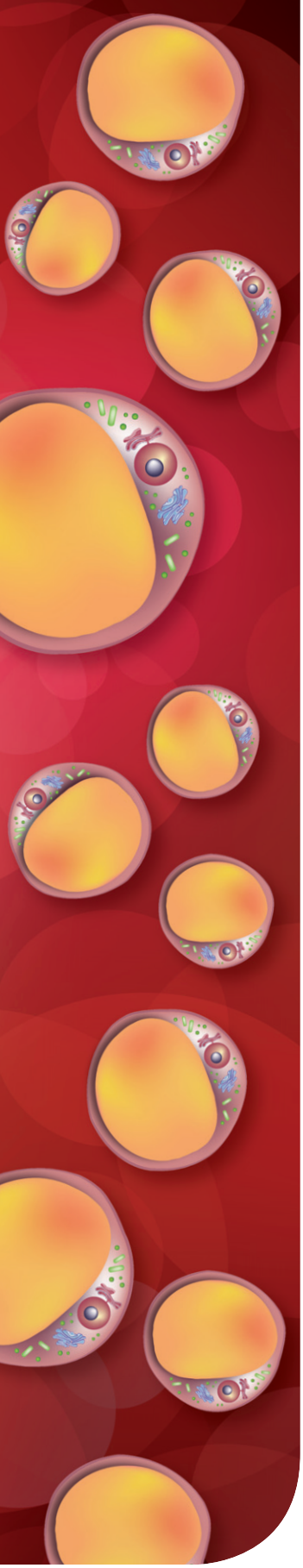

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Adiponectin & the CTRP Family

Linking Immunity to Metabolism

Excess body weight is a major risk factor for cardiovascular diseases, increasing the risk of hypertension, hyperglycaemia and dyslipidaemia, recognized as the metabolic syndrome. Adipose tissue acts as an endocrine organ by producing various signalling cytokines called adipokines. One of the first characterized adipokines, Adiponectin, is a member of the C1q/TNFrelated protein (CTRP) family and has attracted much interest because of its anti-inflammatory and insulin-sensitizing effects. To date, 15 additional CTRP family members have been identified that might also play a role in metabolism and immunity (Figure 2). Several of the CTRPs so far exert insulin-sensitizing effects similar to adiponectin. Therefore, these proteins might compensate for adiponectin deficiency, explaining why adiponec-

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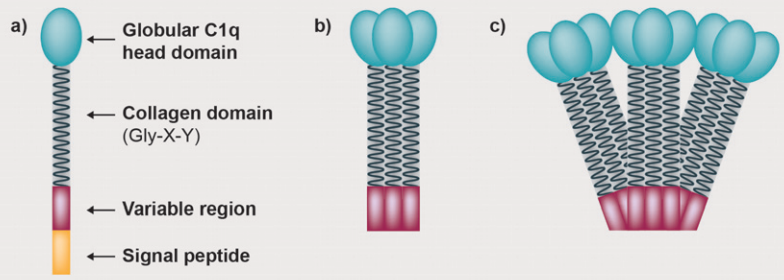

FIGURE 1: Structural organization of the CTRP family members.

a) Domain structure of a CTRP monomeric protein.
b) Homotrimeric CTRP protein structure. CTRP monomeric proteins form homotrimeric or/and heterotrimeric protein structures.
c) Higher-order protein structures of CTRP trimers. CTRP trimeric proteins form higher-order 3D structures.

Contents

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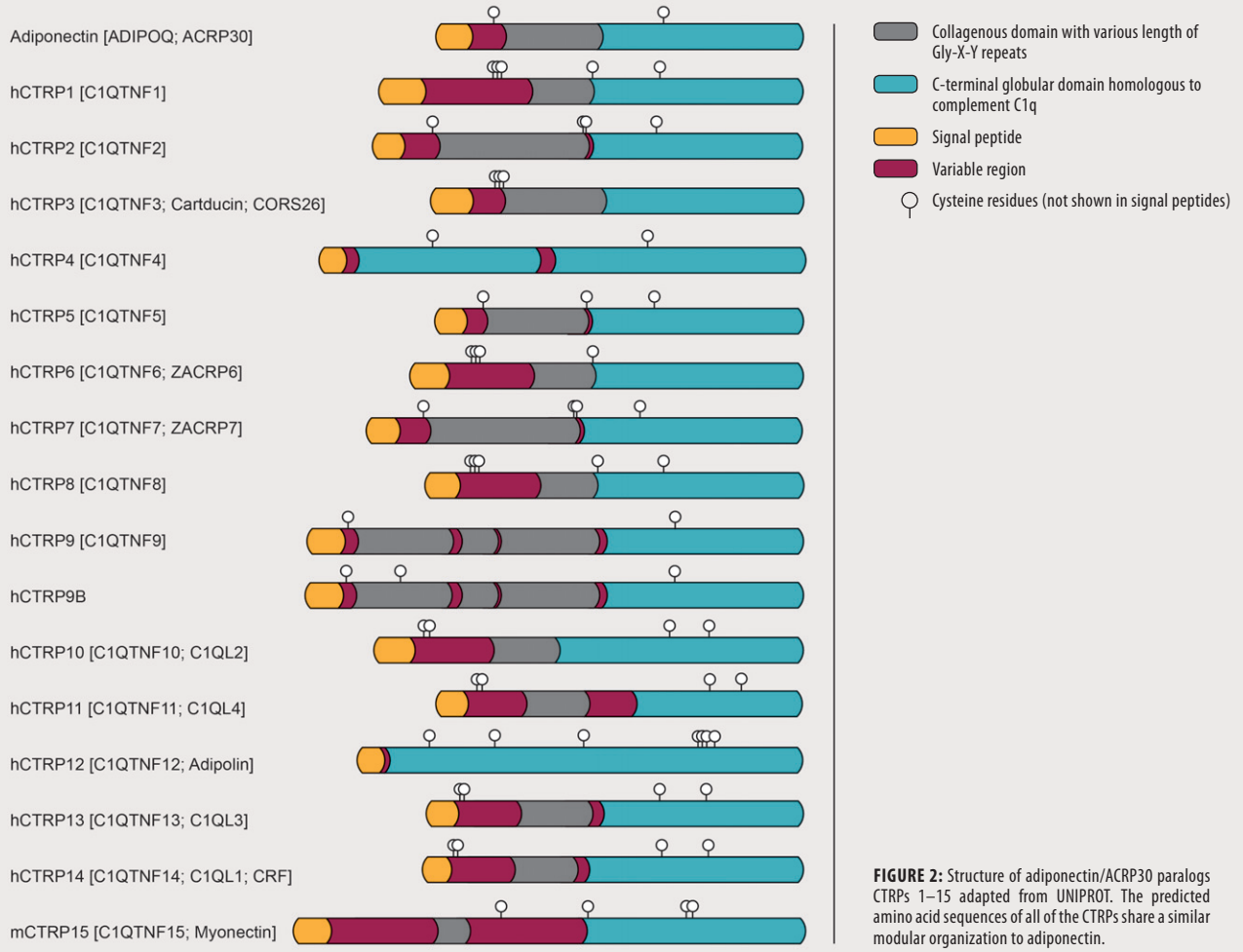

FIGURE 2: Structure of adiponectin/ACRP30 paralogs CTRPs 1–15 adapted from UNIPROT. The predicted amino acid sequences of all of the CTRPs share a similar modular organization to adiponectin.

tin knockout mice have only mild metabolic disturbances, even when fed a high-fat diet [1]. Due to their homology with adiponectin, they might have important implications in energy homeostasis and might provide novel pharmacological targets in type 2 diabetes (T2D) and obesity-related inflammation [2] and could be new molecular mediators connecting inflammatory and metabolic diseases.

CTRP proteins share a common structure composed of four distinct domains: a signal peptide at the N terminus, a short variable region, a collagenous domain and a C-terminal globular domain that is homologous to complement component 1q (C1q) (Figure 1). C1q itself is a component of the classical complement pathway released by the liver, and is crucial for the clearance of pathogens and apoptotic cells [3]. C1q forms trimers composed of A, B and C chains and resembles a bouquet of tulips under electron microscopy (Figure 1) [3]. CTRPs principally form highly stable, biologically active homotrimers. However, recent studies suggest that CTRPs may also form heterotrimers.

The family of CTRPs is rapidly growing and these proteins are widely expressed in human and murine systems. CTRPs are pleiotropic proteins and, similar to adiponectin, have many different physiological functions and are of high clinical interest as drug targets in various diseases. They have highly conserved structural homologies. Diversity, modularity and pleiotropic function are among the most important characteristics of these proteins. Identification of their respective receptors and functional characterization of the low and high MW isoforms will be essential to elucidate the physiological roles of these proteins [4].

LIT: [1] Adiponectin: no longer the lone soul in the fight against insulin resistance? K.E. Davis & P.E. Scherer; Biochem. J. **416,** e7 (2008) • **[2]** A family of Acrp30/adiponectin structural and functional paralogs: G.W. Wong, et al.; PNAS **101,** 10302 (2004) • **[3]** C1q and tumor necrosis factor superfamily: modularity and versatility: U. Kishore, et al.; Trends Immunol. **25,** 551 (2004) • **[4]** CTRP family: linking immunity to metabolism: A. Schaeffler & C. Buechler; TIEM. **23,** 194 (2012) (Review)

Adiponectin:
The best-characterized Member of the CTRP Family

Adiponectin [ACRP30; AdipoQ] is the best-characterized member of the CTRP family and is highly if not exclusively produced in adipocytes (white adipose tissue; WAT). It is secreted into the bloodstream as three oligomeric complexes, including trimer, hexamer and high molecular weight (HMW) multimer comprising at least 18 monomers, which possess distinct biological activities. The HMW oligomer is the major active form mediating insulin-sensitizing and cardiovascular protective effects. Adiponectin differs from most adipokines as it is negatively correlated with obesity.

Adiponectin exerts multiple biological effects throughout the body mediated by the specific receptors AdipoR1, AdipoR2 and T-cadherin. AdipoR1 and AdipoR2 interact with the adaptor protein APPL1, which binds the N-terminal intracellular domains of the receptors. The binding of adiponectin to its receptors provokes the activation of AMPK and the activation of various signaling molecules, such as p38 MAPK, PPAR, the RAS-associated protein Rab5, PI3K and Akt. Activation of AMPK mediates pharmacological actions of adiponectin, including fatty acid oxidation, protein degradation, cytoprotection and glucose uptake. Recently, it was shown that the insulin-sensitizing and anti-apoptotic actions of adiponectin are attributed to the stimulation of ceramidase activity and the formation of the anti-apoptotic metabolite sphingosine-1-phosphate (S1P) (Figure 3).

The physiological role of adiponectin (see Figure 4) is not fully elucidated, but it is believed that it has the ability to reduce glucose, triglycerides and free fatty acids and that it plays a major role in the pathogenesis of metabolic syndrome. Numerous studies have shown decreased adi-

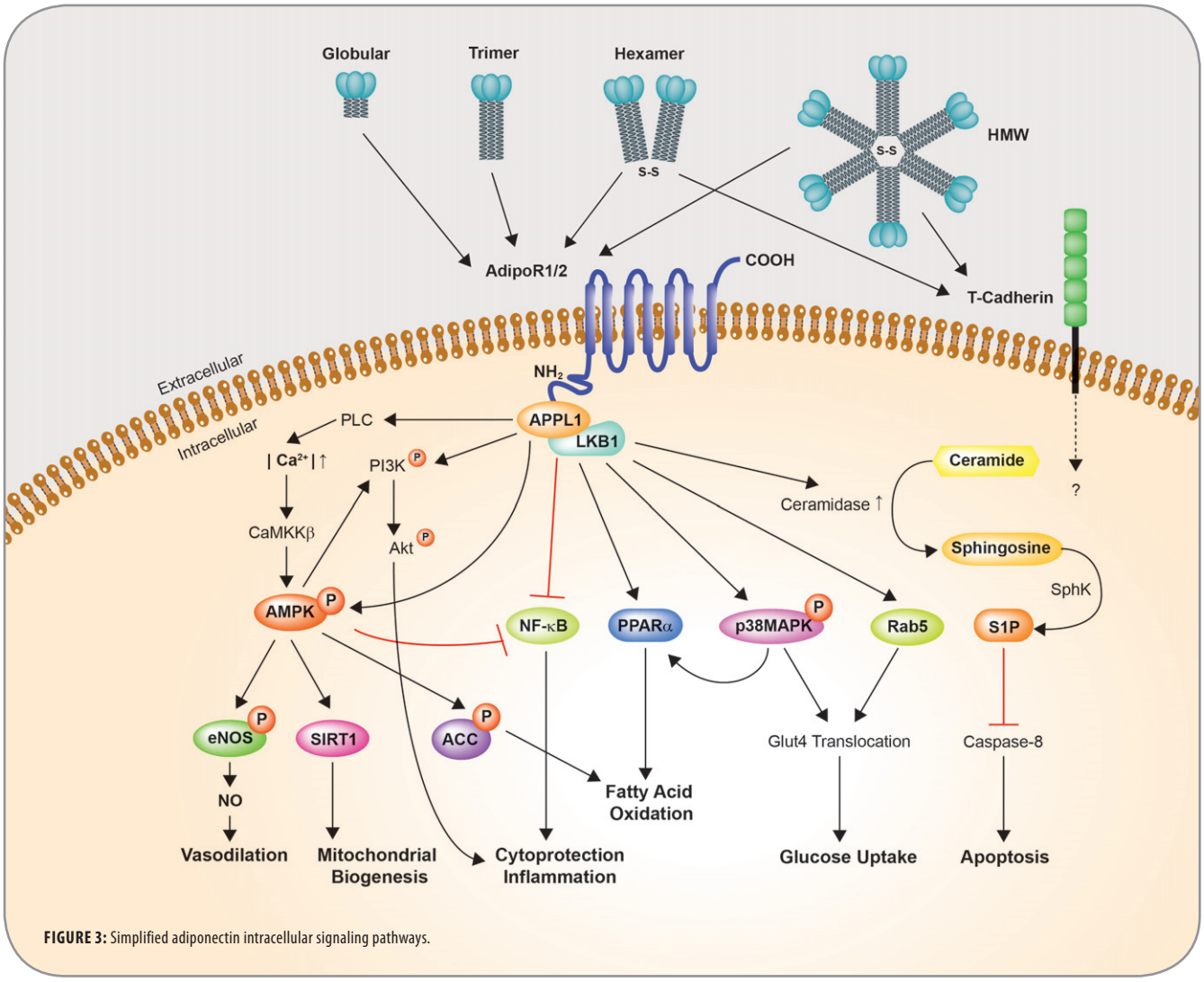

FIGURE 3: Simplified adiponectin intracellular signaling pathways.

ponectin bioactivity in obesity and obesity-related complications, including insulin resistance, diabetes, cardiovascular diseases (CVD) and non-alcoholic fatty liver disease (NAFLD). It is a regulator of immune cell activity, cancer cell proliferation, angiogenesis and many other processes. New findings showed urinary adiponectin excretion as an independent new biomarker of microvascular and macrovascular damage in T2DM and suggested it as a very promising tool for early cardiovascular disease risk assessment. It was also shown that adiponectin has antidepressant-like behavioral effects in normal-weight mice and in obese diabetic mice. Adiponectin levels are critical in determining susceptibility to depressive behaviors and therefore adiponectin could be considered as a potential innovative therapeutic target for depression treatment. Recently, it was shown that adiponectin effectively induces activation of dendritic cells and the release of proinflammatory cytokines, leading to enhanced Th1 and Th17 responses and demonstrating its importance in inflammatory processes.

SELECTED REVIEW ARTICLES

Effect of adiponectin on apoptosis: proapoptosis or antiapoptosis? Y. Sun & X. Chen; Biofactors **36,** 179 (2010) • Adiponectin: a key player in obesity related disorders: Y. Matsuzawa; Curr. Pharm. Des. **16,** 1896 (2010) • Adiponectin receptor binding proteins - recent advances in elucidating adiponectin signalling pathways: C. Buechler, et al.; FEBS Lett. **584,** 4280 (2010) • Adiponectin action from head to toe: K. Brochu-Gaudreau, et al.; Endocrine **37,** 11 (2010) • Inflammation, adiponectin, obesity and cardiovascular risk: H. Mangge, et al.; Curr. Med. Chem. **17,** 4511 (2010) • The therapeutic potential of the adiponectin pathway: W. Gu & Y. Li; BioDrugs **26,** 1 (2012) • Adiponectin and cardiovascular health: an update: X. Hui, et al.; Br. J. Pharmacol. **165,** 574 (2012) • Adiponectin induces dendritic cell activation via PLCγ/JNK/NF-κB pathways, leading to Th1 and Th17 polarization: M.Y. Jung, et al.; J. Immunol. **188,** 2592 (2012)

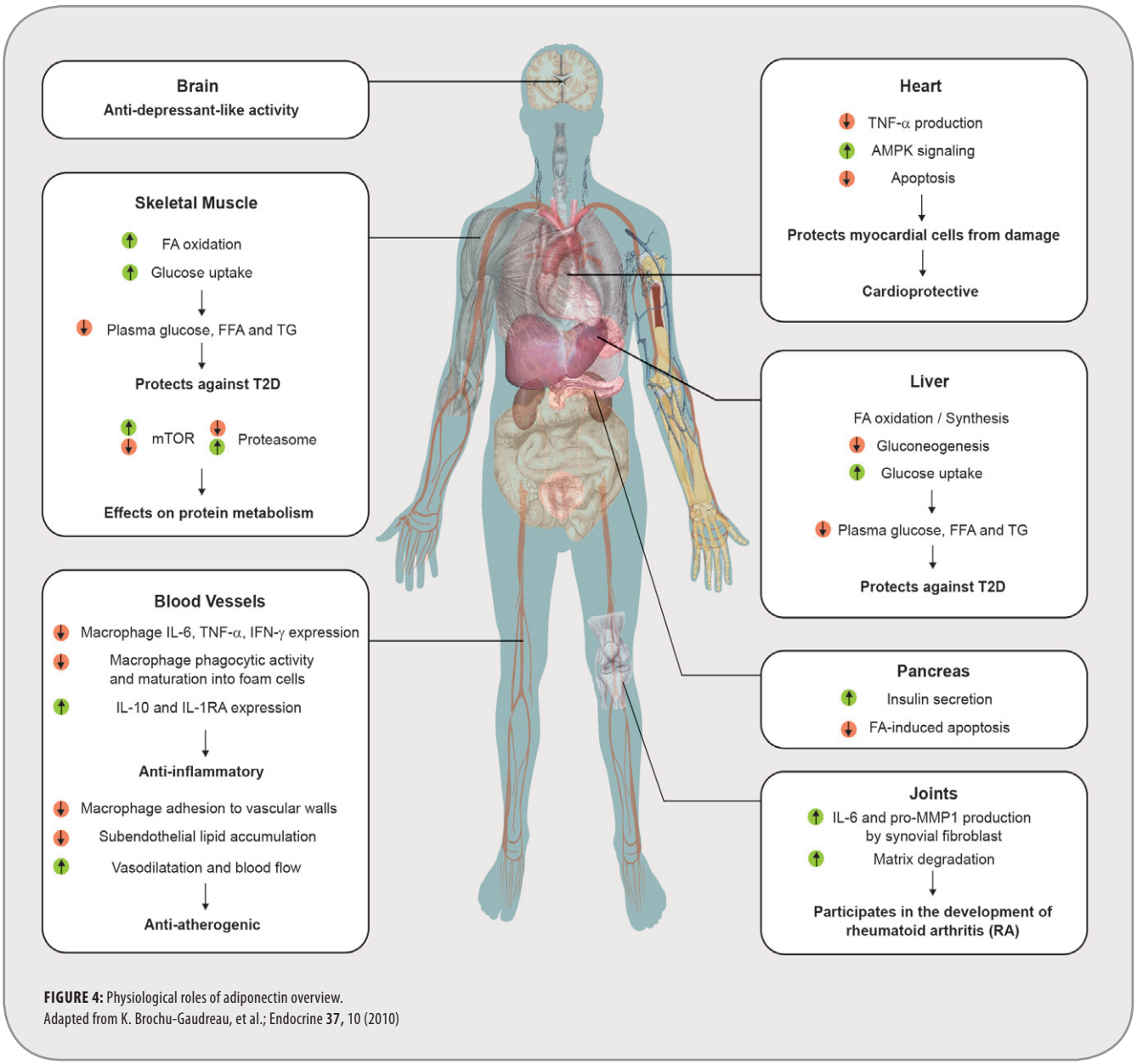

FIGURE 4: Physiological roles of adiponectin overview.
Adapted from K. Brochu-Gaudreau, et al.; Endocrine **37,** 10 (2010)

Proteins

PRODUCT NAME	PID	SIZE	TAG	MW BY SDS-PAGE	SOURCE	SPE-CIES	LIT. REF.
Adiponectin (human) (rec.)	AG-40B-0030	50 µg	FLAG	~33kDa	HEK 293 cells	Hu	
Adiponectin (human) (rec.) (BULK)	AG-40B-0030AA	500 µg	FLAG	~33kDa	HEK 293 cells	Hu	
Adiponectin (human) (rec.)	AG-40A-0001	50 µg	His	~30kDa	*E. coli*	Hu	✓
Adiponectin (trimeric form) (human) (rec.)	AG-40A-0143	10 µg 50 µg	FLAG	~35kDa	HEK 293 cells	Hu	
Adiponectin (GD) (human) (rec.)	AG-40A-0006	50 µg	FLAG	~17kDa	HEK 293 cells	Hu	
Adiponectin (GD) (human) (rec.)	AG-40A-0005	50 µg	His	~17kDa	*E. coli*	Hu	
Adiponectin (mouse) (rec.)	AG-40A-0002	50 µg	FLAG	~30kDa	HEK 293 cells	Ms	✓
Adiponectin (mouse) (rec.) (BULK)	AG-40B-0026AA	500 µg	FLAG	~35kDa	HEK 293 cells	Ms	
Adiponectin (mouse) (rec.)	AG-40A-0003	50 µg	His	~30kDa	*E. coli*	Ms	✓
Adiponectin (GD) (mouse) (rec.)	AG-40A-0007	50 µg	His	~17kDa	*E. coli*	Ms	
Adiponectin (rat) (rec.)	AG-40A-0004	50 µg	FLAG	~30kDa	HEK 293 cells	Rt	
Adiponectin (rat) (rec.)	AG-40A-0021	50 µg	His	~30kDa	*E. coli*	Rt	
Adiponectin (GD) (rat) (rec.)	AG-40A-0022	50 µg	His	~17kDa	*E. coli*	Rt	✓
Adiponectin (dog) (rec.)	AG-40A-0131	10 µg 50 µg	FLAG	~30kDa	HEK 293 cells	Dg	
Adiponectin (GD) (dog) (rec.)	AG-40A-0141	10 µg 50 µg	FLAG	~17kDa	HEK 293 cells	Dg	

GENERAL: **GD:** Globular Domain **SPECIES:** **Hu** = Human; **Ms** = Mouse; **Rt** = Rat; **Dg** = Dog

Antibodies

PRODUCT NAME	LABELS	PID	SIZE	CLONE	SOURCE/ ISOTYPE	APPLICATION	SPE-CIES	LIT. REF.
Adiponectin (human), mAb (ADI 943)		AG-20A-0056	50 µg	ADI 943	Ms IgG1κ	ELISA	Hu	
Adiponectin (human), mAb (HADI 741)		AG-20A-0002	50 µg 100 µg	HADI 741	Ms IgG1κ	ELISA, WB	Hu	✓
Adiponectin (human), mAb (HADI 773)		AG-20A-0001	50 µg 100 µg	HADI 773	Ms IgG1κ	ELISA, IHC (PS), WB	Hu	✓
Adiponectin (human), pAb		AG-25A-0003	100 µg		Rb	ELISA, WB	Hu	✓
Adiponectin (human), pAb	Biotin	AG-25A-0003B	50 µg		Rb	ELISA, WB	Hu	✓
Adiponectin (GD) (human), pAb		AG-25A-0034	100 µg		Rb	ELISA	Hu	
Adiponectin (mouse), mAb (MADI 04)		AG-20A-0005	50 µg 100 µg	MADI 04	Rt IgG1κ	ELISA, IP, WB	Ms	
Adiponectin (mouse), mAb (MADI 1147)		AG-20A-0003	50 µg 100 µg	MADI 1147	Ms IgG1κ	ELISA, IP, WB	Ms	✓
Adiponectin (mouse), pAb		AG-25A-0004	100 µg		Rb	ELISA, IP, WB	Ms	✓
Adiponectin (mouse), pAb	Biotin	AG-25A-0004B	50 µg		Rb	ELISA, IP, WB	Ms	✓
Adiponectin (rat), mAb (RADI 06)		AG-20A-0006	50 µg 100 µg	RADI 06	Ms IgG2bκ	ELISA, WB	Rt	
Adiponectin (rat), mAb (RADI 264)		AG-20A-0036	50 µg 100 µg	RADI 264	Ms IgG1κ	ELISA, WB	Rt	
Adiponectin (rat), pAb		AG-25A-0005	100 µg		Rb	ELISA, IHC (FS), WB	Rt	
Adiponectin (rat), pAb	Biotin	AG-25A-0005B	50 µg		Rb	ELISA, IHC (FS), WB	Rt	

Adiponectin Receptor Antibodies

Adiponectin Receptor 1 (human), pAb (AL238)		AG-25B-0010	100 µl		Rb	IHC (PS), WB	Hu	✓
Adiponectin Receptor 2 (mouse), pAb (AL241)		AG-25B-0012	100 µl		Rb	IP	Ms	

GENERAL: **CCD:** Coiled-coil Domain; **ED:** Ectodomain; **FLD:** Fibrinogen-like Domain; **GD:** Globular Domain; **PF:** Preservative Free
APPLICATIONS: **IHC:** Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); **IP:** Immunoprecipitation; **WB:** Western blot **SPECIES:** **Hu** = Human; **Ms** = Mouse; **Rt** = Rat

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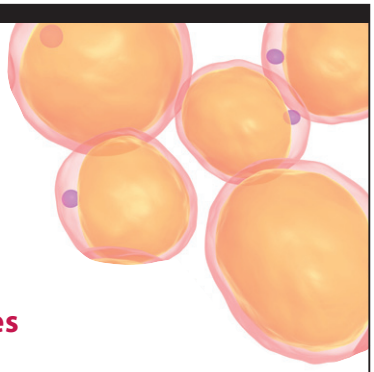


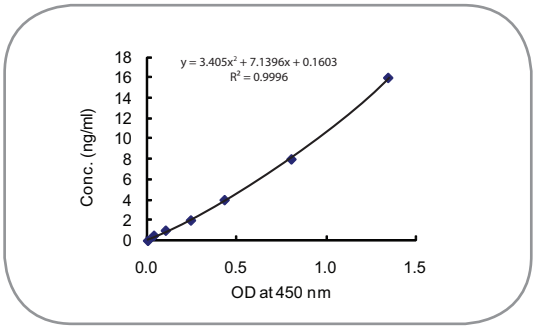
- **ELISA Kits Standards** • **Low inter- and intra-assay variation**
- **High sensitivity** • **Many product specific literature references**

Adiponectin Human ELISA Kits

Adiponectin (human) ELISA Kit

AG-45A-0001EK-KI01		96 wells
AG-45A-0001TP-KI01	TwinPlex	2 x 96 wells
AG-45A-0001PP-KI01	PentaPlex	5 x 96 wells

SPECIES REACTIVITY:	Human
SENSITIVITY:	100 pg/ml
RANGE:	0.5 to 32 ng/m
DETECTION TYPE:	Colorimetric
ASSAY TYPE:	Sandwich
SAMPLE TYPE:	Plasma, Serum, Tissue Supernatant, Urine, Cell Culture Supernatant



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- Association between hypoadiponectinemia and cardiovascular risk factors in nonobese healthy adults. J.A. Im, et al.; Metabolism **55,** 1546 (2006)
- Relationship of serum adiponectin and resistin levels with breast cancer risk: J.H. Kang, et al.; J. Korean Med. Sci. **22,** 117 (2007)
- Improved insulin sensitivity and adiponectin level after exercise training in obese Korean youth: E.S. Kim, et al.; Obesity **15,** 3023 (2007)
- Associations of adiponectin with sex hormone-binding globulin levels in aging male and female populations: T. Yasui, et al.; Clin. Chim. Acta **386,** 69 (2007)
- Crosstalk between high-molecular-weight adiponectin and T-cadherin during liver fibrosis development in rats: K. Asada, et al.; Intl. J. Mol. Med. **20,** 725 (2007)
- Retinol binding protein 4, low birth weight-related insulin resistance and hormonal contraception: A. Zugaro, et al.; Endocrine **32,** 166 (2007)
- Leptin is Associated with Endothelial Dysfunction in Healthy Obese Premenopausal Women: K. Kwon, et al.; Kor. Circ. J. **37,** 251 (2007)
- Correlation between estrogens and serum adipocytokines in premenopausal and postmenopausal women: S.C. Hong, et al.; Menopause **14,** 835 (2007)

Adiponectin (human) Competitive ELISA Kit

AG-45A-0002EK-KI01		96 wells
AG-45A-0002TP-KI01	TwinPlex	2 x 96 wells
AG-45A-0002PP-KI01	PentaPlex	5 x 96 wells

SPECIES REACTIVITY:	Human
SENSITIVITY:	1 ng/ml
RANGE:	0.001 to 1 µg/ml
DETECTION TYPE:	Colorimetric
ASSAY TYPE:	Competitive
SAMPLE TYPE:	Plasma, Serum, Tissue Supernatant, Cell Culture Supernatant

PRODUCT SPECIFIC LITERATURE REFERENCES

- Tumor necrosis factor-related apoptosis-inducing ligand promotes migration of human bone marrow multipotent stromal cells: P. Secchiero, et al.; Stem Cells **26,** 2955 (2008)
- Visceral Obesity is Associated with the Metabolic Syndrome and Elevated Plasma Retinol Binding Protein-4 Level in Obstructive Sleep Apnea Syndrome: S. Makino, et al.; Horm. Metab. Res. **41,** 221 (2009)
- High liver RBP4 protein content is associated with histological features in patients with genotype 1 chronic hepatitis C and with non-alcoholic steatohepatitis: S. Petta, et al.; Dig. Liver Dis. **43,** 404 (2011)

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Adiponectin Mouse & Rat ELISA Kits

Adiponectin (mouse) ELISA Kit

AG-45A-0004EK-KI01		96 wells
AG-45A-0004TP-KI01	TwinPlex	2 x 96 wells
AG-45A-0004PP-KI01	PentaPlex	5 x 96 wells

SPECIES REACTIVITY:	Mouse
SENSITIVITY:	50 pg/ml
RANGE:	0.125 to 8 ng/ml
DETECTION TYPE:	Colorimetric
ASSAY TYPE:	Sandwich
SAMPLE TYPE:	Plasma, Serum, Cell Culture Supernatant

PRODUCT SPECIFIC LITERATURE REFERENCE

- Chop-deficient mice showed increased adiposity but no glucose intolerance: Y. Ariyama, et al.; Obesity 15, 1647 (2007)risk factors in nonobese healthy adults. J.A. Im, et al.; Metabolism **55,** 1546 (2006)

Adiponectin (rat) ELISA Kit

AG-45A-0005EK-KI01		96 wells
AG-45A-0005TP-KI01	TwinPlex	2 x 96 wells
AG-45A-0005PP-KI01	PentaPlex	5 x 96 wells

SPECIES REACTIVITY:	Rat
SENSITIVITY:	50 pg/ml
RANGE:	0.375 to 24 ng/ml
DETECTION TYPE:	Colorimetric
ASSAY TYPE:	Sandwich
SAMPLE TYPE:	Plasma, Serum, Cell Culture Supernatant

PRODUCT SPECIFIC LITERATURE REFERENCE

- A new organotypic culture of adipose tissue fragments maintains viable mature adipocytes for a long term, together with development of immature adipocytes and mesenchymal stem cell-like cells: E. Sonoda, et al.; Endocrinology **149,** 4794 (2008)

Also available:

Adiponectin (rhesus monkey, macaque) Competitive ELISA Kit

AG-45A-0003EK-KI01	96 wells

CTRP Human ELISA Kits

• Newly introduced • Low inter- and intra-assay variation

CTRP3 (human) Competitive ELISA Kit

AG-45A-0042EK-KI01		96 wells
AG-45A-0042TP-KI01	TwinPlex	2 x 96 wells
AG-45A-0042PP-KI01	PentaPlex	5 x 96 wells

SPECIES REACTIVITY:	Human
SENSITIVITY:	1 ng/ml
RANGE:	0.001 to 1 µg/ml
DETECTION TYPE:	Colorimetric
ASSAY TYPE:	Competitive
SAMPLE TYPE:	Plasma, Serum, Cell Culture Supernatant

PRODUCT SPECIFIC LITERATURE REFERENCE

- C1q/TNF-Related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients With Type 2 Diabetes and Metabolic Syndrome: K.M. Choi, et al.; Diabetes **(Epub ahead of print)** (2012)

CTRP5 (human) Competitive ELISA Kit

AG-45A-0031EK-KI01		96 wells
AG-45A-0031TP-KI01	TwinPlex	2 x 96 wells
AG-45A-0031PP-KI01	PentaPlex	5 x 96 wells

SPECIES REACTIVITY:	Human
SENSITIVITY:	1 ng/ml
RANGE:	0.001 to 5 µg/ml
DETECTION TYPE:	Colorimetric
ASSAY TYPE:	Competitive
SAMPLE TYPE:	Plasma, Serum, Cell Culture Supernatant

Biological Functions of CTRPs

CTRP1 [C1QTNF1] mRNA is expressed in heart, placenta, liver, muscle, kidney, prostate and ovary, with highest expression levels in adipose tissue. Stromal vascular cells (SVC) composed of adipose-tissue macrophages, preadipocytes and endothelial cells are the major source of CTRP1, but so far the exact cells which synthesize CTRP1 have not been identified. CTRP1 reduces serum glucose levels in mice [1] by activating the serine/threonine protein kinase Akt and mitogen-activated protein kinase (MAPK) in mouse myotubes. CTRP1 may play a role in blood pressure regulation. It is highly expressed in the zona glomerulosa of the adrenal gland where it enhances aldosterone release and a synergistic effect is observed by coincubation with angiotensin II [2]. The antithrombotic activity of CTRP1 may protect from platelet aggregation following the rupture of atherosclerotic plaques that can cause myocardial infarction and stroke [3]. Systemic CTRP1 is induced by inflammatory cytokines (TNF-α, IL-1β), which may explain higher levels in obesity and hypertension. CTRP1 forms homotrimeric structures and heterooligomers with CTRP6.

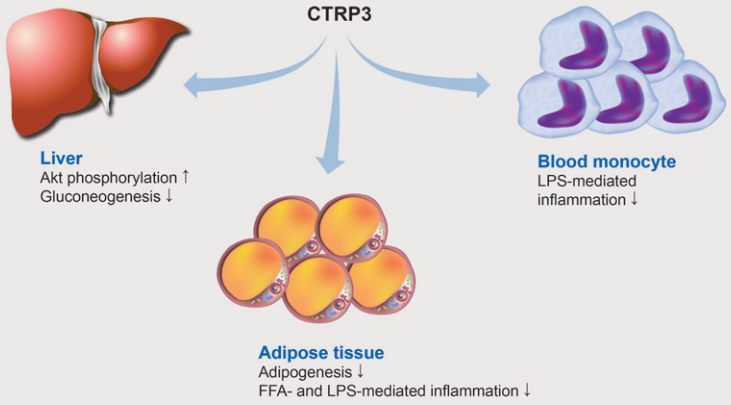

FIGURE 5: Dual effect of CTRP3 on metabolism and immune function.
Adapted from A. Schaeffler & C. Buechler; TIEM **23,** 194 (2012)

CTRP2 [C1QTNF2] mRNA is mainly synthesized in stromal vascular cells (SVC). CTRP2 may theoretically form heteromeric complexes with CTRP7 and adiponectin. CTRP2 induces phosphorylation of AMPK, acetyl-CoA carboxylase (ACC) and p42/44 MAPK in C2C12 myotubes and subsequently increases glycogen accumulation and fatty acid oxidation. It stimulates glucose uptake in muscle and therefore might help to lower blood glucose levels [4, 5].

CTRP3 [C1QTNF3; Cartducin; Cartonectin; CORS26] lowers glucose levels by reducing hepatic gluconeogenesis. The metabolic effects is linked to Akt activation and suppression of the expression of G6Pase and PEPCK [6]. CTRP3 serum levels are inversely correlated with leptin levels. CTRP3 is an adipokine that increases with fasting, decreases in diet-induced obese mice with high leptin levels and increases in leptin-deficient ob/ob mice. CTRP3 is a potential target in metabolic syndrome treatment, that induces adiponectin and resistin release in adipocytes. It is also involved in induction of p-p38 MAPK and p-ERK [6,7]. CTRP3 is a potent anti-inflammatory adipokine that inhibits proinflammatory pathways, such as fatty acid-, LPS- and Toll-like receptor (TLR)-mediated inflammation in monocytes and adipocytes. CTRP3 functions as a novel and endogenous LPS antagonist in adipose tissue [8-10]. The ability of CTRP3 to block LPS-mediated signaling makes it a good candidate for the treatment of acute inflammatory diseases caused by Gram-negative bacteria. CTRP3 may also reduce lipotoxicity, which is a main pathological factor associated with inappropriate lipid storage in peripheral tissues. CTRP3 was shown to promote proliferation and migration of endothelial cells in angiogenesis [11] and has mild effects on vasorelaxation [12].

CTRP4 [C1QTNF4] stimulates IL-6 synthesis, STAT3 and NF-κB activation in HepG2 cells. IL-6 has been shown to upregulate CTRP4 synthesis in HepG2 cells. CTRP4 can promote tumor cell survival and tumor resistance against apoptosis induced by chemotherapeutics [13].

CTRP5 [C1QTNF5] is expressed in adipocytes and myocytes (and is therefore a myokine). CTRP5 induces phosphorylation of AMPK, acetyl-CoA carboxylase (ACC) and p42/44 MAPK in C2C12 myotubes and subsequently increases glycogen accumulation and fatty acid oxidation. It stimulates glucose uptake in muscle and therefore might help to lower blood glucose levels [14]. CTRP5 expression was drastically increased following depletion of mtDNA in myocytes and serum levels are significantly higher in obese/diabetic animals. CTRP5 is a putative biomarker for mitochondrial dysfunction and a mediator for metabolic syndrome, including obesity and insulin resistance [14]. CTRP5 was shown to be associated with late-onset retinal degeneration, based on a missense mutation (Ser163 to Arg) [15, 16]. CTRP5 has mild effects on vasorelaxation [12].

CTRP6 [C1QTNF6; ZACRP 6] mediates the phosphorylation of AMPK and acetyl-CoA carboxylase (ACC) in skeletal muscle cells, subsequently mediating glycogen accumulation and fatty acid oxidation [17]. It induces the expression of the potent anti-inflammatory cytokine IL-10 in macrophages [18]. CTRP6 may be a potential serum marker for hepatocellular carcinoma, contributing to tumor angiogenesis by activating the Akt pathway [19]. CTRP6 was also shown to be associated with obesity, type 1 diabetes mellitus (T1D), vitiligo (depigmentation of the skin) and ASFV (African Swine Fever Virus) [20, 21]. CTRP6 forms homotrimers and higher-order oligomers and it may also form heteromeric complexes with CTRP1.

CTRP7 [C1QTNF7; ZACRP7] is elevated in muscular tissues of old animals and is induced further by caloric restriction. Expression levels of CTRP7 transcripts are up-regulated in 8-week-old obese (ob/ob) mice relative to lean controls [22]. Markers lying within the CTRP7 gene locus were reported to be associated with conduct disorder [23].

CTRP8 [C1QTNF8] is expressed in lung and testis and forms homotrimers as well as heteromeric complexes with C1q-related factor (CRF). There is no ortholog of the CTRP8 gene in the mouse genome, which complicates the analysis of CTRP8 function [24].

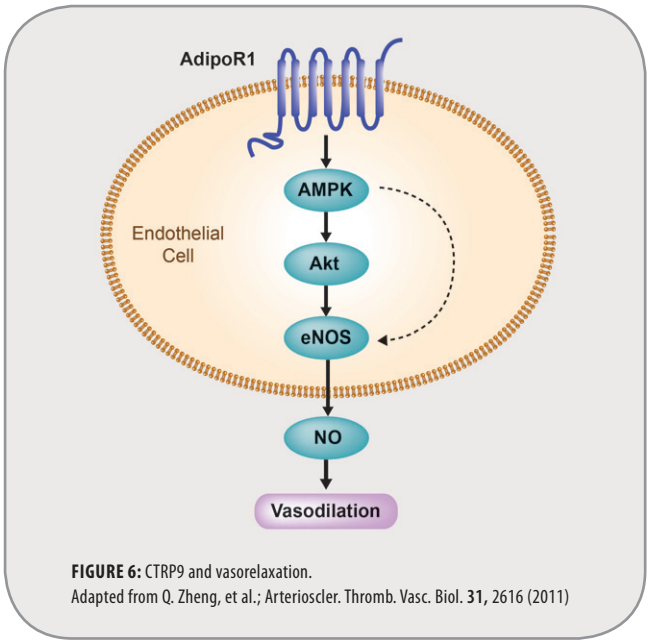

FIGURE 6: CTRP9 and vasorelaxation.
Adapted from Q. Zheng, et al.; Arterioscler. Thromb. Vasc. Biol. **31,** 2616 (2011)

CTRP9 [C1QTNF9] is the closest adiponectin paralog of the CTRP family. Its expression is highest in adipose tissue. CTRP9 activates AMPK, Akt and p42/44 MAPK in cultured myotubes and stimulates glucose uptake in muscle, which might contribute to reduced serum glucose levels in obese (ob/ob) mice [25]. CTRP9 expression might be affected by intracellular magnesium levels, which is suggested to exert beneficial effects on glucose metabolism [26]. CTRP9 is a potent mediator of vasorelaxation via the adiponectin receptor 1, by increasing AMPK/Akt/eNOS phosphorylation and by producing vasorelaxing nitric oxide [27].

CTRP10 [C1QTNF10; C1QL2] is highly expressed in brain, placenta and the eye. CTRP10 in fat is upregulated by rosiglitazone treatment. CTRP10 forms homotrimers or heteromeric complexes with C1q-related factor (CRF)s [1, 28]. It probably plays a role in the regulation of synapse formation and/or maintenance [29].

CTRP11 [C1QTNF11; C1QL4] is a secreted protein that uses BAI-3 as a receptor. Addition of CTRP11 to cultured neurons causes a significant decrease in synapse density. It probably plays a role in the regulation of synapse formation and/or maintenance [29].

CTRP12 [C1QTNF12; Adipolin] is an insulin-sensitizing adipokine that suppresses inflammation in adipose tissue. It may be an anti-inflammatory adipokine that exerts beneficial actions on glucose metabolism. Systemic administration of CTRP12 ameliorates glucose intolerance and insulin resistance and can be potentially useful for the prevention and treatment of obesity-linked insulin resistance and diabetes [30, 31]. CTRP12 administration also reduces macrophage accumulation and pro-inflammatory gene expression in adipose tissue of obese mice [31]. CTRP12 expression is modulated by pro- and anti-inflammatory factors in chondrocytes and might participate in cartilage maturation and development [32].

CTRP13 [C1QTNF13; C1QL3] is an insulin-sensitizing hormone, that promotes glucose uptake in adipocytes, myotubes and hepatocytes via activation of the AMPK signaling pathway. It inhibits the glucose output in hepatocytes, in accordance with lower expression of G6Pase and PEPCK and ameliorates lipid-induced insulin resistance in hepatocytes. CTRP13 reduces phosphorylation of JNK, thereby improving insulin signaling. CTRP13 transcript and circulating levels are elevated in obese male mice, suggesting a potential role in energy metabolism, insulin resistance and obesity [28]. It might probably play a role in the regulation of synapse formation and/or maintenance [29].

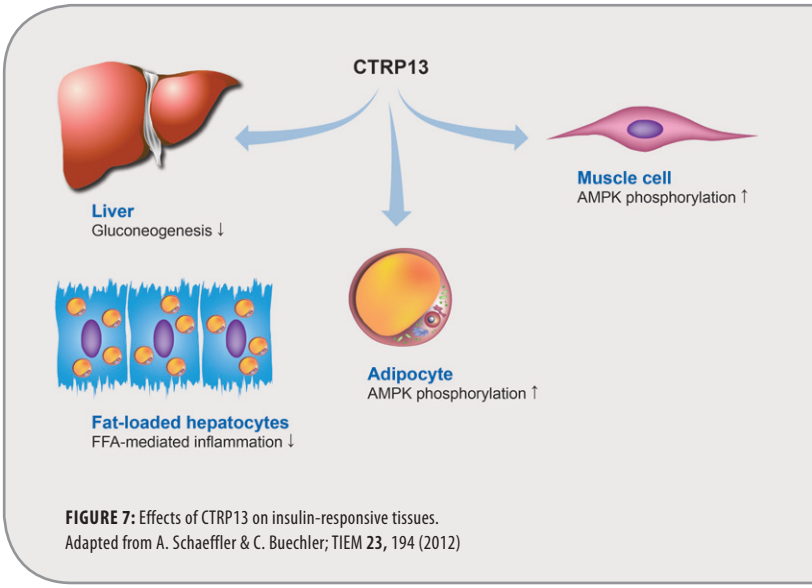

FIGURE 7: Effects of CTRP13 on insulin-responsive tissues.
Adapted from A. Schaeffler & C. Buechler; TIEM **23,** 194 (2012)

CTRP14 [C1QTNF14; C1QL1; CRF] is expressed at highest levels in the brain. It is a secreted protein that uses BAI-3 as a receptor. Addition of CTRP14 to cultured neurons causes a significant decrease in synapse density. It probably plays a role in the regulation of synapse formation and/or maintenance [29].

CTRP15 [C1QTNF15; Myonectin; FAM132B] is a new myokine (cytokine secreted by muscle). CTRP15 mRNA is highly induced in differentiated myotubes and predominantly expressed by skeletal muscle. Its serum levels are

tightly regulated by the metabolic state. Fasting suppresses and re-feeding dramatically increases CTRP15 mRNA levels. CTRP15 levels are reduced in diet-induced obesity and increased by voluntary exercise. In mice, recombinant CTRP15 administration reduces circulating levels of free fatty acids without altering adipose tissue lipolysis. CTRP15 promotes fatty acid uptake in cultured adipocytes and hepatocytes. CTRP15 links skeletal muscle to lipid homeostasis in liver and adipose tissue in response to alterations in energy state, revealing a novel CTRP15 mediated metabolic circuit [33].

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Latest Insight

CTRP3: A Marker for Type 2 Diabetes and Metabolic Syndrome

K.M. Choi, et al. recently examined circulating CTRP3 in 345 subjects with diverse glucose tolerance statuses by using the AdipoGen® CTRP3 (human) Competitive ELISA Kit (AG-45A-0042). They evaluated the involvement of CTRP3 with cardiometabolic risk factors including insulin resistance, high-sensitivity C-reactive protein (hsCRP), estimated glomerular filtration rate (eGFR), and brachial-ankle pulse wave velocity (baPWV). As a result CTRP3 concentrations were significantly higher in patients with type 2 diabetes or prediabetes than the normal glucose tolerance group. Subjects with metabolic syndrome showed significantly higher levels of CTRP3 compared with subjects without metabolic syndrome. Therefore, CTRP3 was significantly associated with cardiometabolic parameters, including waist-to-hip ratio, triglycerides, HDL-cholesterol, alanine aminotransferase, eGFR, hsCRP and baPWV. In summary, they postulate that circulating CTRP3 concentrations were elevated in patients with glucose metabolism dysregulation. It was increased in subjects with metabolic syndrome and associated with various cardiometabolic risk factors.

LIT: C1q/TNF-Related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients With Type 2 Diabetes and Metabolic Syndrome: K.M. Choi, et al.; Diabetes **(Epub ahead of print)** (2012)

Proteins

PRODUCT NAME	PID	SIZE	TAG	MW BY SDS-PAGE	SOURCE	SPE-CIES	LIT. REF.
CTRP1 (GD) (human) (rec.)	AG-40A-0172	10 µg 50 µg	FLAG	~16kDa	HEK 293 cells	Hu	
CTRP2 (GD) (human) (rec.)	AG-40A-0044	10 µg 50 µg	FLAG	~18kDa	HEK 293 cells	Hu	
CTRP2 (GD) (mouse) (rec.)	AG-40A-0061	10 µg 50 µg	FLAG	~25kDa	HEK 293 cells	Ms	
CTRP3 (human) (rec.)	AG-40A-0163	10 µg 50 µg	FLAG	~35kDa	HEK 293 cells	Hu	
CTRP3 (GD) (human) (rec.)	AG-40A-0164	10 µg 50 µg	His	~28kDa	*E. coli*	Hu	
CTRP5 (GD) (human) (rec.)	AG-40A-0134	10 µg 50 µg	His	~16kDa	*E. coli*	Hu	
CTRP5 (human) (rec.)	AG-40A-0142	10 µg 50 µg	His	~26kDa	*E. coli*	Hu	
CTRP6 (human) (rec.)	AG-40A-0166	10 µg	FLAG	~32kDa	HEK 293 cells	Hu	
CTRP6 (GD) (human) (rec.)	AG-40A-0138	10 µg 50 µg	His	~16kDa	*E. coli*	Hu	
CTRP7 (GD) (human) (rec.)	AG-40A-0135	10 µg 50 µg	His	~17kDa	*E. coli*	Hu	
CTRP9 (human) (rec.)	AG-40A-0179	10 µg	His	~35kDa	*E. coli*	Hu	
CTRP9 (GD) (human) (rec.)	AG-40A-0176	10 µg 50 µg	His	~16kDa	*E. coli*	Hu	
CTRP9 (GD) (mouse) (rec.)	AG-40A-0130	10 µg 50 µg	His	~16kDa	*E. coli*	Ms	
CTRP10 (human) (rec.)	AG-40A-0185	10 µg 50 µg	FLAG	~29kDa	HEK 293 cells	Hu	
CTRP10 (GD) (human) (rec.)	AG-40A-0136	10 µg 50 µg	His	~16kDa	*E. coli*	Hu	
CTRP13 (GD) (human) (rec.)	AG-40A-0195	10 µg 50 µg	His	~16kDa	*E. coli*	Hu	

GENERAL: **GD:** Globular Domain
SPECIES: **Hu** = Human; **Ms** = Mouse

Antibodies

PRODUCT NAME	PID	SIZE	CLONE	SOURCE/ ISOTYPE	APPLICATION	SPE-CIES	LIT. REF.
CTRP1 (human), pAb	AG-25A-0114	100 µg		Gp	ELISA, IP, WB	Hu	
CTRP2 (human), pAb	AG-25A-0115	100 µg		Gp	ELISA, IP, WB	Hu	
CTRP3 (human), pAb	AG-25A-0107	100 µg		Gp	ELISA, WB	Hu	
CTRP3 (GD) (human), pAb	AG-25A-0110	100 µg		Rb	ELISA, WB	Hu	
CTRP5 (human), pAb	AG-25A-0103	100 µg		Rb	ELISA, WB	Hu	
CTRP5 (human), pAb	AG-25A-0116	100 µg		Gp	ELISA, IP, WB	Hu	
CTRP5 (GD) (human), pAb	AG-25A-0096	100 µg		Rb	ELISA, WB	Hu	
CTRP6 (human), pAb	AG-25A-0108	100 µg		Gp	ELISA, WB	Hu	
CTRP7 (human), pAb	AG-25A-0117	100 µg		Gp	ELISA, IP, WB	Hu	
CTRP7 (GD) (human), pAb	AG-25A-0097	100 µg		Rb	ELISA, WB	Hu	
CTRP9 (human), pAb	AG-25A-0109	100 µg		Gp	ELISA, WB	Hu	
CTRP9 (GD) (human), pAb	AG-25A-0098	100 µg		Rb	ELISA, WB	Hu	

GENERAL: **GD:** Globular Domain **APPLICATIONS:** **IP:** Immunoprecipitation; **WB:** Western blot
SPECIES: **Hu** = Human; **Gp** = Guinea Pig; **Rb** = Rabbit

Myokines – Muscle, Exercise & Obesity

Exercise training enhances muscular endurance and strength, expends calories, exerts beneficial effects on systemic metabolism and combats the development of common diseases such as obesity and type 2 diabetes, by adaptive structural and metabolic changes in skeletal muscle, including a change in the type of muscle fiber, mitochondrial biogenesis and angiogenesis.

Additionally, skeletal muscle secretes cytokines and growth factors, called myokines, that can potentially act in an autocrine, a paracrine and/or an endocrine manner to modulate metabolic, inflammatory and other processes. The production of myokines may increase during or after exercise due to the activation of contraction-induced signaling pathways, e.g. the calcium signaling pathway or due to changes in energy status within the muscle fibres [1, 2].

Several myokines have been described including CTRP5 [3], CTRP15 [4], FGF-21 [5], IL-6 [6], IL-7 [7], IL-15 [8], LIF [9], BDNF [10] and the very recently described Irisin [11, 12].

LIT: [1] Muscles, exercise and obesity: skeletal muscle as a secretory organ: B.K. Pedersen & M.A. Febbraio; Nat. Rev. Endocrinol. **8,** 457 (2012) (Review) • **[2]** Secreted proteins from adipose tissue and skeletal muscle - adipokines, myokines and adipose/muscle cross-talk: P. Trayhurn, et al.; Arch. Physiol. Biochem. **117,** 47 (2011) (Review) • **[3]** Effects of aerobic exercise training on C1q tumor necrosis factor α-related protein isoform 5 (myonectin): association with insulin resistance and mitochondrial DNA density in women: S. Lim, et al.; J. Clin. Endocrinol. Metab. **97,** E88 (2012) • **[4]** Myonectin (CTRP15), a novel myokine that links skeletal muscle to systemic lipid homeostasis: M.M. Seldin, et al.; J. Biol. Chem. **287,** 11968 (2012) • **[5]** FGF21 is an Akt-regulated myokine: Y. Izumiya, et al.; FEBS Lett. **582,** 3805 (2008) • **[6]** Muscular interleukin-6 and its role as an energy sensor: B.K. Pedersen; Med. Sci. Sports Exerc. **44,** 392 (2012) • **[7]** IL-7 is expressed and secreted by human skeletal muscle cells: F. Haugen, et al.; Am. J. Physiol. Cell Physiol. **298,** C807 (2010) • **[8]** Therapeutic potential of interleukin-15: a myokine involved in muscle wasting and adiposity: J.M. Argilés, et al.; Drug Discov. Today **14,** 208 (2009) (Review) • **[9]** Leukaemia inhibitory factor - an exercise-induced myokine: C. Broholm & B.K. Pedersen; Exerc. Immunol. Rev. **16,** 77 (2010) (Review) • **[10]** The recent understanding of the neurotrophin's role in skeletal muscle adaptation: K. Sakuma & A. Yamaguchi; J. Biomed. Biotechnol. **2011,** 201696 (2011) • **[11]** A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis: P. Boström, et al.; Nature **481,** 463 (2012) • **[12]** Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human: J. Wu, et al.; Cell **150,** 366 (2012)

PRODUCT NAME	PID	SIZE
FGF-21 (human) (rec.)	AG-40A-0091-C010 AG-40A-0091-C050	10 µg 50 µg
FGF-21 (human) (rec.) (His)	AG-40A-0098-C010 AG-40A-0098-C050	10 µg 50 µg
FGF-21 (human):Fc (human) (rec.)	AG-40A-0095-C010 AG-40A-0095-C050	10 µg 50 µg
FGF-21 (mouse) (rec.)	AG-40A-0092-C010 AG-40A-0092-C050	10 µg 50 µg
FGF-21 (mouse) (rec.) (His)	AG-40A-0099-C010 AG-40A-0099-C050	10 µg 50 µg
FGF-21 (mouse):Fc (human) (rec.)	AG-40A-0097-C010 AG-40A-0097-C050	10 µg 50 µg
IL-6 (mouse):Fc (human) (rec.)	AG-40B-0108-C010 AG-40B-0108-3010	10 µg 3 x 10 µg
IL-6 (human):Fc (human) (rec.)	CHI-HF-21006-C050 CHI-HF-21006-3050	50 µg 3 x 50 µg
IL-6 (human):Fc (human) (rec.) (non-lytic)	CHI-HF-22006-C050 CHI-HF-22006-3050	50 µg 3 x 50 µg
IL-6 (mouse):Fc (mouse) (rec.) (non-lytic)	CHI-MF-12006-C050 CHI-MF-12006-3050	50 µg 3 x 50 µg
IL-6R (human):Fc (human) (rec.)	CHI-HF-21006R-C050	50 µg
IL-15 (mutant) (human):Fc (human) (rec.)	CHI-HF-21015M-C050	50 µg
LIF (human) (rec.)	AG-40B-0093-C010 AG-40B-0093-3010 AG-40B-0093-C100	10 µg 3 x 10 µg 100 µg

For CTRP5 products please see page 11.

Just released!

Irisin – A New Myokine & Health Promoting Hormone?

- **Exercise-induced hormone secreted by skeletal muscles • Activates beige fat cells**
- **Improves systemic metabolism by increasing energy expenditure and thermogenesis**

Irisin (rec.) (HEK293)
AG-40B-0102-C010 — 10 µg

Irisin (rec.) (E. coli)
AG-40B-0103-C010 — 10 µg
AG-40B-0103-5010 — MultiPack — 5 x 10 µg

anti-Irisin, pAb (IN102)
AG-25B-0027 –C100 — 100 µg
AG-25B-0027B–C100 — Biotin — 100 µg

SOURCE: Rabbit. IMMUNOGEN: Recombinant irisin. SPECIFICITY: Recognizes human, mouse, rat, monkey irisin. APPLICATION: WB (1:1'000).

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