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Adipose tissue-derived cytokines, CTRPs as biomarkers and therapeutic targets in metabolism and the cardiovascular system

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ABSTRACT

Increasing evidence indicates that adipose tissue-originated cytokines mediate communication between obesity-related exogenous molecules and the molecular events that initiate the metabolic syndrome and the inflammatory responses in the cardiovascular system (CVS). Adipose tissue-derived cytokines including the C1q/tumor necrosis factor-related proteins (CTRPs), a 15-member family of novel adipokines, has attracted much interest due to its metabolic regulatory and anti-inflammatory effect and appear to play a pathophysiological role in metabolism and immunity. To date, 15 members of CTRP family have been identified and they also play a role in the CVS, especially as potent biomarkers or therapeutic targets for modulating metabolic or inflammatory functions. Therefore, this review will focus on the characteristics of CTRPs that influence cardiovascular function and on the potential of CTRPs as biomarkers and therapeutic targets.

INTRODUCTION

During the last decade, a mounting number of adipocyte-originated hormones (adipokines) have been recognized and documented to be discriminately regulated during the onset of metabolic syndrome, obesity, and the inflammatory processes. By acting systemically as circulating hormones or locally on diverse cell types, adipokines are involved in the regulation of many physiological functions, including energy storage, metabolism, and the development of obesity-associated disorders (type 2 diabetes mellitus,

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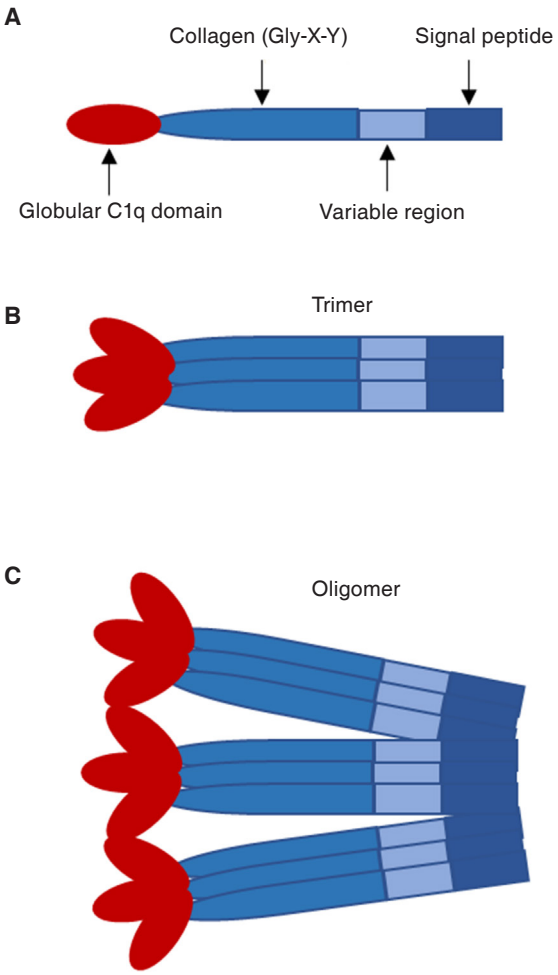

Figure 1: Structural organization of the CTRPs. A: domain structure of CTRP monomeric protein; B: homotrimeric CTRP protein structure. C: CTRP trimeric proteins form higher-order three-dimensional structures. CTRPs: C1q/tumor necrosis factor-related proteins

cardiovascular disease, the inflammatory process).

Adiponectin, discovered as the first member of the C1q/tumor necrosis factor-related proteins (CTRPs) family, has been broadly investigated because of its metabolic regulatory and cardiovascular protective effects. To date, additional CTRP family members, a newly discovered novel family of adipokines, have been identified that may play a role in metabolism and cardiovascular system path-physiological regulation. Hence, in future, the studies on these novel adipokines will provide new understandings into the physiological/pathological mechanisms including the communication of different organs based on energy homeostasis, homeostasis of the internal environment, and prevention of inflammation.

The current review focuses on the main roles of CTRPs in the context of pathophysiology with particular attention to their potential biomarker features and therapeutic roles in the metabolic energy balance regulation, inflammatory responses and in obesity-associated disorders.

WHAT ARE CTRPS?

CTRPs, first identified by the Harvey Lodish laboratory, are considered a new family of secreted proteins from various organs. These 15 secreted proteins (CTRP1 to CTRP15) share common structural and functional characteristics with adiponectin: a N-terminal signal peptide, a short variable region, a collagen domain containing collagen triples (Gly-X-Y), and a C-terminal globular complement factor C1q domain [Figure 1][1,2]. CTRPs display distinct biological and signaling properties by occurring in the circulation as trimers and assembling with their basic structural unit into hexameric and high molecular weight oligomeric complexes [Figure 1]. Most CTRPs are expressed by adipose tissue and circulate in plasma. Their plasma levels vary with the genetic background, age, gender, and metabolic states. In terms of CTRPs sexually dimorphic patterns, female mice express higher levels of CTRP13, CTRP11, CTRP9, CTRP5, and CTRP3 compared to male animals/humans[1-5]. The exact mechanism for these differences is still unclear.

CTRPs are expressed and distributed in a variety of ways that may determine their diverse biological functions [Table 1]. To date, metabolic functions have been established for CTRP1, CTRP2, CTRP3, CTRP5, and CTRP9[2]. Although the functional receptors for CTRPs have not yet been recognized, vascular, liver, muscle, heart and adipose tissue are the likely targets of CTRPs. They share similar structure and function with adiponectin[6], including the regulation of balance of body energy metabolism through enhancing insulin sensitivity in the liver and muscle, exhibition of anti-inflammatory responses, and protection of the cardiovascular system (CVS). Thus, the CTRP family may have parallel implications for energy homeostasis and provides new pharmacological targets in the obesity-related diseases and type 2 diabetes. Meanwhile, they consist of many family members distributed in various organs, hence they have the potential to serve as biomarkers in the obesity-related diseases and may serve as detectable parameters for early prognosis and diagnosis.

CTRPS IN CIRCULATION

Endogenous CTRPs can be detected in the blood by enzyme-linked immunosorbent assay (ELISA), even although they circulate at 1-2 orders of magnitude less than adiponectin. The distribution of CTRPs levels

Table 1: Overview of the function of CTRP family

CTRP	Expression	Function
1	Heart, liver, muscle, kidney, sexual gland	Metabolic regulation: glucose and lipid hemostasis; antithrombotic effects; attenuate plaque formation; increases aldosterone production[18,54,55]
2	Adipose tissue	Metabolic regulation: improve insulin and lipid tolerance[18]
3 (3A,3B)	Kidney, brain, small intestine, adipose tissue	Regulates glucose and lipid metabolism regulates systemic inflammation in obesity and insulin resistance; modulates mitochondrial biogenesis; attenuate liver fibrosis; biomarker for diabetic retinopathy; negative regulator of osteoclastogenesis; independent predictor for atherosclerosis[47,56-60]
4	Hepatic cells	Modulates energy metabolism; novel nutrient-responsive central regulator of food intake and energy balance; reduces colitis; suppresses the pyroptosis of trophoblasts derived from rats with preeclampsia[61-63]
5	Adipose tissue, ocular tissue	Inhibits pro-metabolic insulin signaling; related to the degree of obesity and is associated with obesity-related at alterations; associated with ISR after PCI with DES implantation; associated with obesity and diabetes; Alleviates insulin resistance; circulating markers of metabolic disease, diabetes, nonalcoholic fatty liver disease and age-related macular degeneration[64-67]
6	Adipose tissue, human synoviocytes	Novel metabolic/immune regulator; modulating both inflammation and insulin sensitivity; regulates fat development; alleviates AngII-induced hypertension and vascular endothelial dysfunction; potential therapeutic target for the prevention of skin fibrosis; endogenous complement regulator[5,29,68,69]
7	Adipose tissue, lung	Improves insulin sensitivity; beneficial metabolic outcomes in the setting of obesity and diabetes[9,54]
8 (8B)	Lung, testis, absent in mice	Blocks glioblastoma dissemination within the brain[14,70]
9 (9A,9B)	Cardiac tissue, adipose tissue	Important in the development of type 2 diabetes; novel metabolic regulator and a new component of the metabolic network that links adipose tissue to lipid metabolism in skeletal muscle and liver; prevents vascular restenosis after angioplasty, hepatic steatosis and hypertension; stabilizes plaque, improves endothelial cell survival and function[12,20,48,71-73]
10	Eye, adipose tissue	Regulates metabolism, adipose tissue homeostasis[3,23]
11	Adipose tissue	New regulator of adipogenesis; maintains adipose tissue homeostasis[3,74]
12	Adipose tissue	Novel biomarkers for the prediction and early diagnosis of T2DM; regulates glucose and lipid metabolism and whole-body glucose homeostasis[24,50,51,75,76]
13	Adipose tissue, brain	Associated with increased risk of T2DM and coronary artery disease and non-alcoholic fatty liver disease; negative association with metabolism; modulates whole-body energy balance[2,24,27,77,78]
14	Brain, adipose tissue	Promotes tissue regeneration, and recovery of ischemic heart disease; maintains adipose tissue homeostasis by generating complexes with CTRP11[74]
15	Skeletal muscle	Modulates energy homeostasis and metabolic circuit; modulates inter-tissue crosstalk[21,79]

ISR: in-stent restenosis; PCI: percutaneous coronary intervention; DES: drug-eluting-stent; CTRP: C1q/tumor necrosis factor-related protein; T2DM: type 2 diabetes mellitus

Table 2: C1q/TNF-related proteins traits

Characteristic	Description
Metabolism	Regulation of insulin sensitivity, glucose and lipid metabolism; expression of C1q/TNF-related proteins is various in conditions of obesity and diabetes; promotion of insulin sensitivity, promoting insulin resistance; action is local, action is systemic, exertion of effects via central neuron mechanisms or action on peripheral tissues
Muscle and liver	Regulation of AMPK signaling pathway Inflammation; inhibition of monocyte chemoattractant releasing; inhibition of LPS-induced basic and common proinflammatory pathways
Obesity and type 2 diabetes	Potent inhibition of LPS-induced systemic inflammation; regulation of TLR9 signaling pathway in chronic inflammation[80], biomarker in reflecting the degree of inflammatory response

LPS: lipopolysaccharide; TLR: toll-like-receptor; TNF: tumor necrosis factor; AMPK: AMP-activated protein kinase

varies and is influenced by metabolic hormones, significant signaling and inflammatory states, meanwhile, they can exist in autocrine, paracrine, and endocrine manners that influence the individual susceptibility to the disease and therefore, it provides the possibility that they timely reflect the processing of insulin resistance, obesity, and type 2 diabetes. Accumulated studies reveal that circulating levels of CTRP3, CTRP6, CTRP7, CTRP9, CTRP12, and CTRP15 are reduced in diet-induced diabetes or obese mice or humans[4,5,7-9]. CTRP1 and CTRP5 concentrations are higher in obese and diabetic rodents[10]. The characteristics of CTRPs in various situations are listed [Table 2]. While different CTRP oligomers have distinct distribution properties, the functional significance of CTRPs still remains largely undefined.

CTRPS PERTURBATIONS AND METABOLISM

Inter-organ communication in the organism is necessary to maintain the integrated control of

metabolism and this crosstalk can be realized by the well-orchestrated secreted hormones. The newly discovered CTRPs family has profound significance aiding better understanding of hormonal control of the energy homeostasis based upon the reports from the research group lead by Wong and other researchers in the last decade[11]. They discovered the contributions of various CTRPs hormones to whole-body glucose and lipid metabolic regulation.

CTRPs can dynamically modulate the response to the alterations in short-term nutritional states or the changes in long-term metabolic status. However, the signaling pathways modulated by CTRPs are frequently disrupted by the metabolic perturbations of excess caloric uptake in obesity- and inflammation-induced disorders. Consequently, the hormone dysregulation leads to broad metabolic disorders such as insulin resistance, diabetes, and obesity. Those disruptions include the alterations of structural organization, and post-translational modifications of CTRPs.

For CTRPs structural organization, it has been reported that all CTRPs form trimers, but accumulating reports reveal that CTRP3, CTRP5, CTRP9, CTRP6, CTRP8, CTRP10, CTRP11, CTRP12, CTRP13 and CTRP15 can further assemble into multimeric complexes mediated by the N-terminal Cysteine residues or with the aid of oxidoreductase. Adiponectin, as an insulin sensitizer, assembles with CTRP9 to form heterotrimers[12], by which CTRP9 and adiponectin share the same receptor to exert their cardiovascular protective function[13]. In addition to forming the homo-oligomers, CTRP6/CTRP1, CTRP7/CTRP2, and CTRP2/adiponectin form heterotrimers generating functionally distinct ligands to provide new framework for the action of this family of secreted glycoproteins in normal and diseases states[11]. CTRP9 has 2 isoforms 9A and 9B, whereas CTRP9B requires physical interaction with CTRP9A and adiponectin for completing its function[14]. CTRP8 in addition to forming homotrimers, forms heteromeric complexes with CTRP1, CTRP9 and CTRP10. It effectively activates GPCR relaxin/insulin like family peptide receptor (RXFP1 receptor) to enhance the motility of the glioblastoma through regulating the activity of cathepsin B[15].

CTRPs, as secreted hormones are subjected to multiple functionally relevant post-translational modifications at their highly conserved residues. CTRP12 is glycosylated on the 39th Asparagine amino acid and the 85th Cysteine modified with oligosaccharides which mediates the assembly of oligomeric structure in human embryonic kidney (HEK) 293T cells. However, the exact modification mechanisms are still under investigation[16]. In addition, the two isoforms of CTRP12 differ from the oligomeric structure and are distinct in the regulation of function. Full length CTRP12 preferentially stimulates the Akt signaling in adipocytes, whereas the globular form activates the mitogen-activated protein (MAP) kinase signaling[16]. CTRP9, as a secreted glycoprotein, can be multiple post-translationally modified in multiple ways in its collagen domain. However, since the CTRP9 globular domain is closely similar to that of adiponectin, the interaction between CTRP9 and adiponectin does not need their collagen domains and is independent of posttranslational modification to activate the downstream signaling pathways[12]. Here, we highlight the characteristics of CTRPs and their isoforms; modification of CTRPs could account for the functional diversity of CTRPs.

The circulating levels of CTRPs tend to fluctuate according to sex, age, and alterations in the metabolic states and are sensitive to different responses in mammals. Reports have been made that CTRP6, a protein with fundamentally different modes of action as opposed to other CTRPs characterized to date, is a negative physiological regulator of glucose metabolism in adipocytes, skeletal muscle and liver to control the systemic energy balance. Expression of CTRP6 is upregulated in leptin deficient animals and increases in diabetic animals[8]. However, other researchers have reported that CTRP6 induces fatty acid oxidation in myocytes via AMPK activation[17]. These studies suggest that the newly discovered CTRPs still need to be investigated further in depth to understand their diverse functions. In addition, other CTRPs functional analysis reveals various roles of CTRPs. CTRP2 exerts fatty acid oxidation and glycogen deposition in myotubes[18]. CTRP1 transcript levels are augmented by rosiglitazone in mice, which enhance the insulin sensitizing action on the skeletal muscle via activation of the AMPK and Akt pathways[19]. CTRP3 can be a secreted plasma hormone and regulates hepatic gluconeogenesis. The metabolic regulatory action of CTRP3 is the downregulation of its plasma concentration which indicates that CTRP3 has a significant role in regulation of the lipid metabolism although the exact mechanism has not yet been established. However, CTRP3 deficiency reduces the liver size which indicates that its target organ appears to be the liver. Additionally, reduced circulating level of CTRP3 alters the inflammatory responses in the obese animals and the short-term daily administration of CTRP3 in diet-induced obese mice has been sufficient to improve the fatty liver phenotype, as evidenced by the suppressed triglyceride content and

expression of the triglyceride synthesis genes[1,20]. Hence, CTRP3 shows potent action on the regulation of metabolism. Loss of CTRP5 improves the insulin action states and hepatic steatosis. Deletion of CTRP7 attenuates the obesity-linked glucose intolerance of cytokine expression and circulating levels of cytokine[8]. Overexpression of CTRP9 modestly downregulates the serum glucose and insulin levels. CTRP9 and CTRP15 are considered as cardiokine (the heart-derived proteins are termed cardiokines) due to their high profile in the cardiac tissue and for their protective and preventive actions against cardiovascular injury. Although the CTRP9's functional receptor has not been thoroughly investigated, cadherin family appears to be a potential candidate[21]. Loss of CTRP12 affects the glucose and lipid metabolism in the obese and insulin-resistant mouse models[22]. CTRP13 regulates the metabolism through AMPK activation and decrease of fatty acid-induced JNK signaling[23]. CTRP15 links skeletal muscle and liver to systemic lipid homeostasis[21]. We summarize current understanding of CTRPs metabolic functions and provide insight into the dynamic regulatory role of CTRP on metabolic balance. Although much has been acknowledged since CTRPs were initially defined, many more questions remain to be addressed.

Of all the CTRPs, CTRP1, CTRP3, CTRP9, CTRP12, CTRP13 have been reported to exhibit positive metabolic regulation and cardiovascular effects in animal models. However, in human studies, circulating levels of CTRP1 are elevated, while CTRP12 displayed a decrease in type-2 diabetes patients. Thus, circulating CTRP1 and CTRP12 can serve as potential novel biomarkers for the early diagnosis of type-2 diabetes in humans[24,25]. The measurement of circulating CTRPs in serum is through commercially available ELISA kits provide by Aviscera company (Santa Clara, USA). CTRP3, in recent human studies, was increased in subjects with the cardio-metabolic syndrome and is associated with various cardio-metabolic risk factors including the triglycerides, high-density lipoprotein-cholesterol, waist-to-hip ratio, and eGFR, which indicate the decreased CTRP3 levels that may serve as a predictor of coronary artery disease, while CTRP13 cannot serve as a predictor candidate since there is evidence that CTRP13 mRNA expression is increased in the setting of obesity[26,27]. This contradiction may be attributed to different nature of human and rodent studies.

Collectively, based upon properties of the known and characterized CTRPS, a strategy designed for screening the biomarkers to predict the metabolic-related disease reveals that CTRP1 and CTRP12 can serve as potential novel biomarkers for the prediction and early diagnosis of type-2 diabetes, and furthermore, they represent a new treatment strategy. CTRP3 can be a better predictor for coronary artery disease than other CTRPs.

CTRPS AND INFLAMMATION

Metabolic syndrome such as obesity is associated with the chronic low-level inflammation, and therefore the metabolic regulators connecting obesity and diabetes to the inflammatory response have attracted much attention. In addition, it has been gradually recognized that the imbalance of anti-inflammatory adipokines and pro-inflammatory factors leads to the progression of obesity-related diseases. Disrupted anti-inflammatory adipokines participate in the systemic or local inflammatory reactions contributing to the initiation and development of metabolic dysfunction and cardiovascular events. In this regard, to define the imbalance of anti-inflammatory adipokines (CTRPs) and proinflammatory factors (risks factor) would be valuable in studying the obesity-associated complications. Hence, this section will emphasize the possible associations of CTRPs with cardiovascular inflammation.

CTRPs as a priming potential biomarker for predicting the dysfunctional metabolic status and therapeutic target has drawn much attention. Thus, their capability of regulation of metabolism has been widely investigated and documented. However, the association between CTRPs and inflammation, insulin resistance/obesity-linked inflammation, and pro-inflammatory cytokines needs to be thoroughly investigated even although these relationships between those disorders besides CTRPs have been well documented.

CTRPs protect against the complications of obesity such as cardiovascular diseases (CVDs) via their anti-inflammatory properties. Obesity is characterized by chronic inflammation leading to the obesity-related diseases including hypertension, atherosclerosis, and diabetes, while CTRPs as secretory proteins circulating in the organism can easily reach the site of infection to exert its anti-inflammatory characteristics.

Recent studies have shown new insights into CTRP6. For example, upregulation of CTRP6 in the leptin knock-out mice and under diabetic conditions shows distinct roles of CTRP6 in modulating inflammation[5]. In contrast to other CTRPs, CTRP6 expression is obviously elevated in adipose tissue and vascular cells in obese, diabetic patients and mouse models. Overexpression of CTRP6 not only impairs glucose

disposal in response to glucose challenge in animal models, but also augments local inflammation by targeting the inflammatory cells in production of TNF-α and IL-10[28]. Circulating inflammatory cytokines and pro-inflammatory macrophages were suppressed in the CTRP6-deficient mouse[5]. In addition, CTRP6 exhibits an immune-regulatory role in the complement system as it specifically suppresses the alternative pathway by binding of the finalizing factor-B to treat arthritis[29], where CTRP6 displays ability to cure the arthritis by intra-articulate injection in mice model[29].

Differing from CTRP6, other CTRPs exhibit the inflammatory regulatory role in a distinct way. In contrast to suppression of CTRP6 expression by cytokines, cytokines IL-1β and TNF-α elevate the expression of CTRP1 adaptively in the adipose tissue by which CTRP1 suppresses inflammation[30]. Meanwhile, CTRP1 impedes collagen-induced platelet coagulation, indicating its potent therapeutic value for treating vascular disorders during the inflammatory process[31]. CTRP3 has been shown to be capable of decreasing the secretion of pro-inflammatory mediators by primary human leukocytes, suggesting strongly an anti-inflammatory function, comparable to adiponectin[32-34]. CTRP5 appears to be a better biomarker than CTRP3 for predicting the severity of obstruction of airflow and systemic inflammation in patients with COPD although concentration alteration in response to the obese women[35,36]. CTRP4 can modulate tumor-promoting inflammation in cancer[37]. CTRP12 has been identified as an anti-inflammatory molecule by Enomoto *et al.*[38] in 2013. Even among the diverse types of cells, CTRP12 exhibits similar anti-inflammatory actions through the MAPK/JNK-dependent regulatory pathway to modulate TNF-α production.

Various CTRPs exert beneficial actions on the obesity-associated complications including inflammatory disorders through their anti-inflammatory actions. But, numerous functional, physiological, and mechanistic questions regarding the role of CTRPs in inflammation remain to be answered. The establishment and availability of transgenic and knock-out mice models for investigating inflammatory response of CTRPs will advance the knowledge of functions and mechanisms of action of CTRPs. Meanwhile, the receptor(s) responsible for the CTRP-mediated signal transduction should be thoroughly characterized and established.

CTRPS AND CARDIOVASCULAR SYSTEM

Reports show that CTRPs have beneficial function in the CVS and it is well established that the circulating levels of CTRPs are negatively correlated with the severity of CVDs without or with obesity in animals. Clinic studies indicate close association between CTRPs levels and CVDs. Conversely, the expression of inflammatory mediators in human tissues has been observed to be inversely regulated related to the levels of CTRPs[13,39]. Hence, the reciprocal relationship among CTRPs and the inflammatory mediators may present a dynamic crosstalk in the development of obesity and diabetic complications. Furthermore, the dysregulated production of CTRPs shown in obesity is associated with the pathogenesis of CVDs[40].

In contrast to adiponectin, which is a well-established adipokine for its anti-inflammatory and insulin sensitizer characteristics, CTRPs show diverse biological activities in the setting of normal metabolic condition and CVDs [Figure 2]. In the past decades, adiponectin has been recognized as a member of the CTRP family as it contains the collagen tail and C1q like globular domain. Recent studies reported that CTRPs exhibit stronger effective and sensitive response than adiponectin to different CVDs. Therefore, in this section, we mainly focus on the characteristics of anti-inflammatory and metabolic regulatory actions of the CTRPs in the onset of metabolic dysfunction-related CVDs.

Cardiovascular metabolism plays a pivotal role in the CVDs and the metabolic cascade is particularly important to investigate in the normal and disease processes. Cardiovascular metabolic dysfunction contributes to the progression of obesity-linked cardiovascular events and marks the fate of treatment application. Accumulating studies show that increased levels of CTRP1 are closely associated with the initiation and severity of the coronary arterial disease and can serve as a marker for myocardial infarction[10]. Meanwhile, the inhibition of CTRP1 may slow down the pathogenesis of early stage atherosclerosis and prevent the development of pathological vascular remodeling[41,42]. Circulating levels of CTRP 3 is elevated in patients with dysfunction of glucose metabolism and is associated with numerous cardiovascular metabolic risk factors[26]. It also can serve as a biomarker to predict proliferative retina disorder (PDR) and has beneficial actions for preventing CVDs, providing a promising strategy of vascular remodeling[43]. The levels of CTRP5 are associated with in-stent restenosis after percutaneous coronary intervention (PCI) with drug-eluting-stent implantation. CTRP9 can reflect the pathophysiology of renal involvement and abnormal glucose metabolism besides impairing vasorelaxation in type 2 diabetics[44]. CTRP15, a newly identified myokine, can link skeletal muscle to lipid homeostasis

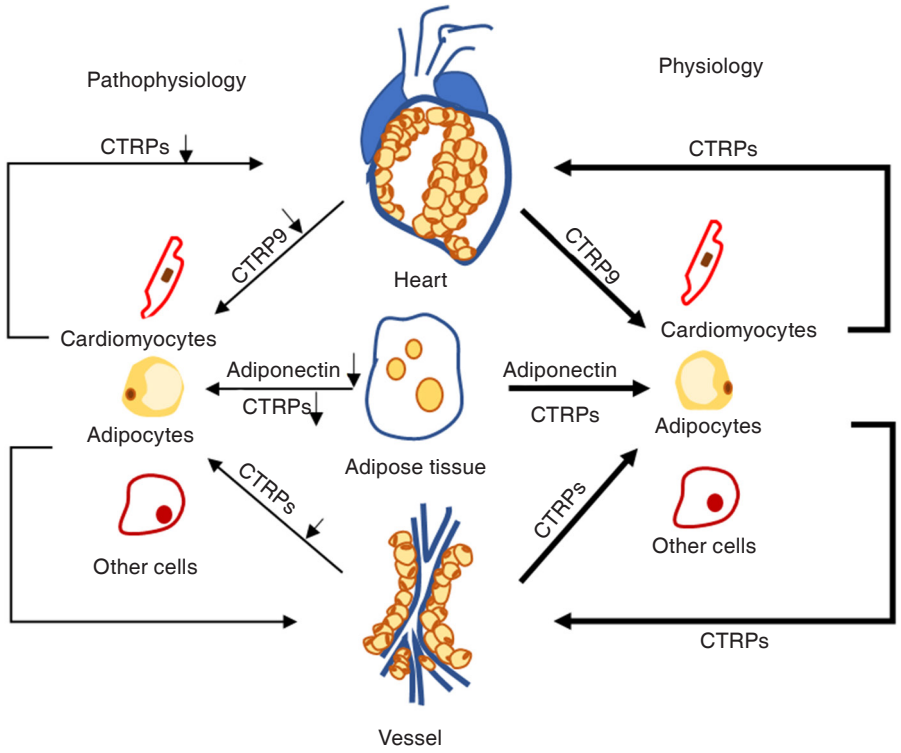

Figure 2: Pathophysiology of CTRPs in cardiovascular system. CTRPs exerts protective effects in cardiovascular system in physiological condition, but unbalanced levels of CTRPs in pathophysiological condition contributes to the development of cardiovascular relevant disease. CTRPs: C1q/tumor necrosis factor-related proteins

in response to alterations in energy state and predicting changes in the metabolic circuit[21].

Therefore, among the CTRPs, CTRP1 displays the potential to serve as a marker and therapeutic target in the vascular system and CTRP3 exhibits biomarker features in patients with diabetic-related PDR[45]. CTRP5 appears to have a greater potential to serve as a biomarker to predict the risks in PCI following the clinical operations.

CTRPS AND CARDIOVASCULAR INFLAMMATION

Inflammation happens in the cardiac tissue and vasculature as an injurious signal in response to the CVDs or risk factors including hypertension, smoking and diabetes. Those situations combined with metabolic dysfunction will amplify the harmful effects to initiate chronic inflammatory reactions resulting in rupture, thrombosis and vulnerable plaque. Basic research and epidemiological clinical studies showed that consistent association between parameters of inflammation and risks of impending cardiovascular event. Emerging advanced techniques can detect locally occurring inflammation by means of screening more reliable and accessible marker systemically, which may provide the best identification of individual at risk for cardiovascular disorders and benefit to prognosis and future treatment.

The alteration in levels of CTRPs is associated with increased risks of cardiovascular event and reflect the progression of CVDs. For better establishment of the relationship between inflammation and CVDs, we will address the recently discovered response of CTRPs to inflammation in the cardiac and vascular systems, respectively to lead the researchers to obtain in depth understanding for the novel strategy for cardiovascular risk.

The levels and actions of circulating CTRPs (CTRP1, CTRP3, CTRP6, CTRP9, CTRP12 and CTRP13) in normal subjects and diabetic patients have been examined in a cross- sectional clinical study which reveals that in chronic inflammatory condition. CTRP1 and CTRP12 show opposite changes in the concentration, while CTRP3 may have a beneficial effect on the prevention of vascular remodeling through anti-inflammatory actions providing a promising strategy for the therapy of vascular disease linked to obesity[42,24]. CTRP6, although it has no effect on collagen or fibroblasts proliferation, does suppress

the cell migration induced by inflammatory factors[46]. CTRP9 has been reported to exert positive effects on endothelium-dependent vasorelaxation in aortic vessel ring with the vasorelaxative effects induced via the activation of nitric oxide synthase. Besides that, CTRP9 inhibits the remodeling of vascular wall in the mouse wire-injured model through attenuating vascular smooth muscle proliferation. It is notable that those actions have been mediated by CTRP9 through sharing the adiponectin receptor[47,48]. Those studies highlight the potential protective roles of CTRPs in response to the inflammatory stress.

It has been reported that CTRP3 may act as an inflammatory molecule to improve the post-ischemic cardiac function and cardiac remodeling in animal model via the ability to reduce apoptosis. Whereas, CTRP6 may affect the inflammatory states in the context of obesity by stimulating the activation of p42/44 mitogen-activated protein kinase-dependent pathway[28]. Meanwhile, it can increase the production of anti-inflammatory cytokine IL-10 in monocyte-derived macrophages in human patients. In protecting against the inflammatory response of oxidative stress, CTRP9 can reduce the myocardial ischemia injury-induced superoxide generation to suppress apoptosis and shrink the infarct size[49]. Although CTRP12 has been reported to be lower in an obese rodent model, the systemic administration of CTRP12 inhibits the macrophage pro-inflammatory factor and attenuates the infiltration of cells in the obese mice. Hence, CTRP12 not only modulates the glucose homeostasis, but also leads to the suppression of the inflammatory response of white blood cells[50,51].

Those new investigations and the numerous epidemiological studies indicate that the CTRPs family has the capability to modulate the metabolic and related inflammation to maintain the cardiovascular homeostasis. This sheds light on the biomarker features of CTRPs in the assessment of obesity relevant diseases or as the therapeutic link for the treatment of metabolic dysfunction-associated disorders. Even so, large-scale clinical trials to investigate the effects/actions of CTRPs on cardiovascular events are required for a better understanding of the potential risks and beneficial roles in the prevention of cardiovascular risks.

LIMITATIONS

Although investigations on the CTRP receptors are ongoing, much work required to be done to understand them better. Adiponectin receptor1 may in part be involved in the effects of CTRP9 on cardiomyocytes and vascular endothelial cells, but research has been limited on the RNA interference approaches. Solid evidence of the CTRP9 interaction with the adiponectin receptor on the cell surface is lacking. A yeast-based assay system for the progestin and adipoQ receptor family (PAQR) receptor activity reveals that the adiponectin receptor is identified as the category of PAQR1 and PAQR2. Adiponectin is identified as an agonist for PAQR3[52,53]. Since CTRP family members share many characteristics with adiponectin, it has been speculated that the CTRP receptors belong to the PAQR family members or share similarity with the adiponectin receptors.

The number of members in the C1q/TNF-related superfamily keeps growing along with the progression of research. C1q engages a broad range of ligands via its globular domain and modulates cells via the collagen region. The members of this new family are involved in processes as diverse as inflammation, metabolism, energy conversation/expenditure, and beyond, including cell differentiation and proliferation. Therefore, the CTRP family is vastly underestimated and its functions need to be further investigated.

CONCLUSION

Research on CTRPs has provided insights into their metabolic roles and their characteristics of vascular protection. Although abundant knowledge has been gained since the CTRPs were first discovered, additional questions still need to be answered. CTRPs possess unique and shared functions that are supported by research using the advanced manipulative techniques, such as the genetic mouse models and gene engineering, and by population research on obese and diabetic patients. Future studies will reveal novel insights into the physiological and pathological functions of CTRPs, their metabolic behavior, and possible redundancy of CTRPs in health and disease. Additionally, studying the CTRPs receptors and the downstream signals that transduce the actions of CTRP in the cell are major challenges but the research will provide tremendous insights into drug design and identification of biomarker.

DECLARATIONS

Authors' contributions

Structure design, and finalized the manuscript: Y.J. Wang

Collected data and worked on the revision: W.B. Lau, X.L. Ma

Composed the first draft of the article: J.L. Zhao

Drew figures and collated literatures: J. Liu, R. Guo

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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