**Autophagy regulation by adiponectin and associated mechanism**

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**Abstract**

Adiponectin is a multifunctional adipocytokine produced predominantly by adipocytes，with potent anti-inflammatory, insulin-sensitizing, and cardiovascular protective properties. A decrease in the circulating level of adiponectin has been linked to insulin resistance, type 2 diabetes, atherosclerosis, and metabolic syndrome. Autophagy is a highly conserved homeostatic cellular mechanism that mediates the degradation of damaged organelles, protein aggregates and invading pathogens through a lysosome-dependent pathway. Accumulating evidence demonstrated that adiponectin performs different biological functions via the regulation of autophagy. Consequently, this review is aiming to elucidate the biological responses and the potential mechanisms underlying autophagy induction by adiponectin. Understanding the association and mechanism between adiponectin and autophagy is essential for developing new diagnostic biomarkers and identifying new therapeutic targets in related diseases.

**Keywords:** Adiponectin; Adiponectin Receptors; Autophagy

**Introduction**

Adiponectin has been generally considered a healthy adipokine with positive metabolic effects, such as insulin-sensitizing, anti-inflammatory, anti-tumor activity as well as cardiovascular protective functions. Accumulating evidence demonstrated that adiponectin and its binding receptors play an important role in regulating autophagy.

Autophagy is a highly conserved homeostatic cellular mechanism that mediates the degradation of damaged organelles, protein aggregates, and invading pathogens through a lysosome-dependent pathway. The dysregulation of autophagy has been considered as an attribute of a variety of pathologic conditions, including cancer，neurodegenerative disorders, and metabolic diseases[1]. Recent research showed that inhibition of autophagy significantly reduced the degradation of lipid droplets in brown adipose tissue in mice with autophagy-associated proteins knockdown[2]. Adiponectin-induced autophagy in skeletal muscle cells alleviated ER stress and insulin resistance, indicating that adiponectin mediates anti-diabetic effects in an autophagy-dependent manner[3]. There is evidence suggesting that globular adiponectin induces Beclin-1 phosphorylation, inhibiting Beclin-1/Bcl-2 association and mediates the induction of autophagy in macrophages [4].

 Herein, we describe the role of adiponectin and its binding receptors on the process of autophagy and involved molecular signaling pathways. We hope to provide a better understanding of the relationship between adiponectin and autophagy mediation, which may contribute to the discovery of new therapeutic agents for the treatment of related diseases.

**Adiponectin and Adiponectin Receptors**

Adiponectin is an adipokine secreted primarily by white adipose tissue, also known as AdipoQ , apM1 and GBP28[5]. It is a 30-kDa complement C1q-related protein with a globular C-terminal domain and a collagenous N-terminal domain, usually circulates in oligomeric complexes as trimers, hexamers, and multimers[5, 6]. Adiponectin plays important role in the regulation of a variety of molecular and cellular events, including maintaining energy homeostasis, lipid metabolism, insulin sensitivity, immune response and inflammation[7].

Adiponectin carries out its pleiotropic functions through two widely expressed receptors, AdipoR1 and AdipoR2, found in skeletal muscle, liver, and endothelial cells[8]. AdipoRon has been identified as the first orally active adiponectin receptor agonist with the ability to activate AMPK and bonding AdipoR1 and AdipoR2[9]. The function of these receptors varies depending on the target tissue. In this review, we highlight the relationship between Adiponectin/AdipoRs and autophagy modulation and its biological effects.

**Adiponectin and Autophagy induction**

Mounting evidence supports that autophagy plays a critical role in maintaining cellular homeostasis in response to intracellular stress, including oxidative stress, inflammation and endoplasmic reticulum stress. Impairment of autophagy results in further aggravation of diabetes-related metabolic disorders in insulin target tissues, including the liver, skeletal muscle and adipose tissue, as well as in pancreatic β-cells[10, 11]. There has been increasing evidence demonstrating that adiponectin, which generally presents positive metabolic effects, plays a critical in autophagy regulation in various types of cells or tissue, thus exerting different biological effects. A study showed that adiponectin inhibits high glucose-induced angiogenesis of RF/6A cells by inhibiting autophagy[12]. It is reported that adiponectin receptor PAQR-2 signaling acts as a regulator linking low temperature with autophagy to promote C. elegans longevity[13]. Autophagy induction would be one of the key mechanisms for the modulation of the various biological responses by adipokines. We will discuss the role of adiponectin on autophagy induction in different cells or tissue respectively and elucidate the underlying mechanism.

***Effects of adiponectin in inflammation modulation during autophagy induction***

Adipose tissue is an endocrine organ that secretes adipokines and hormones, many of which are involved in inflammation, glucose homeostasis and lipid metabolism. At present, evidence proved that autophagy could affect lipid metabolism in adipose tissue and regulate cellular energy and nutrient storage.

Collective evidence indicated the prominent role of autophagy in regulating inflammation. There is evidence revealed that autophagic flux is an important mechanism for various beneficial biological responses by adiponectin[14]. Accumulating evidence has indicated that the anti-inflammatory effects by globular adiponectin can be mediated by the induction of autophagy. For instance, globular adiponectin has been shown to suppressed lipopolysaccharide (LPS)-primed inflammasomes activation and production of active IL-1β and pyroptosis in murine peritoneal macrophages through the modulation of autophagy and AMPK signaling[15]. In addition, inhibition of autophagy in adipocytes was associated with significant up-regulation of adiponectin expression and a decrease of pro-inflammatory markers [16]. A previous study showed that defects of autophagy genes such as Atg3 and Atg16L1 in fully differentiated adipocytes cause inflammation, insulin resistance the dysfunction of mitochondria[17]. Autophagy is critical for lipid accumulation and adipocyte differentiation factors[18]. Moreover, autophagy proteins Atg3 and Atg16L1 are required for proper mitochondrial function in mature adipocytes, post-developmental ablation of autophagy causes peripheral insulin resistance independently of diet or adiposity[17]. Adiponectin possesses cell-protective properties. Adipocyte-specific Atg5 knockouted mice had increased circulating levels of adiponectin and were resistant to alcohol-induced adipose atrophy and liver injury[19]. Study showed that Beclin-1 phosphorylation and Bcl-2 mRNA destabilization are critical for the suppression of inflammatory mediators by gAcrp in macrophages. The interaction between Beclin-1 and Bcl-2 is considered a critical step in the regulation of autophagy induction, and inhibition of such an interaction is a plausible mechanism for the initiation of autophagy. Furthermore, adiponectin induced autophagy activation via Bcl-2 mRNA destabilization in macrophages[20]. In order to elucidate the effects of globular adiponectin(gAcrp) on the Beclin-1/Bcl-2 association and its underlying mechanisms, a study determined the effects of gAcrp on Beclin-1 phosphorylation and Bcl-2 mRNA stability, and investigated their role in the suppression of inflammatory mediators. The results demonstrated that gAcrp suppress LPS-stimulated inflammatory by inhibiting the formation of Beclin-1 and Bcl-2 complexes and induced autophagy in macrophages[4]. Adiponectin exhibits protective effects against hepatotoxicity, further study showed that ER stress acts as signaling event leading to the inflammasome activation in hepatocytes. Moreover, gAcrp significantly suppressed expression of ER stress marker genes in vitro, demonstrated that gAcrp protects hepatocytes against cell death by modulating ER stress and the inflammasome activation, at least in part, via autophagy induction[21].

These findings not only elucidate the physiological role of adiponectin in the modulation of inflammasomes but also provide novel insight into the molecular mechanisms underlying the relationship between autophagy and inflammasomes activation. Adiponectin potently suppresses inflammatory mediator production. Based on the previous reports, it is well established that autophagy induction plays a crucial role in anti-inflammatory responses by adiponectin，and study of the modulatory effect of adiponectin on the inflammasome would be a novel area for treatment of inflammatory diseases.

***Effects of adiponectin on autophagy induction via regulating AMPK signaling pathway***

As is known that AMP-activated protein kinase (AMPK) is a central regulator of energy homeostasis. Evidence showed that in many cases autophagy induced by adiponectin is related to AMPK signaling pathway. Autophagy dysregulation is implicated in various diseases, including type 2 diabetes, renal damage and myocardial injury, deficiency in autophagy is associated with metabolic disorders. Regulated autophagy is a critical component for a healthy skeletal muscle mass. Globular adiponectin activates autophagy in myoblasts and promotes myoblast survival and apoptosis via an AMPK-dependent mechanism[22].

Cardiomyocytes autophagy is essential for maintaining cardiac function. Evidence showed that decreased myocardial autophagic flux resulted in cardiomyocyte death and cardiac dysfunction. AdipoRON is proved to be a cardioprotective molecule, deficiency of ADIPOQ, markedly increases MI-R injury. Hypoadiponectinemia impairs autophagic flux, contributing to enhanced MI-R injury in the diabetic state. ADIPOR activation restores AMPK-mediated autophagosome formation and antioxidant-mediated autophagosome clearance, representing a novel intervention effective against MI-R injury in diabetic conditions[23]. A study confirmed that adiponectin up-regulated autophagic flux via promoting AMPK phosphorylation. Adiponectin deficiency could aggravate the decrease of myocardial AMPK phosphorylation level, autophagic flux and cardiac function, while exogenous adiponectin could reverse the decline of AMPK phosphorylation level and autophagic flux and eventually reduce cardiomyocyte death[24]. In vitro and in vivo studies demonstrate that AdipoRon promotes autophagic flux through activation of AMPK/ULK1 pathway, thus inhibiting renal fibrosis[25]. A previous study showed that adipose tissue specifically secretes autophagy protein Becn1，and then facilitates the secretion of adiponectin[26]. Furthermore, Becn1 regulates systemic AMPK activity and insulin sensitivity by promoting adiponectin secretion [27]. In addition, adiponectin knockout(Ad-KO) mice induce insulin resistance and autophagy, when fed with exogenous adiponectin, the expression of autophagy-related gene LC3-II and Beclin1 upregulated. In vitro, adiponectin could enhance autophagic flux in cultured muscle cells in an AMPK-dependent manner. Taking together, these studies demonstrated that adiponectin stimulated skeletal muscle autophagy and alleviates HFD-induced insulin resistance and metabolic dysfunction in skeletal muscle[28]. In vitro study showed that AdipoRon upregulated LC3-II/LC3-I level and down-regulated the protein level of p62 of multiple myeloma cells, at the same time significantly inhibited the proliferation and increase the expression levels of apoptosis-related proteins of MM cell lines. Besides, AdipoRon upregulated p-AMPK and its downstream p-ACC in MPC-11. AdipoRon, an adiponectin receptor agonist, can inhibit myeloma cell proliferation and induce apoptosis, and AMPK/autophagy pathway may be one of its mechanisms[9]. Evidences showed that the antiapoptotic effect of gAPN in chondrocytes was related to gAPN-induced autophagy by increased formation of Beclin-1 and LC3B and P62 degradation, indicating that global adiponectin (gAPN) possesses antiapoptotic properties by induce autophagy. In this study, the authors demonstrate that gAPN induced a high expression of p-AMPK accompanying with a high expression of Beclin-1 and LC3-Ⅱ in chondrocytes. Further more, the application of the inhibitor of AMPK, significantly blocked the gAPN-induced autophagy in chondrocytes[29].

In order to investigate the therapeutic value and the molecular mechanism of AdipoRon, an adiponectin receptor agonist, on the chondrocytes calcification, Duan, Z. X., et al. reported that AdipoRon induced autophagy of chondrocytes in vitro, and eventually decreased calcification and ALP activity. However, these activity were blocked by were blocked by AMPK inhibitor[30]. Epidemiological studies have indicated that low levels of circulating plasma AdipoQ portend poor prognosis in patients with breast cancer. What’s more, elevated expression levels of AdipoQ in breast tissue are correlated with advanced stages of the disease. A study showed that globular adiponectin increased the expression levels of microtubule-associated protein 1 light chain 3 beta (LC3B)-II and intracellular LC3B puncta, which are indicators of autophagosome formation, suggesting autophagic induction by gAd, thus promoing invasive cell morphology and significantly increased the migration and invasion abilities of breast cancer cells[31]. In consistent with the above study, Chung, S.J., et al. reported that ADIPOQ/adiponectin induces a robust accumulation of autophagosomes in breast cancer cells, and significantly inhibits breast cancer growth and induces apoptosis both in vitro and in vivo. AMPK-inhibition abrogates ADIPOQ/adiponectin-induced ULK1-activation, LC3B-turnover and SQSTM1/p62-degradation while AMPK-activation potentiates ADIPOQ/adiponectin’s effects[32]. Collectively, these data presented that ADIPOQ/adiponectin induces autophagic cell death in breast cancer through modulation of the STK11/LKB1 and AMPK-ULK1 axis.

***Effects of adiponectin on autophagy induction via regulating oxidative stress and ER stress***

Oxidative stress in cardiac myocytes is an important pathogenesis of cardiac lipotoxicity. Adiponectin (APN) is reported to become a potential cardioprotective molecule，studies showed that the mechanism may related to modulation of mitochondrial function or ER stress. A study showed that globular adiponectin (gAcrp) significantly increased the expression of various ER stress markers in macrophages, and inhibition of ER stress prominently suppressed gAcrp-induced autophagy[33]. It is reported that exogenous APN pretreatment inhibited ER stress and activated autophagy via AMP-activated protein kinase (AMPK) activation and protected HL-1 cardiomyocytes against apoptosis[34]. Another study demonstrated that Exogenous administration of APN significantly reduced oxidative stress and increased the expression of anti‑oxidative enzyme, resulting in the stimulation of autophagy, inhibition of apoptosis and reduced brain tissue injury[35].

Evidence showed that Globular CTRP9 (gCTRP9) , a newly identified adiponectin paralog, increased the ratio of LC3II/I and the expression of ATG5 which was vital to the formation of autophagosomes and decreased the level of P62. Moreover, gCTRP9 reestablished the loss of mitochondrial membrane potential, suppressed ROS generation, and reduced myocyte death. These results suggest that adiponectin paralog protect against oxidative stress-mediated damage in cardiomyocytes through enhancing autophagy[36]. Shi, W., et al. demonstrated that globular adiponectin up-regulated the expression of autophagy related protein while inhibiting the expression of NAD(P)H-quinone oxidoreductase 1(NQO1), heme oxygenase-1 (HO-1) and superoxide dismutase (SOD) in the testes of diabetic mice, suggesting that globular adiponectin may produce the protective effect on the testes of diabetic mice by inducing autophagy and inhibiting ER stress and oxidative stress[37]. The above two studies suggest that globular adiponectin may induced autophagy both in vivo and in vitro. However, the relationship between globular adiponectin and ER stress seems to be different.

To make a conclusion, adiponectin may have protective effect on different tissue, and he mechanism greatly related to inducing autophagy via modulation of oxidative stress and ER stress.

**Selective Form of autophagy induced by Adiponectin**

Accumulating studies demonstrated that adiponectin targets specific forms of autophagy, including mitophagy, lipopagy and endoplasmic reticulum autophagy(ER-phagy). We will elaborate the association and the underlying mechanism involved as following.

The elimination of damaged mitochondria is essential for ensuring efficient energy supply and maintaining mitochondrial quality. Mitochondrial autophagy (mitophagy), characterized by selectively excludes damaged mitochondria via a specific autophagic pathway, is one of the catabolic processes by which dysfunctional mitochondria are degraded[38]. It has also proved to be crucial for mitochondrial quality control as well as moderating mitochondrial homeostasis, and showed to play a critical role in cell protection [39, 40]. Emerging evidence show that adiponectin participate in modulate insulin responsiveness, through regulation of mitophagy and play a beneficial role in maintaining mitochondrial homeostasis, but the mechanism remains unknown. Evidence showed that adiponectin induced mitophagy and attenuated subsequent diabetic lung IR injury by improving lung functional recovery in type 2 diabetic rats，by suppressing oxidative damage, diminishing inflammation, decreasing cell apoptosis, and preserving mitochondrial function[41]. Another study demonstrated that chronic intermittent hypoxia causes disturbances of genioglossal mitophagy, while supplementation of exogenous adiponectin alleviated the damage of mitochondrial structure and function via increasing mitophagy[42]. In vitro study demonstrated that APN pretreatment suppressed the over-production of ROS by activating the Nrf2/HO-1 pathway, suppressed H2O2-induced mitophagy and partially inhibited the colocalization of mitochondria with autophagosomes/lysosomes. In addition, APN downregulates the transcript levels of both Bax and Bax/Bcl-2 protein induced by oxidative stress[43]. These findings suggest that APN has a moderate regulatory role in oxidative stress-induced mitophagy and suppresses apoptosis. Howerer, the interactions between autophagy and oxidative stress should also be further investigated. Globular adiponectin upregulated mitophagy while reduced the rate of hepatocyte apoptosis induced by intermittent hypoxia [44]. In summary, we can infer that adiponectin may protect against tissue damage via upregulate mitophagy. However, concrete mechanism remains to be further explored.

 Lipophagy is a selective form of autophagy characterized by selective degradation of lipid droplets (LDs). Evidence suggests that lipophagy may play a key role in lipid homeostasis. Increased lipophagy could be effective to decrease abnormal lipid accumulation that leads to insulin resistance and β-cell impairment by removing ectopic LDs[45]. While disturbances in lipophagy have been linked to NAFLD and hepatic TG accumulation, liver steatosis, obesity, atherosclerosis[46, 47]. A recent study also confirm this point of view. In their study, lipophagy deficiency was observed in the tubular cells of patients with diabetic nephropathy(DN) and db/db mice, which was accompanied by significantly ectopic lipid deposition(ELD), oxidative stress, apoptosis. Intrestingly, they find that these damages were ameliorated as the levels of lipophagy was increased by AdipoRon administration, while the effects were blocked partially by AdipoR1 siRNA, autophagy inhibitor and enhanced by AMPK activator[48]. The results indicated that AdipoRon has the potential to reduce intrarenal lipotoxicity-associated renal injury in DN through increasing lipophagy by activating AdipoR1/AMPK pathway.

 Endoplasmic reticulum autophagy(ER-phagy) is another selective form of autophagy. ER-phagy is a process that enabling protein and lipid synthesis, ion homeostasis, quality control of newly synthesized proteins and organelle communication via constant ER turnover and modulation[49]. A study suggests that globular adiponectin upregulated ER-phagy to extenuate ER stress, and mitigated H9C2 cardiomyocytes apoptosis induced by CIH through AMPK activation[50]. Studies showed that disruption of adiponectin signalling mimics perturbed or inadequate nutrient intake, triggers catabolic processes such as selective form of autophagy, including selective ER-phagy and lipophagy, to access and mobilize internal nutrient stores, enhances survival and promotes longevity in C. elegans[51].

**Conclusions and perspectives**

In summary, adiponectin was generally considered as a healthy adipocytokine because of its anti-inflammatory properties, anti-apoptosis, favorable effects on intermediary metabolism, cardiovascular protection, renal or liver protection. Accumulating evidence have showed that adiponectin has multi-biological effects on a wide variety of metabolic pathways many of which are mediated via autophagy induction. Inflammation response，AMPK activation, Oxidative stress and ER stress and related signaling pathways are the main routes in which adiponectin may be effective to modulate the process of autophagy. However, most of the current research were focused on molecular or cellular biological reaction. It will be important to determine the precise mechanisms via which adiponectin/adipoRs regulate autophagy and the potential physiological functions in vivo and in vitro. Better understanding of the regulation of autophagy by adiponectin and the mechanism could be an interesting target in preclinical and clinical studies for metabolic diseases and cancer.

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The author contributed solely to the article.

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