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Review paper

New advances of adiponectin in regulating obesity and related metabolic syndromes

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ABSTRACT

Obesity and related metabolic syndromes have been recognized as important disease risks, in which the role of adipokines cannot be ignored. Adiponectin (ADP) is one of the key adipokines with various beneficial effects, including improving glucose and lipid metabolism, enhancing insulin sensitivity, reducing oxidative stress and inflammation, promoting ceramides degradation, and stimulating adipose tissue vascularity. Based on those, it can serve as a positive regulator in many metabolic syndromes, such as type 2 diabetes (T2D), cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), sarcopenia, neurodegenerative diseases, and certain cancers. Therefore, a promising therapeutic approach for treating various metabolic diseases may involve elevating ADP levels or activating ADP receptors. The modulation of ADP genes, multimerization, and secretion covers the main processes of ADP generation, providing a comprehensive orientation for the development of more appropriate therapeutic strategies. In order to have a deeper understanding of ADP, this paper will provide an all-encompassing review of ADP.

1. Introduction

Along with economic development and changes in people's lifestyles, obesity and its associated metabolic diseases have become increasingly serious global public health issues. Obesity is a chronic metabolic disease caused by numerous factors, characterized by an excessive accumulation and an abnormal distribution of fat, and therefore weight gain. According to some studies, obesity has been linked to an increased risk of type II diabetes (T2D), cardiovascular illness, hypertension, certain cancers, and Alzheimer's disease (AD) [1]. The estimated global prevalence of diabetes among individuals aged 20–79 was 10.5% (536.6 million people) in 2021, with a projected increase to 12.2% (783.2 million) in 2045 [2]. Concurrently, the prevalence of non-alcoholic fatty liver disease (NAFLD) has risen from 24% in 1991–2006 to 38% in 2021, with a predicted continued increase. Obesity and T2D are closely linked to a higher risk of NAFLD [3]. According to a serial cross-sectional analysis of US adults aged 20–44 years, the age-adjusted prevalence of hypertension within this group was 9.3% in 2009–2010 and increased to 11.5% in 2017–2020. Over the same period, obesity prevalence rose significantly from 32.7% to 40.9%, while hyperlipidemia prevalence decreased from 40.5% to 36.1% [4].

Dysregulation of adipocytokines such as adiponectin (ADP), leptin, and resistin is a crucial cause of obesity and related metabolic disorders. Among those factors, ADP shows beneficial regulatory effects on obesity and associated metabolic syndromes, including coordinating adipose tissue expansion and vascularization, reducing inflammation, improving metabolic flexibility, increasing insulin sensitivity, modulating skeletal muscle, regulating cardiovascular, regulating liver function and so on.

In this review, we systematically queried the prominent research databases, including PubMed, Google Scholar, ScienceDirect, SpringerLink and Wiley Online Library, to identify pertinent studies that investigated ADP levels and obesity associated with metabolic syndromes. The search was extended to encompass original articles published in the last 20 years. Medical Subject-Heading (MeSH) and

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text words “adiponectin”, “obesity”, “metabolic syndrome”, “glucose metabolism”, “lipid metabolism”, “insulin sensitivity”, “inflammation”, “oxidative stress”, “multimerization”, and their matching synonyms were used for an adequate search strategy.

Many reviews have been published to describe the role of ADP in various metabolic diseases, its molecular and cellular cascades, and interactions among different adipokines [5–10]. Numerous preclinical and clinical studies have revealed the pivotal role of ADP in the pathogenesis of metabolic syndrome and its therapeutic potential. Thus, a comprehensive and systematic understanding of ADP is crucial. This comprehensive review provides a holistic view, which will connect the role of ADP across various organs in the body. This review will elaborate on the regulation of ADP from genetic aspects to its multimerization as well as the secretion, incorporating the latest research developments. Here, the first section will introduce the fundamental features of ADP and its receptors. Then the article will further explore ADP's regulatory mechanisms and its pharmacological effects on obesity and various metabolic syndromes. Finally, this review will provide an overview of the mechanisms of clinical drugs associated with ADP and ADP receptor agonists. Herein, we hope this review can be helpful in designing new drug development as well as drug delivery system targeting ADP.

2. Adiponectin introduction

2.1. Adiponectin features

ADP is a 28 kDa adipokine specifically secreted by adipose tissue, but possibly also by skeletal muscle cells, cardiomyocytes, endothelial cells, etc. Moreover, ADP is usually highly expressed in lean and healthy individuals and its expression gradually decreases with increasing body weight. ADP is a relatively abundant serum protein, accounting for up to 0.05% of the total serum proteins [11]. It is at least three orders of magnitude higher than other hormones, such as insulin and leptin. ADP structurally belongs to the complement 1q family and is composed of an amino-terminal signal sequence, variable region, collagenous domain, and a carboxyl-terminal globular domain (Fig. 1). Full-length human ADP contains 244 amino acids, and murine-derived ADP contains 247 amino acids. It has been reported that there are three main forms of full-length ADP *in vivo*: trimers (low molecular weight, named as LMW multimers), hexamers (middle molecular weight, MMW multimers) and 12–18 monomers (high molecular weight, HMW multimers). Different polymeric forms of ADP have different mechanisms and tissue-specific biological functions, but they can not interconvert during circulation. In particular, HMW multimers usually exhibit higher activities and effects on glycolipid metabolism. Interestingly, there is a cleaved form of ADP present *in vivo* called globular adiponectin (gADP, 18 kDa), which is cleaved by thrombin from the C-terminal globular domain of full-length ADP [12]. Although gADP circulates in low abundance in human plasma, it may influence energy balance by promoting mitochondrial free fatty acid (FFA) oxidation in the muscles, which may lead to weight loss [13]. ADP is primarily eliminated by the liver and excreted via the kidneys. The half-life of ADP diverges among its LMW, MMW, and HMW multimers; for example, HMW multimers show a minimum clearance of 83.3 ± 7 min, followed by MMW multimers at 54.5 ± 3.7 min, and LMW multimers at 32.4 ± 1.2 min. Generally speaking, ADP shows delayed clearance and therefore, higher concentrations within the plasma of those with high-fat diets and in ob/ob T2D animal models than normal models. However, plasma ADP levels are generally low in obese mice, which may result from the reduced rate of ADP production [14].

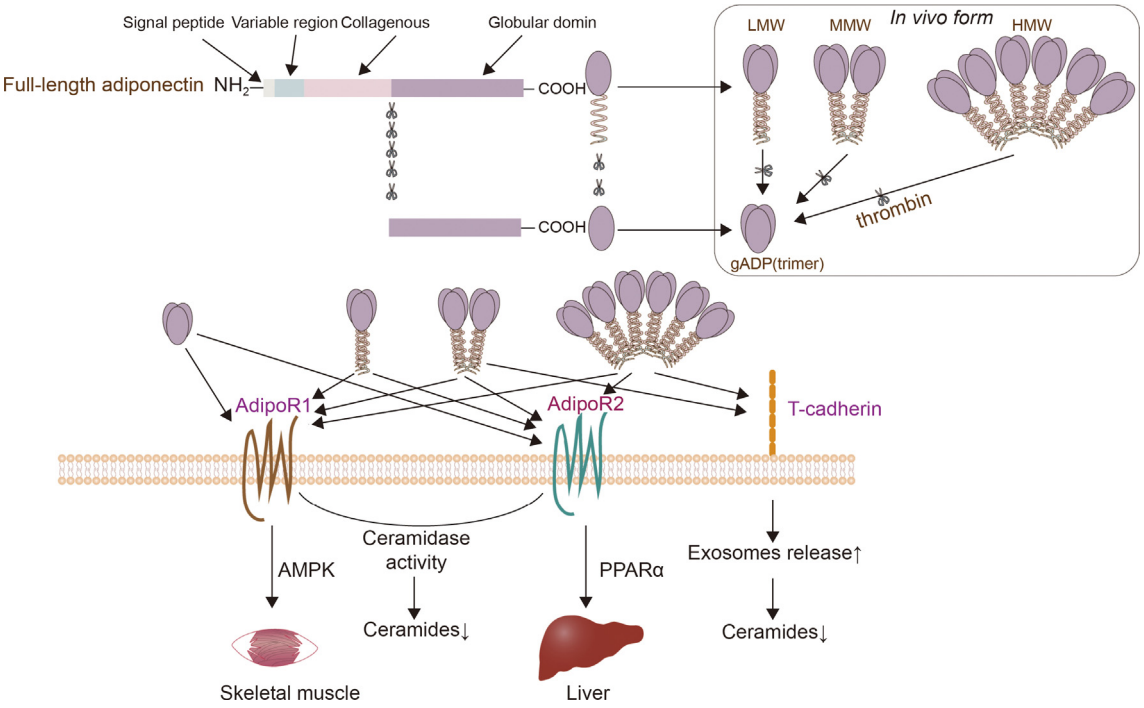

Fig. 1. Characterization of full-length ADP: an amino-terminal signal sequence, a variable region, a collagenous domain, and a carboxyl-terminal globular domain. ADP monomers form three main forms of full-length ADP *in vivo*, including trimers (low molecular weight (LMW) multimers), hexamers (middle molecular weight (MMW) multimers) and 12–18 monomers (high molecular weight (HMW) multimers). In plasma, full-length ADP can be cleaved by thrombin, forming gADP. ADP receptors include AdipoR1, AdipoR2 and T-cadherin. AdipoR1 is primarily expressed in skeletal muscle and mainly activates AMP-activated protein kinase (AMPK), while AdipoR2 is primarily expressed in the liver and mainly activates peroxisome proliferator-activated receptor α (PPARα). AdipoR1 and AdipoR2 have inherent ceramidase activity. MMW and HMW multimers bind with high affinity to T-cadherin, which induces decreased ceramides.

2.2. Adiponectin receptors

AdipoR1 and AdipoR2 are the primary ADP receptors *in vivo*, and are both composed of seven transmembrane domains (Fig. 1). Unlike G protein-coupled receptors, both AdipoR1 and AdipoR2 have an inverted topology with the extracellular C-terminus. AdipoR1 is a high-affinity receptor for gADP and is predominantly expressed in skeletal muscles, but it can also bind to full-length ADP. AdipoR2 is an intermediate-affinity receptor for both gADP and HMW multimers and is found mostly in the liver. AdipoR1 appears to be related to AMP-activated protein kinase (AMPK) pathways, while AdipoR2 appears to be involved in peroxisome proliferator-activated receptor α (PPARα) pathways in AdipoR1/2-knockout (KO) mice [15]. Although the relative abundance of AdipoRs differs in the target tissues, they are widely expressed. In addition, AdipoR1 and AdipoR2 have inherent ceramidase activities that catalyze the hydrolysis of ceramides to generate sphingosine and FFA. Insulin-stimulated glucose transporter 4 (GLUT4) redistribution can be inhibited by ceramides, contributing to insulin resistance (IR) and cardiometabolic diseases based on some rodent studies [16]. The resulting sphingosine is phosphorylated by sphingosine kinases 1 and 2 (SphK1/2) to produce sphingosine 1-phosphate (S1P). Utilizing mouse embryonic fibroblasts sourced from AdipoR1/2-KO embryos, human cell lines, and the model organism *C. elegans*, it was found that S1P upregulates stearoyl-CoA desaturase (SCD) by activating the S1P receptor 3-sterol regulatory element-binding protein-1 (S1PR3-SREBP1) and peroxisome-proliferator activated receptor γ (PPARγ) pathways, promoting membrane homeostasis and thus regulating lipid metabolism [17].

ADP can also interact with T-cadherin, a glycosyl phosphatidylinositol-anchored protein without transmembrane and cytoplasmic regions. T-cadherin is comprised of five extracellular cadherin domains and a propeptide, and is highly expressed in the cardiovascular system, particularly in vascular endothelial cells, smooth muscle cells, and pericytes. Because of the oligomeric state and unique C1q-like geometry of full-length ADP, only MMW and HMW multimers show a high affinity for T-cadherin [18]. The ADP/T-cadherin system stimulates exosome biogenesis and secretion, accompanied by decreased cellular ceramides through ceramide efflux in exosomes. Exosomal release mitigates cellular stress and sustains cellular homeostasis by exporting diverse profitless components. The adiponectin/T-cadherin-mediated effect plays an important role in cardiovascular protection [19]. Based on recent studies, circadian rhythm disruption may become a noteworthy risk indicator for the emergence of metabolic diseases. Meanwhile, serum ADP levels and AdipoR expression levels exhibit diurnal variations. Therefore, an effective therapeutic approach may be to target the regulation of ADP signaling rhythms to alter the circadian rhythms of related glucose and lipid metabolism, as well as counteract the obesogenic effects [20,21].

3. The regulatory mechanisms of adiponectin

3.1. Reduced adiponectin levels in obesity and associated metabolic diseases

A novel longitudinal weight gain model in healthy adults demonstrates that modest weight gain improves ADP levels. However, more significant weight gain, especially some degree of obesity, causes a decrease in ADP expression. Moreover, the decline of HMW multimers (5-fold decrease) is greater than that of MMW multimers (3.5-fold decrease) and LMW multimers (2-fold decrease) in obese subjects [22].

In healthy individuals with a normal metabolism, leptin levels gradually increase with weight gain and stimulate ADP mRNA expression via the extracellular-signal-regulated kinase (ERK)-dependent activation of signal transducer and activator of transcription 3 (STAT3). Research on ADP in adipo-transgenic mice suggests that at early stages of adipogenesis, the aP2 promoter can drive the over-expression of ADP and promote adipogenesis by raising cAMP levels. Singh et al. proposed that the turning point in altered ADP levels may be linked to its threshold effect. After a certain level of body fat builds up, leptin-dependent increases in caveolin-1 cause impairment of leptin signaling, which makes leptin unable to trigger ADP release, ultimately resulting in reduced ADP levels in obese individuals [23,24]. Currently, rather than focusing on changes in ADP or leptin expression levels alone, researchers place more emphasis on the ratio of ADP to leptin. It has been reported that in obese mice, the ADP/leptin ratio is significantly reduced, and this decrease is prone to induce dysfunction of adipose tissue and cardiovascular disease [25].

Accompanied by weight gain, adipose tissue homeostasis is destroyed through hypoxia, oxidative stress, inflammation, and fibrosis, which in turn causes imbalances in adipokine secretion and therefore a decrease in ADP expression. As shown in Fig. 2, ADP depression in obese patients can be related to many factors. First, the comparative results of adipose tissue between C57BL/6J mice on a regular diet and those on a high-fat diet (HFD) showed that lipid accumulation in adipose tissue causes lipid droplets to grow progressively larger, with adipocyte diameter reaching 140–180 μm. However, the maximum diffusion distance of oxygen is 100 μm, and the sparse vascularity of adipose tissue results in restricted blood flow. This causes the adipocytes to eventually fall into a hypoxic state after expanding to a limited size [26]. Hypoxia triggers an imbalance in adipokines, including inhibition of ADP expression and enhanced mRNA degradation of ADP, ultimately leading to ectopic deposition of fat in non-adipose tissue. Second, massive accumulation of lipids elicits an increase in reactive oxygen species (ROS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, as well as a decrease in the expression of antioxidant enzymes. It also induces oxidative stress and suppresses PPARγ mRNA expression in 3T3-L1 adipocytes, which subsequently downregulates ADP expression [27]. Third, insulin sensitivity will be decreased by excessive and prolonged exposure to ROS, accompanied by impaired glucose and lipid metabolism, thus further inducing damage to high-density lipoprotein (HDL) signaling observed in obese female participants, which has vasoprotective effects. This leads to decreased NO and increased oxidative and inflammatory factors [28,29]. Meanwhile, in the mouse model of HFD-induced, elevated endothelin-1 in adipose tissue inhibits ADP production and insulin sensitivity [30]. Fourth, inflammation is a significant problem in obesity and related metabolic syndromes, and impairs the function of endothelial cells and some cytokines, such as ADP and HDL [31]. Study on 32-week HFD/chow diet of ADP deficient mice, ADP transgenic over-expressing mice and wild type mice, resepectively showed that large-volume adipocytes secrete low levels of ADP and high levels of pro-inflammatory agents, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [32]. Meanwhile, hypoxia, TNF-α, endoplasmic reticulum (ER) stress, ROS, and FFA induce adipocyte necrosis, which later provokes macrophage recruitment. At this point, as shown in Fig. 2, the macrophages in adipose tissue also transit from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype, which promoted the release of IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1) [33]. Macrophages surround necrotic adipocytes with crown-like structures (CLS) that eventually fuse into multinucleate giant cells (MGCs). As it is shown in Fig. 2, MGCs actively phagocytose debris and create large amounts of pro-inflammatory cytokines. The free lipid droplets released after adipocyte necrosis act as sites

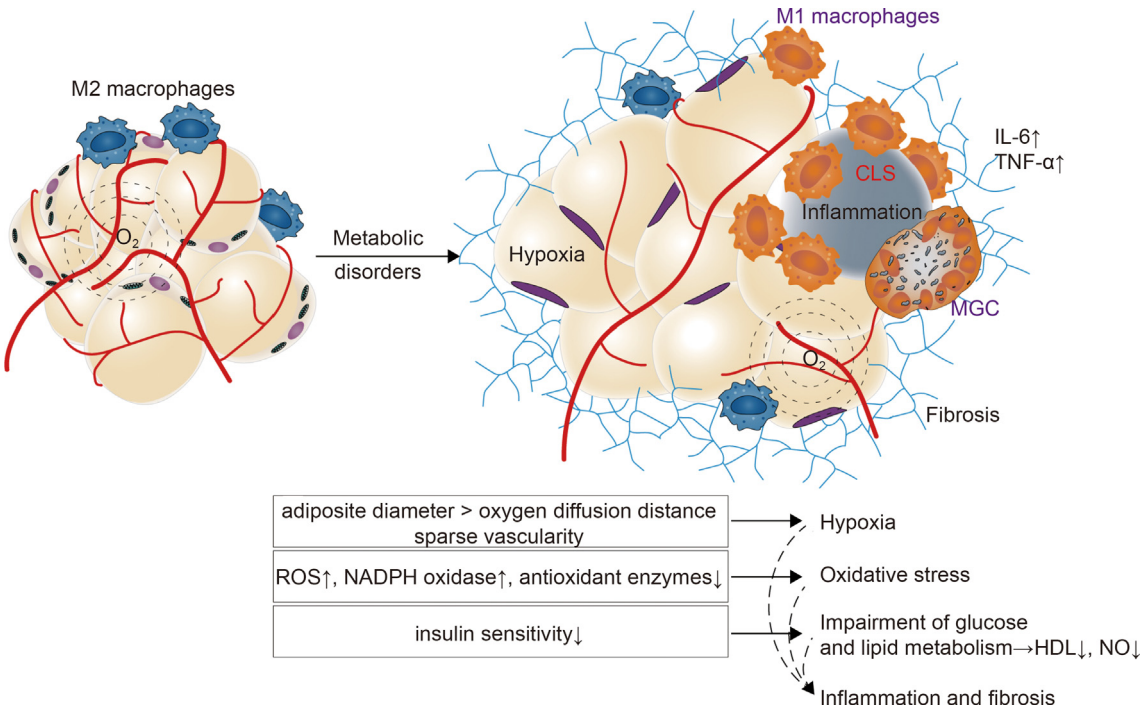

Fig. 2. In the pathological conditions associated with obesity and metabolic disorders, the adipose tissue expands to a limited size, and are accompanied by hypoxia, oxidative stress, impairment of glucose and lipid metabolism, M2 macrophages to M1 macrophages transformation, inflammation, and fibrosis. These factors may decrease ADP levels. Refer to Section 3.1 for detailed information. IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; MGC: multinucleate giant cell; ROS: reactive oxygen species; NADPH: nicotinamide adenine dinucleotide phosphate; HDL: high-density lipoprotein; CLS: crown-like structures; MGC: multinucleate giant cell.

that maintain macrophage fusion, lipid uptake, and MGC persistence [34]. Feedback on the inflammatory response activates self-repair of adipose tissue. Collagen aggregates around adipocytes to form pericellular fibrotic structures. Fibrous bundles of different thicknesses are subsequently formed. Gradually, adipose tissue is transformed into a fibrotic state [35]. These pathological changes in adipose tissue further accelerate adipokine disorders, which consequently downregulate ADP levels.

3.2. Regulation of adiponectin genes

Since the altered ADP levels in patients with obesity and metabolic syndromes, attention has been drawn to the ADP regulation and its potential as a therapeutic target. ADP gene expression is tightly regulated by numerous transcription factors, including PPARγ, sterol regulatory element-binding protein 1c (SREBP1c), CCAAT/enhancer-binding protein (C/EBP) sites, retinoid X receptor (RXR), liver receptor homolog-1 (LRH-1) and so on (shown in Fig. 3).

PPARγ is an essential transcription factor that modulates glucose and lipid metabolism, adipogenesis, and adipokine production. The co-expression of LRH-1 augments PPARγ/RXR-induced transactivation of the ADP promoter in 3T3-L1 adipocytes [36]. In physiological diurnal rhythms, PPARγ acetylation in adipose tissue varies dynamically. In pathological states of obesity, aging, and circadian disruption, PPARγ acetylation increases. Metabolic oscillations in daily rhythms may be regulated by the dynamics of PPARγ acetylation in adipose tissue. Mutations in PPARγ K293Q (aKQ) within adipocytes mimic PPARγ acetylation. It has been shown that adipose plasticity is restrained during calorie restriction and diet-induced obesity, and this is related to BMAL1 (a critical circadian component). An additional study based on silent information regulator sirtuin 1 (SIRT1) overexpression mice has also implicated SIRT1 in promoting PPARγ deacetylation [37]. The destabilization of BMAL1

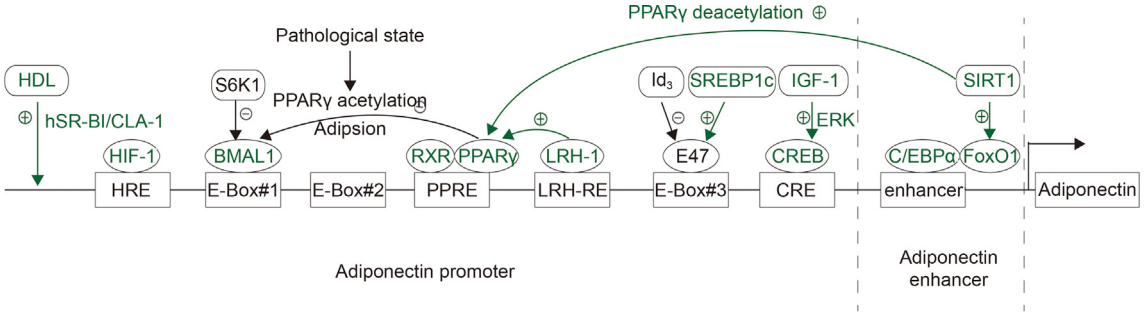

Fig. 3. Schematic diagram of the regulatory mechanisms of adiponectin. Various cytokines or proteins act directly or indirectly by binding to adiponectin gene promoter or enhancer regions. These designators in the figure represent the binding sites in the adiponectin gene sequence, including hexanucleotide repeat expansions (HRE), E-Box, peroxisome proliferator response element (PPRE), LRH-RE, CRE, enhancer, and so forth. The specific details of the mechanisms are described in Section 3.2. HIF-1: hypoxia-inducible factor-1; BMAL1: brain and muscle Arnt-like protein-1; S6K1: ribosomal protein S6 kinase 1; RXR: retinoid X receptor; PPARγ: peroxisome-proliferator activated receptor; LRH-1: liver receptor homolog-1; SREBP1c: sterol regulatory element-binding protein 1c; IGF-1: insulin-like growth factor 1; CREB: cAMP-response element binding protein; C/EBPα: CCAAT/enhancer-binding protein α; FoxO1: forkhead box transcription factor O1; SIRT1: sirtuin 1.

by adipsin connects PPARγ acetylation to daily rhythms in acetylation-mimetic mutation of PPARγ K293Q (aKQ) mice [38]. Furthermore, ribosomal protein S6 kinase 1 (S6K1) can control ADP expression by activating a transcriptional switch between the transcriptional machinery of BMAL1 and enhancer of zeste homolog 2 (EZH2) according to the model of S6K1-deficient C57BL/6 mice. Active S6K1 phosphorylates BMAL1, leading to its dissociation from the ADP promoter region. Subsequently, EZH2 recruitment and H3K27me3 modification occur, resulting in suppressed ADP expression. Nuclear S6K1 can also trigger early adipogenesis by inhibiting Wnt gene expression via H2BS36 phosphorylation [39,40]. Some pathological mechanisms in AD and aging-related diseases are significantly related to BMAL1 deficiency [41].

SREBP1c is a major regulator of fatty acid biosynthesis. SREBP1c and E47 (an E-protein) can bind with the endogenous ADP promoter and synergistically activate it. The inhibitor of differentiation (Id3) regulates SREBP-1c activity by interacting with E47, thus suppressing E47 binding to the ADP promoter and suppressing ADP expression in an atherogenic model of ApoE$^{-/-}$ and Id3$^{-/-}$ApoE$^{-/-}$ mice [42]. C/EBPα interacts with response elements in the intronic enhancer of the human ADP gene to activate ADP gene transcription [43]. Forkhead box transcription factor O1 (FoxO1) interacts with C/EBPα to form a transcription complex in the mouse ADP promoter, which upregulates ADP gene transcription in 3T3-L1 adipocytes. Furthermore, SIRT1 promotes ADP transcription in adipocytes by activating FoxO1 and improving FoxO1 and C/EBPα interactions [44]. The cAMP-response element binding protein (CREB) is not only an important regulator of ADP gene expression but also a fundamental transcriptional activator of adipocyte differentiation. Insulin-like growth factor (IGF-1), which stimulates CREB via the ERK pathway, increases ADP promoter activity in 3T3-L1 adipocytes [45].

Hypoxia-inducible factor-1 (HIF-1) is a transcription factor responsible for the induction of genes that foster cellular adaptation to hypoxic conditions. It causes a substantial ADP increase both *in vivo* and *in vitro*, with potent biological benefits in the diabetic vasculature [46]. HDL enhances ADP gene expression in 3T3-L1 adipocytes through a homolog of the B-class type I scavenger receptor/CD36 and LIMPII analogous-1 (hSR-BI/CLA-1). The Ca^{2+}/calmodulin (CaM)-dependent protein kinase IV (CaMKIV) cascade plays a key role in this process [47].

3.3. Regulation of adiponectin multimerization

Clinical studies have shown that impaired ADP multimerization, especially the selective reduction in HMW ADP concentrations, is associated with various metabolic diseases. HMW ADP and the HMW-to-total ADP ratio have superior predictive potential in patients with insulin resistance (IR) and related metabolic syndromes [48]. Hence, it is essential to deeply explore the mechanistic processes that promote and inhibit ADP expression as well as the multimerization, stability, and secretory functions of ADP.

The amino-terminal cysteines (Cys^{36} in humans and Cys^{39} in mice) of ADP form an intermolecular disulfide bond, which acts as a key site for ADP succinylation. Succinylated ADP ceases to polymerize into a multimeric form and is no longer secreted from adipocytes, indicating that the intermolecular disulfide bond site is critical for ADP multimerization and secretion. Another highly conserved amino acid residue at the amino-terminus is tryptophan (W42). Residue W42 affects ADP assembly and maintains full-length ADP in an oxidized trimeric or hexameric state, possibly because of a reduction in the rate of Cys^{39} oxidation owing to proximity effects. Additionally, hydroxylation and subsequent glycosylation of lysine residues in the collagenous region and hydroxylation of proline residues also play an important role in the aggregation of ADP from LMW into HMW multimers [49–51].

In obese patients, there is an increased demand for ER function by the body. High FFA levels and mitochondrial oxidative stress can lead to ER stress. ER stress promotes protein synthesis to meet demands or functional overload when elimination of misfolded proteins is reduced. It also facilitates autophagy-dependent ADP degradation, thus profoundly affecting the downregulation of ADP levels. To ameliorate ER stress, the expression of the disulfide bond oxidoreductase A-like protein (DsbA-L) can be increased to further regulate the expression of ER membrane-associated oxidoreductase 1-α (Ero1-α) and ER protein of 44 kDa (ERp44), ultimately promoting ADP multimerization in 3T3-L1 adipocytes overexpressing DsbA-L. ERp44 and ADP connect via a mixed disulfide bond created by a cysteine residue within their variable regions. It prolongs the resident time of ADP in the secretory pathway, improving the likelihood that it will properly fold into higher-order complexes. In contrast, Ero1-α, a privileged partner of ERp44, replaces ERp44-retained ADP and enhances ADP release from the ER [52]. PPARγ agonists selectively enhance the circulating levels of HMW multimers through two critical ER chaperones in the secretory pathway [53]. Moreover, the spliced form of X-box-binding protein 1 (XBP1s) is a vital transcription factor that responds to ER stress, likely by directly regulating the expression levels of ER chaperones involved in ADP maturation in white adipose tissue of XBP1s transgenic ob/ob mice, such as the protein disulfide isomerase family A member 6 (PDIA6), glucose-regulated protein 78 kDa, ERp44, and DsbA-L [54]. However, protein disulfide isomerase family A member 4 (PDIA4) downregulates ADP levels and impairs ADP folding and multimerization [55]. The above ER stress-associated components serve an important role in modulating the assembly and secretion of the ADP complex. Brännmark et al. [56] reported that elevated HMW ADP depended on caveolin 1 and/or intact caveolae structures to exocytose in caveolin-1 deficient mice. The loss of caveolin 1 may shorten resident ADP time in the ER, favor synthesis and the release of smaller ADP forms, and be adverse to the synthesis and secretion of HMW multimers.

Mitochondrial dysfunction also impairs ADP synthesis, secretion, and multimerization, as it causes elevation of intracellular ROS levels and induces ER stress [57]. The mitochondrial chaperonin HSP60, located in the mitochondria, cytosol, cell membranes, and body fluids, plays an important role in protein folding and the mitochondrial stress response. Reduced HSP60 is associated with pronounced steatosis in human NAFLD biopsies and HFD obese mice. HSP60 loss contributes to misfolding of sirtuin-3 (SIRT3). SIRT3 can deacetylate HSP10 and regulate the biological activity of the HSP60/HSP10 complex, which improves the folding of medium-chain acyl-CoA dehydrogenase, a fatty acid oxidation enzyme. It can also promote fatty acid oxidation and lipolysis, while inhibiting ROS, lipotoxicity, and mitochondrial dysfunction. HSP60 reverses the mitochondrial unfolded protein response (UPR) and improves electron transport chain function. HSP60 also ameliorates HFD-induced oxidative stress, hepatic steatosis, and the M1/M2 macrophage switch [58]. Moreover, metallothionein expression is lower in hypertrophic adipocytes than in mature adipocytes. Metallothioneins act as non-enzymatic antioxidants through the suppression of superoxide radicals and ER stress [59].

3.4. Regulation of adiponectin secretion

Many cytokines or proteins in the physiological environment regulate ADP levels. Autophagy dysregulation is associated with metabolic disorders, including T2D. In the autophagy hyperactive knock-in (KI) mouse model with disrupted Becn1 downstream pathway, the autophagy protein Beclin 1/Becn1 in adipose tissue was proved to promote ADP secretion via binding to the exocyst complex in adipose tissue, activating the AMPK pathway, and

increasing insulin sensitivity systemically [60]. Insulin stimulates the release of ADP and inhibits its ubiquitination and degradation in differentiated 3T3-L1 adipocytes, but the impaired insulin pathway in obese patients depresses its stimulatory effect on ADP. TNF-α is one of the factors the triggers insulin-stimulated ADP secretion, and the secretion of HMW multimers is significantly lower than that of MMW and LMW [22,61]. Under normal circumstances, leptin can upregulate ADP expression. However, elevated leptin-dependent caveolin-1 (Cav1) in obesity impairs the leptin signaling pathway after a specific quantity of body fat accumulation and subsequently decreases ADP levels [23]. Although Cav1 might restrict total ADP release, Brännmark et al. [56] suggests that Cav1-depletion decreases the levels of HMW ADP in white adipocytes. ADP vesicles themselves may have no need to interact with Cav1 during the exocytosis process, but their release requires the help of Cav1. Cav1 dysfunction might lead to decreased serum HMW multimers, which is associated with diabetes. The expression of resistin and ADP is highly correlated and may be regulated by similar molecular mechanisms [62]. Resistin reduces plasma ADP levels and AdipoR expression in the hypothalamus and peripheral tissues based on the models of adrenalectomized male ob/ob mice and HFD-induced obese mature male C57Bl/6J mice. In addition, Benomar revealed that the central resistin/TLR4 pathway can induce whole-body IR by impairing ADP signaling and increasing fibroblast growth factor 21 (FGF21) resistance [63]. FGF21 significantly stimulates ADP secretion in rodents, while decreasing ceramides buildup in obese animals. FGF21 relies heavily on ADP to exert its glucose-regulating and insulin-sensitizing effects [64,65]. Han et al. [66] demonstrated that the cJun NH_2-terminal kinase (JNK) signaling pathway in adipocytes caused an increased circulating concentration of FGF21, which then enhanced circulating ADP via PPARγ activation. ADP triggers FGF21 expression in the liver. In several C57BL/6J mouse models being knocked out the above genes, this regulatory loop illustrates that JNK signaling in adipocytes is an instance of adipose tissue crosstalk with the liver. Maruyama and his group [67] conducted research on NAFLD mice models treated with recombinant human serum albumin-FGF21 analog fusion protein (HSA-FGF21). Their results indicate that in adipose tissue, HSA-FGF21 can increase adipocyte hypertrophy, decrease inflammatory cytokines, and facilitate the expression of ADP and thermogenic factors [67].

ADP can also be reversibly downregulated partly via p44/42 mitogen-activated protein (MAP) kinase [68]. Pleckstrin homology domain leucine-rich repeat protein 1 phosphatase 2 (PHLPP2) in adipocytes from obese mice was higher than that in normal mice. Kim et al. [69] found that PHLPP2 levels in adipose tissue were negatively correlated with serum ADP levels in obese patients. Owing to prolonged hormone-sensitive lipase (HSL) phosphorylation, adipocyte PHLPP2 ablation causes an increase in adipose lipolysis. Some ER stress-associated components can modulate the multimerization and secretion of ADP complexes, including PDIA4, Ero1-α, ERp44, and DsbA-L [52,53,55,70]. ADP secretion can be induced by Ca^{2+}-independent and protein kinase A (PKA)-independent cAMP activation, which is enhanced by both Ca^{2+} and ATP. Epac acts as an exchange protein activated by cAMP and participates in white adipocyte exocytosis. Similar to cAMP, Epac agonists can stimulate exocytosis and ADP secretion. Although cooling has no impact on cAMP-stimulated ADP secretion, it fully eliminates Ca^{2+}-induced ADP exocytosis in 3T3-L1 adipocytes [71,72]. Furthermore, ADP expression levels in breast, prostate, and colorectal minority cancer survivors can be improved by circuit, interval-based aerobic, and resistance exercise interventions [73].

ADP does not show an effect until it leaves the circulation and crosses the endothelial barrier into the target tissue. Hence, vascular permeability also influences ADP and should be considered. ADP has multiple forms of aggregation and its radial size is estimated to be 3.96–10.1 nm [74]. This is the exact range where tight junctions with dimensions of approximately 4 nm can be predicted to influence ADP flux. Tight junctions show loose endothelial barrier tightness and decreased levels of claudin-7 in high glucose-treated cells, which can result in a high flux of ADP across endothelial monolayers [75]. Indeed, transendothelial movement of ADP can be reduced by glucocorticoids, thus leading to impaired ADP action in target tissues [76]. The whole process of ADP regulatory mechanisms is summarized in Fig. 4.

3.5. Downstream regulation of adiponectin

ADP is one of the key adipokines triggering diverse downstream mechanisms, such as PPARα and AMPKsignaling pathways. Many reviews have summarized the downstream pathways of ADP. In which, the above two pathways are the most extensively reported. Herein, we will primarily highlight several recently published downstream pathways of ADP.

The recently identified adipokines, secreted frizzled-related protein (Sfrp)-5 and wingless-related integration site 5A (Wnt5a), constitute a distinctive duo renowned for their anti-inflammatory properties. Wnt5a, secreted by adipose tissue macrophages, is implicated in inflammation, atherosclerosis, and insulin resistance. Sfrp5, expressed in various insulin target tissues, modulates metabolic homeostasis by inhibiting Wnt5a signaling. Sfrp5 could potentially be a target gene regulated by PPARγ. Furthermore, based on a clinical study, the connection between Sfrp5 and insulin sensitivity is predominantly influenced by ADP [77–79]. Duan et al. [80] also found CD44 as an antigen on the cell surface, was a novel target gene of ADP. Their study indicated that ADP mitigated inflammation induced by hyperglycemia through the leucine zipper motif 1 (APPL1)/Wnt/β-catenin/CD44 signaling axis.

In addition, by overexpressing the transcription factor of hepatocyte nuclear factor 4α (HNF4α) and PPARα inducibly specifically in pancreatic β cells of C57/BL6 mice, Scherer' group [81] uncovered a cascade of ADP-HNF4α-PPARα in pancreatic β cells. The latter two factors are recognized for their role in regulating fatty acid oxidation and cholesterol metabolism. They further examined genes downstream consistently regulated by this axis. Among these, the islet amyloid polypeptide (IAPP) gene is a significant target and accumulates in ADP KO mice [81].

4. Regulating effects of adiponectin on obesity and metabolic syndromes

In 2009, the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute unified the criteria for metabolic syndromes. A diagnosis of metabolic syndrome is made when any three of the following five risk factors are observed: large waist circumference, high triglycerides, low high-density lipoprotein cholesterol (HDL-C), high blood pressure, and high fasting glucose [82]. Ectopic storage of fat in non-adipose tissue is commonly recognized as the causative agent of obesity and related metabolic syndromes, such as T2D, cardiometabolic disorders, NAFLD, sarcopenia, osteoporosis, diabetic kidney disease (DKD), polycystic ovary syndrome (PCOS) and so on. Overall, ADP displays a positive regulatory role in preventing and reversing metabolic disorders (Fig. 5).

4.1. Coordination of adipose tissue expansion and vascularization

Obesity, a manifestation of excessive adipose tissue, is caused by hypertrophy and hyperplasia of adipocytes. When adipose tissue

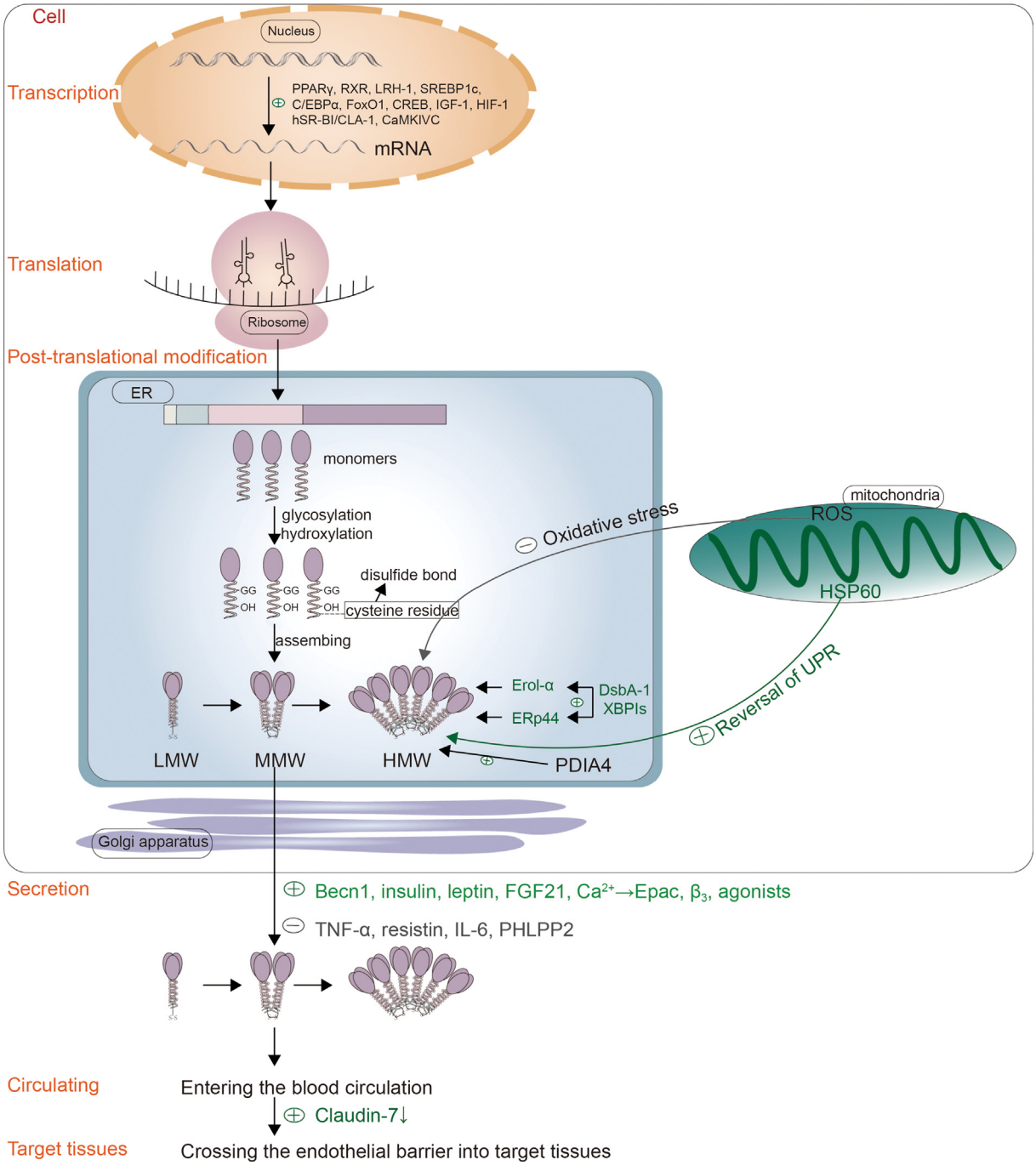

Fig. 4. The regulation of adiponectin extends through all stages of its production, including ADP gene expression, multimerization, secretion and circulation in blood after crossing the endothelial barrier. Refer to the Section of 3.2–3.4 for detailed information. hSR-BI/CLA-1: a homolog of the B-class type I scavenger receptor/CD36 and LIMPII analogous-1; CaMKIV: Ca^{2+}/calmodulin (CaM)-dependent protein kinase IV; ERp44: ER protein of 44 kDa; Ero1-α: ER membrane-associated oxidoreductase 1-α; DsbA-L: disulfide bond oxidoreductase A-like protein; XBP1s: the spliced form of X-box-binding protein 1; PDIA4: protein disulfide isomerase family A member 4; HSP60: heat shock protein 60; Becn1: beclin 1; FGF21: fibroblast growth factor 21; PHLPP2:pleckstrin homology domain leucine-rich repeat protein 1 phosphatase 2.

expands excessively but vascular oxygen delivery is insufficient, it will lead to a hypoxic state, and marks the onset of metabolic imbalance. ADP can promote adipocyte differentiation, reduce adipocyte size, increase adipocyte number, and to some extent, foster adipocyte browning. ADP can also facilitate the preferential storage of triglycerides in adipose tissue. These effects suggest that ADP acts as a "starvation signal" emitted by adipocytes, indicating that the average adipocyte volume is relatively small and higher levels of triglyceride are required in the adipose tissue [83]. ADP can mediate peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) by cAMP regulation, increase mitochondrial density, accelerate the cleavage rate of fatty acid oxidation, and balance the expansion of subcutaneous adipose tissue in ADP deficient or over-expressing mice [84].

It was found that in fully differentiated adipocytes, lipid droplets of adipocytes over-expressing ADP were larger than those of control cells. ADP promoted the augmentation of lipid accumulation and insulin-responsive glucose transport. Li *et al.* [85] revealed that ADP

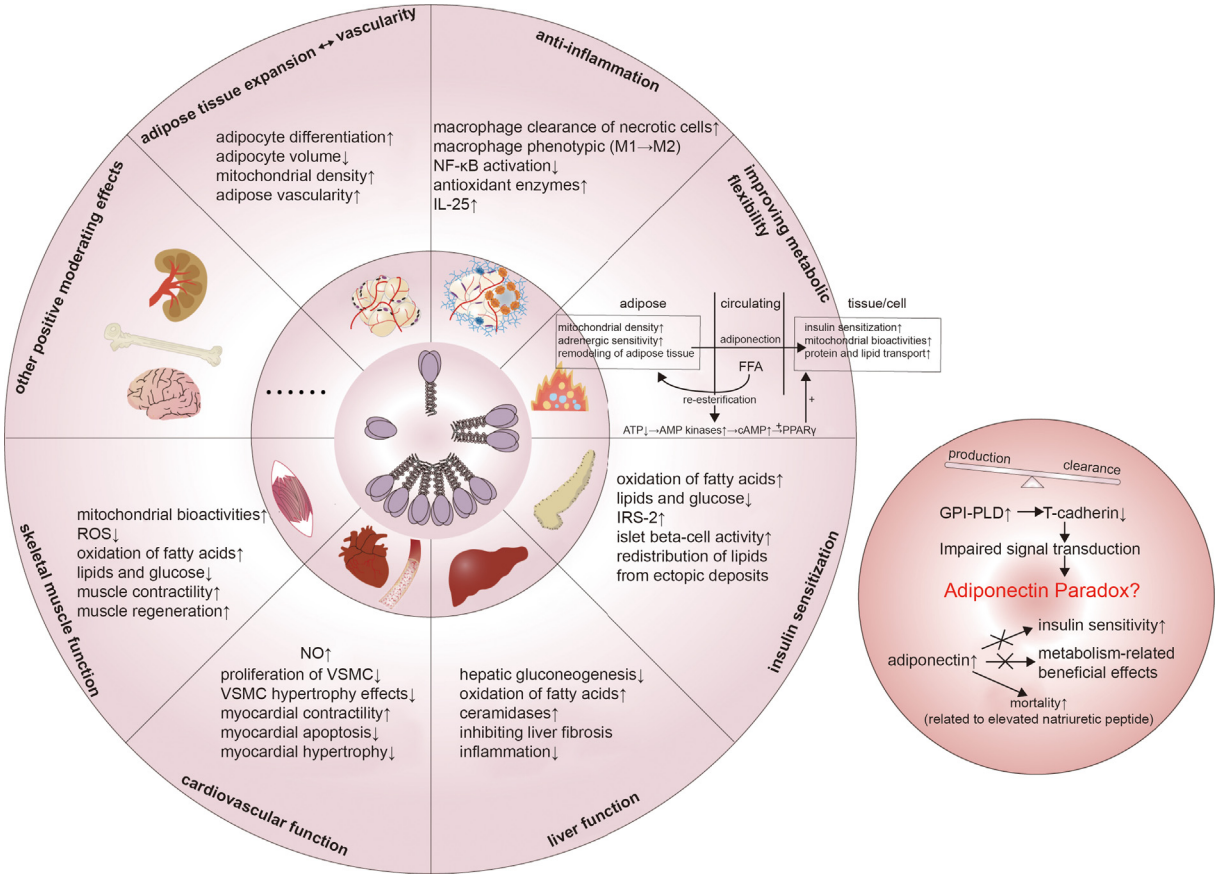

Fig. 5. Adiponectin has pleiotropic effects on obesity and related metabolic syndromes, such as the coordination of adipose tissue expansion and vascularization, anti-inflammatory, increased metabolic flexibility, enhanced insulin sensitivity, and improved skeletal muscle function, cardiovascular function and liver function. In addition, the adiponectin paradox has become a noteworthy problem. Refer to the Section of 4.1–4.11 for details. NF-κB: nuclear factor κB; IL-25: interleukin-25; FFA: free fatty acid; IRS-2: insulin receptor substrate 2; VSMC: vascular endothelial smooth muscle cells; GPI-PLD: glycosylphosphatidylinositol phospholipase D.

treatment increased epididymal white adipose tissue mass but did not change total fat mass in HFD induced mice [85]. This indicates that ADP may have potential for adipocyte expansion. Kim *et al.* [83] revealed that metabolic levels were normal in ADP transgenic ob/ob mice under high-fat induction, but adipose tissue mass and body weight were substantially higher than those in ob/ob mice controls. The study also showed that increases in subcutaneous adipose tissue were predominantly responsible for the increase in overall adiposity. Visceral fat did not change significantly in ADP transgenic ob/ob mice compared to that in obese littermates. This suggests that the metabolic improvement of ADP is closely related to the compensatory growth of subcutaneous adipose tissue. Elevated ADP levels stimulate angiogenesis and blood flow in the adipose tissue, which can mitigate the degree of hypoxia exhibited by adipose tissue expansion. The role of ADP in maintaining the balance between the vascular system and adipose tissue expansion may result from the elevation of vascular endothelial growth factor (VEGF), which is mediated by the sonic hedgehog (Shh) pathway [32].

4.2. Anti-inflammatory effect

It is currently recognized that chronic inflammation induced by overnutrition is a pivotal mechanism contributing to metabolic diseases associated with obesity. ADP can significantly suppress inflammation by reducing the number of macrophages in the inflammatory state of white adipose tissue in transgenic overexpressing mice compared with ADP deficient mice [32]. This animal model also demonstrated that ADP could inhibit local inflammation by regulating macrophage phenotypic transition from a pro-inflammatory M1-like state to an anti-inflammatory M2-like state. In the M1-like state, macrophages secrete more pro-inflammatory factors such as IL-6, TNF-α, and MCP-1. While in the M2-like state, anti-inflammatory factors are increased, such as arginase-1, macrophage galactose N-acetyl-galactosamine-specific lectin-1, and IL-10 [33]. In addition, ADP decreases the inflammatory stimuli-induced nuclear factor κB (NF-κB) and inflammatory genes via the AdipoR1 and the AMPK-SIRT1-PGC-1α signaling pathways. During adipocyte differentiation, IL-25 expression is upregulated, which promotes ADP secretion through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway. ADP further attenuates IL-6 and chemokine ligand 5 (CCL5) expression [86]. JT003, an adiponectin-based agonist, alleviates non-alcoholic steatohepatitis (NASH) and associated liver fibrosis in mice models via the AMPK, PPARα, and PI3K-AKT signaling pathways. It can considerably suppress the overexpression of HFD-induced genes for inflammation such as IL-6 and inducible nitric oxide synthase (iNOS), as well as genes for ER stress such as X-box binding protein-1 (XBP1), together with alleviating mitochondrial dysfunction [87].

4.3. Increased metabolic flexibility

Metabolically sound individuals adeptly respond to variations in nutritional status, while those with metabolic disorders lose this ability. ADP serves as a key factor augmenting the metabolic adaptability of adipose tissue, thereby fortifying its capacity to sustain optimal functionality amid metabolically demanding

circumstances. Higher ADP levels enhance not only the sensitivity of adrenergic receptor agonists to lipolytic effects but also the clearance of FFA and the expansion of subcutaneous fat induced by HFD. ADP reduces ectopic accumulation of fat in skeletal muscles and the liver of C57BL/6J mice by increasing lipoprotein lipase (LPL) activity, ultimately improving triglyceride uptake and increasing the storage capacity of white adipose tissue [85]. In the HFD induced models of ADP deficient mice, ADP over-expressing mice and wild type mice, researchers have discovered that adaptive changes caused by ADP in response to high lipid induction are associated with increased mitochondrial density in adipocytes, decreased average adipocyte size, and the overall upregulation of adipokines connected to FFA re-esterification. Lipolysis (in particular, the subsequent re-esterification of fatty acids) burns a lot of energy and lowers cellular ATP levels, thus indirectly activating AMPK. The physiological effects of ADP overexpression are similar to those of chronic β3 receptor agonists, which can improve insulin sensitivity, enhance adipose tissue metabolic flexibility, and promote adipose tissue remodeling. Moreover, the generation of cAMP can further activate the PPARγ pathway to exert adrenergic effects. Simultaneously, cAMP also regulates mitochondrial function, which stimulates adipocyte differentiation and adipogenesis [84]. Furthermore, ADP potentiates mitochondrial bioenergetics of neonatal rat cardiac myocytes, including enhanced ATP generation, basal mitochondrial oxygen consumption rate, and spare respiratory capacity, all of which are inhibited by the knockdown of AMPKγ1 and the suppression of succinate dehydrogenase complex assembly [88]. Ye *et al.* [89] found that ADP could selectively bind to some anionic phospholipids and sphingolipids in Expi293 cells to clear unwanted lipids, such as glucosylceramide, ceramide-1-phosphate, phosphatidylserine, and sulfatide, through its C1q region, depending on oligomerization to regulate protein or lipid transport.

4.4. Enhanced insulin sensitivity (T2D)

The mechanisms underlying the relationship between obesity, dyslipidemia, and cardiometabolic disorders have focused on IR. This may stem from the fact that insulin in obese patients cannot effectively clear glucose from the blood, which in turn directly or indirectly leads to diverse metabolic syndromes. IR can result from several factors. Increased triglyceride levels affect phosphatidylinositol-3 kinase activation, glucose uptake, and translocation of GLUT4, both of which contribute to IR. Clinical studies have found that IL-6 and TNF-α could impair the insulin signaling pathway by affecting insulin receptor substrate-1 (IRS-1), IRS-1 tyrosine phosphorylation, and GLUT4 expression levels [90]. Oxidative stress triggered by mitochondrial dysfunction also reduces GLUT4 expression in 3T3-L1 adipocytes and C2C12 myotubes, leading to insufficient ADP secretion and decreased insulin sensitivity [57]. In addition, a clinical study suggests that dipeptidyl peptidase-4 (DPP-4) levels in visceral adipose tissue are usually elevated in obesity, which can inhibit glucagon-like peptide-1 (GLP-1) secretion, subsequently inducing IR [91].

ADP can enhance insulin sensitivity and improve islet β-cell function mainly by increasing fatty acid oxidation and inhibiting hepatic glucose production, which redistributes the ectopic deposition of lipids from the liver or muscles to subcutaneous fat in ADP transgenic ob/ob mice [83]. The AMPK-α and PPARα signaling pathways are key regulators of lipid and glucose homeostasis based on the data of ADP transgenic ob/ob mice. They can reduce skeletal muscle and hepatic triglyceride levels and promote acetyl CoA carboxylase (ACC) phosphorylation, lipid consumption, and glucose uptake *in vivo* and *in vitro* [92]. ADP inhibits gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase and glucose 6-phosphatase [93]. Additionally, independent of the AdipoR1 and AdipoR2 pathways, ADP increases the expression levels of hepatic IRS-2 through a macrophage-derived IL-6-dependent pathway due to a mouse model with the IL-6 gene knocked out, which consequently enhances insulin sensitivity. This suggests that there may be unknown ADP receptors from macrophages that can contribute to ADP-mediated insulin sensitivity [94]. Moreover, a study with the model of ADP transgenic mice suggests that ADP reverses β-cell damage induced by obesity and restores β-cell functional integrity with increased insulin secretion from the pancreatic islets [95].

4.5. Effect on skeletal muscle function (sarcopenia)

The decline in muscle regenerative capacity with age is proposed to be a contributing factor to the loss of muscle mass in the elderly. In addition, it was also found that obesity and related metabolic disorders have been associated with a decline in muscle regeneration. Through binding to AdipoR1 and AdipoR2 in an autocrine or paracrine fashion, ADP can modify skeletal muscle function by enhancing mitochondrial bioactivity, reducing ROS production, promoting fatty acid oxidation, increasing insulin-induced glucose uptake and triglyceride clearance, improving muscle contractility, attaining increased muscle regeneration, and reducing protein hydrolysis and other pathways [96]. ADP can also reverse sarcopenia, which may originate in the elderly or be secondary to diabetes, chronic inflammatory states, hormonal alterations, and vascular disturbances [97,98]. At the histological level, sarcopenia exhibits hypotrophic myofibers (mainly type II myofibers) in human skeletal muscle tissue, infiltration with adipose, along with later fibrotic tissue, and diminished satellite cells [99]. Excessive ROS production due to mitochondrial dysfunction is a major cause of muscle loss. The transition from C2C12 myoblasts to brown adipocytes occurs because of chronic oxidative stress, which results from NF-κB (p65)-dependent upregulation of S100B (a Ca^{2+}-binding protein of the EF-hand type) and bone morphogenetic protein 7 (BMP-7). Morozzi et al. [100] revealed that the knockdown of S100B or the inhibition of NF-κB in brown adipocytes derived from myoblasts would reconvert them into fusion-competent myoblasts. ADP may facilitate muscle regeneration by binding T-cadherin from the model of ADP KO mice and T-cadherin KO mice [101]. It has also been proposed that gADP could activate autophagy in the myoblasts of skeletal muscles through an AMPK-dependent mechanism, boosting myoblast survival and preventing apoptosis during serum starvation [97]. Simultaneously, myokines like irisin and IL-6 secreted by skeletal muscles can promote the browning of white adipose tissue, regulate glucose and lipid metabolism, and alleviate low-grade inflammation [102].

4.6. Effect on cardiovascular function (hypertension, restenosis, atherosclerosis, heart disease)

Endothelial dysfunction is a recognized precursor to hypertension and atherosclerosis, characterized by reduced NO and compromised endothelium-dependent vasodilation. ADP produces NO in human umbilical vein endothelial cells (HUVECs) by activating vascular endothelial NO synthase (eNOS) to maintain the stability of cardiovascular function, which involves heat shock protein (HSP) 90 [103]. Farah *et al.* [104] review the effects of NO, including angiogenesis, mitochondrial biogenesis, intercellular information exchange, vasodilation, and upregulation of telomerase activity, as well as a decrease in oxidative stress and inflammatory cell infiltration. ADP also suppresses the proliferation and migration of vascular endothelial smooth muscle cells (VSMC) and induces apoptosis. Meanwhile, under the pathological conditions of excessive cell proliferation, ADP can inhibit the formation of the neoplastic endothelium. Furthermore, endothelial NO production

can attenuate Ang II-mediated vascular smooth muscle hypertrophic effects and improve hypertension, restenosis, and atherosclerosis based on the model of Ang II induced mice [105–107]. ADP enhances myocardial contractility, suppresses cardiac sympathetic remodeling, and alleviates cardiac remodeling after myocardial infarction *in vivo* and *in vitro*. ADP can also inhibit NF-κB and TNF-α to prevent myocardial inflammation, accelerate fatty acid oxidation to prevent diabetic cardiomyopathy, promote ceramides degradation to prevent apoptosis and myocardial hypertrophy, and activate sphingosine kinase-1/COX-2 (SphK1/COX-2) signaling to protect the myocardium during myocardial infarction [108–112].

4.7. Effect on liver function (NAFLD)

The excessive elevation of hepatic gluconeogenesis significantly contributes to hyperglycemia observed in diabetes. ADP can exert hepatoprotective effects by reducing hepatic lipid biosynthesis, gluconeogenesis, inflammation, and oxidative stress [113]. Inhibition of gluconeogenesis by ADP is mainly modulated by stimulation of the liver kinase B1/AMPK axis in hepatocytes, suppressing the transcription of two gluconeogenesis-limiting enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase [114,115]. ADP then activates PPARα, inducing the upregulation of acyl-CoA oxidase and mitochondrial uncoupling protein 2 (UCP2), inhibiting ACC transcription, and activating carnitine palmitoyltransferase-1. Ultimately, it promotes the β-oxidation of fatty acids in hepatocytes and suppresses triglyceride production [116,117]. MCP-1, an attractive factor for recruiting immune cells, can be blocked by ADP, which can alleviate diet-induced chronic inflammation in the liver [118]. ADP also activates ceramidase and attenuates ceramide-mediated IR and hepatocyte apoptosis [119]. JT003, an adiponectin-based agonist, was reported to be effective in improving insulin sensitivity in HFD-induced NASH mice and reducing hepatic stellate cell (HSCs) activation in CCl_4 induced liver fibrosis [87]. ADP levels are highly correlated with the degree of liver fibrosis. Either ADP itself or ADP-inducing agents might be crucial therapeutic treatments for NAFLD.

4.8. Effect on bone, kidney, ovary (osteoporosis, DKD, PCOS)

ADP has pleiotropic effects and is possibly involved in the progression of many metabolic syndromes. Besides the above-mentioned functions, ADP also exerts positive regulatory functions on bones, kidneys, and many other organs. In terms of bone regulation, ADP can restrain osteoclast-mediated bone resorption and increase osteoblast-mediated bone formation in bone mesenchymal stem cells through Wnt/β-catenin pathway, thereby elevating bone mineral density and treating osteoporosis [120]. High ADP expression also activates the mechanistic target of rapamycin (mTOR)/p-mTOR/SIRT1 pathway to reduce renal cell death, while achieving renal protection during the development of overt DKD against lipotoxicity and oxidative stress by inducing the AMPK/PPARα pathway and improving the ceramidase activities of AdipoRs [121,122]. Additionally, it has been shown that increasing circulating levels of ADP might be a promising treatment for improving metabolic and endocrine disorders in patients with PCOS. Follistatin, a key etiological factor in PCOS, is inversely correlated with HMW-ADP and positively with insulin during an oral glucose tolerance test [123].

4.9. Effect on brain (Parkinson's disease (PD), AD, anti-aging)

ADP exhibits neuroprotective properties in the central nervous system (CNS). The LMW and MMW multimers of ADP have been verified to cross the blood-brain barrier and mostly bind with AdipoR1. Elevated ADP or chronic AdipoRon treatment in the brain partially mimics hippocampal neuroplasticity benefits of physical exercise in diabetic individuals. Meanwhile, they could induce antidepressant- and anxiolytic-like effects, irrespective of alterations in hippocampal structural and synaptic function. The subsequent activated ADP signaling cascade including AMPK/PGC-1α may potentially elevate the level of brain-derived neurotrophic factor (BDNF) in streptozotocin-induced diabetic mice, which may reverse cognitive deficits linked to diabetes [124–126]. PD and AD are prevalent neurological disorders associated with old age. The circadian rhythm disturbances are one of their clinical manifestations. Brain and muscle Arnt-like protein-1 (BMAL1), a central regulator of the circadian clock, orchestrates the cyclic activation of circadian clock genes like ADP. BMAL1 deficiency can contribute to circadian rhythm disorders, worsen neuropathological conditions and synaptic degeneration and accelerate aging [41].

Some studies have shown that increased circulating ADP is linked to extended lifespan, accompanied by a healthier metabolic phenotype [127]. ADP deficiency contributes to accelerated brain aging through mechanisms involving mitochondria-associated neuroinflammation. The cerebral cortex and hippocampus of aged ADP KO mice display pronounced upregulation of aging-associated senescence markers, including β-galactosidase, p16, and p21. Chronic inflammation and mitochondrial impairment are key features of aging. The proinflammatory cytokines, mitochondrial membrane potential, ATP, malonaldehyde, glutathione and some proteins related to mitochondrial dynamics, mitochondrial biogenesis, and autophagy such as dynamin-related protein 1 (Drp1), p62, optic atrophy 1 (OPA1) are significantly different between aged ADP KO and wild-type mice. There is a plausible causal relationship between histone deacetylase 1 and mitochondrial dysfunction in ADP-deprived conditions [128]. In addition, enhanced autophagy also serves as an important mechanism promoting longevity. A proper initiation of autophagy is necessary for eliminating aggregated proteins and maintaining skeletal muscle homeostasis during the regular aging process. Autophagy can be induced at low temperatures or through physical exercise, which is closely associated with elevated ADP levels and upregulated adiponectin receptor expression. The ω-6 polyunsaturated fatty acids and forkhead box O3 (FoxO3a) operates in the downstream pathway to facilitate autophagy [129,130].

4.10. Cancer treatment

Clinical studies have revealed an association between decreased ADP concentrations and an augmented susceptibility to the proliferation of breast cancer, characterized by a heightened aggressive phenotype [131,132]. Increasingly compelling evidence suggests that ADP might exert a preventive and protective role against the onset of breast cancer in individuals. The role of estrogen receptor-α (ERα) in the course of cancer treatment might be significant due to the effect on cellular proliferation and polarity, yet it remains a topic of debate [131,133]. In addition, ADP also exerts a role in impeding the advancement of cancer diseases such as colorectal cancer [134], nasopharyngeal carcinoma [135], endometrial carcinoma [136].

4.11. The paradox about adiponectin regulating effection

Many previous studies have shown that hypoadiponectinemia is a typical feature of obesity and associated metabolic syndromes. Nevertheless, clinical studies have recently found that some patients with obesity and associated metabolic syndromes had high ADP levels [137], but high ADP levels could not improve insulin sensitivity or attain other beneficial effects, termed as the “adiponectin paradox”.

For instance, ADP and leptin levels are elevated in patients with cirrhotic or non-cirrhotic viral-infected liver cancer. Herein, serum ADP levels were correlated with the stage of liver fibrosis, degree of cirrhosis in patients with chronic liver disease, and the extent of deterioration in the overall survival of patients with hepatocellular carcinoma [138–141]. Serum ADP levels may be an effective parameter in differentiating early NASH (decreased ADP levels) from more advanced stages such as cirrhosis and hepatocellular carcinoma (elevated ADP levels) [142]. On the other hand, there are many explanations for high ADP levels in patients with severe cardiovascular or other metabolic diseases (liver and kidney disorders) that are yet to be fully corroborated. One explanation is that it may be due to an imbalance in the release and clearance of ADP. Severe damage to adipose tissue function affects ADP release [143], but inflammation and hepatic and renal impairment can cause delayed ADP clearance [138]. Elevated ADP levels, acting as a signal reflecting the development of functional ADP resistance, may also be due to adipose tissue attempting to compensate for the energy deficiency caused by myocardium failure. In addition, the ADP paradox may be related to an increase in glycosylphosphatidylinositol phospholipase D (GPI-PLD). Under normal conditions, the functional ADP signaling pathway can suppress plasma GPI-PLD levels. However, abnormal ADP signaling induced by overnutrition may arouse a vicious circle. Impaired ADP signaling leads to elevated GPI-PLD levels, which result in the absence of membrane-bound T-cadherin, further diminishing ADP signaling. When ADP is no longer bound to T-calmodulin and is thus sequestered, ADP levels in the blood rise. The elimination of cellular ceramides is carried out through the interaction of ADP and T-cadherin, and metabolic issues worsen when this mechanism is dysfunctional [144,145].

In many studies, ADP has been shown to be positively related to mortality rate in some clinical sets, with only very few studies revealing the expected inverse association. Such cases may be affected by the direct and significant link between ADP itself and natriuretic peptides, which are well-established risk factors for mortality rate [146]. The paradox may also be mediated by growth differentiation factor 15 (GDF-15), a cardiac endocrine factor [147]. Interestingly, the “adiponectin paradox” has only been observed in human prospective studies but not in rodent models. It is well established that further well-designed multifactorial indicators or randomized double-blind controlled trials are required in human clinical studies [137].

5. Drugs used to regulate adiponectin levels

5.1. Conventional chemical drugs

5.1.1. Drugs for treating T2D

Many drugs employed in the treatment of metabolic disorders such as T2D, cardiovascular diseases, as well as hepatic and renal dysfunction, have mechanisms of action closely associated with ADP. Given its regulatory role in glucose and lipid metabolism, ADP holds significant promise for the treatment of T2D. Currently, classic drugs used in clinical practice to treat T2D include metformin, PPARγ agonists (thiazolidinediones), GLP-1 receptor agonists, and DPP-4 inhibitors.

Metformin is a first-line treatment medication for clinical management of T2D. Its beneficial effects, such as blood glucose reduction, weight loss, and immune modulation, are mainly achieved through AMPK activation. Metformin has also been observed to upregulate ADP in HFD induced mice or deregulate leptin/HMW ADP in obese children, which may potentially in connection with the ER stress component PDIA4 [55,148].

In a rodent model of KKAy mice and clinical studies, PPARγ agonists, such as rosiglitazone, enhance the action of ADP by increasing AdipoRs expression and the ratio of HMW multimers to total ADP. This may be related to improved DsbA-L levels [52,149].

GLP-1 enhances glucose-triggered insulin secretion from β cells while inhibiting glucagon release. GLP-1 receptor agonists ameliorate glucolipid metabolism, resulting in weight loss and decreasing IR due to some preclinical and clinical evidence. Among these, liraglutide has been shown to lower the levels of pro-inflammatory cytokines by suppressing activation of the JNK pathway, which is accompanied by elevated ADP [150,151].

DPP-4 inhibitors (Sitagliptin and Repagliptin) can also act as promoters of ADP expression. The primary mechanism of reducing glucose levels is by restraining DPP-4 based on some clinical data, which is an enzyme responsible for cleaving the incretin hormones GLP-1 and GIP [152,153].

5.1.2. Drugs for treating cardiovascular diseases

Some therapeutic agents for cardiovascular diseases also possess the ability to influence ADP-related signaling, including Cilostazol, AngII receptor blockers, fibrates, and statins.

Cilostazol is an antiplatelet medication that exerts vasodilatory effects by elevating intracellular cAMP levels. It activates PPARγ and further upregulates ADP/AdipoRs in a db/db mouse model of T2D. The following SIRT1/AMPK downstream signaling pathway leads to the improvement of high glucose-induced endothelial dysfunction and reduction of inflammatory factors [154,155]. Cilostazol also offers therapeutic advantages for managing ischemic conditions in diabetic patients.

Chronic activation of the renin-angiotensin-aldosterone system (RAAS) has extensive implications for cardiometabolic risk and significantly contributes to this clinical state. AngII receptor blockers, like irbesartan, can also give rise to ADP possibly by promoting the PPARγ pathway in obese Zucker rats [156,157].

A notable inverse correlation exists between ADP and both dyslipidemia and the accumulation of lipids within atherosclerotic plaques. Fibrates are primarily prescribed as PPARα agonists for the treatment of hypertriglyceridemia. For example, fenofibrate has been shown to increase total ADP and HMW multimers, and AdipoRs according to some clinical trials. The ability of fibrates to induce ADP may result from their capacity to stimulate FGF21 [158–160].

Rosuvastatin increases ADP and decreases hemoglobin A1c (HbA1c) levels in treating non-ischemic chronic heart failure (NICHF) patients, as well as improving insulin sensitivity mediated by the increase in SIRT1 due to the model of HFD induced Wistar rats [161,162].

5.2. Natural products

Some natural products also have an effect on regulating ADP levels. In the presence of excess FFAs, stinging nettle (*Urtica dioica* L.) increases ceramidase activity in 3T3-L1 adipocytes, which is dependent on enhanced ADP expression, and is accompanied by improved AKT phosphorylation, independent of ADP [163].

Quercetin, with its antioxidative, insulin-sensitizing, and anti-inflammatory properties, is used in the treatment of T2D, cardiovascular disorders and NAFLD [164]. It significantly decreases glucose and lipid levels, preventing metabolic syndromes in HFD induced male Wistar rats or ob/ob mice partly through overexpression of ADP and reduction of inflammatory factors [165,166].

D-Chiro-Inositol (DCI), an active component of tartary buckwheat, can enhance insulin sensitivity by inhibiting hepatic gluconeogenesis related to the protein kinase C epsilon (PKCε)-IRS/PI3K/AKT signaling pathway in mice fed a high-fat diet and saturated palmitic acid-treated hepatocytes. In addition, DCI could potentially reduce liver lipid accumulation by activating the AMPKα/PPARα pathway [167,168].

Danthron profoundly mitigates obesity and related hepatic steatosis in HFD induced C57BL/6J mice, suggesting its potential for metabolic associated fatty liver diseases (MAFLD). Danthron promotes AdipoR2 expression and dramatically facilitates the interaction between the PPARα/RXRα heterodimer and AdipoR2, causing activation of AMPKα [169].

Recently, Ramulus Mori (Sangzhi) alkaloid (SZ-A) tablets have been approved in China for the medical management of T2D. Besides the hypoglycemic effects, SZ-A can enhance lipid metabolism and prevent weight gain in HFD-induced obese mice. This is by promoting lipolytic enzyme expression and hindering fatty acid synthase to inhibit fat buildup. SZ-A also stimulates ADP expression and exerts multiple pharmacological effects [170,171].

5.3. Adiponectin receptor agonists

The clinical application of ADP carries certain risks, as the administration of megadoses via intravenous delivery can lead to significant side effects and ADP multimers present challenges for large-scale production [172]. Several studies have consolidated drugs screened with ADP and its receptors as active sites.

Compared to full-length ADP, gADP may have greater potential in being used as a direct therapeutic agent. There have been relevant studies on the modification of gADP to improve its half-life and control its production by linking the gADP trimer to a single polypeptide chain [173]. In addition, based on the potent metabolic effects of globular domain (gADP) in various tissues, multiple peptide-based drugs have been developed targeting its functional region. The peptidomimetic ADP355 was developed to enhance metabolic stability and solubility, and it has been employed for the treatment of breast cancer, and hepatic fibrosis in some researches. It demonstrates the capacity to bind to both AdipoR1 and AdipoR2, showing a higher affinity for AdipoR1. However, subsequent efforts to optimize ADP355 (*e.g.*, ADP399) did not result in the development of derivatives with significantly enhanced cellular activities.

Moreover, utilizing the crystal structure of AdipoR1, a peptide agonist named BHD-1028 was designed. This peptide exhibits its biological activity by stimulating AMPK phosphorylation within a mouse myotube model. Additionally, during compound screening, an orally active AdipoR agonist termed AdipoRon was identified, emerging as an extensively explored non-peptide solution in ADP replacement therapy. AdipoRon mirrors ADP-like activities in diverse pathological frameworks, spanning obesity, inflammatory disorders, diabetes, thrombosis, and certain cancers like pancreatic cancer [172,174,175]. Qiu et al. recently identified a novel ADP receptor agonist AdipoAI (adipo anti-inflammation agonist), which is an analog of AdipoRon. Remarkably, AdipoAI exhibits an anti-inflammatory effectiveness approximately eightfold greater than that of AdipoRon in macrophages. Subsequently, AdipoAI has been demonstrated the capacity to mitigate periodontitis in diabetic rats [176,177]. Furthermore, ADP clinical alternative therapy-receptor agonists have been developed based on ADP active sites, and the potential to further optimize their structure makes them potentially useful in clinical applications [175,178,179].

The drugs associated with adiponectin are shown in Table 1 [52,55,148–163,165–171].

Table 1
Drugs associated with adiponectin.

Category	Metabolic syndrome	Drug name	ADP-related indicators	Regulatory mechanisms possibly related to ADP	Refs.
Conventional chemical drugs	T2D	Metformin	Leptin/HMW↓	AMPK↑	[55,148]
		Thiazolidinediones (Rosiglitazone)	HMW/total ADP↑	PPARγ↑ → ADP↑ DsbA-L↑ → ADP multimerization↑	[52,149]
		GLP-1 receptor agonists (Liraglutide)	/	GLP-1↑ JNK↓ Inflammatory factors↓ Glycolipid metabolism↑ ADP↑	[150,151]
		DPP-4 inhibitors (Sitagliptin, Repagliptin)	/	DPP-4↓ ADP↑	[152,153]
	Cardiovascular disorders	Cilostazol	/	PPARγ↑ → ADP/AdipoRs↑ SIRT1/AMPK↑ inflammatory factors↓	[154,155]
		AngII receptor blockers (Irbesartan)	/	PPARγ↑ → ADP↑	[156,157]
		Fenofibrate	HMW↑ total ADP↑	PPARα↑	[158–160]
		Rosuvastatin	Leptin/HMW↓	ADP↑ HbA1c↓ SIRT1↑	[161,162]
Natural products	T2D	Stinging Nettle (*Urtica dioica* L.)	/	ADP↑ → Ceramidase activity↑ AKT phosphorylation↑(Independent of ADP)	[163]
	T2D, NAFLD, cardiovascular disorders	Quercetin	/	Glycolipid metabolism↑ Inflammatory factors (TNF-α/MCP-1)↓ PPAR γ↑ → ADP↑	[165,166]
	NAFLD	D-Chiro-Inositol	/	PKCε-PI3K/AKT↑ → hepatic gluconeogenesis↓ AMPKα/PPARα↑	[167,168]
	MAFLD	Danthron	/	PPARα/RXRα-AdipoR2↑ → AMPKα↑	[169]
	T2D	Ramulus Mori (Sangzhi) Alkaloids	/	ADP↑Leptin↓ Inflammatory factors↓ Glycolipid metabolism↑ Lipid accumulation↓ Oxidative stress↓	[170,171]

ADP: adiponectin; T2D: Type II diabetes; HMW: high molecular weight; AMPK: AMP-activated protein kinase; PPAR: peroxisome proliferator-activated receptor; DsbA-L: disulfide bond oxidoreductase A-like protein; GLP-1: glucagon-like peptide-1; JNK: cJun NH_2-terminal kinase; DPP-4: dipeptidyl peptidase-4; HbA1c: hemoglobin A1c; SIRT1: sirtuin 1; AKT: protein kinase B; PKC: protein kinase B; PI3K: phosphatidylinositol 3-kinase; TNF-α: tumor necrosis factor-α; MCP-1: monocyte chemoattractant protein-1; RXR: retinoid X receptor.

6. Conclusions and future perspective

As one of the important biomarkers for the diagnosis of metabolic syndromes, there is a significant difference in ADP levels between healthy and metabolically disordered states. With the gradual development of its physiological mechanisms, ADP research is receiving increased attention. Because of the uncertainty in the degree of polycondensation of ADP, it is difficult to control its polymerization and quality if directly used as a therapeutic medicine. Therefore, exploring the upstream and downstream pathways of ADP; the regulatory mechanisms of ADP expression, secretion, and multimerization; and tapping into the regulatory effects of drugs on ADP may provide a new direction in broadening the treatment of obesity and related metabolic syndromes. This may open new possibilities for ADP treatment.

In conclusion, while this review aims to provide a comprehensive overview of the current state of knowledge in ADP, it is essential to acknowledge the challenge of information overload due to a broad literature search spanning several years rather than the most recent five years. The review provides readers with a holistic understanding of ADP, offering a feasible direction for the future treatment of metabolic syndromes. ADP is a promising target for the treatment of obesity and related metabolic syndromes, and it is crucial for constructing targeted drug delivery systems for metabolic disorders.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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