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REVIEWS

# T-Cadherin as a Novel Receptor Regulating Metabolism in the Blood Vessel and Heart Cells: from Structure to Function

**M. N. Balatskaya, A. V. Balatskii, G. V. Sharonov, and V. A. Tkachuk**

*Lomonosov Moscow State University, Moscow, Russia*
*e-mail: m.balatskaya@gmail.com*

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**Abstract**—The review discusses structural features of T-cadherin (T-cad) that allow it to perform functions other than cell–cell adhesion. T-cad is a receptor of the significant metabolic components, low-density lipoproteins and high-molecular-weight adiponectin. Association of cardiovascular and metabolic diseases with the T-cad gene polymorphism, as well as predominant T-cad expression in the cardiovascular system, cardioprotection and ischemic limb revascularization, depending on T-cad interaction with adiponectin, suggest a major role of this receptor in vascular and cardiac cell functioning. Possible mechanisms of T-cad-mediated regulation of metabolic processes are discussed.

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*Key words*: T-cadherin, low-density lipoprotein, adiponectin.

## INTRODUCTION

T-cadherin, T-cad (derived from "truncated"), also known as H-cadherin (derived from "heart") or cadherin-13, was first discovered in the chicken embryonic brain and later in the adult human brain as a protein of the glycosyl phosphatidylinositol (GPI)-anchored cadherin superfamily [1, 2]. In our laboratory, T-cad was isolated from the human aorta as a result of the search for the receptor mediating lipoprotein signaling (stimulation of phosphoinositide metabolism, activation of phospholipase C, mobilization of intracellular $Ca^{2+}$) [3–6]. In 2004, the interaction of T-cad with adiponectin, a key adipose tissue hormone regulating insulin sensitivity and reducing the risk of cardiovascular diseases, was found [7]. In this review we survey the current ideas on the role of T-cad in regulation of the cardiovascular system, as well as our data on its possible involvement in the regulation of metabolism.

At first, we consider the associations, revealed in clinical studies, of the T-cad gene polymorphism with cardiovascular diseases that indirectly indicate its involvement in the regulation of metabolism and the functions of the cardiovascular system. At second, we specify the structural features which distinguish T-cad from other cadherins and allow it to perform functions other than cell–cell adhesion. At third, we present the data on T-cad expression in the organism in proof of its tissue-specific effect. At fourth, we consider the T-cad cellular localization and ligands, as well as their role in metabolism. In the last section of the review, we provide the variants of T-cad-mediated regulatory pathways in the cardiovascular system's cells. Thus, our review treats T-cad as a receptor which regulates metabolic processes in the blood vessel and heart cells.

Associations of mononucleotide replacements in CDH13 gene with T-cad expression and adiponectin level as well as with cardiovascular diseases and their risk factors

| CDH13 polymorphism | T-cadherin expression | Adiponectin blood level | Association with cardiovascular diseases and their risk factors |
|---|---|---|---|
| rs12444338 | ↑expression 2.2-fold (G-allele) [18] | ↑(T-allele linked to A rs3865188 allele) [17, 18, 30] | T-allele: ↓ IMT, ↑ AH risk [13], ↑ HDL [30] |
| rs4783244 | no data | ↓(T-allele) [8, 31] | T-alele: ↓ BMI, IR, TG, ↑ HDL [32], ↓ TG, AH, fasting glucose, MS and ischemic stroke risk [8] |
| rs12051272 | no data | ↓ (T-allele) [8, 31] | T-allele: ↑ HDL, ↓ IR, TG, DAP, fasting glucose, MS risk [33] |
| rs8060301 | no data | ↓ (A-allele) [30] | A-allele: ↑ HDL, ↓ SAP, DAP [30] |
| rs2239857 | no data | CG/CT genotype: ↓ 4.5-fold [30] | no data |
| rs77068073 | no data | | no data |
| rs3865188 | no data | ↓ (T-allel) [17, 19] | no data |
| rs11646213 | no data | no data | A-allele: ↓ AH risk [12], HDL [34], ↑ TG, MS risk [34] |
| rs1048612 | no data | no data | AA genotype: ↑ IHD [13] |
| rs3096277 | no data | no data | Raised AP (long-term basis) [11] |
| rs12443878, rs62040565 | no data | no data | Alleles C, A respectively: ↑ HDL [30] |
| rs6565105 | no data | no data | AA genotype: ↑ LDL [13] |
| rs8055236 | no data | no data | G-allele: ↑ IHD risk [9] |

Note: AH—Arterial hypertension, DAP—diastolic arterial pressure, IHD—ischemic heart disease, BMI—body mass index, IR—insulin resistance, HDL—high-density lipoproteins, LDL—low-density lipoproteins, MS—metabolic syndrome, TG—triglycerides, IMT—intima-media complex thickness in carotid arteries.

## ASSOCIATIONS OF T-CAD GENE POLYMORPHISM WITH CARDIOVASCULAR DISEASES

The genome-wide association studies revealed the association of single-nucleotide replacements in the T-cad gene (CDH13) with stroke [8] and ischemic heart disease (IHD) [9]. It was also found that T-cad gene insertion (variation in the number of copies) is associated with the risk of myocardial infarction [10], and that there is a relationship between single-nucleotide replacements and such the known cardiovascular disease risk factors as arterial blood pressure [11–13] and the lipid profile [10, 13, 14]. The data on the association between cardiovascular diseases and T-cad gene single-nucleotide replacements are summarized in the Table. Our findings indicate a cumulative effect of single-nucleotide replacements on the body weight in cardiovascular disease sufferers [15].

Many studies support the relationship between the T-cad gene polymorphism and adiponectin blood level (see Table) [16–21]. Less unambiguous are the data on the other adiponectin receptors: in a few papers significant associations of AdipoR1 and AdipoR2 with adiponectin blood level and various pathologies were detected, although other studies failed to reveal such a dependence [26–29].

Adiponectin, an adipose tissue hormone, was found in several laboratories to be a tissue-specific soluble factor and gene product expression of which increases 100 times during preadipocyte differentiation, while remaining at the highest level in adipocytes in the normal state [35, 36]. However, under obesity adiponectin gene expression and its blood level decrease [37, 38]. A drop in the adiponectin level occurs under insulin resistance, type 2 diabetes, metabolic syndrome, dyslipidemia, hypertension, cardiovascular diseases (for more details see the reviews [39, 40]). It was shown on mice that administration of full-length adiponectin or its globular form leads to a reduction in blood levels of fatty acids, glucose and triglycerides, as well as to body weight loss versus control even under high-fat diet [41]. Further studies showed that elevation of the level exactly of the high-molecular-weight (HMW) adiponectin form correlates with body weight loss in humans, while its reduction—with insulin resistance and ischemic heart disease [42–44]. T-cad not only selectively binds HMW adiponectin, but also mediates its cardioprotective effects: deletion of the T-cad gene in null mutant mice abolishes the protective effect of adiponectin, as manifested in exacerbated cardiac hypertrophy and increased infarct size [45]. T-cad is implicated in adiponectin binding with the heart, aorta and muscles, since without T-cad these tissues cannot bind adiponectin [46]. The inverse relationship was also demonstrated: adiponectin was found to be essential for stabilization of the T-cad protein on the membrane, probably, because it can prevent GPI-anchor cleavage by phospholipase [46].

Thus, a direct relationship between T-cad and adiponectin was proved both on the mouse model and in genome-wide studies of different populations. The clinically revealed correlations suggest that T-cad plays a certain role in the pathogenesis of cardiovascular diseases, but deeper understanding of the cause-and-effect relations requires the identification of molecular mechanisms of interactions between T-cad and its ligands.

## T-CADHERIN STRUCTURAL FEATURES AND MATURATION

Studying the structural features of T-cad is one of the ways to understand its role in the organism and the molecular mechanisms of its functioning. T-cad in humans is synthesized as a preproprotein with the length of 713 animo acid residues (Fig. 1a).

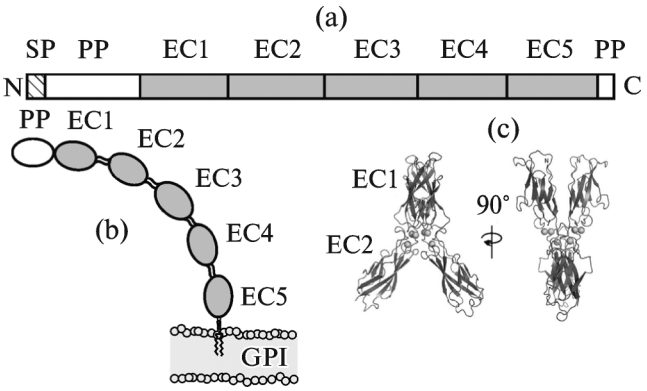


**Fig. 1.** T-cad structural features. (a) Domain organization of T-cad preproprotein; (b) schematic representation of T-cad structure on the membrane surface. SP—Signaling peptide, PP—propeptide, EC1–EC5—extracellular cadherin domains, GPI—glycosyl phosphatidylinositol anchor; (c) X-dimer structure in first two domains with bound calcium ions (modified from [47]).

At the N-terminus of the immature protein there is a 22-residue signaling peptide, characteristic of many membrane-bound (including cadherins) and most secreted proteins [1]. After the maturing protein comes to the endoplasmic reticulum (ER), peptidase splits off the signaling peptide from the proprotein. Like in classical cadherins, the signaling peptide is followed in T-cad by the N-terminal 116-residue propeptide. It was shown experimentally that usually in cells, expressing T-cad, both the heavier T-cad proprotein form (p130) and the mature form (p105) can be detected on the membrane [48, 49]. Classical cadherins, E- and N-cadherins, require a proteolytic cleavage of the propeptide to perform their function, i.e. calcium-dependent cell adhesion (that is why they are called a "cadherin" superfamily) [50–52]. Presumably, propeptide cleavage is executed by endoprotease furin (EC 3.4.21.75) in the distal parts of the Golgi apparatus (trans-Golgi) [47], as well as on the cell surface and in endosomes [53]. Interestingly, in adiponectin gene null mice only T-cad form p105 was detected in skeletal muscles and myocardium at the invariable

mRNA level, i.e. adiponectin is likely to prevent the T-cad propeptide cleavage in the normal state [45, 54].

T-cad, like other cadherins, has extracellular cadherin domains EC1–EC5, each composed of about 110 amino acid residues, which adopt a beta-barrel structure with a Greek key folding topology [55] (Fig. 1c). T-cad has 30–58% of identical amino acids in the EC1 domain as compared with E-, N- and C-cadherin, while EC1–EC5 show 47% sequence identity with N-cadherin [1, 2, 55–57]. The T-cad sequence contains amino acid groups required for binding $Ca^{2+}$: Glu-11 (numeration without propeptide), LDRE, DQNDN, DADD and others [56]. In all cadherins, the conserved $Ca^{2+}$-binding sites, stabilized by three $Ca^{2+}$ ions, reside in the interdomain position [58]. Due to high-affinity $Ca^{2+}$ binding, five protein domains are occupied under physiological conditions with twelve ions. $Ca^{2+}$ allows coordination of the cadherin domain structure in such a way that the protein adopts a crescent shape [59]. This shape is essential for adhesive binding: EC1 and EC5 should be spaced at an angle of ca 90° to each other to form trans bonds between the molecules on the surface of different cells [60]. The structures of the first two cadherin domains, obtained at atomic resolution, and various experiments with mutants allowed identification of how cis-homodimers and trans-homodimers of classical cadherins form, respectively, on the membrane of the same cell and different cells [52, 60–62]. By simultaneous formation of cis- and trans-bonds, classical cadherins generate oligomeric complexes in the cell–cell contacts, while the cytoplasmic domains indirectly interact with the actin cytoskeleton and stabilize them [60, 63]. In the EC1 domain of type I cadherin, tryptophan in the second position (Trp-2) enters the conserved hydrophobic pocket EC1 in the partner molecule and forms a "strand-swap" dimer [62]. However, in T-cad amino acids required for the formation of dimers by such a mechanism are replaced in EC1 (for example, the HAV motif is missing, while Ile resides in the second position) [1, 47, 55]. These modifications of the first domain lead to stabilization of the monomeric form and reduction in T-cad adhesiveness as compared with type I cadherins [55]. The studies conducted on cells hyperexpressing T-cad showed that this protein can be involved in homophylic adhesion [64]. The $Ca^{2+}$-binding sites EC1–EC2 participate in the formation of T-cad dimers, resulting in the X-dimer formation (Fig. 1c). The same structure forms from type I cadherin monomers, but in contrast to T-cad, it comes to another stabile complex [62].

Most significant distinction of T-cad amongst other cadherins is the lack of the transmembrane and cytoplasmic regions [1]. Instead, a 20-residue hydrophobic propeptide resides at the C-terminus of T-cad (Fig. 1a), being replaced in the ER by the GPI-anchor with the involvement of transamidase. The mature protein is anchored on the outer surface of the plasma membrane by two fatty acid residues of the GPI-anchor: after treatment with phosphatidylinositol-specific phospholypase C the GPI-anchor splits off and T-cad goes to culture medium [1].

Another T-cad isoform, T-cadherin 2, was isolated from chicken embryonic cDNA; it is distinguished by its C-terminus sequence, although its mature form also contains the GPI-anchor [65]. Current data, accumulated due to isolation of human cDNA, predict the existence of several other T-cad isoforms in addition to the main human T-cad isoform (P55290 according to UniProtKB/Swiss-Prot, 713 amino acid residues, calculated mass of 78287 Da) discussed herein. The primary sequence of this protein, predicted using the NCBI RefSeq and UniProtKB/Swiss-Prot data bases, consists of 175 to 760 amino acid residues, although it is not proved experimentally as yet.

T-cad undergoes a number of post-translational modifications during which its molecular weight increases up to 130 kDa (with N-terminal propeptide) and 105 kDa (mature form) in endothelial and smooth muscle cells (SMC) as well as in myocardium [49, 66]. Interestingly, the molecular weight of classical cadherins with transmembrane and cytoplasmic domains is ca 120 kDa, and normally a single mature propeptide-free form is detectable [2, 51, 67]. Treatment of cell lysates, hyperexpressing T-cad, with a deglycosylase mixture decreases the T-cad molecular weight by 20–40 kDa, indicative of a high degree of its glycosylation (our unpublished data). Inhibition of N-glycosylation by tunicamycin leads to the accumulation of immature 75-kDa form, which is not translocated to the

cell surface [68]. This evidences an importance of glycosylation for the maturation of T-cad. Based on the sequence analysis, it was ascertained that T-cad has eight N-glycosylation sites of which four were confirmed experimentally using mass spectrometry: one resides in the propeptide, two in the EC4 domain, one in the EC5 domain [69, 70]. Recently, unusual O-glycosylation of T-cad by a single mannose residue was found in the skeletal muscle [71]. ADP-ribosylation was also demonstrated experimentally in the cardiac muscle sarcolemma [72]. During induction of neuronal differentiation in the pheochromocytoma PC12 cell line by the nerve growth factor (NGF) there occurs tyrosine-327 phosphorylation in the EC2 domain, leading to proteasomal protein degradation [73]. The T-cad isoforms and post-translational modifications are poorly studied so far: there are no data on the tissue-specific forms and modifications. The 45 to 139 kDa data spread in assessing T-cad molecular weight by immunoblotting [68] also remains unexplained.

Thus, the T-cad domain structure is similar in many respects to that of classical cadherins, although some peculiarities, as well as the GPI-anchor, impart to this protein the unique properties which distinguish them from cadherins responsible for cell–cell adhesion.

## T-CADHERIN EXPRESSION IN THE ORGANISM

T-cad was first discovered in the nervous system of chicken embryo and named because of its truncated structure [1]. During embryogenesis T-cad is expressed at strictly determined time and in the limited number of cells, promoting axon guidance [74–77]. The human homolog with 82% sequence identity to chicken T-cad, called by Tanihara et al. cadherin-13, was also derived from the brain [2]. The T-cad amino acid sequence is highly conserved (interspecies degree of identity is higher than in E-cadherin) in the evolution of vertebrates, but, in contrast to other cadherins, has no homologs amongst invertebrates [78, 79]. This indirectly indicates the importance of T-cad functions for vertebrates.

In the adult organism, T-cad is also expressed in the nervous system with the level of expression higher than in embryos [80]. The highest level of the protein was found in the heart, aorta and arteries [66, 81]. In our laboratory it was shown that T-cad is expressed in the vascular intima and media: in endothelial cells, SMC and pericytes [66]. In the adventitia, T-cad occurs in the vasa vasorum walls. During the development of atherosclerotic injury of the vascular wall T-cad expression in SMC increases [66]. During the vascular wall injury caused by angioplasty, a rise in the SMC T-cad level temporally coincides with the phase of active migration and proliferation of the vascular cells [82]. *In vitro* experiments confirm that T-cad synthesis in SMC depends on the cell spacing density and their proliferative status [83]. In endothelial cells, like in SMC, the T-cad level depends on the cell cycle phase (more in G2/M), while T-cad hyperexpression leads to an increase in the number of cells [84].

Analysis of blood vessels in different tissues showed that normally T-cad is expressed not in all endothelial cells in the lungs, heart, spleen and kidneys [85]. T-cad synthesis increases in tumor endothelial cells [85], while in most cancer cells its expression decreases as compared with healthy cells [81] (for more details on the role of T-cad in tumorigenesis see review [86]).

T-cad is expressed copiously in the heart and is detected in skeletal muscles, but the studies of its role in muscle cells are still few [45, 54, 72]. T-cad is detected in endothelial cells of the mammary gland, intestine and in keratinocytes [81, 87, 88]. However, in most organs (liver, spleen, stomach, adrenal and thyroid glands, lymph nodes) T-cad is not detected [66, 81, 82, 89, 90].

Thus, in the healthy organism T-cad is expressed to the highest degree in the cerebrovascular system: in SMC, endothelium and cardiomyocytes.

## CELLULAR LOCALIZATION, HOMO- AND HETEROPHYLIC INTERACTIONS

In contrast to classical cadherins, localized at intercellular contacts, T-cad occurs in endothelial cells and SMC both on the plasma membrane and in the intracellular structures [67, 91–93]. During migration of these cells, T-cad is relocated to the leading edge [91]. In the polarized intestinal epithelial cells T-cad resides on the apical, but

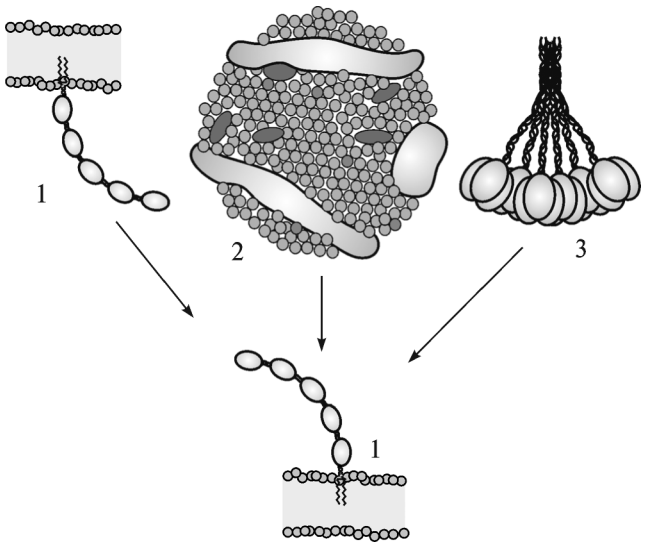


**Fig. 2.** Diagram of T-cad extracellular molecular partners. (1) T-cad, (2) LDL, (3) high-molecular-weight adiponectin.

not basolateral (as N-cadherin), part [87]. In the experiments on the MDCK-line epithelial cells, the chimera with five N-cadherin ectodomains and the 76-residue C-terminal part of T-cad is localized to the apical part (like native T-cad), while the chimera of EC1–EC5 T-cad domains and transmembrane domains with the part of cytoplasmic N-cadherin resides on the basolateral pole [87]. From this, it follows that T-cad localization is determined not by ectodomains, but by the GPI-anchor which promotes apical distribution of this protein on the plasma membrane. The GPI-anchor composition influences the ability of the protein to oligomerization and apical sorting [94]. Meanwhile, an indispensable requirement is the location of the GPI-anchored proteins in the lipid rafts, detergent-resistant domains [95]. For example, T-cad is located in the Triton X-100 insoluble rafts in rat atrial myocytes, human vascular SMC and endothelial cells [72, 96].

Although hyperexpressed T-cad in the line cells can be involved in $Ca^{2+}$-dependent adhesion, the above-mentioned data obtained *in vivo* and on primary cells argue in favor of trans-homophylic interaction being not a basic T-cad property, as shown for other cadherins [64]. Membrane localization of T-cad appears to be prevalent only in cardiomyocytes and skeletal muscles, but this issue is not studied in detail [45, 46]. Nevertheless, it is known that homophylic interaction may occur during the growth of nerves and blood vessels [47, 97]. In the embryonic state, there occurs a contact inhibition of axon growth due to homophylic interaction between T-cad at the end of the growing axon and the surface of surrounding cells [75]. It appears that the same repulsion occurs during angiogenesis as well: less blood vessels, compared to control, ingrow into Matrigel implant containing cells which hyperexpress T-cad [97]. Formation of capillary-like structures by HUVEC endothelial cells *in vitro* is significantly reduced if the surface is covered with EC1, but not EC5, domain. The same effect can be observed during vascular growth from the aorta *ex vivo* [97]. Endothelial cells migrate across the Boyden chamber membrane twice worse when covered by the EC1, not EC5, domain. At the same time, no effect of T-cad on apoptosis was revealed [29]. Adhesion and spreading of endothelial cells and SMC decrease if the surface is covered by EC1 or the anti-EC1 antibody [98]. Inclusion of full-length recombinant T-cad to the gel promotes the VEGF-stimulated growth of processes in the spheroid model and Nicosia tissue assay [99]. If the T-cad endogenous level in cells is increased or decreased by adenoviral constructs, it leads, respectively, to an increase or decrease in sprouting from spheroids. These findings suggest that *in vivo* T-cad–T-cad interaction is involved in angiogenesis through its effect on adhesion and migration of endothelial cells. Angio- and neurogenesis are most active during embryogenesis and regeneration after tissue injury. What is the normal role of T-cad in the adult organism?

T-cad is expressed predominantly in cells of the cardiovascular system and interacts with two molecules, permanently circulating in the blood: low-density lipoproteins (LDL) and HMW adiponectin form (Fig. 2). In our laboratory, the signaling effects of high-density lipoproteins (HDL) and LDL were detected: activation of phosphoinositide metabolism, elevation of the intracellular $Ca^{2+}$ level, protein phosphorylation in platelets and vascular SMC [3, 4, 100–105]. We isolated from the human aorta the LDL-binding protein identified by mass spectrometry as T-cad [6]. Hyperexpression of T-cad in the line cells enhances their specific LDL binding [106, 107].

To elucidate the mechanisms of lipoprotein binding to T-cad, the agents were used that inhibited LDL binding to apolipoprotein B/E (apoB/E) receptor, scavenger receptor, extra LDL receptor and protein related to LDL receptor; however, specific LDL binding to T-cad was managed to be decreased only upon addition of the anti-apoB antibody [104]. LDL modifications (acetylation, carbamylation, modification of lysine residues) practically did not change the ligand-binding properties of T-cad, but not apoB/E receptor [103, 105]. LDL binding to T-cad during ligand blotting considerably decreases in the presence of the divalent ion chelator, EDTA, and the reducing agent, β-mercaptoethanol; this indicates that calcium ions and disulfide bonds are required for the maintenance of the T-cad structure [105]. In the Resnik's laboratory it was demonstrated that after treatment with phosphatidylinositol-specific phospholypase C the supernatant specimen, containing T-cad, does not bind LDL [108]. Eukaryotic T-cad deprived of propeptide (replaced by GPI-anchor during processing), as well as T-cad synthesized in *E. coli* without the GPI-anchor, also do not bind LDL, suggesting that the GPI-anchor is essential for LDL binding. It might be assumed that GPI, containing the fatty acid residues, dissolves in LDL. However, neither the mass spectrometry data [109] nor immunoblotting analysis (our unpublished data) revealed T-cad in native LDL. Thus, the issue of LDL–T-cad interaction sites remains open.

Hug et al. found that T-cad is a receptor of the hexameric and HMW forms of adiponectin, the adipose tissue hormone [7]. Having revealed the specific adiponectin binding to the undifferentiated myoblast C2C12 line, the authors transfected by cDNA library the C2C12 cell line that originally did not bind adiponectin. It turned out that clones, binding adiponectin after transfection, contain T-cad. The selective T-cad interaction with hexameric and HMW adiponectin forms, but not with trimeric or globular forms, was shown. Only adiponectin derived from eukaryotic cells binds to T-cad, indicative of the importance of post-translational modifications for this interaction. The adiponectin mutant lacking the N-terminal cysteine residue, required for the formation of hexamers and larger oligomers, demonstrates during immunoprecipitation a significant decrease in T-cad binding as compared with wild-type adiponectin. In *in vivo* experiments on mice, T-cad was shown to co-localize with adiponectin in the cardiac muscle (both by microscopy and immunoprecipitation) [45]. Cardiomyocytes and skeletal muscles in T-cad knockout mice do not bind adiponectin, and because of this its blood level increases [45]. For binding adiponectin by the HEK293 cells, it is enough to transfect them with the T-cad cDNA construct, but not with constructs of other adiponectin receptors (AdipoR1 and AdipoR2) [45]. All these data prove that T-cad is a specific adiponectin-binding protein.

Thus, T-cad can interact homophylically with T-cad and heterophylically with LDL and adiponectin.

## POSSIBLE MECHANISMS OF METABOLISM REGULATION INVOLVING T-CADHERIN

LDL not only transfer lipids into cells, but also regulate various processes: in SMC they stimulate an increase in the intracellular $Ca^{2+}$ level, DNA and protein synthesis, and as a result—cell proliferation [110, 111]. The LDL binding parameters (concentration dependencies, association/dissociation kinetics, sensitivity to inhibitors) in SMC coincide with those for T-cad, while T-cad hyperexpression in the HEK293 and L929 line cells significantly increases LDL-induced elevation of intracellular $Ca^{2+}$ [106]. T-cad promotes cell migration towards a LDL gradient [106]. LDL–T-cad interaction leads to mitogenic cell response in cells with endothelial and epithelial morphology, triggering intracellular signaling via $Ca^{2+}$ mobilization, Erk1/2 phosphorylation and NFkB translocation to the nucleus [107]. The T-cad-mediated influence of LDL on SMC and endothelial cells is shown schematically in Fig. 3a.

The necessity for T-cad for the realization of adiponectin cardioprotective functions was reported [45]. In wild-type mice, the myocardial infarction area under acute injury caused by ischemia-reperfusion, as well as the number of apoptotic cardiomyocytes, are smaller compared with T-cad or adiponectin null mice. Under chronic stress induced by pressure overload, T-cad–adiponectin

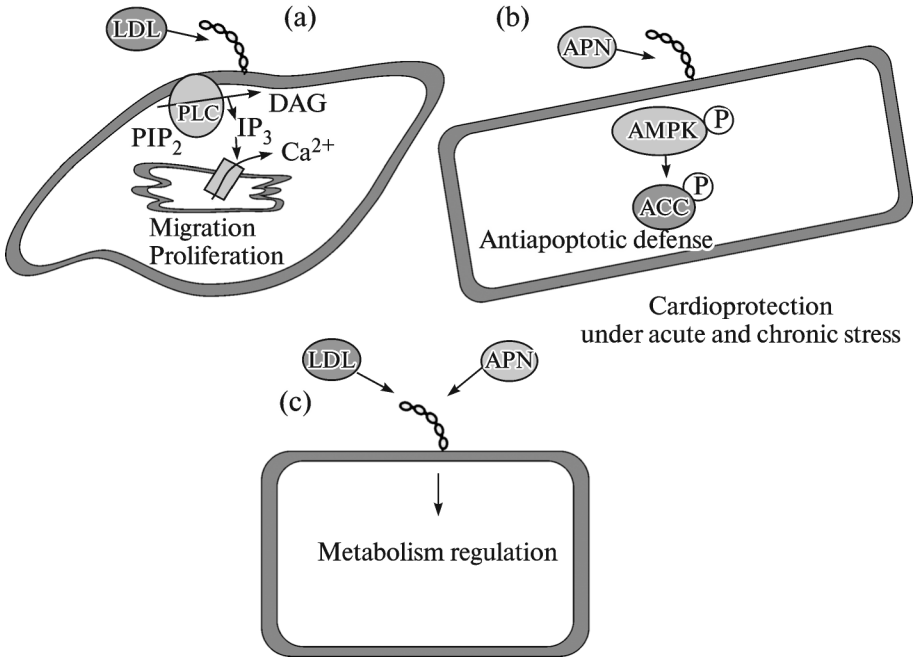


**Fig. 3.** Ligand-dependent signaling and physiological responses of T-cad receptor during interaction with LDL (a) and adiponectin (b). Competitive effects of LDL and adiponectin on T-cad-expressing cells (c). ACC—Acetyl-CoA carboxylase, AMPK—adenosine monophosphate-activated protein kinase, APN—adiponectin, DAG—diacylglycerol, $IP_3$—inositol triphosphate, LDL—low-density lipoproteins, $PIP_2$—phosphatidylinositol 4,5-diphosphate, PLC—phospholypase C.

interaction allows avoiding excess hypertrophy. T-cad-mediated adiponectin signaling pathway is not investigated in detail, but their interaction was shown to an increase in AMPK (adenosine monophosphate-activated protein kinase) and ACC (acetyl-CoA carboxylase) phosphorylation (Fig. 3b) [45]. A key role of T-cad in adiponectin-mediated revascularization was proved: T-cad is implicated in adiponectin-mediated migration and proliferation of endothelial cells because the suppression of its expression mitigates these effects [54].

Of particular notice is the fact that LDL and HMW adiponectin represent large molecular complexes. Diameter of LDL particles is 18–25 nm [112]. Adiponectin is present in blood as homo-oligomeric complexes. Adiponectin monomers in adipocytes, due to their collagen and globular domains, assemble into trimers and then into hexamers and 12–18-meric complexes (HMW form) [113, 114]. HMW adiponectin can form a fan-shaped or more compact bunch-shaped complex (Fig. 2) [115]. The collagen base of such a "bunch" circumscribes a $6 \times 4.5 \times 4.5$ nm ellipsoid, while the globular domains may occupy from 25 to 32 nm [115, 116]. Thus, both LDL and HMW adiponectin represent complexes sized about 25 nm, suggesting a competition between these two protein complexes during interaction with T-cad. In blood of healthy humans, the LDL concentration is 0.6 mg/ml (by protein), while the adiponectin concentration is also exceedingly high for a hormone (about 10 μg/ml) [38, 117]. Under metabolic syndrome the LDL blood level increases to exceed 2 mg/ml, while the adiponectin level may decrease below 1 μg/ml [38, 118], i.e. the T-cad ligand ratio changes more than tenfold. The dissociation constant of T-cad with LDL is about 40 μg/ml (as assayed by protein), while half-maximal binding with adiponectin is attained at 2.2 μg/ml (25 nM in trimer equivalent) [4, 7]. However, it is worth remembering about other LDL and adiponectin receptors which may locally reduce the concentration of these ligands. Thus, one may suggest that LDL prevents T-cad binding to adiponectin, which is essential for cardioprotection from acute and chronic stress (Fig. 3c) [45]. Our tentative results argue in favor of this suggestion:

in the HEK293 line cells with T-cad hyperexpression we found that adiponectin can inhibit LDL-stimulated $Ca^{2+}$ signaling.

Changes in T-cad expression in the cardiovascular system also affect metabolism. Firstly, the lack of T-cad synthesis deprives skeletal and cardiac muscles of the ability to bind adiponectin, resulting in a considerable increase in the adiponectin blood level [46]. Thus, by changing the adiponectin blood level T-cad may change its accessibility for muscle (AdipoR1) and liver (Adipo R2) receptors, which are basically responsible for metabolic effects [119, 120]. Secondly, T-cad may be involved in regulation of the same PI3K/Akt/mTOR cascade as is regulated by insulin [121]. On endothelial cells it was shown that T-cad hyperexpression leads to chronic activation of PI3K/Akt pathway and degradation of the insulin receptor substrate (IRS-1), resulting in a decreased insulin sensitivity of cells. Suppression of T-cad expression brings about an increased insulin sensitivity [122]. T-cad immunoprecipitation revealed its binding to insulin receptor. Filipin, which wrecks lipid rafts, abolishes the inhibitory effect of T-cad on insulin signaling, indicative thereby of the importance of rafts for signal transmission. Hyperinsulinemia, it turn, increases T-cad expression at the level both of mRNA and protein. Thus, there is a tight relationship between T-cad and insulin signaling. In this connection, it is worth noticing that T-cad occurs in pancreatic β-cells, specifically within insulin granules [123]. A comparison between wild-type and T-cad null mice revealed that T-cad affects the second phase of insulin secretion [123].

Obesity is known to cause ER stress by disturbing protein maturation therein [124]. This process involves activation of the unfolded protein response, which is regulated chiefly by BiP/Grp78 chaperone. There is evidence that T-cad interacts with Grp78 in endothelial cells, leading to protection from stress-induced apoptosis [125, 126]. Moderate ER stress stimulates neovascularization as a result of the T-cad/Grp78 complex formation [127]. Thus, T-cad can be involved in metabolism regulation through binding adiponectin in tissues and changing thereby its blood level. This binding may also be influenced by another T-cad ligand, LDL. The possible mechanism of how T-cad may affect insulin signaling in endothelial cells was demonstrated *in vitro*. T-cad was found to affect insulin secretion, which, in its turn, regulates the key metabolic pathways. Under ER stress, the T-cad/Grp78 complex forms regulating vasculaization.

## CONCLUSION

T-cadherin is a receptor of the key participants of metabolic processes: low-density lipoproteins and high-molecular-weight adiponectin. Its expression in the cardiovascular system is necessary for the provision of such adiponectin effects as cardioprotection under myocardial infarction and stimulation of limb revascularization. Molecular mechanisms of T-cad–LDL interaction are not identified as yet, but further investigation of the competition between these ligands for T-cad binding, as well as of the downstream processes of intracellular signaling, may disclose how obesity and metabolic syndrome affect the cardiovascular system. Understanding these effects is definitely of prime importance.

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