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## Metabolic function of the CTRP family of hormones

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### Abstract

Maintaining proper energy balance in mammals entails intimate crosstalk between various tissues and organs. These inter-organ communications are mediated, to a great extent, by secreted hormones that circulate in blood. Regulation of the complex metabolic networks by secreted hormones (e.g., insulin, glucagon, leptin, adiponectin, FGF21) constitutes an important mechanism governing the integrated control of whole-body metabolism. Disruption of hormone-mediated metabolic circuits frequently results in dysregulated energy metabolism and pathology. As part of an effort to identify novel metabolic hormones, we recently characterized a highly conserved family of fifteen secreted proteins, the C1q/TNF-related proteins (CTRP1–15). While related to adiponectin in sequence and structural organization, each CTRP has its own unique tissue expression profile and non-redundant function in regulating sugar and/or fat metabolism. Here, we summarize the current understanding of the physiological functions of CTRPs, emphasizing their metabolic roles. Future studies using gain-of-function and loss-of-function mouse models will provide greater mechanistic insights into the critical role CTRPs play in regulating systemic energy homeostasis.

### Keywords

adipokine; obesity; type 2 diabetes; insulin resistance; gluconeogenesis; fat oxidation

### Introduction

Mammals use complex central and peripheral mechanisms to maintain proper energy balance (1, 2). Among peripheral mechanisms, secreted hormones play a particularly important role (2–5). They mediate inter-organ communication and tissue crosstalk to coordinate the integrated control of whole-body metabolism. Circulating levels of many secreted hormones, such as insulin, leptin, adiponectin, and FGF21, are dynamically regulated in response to short-term changes in nutritional status or long-term changes in metabolic state (2–6). Sustained metabolic perturbations due to excess caloric intake, as in obesity, frequently disrupt the signaling pathways regulated by these circulating hormones. Consequently, hormonal axis deregulation is mechanically linked to common metabolic disorders such as obesity, insulin resistance, and type 2 diabetes (7).

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#### Competing Interests

The authors have declared that no competing interests exist.

## Adiponectin and the C1q family

Among peripheral tissues, adipose fulfills two critical roles—as the major storage depot for triglycerides and as an endocrine organ that secretes active polypeptide hormones into circulation (8). Adipose-derived secretory proteins are collectively called adipokines and act in an autocrine, paracrine, and/or endocrine manner to modulate insulin sensitivity and glucose and fatty acid metabolism (7). Adipokines may also influence whole-body metabolism by indirectly modulating inflammatory processes in adipose and other metabolic tissues (9). Adiponectin is a pleiotropic insulin-sensitizing adipokine that has been the subject of extensive genetic and correlative studies in humans and mechanistic studies in transgenic and knockout (KO) mice (10, 11). Despite the widely described anti-diabetic, antiatherogenic, and anti-inflammatory properties of adiponectin (10–12), adiponectin KO mice exhibit highly variable phenotypes (13–17). Three independent adiponectin KO mouse lines develop some degree of insulin resistance when fed a high-fat diet, while another line exhibits enhanced fat oxidation; all four KO mouse lines have mild or undetectable metabolic abnormalities when fed a standard chow diet (13–16). The generally mild metabolic phenotypes of adiponectin KO mice have been partially attributable to enhanced leptin sensitivity (18). However, despite attempts to provide a unifying mechanism of action for adiponectin (19, 20), a clear understanding of the pleiotropic functions of adiponectin has been confounded by conflicting studies concerning its role in glucose metabolism (21), atherosclerosis (17), food intake (22, 23), inflammation (24–26), and tumor angiogenesis (27, 28). Additional mechanisms may partially account for the variable and mild metabolic alterations of adiponectin KO mice (29, 30).

Adiponectin belongs to the larger C1q protein family, defined by the presence of a C-terminal globular domain with sequence homology to the immune complement protein C1q (31). Human and mouse genomes encode >30 C1q domain-containing proteins (31, 32). These include the founding immune complement C1q (A-, B-, and C-chain) (33), as well as multimerins (34), emilins (35), C1q/TNF-related proteins (CTRPs) (36), cerebellins (37), adiponectin (38), otolin (39), C1q-related factor (CRF) (40), C1qDC1/caprin-2 (41), and nonfibrillar collagen VIII (42, 43) and collagen X (44). With the exception of cytosolic C1qDC1 (41), all C1q family members are secreted proteins that likely evolved from a common C1q domain-containing ancestral protein. C1q proteins play diverse roles in mammalian physiology, including immunity, development, and metabolism (31, 34, 35, 37, 45, 46). Of the C1q family members, CTRP1-15 share strikingly similar structural organization and biochemical properties with adiponectin (29, 36, 47–55). Here, we highlight the unique and shared characteristics between CTRPs and adiponectin; overlapping metabolic functions with CTRPs could account for the mild phenotypes of adiponectin KO mice (30).

### CTRP characteristics

CTRPs were identified by sequence homology with the globular domain of adiponectin (36). Further, the overall CTRP domain organization is similar to adiponectin; every CTRP contains a signal peptide to direct protein secretion, an N-terminal domain with one or more conserved Cys residues, a collagen-like domain with variable numbers of Gly-X–Y repeats,

and a C-terminal globular C1q domain (Fig. 1). All CTRPs are highly conserved throughout vertebrate evolution, and clear orthologs can be identified from zebrafish, frog, mouse, and human genomes. Of the CTRPs, CTRP9 shares the highest degree of sequence identity (54%) with adiponectin at the presumed functional globular domain (47). Unlike adiponectin, whose transcript is expressed almost exclusively by adipocytes (38), CTRPs are widely expressed in human and mouse tissues (29, 36, 47–55). Although adipose predominantly expresses CTRP1, CTRP2, CTRP3, CTRP5, CTRP7, CTRP9, CTRP12, and CTRP13, each CTRP has a unique tissue expression profile that may reflect unique functions (29, 47, 50, 51).

## CTRP structural organization

All characterized C1q members, including CTRPs, form trimers (56–61). Adiponectin trimers can be further assembled into higher-order hexameric and octadecameric complexes (62–67). Assembly of these structures requires the conserved N-terminal Cys-39 residue and is achieved with the help of endoplasmic reticulum proteins such as ERp44 and DsbA-L (68, 69). CTRP3, CTRP5, CTRP6, CTRP9, CTRP10, CTRP12, CTRP13, and CTRP15/myonectin also form multimeric complexes that are assembled through the conserved N-terminal Cys residues (29, 47, 50–53). CTRP11 forms multimeric complexes through an interaction with the oxidoreductase ERp44, but conserved N-terminal Cys-28 and Cys-32 residues are not required for assembly (52). While different adiponectin oligomers may have distinct signaling properties (62, 70, 71) that correlate with insulin sensitivity in humans (66, 72–74), the functional significance of CTRP oligomers remains largely undefined, with the exception of CTRP12 (75).

## CTRP posttranslational modifications

When secreted from mammalian cells, CTRP1, CTRP2, CTRP6, CTRP12, and CTRP15/myonectin contain *N*-linked glycans, but CTRP3, CTRP5, CTRP9, CTRP10, CTRP11, and CTRP13 contain other carbohydrate moieties (29, 47, 50–53). Mass spectrometry revealed that proline residues within the Gly-X-P repeats and lysine residues within the consensus GXKG(E/D) motif in the N-terminal collagen domain of CTRP9 are hydroxylated and glycosylated, respectively (47). Proline hydroxylation and lysine glycosylation within the collagen domain affect the stability, function and biological potency of adiponectin (76–78). One or more GXKG(E/D) motifs are present in the collagen domain of all CTRPs except CTRP4, CTRP12, and CTRP15/myonectin, suggesting these modifications may occur in other CTRPs to affect protein stability and/or function. Adiponectin also contains sialic acids important for stability (79, 80), although it is presently unknown whether any CTRPs are modified with sialic acid. The potential influence of posttranslational modifications on assembly of higher-order CTRP structures underscores the importance of using recombinant CTRPs produced in mammalian expression systems to conduct functional studies. Recombinant proteins produced in mammalian cells, rather than bacteria, are likely to possess native posttranslational modifications and higher-order structures to confer biological activity.

## CTRPs in circulation

When specific antibodies are available, endogenous CTRPs can be detected circulating in the blood (29, 47, 50, 53). Although adiponectin circulates in human plasma at high concentrations (10–30 µg/mL), CTRPs circulate at 1–2 orders of magnitude less than adiponectin (81–84). In both humans and mice, sex and genetic background influence metabolic hormone levels and signaling pathways, and thus variably influence the development of obesity, insulin resistance, and type 2 diabetes (85–88). Females have significantly higher circulating adiponectin levels (63, 89, 90), which may be due to the ability of testosterone to suppress adiponectin (89–91). Likewise, the expression and circulating levels of some CTRPs also exhibit sexually dimorphic patterns, with female mice expressing higher levels of CTRP5, CTRP9, CTRP11, and CTRP13 relative to males (29, 47, 51, 52). However, it is unclear whether sex hormones directly modulate CTRP expression levels. Alterations in metabolic state also affect circulating CTRP levels consistent with metabolic function (47–51, 53). Adiponectin expression levels are consistently reduced in obesity and type 2 diabetes (92–97); similarly, circulating levels of CTRP1, CTRP3, CTRP9, CTRP12, and CTRP15/myonectin are also reduced in diet-induced obese (DIO) mouse models (48–50, 53).

## CTRP metabolic functions

The metabolic function and regulation of adiponectin has been extensively studied in the past decade (10, 11); however, much less is known about the regulation and function of CTRPs. Here, we summarize current understanding of CTRP metabolic functions (Table 1), as non-metabolic roles have been reviewed elsewhere (45).

## CTRP1

CTRP1 is predominantly expressed by adipose tissue (29). Circulating CTRP1 levels decrease in DIO (48) and increase in adiponectin KO mice or mice given daily injections of the anti-diabetic drug rosiglitazone (29), suggesting that increased circulating CTRP1 levels may have a positive metabolic effect. Concordantly, administration of physiological amounts of recombinant CTRP1 to wild-type mice acutely and substantially lowers blood glucose (29). Further, a two-fold increase in circulating CTRP1 levels modestly improves insulin sensitivity and decreases high-fat diet-induced weight gain in transgenic mouse models (48). Reduced weight gain in response to high-fat feeding is primarily due to increased energy expenditure from enhanced fat oxidation in skeletal muscle (48). These *in vivo* effects are mediated by the highly conserved AMP-activated protein kinase (AMPK). In skeletal muscles of transgenic mice, AMPK $\alpha$  and its downstream target acetyl-CoA carboxylase (ACC) are hyperphosphorylated (48). Phosphorylation of AMPK $\alpha$  at Thr-172 activates the kinase, whereas AMPK phosphorylation of ACC at Ser-79 inactivates the carboxylase (98). Inactivation of ACC reduces malonyl CoA levels to promote fatty acyl-CoA import into mitochondria for  $\beta$ -oxidation (98), reflecting a direct action of CTRP1 on AMPK signaling in muscle cells. In addition, recombinant CTRP1 can recapitulate increases in skeletal muscle AMPK $\alpha$  (Thr-172) and ACC (Ser-79) phosphorylation in wild-type mice

(48). These studies collectively indicate that CTRP1 is a novel secreted regulator of skeletal muscle fat oxidation.

## CTRP3

CTRP3, also known as CORS26/cartducin (99), is expressed by adipocytes (100–102) and adipose stromal cells (29) and in other tissues (29, 100, 103–105). Overnight fasting increases circulating CTRP3 levels relative to mice fed *ad libitum*, while high-fat feeding reduces CTRP3 levels by ~50% (49). In humans, circulating CTRP3 levels positively correlate with adiponectin and negatively correlate with waist circumference, blood pressure, fasting glucose, triglycerides, and cholesterol (82). Additionally, CTRP3 regulates glucose metabolism. Increased circulating CTRP3 levels substantially lower blood glucose in wildtype and insulin-resistant, leptin-deficient obese *ob/ob* mice (49). These results suggest CTRP3 influences metabolism independently of insulin. CTRP3 targets liver hepatocytes to suppress gluconeogenic gene expression (*G6Pase* and *PEPCK*) and gluconeogenesis via the activation of protein kinase B/Akt signaling (49). This differs from the mechanism of adiponectin in liver which activates AMPK to suppress hepatic glucose output (106, 107), although the role of AMPK in this process has been recently challenged (108).

We generated transgenic mice with elevated circulating CTRP3 levels (109). When challenged with a high-fat diet, CTRP3 transgenic mice exhibit remarkable resistance to the development of hepatic steatosis despite similarities in body weight, food intake, and energy expenditure (109). Further, DIO mice administered daily physiological amounts of recombinant CTRP3 for five consecutive days exhibit reduced hepatic triglyceride content, confirming the direct action of CTRP3 in the liver (109). Mechanistically, CTRP3 reduces hepatic triglyceride content by inhibiting the expression of enzymes involved in triglyceride synthesis (GPATs, AGPATs, and DGATs) (109); it has no appreciable effect on hepatic fat oxidation, unlike adiponectin (110). Adiponectin also improves alcoholic and non-alcoholic fatty liver phenotypes, although triglyceride synthesis enzymes were not examined (110).

Given the importance of chronic inflammation in obesity (111), it is interesting to note that CTRP3 may also modulate metabolism indirectly through anti-inflammatory processes (45). Recombinant CTRP3 reduces lipopolysaccharide-induced inflammation in monocytes (112), adipocytes (113) and colonic fibroblasts (114); however, the physiological relevance of these *in vitro* studies awaits *in vivo* confirmation.

CTRP3 also has non-metabolic functions in the vasculature and heart. Recombinant CTRP3 induces endothelial cell proliferation and migration *in vitro* by activating ERK1/2 and p38 MAPK signaling (115), implying a potential role of CTRP3 in regulating angiogenesis. Myocardial infarction induced by coronary artery occlusion substantially reduces CTRP3 expression in adipose tissue and in circulation in mice, although reconstitution of CTRP3 expression significantly restores cardiac function and survival rates (116). CTRP3 activation of Akt, but not AMPK, signaling attenuates cardiomyocyte apoptosis, suppresses interstitial fibrosis, and increases revascularization following myocardial infarction (116). Together,

these studies highlight a novel and important role for CTRP3 in modulating metabolic, immune, and cardiovascular functions.

## CTRP5

CTRP5 is widely expressed, with highest levels detected in the eye and adipose tissue (29). Prolonged mitochondrial depletion induces CTRP5 expression in rat L6 myocytes (117). Further, expression of recombinant GST-tagged CTRP5 or an un-tagged C-terminal globular head stimulates AMPK signaling to translocate GLUT4 and enhances fat oxidation via the AMPK-ACC pathway *in vitro* (117). These studies imply an autocrine function for CTRP5 in muscle in response to reduced mitochondrial content. CTRP5 is also expressed by cultured mouse and human adipocytes and circulates in human serum (84). Saturated fatty acids upregulate CTRP5 expression in adipocytes, where CTRP5 acts in an autocrine fashion to reduce adiponectin and resistin secretion (84). While the physiological relevance of CTRP5 in metabolism remains uncertain, a point mutation (S163R) impairs folding and secretion of human CTRP5 to cause an autosomal dominant form of late-onset retinal macular degeneration (L-ORD) (118–121). S163R knock-in mouse models of L-ORD have yielded conflicting results—one model successfully recapitulates the retinal degeneration phenotype (122), while another does not (123).

## CTRP9

CTRP9 is the closest paralog of adiponectin and shares the highest degree of amino acid identity (54%) at the globular domain. Adipose predominantly expresses CTRP9 (47). In leptin-deficient obese *ob/ob* mice, CTRP9 expression is elevated in adipose tissue and in circulation at 8 weeks of age relative to lean controls, but subsequently normalizes by 12 weeks of age (47). This observation suggests a possible compensatory response in young *ob/ob* mice prior to developing severe obesity and insulin resistance. Concordantly, circulating CTRP9 levels are significantly reduced in DIO mice, a model more closely resembling the common form of human obesity induced by excess caloric intake (Peterson and Wong, unpublished data). A modest (~40%) increase in circulating CTRP9 levels by adenoviral-mediated expression acutely reduces serum glucose levels in *ob/ob* mice without altering body weight and plasma insulin levels (47). In transgenic mouse models where circulating CTRP9 levels are chronically elevated, animals have reduced caloric intake and increased metabolic rate in response to high-fat feeding (124). Consequently, CTRP9 transgenic mice are strikingly resistant to weight gain when challenged with a high-fat diet for 12 weeks (124). The observed reduction in adiposity is due to chronic activation of AMPK in the skeletal muscle, increased mitochondrial content and up-regulated expression of genes that mediate fat oxidation. As expected, lean CTRP9 transgenic mice fed a high-fat diet exhibit improved systemic insulin sensitivity and fail to develop hepatic steatosis (124). These observations suggest CTRP9 enhances fat oxidation in an AMPK-dependent manner.

The metabolic roles of CTRP9 functionally overlap with those of adiponectin. Adiponectin, in particular its globular domain, enhances skeletal muscle fat oxidation by activating the AMPK signaling pathway (107, 125, 126). Over-expression of adiponectin also improves insulin function in rat skeletal muscle (127); however, other studies concluded that liver, not

skeletal muscle, is the predominant adiponectin target *in vivo* (106, 128). It remains to be confirmed, using skeletal muscle-specific adiponectin receptor KO mice, whether adiponectin acts directly on skeletal muscle to exert some of its whole-body metabolic effects (129).

CTRP9 also controls cardiac and endothelial cell functions. In human umbilical vein endothelial cells and in freshly isolated vascular rings, recombinant CTRP9 increases nitric oxide production to induce vasodilatation through the AMPK/eNOS pathway (130). CTRP9 also benefits cardiac function in response to stress. Overexpression of CTRP9 reduces myocardial infarct size and hypoxia-induced apoptosis of cardiac myocytes following myocardial ischemia/reperfusion through AMPK signaling (131). Expression of only the C-terminal globular domain of CTRP9 also attenuates oxidative stress and myocardial infarct size induced by ischemia/reperfusion injury and enhances cardiac output in DIO mice (132). In another model of femoral artery injury, adenoviral CTRP9 overexpression substantially reduces neointimal formation by suppressing vascular smooth muscle cell proliferation and migration through the cAMP/PKA/ERK pathway (133). Since obesity and insulin resistance are risk factors for vascular and cardiac dysfunction (134–136), these studies highlight the potential protective roles of CTRP9 in the heart in response to stress.

## CTRP11

CTRP11 is predominantly expressed by white and brown adipose tissues (52). Sequence alignment indicates a striking degree of amino acid identity between CTRP11 of different vertebrate species (52). Within white adipose tissue, CTRP11 is primarily produced by stromal vascular cells (52). CTRP11 expression is acutely regulated by changes in metabolic state, as overnight fasting followed by re-feeding upregulates expression (52). The lack of a CTRP11-specific antibody precludes analysis of the endogenous protein; hence, it remains uncertain whether CTRP11 also circulates in blood. Functional studies suggest a role for CTRP11 in regulating adipogenesis (52). CTRP11 suppresses 3T3-L1 mouse cell differentiation into mature adipocytes by inhibiting the expression of PPAR- $\gamma$  and C/EBP- $\alpha$ , two major transcriptional regulators that drive adipogenesis (137–139). Further, CTRP11 inhibits mitotic clonal expansion of 3T3-L1 pre-adipocytes (52), a process essential for adipocyte differentiation in culture (140). Suppression of adipogenesis is specific, as expression of other structurally-related proteins such as CTRP1, CTRP10, and adiponectin do not influence 3T3-L1 differentiation. These *in vitro* studies indicate that CTRP11 likely acts in a paracrine manner to mediate crosstalk between adipocytes and cells of the stromal vascular compartment to maintain adipose tissue homeostasis (52).

## CTRP12

Sequence alignments between CTRP12 and other members of the C1q family indicate only modest sequence identity at the globular C1q domain (50, 54). Human adipose tissue predominantly expresses CTRP12, although expression is more widespread in mice (50). Unlike other CTRPs, endogenous CTRP12 exists in two differently sized isoforms—a full-length and a cleaved globular isoform. Furin/PCSK3, a member of the proprotein convertase family, cleaves CTRP12 at Lys-91 within the N-terminal KKXR motif (75). The two

CTRP12 isoforms differ in oligomeric structure and signaling specificity; full-length protein preferentially activates Akt signaling, whereas the globular gCTRP12 isoform preferentially activates p44/42-MAPK and p38-MAPK signaling (75). While CTRP12 expression in the adipose tissue of DIO mice is significantly reduced (50, 54), its expression in cultured adipocytes is acutely induced by insulin or rosiglitazone treatment (50, 75). Cleavage of CTRP12 appears to be enhanced in DIO mice (141).

A modest increase in circulating CTRP12 levels by adenoviral expression or recombinant protein administration is sufficient to lower blood glucose and improve insulin sensitivity in three different mouse models—lean wild-type, DIO, and leptin-deficient *ob/ob* mice (50). These metabolic improvements are mediated by enhanced insulin signaling in the liver and adipose tissue, but not in skeletal muscle (50). Independent of insulin, recombinant CTRP12 suppresses gluconeogenesis in cultured hepatocytes and promotes glucose uptake in adipocytes. Thus, CTRP12 improves metabolic function through both insulin-dependent and -independent mechanisms. Adipose tissue inflammation is dampened in obese mice overexpressing CTRP12, suggesting the anti-inflammatory action of CTRP12 is responsible for whole-body insulin sensitivity improvements (54). In contrast, adenoviral overexpression of CTRP12 does not alter adipose tissue histomorphology or inflammatory gene expression (e.g., *IL-1 $\beta$* , *IL-6*, *TNF- $\alpha$* ) despite remarkable improvements in systemic insulin sensitivity and glucose homeostasis (50). CTRP12 is thus a novel adipokine with beneficial anti-diabetic properties, although future studies using loss-of-function mouse models will help clarify its mechanism of action.

## CTRP13

CTRP13 is preferentially expressed in adipose and brain tissues of mice and in adipose tissue of humans (51). Within mouse adipose tissue, CTRP13 is also mainly produced by cells of the stromal vascular compartment. In cultured adipocytes, myotubes, and hepatocytes, recombinant CTRP13 activates AMPK signaling to promote glucose uptake. CTRP13 also partially reverses lipid-induced insulin resistance in hepatocytes by suppressing SAPK/JNK stress signaling, which impairs insulin signaling (51). Further, CTRP13 activates AMPK signaling to reduce gluconeogenesis in H4IIE hepatocytes by inhibiting gluconeogenic enzymes G6Pase and PEPCK. However, the physiological relevance of CTRP13 in peripheral tissues remains to be determined *in vivo*.

In the brain, CTRP13 modulates food intake as an anorexigenic factor (142). Wild-type mice given restricted access to food downregulate hypothalamic CTRP13 expression, whereas this expression is upregulated in similarly-treated DIO mice. Further, recombinant CTRP13 administered via intracerebroventricular cannulae suppresses food intake and reduces body weight in mice (142). Interestingly, CTRP13 and the orexigenic neuropeptide AgRP reciprocally regulate each other's expression in the hypothalamus; central CTRP13 delivery suppresses *AgRP* expression, while AgRP delivery increases *Ctrp13* expression. Food-restricted mice have reduced CTRP13 and increased orexigenic neuropeptide (NPY and AgRP) expression in the hypothalamus. In contrast, when food restriction is coupled to enhanced physical activity in an activity-based anorexia mouse model, hypothalamic expression of both CTRP13 and AgRP increases (142). These results suggest that CTRP13



and AgRP form a hypothalamic feedback loop to modulate food intake and that this neural circuit may be disrupted in anorexia.

### CTRP15/myonectin

Unlike other CTRPs, CTRP15 is a myokine expressed predominantly by mouse and human skeletal muscle (53). The term myonectin was used for CTRP5 in a recent study (143). To prevent confusion in nomenclature, CTRP5 retains its original designation (36, 117, 118), while CTRP15 is now referred to as myonectin (53). Expression and circulating levels of CTRP15/myonectin are upregulated upon re-feeding after fasting and significantly downregulated in DIO mice (53). Interestingly, CTRP15/myonectin expression is differentially regulated in different muscle fiber types. At basal levels, CTRP15/myonectin is expressed more in oxidative slow-twitch fibers compared to fast-twitch glycolytic fibers. Re-feeding after fasting increases CTRP15/myonectin expression ~80-fold in slow-twitch fibers but only ~4-fold in fast-twitch fibers (53). Administration of glucose or lipid after overnight fasting increased serum CTRP15/myonectin levels four-fold; likewise, nutrient-starved myotubes upregulated CTRP15/myonectin expression similarly to glucose or fatty acid supplementation. These observations suggest that CTRP15/myonectin is a postprandial hormone produced and secreted by skeletal muscle in response to nutrient flux. Consistent with this notion, administration of recombinant CTRP15/myonectin to mice significantly lowered circulating free fatty acids by promoting hepatocyte uptake through upregulation of CD36, fatty acid binding proteins, and fatty acid transport proteins (53).

### CTRP receptors

Three adiponectin receptors—adipoR1, adipoR2, and T-cadherin—have been identified by expression cloning strategies (144, 145). An additional distinct macrophage receptor for adiponectin is thought to exist, although this receptor remains elusive (146). In addition, the calreticulin/CD91 complex may bind adiponectin on the plasma membrane of macrophages to facilitate the removal of apoptotic cells (147). Since T-cadherin is a GPI-anchored plasma membrane protein (148), it is unclear how T-cadherin transduces a signal in response to adiponectin binding. Nonetheless, KO mice demonstrate that T-cadherin largely mediates the cardioprotective effects of adiponectin (149). AdipoR1 and adipoR2 contain seven transmembrane domains with inverse GPCR topologies. APPL1 is an intracellular adaptor protein that couples adiponectin binding to adipoR1/2 to intracellular signal transduction (150–153). Mice lacking adipoR1 or adipoR2 show variable and opposing phenotypes (154–156). In general, the metabolic phenotypes of adipoR1/2 KO mice are more striking than the relatively mild metabolic phenotypes of adiponectin KO mice. This complex story is ongoing (20, 157).

No CTRP receptors have been definitively identified. AdipoR1 may partially mediate the effects of CTRP9 on vascular endothelial cells (130) and cardiomyocytes (131), although these studies relied entirely on RNA interference approaches. No evidence demonstrates that CTRP9 interacts with adipoR1 on the plasma membrane of intact cells. FACS analysis can monitor receptor-ligand interactions on live cells, suggesting these experiments are feasible. Since adipoR1 and adipoR2 belong to the 11-member PAQR family of transmembrane

proteins (158), it is tempting to speculate that other PAQR family members may be CTRP receptors.

## Concluding remarks

Recent studies have provided insight into the metabolic roles of CTRP proteins. Although much has been learned since CTRPs were initially described, many more questions remain to be addressed. CTRPs possess unique and shared functions supported by a high degree of vertebrate conservation. Future studies with gain-of-function and loss-of-function mouse models will reveal novel insights into the physiological function, mechanism of action, and possible redundancy of each CTRP in normal and disease states. Going forward, identifying CTRP receptors will remain a major challenge but will provide enormous insights into the signaling pathways controlled by each CTRP to mediate its unique biological function.

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## Abbreviations

|                                  |  |
|----------------------------------|--|
| <b>ACC</b>                       | acetyl Co-A carboxylase                                |
| <b>AgRP</b>                      | agouti-related protein                                 |
| <b>AMPK</b>                      | AMP-activated protein kinase                           |
| <b>CTRP</b>                      | C1q/TNF-related protein                                |
| <b>C/EBP-<math>\alpha</math></b> | CCAAT/enhancer binding protein alpha                   |
| <b>DIO</b>                       | diet-induced obese                                     |
| <b>Erk1/2</b>                    | extracellular signal-regulated protein kinases 1 and 2 |
| <b>eNOS</b>                      | endothelial nitric oxide synthase                      |
| <b>FACS</b>                      | fluorescent activated cell sorter                      |
| <b>GLUT4</b>                     | glucose transporter 4                                  |
| <b>G6Pase</b>                    | glucose-6-phosphatase                                  |
| <b>GPCR</b>                      | G-protein coupled receptor                             |
| <b>GPI</b>                       | Glycosylphosphatidylinositol                           |
| <b>JNK</b>                       | c-Jun N-terminal kinase                                |
| <b>KO</b>                        | knock-out  |
| <b>LKB1</b>                      | liver kinase B1  |
| <b>L-ORD</b>                     | late-onset retinal macular degeneration                |
| <b>MAPK</b>                      | mitogen activated protein kinase                       |
| <b>NPY</b>                       | neuropeptide Y   |

|                                 |  |
|---------------------------------|--|
| <b>PPAR-<math>\gamma</math></b> | peroxisome proliferator-activated receptor gamma |
| <b>PCSK</b>                     | proprotein convertase subtilisin/kexin           |
| <b>PEPCK</b>                    | phosphoenolpyruvate carboxykinase                |
| <b>SAPK</b>                     | stress-activated protein kinase                  |

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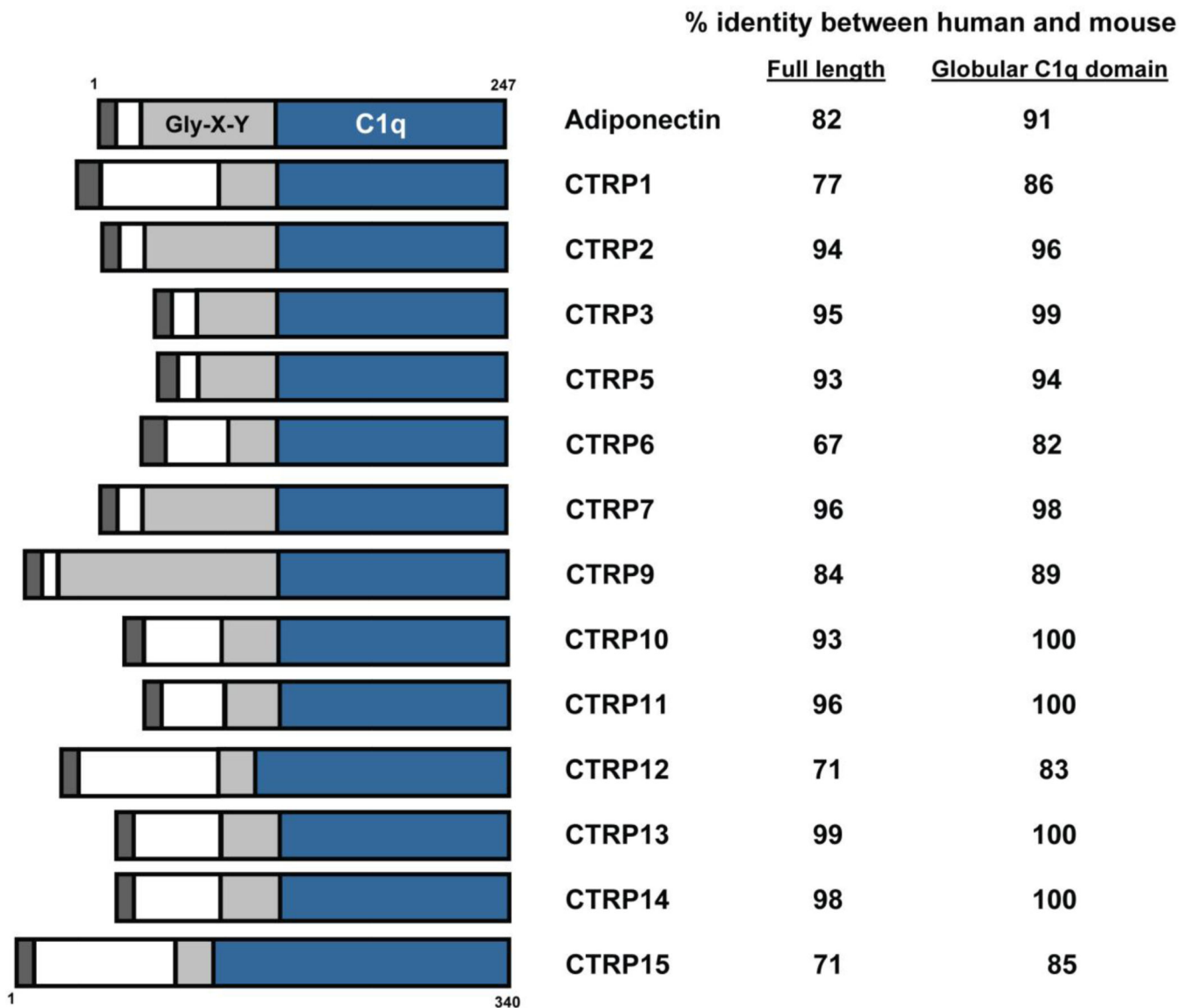


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**Figure 1. Schematic of CTRPs**

With the exception of CTRP4, every CTRP consists of four domains: a signal peptide for secretion (dark grey), an N-terminal domain with one or more conserved Cys residues (white), a collagen domain with varying numbers of Gly-X-Y repeats (light gray), and a C-terminal globular domain homologous to the immune complement C1q (blue). The numbers on the right refer to the percent amino acid identity between human and mouse orthologs when comparing the full-length protein (first column) or the C-terminal globular domain (second column). CTRP4 and CTRP8 are omitted—the former consists of only two tandem C1q domains, while the latter is absent in the mouse genome.

Table 1

Summary of CTRPs and their potential metabolic functions.

| CTRP  | Tissue distribution   | Regulation   | Signaling specificity | Sites of action                               | Physiological function   | Reference               |
|-------|---|--|-----------------------|---|--|-------------------------|
| CTRP1 | Primarily adipose tissue and placenta   | Decreased expression and circulating levels in DIO mice; increased expression in adiponectin KO mice                               | AMPK 44/42-MAPK       | Skeletal muscle                               | Promotes glucose uptake and skeletal muscle fat oxidation; decrease fat mass and enhances insulin sensitivity in transgenic mice fed a high-fat diet       | 29, 36, 48              |
| CTRP2 | Primarily adipose tissue; lower levels in lung, liver, testis, uterus                           | Increased expression in the adipose tissue of <i>ob/ob</i> mice  | AMPK                  | Skeletal muscle ?                             | Promotes fatty acid oxidation in cultured C2C12 myotubes   | 36                      |
| CTRP3 | Adipose tissue, kidney, testis, uterus, bone  | Decreased expression and circulating levels in DIO mice; increased expression in overnight fasted mice                             | AKT                   | Liver   | Suppresses hepatic gluconeogenic gene expression and glucose output; ameliorates diet-induced hepatic steatosis by inhibiting liver triglyceride-synthesis | 36, 49 99, 109, 112-116 |
|       |   |  | p44/42-MAPK p38-MAPK  | Endothelial cells                             | Increases migration and proliferation of endothelial cells in vitro  |                         |
|       |   |  | AKT                   | Heart   | Increases survival and decreases infarct size following myocardial infarction  |                         |
| CTRP5 | Adipose tissue, eye, testis skeletal muscle, brain spleen, uterus                               | Circulating levels of CTRP5 are increased in db/db and <i>ob/ob</i> mice, and OLETF rats   | ?                     | Monocytes, adipocytes and colonic fibroblasts | Decreases LPS-induced inflammatory response  | 29, 36, 84, 117-123     |
|       |   |  | AMPK                  | Skeletal muscle ?                             | Increases glucose uptake and fatty acid oxidation in mitochondria-depleted myotubes in vitro   |                         |
| CTRP6 | Primarily placenta; much lower levels in spleen, lung, testis, prostate, uterus, adipose tissue | Increased expression in the adipose tissue of <i>ob/ob</i> mice; rosiglitazone treatment decrease expression in the adipose tissue | ?                     | ?   | ?  | 29, 36                  |
| CTRP7 | Primarily adipose tissue and lung   | ?  | ?                     | ?   | S163R mutation results in late-onset retinal macular degeneration in humans  | 29, 36                  |

| CTRP               | Tissue distribution   | Regulation   | Signaling specificity | Sites of action                       | Physiological function  | Reference         |
|--------------------|---|--|-----------------------|---------------------------------------|---|-------------------|
| CTRP9              | Primarily adipose tissue  | Decreased circulating levels in DIO mice; Increased expression and circulating levels in fasted/re-fed mice  | AMPK                  | Skeletal muscle                       | Promotes fat oxidation  | 47, 124, 130-133, |
|                    |   |  | AMPK/eNOS             | Endothelial cells                     | Vasorelaxation  |                   |
| CTRP11             | Primarily adipose tissue and testis; lower levels in brain and kidney                         | Increased expression in the adipose tissue of fasted/re-fed mice   | AMPK                  | Heart                                 | Improved cardiac function following ischemia/reperfusion injury   | 52                |
|                    |   |  | p44/42-MAPK PKA       | Vascular smooth muscle cells          | Increased migration and cell proliferation; reduces neointima formation   |                   |
| CTRP12             | Primarily adipose tissue in humans; primarily testis, adipose, kidney, spleen, uterus in mice | Decreased expression and circulating levels in <i>ob/ob</i> and DIO mice                                     | p44/42-MAPK           | Pre-adipocytes                        | Inhibit adipogenesis  | 50, 54,75, 141    |
|                    |   |  | AKT                   | Adipose tissue                        | Promotes glucose uptake in adipocytes   |                   |
|                    |   |  | AKT                   | Liver                                 | Suppresses hepatic gluconeogenic gene expression and glucose output   |                   |
|                    |   |  | ?                     | Pancreatic $\beta$ -cells ?           | Enhances insulin secretion in lean but not DIO mice; increases glucose-induced insulin secretion in INS-1 cells |                   |
| CTRP13             | Primarily adipose, brain, and kidney  | Increased expression in the adipose tissue of <i>ob/ob</i> mice and in adipocytes treated with rosiglitazone | ?                     | Adipose tissue                        | Suppresses adipose tissue inflammation  | 51, 142           |
|                    |   |  | AMPK                  | Adipocytes, myotubes, and hepatocytes | Promotes glucose uptake in cultured adipocytes, myotubes, and hepatocytes                                       |                   |
|                    |   |  | AMPK                  | Liver ?                               | Suppressed gluconeogenic gene expression and glucose production in cultured H4IIEhepatocytes                    |                   |
|                    |   |  | ?                     | Liver ?                               | Decreased palmitate-induced insulin resistance in cultured hepatocytes by suppressing JNK signaling             |                   |
| Myonectin (CTRP15) | Primarily skeletal muscle   | Decreased expression and circulating levels in fasted mice and strikingly induced in fasted/re-fed mice      | ?                     | Hypothalamus                          | Suppressed food intake in mice by inhibiting orexigenic neuropeptide (NPY) expression                           | 53                |
|                    |   |  | ?                     | Adipose tissue and liver              | Promotes lipid uptake by increasing the expression of molecules (FATP, FABP) involved in fatty acid uptake      |                   |