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Regulation of adiponectin multimerization, signaling and function

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Adiponectin, which exists in serum in three major complexes including trimer, hexamer, and the high molecular weight (HMW) form, has strong insulin sensitizing, anti-inflammatory and anti-diabetic functions. Different adiponectin complexes exert tissue-specific biological functions and activate distinct signaling pathways. In this review, we summarize our current understanding on the mechanisms regulating adiponectin multimerization. We also describe the major target tissues in which distinct adiponectin multimers exert their functional roles. Finally, we discuss the potential involvement of endoplasmic reticulum stress and mitochondrial stress in diet-induced adiponectin downregulation and highlight the roles of Disulfide bond A oxidoreductase-like protein (DsbA-L) in the prevention of endoplasmic reticulum stress and promotion of adiponectin multimerization, stability, and function.

Introduction

Adiponectin has great potential as a therapeutic target for a variety of obesity-associated diseases, including type 2 diabetes, non-alcoholic steatotic hepatitis (NASH), and atherosclerosis [1–4]. However, manipulation of circulating adiponectin has been quite challenging due to its complicated multimeric structure and the presence of high concentrations of this adipokine in serum, which is roughly 3 orders

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of magnitude greater than most other hormones in humans [5]. The successful development of adiponectin as an effective therapeutic drug, therefore, is critically dependent upon our understanding of the cellular mechanisms regulating adiponectin biosynthesis, secretion, and action.

Adiponectin circulating in plasma exists in three major forms: trimer, hexamer, and high molecular weight (HMW) multimer [6–9], as well as a proteolytically cleaved form, globular adiponectin [10,11]. The percentage of the HMW and hexamer multimers was relatively higher in the plasma of mice than in human subjects [12,13]. Different adiponectin multimers, which have been shown to exert distinct biological properties, do not interconvert once in circulation [13]. The HMW form of adiponectin has been shown to be the more active form of the protein and has a more relevant role in improving insulin sensitivity and protecting against diabetes [14–17]. Impaired adiponectin multimerization, particularly selective reduction of the HMW adiponectin concentrations, was found to be associated with various metabolic diseases such as obesity, insulin resistance, type 2 diabetes, and arteriosclerosis [5,17–20] and contributed to the worsening of insulin resistance and its metabolic complications in myotonic dystrophy type 1 patients [21]. An increase in the HMW form, rather than the total level of adiponectin, was found to be associated with insulin-sensitizing effect of Thiazolidinediones (TZDs) in both mice and human diabetic patients [20]. Consistent with this finding, increasing the HMW form of adiponectin by fat-specific overexpression of DsbA-L protected mice from diet-induced insulin resistance [12]. In fact, it has been suggested that reduced levels of the HMW form rather than total levels of adiponectin could be a superior biomarker for insulin resistance, the metabolic syndrome, and type 2 diabetes [17]. However, how adiponectin multimerization is regulated and whether impaired adiponectin multimerization has a causative role in insulin resistance and metabolic dysfunction remains largely unclear, which greatly hinders the development of adiponectin-based therapeutic treatments. This review describes the most recent advances in the understanding of the mechanisms regulating adiponectin biosynthesis and function.

Molecular structure and multimerization of adiponectin

Adiponectin, a member of the complement 1q family, consists of a signal sequence at the N-terminus, followed by a variable region, a collagenous domain, and a C-terminal globular domain [22,23]. A number of studies have demonstrated that the N-terminal region of adiponectin plays an essential role in the multimerization of this adipokine. There is a conserved cysteine residue at the N-terminus (Cys^{36} in human and Cys^{39} in mouse) and the formation of an intermolecular disulfide bond via this residue is essential for adiponectin multimerization and secretion [8]. Replacing Cys^{39} with serine completely disrupted the assembly and secretion of hexamer and HMW adiponectin, but had very little effect on the formation of the trimer [8]. Cys^{39} was also identified as a key site of succination of adiponectin which blocks adiponectin multimerization, and may contribute to the decrease in plasma adiponectin in diabetes [24]. Another highly conserved amino acid residue within the N-terminus is tryptophan (W^{42}) and a mutation of this residue profoundly affects adiponectin assembly by trapping full-length adiponectin in the oxidized trimeric or hexameric states, probably due to a proximity effect causing a reduction in the rate of Cys^{39} oxidation [25]. In addition to disulfide bond formation, adiponectin multimerization is also regulated by hydroxylation and glycosylation [26]. There are four conserved lysine residues in the collagenous domain of adiponectin (Lys^{65}, Lys^{68}, Lys^{77}, and Lys^{101} for human adiponectin) and hydroxylation and subsequent glycosylation at these sites are required for intracellular assembly of the trimer of adiponectin into the HMW multimer [26–28]. Hydroxylation is also detected at several proline residues in human adiponectin including Pro^{71}, Pro^{76}, and Pro^{95}. Inhibition of proline hydroxylation results in a more severe impairment of adiponectin multimerization, although the physiological role of this hydroxylation remains to be further clarified [28]. A number of mutations have been identified in human adiponectin that are associated with impaired adiponectin multimerization and metabolic diseases [8]. The G84R and G90S mutants of adiponectin do not form HMW multimers and are associated with diabetes and hypoadiponectinemia [8]. R112C and I164T mutants, which are associated with hypoadiponectinemia, fail to assemble into trimers, resulting in impaired secretion from the cell [8]. These data provide evidence for a link between impaired adiponectin multimerization and the causes of a diabetic phenotype in humans and suggest that not only total concentrations, but also multimer distribution should always be a consideration in the interpretation of plasma adiponectin levels in health as well as various disease states.