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Review

Back to the heart: The protective role of adiponectin

C. Caselli[a,*], A. D'Amico[b], M. Cabiati[a], T. Prescimone[a], S. Del Ry[a], D. Giannessi[a]

[a] Consiglio Nazionale delle Ricerche (CNR), Institute of Clinical Physiology, Laboratory of Cardiovascular Biochemistry, Pisa 56100, Italy
[b] Scuola Superiore S. Anna, Pisa, Italy

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death worldwide and the prevalence of obesity and diabetes are increasing. In obesity, adipose tissue increases the secretion of bioactive mediators (adipokines) that may represent a key mechanism linking obesity to CVD. Adiponectin, extensively studied in metabolic diseases, exerts anti-diabetic, anti-atherogenic and anti-inflammatory activities. Due to these positive actions, the role of adiponectin in cardiovascular protection has been evaluated in recent years. In particular, for its potential therapeutic benefits in humans, adiponectin has become the subject of intense preclinical research. In the cardiovascular context, understanding of the cellular and molecular mechanisms underlying the adiponectin system, throughout its secretion, regulation and signaling, is critical for designing new drugs that target adiponectin system molecules. This review focused on recent advances regarding molecular mechanisms related to protective effects of the adiponectin system on both cardiac and vascular compartments and its potential use as a target for therapeutic intervention of CVD.

Contents

* Corresponding author at: Institute of Clinical Physiology, Via Moruzzi, 1, 56124 Pisa, Italy. Tel.: +39 0503153551.
E-mail address: chiara.caselli@ifc.cnr.it (C. Caselli).

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1. Obesity, adipokines and adiponectin

Obesity is a risk factor in several CVD such as atherosclerosis, heart failure, hypertension, and stroke [1–3]. Adipose tissue is considered an endocrine organ, secreting a large number of bioactive molecules called adipokines [4,5]. Due to the development of obesity and consequent macrophage infiltration, adipose tissue increases the secretion of these bioactive mediators, including adiponectin, resistin, leptin, and PAI-1, that are involved in many biological processes, such as metabolism, inflammation and vascular diseases [6–8]. Adipokines could be a key mechanism linking obesity to CVD [1,8–10].

Adiponectin, the major adipocyte-secreted protein, links visceral adiposity with insulin resistance and atherosclerosis [9,11]. Unlike other adipokines, adiponectin circulating concentrations are inversely proportional to adiposity, and low adiponectin levels predict the development of T2DM and CVD [10–12]. Adiponectin production is primarily determined by adipocyte size and insulin sensitivity, with larger, insulin-resistant adipocytes producing less adiponectin [13]. While plasma adiponectin is unchanged after meal ingestion, it is increased by significant weight loss, including after bariatric surgery [1–8,14]. Adiponectin is secreted also by other different cells and tissues, including cardiomyocytes [15–18]. Again, unlike other adipokines, adiponectin exerts antidiabetic, anti-atherogenic and anti-inflammatory activities [11,19–23]. Due to these positive actions, adiponectin has been extensively studied in cardiovascular protection in recent years, becoming the subject of intense preclinical research [24–28]. This review focuses on recent advances in understanding the molecular mechanisms related to the protective effects of adiponectin on cardiac and vascular compartments. Understanding the molecular and cellular mechanisms underlying the adiponectin system is critical in the cardiovascular context for designing new drugs with adiponectin system as target.

2. The pathways of adiponectin biosynthesis

Adiponectin biosynthesis, from gene transcription to secretion into circulation as well as adiponectin signaling, including receptor and post-receptor mechanisms, are summarized in Fig. 1.

2.1. Structure and biosynthesis

Adiponectin, also called Acrp30, AdipoQ, apM1 or GBP28, was discovered in both mice and humans by four independent groups employing different experimental approaches [29–32]. The gene encoding human adiponectin is located on chromosome 3q27 [33], a locus linked with susceptibility to diabetes and CVD [34]. The full-length protein (fAd) consists of 247 aminoacids, including the N-terminal hypervariable region, a conserved collagenous domain comprising 22 Gly-Xaa-Yaa repeats and a C-terminal C1q-like globular domain [35]. Adiponectin is present in peripheral circulation as three oligomeric complexes. The trimeric adiponectin represents the basic unit and is called LMW adiponectin. Two subunits of the trimer are linked by a disulfide bond mediated through a cysteine residue in the collagen-like domain to form a hexamer, also termed MMW adiponectin. The hexamer provides the building block for the formation of a bouquet-like HMW adiponectin [36–38]. Leukocyte elastase secreted from activated monocytes and/or neutrophils can cleave the fAd, generating the 17 kDa globular fragment of adiponectin (gAd) which is found at lower levels (about 1% of total adiponectin) in the circulation [15]. Post-translational modifications, especially hydroxylation and subsequent glycosylation of several conserved lysine residues within its collagen-like domain, are required for the intracellular assembly of the HMW oligomeric

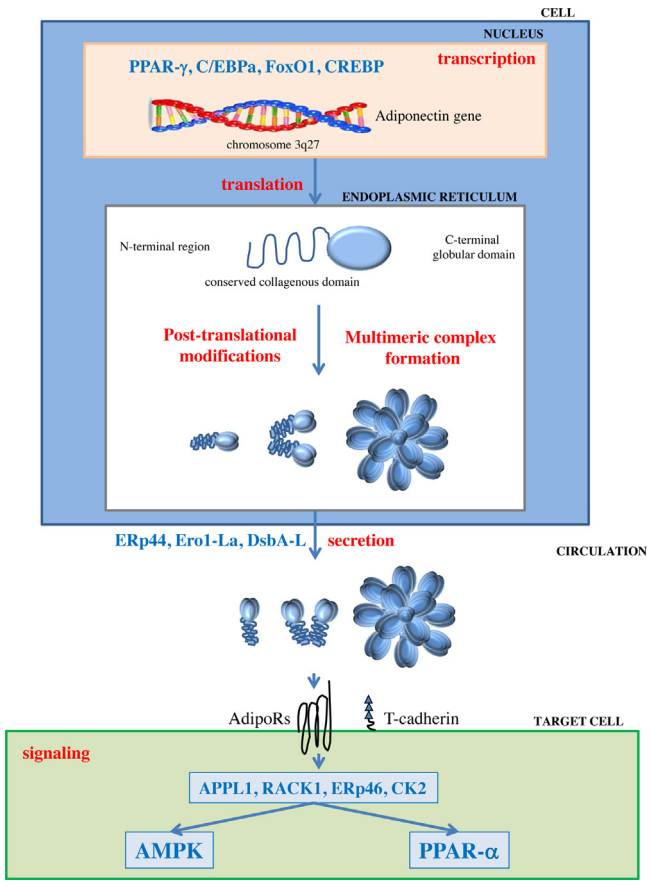

Fig. 1. Gene regulation, synthesis, secretion and signaling of adiponectin.

complex in adipocytes and for its secretion [39]. The biosynthesis and secretion of adiponectin in adipocytes are regulated by several molecular chaperones in the ER, including ERp44, Ero1-La and DsbA-L [40–42]. Multimeric complex formation of adiponectin is recognized as an important mechanism modulating its biological functions [38]. HMW is considered the biologically active form and, rather than total adiponectin, may exert anti-atherogenic, anti-diabetic and anti-inflammatory actions that would prevent the development of metabolic and CVD [43]. Extensive post-translational modifications are also required for maintaining its stability in the circulation [44]. For example, the extent of succination of adiponectin is elevated in diabetes, possibly contributing to impaired adiponectin secretion in obesity-related disorders [45]; yet, adiponectin is also modified by sialic aids through O-linked glycosylation within its hyper-variable region, modulating its plasma half-life and concentration [46].

Adiponectin shows abundant levels and a rapid turnover in peripheral circulation, representing about 0.01% of total plasma protein [26,47] and it is rapidly cleared within 1 h after its secretion. Different immunometric assays, developed in the last years for measuring adiponectin in plasma, use different antibodies and standard preparations to build the calibration curve, mainly performed using recombinant adiponectin or human serum stabilized in pre-treatment buffer. A complete standardization of adiponectin assay as well as a clear definition of reference ranges is so far lacking. These issues are of pivotal importance for evaluating its role in different patho-physiological conditions, especially in CVD [47,48].

2.2. Gene transcription, inflammation and ER stress

The adiponectin gene promoter contains multiple transcription factor binding sites through which a number of factors modulate