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Review article

C1q tumor necrosis factor-related protein 9 in atherosclerosis: Mechanistic insights and therapeutic potential

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ABSTRACT

C1q tumor necrosis factor-related protein 9 (CTRP9), a newly discovered adipokine, is the closest paralog of adiponectin. After proteolytic cleavage, it can release the globular domain (gCTRP9) that serves as the major circulatory isoform. Upon binding to adiponectin receptor 1 (AdipoR1) and N-cadherin, CTRP9 can activate a variety of signaling pathways to regulate glucose and lipid metabolism, vascular relaxation and cell differentiation. Circulating CTRP9 levels are significantly decreased in patients with coronary atherosclerosis disease. Data obtained from *in vitro* experiments and animal models suggest that CTRP9 exerts an atheroprotective effect by altering multiple pathological processes involved in atherosclerosis, including inflammation, foam cell formation, endothelial dysfunction, insulin resistance, and vascular smooth muscle cell dedifferentiation, proliferation and migration. In this review, we summarize the latest advances regarding the roles of CTRP9 in atherosclerosis with an emphasis on its potential as a novel therapeutic target in cardiovascular disease.

1. Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in the developed countries. Epidemiological studies have suggested that CVD accounts for >17 million deaths globally every year, which is predicted to rise to >23 million by 2030 [1]. Atherosclerosis has long been thought to be the common pathological basis of most cardiovascular diseases such as myocardial infarction, stroke, and peripheral arterial disease. The formation of atherosclerotic lesions is a chronic process involving a complicated signaling network and various effector molecules [2,3]. Although statin monotherapy or its combination with other drugs has obtained considerable improvement in clinical outcomes of CVD patients, the residual risk is still a major challenge [4]. Thus, a more detailed understanding of the roles of key molecules in atherogenesis is essential to develop novel therapeutic strategies for CVD.

Adipokines are bioactive substances secreted by adipose tissue, including adiponectin, leptin, omentin, and C1q tumor necrosis factor-related proteins (CTRPs). Among them, adiponectin is the most extensively investigated adipokine and confers a variety of beneficial effects on cardiovascular system [5]. As the paralogs of adiponectin, CTRPs are a highly conserved family containing 15 members from CTRP1 to CTRP15 [6,7]. Of all members, CTRP9, a secreted glycoprotein discovered in 2009, has the highest similarity to adiponectin [8]. Several lines of evidence have shown that CTRP9 can attenuate myocardial ischemia-reperfusion injury, inhibit adverse cardiac remodeling after acute myocardial infarction (AMI), and ameliorate pulmonary arterial hypertension in rodents [9–11].

Abbreviations: CVD, cardiovascular disease; CTRPs, C1q tumor necrosis factor-related proteins; AMI, acute myocardial infarction; HMW, high molecular weight; AMPK, adenosine monophosphate-activated protein kinase; eNOS, endothelial nitric oxide synthase; AdipoR, adiponectin receptor; ECs, endothelial cells; MSCs, mesenchymal stem cells; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor-coactivator-1α; NF-κB, nuclear factor-κB; ACC, acetyl-CoA carboxylase; LXRα, liver X receptor α; ABCA1, ATP-binding cassette transporter A1; VSMCs, vascular smooth muscle cells; ERK, extracellular signal-regulated kinase; MMP-9, matrix metalloproteinase-9; Nrf2, nuclear factor erythroid-derived 2-like 2; CAD, coronary atherosclerosis disease; HDL-C, high-density lipoprotein cholesterol; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; T2DM, type 2 diabetes mellitus; ICAM-1, ntracellular adhesion molecule-1; VCAM-1, vascular cellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; ox-LDL, oxidized low-density lipoprotein; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; PDGF-BB, platelet-derived growth factor-BB.

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Recently, accumulating studies reveal that CTRP9 is protective against atherosclerosis through multiple mechanisms including inhibition of inflammatory response, regulation of lipid metabolism, and amelioration of endothelial dysfunction, suggesting this adipokine as a novel and promising target to prevent and treat atherosclerosis-associated disease [12,13]. In this review, we summarized the current knowledge about the roles of CTRP9 in atherosclerosis to provide a rationale for future investigation and therapeutic intervention.

2. Structural features and post-translational modifications of CTRP9

Both human and mouse *CTRP9* genes have similar exon and intron structures [8]. Human *CTRP9* gene (12.6 kb) contains 4 exons and is located on chromosome 13q12.12. Mouse *CTRP9* gene (12.7 kb) also consists of 4 exons and is mapped to chromosome 14. Human CTRP9 protein contains 333 amino acid residues with a predicted molecular mass of 32 kDa. Similar to adiponectin, CTRP9 is composed of a signal peptide (residues 1–19) to direct protein secretion, a short N-terminal domain (residues 20–28), a collagen-like domain with 56 Gly-X-Y repeats (residues 29–196), and a C-terminal globular C1q domain (residues 197–333, Fig. 1). These 4 domains also exist in other CTRPs except CTRP4. However, CTRP9 shares the highest degree of amino acid identity (54%) with adiponectin in the C-terminal globular C1q domain, suggesting that both adipokines may have similar functions [8]. CTRP9 is also evolutionarily highly conserved among dogs, chickens, zebrafishes, frogs, mice, and humans.

There are 22 Gly-X-Y repeats and one consensus GXKG(E/D) motif in the collagen-like domain of adiponectin. It has been reported that proline residues in its Gly-X-Y repeats undergo hydroxylation for structural stabilization [14,15]. Lysine residues in the consensus GXKG(E/D) motif are hydroxylated and subsequently glycosylated with a glucosyl-galactosyl group, leading to enhancement of its function [16,17]. CTRP9 has a longer collagen-like domain with 56 Gly-X-Y repeats. In line with adiponectin, mass spectrometry showed that 10 of the 13 proline residues in the Gly-X-Y repeats of CTRP9 are hydroxylated, and two of the seven lysine residues in its consensus GXKG(E/D) motif are hydroxylated and glycosylated [8]. However, the effects of these post-translational modifications on CTRP9 structure and function remain largely unknown. Future research in this area will help deepen the understanding of its role in cardiovascular system. Proteolysis, a common post-translational modification, frequently occurs in the CTRPs. For example, furin mediates endogenous cleavage of full-length CTRP12 to liberate the globular domain with different structure and function [18]. Similarly, CTRP9 monomers form the trimeric complexes, which undergo proteolytic cleavage to release their globular domain (gCTRP9) as the major circulatory isoform (Fig. 2) [19]. Moreover, gCTRP9 has stronger effects on the activation of adenosine monophosphate-activated protein kinase (AMPK), Akt and endothelial nitric oxide synthase (eNOS) than full-length CTRP9 [19]. Thus, promoting gCTRP9 production may be an effective approach for enhancing the biological function of CTRP9.

3. CTRP9 expression profile

CTRP9 is predominantly produced by adipocytes, but other types of cells, such as cardiomyocytes, can also synthesize this molecule [20]. This raises an intriguing possibility that CTRP9 is not only an adipokine but also a cardiokine. In accordance with adiponectin, higher levels of CTRP9 transcripts are found in female

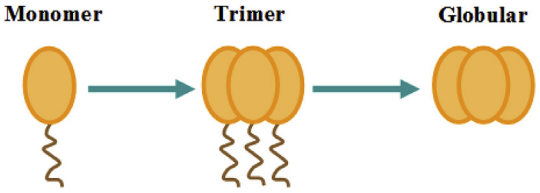

Fig. 2. A schematic showing CTRP9 isoform production.
CTRP9 is first synthesized as a monomer. Three monomers are assembled into a trimeric complex. These trimers are proteolytically cleaved to form gCTRP9, the primary circulatory isoform.

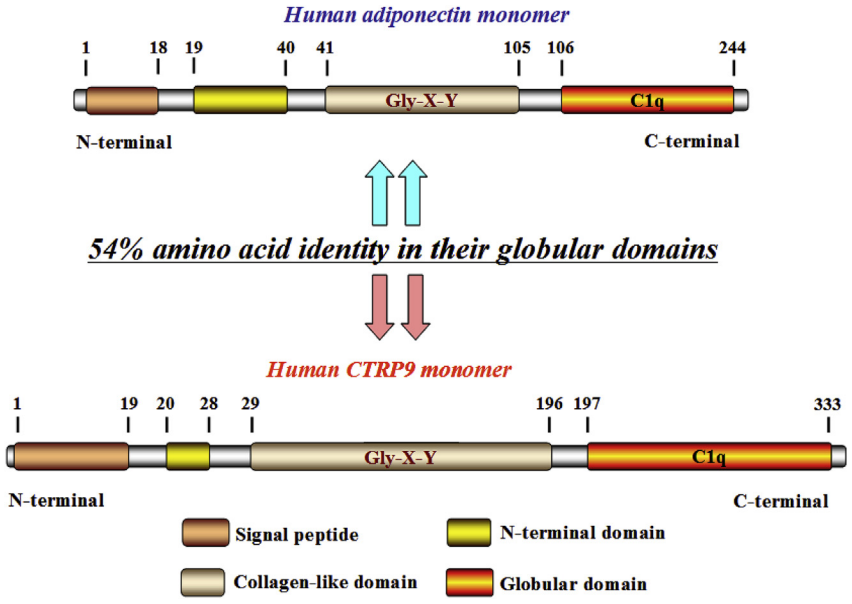

Fig. 1. Schematic of human adiponectin and CTRP9 monomer structure.
Human adiponectin and CTRP9 monomers are composed of four regions: a signal peptide, an N-terminal domain, a collagen-like domain with multiple Gly-X-Y repeats, and a C-terminal globular domain homologous to the immune complement C1q. These two adipokines share 54% amino acid identity in their globular domains.