Regulatory Mechanisms of Adiponectin and Its Receptors on Lipid Metabolism Signal Transduction Pathways: Postprint

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Abstract

Adiponectin (AdipoQ) is a cytokine secreted by adipose tissue that plays an important role in regulating lipid metabolism in livestock and poultry. AdipoQ primarily regulates signaling pathways such as adenosine monophosphate-activated protein kinase α (AMPKα), p38 mitogen-activated protein kinase (p38MARK), and peroxisome proliferator-activated receptor α (PPARα) by binding to two receptors, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), thereby participating in lipid metabolism pathways in the organism. Currently, research on adiponectin-mediated lipid metabolism signaling pathways has made certain progress. This article reviews the structure of adiponectin and its receptors, as well as the regulatory mechanisms of adiponectin and its receptors on lipid metabolism.

Full Text

Regulation Mechanism of Adiponectin and Its Receptors on Lipid Metabolism Signal Transduction Pathways

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Abstract

Adiponectin (AdipoQ) is a cytokine secreted by adipose tissue that plays an important role in regulating lipid metabolism in livestock and poultry. AdipoQ primarily exerts its effects by binding to two receptors—adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2)—to regulate signaling transduction pathways including adenosine 5’ -monophosphate-activated protein ki-

nase α (AMPKα), p38 mitogen-activated protein kinase (p38MAPK), and peroxisome proliferator-activated receptor α (PPARα), thereby participating in lipid metabolism pathways. Research on AdipoQ-mediated lipid metabolism signaling transduction pathways has made considerable progress. This review summarizes the structures of AdipoQ and its receptors, as well as the regulatory mechanisms of lipid metabolism mediated by AdipoQ and its receptors.

Keywords: adiponectin; adiponectin receptor; lipid metabolism; signal transduction pathway

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Adipose tissue functions as an endocrine organ that plays a crucial role in regulating various metabolic processes. Adiponectin (AdipoQ) is a cytokine secreted by adipose tissue that exists in multiple forms in plasma and exerts diverse biological functions primarily through binding to adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). Through circulatory, paracrine, and autocrine mechanisms, AdipoQ acts on target tissues involved in lipid metabolism, including the liver, skeletal muscle, and adipose tissue, thereby regulating and maintaining lipid homeostasis. This regulatory function is achieved through two main mechanisms: promoting fatty acid oxidation and inhibiting fatty acid synthesis. While numerous studies have reported on AdipoQ' s role in promoting fatty acid oxidation, relatively few have focused on its inhibitory effects on fatty acid synthesis. Given that AdipoQ and its receptors are indispensable for regulating lipid metabolism in livestock and poultry, this review examines the structures of AdipoQ and its receptors, along with their mechanisms for regulating lipid metabolism.

1.1 Structure of AdipoQ

AdipoQ, also known as GBP28, Acrp30, and apM1, exhibits slight variations in amino acid number across species. Rhesus monkey AdipoQ consists of 243 amino acids, while human, rat, chicken, and canine AdipoQ each contain 244 amino acids, and mouse AdipoQ comprises 247 amino acids. AdipoQ contains four structural domains: an N-terminal signal peptide, an N-terminal non-helical functional region, a collagen domain, and a C-terminal globular domain. Following post-translational modifications, AdipoQ forms eight different homologous proteins. As a member of the collagen superfamily, AdipoQ circulates in plasma in three forms: low-molecular-weight (LMW) trimers, medium-molecular-weight (MMW) hexamers, and high-molecular-weight (HMW) polymers, with the polymeric forms being the primary physiologically active configurations. Notably, Ramachandran et al. found that the polymeric forms of chicken AdipoQ differ from those in mammals, existing predominantly as polymers larger than 669 kDa in both plasma and adipose tissue, whereas mammalian AdipoQ simultaneously exists as three distinct polymeric forms. Full-length adiponectin (fAd) and globular adiponectin (gAd) represent the two active forms of AdipoQ, each exerting distinct biological effects.

1.2 Structure of AdipoQ Receptors

AdipoQ primarily functions through two receptors, AdipoR1 and AdipoR2, which were first identified in 2003 when Yamauchi et al. extracted their cDNA from Ba/F3 cells using genetic engineering techniques. AdipoR1 and AdipoR2 are isoforms with 67.5% protein sequence homology and high structural similarity. Both are transmembrane proteins containing seven transmembrane domains, but their topology is opposite to that of G protein-coupled receptor families, with the N-terminus located intracellularly and the C-terminus extracellularly. The homology of human and mouse AdipoR1 and AdipoR2 genes reaches 96.80% and 95.52%, respectively.

T-cadherin (T-cad) represents another AdipoQ receptor discovered by Hug et al. in 2004. T-cadherin can bind to MMW hexamers and HMW polymers of AdipoQ but not to LMW trimers or the globular domain. Lacking a transmembrane region, T-cadherin attaches to the cell membrane via glycosylphosphatidylinositol (GPI) and belongs to the GPI-anchored protein family. T-cadherin is expressed in various tissues, with the highest expression levels observed in the cardiovascular system.

2 Regulation of Lipid Metabolism Signaling Pathways by AdipoQ and Its Receptors

AdipoQ and its receptors play a vital role in regulating lipid metabolism in animals, primarily by modulating fatty acid oxidation and synthesis pathways. AdipoQ receptors interact with several key proteins in lipid metabolism pathways, including adaptor protein containing PH domain, PTB domain and leucine zipper motif 1 (APPL1), receptor for activated C kinase 1 (RACK1), casein kinase 2 (CK2), and endoplasmic reticulum protein 46 (ERp46), thereby mediating AdipoQ' s regulatory effects on lipid metabolism.

2.1.1 APPL1 APPL1, composed of 709 amino acids, was the first adaptor protein identified to bind AdipoQ receptors and mediate their functions. APPL1 contains multiple regulatory modules, including a BAR (bin-amphiphysin-rvs domain), PH (pleckstrin homology domain), and PTB (phosphotyrosine-binding domain). As a signaling molecule involved in mediating various cellular signaling pathways, APPL1 regulates glucose homeostasis and lipid metabolism upon binding to AdipoQ receptors. The interaction between AdipoQ and the C-terminus of AdipoR facilitates subsequent binding between the N-terminus of AdipoR and the PTB domain of APPL1, thereby modulating the activity of downstream molecules in the AdipoQ signaling pathway. Additionally, the interaction between APPL1 and AdipoR enhances the phosphorylation of downstream signaling molecules such as AMPK and p38MAPK, accelerating fatty acid oxidation in skeletal muscle and promoting GLUT4 translocation to the cell membrane and glucose uptake.

2.1.2 RACK1 RACK1 is an intracellular adaptor protein with a molecular weight of 36 kDa that contains seven WD40 repeat sequences, enabling it to regulate protein-protein interactions and integrate information from different signaling pathways. RACK1 was identified as another protein that directly binds AdipoR1 after APPL1, though the specific binding site remains unclear. However, studies using RNAi technology to knock down RACK1 in HepG2 cells demonstrated that reduced adaptor protein levels inhibited downstream signaling pathways of AdipoQ, suggesting that RACK1 plays a significant role in AdipoQ-mediated glucose metabolism in hepatocytes.

2.1.3 CK2 CK2 is a serine/threonine protein kinase composed of two catalytic subunits and two regulatory subunits that plays an important role in cellular regulation. CK2 was identified as the third adaptor protein capable of binding AdipoR1. Genetic studies in knockout mice have shown that as long as one CK2 catalytic subunit remains, metabolic activities proceed normally. In other words, compared with other genotypes, knockout mice exhibit altered lipid metabolism, indicating that CK2 plays a role in regulating lipid metabolism.

2.1.4 ERp46 ERp46 is another adaptor protein that interacts with AdipoR1, in addition to APPL1, RACK1, and CK2. Research has shown that ERp46 can inhibit the interaction between AdipoQ and AdipoR1 in HeLa cells, thereby regulating the AdipoQ signaling pathway. Inhibition of ERp46 expression leads to decreased endocytosis of AdipoR1, causing AdipoR1 to accumulate on the cell membrane surface. However, following AdipoQ stimulation, AMPK phosphorylation is enhanced, suggesting that AdipoQ-mediated metabolism may be influenced by ERp46.

2.2.1 Regulation of Fatty Acid Oxidation Pathway by AdipoQ Studies have demonstrated that AdipoQ is associated with obesity, type II diabetes, and metabolic syndrome in humans and other mammals, highlighting its important role in lipid metabolism. In various tissues, AdipoQ participates in lipid metabolism and promotes fatty acid oxidation through pathways involving AdipoR, APPL1, AMPKα, p38MAPK, and PPARα. Upon binding of AdipoQ to the C-terminus of AdipoR, APPL1 is recruited, enhancing phosphorylation of downstream signaling molecules such as AMPKα and p38MAPK. Phosphorylated AMPKα inhibits the nuclear factor-kappa B (NF- B) and phosphatidylinositol 3-kinase (PI3K) pathways while promoting lipolysis. Activated p38MAPK stimulates the PPARα pathway, accelerating fatty acid oxidation in skeletal muscle. Yamauchi et al. found that in skeletal muscle, both fAd and gAd can stimulate AMPKα phosphorylation, whereas in hepatocytes, only fAd can stimulate AMPKα phosphorylation—even high doses of gAd have no effect on AMPKα phosphorylation in liver cells. AdipoQ regulates fatty acid oxidation by activating AMPK, which mediates lipid metabolism signaling pathways through PPARα elements. PPARα is a nuclear receptor whose target genes include multiple lipid metabolism-related genes. PPARα promotes expression of fatty acid

transport protein (FATP) and fatty acid translocase (FAT/CD36) to enhance fatty acid transmembrane transport and is essential for transcription of fatty acid oxidation genes. Therefore, AdipoQ-mediated activation of PPARα may promote fatty acid oxidation. In skeletal muscle, reduced malonyl-CoA content also contributes to AdipoQ-regulated AMPKα activation and phosphorylation.

2.2.2 Regulation of Fatty Acid Synthesis Pathway by AdipoQ In addition to promoting fatty acid oxidation, AdipoQ can inhibit fatty acid synthesis through pathways mediated by AdipoR1, liver kinase B1 (LKB1), AMPKα, and sterol regulatory element-binding protein 1c (SREBP-1c). Using leptin receptor knockout mice, Awazawa et al. confirmed AdipoQ' s role in hepatic lipid metabolism and elucidated that AdipoQ suppresses SREBP-1c expression through AdipoR1-mediated activation of AMPKα. SREBP-1c participates in fatty acid synthesis and helps maintain stable lipid content in non-adipose tissues. In their experiments, Awazawa et al. first administered recombinant AdipoQ via intraperitoneal injection to mice and observed significantly reduced SREBP-1c expression in the liver after 4 hours. After 8 hours, the mRNA expression levels of acetyl-CoA carboxylase α (ACCα) and stearoyl-CoA desaturase-1 (SCD1) also began to decrease. These inhibitory effects of recombinant AdipoQ were independent of serum insulin and glucose concentrations. The researchers further investigated which receptor—AdipoR1 or AdipoR2—mediates SREBP-1c suppression, concluding that AdipoQ inhibits SREBP-1c expression through its functional receptor AdipoR1. AdipoQ binding to AdipoR1 activates AMPKα, which suppresses SREBP-1c expression in hepatocytes. Conversely, disruption of LKB1, the primary upstream kinase of AMPKα, abolishes AMPKα phosphorylation in hepatocytes and increases the content of lipogenic genes, demonstrating that AdipoQ inhibits fatty acid synthesis through AdipoR1/LKB1/AMPKα signaling pathways to regulate lipid metabolism.

As a multifunctional adipokine, AdipoQ plays crucial roles in the body through binding to its receptors. While significant progress has been made in understanding AdipoQ signaling transduction pathways, many questions remain, particularly regarding lipid metabolism regulation. Further investigation into the mechanisms by which AdipoQ regulates lipid metabolism signaling pathways will not only facilitate artificial intervention in animal production but also hold important implications for disease treatment.

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Note: Figure translations are in progress. See original paper for figures.