phosphorylation of its receptor, binding of STAT3, and phosphorylated by JAK2 [72]. Activated STAT3 enters the nucleus and binds to target sites on DNA; and so cellular activity takes place (**Figure 2**).

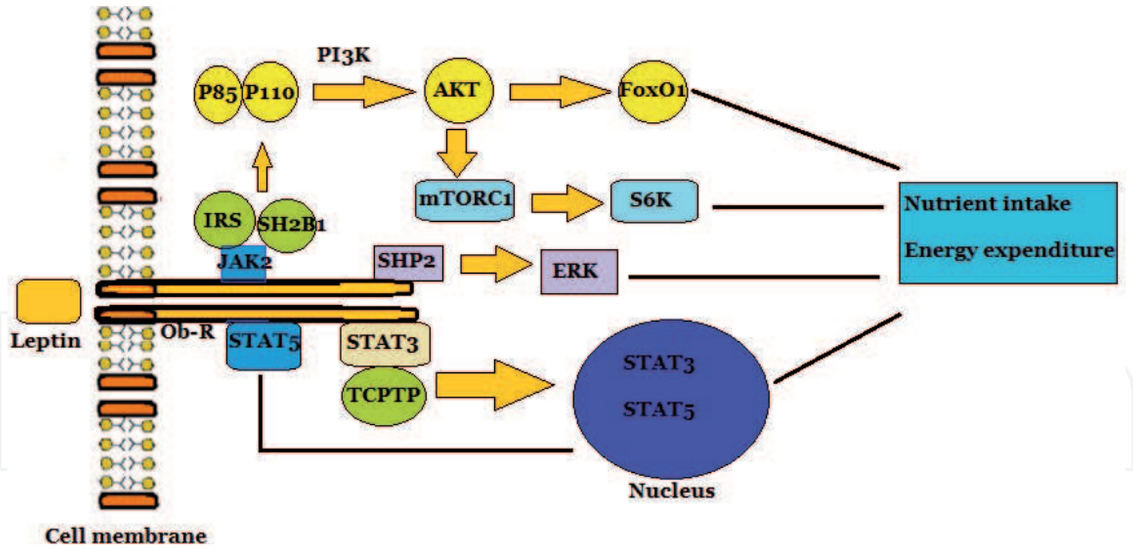

Figure 2.
Leptin signaling pathways. POMC;pro-opiomelanocortin, SOCS3; intracellular suppressor of cytokine signal 3, PTP1B; protein tyrosine phosphatase 1B, SHP2; tyrosine phosphatase 2, IRS; (insulin receptor substrate)/PI3K; (phosphoinositol 3 kinase), FoxO1; (forkhead box O1) and mTOR; (mammalian target of rapamycin), S6K; ribosomal S6 kinase, ERK; extracellular signal-regulated kinase [73].

6.2 SHP2/ERK signaling pathway

Stimulation of the leptin receptor activates the protein tyrosine phosphatase 2 (SHP2), contributing to the activation of the ERK signaling pathway, resulting in a cellular response [72, 74].

6.3 JAK2/STAT5 signaling pathway

As a result of the stimulation of the receptor, it provides activation of STAT5 by JAK2. Activated STAT5 acts by binding to the target region in the nucleus [75].

6.4 IRS/ PI3K Signaling pathway

Leptin also activates the IRS (insulin receptor substrate)/PI3K (phosphoinositol 3 kinase) pathway [76, 77] (**Figure 2**). The SH2B1 adapter protein mediates activation of the PI3K pathway by linking the JAK2 and IRS protein via the SH2 domain [78]. In addition, the IRS/PI3K pathway proceeds in two substeps, FoxO1 (forkhead box O1) and mTOR (the mammalian target of rapamycin) (**Figure 2**).

7. The relationship between leptin and oxidative stress

Oxidative stress results from an imbalance between reactive oxygen species (ROS) and the organism's antioxidant defense. Due to oxidative stress, peroxidative damage to macromolecules and membranes of cells occurs in organisms. Moreover, their metabolic activities in cell components are impaired. Known to tissue and organ pathologies occur in the presence of oxidative stress in the organism [79–86]. It has been reported that high leptin levels can induce the formation of ROS, mainly due to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation [87, 88]. However, leptin replacement therapy has also been shown to significantly downregulate NADPH oxidase expression in AT of leptin-deficient *ob/ob* mice [89]. This indicates that leptin has a protective role at normal levels.

Free radical-mediated peroxidation of membrane lipids loses its integrity, increasing membrane fluidity and permeability. The lipid peroxidation process is one of the oxidative conversions of PUFAs to products known as malondialdehyde (MDA). MDA is a highly toxic molecule and its secondary products such as thiobarbituric acid reactive agent are commonly used to assess lipid peroxidation [90–94]. Glutathione (GSH) is an important nonenzymatic component of the cellular antioxidant system and plays an important role in ROS antioxidation [95–97]. It has been suggested that leptin modulates the activity of various antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in patients with leptin gene mutations [98]. Leptin production is increased by overexpression of the endogenous antioxidant enzyme catalase and correlates with markers of oxidative stress and inflammatory in *ob/ob* mice [99]. In another study, enzymatic antioxidants including catalase and GSH levels were increased by leptin treatment in *ob/ob* mice, and leptin treatment decreased MDA levels in rats exposed to oxidative stress [100, 101]. It is noted that leptin treatment reverses the effect of streptozotocin (STZ)-induced diabetes by lowering glutathione and catalase levels and increasing lipid peroxidation [102, 103] It has been reported that defective antioxidant enzyme activity is recovered after leptin treatment in the plasma of humans with leptin gene mutations and ob/ob mice [97, 104]. They are most likely the result of the modulatory effect of leptin on metabolic and hormonal disorders. Recombinant leptin treatment leads to weight loss by reducing food intake and has a reducing effect on oxidative stress caused by a high-fat diet [105].

Hyperleptinemia is the most prominent feature of obesity and is likely to be involved in the pathogenesis of obesity-related pathologies [19]. Studies in obese individuals have shown a correlation between leptin levels and oxidative stress parameters such as nitric oxide (NO), superoxide anion (O_2^-.), peroxynitrite, MDA, hydroperoxides, protein carbonyl (PC) contents, GSH, and SOD [106–108]. Studies in which hyperleptinemia was induced by the administration of exogenous leptin in nonobese animals suggest that leptin increases the level of systemic oxidative stress [109, 110]. In addition, some *in vitro* studies have shown that in the presence of high leptin concentration, ROS production is stimulated by endothelial cells, inflammatory cells, and other cell types [111–113]. In another *in vitro* study, it was noted that leptin significantly decreased pro-oxidant biomarkers such as MDA and NO and increased antioxidant markers such as total antioxidant capacity (TAC), SOD, and GPx against cryopreservation-induced oxidative stress in rabbit embryos. It has been suggested that leptin can be used as an antiapoptotic and antioxidant promoter to support embryonic development *in vitro* under oxidative stress induced by cryopreservation [114]. In one study, treatment with high glucose caused an increase in oxidative stress in pheochromocytoma (PC12) cells with excessive ROS and MDA production and depletion of GSH content, however, leptin treatment caused a decrease in MDA and ROS levels and an increase in GSH content, resulting in hyperglycemic PC12 cells. It has been reported to significantly reduce the oxidative damage mediated by reactive oxygen species caused by the condition. Therefore, it was stated that leptin may have a protective effect against oxidative stress and apoptosis mediated by reactive oxygen species caused by the hyperglycemic state [115]. In addition, hypothalamic oxidative stress induces leptin resistance, which leads to the induction of insulin resistance and obesity. Activation of nuclear factor erythroid 2–related factor 2 (Nrf2) suppresses hypothalamic oxidative stress and improves leptin resistance in the hypothalamus [116].

8. The relationship between leptin and apoptosis

Recently, some studies have shown that there is an important relationship between leptin and apoptosis; such as in a study, it was determined that there is a

leptin receptor (Ob-R) on the surface of breast cancer cells. Leptin is thought to stimulate these cancer cells with various effects, such as migration and spread. It has been determined that the expression of Ob-R increases as the tumor grows [117]. Another study reported that leptin may affect the risk of breast cancer by increasing estrogen synthesis [118, 119]. It is believed that leptin, which is associated with breast cancer, exerts this effect by affecting the JAK/STAT and MAPK pathways, as well as increasing the transcriptional expression of vascular endothelial growth factor receptor-2 (VEGFR-2) and VEGF [120]. In another study, it was determined that the ratio between leptin and adiponectin is important in regulating the development of breast cancer [121]. Again, in some studies, it has been determined that leptin triggers cell proliferation by stimulating the MAPK pathway in breast cancer cells [122]. It has been observed that leptin also stimulates estrogen receptors via MAPK in breast cancer cells [123].

It has also been reported that leptin is associated with lung cancer. Ob-Ra and Ob-Rb were expressed on the surface of lung cancer cells. It has been determined that leptin plays a role in the development and progression of lung cancer as well as its migration [124, 125]. It has been reported that leptin also increases cytokine production by stimulating JAK/STAT3, PI3K/AKT, and MEK1/2 signaling pathways [126]. In a study, it was determined that the removal of leptin from the medium in non-small cell lung cancer cell lines inactivates the JAK/STAT3 and Notch signaling pathways, thus stopping cell proliferation and stimulating apoptosis (**Figure 3**) [128].

In some studies, leptin has been shown to stimulate cell proliferation and prevent apoptosis by activation of the PI3K/AKT signaling pathway in thyroid cancer cells [129, 130].

Leptin has been reported to be associated with liver cancer [131]. In one study, they reported elevated leptin levels in patients with hepatocellular carcinoma [132]. It has been determined that leptin increases liver fibrosis by stimulating transforming growth factor-β (TGF-β) synthesis and release. It has also been reported that leptin stimulates the production of a tissue inhibitor of metalloproteinase1 through the JAK/STAT pathway in hepatic stellate cells [133]. Leptin has also been reported to cause the proliferation of hepatocellular cancer cells by altering cyclin D1, *Bcl-2* (B-cell lymphoma-2)-related X protein (Bax), and apoptotic gene activity [134].

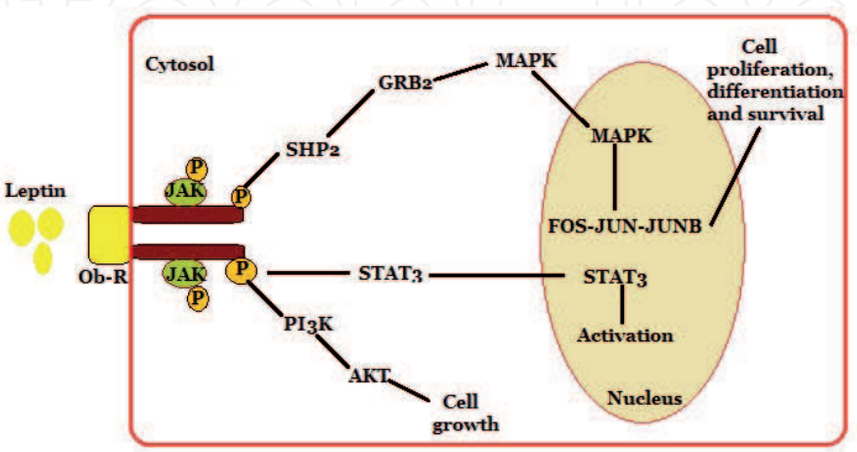

Figure 3.
Leptin signaling. AKT; protein kinase B, GRB2; growth factor receptor-bound protein 2, JAK; Janus kinase, Ob-R; leptin receptor, MAPK; mitogen-activated protein kinase, FOS, JUN, JUNB; GENES PI3K; phosphatidylinositol 3 kinase, SHP2; Src homology 2-containing tyrosine phosphatase, STAT3; signal transducer and activator of transcription 3 [127].

Another study demonstrated the presence of leptin receptors on the surface of human colon tumor cells [135]. In colorectal cancer, leptin acts as a very potent mitogen and antiapoptotic cytokine. It has been determined that leptin plays a role in many stages of this type of cancer [136, 137]. It has been reported that leptin increase is proportional to tumor development and tumor metastasis [138]. It has been determined that leptin exerts this effect via JAK and the extracellular signal-regulating kinase (ERK) pathway [139]. In another study, they found that leptin prevented apoptosis and stimulated cell proliferation via PI3K/AKT/mTOR pathways in colon cancer cells (**Figure 4**) [141].

In a study conducted in ovarian cancer, it was determined that leptin is directly related to PI3K/AKT signaling pathways, antiapoptotic proteins XIAP (X-linked inhibitor of apoptosis), and Bcl-XL. By activating these pathways, leptin has been reported to suppress cell proliferation and apoptosis [142]. In another study, it was determined that leptin administration to epithelial ovarian cancer cells increases cancer cell proliferation in a dose-dependent manner, and this increase is done by suppressing genes that inhibit cell proliferation [143].

An increase in leptin levels has been found to be associated with the development of prostate cancer [144]. It has been determined that leptin suppresses apoptosis in prostate cancer cells. Leptin has been reported to exert this effect via the MAPK and PI3K pathways [145]. It has also been reported that leptin stimulates the increase of (hypoxia-inducible factor 1), which is known to play an important role in carcinogenesis in prostate cancer cell culture and stimulates the spread and adhesion of these cells [146].

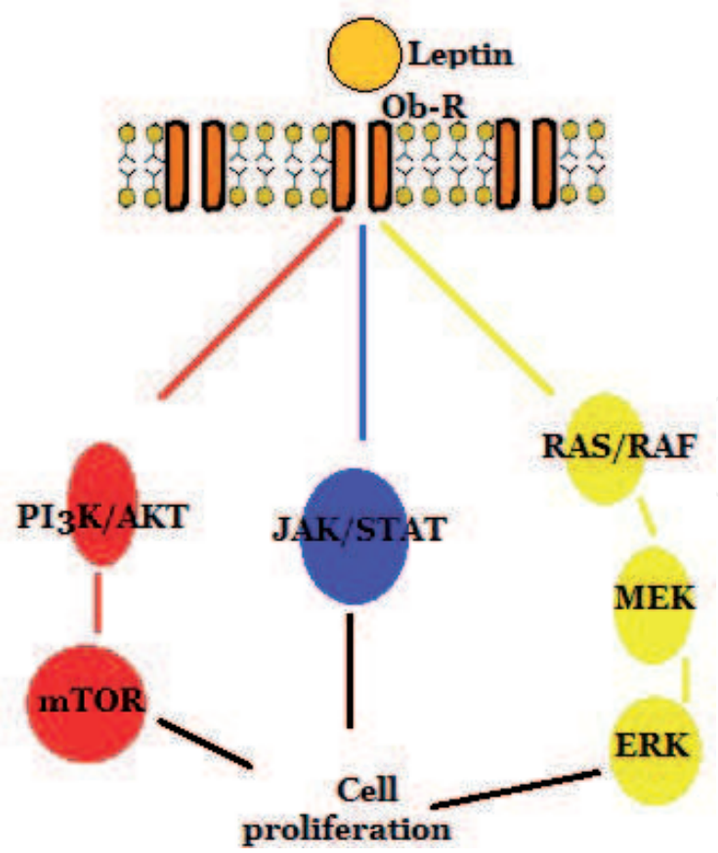

Figure 4.
Intracellular signaling pathways of leptin in connection with cellular proliferation. AKT: Protein kinase B/serine–threonine kinase, ERK: Extracellular signal-regulated kinase, JAK: Janus kinases, MAPK: Mitogen-activated protein kinase, MEK: Mitogen-activated protein kinase, mTOR: Mechanistic/mammalian target of rapamycin, Ob-R: Leptin receptor, PI3K: Phosphatidylinositol3-kinase, STAT: Signal transducer and activator of transcription [140].

9. Conclusion

In conclusion, leptin is adiponectin released from AT. As a result of studies, it has been reported that leptin is associated with oxidative stress and apoptosis, as well as regulating body energy metabolism and food intake. Knowing the release of leptin, its receptor, cellular effects, and especially the relationship between oxidative stress and apoptosis will guide various studies on this subject.

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