Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1923–1927

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

C1q/TNF-related protein-3 and glucose homeostasis

Habib Yaribeygi [a, **], Farin Rashidfarrokhi [a], Stephen L. Atkin [b], Amirhossein Sahebkar [c, d, e, *]

[a] Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Weill Cornell Medicine Qatar, Doha, Qatar
[c] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[e] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article history:
Received 9 April 2019
Accepted 24 April 2019

Keywords:
C1q/TNF-Related protein-3
CTRP3
Adipokine
Adiponectin
Inflammation
TNF-α
Insulin resistance
Insulin sensitivity
Glut-4

ABSTRACT

Adipokines are cytokines produced by adipocytes that may mediate inflammatory processes, whilst adipocyte-derived proteins may have the converse effect. C1q/TNF-related protein-3 or CTRP3 is a novel adipokine that is expressed and released by most types of human tissues including adipose tissue. This adipokine, considered as an adiponectin, can normalize blood glucose by several mechanisms. In addition, it can modulate the expression/secretion of other cytokine and adipokines leading to lower insulin resistance in peripheral tissues. Beneficial effects of CTRP3 against hyperglycemia-induced complications in the kidney and eye have been reported. In this review, we have presented the latest findings on the in vitro and in vivo hypoglycemic effects of CTRP3, followed by the findings on the preventive/therapeutic effects of CTRP3 adipokines against diabetes related complications.

1. Introduction

The global incidence of diabetes mellitus (DM) is increasing resulting in diabetes related complications [1], with increased morbidity and mortality due to diabetes related kidney disease and cardiovascular disease [2–4]. The pathophysiology of DM is not fully understood though the role of the inflammatory responses appears to be important [5–7]. Indeed there is evidence suggesting that inflammatory mediators play a major role in the pathophysiology of DM by impairing beta cell function and impairing insulin signal transduction leading to insulin resistance and DM [8,9]. In this context, different inflammatory mediators such as interleukin (IL)-1, IL-6, IL-18, TNF-α (tumor necrosis factor alpha), ICAM (intracellular cell adhesion molecules), VCAM (vascular cell adhesion molecules) have been introduced as markers of insulin resistance [8–10]. Less commonly cytokines may improve insulin sensitivity [11] and in this context we have evaluated the effects of a newly introduced adipocyte derived cytokine named C1q/TNF-related protein-3 in modulating the insulin signaling pathway and how it may be involved in DM pathophysiology.

2. C1q/TNF-related Protein-3

Adipocytes are able to express and release a wide variety of proteins such as adipokines and adiponectins that have hormone properties, and so introducing adipose tissue as the largest endocrine organ within the human body [12]. After discovering leptin by Scherer and coworkers in 1994 as the first protein expressed and secreted by adipocytes, hundreds of proteins have been subsequently identified and purified [13]. These proteins are mainly of two classes of adipokines or adiponectins that can modulate insulin sensitivity and are therefore involved in the molecular pathophysiology of DM [11].

C1q/TNF-related protein-3 or CTRP3 is a novel adiponectin protein secreted by adipose tissue that may have modulatory effects on insulin sensitivity [14,15]. CTRP3 was discovered and

* Corresponding author. Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, P.O. Box: 91779-48564, Iran.
** Corresponding author. Chronic Kidney Disease Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail addresses: habib.yari@yahoo.com (H. Yaribeygi), sahebkara@mums.ac.ir, amir_saheb2000@yahoo.com (A. Sahebkar).

https://doi.org/10.1016/j.dsx.2019.04.047
1871-4021/

cloned by Maeda et al., in 2001 as an inducer for chondrocyte growth and skeletal development in mice and was named as CORS26 (Collagenous repeat-containing sequence 26 kDa protein) due to the 23 Gly-X-Y repeats at its *N*-terminal domain [16]. Later, Wong et al., in 2004 reported seven highly conserved isoforms of CTRPs all of which have C1q-like globular domains at the C terminus similar to the globular domain homology of TNF-α, therefore named as C1q/TNF-related protein-3 or CTRP3 1–7 [16]. However, additional types of CTRPs such as CTRP 8–15 have been identified subsequently [17]. Because of the high expression of CTRP3 in developing cartilage, it is also so-called as cartonectin or cartducin [12,17].

In addition to chondrocytes in cartilage, CTRP3 is highly expressed by adipose tissue and secreted into the blood where it circulates and acts in the same manner as an endocrine hormone [16,18–20]. There are two variants of CTRP3 that differ by molecular weight, CTRP3-A (40 kD) and CTRP3-B (32 kD) that are both formed by variant splicing [19]. They differ in structure since CTRP3B has a highly conserved *N*-linked glycosylation site with an additional 73 amino acids at the *N*-terminal region, whilst this is absent in CTRP3A, the original isoform [12,19]. However, both isoforms are expressed by human adipocytes, and both form heterooligomers that affords protection from proteolytic enzymes and both are detectable in human plasma as well as in peritoneal fluid surrounding visceral adipose tissue [12,20,21]. CTRP3B has a shorter half-life than CTRP3A and is quickly removed from the circulation if not bound with the A isoform [20]. In mammalian cell lines, CTRP3 forms higher-order oligomers by disulfide bonds via its *N*-terminal cysteine residues [17,20]. CTRP3 is expressed by most human tissues such as lung, liver, bone, chondrocytes, testis, kidneys, vascular smooth muscle cells, spleen, macrophages, monocytes, ovary, brain, heart, small intestine, placenta, skeletal muscle as well as adipocytes [12], and its serum concentration is estimated to be about 1 ± 0.3 μg/ml [19].

The mechanism of action is not clear for CTRP3, but there is evidence that it may bind or inhibits a variety of proteins such as lysosomal-associated membrane protein 1 (LAMP-1), lysosome membrane protein 2 (LIMP II), toll-like receptor 4 (TLR4) and lipopolysaccharide (LPS) [22,23]. CTRP3 has a long untranslated upstream segment in its gene and a wide variety of macromolecules and enzymes such as Peroxisome proliferator-activated receptors (PPARs); cAMP response element-binding protein (CREB); specificity protein 1 (SP-1); GATA-binding factor-1 (GATA-1); cytomatosis viral oncogene (*c*-Myc); transcription factor II D – "TATAA" box (TY-IID); Fos proto-oncogene (*c*-FOS); transcription factor-1 (Pit-1a); CCAAT-enhancer-binding proteins-alpha/beta (C/EBP-α/β); *c*-JUN; Protein kinase A (PKA); Activator protein 1 (AP-1); sex-determining region Y (SRY); SRY-related HMG-box 5 (Sox-5); myogenic differentiation (MyoD) and Retinoid X receptor (RXR) can modulate its expression or regulate related signaling pathways [12,24–28].

3. CTRP3 and metabolism

CTRP3 is highly expressed in adipose tissue suggesting a role in modulation of metabolic pathways and regulation of lipid metabolism [17,29]. In vitro and in vivo studies have established that CTRP3 induces adiponectin release, stimulates lipid peroxidation in liver tissue, induces cellular proliferation and differentiation, and inhibits of inflammatory responses [12,17,19]. CTRP3 release and the induction of resistin release by adipocytes, increase triglyceride storage by Phospho-p38 mitogen-activated protein kinases (p-p38 MAPK) and phospho-extracellular signal–regulated kinases (*p*-ERK) dependent pathways, Akt (Protein kinase-B (PKB)) activation and reduction in hepatic gluconeogenesis are suggested [15,17,22,30,31]. Moreover, it has been demonstrated by Wolf et al., in 2015 that lower circulatory levels of CTRP3 are correlated to lipid metabolism dysregulation and obesity [32]. Therefore, CTRP3 has important regulatory effects on metabolic pathways especially on lipid metabolism and plays a significant role in the pathophysiology of metabolic dysfunction such as in nonalcoholic fatty liver disease (NAFLD) and DM [17,32,33].

4. CTRP3 and glucose homeostasis

Recent evidence has suggested that CTRP3 plays a major role in glucose homeostasis and stabilizing blood glucose within the normal physiological range [19]. Reduced levels of CTRP3 gene expression are associated with impaired insulin signaling and lower insulin sensitivity [34]. Circulatory levels of CTRP3 are lower in diabetic patients compared to normoglycemic subjects, suggesting that CTRP3 may be a novel biomarker of impaired normal homeostasis of glucose and chronic hyperglycemic [34–36] (Table 1).

As noted above, adiponectins can improve insulin resistance and may induce insulin sensitivity in insulin-dependent peripheral tissues [36]. Choi and coworkers in 2013 reported that the beneficial effects of exercise on insulin sensitivity are related to CTRP3 expression [43]. They demonstrated that a combined exercise program improved insulin sensitivity by induction of CTRP3 expression in adipocytes [43]. Moreover, Fadaei et al., in 2016 suggested that decreased levels of CTRP3 are associated with higher insulin resistance, TNF-α, HbA1c (Glycosylated hemoglobin) and a greater risk of DM [44]. Tan et al., in 2013 reported that circulatory levels of insulin were inversely related to CTRP3 expression, suggesting positive effects of CTRP3 in insulin sensitivity [45]. Also, they found that treatment by metformin; that is a known insulin sensitizer; increased CTRP3 expression level suggesting that metformin may acts at least partly via CTRP3 expression [45].

Promotion of the Akt signaling pathway and subsequent downstream effects is another possible way by which CTRP3 induces insulin sensitivity in peripheral tissues [12,29,41]. Hou and coworkers in 2014 demonstrated that CTRP3 induces the Akt signaling pathways [41], and Peterson and colleagues in 2010 reported that recombinant CTRP3 induced Akt/PKB signaling pathways lead to more insulin sensitivity [19]. Hou et al., in 2015 reported that CTRP3 promoted the PI3K/Akt signaling molecular pathway that may improve insulin signaling [42].

Li and coworkers recently reported that insulin resistance and beta cell dysfunction occurring in gestational diabetes were associated with lower CTRP3 levels [40]. They also found that a higher body mass index (BMI) was correlated to lower fasting and postprandial CTRP3 plasma levels [40]. Deng and coworkers in 2015 demonstrated that CTRP3 is an independent factor affecting insulin resistance and related cardiovascular complications [46]. They compared the parameters of insulin resistance between diabetic patients and normal subjects and found that C1q/TNF-related protein-3 circulatory levels were inversely correlated to insulin resistance related parameters in obese patients [46]. Li and colleagues in 2014 reported that CTRP3 is a potent modulator for the release of other adipokines such as leptin, visfatin, resistin and adiponectin [39], and treatment with CTRP3 improved insulin sensitivity by inducing adiponectin expression/secretion in insulin resistant 3T3-L1 adipocytes [39].

Insulin sensitizing effects of CTRP3 may be related to its anti-inflammatory properties in adipocytes since it can inhibit lipopolysaccharide (LPS) signaling; a toxic molecule involved in inflammation in adipose tissues [22]. Kopp et al., in 2010 suggested that CTRP3 significantly suppressed inflammatory responses in obese patients with DM by the prevention of LPS binding to its

Table 1
Possible molecular mechanisms by which CTRP3 exerts its hypoglycemic effects (TLR4 = toll like receptor type 4, MD-2 = myeloid differentiation factor 2, MCP-1 = monocytes chemoattractant protein-1, PBK = protein kinase b, IL-6- interleukin 6, TNF-α = tumor necrosis factor alpha, LPS = lipopolysaccharide, Glut4 = Glucose transporter type 4, G6pase = gluconeogenesis as glucose-6-phosphatase, PEPCK= Phosphoenolpyruvate carboxykinase).

Possible Hypoglycemic Potential	Effects	References
Anti-inflammation	Inhibits LPS binding to TLR4/MD-2 and so suppresses further toxic effects, reduces TNF-α, MCP-1, and IL-6 expression/release	[22,37,38]
Correction of Serum Lipid Profile	Corrects lipid metabolism leading to better serum lipid profile	[29,32]
Hepatic Gluconeogenesis	Reduces hepatic glucose output by suppressing G6Pase and PEPCK expression	[19]
Modulation of other adipokines	Modulates leptin, visfatin, apelin, resistin and adiponectin release leading to more insulin sensitivity	[39]
Beta Cell Function	Improves islets cells and induces more insulin secretion	[40]
Glu 4-4 Expression	Increases Glut4 and PKB mRNA expression	[37]
Insulin Signaling Activation	Induces Akt/PKB signaling pathways leading to more insulin sensitivity, increases PKB mRNA expression, induces p-p38 MAPK and *p*-ERK signaling pathways leading to more insulin sensitivity in adipocytes	[12,22,29,37,41,42]

receptor, TLR4/MD-2 and so reducing monocyte chemoattractant protein-1 (MCP-1), TNF-α and IL-6 in adipocytes [22]. They observed that CTRP3 induced p-p38 MAPK and *p*-ERK signaling pathways leading to enhanced insulin sensitivity in adipocytes [22]. Li et al., in 2014 found that CTRP3 increased glucose consumption and induced insulin sensitivity via a decrease of the inflammatory mediators of TNF-α and IL-6 in 3T3-L1 insulin resistant adipocytes [37]. They demonstrated that treatment with recombinant CTRP3 protein increased GLUT4 (glucose transporter type 4) and PKB mRNA expression resulting in insulin sensitivity [37]. Supporting evidence was provided by Wolf et al., in 2015 who reported that CTRP3 knockout mice have higher circulatory inflammatory cytokines such as IL-6 and TGF-β than wild type, suggesting that CTRP3 regulates systemic inflammation and may inhibit inflammation-induced disorders such as insulin resistance and DM [38].

In addition to anti-inflammatory effects, CTRP3 may improve hyperglycemia via a reduction of hepatic glucose output [19]. Peterson et al., in 2010 showed that CTRP3 markedly reduced hepatic gluconeogenesis and glucose delivery independent of insulin sensitization by down-regulation of gluconeogenic enzymes in liver tissue [19]. They reported that CTRP3 markedly suppressed the expression of two key enzymes involved in hepatic gluconeogenesis, namely glucose-6-phosphatase (G6Pase) and Phosphoenolpyruvate carboxykinase (PEPCK), thus reducing glucose synthesis by hepatic cells [19].

CTRP3 may provide a new therapeutic target for DM [47], and it was shown that a reduction of CTRP3 expression/secretion was accompanied with a greater risk of DM in both normal and obese young adults, suggesting that CTRP3 may play an essential role in its pathophysiology [47]; therefore, modulation of CTRP3 expression/release may provide preventive effects against metabolic disorder as well as DM [47]. In this context, CTRP3 can reduce glucose output and decrease blood glucose in both normal and insulin-resistant animals by inhibition of hepatic gluconeogenesis and inflammatory responses [19,38].

5. CTRP3 and diabetic complications, a new possible therapeutic target

CTRP3 may be important in the pathophysiology of diabetes complications such as. diabetic retinopathy and diabetic nephropathy [48] (Table 2). Ma and coworkers in 2017 showed that CTRP3 prevented diabetic cardiomyopathy by the amelioration of inflammatory responses and AMPKα (Adenosine mono phosphate-activated protein kinase α) and Akt activation leading to better insulin signaling in the H9c2 cells of diabetic rats [48]. Yan and colleagues in 2017 reported that CTRP3 deficiency was correlated to proliferative diabetic retinopathy and also, had an inverse association with VCAM-1 expression [36]. They also found that treatment with recombinant CTRP3 in cultured human retinal microvascular endothelial cells (HRMECs) reduced high glucose high lipid (HGHL)-dependent VCAM-1 production via an AMPK-dependent mechanism [36].

Recently, Hu and coworkers in 2018 reported that CTRP3 overexpression inhibited the proliferation of glomerular mesangial cells, attenuated reactive oxygen species generation, and reduced extracellular matrix expansion, resulting in the prevention of diabetic nephropathy by inactivation of the JAK2/STAT3 (Janus kinases 2/Signal Transducer and Activator of Transcription proteins) signaling pathway [49]. In addition, it has been shown that CTRP3 treatment in animals fed a high fat diet protected them against NAFLD [29,50]: Peterson and colleagues in 2013 observed that treatment with CTRP3 can potentially protect animals fed a high fat diet from NAFLD by improvement of lipid metabolism through the down-regulation of three key enzymes involved in triglyceride synthesis, namely Glycerol-3-phosphate Acyltransferase (GPAT), acylglycerolphosphate acyltransferase (AGPAT), and Diacylglycerol *O*-acyltransferase (DGAT) resulting in an improvement of the serum lipid profile and reduction of triglyceride content in the liver [29].

This recent evidence suggests that CTRP3 may be considered as a new therapeutic target in the prevention/treatment of diabetic complications [49]; however, further clarification is needed.

Table 2
Some beneficial effects of CTRP3 against diabetic complications (AMPK = Adenosine mono phosphate-activated protein kinase α, JAK2/STAT3 = Janus kinases 2/Signal Transducer and Activator of Transcription proteins, NAFLD = non-alcoholic fatty liver disease, GPAT = Glycerol-3-phosphate Acyltransferase, AGPAT = acylglycerolphosphate acyltransferase, DGAT = Diacylglycerol *O*-acyltransferase).

Diabetic Complications	Possible Beneficial Effects of CTRP3	Reference(s)
Diabetic Cardiomyopathy	Prevents of diabetic cardiomyopathy by amelioration of inflammatory responses and AMPKα and Akt activation leading to better insulin signaling,	[48]
Diabetic Nephropathy	Inhibits of proliferation of glomerular mesangial cells, oxidative stress, reduces extracellular matrix expansion, inactivates JAK2/STAT3 signaling pathway	[49]
Diabetic Retinopathy	Prevents of diabetic retinopathy by amelioration of VCAM-1 expression via an AMPK-dependent mechanism,	[36]
NAFLD	Protects from NAFLD by improve of lipid metabolism, down-regulation of GPAT, AGPAT, and DGAT and so improve of serum lipid profile and reduction of triglyceride content in liver	[29,50]

6. Conclusion

C1q/TNF-related protein-3 or CTRP3 is a novel adipokine that is expressed and secreted by diverse tissues, including adipocytes that has potent modulatory influences on glucose homeostasis. Recent evidence has shown that CTRP3 significantly induced insulin sensitivity and normalized blood glucose by mechanisms that are still not completely understood. However, CTRP3 has potent anti-inflammatory properties that may contribute its hypoglycemic properties. In addition, CTRP3 may increase GLUT4 expression and enhance Akt signaling pathways involved in insulin signaling, thereby increasing insulin sensitivity in insulin-dependent tissues. Moreover, CTRP3 may potentially improve plasma lipids resulting in an improvement in insulin resistance. In addition to normalizing glucose levels CTRP3 may modulate the underlying molecular mechanisms involved in diabetic complications (through a reduction in inflammation) and thus may have potential as a new therapeutic target against DM and its complications.

Compliance with ethical standards

Funding

None.

Conflict of interest

The authors declare that they have no conflict of interest in this study.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.04.047.

References

[1] Candler T, Mahmoud O, Lynn R, Majbar A, Barrett T, Shield J. Continuing rise of Type 2 diabetes incidence in children and young people in the UK. Diabet Med 2018;35(6):737–44.
[2] Helve J, Sund R, Arffman M, Harjutsalo V, Groop P-H, Grönhagen-Riska C, Finne P. Incidence of end-stage renal disease in patients with type 1 diabetes. Diabetes Care 2018;41(3):434–9.
[3] Mostafa S, Coleman R, Agbaje O, Gray A, Holman R, Bethel M. Modelling incremental benefits on complications rates when targeting lower HbA1c levels in people with Type 2 diabetes and cardiovascular disease. Diabet Med 2018;35(1):72–7.
[4] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14(2):88.
[5] Yaribeygi H, Atkin SL, Pirro M, Sahebkar A. A review of the anti-inflammatory properties of antidiabetic agents providing protective effects against vascular complications in diabetes. J Cell Physiol 2019;234(6):8286–94.
[6] Yaribeygi H, Atkin SL, Sahebkar A. Mitochondrial dysfunction in diabetes and the regulatory roles of antidiabetic agents on the mitochondrial function. J Cell Physiol 2019;234(6):8402–10.
[7] Yaribeygi H, Butler AE, Barreto GE, Sahebkar A. Antioxidative potential of antidiabetic agents: a possible protective mechanism against vascular complications in diabetic patients. J Cell Physiol 2019;234(3):2436–46.
[8] Yaribeygi H, Farrokhi FR, Butler AE, Sahebkar A. Insulin resistance: review of the underlying molecular mechanisms. J Cell Physiol 2019;234(6):8152–61.
[9] Yaribeygi H, Katsiki N, Butler AE, Sahebkar A. Effects of antidiabetic drugs on NLRP3 inflammasome activity, with a focus on diabetic kidneys. Drug Discov Today 2019;24(1):256–62.
[10] Yaribeygi H, Atkin SL, Sahebkar A. Interleukin-18 and diabetic nephropathy: a review. J Cell Physiol 2019;234(5):5674–82.
[11] Kou H, Deng J, Gao D, Song A, Han Z, Wei J, Jin X, Ma R, Zheng Q. Relationship among adiponectin, insulin resistance and atherosclerosis in non-diabetic hypertensive patients and healthy adults. Clin Exp Hypertens 2018:1–8.
[12] Li Y, Wright GL, Peterson JM. C1q/TNF-Related protein 3 (CTRP3) function and regulation. Compr Physiol 2011;7(3):863–78.
[13] Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270(45):26746–9.
[14] Schmid A, Kopp A, Hanses F, Bala M, Müller M, Schäffler A. The novel adipokine C1q/TNF-related protein-3 is expressed in human adipocytes and regulated by metabolic and infection-related parameters. Exp Clin Endocrinol Diabetes 2012;120(10):611–7.
[15] Wölfing B, Buechler C, Weigert J, Neumeier M, Aslanidis C, Schöelmerich J, Schäffler A. Effects of the new C1q/TNF-related protein (CTRP-3)"cartonectin" on the adipocytic secretion of adipokines. Obesity 2008;16(7):1481–6.
[16] Maeda T, Abe M, Kurisu K, Jikko A, Furukawa S. Molecular cloning and characterization of a novel gene, CORS26, encoding a putative secretory protein and its possible involvement in skeletal development. J Biol Chem 2001;276(5):3628–34.
[17] Schäffler A, Buechler C. CTRP family: linking immunity to metabolism. Trends Endocrinol Metabol 2012;23(4):194–204.
[18] Maeda T, Jikko A, Abe M, Yokohama-Tamaki T, Akiyama H, Furukawa S, Takigawa M, Wakisaka S. Cartducin, a paralog of Acrp30/adiponectin, is induced during chondrogenic differentiation and promotes proliferation of chondrogenic precursors and chondrocytes. J Cell Physiol 2006;206(2):537–44.
[19] Peterson JM, Wei Z, Wong GW. C1q/TNF-related protein-3 (CTRP3): a novel adipokine that regulates hepatic glucose output. J Biol Chem 2010;285(51):39691–701.
[20] Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Revett T, Gimeno R, Lodish HF. Molecular, biochemical and functional characterizations of C1q/TNF family members: adipose-tissue-selective expression patterns, regulation by PPAR-γ agonist, cysteine-mediated oligomerizations, combinatorial associations and metabolic functions. Biochem J 2008;416(2):161–77.
[21] Wiest R, Leidl F, Kopp A, Weigert J, Neumeier M, Buechler C, Schoelmerich J, Schäffler A. Peritoneal fluid adipokines: ready for prime time? Eur J Clin Investig 2009;39(3):219–29.
[22] Kopp A, Bala M, Buechler C, Falk W, Gross P, Neumeier M, Scholmerich J, Schaffler A. C1q/TNF-related protein-3 represents a novel and endogenous lipopolysaccharide antagonist of the adipose tissue. Endocrinology 2010;151(11):5267–78.
[23] Li Y, Ozment T, Wright GL, Peterson JM. Identification of putative receptors for the novel adipokine CTRP3 using ligand-receptor capture technology. PLoS One 2016;11(10):e0164593.
[24] Kim M-J, Park E-J, Lee W, Kim J-E, Park S-Y. Regulation of the transcriptional activation of CTRP3 in chondrocytes by c-Jun. Mol Cell Biochem 2012;368(1–2):111–7.
[25] Schäffler A, Ehling A, Neumann E, Herfarth H, Paul G, Tarner I, Gay S, Buechler C, Schölmerich J, Müller-Ladner U. Role of specificity protein-1, PPARγ, and pituitary protein transcription factor-1 in transcriptional regulation of the murine CORS-26 promoter. Biochim Biophys Acta Gene Struct Expr 2004;1678(2–3):150–6.
[26] Schäffler A, Ehling A, Neumann E, Herfarth H, Paul G, Tarner I, Gay S, Schölmerich J, Müller-Ladner U. Genomic organization, promoter, amino acid sequence, chromosomal localization, and expression of the human gene for CORS-26 (collagenous repeat-containing sequence of 26-kDa protein). Biochim Biophys Acta Gene Struct Expr 2003;1630(2–3):123–9.
[27] Schäffler A, Ehling A, Neumann E, Herfarth H, Tarner I, Gay S, Schölmerich J, Müller-Ladner U. Genomic organization, chromosomal localization and adipocytic expression of the murine gene for CORS-26 (collagenous repeat-containing sequence of 26 kDa protein). Biochim Biophys Acta Gene Struct Expr 2003;1628(1):64–70.
[28] Schäffler A, Weigert J, Neumeier M, Schölmerich J, Buechler C. Regulation and function of collagenous repeat containing sequence of 26-kDa protein gene product "cartonectin". Obesity 2007;15(2):303–13.
[29] Peterson JM, Seldin MM, Wei Z, Aja S, Wong GW. CTRP3 attenuates diet-induced hepatic steatosis by regulating triglyceride metabolism. Am J Physiol Gastrointest Liver Physiol 2013;305(3):G214–24.
[30] Hofmann C, Chen N, Obermeier F, Paul G, Büchler C, Kopp A, Falk W, Schäffler A. C1q/TNF-related protein-3 (CTRP-3) is secreted by visceral adipose tissue and exerts antiinflammatory and antifibrotic effects in primary human colonic fibroblasts. Inflamm Bowel Dis 2011;17(12):2462–71.
[31] Kopp A, Bala M, Weigert J, Büchler C, Neumeier M, Aslanidis C, Schölmerich J, Schäffler A. Effects of the new adiponectin paralogous protein CTRP-3 and of LPS on cytokine release from monocytes of patients with type 2 diabetes mellitus. Cytokine 2010;49(1):51–7.
[32] Wolf RM, Steele KE, Peterson LA, Magnuson TH, Schweitzer MA, Wong GW. Lower circulating C1q/TNF-related protein-3 (CTRP3) levels are associated with obesity: a cross-sectional study. PLoS One 2015;10(7):e0133955.
[33] Zhou W, Wang Y, Wu Y, Yang J, Xu L, Yang Y. Serum CTRP3 level is inversely associated with nonalcoholic fatty liver disease: a 3-y longitudinal study. Clin Chim Acta 2018;479:79–83.
[34] Li X, Jiang L, Yang M, Wu YW, Sun JZ. Impact of weight cycling on CTRP3 expression, adipose tissue inflammation and insulin sensitivity in C57BL/6J mice. Exp Ther Med 2018;16(3):2052–9.
[35] Ban B, Bai B, Zhang M, Hu J, Ramanjaneya M, Tan BK, Chen J. Low serum cartonectin/CTRP3 concentrations in newly diagnosed type 2 diabetes

mellitus: in vivo regulation of cartonectin by glucose. PLoS One 2014;9(11):e112931.
[36] Yan Z, Zhao J, Gan L, Zhang Y, Guo R, Cao X, Lau WB, Ma X, Wang Y. CTRP3 is a novel biomarker for diabetic retinopathy and inhibits HGHL-induced VCAM-1 expression in an AMPK-dependent manner. PLoS One 2017;12(6):e0178253.
[37] Li X, Jiang L, Yang M, Wu Y-w, Sun J-z, Sun S-x. CTRP3 improves the insulin sensitivity of 3T3-L1 adipocytes by inhibiting inflammation and ameliorating insulin signalling transduction. Endokrynol Pol 2014;65(4):252–8.
[38] Wolf RM, Lei X, Yang Z-C, Nyandjo M, Tan SY, Wong GW. CTRP3 deficiency reduces liver size and alters IL-6 and TGFβ levels in obese mice. Am J Physiol Endocrinol Metab 2015;310(5):E332–45.
[39] Li X, Jiang L, Yang M, Wu Y-w, Sun S-x, Sun J-z. CTRP3 modulates the expression and secretion of adipokines in 3T3-L1 adipocytes. Endocr J 2014;61(12):1153–62.
[40] Li J, Wu G, Hou Z, Cao Y. Expression of C1q/TNF-related protein-3 (CTRP3) in serum of patients with gestational diabetes mellitus and its relationship with insulin resistance. Eur Rev Med Pharmacol Sci 2017;21:5702–10.
[41] Hou M, Liu J, Liu F, Liu K, Yu B. C1q tumor necrosis factor-related protein-3 protects mesenchymal stem cells against hypoxia-and serum deprivation-induced apoptosis through the phosphoinositide 3-kinase/Akt pathway. Int J Mol Med 2014;33(1):97–104.
[42] Hou Q, Lin J, Huang W, Li M, Feng J, Mao X. CTRP3 stimulates proliferation and anti-apoptosis of prostate cells through PKC signaling pathways. PLoS One 2015;10(7):e0134006.
[43] Choi HY, Park JW, Lee N, Hwang SY, Cho GJ, Hong HC, Yoo HJ, Hwang TG, Kim SM, Baik SH. Effects of a combined aerobic and resistance exercise program on C1q/TNF-related protein-3 (CTRP-3) and CTRP-5 levels. Diabetes Care 2013;36(10):3321–7.
[44] Fadaei R, Moradi N, Baratchian M, Aghajani H, Malek M, Fazaeli AA, Fallah S. Association of C1q/TNF-related protein-3 (CTRP3) and CTRP13 serum levels with coronary artery disease in subjects with and without type 2 diabetes mellitus. PLoS One 2016;11(12):e0168773.
[45] Tan BK, Chen J, Hu J, Amar O, Mattu HS, Adya R, Patel V, Ramanjaneya M, Lehnert H, Randeva HS. Metformin increases the novel adipokine cartonectin/CTRP3 in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2013;98(12):E1891–900.
[46] Deng W, Li C, Zhang Y, Zhao J, Yang M, Tian M, Li L, Zheng Y, Chen B, Yang G. Serum C1q/TNF-related protein-3 (CTRP3) levels are decreased in obesity and hypertension and are negatively correlated with parameters of insulin resistance. Diabetol Metab Syndrome 2015;7(1):33.
[47] Elsaid HH, Elgohary MN, Elshabrawy AM. Complement c1q tumor necrosis factor-related protein 3 a novel adipokine, protect against diabetes mellitus in young adult Egyptians. Diabetes, Metab Syndrome : Clin Res Rev 2019;13(1):434–8.
[48] Ma Z-G, Yuan Y-P, Xu S-C, Wei W-Y, Xu C-R, Zhang X, Wu Q-Q, Liao H-H, Ni J, Tang Q-Z. CTRP3 attenuates cardiac dysfunction, inflammation, oxidative stress and cell death in diabetic cardiomyopathy in rats. Diabetologia 2017;60(6):1126–37.
[49] Hu Ty, Li Lm, Pan Yz. CTRP3 inhibits high glucose–induced human glomerular mesangial cell dysfunction. J Cell Biochem 2019;120(4):5729–36.
[50] Peterson JM. Identification of cell surface receptors for the novel adipokine CTRP3. FASEB J 2016;30(1_supplement). 1249.1242-1249.1242.