Anatomy & Physiology: Current Research
ISSN: 2161-0940

Ishola et al., Anat Physiol 2015, 5:2
DOI: 10.4172/2161-0940.1000173

Review Article Open Access

Leptin and Autophagy: When the Two Masters Meet

Peter Ishola[1], Elizabeth Greene[1], Phuong Nguyen[1], Walter Bottje[1], Mark Cline[2], Nicholas Anthony[1] and Sami Dridi[1]*,

[1]*Center of Excellence for Poultry Science, University of Arkansas, Fayetteville, AR 72701, USA*
[2]*Department of Animal and Poultry Sciences, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA*

Abstract

Autophagy or cellular self-digestion, a lysosomal degradation pathway that is conserved from yeast to human, plays a key role in recycling cellular constituents, including damaged organelles. It also plays a pivotal role in the adaptation of cells to a plethora of distinct stressors including starvation. Leptin is an adipocytokine that is mostly produced by white adipose cells in mammals and functions as a hormonal sensing mechanism to inhibit feed intake and increase energy expenditure. In this review, we will describe the autophagy and leptin systems and summarized recent advances regarding their interactions in the regulation of energy homeostasis.

Keywords: Leptin; Autophagy; Food intake; Energy homeostasis; Molecular mechanisms

Introduction

The hormone Leptin, also called obese hormone, is the central mediator in a negative feedback loop regulation of energy homeostasis. Mammalian adipocytes produce and secrete more leptin in bloodstream as fat storage increases [1] signalling the brain via leptin receptors [2-5] and modulating the feeding-related (an) orexgenic hypothalamic neuropeptide system to suppress appetite and increase energy expenditure [3-4]. Leptin gene and its related receptors are expressed in a wide range of tissues indicating various potential physiological functions. Leptin has been reported to play a key role in reproduction [6], immunity [5], bone mass [7], blood pressure [4], hematopoiesis [4], and lipid metabolism [3,4].

Hyperphagy, morbid obesity and diabetes were observed in rodents that were deficient in leptin (ob/ob mouse), or that lack certain isoform of leptin receptor (db/db mouse and fa/fa rat) [2,4,8,9]. Interestingly a dysfunctional autophagic activity has been observed in these obese models, suggesting a potential interaction between leptin and autophagy.

Autophagy is a highly conserved cellular mechanism that is responsible for the degradation and recycling of damaged organelles. It is also considered as an alternative to apoptosis in programmed cell death. In recent years though autophagy has appeared to play critical roles in several cellular functions and physiological processes including reproduction, development [10] immunity [11], inflammation [11] neurodegenerative diseases [12], cardiovascular diseases [5] , metabolic syndrome [13,14], and energy homeostasis [15].

There are three major types of autophagy; micro-, macro-autophagy, and chaperone-mediated autophagy [16-18]. Micro- and macro-authophagy can selectively engulf large structures such as mitochondria and endoplasmic reticulum (referred to as mitophagy or reticulophagy, respectively [17,18] or by non-selective mechanisms (e.g. bulk cytoplasm), whereas chaperone-mediated autophagy degrades only soluble proteins [18]. Micro-autophagy refers to the sequestration of cytosolic components directly by lysosomes through invaginations in their limiting membrane. However, macro-autophagy that we will address in the present review refers to the sequestration of material within an autophagosome, a unique double membrane cytosolic vesicle. Autophagosomes fuse with late endosomes and lysosomes, promoting the delivery of organelles, aggregated proteins and cytoplasm to the luminal acidic degradative milieu that enables their breakdown into constituent molecular building blocks that can be recycled by the cell [19]. In recent years, interaction between leptin and autophagy has been a focus of research interest. After a brief description of leptin and autophagy systems, we will review here studies on the biological interaction between leptin and autophagy in the regulation of energy homeostasis.

Leptin System

The ob (leptin) gene has been previously cloned and characterized in rodent and human by Friedman and co-workers [20]. It consists of three exons with the two coding regions separated by two introns. It was assigned to mouse chromosome 6 [21] and human chromosome 7q31.3 [21]. The ob product, leptin (derived from the Greek word "leptos" meaning lean) contains 167 amino acids (AA) and a 21 AA signal peptide cleaved during translocation into the microsome. The 16-kDa mature leptin circulates in serum both as a free and as a protein-bound entity. Mammalian white adipose tissue is the main site of ob gene expression and leptin secretion. Expression and secretion occur exclusively within the differentiated adipocytes [1,22]. Leptin, however, is also produced in several cell types in other organs. In fact, it is produced by gastric cells in the walls of the stomach [23], in follicular papilla cells of hair follicles [1], in osteoblasts [7], in the placenta [6], in skeletal muscle [1], in the brain [1], and in the pituitary [22]. Additionally, leptin has been localized in the ovary (granulosa and theca cells, corpora lutea, and interstitial gland) [6] and in the mammary gland [22]. Intriguingly, leptin has been shown to particularly be expressed in the liver of several non-mammalian oviparous species such as chicken [24,25], dunlin [26], thin-billed prions [24], fishes [26], amphibians [26] and reptiles [23].

Leptin exerts its function through its receptor Ob-R which is first

***Corresponding author:** Sami Dridi, Center of Excellence for Poultry Science, University of Arkansas, 1260 W. Maple Street, Fayetteville AR 72701, USA, Tel: 479-575-2583; E-mail: dridi@uark.edu

Received February 28, 2015; **Accepted** March 28, 2015; **Published** March 30, 2015

Citation: Ishola P, Greene E, Nguyen P, Bottje W, Cline M, et al. (2015) Leptin and Autophagy: When the Two Masters Meet. Anat Physiol 5: 173. doi:10.4172/2161-0940.1000173

identified in mouse choroids plexus by expression cloning techniques and then in human using infant total brain library [8]. It is a single transmembrane-spanning receptor and a member of the cytokine receptor superfamily that includes the gp130 signal-transducing component of the receptors for interleukin 6 (IL-6), granulocyte colony stimulating factor (G-CSF), and leukemia-inhibitory factor (LIF) [13]. The Ob-R extracellular domain consists of 816 AA and is followed by a 23-AA transmembrane domain and intracellular domain which varies in length from 30 to 303 AA, depending on alternative splicing. The alternate splicing of the Ob-R gene generates multiple variants of leptin receptor mRNA that encode at least six Ob-R (Ob-Ra,b,c,d,e and f) isoforms [4,5]. Ob-R is primarily expressed in the hypothalamus. It is particularly prominent in areas important in regulation of energy balance such as arcuate (ARC) and paraventricular (PVN) nucleus [4,5]. Expression of Ob-R was also detected at lower levels in a large number of peripheral tissues including skeletal muscle, heart, adrenals, kidney, adipose tissue, liver, pancreatic β cells and immune cells [22]. The short isoforms are expressed at higher levels in a variety of tissues and were elegantly reviewed by Friedman and Halaas [27]. The ubiquitous expression of leptin and its related receptors indicates that leptin may have several physiological roles. It is well established that leptin has potent food intake and body weight reducing effects in mammals [1,5] and this effect is mediated via the activation of POMC/CART and inhibition of NPY/AgRP neurons [5]. The molecular basis for stimulation of POMC gene expression likely involves Janus kinase and signal transducer and activator of transcription (JAK-STAT) activation [5,8] while the phosphoinositol 3-kinase (PI3K) pathway may play a specific role in the repression of NPY and AgRP gene expression by leptin [5,8]. Leptin has been reported to interact also with other hypothalamic peptides including orexin, melanocortin receptors (MCR), corticotropin releasing factor (CRF), glucagon-like peptide (GLP-1), ghrelin, cholecystokinin (CCK), and bombesin to regulate feeding behavior [1,27]. Leptin also increases energy expenditure [2,25,27], induces lipolysis, reduces lipogenesis [27], regulates reproduction [6], immunity [22], and bone mass [7].

Autophagy System

Autophay has been described as a highly conserved self-eating process during which cells degrade and recycle their own components (cytosol and organelles) within the lysosomes [28]. The word autophagy was coined from Greek Word "auto" which means self, and "phagein", meaning to eat. Autophagy, which is a unique morphological feature or process in a dyeing cell was often erroneously presumed to be a preceding pathway to cell death, but on the contrast, it has now been evidently and clearly clarified that, one of its major function is to fight the cell death and consequently keep it alive even when undergoing stressful and life-threatening conditions [29]. Autophagy is induced upon nutrient depletion or starvation, thereby leading to the response of more than 30 autophagy-related genes (Atg) [30]. However, how Atg proteins are regulated is still under investigation, but it's clear that all signals reporting on availability of carbon and nitrogen sources converge on the mTOR signaling pathway, and that, Atg proteins are downstream effectors of mTOR pathway [30,31]. There are three steps involved in formation of autphagosome, and the first is initiation, during which phagophore (outer mitochondrial membrane, plasma membrane, endoplasmic reticulum membrane, etc) undergo nucleation [19]. The second step undergoes elongation, cycling, expansion and closure, forming autophagosome [19]. The third and final step is referred to as maturation, which involves the advancement of autophagosome into amphiosome (fusion of autophagosome and endosome), which is acidic and hydrolytic vacuole. It is this hydrolytic vacoule that is ripe for degradation and recycling of nutrients [19].

Under fed (normal nutrient-energy) state, the nutrient sensor mechanistic target of rapamycin (mTOR) is activated and in turn phosphorylates ULK1 and thereby sequestering the ULK1-Atg13-FIP200 complex in an inactive state at the mTOR complex [32]. In contrast when nutrients are limited (e.g. during stress or starvation), the energy sensor AMPK is activated. AMPK activation inhibits mTOR activity leading to a reduced ULK1 phosphorylation and consequently releases the ULK1-Atg13-FIP200 complex from mTOR to the site of autophagosome formation and induction of autophagy. In the second step of autophagy, Beclin1 forms a lipid kinase complex with Vps15, Vps34 and Atg14 that phosphorylates phosphatidylinositol (PI) to form inositol-3-phosphate (PI3P) and is essential for induction of autophagy [33]. Accumulation of PI3P in specific sub-domains of the ER increases membrane curvature at the site of autophagosome formation. The elongation step involves two ubiquitin like reactions of the pre-autophagosomal structures. First, the ubiquitin-like protein Atg12 is conjugated to Atg5 by the action of Atg7 and Atg10 after which Atg16 multimerizes to form the Atg12-Atg5-Atg16 complex. Next, Atg4 cleaves soluble microtubule-associated protein light chain 3-I (LC3-I) to form the membrane-bound LC3-II [34]. Both of these two ubiquitin-like systems are required for elongation and closure of the phagophore. During maturation and fusion, autophagosomes will first fuse with endosomes then with lysosomes. Any mutation or loss of proteins important for formation of multivesicular bodies (MVBs) can lead to inhibition of maturation of autophagosomes [28]. Some genes involved in this step include UVRAG, a Beclin 1 interacting protein that recruits the fusion machinery on the autophagosomes. Another Beclin 1 interacting protein, Rubicon, also functions in the maturation of autophagosomes where it is thought to be a part of a distinct Beclin 1 complex containing Vps34, Vps15, and UVRAG that suppresses autophagosome maturation [35]. Working together, these steps complete the formation of the autolysosome and its lysis, that releases proteins and amino acids that can be used as an energy source during times of low energy availability or increased energy demand (stress) for the organism (Figure 1).

Interaction between Leptin and Autophagy in the Regulation of Energy Homeostasis

Since both leptin and autophagy are dysfunctional in obese models and both are implicated in the regulation of lipid metabolism, increasing studies investigating the leptin-autophagy interaction have received considerable attention over the last few years. Activation of hypothalamic mTOR has been shown to regulate feeding behavior and energy homeostasis [2,25] and mTOR pathway has been shown to be a downstream effector of leptin and upstream regulator of autophagy [36]. Leptin, mTOR and autophagy are all regulated by starvation and nutritional state [36]. In addition, appetite, energy expenditure and metabolism are tightly regulated by the central nervous system (CNS) particularly the POMC and AgRP neurons in the hypothalamic arcuate nucleus. These neurons act as major negative (anorexigenic) and positive (orexigenic) regulators of feed intake. In 2012, three recent studies have implicated CNS autophagy in the regulation of energy homeostasis. Conditional specific depletion of Atg7 in POMC neurons resulted in higher body weight, hyperphagia, impaired glucose tolerance, increased adiposity and leptin resistance [37]. Moreover, deficient Atg7 in hypothalamic POMC neurons impaired leptin-induced signal transducer and activation of transcription 3 activation. In line with these data, Malhotra and coworkers [38], recently showed

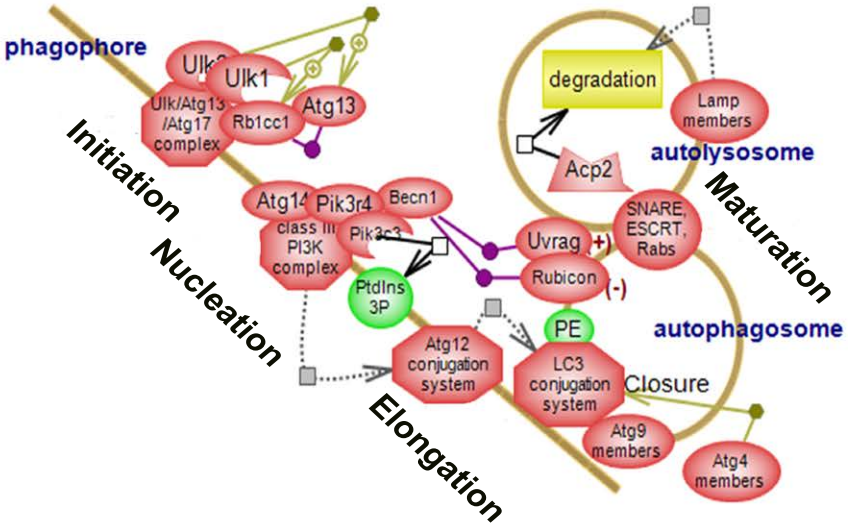

Figure 1: Steps of autophagosome formation: Autophagosome formation can be initiated via mTOR inhibition or AMPK activation during starvation or nutrient limitation. This results in the activation of ULK1 which in turn phosphorylates Atg13, Atg101 and FIP200. When autophagy is activated, Beclin 1 is liberated from Bcl-2 and is associated with Vps34, Vps15 and Atg14. ULK1 phosphorylates also AMBRA, a component of the PI3K CIII complex enabling it to relocate from the cytoskeleton to the isolation membrane. The activation of Vps34 generates PI3P which catalyzes the first of two types of ubiquitination-like reactions that regulates membrane elongation. Firstly, Atg5 and Atg12 are conjugated to each other in the presence of Atg7 and Atg10. Attachment of the Atg5-Atg12-Atg16L1 complex on the isolation membrane induces the second complex to covalently conjugate PE to LC3 which facilitates in turn the closure of the isolation membrane. The complex Atg9-Atg2-atg18 cycles between endosomes, the Golgi and the phagophore possibly carrying lipid components for membrane expansion. LC3-II is formed by LC3 conjugation to its lipid target PE and Atg4 removes LC3-II from the outer surface of newly formed autophagosome, and LC3 on the inner surface is degraded when the autophagosome fuses with lysosomes. Atg, autophagy-related genes; LC3, microtubuleassociated protein light chain; PE, phosphatidylethanolamine; PI3K, phosphatidylinositol 3 kinase; PIP3, phosphatidylinositol 3-phosphate; ULK1, UNC51-like kinase 1. The figure was produced by the Pathway Studio software from Ariadne/Elsevier and is used by permission of the Rat Genome Database [47].

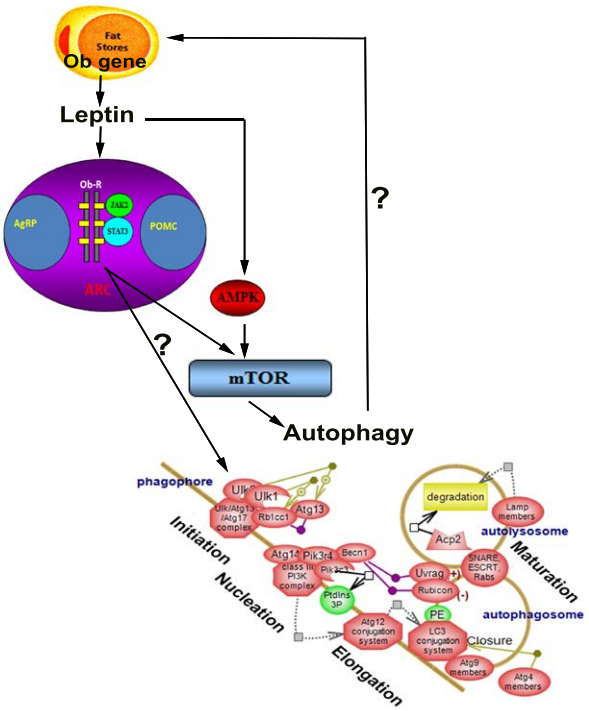

Figure 2: Potential model of leptin-autophagy interaction in the regulation of energy homeostasis. Leptin is secreted from adipocytes, binds to the extracellular domain of its Ob-Rb receptor dimmer and activates the JAK2 tyrosine kinase and STAT3. In ARC neurons that coexpress Ob-Rb and POMC/CART, leptin increases POMC production via STAT3, which 17 generates an anorectic signal via α-MSH and MCR3/4. In ARC neurons that co-express Ob-Rb and NPY/AgRP, leptin inhibits AgRP production partly through STAT3 pathway, which disinhibits melanocortin signaling. Additionally, leptin can act through IRS-PI3K pathway. Leptin can alter autophagy directly via JAK-STAT, AMPK-mTOR or via other downstream signaling cascades that are not known yet. Whether autophagy alters the leptin expression in peripheral tissues directly or indirectly is unknown and warrant further investigations. AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; ARC, arcuate nucleus; JAK2, janus kinase 2; mTOR, mechanistic target of rapamycin; Ob gene, obese gene; OB-R, leptin receptor; POMC, pro-opiomelanocortin.

that upon high-fat diet consumption mice lacking Atg12 in POMC-positive neurons exhibit accelerated weight gain, adiposity and glucose intolerance which is associated with increased food intake and decreased leptin sensitivity. Interestingly, mice lacking Atg5 in POMC neurons do not exhibit these phenotypes observed in Atg7 and Atg12 deficient mice [38].

These results indicated that autophagy-related genes might exert different physiological function depending on tissue or cell type. Kaushik et al. [39] proposed that autophagosome-mediated form of secretion in POMC neurons controls energy homeostasis by regulating α-MSH production. The same group demonstrated a role for autophagy in hypothalamic agouti-related peptide (AgRP) neurons in the regulation of food intake and energy balance [40]. They showed that starvation-induced hypothalamic autophagy mobilizes neuronintrinsic lipids to generate endogenous free fatty acids which in turn regulate AgRP levels. Depletion of Atg7 in hypothalamic AgRP neurons promotes neuronal lipid accumulation, reduced AgRP levels, feed intake and adiposity [40]. Plasma leptin levels have been reported to be altered in Zmpste24-null mice, which show accelerated aging and exhibit an extensive basal activation of autophagy [41]. Mice with specific deletion of Atg7 in adipocytes exhibited markedly decreased plasma concentration of leptin [42]. In vitro treatment with recombinant leptin inhibited autophagy in human CD4(+)CD25(-) conventional (T conv) T cells and this effect was mediated via mTOR activation [43]. However, leptin knockdown attenuated hypoxic-preconditioning-induced autophagy in bone marrow derived mesenchymal stem cells [44] indicating that the effect of leptin on autophagy might be tissue- and cell-specific. Enteral leptin administration has also been shown to inhibit intestinal autophagy in piglets [28]. In heart, however, leptin promoted autophagosome formation as evidenced by increased LC3-II, beclin 1 and Atg5 expression [45]. Malik and co-workers reported that peripheral administration of recombinant leptin induced autophagy in peripheral tissues including skeletal muscle, liver and heart [2]. Moreover, leptin stimulated autophagy in cultured human and mouse cell lines and this effect was likely mediated through the activation of AMPK and inhibition of mTOR [46,47].

Together these elegant studies suggest that the interaction between the two masters leptin and autophagy underscore a novel link that plays a crucial role in the regulation of energy balance and many other cellular processes (Figure 2).

References

1. Trayhurn P, Bing C (2006) Appetite and energy balance signals from adipocytes. Philos Trans R Soc Lond B Biol Sci 361: 1237-1249.
2. Malik SA, Mariño G, BenYounès A, Shen S, Harper F, et al. (2011) Neuroendocrine regulation of autophagy by leptin. Cell Cycle 10: 2917-2923.
3. Cassy S, Picard M, Crochet S, Derouet M, Keisler DH, et al. (2004) Peripheral leptin effect on food intake in young chickens is influenced by age and strain. Domest Anim Endocrinol 27: 51-61.
4. Beltowski J (2006) Leptin and atherosclerosis. Atherosclerosis 189: 47-60.
5. Anthony RM (2004) Recent Progress in Hormone Research: Cardiovascular Endocrinology & Obesity. Endocrine Society.
6. Archanco M, Muruzábal FJ, Llopiz D, Garayoa M, Gómez-Ambrosi J, et al. (2003) Leptin expression in the rat ovary depends on estrous cycle. J Histochem Cytochem 51: 1269-1277.
7. Williams GA, Callon KE, Watson M, Costa JL, Ding Y, et al. (2011) Skeletal phenotype of the leptin receptor-deficient db/db mouse. J Bone Miner Res 26: 1698-1709.
8. Sandowski Y, Raver N, Gussakovsky EE, Shochat S, Dym O, et al. (2002) Subcloning, expression, purification, and characterization of recombinant human leptin-binding domain. J Biol Chem 277: 46304-46309.
9. Shell ER (2002) The Hungry Gene: The Inside Story of the Obesity Industry. Grove Press.
10. Kanninen TT, de Andrade Ramos BR, Witkin SS (2013) The role of autophagy in reproduction from gametogenesis to parturition. Eur J Obstet Gynecol Reprod Biol 171: 3-8.
11. Levine B, Kroemer G (2008) Autophagy in the pathogenesis of disease. Cell 132: 27-42.
12. Radad K, Moldzio R, Al-Shraim M, Kranner B, Krewenka C, et al. (2015) Recent advances in autophagy-based neuroprotection. Expert Rev Neurother 15: 195-205.
13. Chaudhari N, Talwar P, Parimisetty A, Lefebvre d'Hellencourt C, Ravanan P (2014) A molecular web: endoplasmic reticulum stress, inflammation, and oxidative stress. Front Cell Neurosci 8: 213.
14. Yorimitsu T, Nair U, Yang Z, Klionsky DJ (2006) Endoplasmic reticulum stress triggers autophagy. J Biol Chem 281: 30299-30304.
15. Zarzynska JM (2014) The importance of autophagy regulation in breast cancer development and treatment. Biomed Res Int 2014: 710345.
16. Fader CM, Colombo MI (2009) Autophagy and multivesicular bodies: two closely related partners. Cell Death Differ 16: 70-78.
17. Mizushima N, Ohsumi Y, Yoshimori T (2002) Autophagosome formation in mammalian cells. Cell Struct Funct 27: 421-429.
18. ÄŒesen MH, Pegan K, Spes A, Turk B (2012) Lysosomal pathways to cell death and their therapeutic applications. Exp Cell Res 318: 1245-1251.
19. Mehrpour M, Botti J, Codogno P (2012) Mechanisms and regulation of autophagy in mammalian cells. Atlas Genet Cytogenet Oncol Haematol 16: 165-182.
20. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, et al. (1994) Positional cloning of the mouse obese gene and its human homologue. Nature. 372: 425-32.
21. Isse N, Ogawa Y, Tamura N, Masuzaki H, Mori K, et al. (1995) Structural organization and chromosomal assignment of the human obese gene. J Biol Chem 270: 27728-27733.
22. Muhammad AH (2006) Leptin: fights against obesity. Pakistan J Physiol 2: 54-60.
23. Muruzábal FJ, Frühbeck G, Gómez-Ambrosi J, Archanco M, Burrell MA (2002) Immunocytochemical detection of leptin in non-mammalian vertebrate stomach. Gen Comp Endocrinol 128: 149-152.
24. Quillfeldt P, Everaert N, Buyse J, Masello JF, Dridi S (2009) Relationship between plasma leptin-like protein levels, begging and provisioning in nestling thin-billed prions Pachyptila belcheri. Gen Comp Endocrinol 161: 171-178.
25. Bhagwat VM, Ramachandran BV (1975) Malathion A and B esterases of mouse liver-I. Biochem Pharmacol 24: 1713-1717.
26. Dridi S, Raver N, Gussakovsky EE, Derouet M, Picard M, et al. (2000) Biological activities of recombinant chicken leptin C4S analog compared with unmodified leptins. Am J Physiol Endocrinol Metab 279: E116-123.
27. Gambardella C, Gallus L, Ravera S, Fasulo S, Vacchi M, et al. (2010) First evidence of a leptin-like peptide in a cartilaginous fish. Anat Rec (Hoboken) 293: 1692-1697.
28. Friedman JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395: 763-770.
29. Słupecka M, Woliński J, Gajewska M, Pierzynowski SG (2014) Enteral leptin administration affects intestinal autophagy in suckling piglets. Domest Anim Endocrinol 46: 12-19.
30. Mizushima N, Yoshimori T, Levine B (2010) Methods in mammalian autophagy research. Cell 140: 313-326.
31. Lipinski MM, Hoffman G, Ng A, Zhou W, Py BF, et al. (2010) A genome-wide siRNA screen reveals multiple mTORC1 independent signaling pathways regulating autophagy under normal nutritional conditions. Dev Cell 18:1 041-1052.
32. Jung CH, Ro SH, Cao J, Otto NM, Kim DH (2010) mTOR regulation of autophagy. FEBS Lett 584: 1287-1295.
33. Kim J, Kundu M, Viollet B, Guan KL (2011) AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk. Nat Cell Biol 13: 132-141.

34. Vergne I, Deretic V (2010) The role of PI3P phosphatases in the regulation of autophagy. FEBS Lett 584: 1313-1318.

35. Mizushima N, Yoshimori T (2007) How to interpret LC3 immunoblotting. Autophagy 3: 542-545.

36. Ravikumar B, Sarkar S, Davies JE, Futter M, Garcia-Arencibia M, et al. (2010) Regulation of mammalian autophagy in physiology and pathophysiology. Physiol Rev 90: 1383-1435.

37. Chi H (2012) Regulation and function of mTOR signalling in T cell fate decisions. Nat Rev Immunol 12: 325-338.

38. Zhou Y, Rui L (2013) Leptin signaling and leptin resistance. Front Med 7: 207-222.

39. Malhotra R, Warne JP, Salas E, Xu AW, Debnath J (2015) Loss of Atg12, but not Atg5, in pro-opiomelanocortin neurons exacerbates diet-induced obesity. Autophagy 11: 145-154.

40. Kaushik S, Arias E, Kwon H, Lopez NM, Athonvarangkul D, et al. (2012) Loss of autophagy in hypothalamic POMC neurons impairs lipolysis. EMBO Rep 13: 258-265.

41. Kaushik S, Rodriguez-Navarro JA, Arias E, Kiffin R, Sahu S, et al. (2011) Autophagy in hypothalamic AgRP neurons regulates food intake and energy balance. Cell Metab 14: 173-183.

42. Mariño G, Ugalde AP, Salvador-Montoliu N, Varela I, Quirós PM, et al. (2008) Premature aging in mice activates a systemic metabolic response involving autophagy induction. Hum Mol Genet 17: 2196-2211.

43. Zhang Y, Goldman S, Baerga R, Zhao Y, Komatsu M, et al. (2009) Adipose-specific deletion of autophagy-related gene 7 (atg7) in mice reveals a role in adipogenesis. Proc Natl Acad Sci U S A 106: 19860-19865.

44. Cassano S, Pucino V, La Rocca C, Procaccini C, De Rosa V, et al. (2014) Leptin modulates autophagy in human CD4+CD25- conventional T cells. Metabolism 63: 1272-1279.

45. Wang L, Hu X, Zhu W, Jiang Z, Zhou Y, et al. (2014) Increased leptin by hypoxic-preconditioning promotes autophagy of mesenchymal stem cells and protects them from apoptosis. Sci China Life Sci 57: 171-180.

46. Kandadi MR, Roe ND, Ren J (2014) Autophagy inhibition rescues against leptin-induced cardiac contractile dysfunction. Curr Pharm Des 20: 675-683.

47. Shimoyama M, De Pons J, Hayman GT, Laulederkind SJ, Liu W, et al. (2015) The Rat Genome Database 2015: genomic, phenotypic and environmental variations and disease. Nucleic Acids Res 43: D743-750.