**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. Decreasing adiponectin has been proved to promote metabolic syndrome. Autophagy is a lysosome-dependent self-degradative process that mediates the degradation of damaged organelles, invading pathogens and protein aggregates, thus maintaining cellular homeostatic. 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 necessary for identifying new therapeutic targets of related diseases.

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

**Introduction**

Adiponectin has been generally considered as 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 lysosome-dependent self-degradation process, through mediating the degradation of damaged organelles, invading pathogens and protein aggregates, hence maintaining cellular homeostatic. The dysregulation of autophagy has been considered as an attribute of varieties of pathologic conditions, including cancer，neurodegenerative disorders, and metabolic diseases[1]. Recently, evidence showed that inhibition of autophagy significantly reduced the degradation of lipid droplets in brown adipose tissue in mice with autophagy-associated proteins knockdown[2]. Another research displayed that adiponectin induced autophagic flux in skeletal muscle cells, and diminished insulin resistance by alleviating ER stress, indicating that adiponectin mediates anti-diabetic effects in an autophagy-dependent manner[3]. Furthermore, there is evidence suggesting that globular adiponectin induces Beclin-1 phosphorylation, inhibiting Beclin-1/Bcl-2 combination and mediates the induction of autophagy in macrophages [4]. Herein, we describe the function 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 interrelation between adiponectin and autophagy mediation, which may provide novel therapeutic directions for the treatment of related diseases.

**Adiponectin and Adiponectin Receptors**

Adiponectin is an adipokine primarily secreted 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 in the manner of trimers, hexamers, and multimers[5, 6]. Adiponectin plays important role in the regulation of multiple molecular and cellular events, including maintaining energy homeostasis, lipid metabolism, insulin sensitivity, immune response and inflammation[7].

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

**Adiponectin and Autophagy induction**

A bounding evidence manifested that autophagy plays a critical role in maintaining cellular homeostasis and ease intracellular stress, including inflammation response, oxidative stress, and endoplasmic reticulum stress. Some evidence revealed that impairment of autophagy results in exacerbated of diabetes-related metabolic disorders in insulin target tissues, including the liver, adipose tissue and skeletal muscle, as well as pancreatic β-cells[10, 11]. There has been increasing evidence indicating 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 via suppression of autophagy[12]. Taken together, accumulating evidence have indicated that autophagy may possibly be one of the key mechanisms for the modulation of the various biological responses by adiponectin/adipoRs. Accordingly, we will discuss the role of adiponectin on autophagy regulation in different cells or tissue respectively and elucidate the underlying mechanism.

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

Adipose tissue is an know as endocrine organ that capable of secreting adipokines and hormones, many of which are involved in inflammation, glucose homeostasis and lipid metabolism. At present, there is evidence pointed out that autophagic flux is an important mechanism for various beneficial biological responses by adiponectin[13]. For example, autophagy could affect lipid metabolism in adipose tissue and regulate cellular energy and nutrient storage[2]. Furthermore, multiplied evidence suggest that the anti-inflammatory effects by globular adiponectin can be mediated by the induction of autophagy. For instance, globular adiponectin suppressed lipopolysaccharide-primed inflammasomes activation and generation of active IL-1β in murine peritoneal macrophages through up-regulated of autophagy and active AMPK signaling[14]. On the contrary, inhibition of autophagy in adipocytes was associated with significant up-regulation of adiponectin expression and a decreased of pro-inflammatory markers [15]. A previous study showed that defects of autophagy related genes such as Atg3 and Atg16L1 in fully differentiated adipocytes cause inflammation, insulin resistance the dysfunction of mitochondria. Moreover, Atg3 and Atg16L1 are required for proper mitochondrial function in mature adipocytes, yet post-developmental ablation of autophagy causes peripheral insulin resistance regardless of diet or adiposity[16]. To make a conclusion, evidence proved that autophagy is critical for lipid accumulation and adipocyte differentiation factors[17].

Adiponectin is generally considered to possess cell protective properties. For example, adipocyte-specific gene Atg5 knockouted mice had increased circulating levels of adiponectin and protect against alcohol-induced adipose atrophy and liver injury[18]. Moreover, some evidence showed that adiponectin carried out cell-protective and anti-inflammation properties via inhibition of autophagy. In vitro study showed that globular adiponectin contribute to Beclin-1 phosphorylation and Bcl-2 mRNA destabilization in macrophages, and exert anti-inflammatory effect. The interaction between Beclin-1 and Bcl-2 is regarded as a critical step in the regulation of autophagy induction, inhibition of such an interaction is a plausible mechanism for the initiation of autophagy. In consistent with the above research, another study showed that adiponectin caused Bcl-2 mRNA destabilization and consequently activate autophagy in macrophages[19]. Apart from this, a study further determined the effects of globular adiponectin on Beclin-1 phosphorylation and Bcl-2 mRNA stability, and investigated their role in the suppression of inflammatory mediators. Interestingly and consistent with expectations, the results demonstrated that globular adiponectin suppress inflammation response 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. For instance, globular adiponectin significantly suppressed expression of ER stress marker genes, and promote inflammasome activation hence protects hepatocytes against cell death by autophagy induction, indicating that adiponectin possess hepatocyte protection at least in part, via autophagy induction[20].

Adiponectin potently suppresses the production of inflammatory mediator. Based on the previous reports, it is well established that adiponectin promote autophagy induction via inhibition of inflammatory responses and thus exhibit cell protective properties. Further study of the modulatory effect of adiponectin on the inflammasome would be a novel area for treatment of inflammatory related 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 responsible for various diseases, including type 2 diabetes, myocardial injury and renal damage, deficiency in autophagy is associated with metabolic disorders. Otherwise, regulated autophagy is a critical component for a healthy skeletal muscle mass.

Cardiomyocytes autophagy is vital for maintaining cardiac function. Evidence showed that decreased myocardial autophagic flux resulted in cardiac dysfunction and cardiomyocyte death. In contrast, activates autophagy by globular adiponectin in myoblasts and promotes myoblast survival and apoptosis via an AMPK-dependent mechanism[21]. A study confirmed that adiponectin increase autophagic flux via promotion of AMPK phosphorylation. While adiponectin deficiency could aggravate the down-regulation of myocardial AMPK phosphorylation, autophagic flux and cardiac function. In contrast, exogenous administration of adiponectin reverse the decline of AMPK phosphorylation and autophagic flux and eventually reduce cardiomyocyte death[22]. AdipoRon, as an adiponectin receptor agonist, is potent to inhibit myeloma cell proliferation and induce apoptosis, and AMPK/autophagy pathway may be one of its mechanisms[9]. Besides, AdipoRON is proved to be a cardioprotective molecule, deficiency of ADIPOQ, markedly increases myocardial ischemia-reperfusion(MI-R) injury. A report showed that hypoadiponectinemia in diabetic model impairs autophagic flux, and consequently enhance MI-R injury. Additionally, ADIPOR activation restores AMPK-mediated autophagosome formation and antioxidant-mediated autophagosome clearance, manifesting a novel intervention effective against MI-R injury in diabetic conditions[23]. In vitro studies demonstrated that AdipoRon promotes autophagic flux through activation of AMPK/ULK1 pathway, thus inhibiting renal fibrosis[24]. A previous study showed that adipose tissue specifically secretes autophagy protein Becn1，and then facilitates the secretion of adiponectin[25]. Furthermore, Becn1 regulates AMPK activity and improves insulin sensitivity by promoting adiponectin secretion [26]. 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, the study demonstrated that adiponectin stimulated skeletal muscle autophagy and alleviates HFD-induced insulin resistance and metabolic dysfunction in skeletal muscle[27]. Moreover, 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. Evidences showed that globular adiponectin induced autophagy in chondrocytes by increased formation of Beclin-1 and LC3B and P62 degradation, hence exhibit antiapoptotic effect, indicating that global adiponectin possesses antiapoptotic properties by induce autophagy. In this study, the authors demonstrate that global adiponectin 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 global adiponectin induced autophagy in chondrocytes[28].

AdipoRon is know as an adiponectin receptor agonist. In order to investigate its therapeutic value and the molecular mechanism on the chondrocytes calcification, an in vitro study investigate the effect on autophagy by AdipoRon in chondrocytes, eventually found that adiponRon decreased calcification and ALP activity by promoting autophagy. However, these activites were blocked by AMPK inhibitor[29]. Epidemiological studies revealed that patients with breast cancer generally have low levels of AdipoQ in circulating, which indicate poor prognosis. What’s more, elevated expression of AdipoQ in breast tissue are close associated with advanced stages of the disease. Moreover, another study showed that globular adiponectin up-regulated microtubule-associated protein 1 light chain 3 beta (LC3B)-II and intracellular LC3B puncta, which are indicators of autophagosome formation, suggesting adiponectin contribute to autophagic induction, hence promoting the migration and invasion abilities of breast cancer cells[30]. In consistent with the above study, Chung, S.J., et al. reported that ADIPOQ/adiponectin induces accumulation of autophagosomes in breast cancer cells, and evidently inhibits breast cancer growth and induces apoptosis. Otherwise, AMPK-inhibition abrogates ADIPOQ/adiponectin-induced ULK1-activation, LC3B-turnover and p62-degradation yet AMPK-activation reverse those effects[31]. These data presented that ADIPOQ/adiponectin induces autophagic in breast cancer through modulation of AMPK-ULK1 axis. Collectively, these evidence suggested that autophagy modulation by adiponectin is possibly via the AMPK signaling pathway.

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

Adiponectin is reported to possess cardioprotective properties, studies showed that the mechanism may related to modulation of mitochondrial function or ER stress. ER stress promotes cardiac lipotoxicity in cardiac myocytes. A study showed that globular adiponectin (gAcrp) significantly up-regulate the expression of various ER stress markers in macrophages, inhibition of ER stress prominently suppressed gAcrp-induced autophagy[32]. It is reported that pretreatment of exogenous APN inhibited ER stress and activated autophagy, therefore protected cardiomyocytes against apoptosis via AMPK activation [33]. Similarly, another study showed that exogenous administration of adiponectin significantly reduced oxidative stress and increased the expression of anti‑oxidative enzyme, resulting in autophagy stimulation, hence inhibiting apoptosis and diminish brain tissue injury[34].

Globular CTRP9 (gCTRP9) , a newly identified adiponectin paralog, is proved to increased the ratio of LC3II/I and upregulate autophagy related gene ATG5, and decreased the level of P62, which were vital to the formation of autophagosomes. Moreover, gCTRP9 restored 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[35]. 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, heme oxygenase-1 and superoxide dismutase in the testes of diabetic mice, suggesting that globular adiponectin exhibit protective effect on diabetic mice by inhibiting oxidative stress and ER stress and inducing autophagy [36]. 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. However, the detailed mechanism still needs to be explored.

**Selective Form of autophagy induced by Adiponectin**

Adiponectin targets specific forms of autophagy, including mitophagy, lipopagy and endoplasmic reticulum autophagy(ER-phagy). Herin, we will elucidate the association and the underlying mechanism involved as following.

The elimination of damaged mitochondria is critical for ensuring 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[37]. 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 [38, 39]. 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. Further evidence showed that adiponectin promote mitophagy and improving lung functional recovery in type 2 diabetic rats, and suppressing oxidative damage, decreasing inflammation response, diminishing cell apoptosis, and preserving mitochondrial function[40]. 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[41]. In vitro study demonstrated that adiponectin suppressed the over-production of ROS through activating the Nrf2/HO-1 pathway, suppressed H2O2-induced mitophagy and partially inhibited the colocalization of autophagosomes/lysosomes with mitochondria. Otherwise, adiponectin downregulates the expression of both Bax and Bax/Bcl-2 protein induced by oxidative stress[42]. These findings suggest that APN moderately regulate oxidative stress-induced mitophagy and suppresses apoptosis. Like wise, globular adiponectin upregulated mitophagy while reduced the rate of hepatocyte apoptosis induced by intermittent hypoxia [43]. In summary, we can infer that adiponectin may protect against tissue damage via upregulate mitophagy and concrete mechanism remains to be further explored.

Lipophagy is another selective form of autophagy with the characteristic of selectively degradation of lipid droplets (LDs). Evidence suggests that lipophagy is beneficial in maintaining lipid homeostasis. Increased lipophagy is potent to decrease abnormal lipid accumulation by removing ectopic LDs, thus alleviating insulin resistance and β-cell impairment [44]. While disturbances in lipophagy have been linked to NAFLD and hepatic TG accumulation, obesity, liver steatosis as well as atherosclerosis[45, 46]. A recent study also confirm this point of view. The authors reported to observe lipophagy deficiency in the tubular cells of patients with diabetic nephropathy and db/db mice, which was accompanied by significantly ectopic lipid deposition, oxidative stress, apoptosis. Interestingly, hey find that AdipoRon administration moderated these damages by increase lipophagy, yet the effects were blocked partially by AdipoR1 siRNA, autophagy inhibitor and enhanced by AMPK activator[47]. The results indicated that AdipoRon has the potential to reduce intrarenal lipotoxicity-associated renal injury through up regulate lipophagy by activating AdipoR1/AMPK pathway.

Endoplasmic reticulum autophagy(ER-phagy) is known as another selective form of autophagy. ER-phagy is a process that enabling protein and lipid synthesis, ion homeostasis and organelle communication via constant ER turnover and modulation[48]. A study suggests that globular adiponectin upregulated ER-phagy to alleviate ER stress, and attenuated H9C2 cardiomyocytes apoptosis induced by CIH through AMPK activation[49]. Studies showed that interruption of adiponectin signalling pathway mimics perturbed or inadequate nutrient intake, triggers catabolic processes like selective form of autophagy, including ER-phagy and lipophagy, to acquire and mobilize internal nutrient stores, enhances survival and promotes longevity in C. elegans[50].

**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. Up till now, evidence 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 pathways by 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 significant to determine the precise mechanisms via which adiponectin/adipoRs regulate autophagy and the potential physiological functions. 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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