T-cadherin and its impact on human diseases (Review)

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Abstract. Truncated-cadherin (T-cadherin) is a distinct glycosylphosphatidylinositol-anchored atypical cadherin that differs from classical cadherins since it does not have transmembrane and intracellular domains. It primarily functions as a dual receptor, serving as a physiological receptor for low-density lipoprotein (LDL) and a specific receptor for high-molecular-weight (HMW) adiponectin. Upon binding to LDL, T-cadherin activates calcium signaling, thereby promoting cell proliferation and migration and contributing to the development of atherosclerotic plaques. Conversely, its interaction with HMW adiponectin mediates cardiovascular protective effects through various mechanisms, such as increased exosome secretion, reduced intracellular ceramide accumulation, improved insulin sensitivity and anti-inflammatory actions. T-cadherin is predominantly expressed in cardiovascular tissues, such as endothelial cells, smooth muscle cells, pericytes and cardiomyocytes. Genetic polymorphisms in *cadherin-13*, the gene encoding T-cadherin, are notably associated with the risk of hypertension, type 2 diabetes and end-stage renal disease. In cancer, T-cadherin generally has tumor-suppressive effects, particularly in gastric, ovarian and breast cancers. This function is often compromised by promoter region hypermethylation, which leads to gene silencing and subsequently inhibits key signaling pathways, such as the PI3K/Akt, Wnt/β-catenin and epithelial-mesenchymal transition pathways. The present review provided a comprehensive overview of the molecular mechanisms, regulation of expression and potential clinical importance of T-cadherin as a diagnostic biomarker and therapeutic target for cardiovascular diseases, including atherosclerosis, hypertension and heart failure, metabolic disorders, such as diabetes, and various cancers. Further research is required to fully elucidate the signal transduction pathways and competitive dynamics of T-cadherin ligand binding.

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Contents

1. Introduction

Considering incidence and mortality rates, cardiovascular diseases, diabetes and cancer have become the most notable diseases worldwide (1-3). Despite notable progress in prevention approaches and treatment modalities, the incidence rates of these diseases continue to increase steadily and are gradually shifting toward younger populations (4-7). Besides known risk factors, some risks cannot be explained by traditional factors, indicating the presence of unknown variables (8,9). This emphasizes how important it is to find and understand novel molecular regulators at the pathophysiological nexus of metabolic, cancer and cardiovascular diseases.

An atypical member of the cadherin superfamily, truncated-cadherin (T-cadherin), also known as heart-cadherin or cadherin-13 (*CDH13*), was first discovered in the embryonic brains of chicks (10). T-cadherin contains five Ca^{2+}-binding extracellular structural domains, which are typical components of cadherins. However, it lacks transmembrane and cytoplasmic structural domains and binds to the plasma membrane via glycosylphosphatidylinositol (GPI) anchors (11,12). In the embryonic nervous system, T-cadherin-mediated homophilic cell adhesion regulates angiogenesis and tumor neoangiogenesis, and negatively affects motor neuron axon projections and neural crest cell migration (13). Owing to the unique structure of T-cadherin, T-cadherin-mediated homophilic cell adhesion fundamentally alters its mechanism of action, preventing it from forming stable intercellular junctions in the same way as a traditional adhesion molecule; specifically, its distinct modes of action are determined by its GPI anchor, which enables it to function as both a receptor and a ligand, thereby allowing

it to participate in regulating intracellular signaling pathways governing proliferation, differentiation, migration and regeneration (11). T-cadherin, as a physiological receptor, can bind to hexameric and high molecular weight (HMW) forms of the cardiovascular preventive factor adiponectin, while it can also independently serve as a receptor for atherosclerotic low-density lipoprotein (LDL); this paradoxical ligand affinity thereby positions T-cadherin at a critical signaling hub (11,12). The present study reviewed the current research progress on the structure, regulation, expression, function, signaling and role of T-cadherin in cardiovascular diseases, metabolic disorders and cancer.

2. Molecular foundation of T-cadherin

T-cadherin: Structure and function. A comprehensive understanding of the molecular structure, ligand interactions and regulation of T-cadherin expression is necessary to fully understand its multifaceted roles in various diseases. This information lays the groundwork for investigating the specific contribution of T-cadherin to cardiovascular diseases, metabolic disorders and cancer.

The 3' untranslated region of the T-cadherin-encoding gene *CDH13* has a microRNA (miR)-377-3p binding site that controls T-cadherin protein expression (14). T-cadherin is a member of the 'atypical cadherin' subgroup of the cadherin superfamily. The five Ca^{2+}-binding domains present in T-cadherin are important for homo- and hetero-dimerization and interactions with other T-cadherin molecules in the vascular and neurological systems (12) (Fig. 1). Similar to other traditional cadherins, such as epithelial-cadherin (E-cadherin) and neural-cadherin (N-cadherin), T-cadherin is linked to the cell membrane by a GPI anchor; however, T-cadherin does not have intracellular and transmembrane structural domains (15). Protein distribution of T-cadherin within plasma membrane rafts is often guided by the presence of the GPI anchor (11), a structural component that provides dynamic modulation of cell adhesion and may play a role in signal transduction via lipid raft microregions. The dual ligand-binding capability of T-cadherin implies that its extracellular domain may contain multiple binding sites, as its extracellular region acts as a receptor for both LDL and HMW adiponectin (16). *In vitro* experiments have shown that adiponectin binds to cells expressing T-cadherin but not adiponectin receptor (AdipoR)1 or calreticulin. AdipoR and calreticulin may require additional co-receptors or accessory proteins to acquire the ability to bind natural HMW adiponectin. T-cadherin knockout notably reduces adiponectin binding to cells of the 293 cell line, Chinese hamster ovary cells and C2C12 myotubes. These findings indicate that T-cadherin is the primary binding partner of native adiponectin (17,18) Importantly, T-cadherin is a receptor for hexameric and HMW adiponectin, but not for trimeric or globular adiponectin (19). A study by Fukuda *et al* (20) showed that the binding of adiponectin to T-cadherin required the extracellular EC1-EC2 region of T-cadherin, and that the pro-domain of T-cadherin played a role in binding with adiponectin. The extracellular cadherin repeat (EC1-EC2) region overlaps with the reported homologous transmembrane region of T-cadherin (21). Notably, compared with the mature form comprising 100 kDa T-cadherin without the pro-domain, the 130 kDa T-cadherin form with the pro-domain shows a greater binding affinity for adiponectin. The 130 kDa form is also more likely to be expressed on the surface of endothelial cells both *in vitro* and *in vivo* than the mature form, demonstrating positive feedback regulation of T-cadherin by adiponectin (20). Adiponectin binding further increases membrane expression and functional activity of 130 kDa T-cadherin, continuously elevating T-cadherin abundance at the post-translational level. A study by Bochkov *et al* (22) primarily showed that the atypical lipoprotein-binding protein P105 that is present on the vascular smooth muscle membrane of humans and rats was T-cadherin, providing evidence that the mechanism underlying binding of LDL to T-cadherin may be similar to that mediating homophilic cadherin-cadherin interactions. A subsequent study revealed that T-cadherin is expressed in *Escherichia coli* with a GPI anchor signal sequence but without GPI modification, and that recombinant human T-cadherin expressed in 293 cells without a GPI anchor signal sequence cannot bind to lipoproteins, providing evidence that the GPI anchor of T-cadherin is important for lipoprotein binding (23). Previous studies have provided evidence that T-cadherin is a physiological receptor for LDL (24-26). T-cadherin binds to LDL on the cell surface, triggering intracellular calcium ion mobilization, increasing tyrosine phosphorylation and stimulating ERK1/2 and NF-κB to promote cell proliferation, thereby converting extracellular LDL into mitogenic signals (25,27).

T-cadherin accumulation in cardiovascular tissues, such as the aorta, heart and skeletal muscles, allows adiponectin to exert cardioprotective effects (28). Clinical research has shown a notable association between serum HMW adiponectin levels and T-cadherin expression. The binding between T-cadherin in HMW adiponectin is specific and independent of other known adiponectin receptors, such as AdipoR1 and AdipoR2 (17,29). In addition to its role as a receptor for adiponectin, T-cadherin contributes to the pleiotropic organ-protective effects of adiponectin. T-cadherin-dependent secretion of adiponectin via exosomes in the cardiovascular system improves vascular homeostasis and myocardial regeneration, and is the predominant mechanism underlying therapeutic effects of mesenchymal stem cells (MSCs) (30). In muscle and endothelial cells, T-cadherin binds to adiponectin to activate exosome secretion. Additionally, inhibition of the AdipoR1/R2 signaling pathway, potentially mediated by competitive binding of adiponectin to T-cadherin, activates the ERK1/2/MAPK pathway, promoting tissue repair and cell proliferation (Fig. 1) (30,31).

T-cadherin expression and control in the cardiovascular system. Vascular endothelial cells, vascular smooth muscle cells and pericytes are the primary cells of the cardiovascular system that express T-cadherin (32,33). Immunofluorescence results in a previous study showed that T-cadherin is markedly expressed in the basal layer of healthy arteries and is closely linked to the functional control of pericytes (33). Furthermore, its presence in cardiac tissues, particularly in the coronary endothelium and cardiomyocytes, raises the possibility that T-cadherin plays a cardioprotective role (20,34).

As a receptor for LDL and HMW adiponectin, T-cadherin possesses dual ligand-binding capabilities (12,16,25). These two ligands exert opposing effects on the cardiovascular

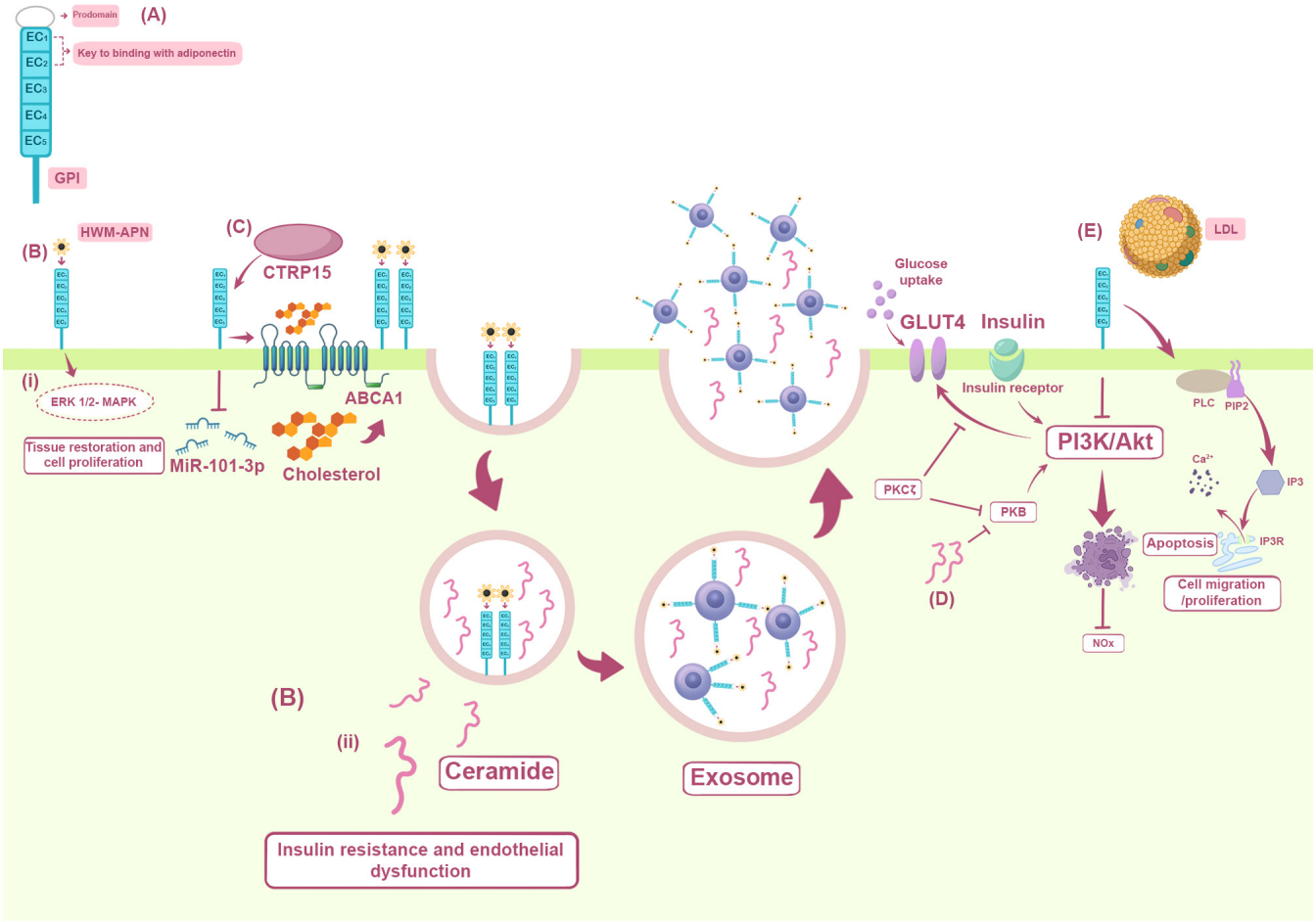

Figure 1. T-cadherin modulates atherosclerosis through adiponectin signaling, insulin sensitivity and cholesterol transport. The figure summarizes the structure and pleiotropic functions of T-cadherin. (A) Molecular architecture of T-cadherin. The preproprotein consists of a signal pre-peptide, five extracellular cadherin repeats, EC1-EC5, and a C-terminal GPI anchor. The EC1 and EC2 domains are necessary for adiponectin binding and the GPI anchor targets the protein to membrane lipid rafts. (B) Adiponectin signaling and ceramide export. The binding of HMW-APN to T-cadherin triggers two important events: i) Activation of the ERK1/2/MAPK pathway, which promotes tissue repair and cell proliferation; and ii) adiponectin sequestration into multivesicular bodies, enhancing exosome biogenesis and secretion. This process concurrently exports intracellular ceramide, a lipid that inhibits insulin signaling. (C) Promotion of macrophage cholesterol efflux. The CTRP15/T-cadherin axis downregulates miR-101-3p, which directly represses the cholesterol transporter ABCA1. This enhances ABCA1-mediated cholesterol efflux, reducing lipid accumulation in macrophages and slowing the progression of atherosclerosis. (D) Inhibition of insulin signaling by ceramide. High intracellular ceramide levels block the PI3K/Akt pathway either by inhibiting the PKB/Akt pathway or by activating PKCζ, ultimately preventing GLUT4 translocation to the membrane and reducing cellular glucose uptake, which fosters insulin resistance. (E) Consequences of T-cadherin loss. T-cadherin deficiency: i) Promotes apoptosis and reduces bioavailable nitric oxide via diminished Akt phosphorylation and endothelial nitric oxide synthase activity; and ii) ablates T-cadherin binding to LDL, preventing the activation of PLC/PIP2/IP3 signaling and subsequent calcium release, which are important for normal endothelial function and cell motility. LDL, low-density lipoprotein; miR, microRNA; ABCA1, ATP-binding cassette transporter A1; Akt, Protein kinase B; CTRP15, C1q/TNF-related protein 15; EC1-EC5, extracellular cadherin repeats 1-5; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal-regulated kinases 1 and 2; GLUT4, glucose transporter type 4; GPI, glycosylphosphatidylinositol; HMW-APN, high-molecular-weight adiponectin; IP3, inositol trisphosphate; MAPK, mitogen-activated protein kinase; miR-101-3p, microRNA-101-3p; NO, nitric oxide, PI3K, phosphoinositide 3-kinase; PIP, phosphatidylinositol 4,5-bisphosphate; PKB, protein kinase B; PKCζ, protein kinase C ζ; PLC, phospholipase C.

system. When LDL binds to T-cadherin, it triggers the calcium signaling cascade, accelerating the formation of atherosclerotic plaques by promoting endothelial cell migration, proliferation and inflammatory responses (25,35). HMW adiponectin accumulation in cardiovascular tissues via T-cadherin improves insulin resistance and inhibits vascular inflammation by increasing exosome production and release while decreasing cellular ceramide accumulation (20,34,36) (Fig. 1). This process activates Notch signaling (37), a pathway closely associated with adiponectin-dependent vascular regeneration and myocardial protection (38,39). Although T-cadherin is generally associated with the cardiovascular protective effects of adiponectin, it also displays an association with non-alcoholic fatty liver disease (NAFLD) due to shared metabolic dysfunction. Reduced adiponectin signals via its receptors, including T-cadherin, cause insulin resistance and hepatic fat accumulation in NAFLD (40). Additionally, a study has shown that genetic variations, known as polymorphisms, in *CDH13* are associated with NAFLD-related metabolic diseases, such as type 2 diabetes (T2D) and metabolic syndrome (40). A previous study has shown that a high fatty liver index score can predict the risk of T2D. It is plausible that *CDH13* alleles are associated with T2D through liver indicators (41).

Atherosclerosis, assessed using carotid intima-media thickness (IMT), is closely associated with NAFLD (42). The dual role of T-cadherin as a receptor for both cardioprotective

adiponectin and atherogenic LDL suggests that it is an important metabolic sensor that may influence NAFLD and its associated cardiovascular risk. T-cadherin is uniquely expressed on the plasma membranes of vascular endothelial cells, smooth muscle cells and cardiomyocytes. Its distribution is not uniform but rather concentrated at signaling hubs such as membrane microdomains rich in caveolin proteins. This 'strategic localization' enables efficient binding to ligands in the bloodstream (such as adiponectin) and initiates signaling pathways that regulate cell growth, survival and function. Due to the strategic placement and dual ligand-binding capabilities of T-cadherin within the cardiovascular system, its dysregulation or altered expression is expected to contribute towards the development of major cardiovascular disorders (19,43,44). The following sections discuss the evidence linking T-cadherin to atherosclerosis, hypertension, heart failure and diabetes.

3. T-cadherin and cardiovascular diseases

T-cadherin and atherosclerosis. T-cadherin regulates lipid metabolism, which directly affects the development of atherosclerotic plaques (45). A study by Göddeke *et al* (45), while studying the role of T-cadherin in 3T3-L1 adipocyte differentiation, observed that T-cadherin expression was highest in undifferentiated adipocytes and almost undetectable in mature adipocytes. During adipogenesis, T-cadherin knockdown has been shown to reduce the expression of adipogenic genes, including *peroxisome proliferator activated receptor γ* and *CCAAT enhancer binding protein α*. Additionally, the authors of the study noted that T-cadherin knockdown resulted in a reduction in both fatty acid uptake and lipid content in developing adipocytes (45). Another study by Sysoeva *et al* (16) subsequently reported that LDL stimulated adipogenic differentiation, whereas T-cadherin expression appears to mitigate the promotional effect of LDL on lipid droplet accumulation. When LDL was added to adipogenic and standard media, the proportion of lipid droplet-positive cells in both T-cadherin$^{-/-}$ MSCs and wild-type MSCs markedly increased, suggesting that LDL promotes lipid droplet accumulation. However, the proportion of lipid droplet-positive cells in wild-type MSCs was lower compared with that in T-cadherin$^{-/-}$ MSCs, indicating that T-cadherin plays a specific role in mitigating the impact of LDL on adipogenic differentiation (16).

Atherosclerosis is characterized by excessive accumulation of lipids in the intima of the cardiovascular system (46). By inhibiting the expression of miR-101-3p, erythroferrone can increase phospholipid-transporting ATPase ABCA1 expression and cholesterol efflux, thereby increasing T-cadherin expression and high-density lipoprotein cholesterol levels in the circulation, as well as the efficiency of reverse cholesterol transport, thereby inhibiting the development of atherosclerosis (Fig. 1) (39). Furthermore, a study on T-cadherin/apolipoprotein E dual-knockout model mice demonstrated markedly elevated plasma lipocalin levels in T-cadherin-deficient mice reared on a high-cholesterol diet compared with T-cadherin-expressing mice, alongside a notable increase in atherosclerotic plaque area and neointimal thickness, indicating that T-cadherin is an important receptor for the protective function of adiponectin (47).

Atherosclerosis is often accompanied by neovascularization, a process induced by inflammation and tissue ischemia. Neovascularization within the plaque extends to the intima at the site of vascular injury, which may lead to intra-plaque hemorrhage and rupture, thereby promoting the progression and acute onset of atherosclerosis (48-50). Notably, T-cadherin promotes angiogenesis by facilitating vascular cell cycle progression and inducing cell de-adhesion, thereby promoting the migration of smooth muscle and endothelial cells (33,48,51). In human umbilical vein endothelial cells, T-cadherin overexpression leads to impaired endothelial barrier function through chloride-dependent endocytosis and lysosomal degradation of vascular endothelial-cadherin (VE-cadherin), activation of Rho GTPase and increased actin stress fiber assembly (52). It has been further demonstrated that increased T-cadherin expression negatively affects endothelial barrier functions. A study on the human endothelial cell line Ea.hy926 showed that overexpression of T-cadherin is linked to lower VE-cadherin and β-catenin mRNA levels, resulting in the loss of endothelial barrier function (53). The present review speculates that under pathological conditions, overexpression of T-cadherin further suppresses endothelial function and increases endothelial permeability. Additionally, a previous study has shown that the extracellular cadherin repeats EC1 and EC5 of T-cadherin are necessary for its ability to stimulate endothelial cell angiogenic behavior (51). These findings suggest that T-cadherin promotes the progression of atherosclerosis.

The severity of atherosclerotic lesions is closely associated with immune cell infiltration (54). It is hypothesized that T-cadherin may influence plaque progression by modulating CD8$^+$ T cell functions. In advanced plaques, depletion of CD8$^+$ T cells reduces smooth muscle apoptosis and improves plaque stability (54). Furthermore, animal experiments have demonstrated that T-cadherin deficiency causes endothelial cell death by inhibiting the PI3K/Akt pathway, which leads to decreased Akt phosphorylation, rather than by inhibiting endothelial nitric oxide synthase, which leads to decreased production of endothelial cell nitrogen oxides and a marked reduction in vasodilatory function. These changes in endothelial cells (55) (Fig. 1) exacerbate oxidative stress and the release of inflammatory factors, such as IL-1β and IL-6, which further encourage macrophage infiltration into the plaque (53). Adiponectin reduces the intra-plaque inflammatory response by blocking inflammatory signaling pathways, such as the NF-κB signaling pathway, via mechanisms dependent on T-cadherin (56). A clinical study has shown that patients with particular genotypes, for example the thymine allele, carrying the *CDH13* rs12444338 single-nucleotide polymorphism (SNP), have lower plasma T-cadherin levels, although the carotid IMT of these patients was lower than patients without these SNPs. These findings suggest that this particular genotype may have a protective effect against atherosclerosis (56). Furthermore, T-cadherin plays dual roles in diabetes-related vasculopathy; increases in T-cadherin expression increase insulin secretion, while the excessive upregulation of T-cadherin may worsen endothelial insulin resistance (35,37).

Several studies have proposed treatment options for atherosclerosis based on the regulatory mechanisms of T-cadherin. Supplementation with recombinant adiponectin or increased

T-cadherin expression can prevent lipid accumulation and inflammatory responses in plaques, protecting the heart from stress-induced pathological remodeling (39,47,57). Generating specific antibodies or small molecule inhibitors to prevent LDL from binding to T-cadherin can reduce its pro-atherosclerotic effects (25,56). Furthermore, CRISPR/Cas9 technology can be used to alter *CDH13* polymorphisms (58), while miRs, such as miR-101-3p, can be used to modify T-cadherin expression for improving the efficacy of reverse cholesterol transporters (16,39).

Hypertension and T-cadherin. In total, ~30% of adults have hypertension, one of the most prevalent cardiovascular conditions worldwide. Hypertension is closely associated with metabolic irregularities and the risk of cardiovascular events (59). SNPs in *CDH13* have been linked to hypertension in genome-wide association studies (GWASs). Reduced circulating T-cadherin levels and carotid IMT are linked to the *CDH13* SNP rs12444338, indicating that this genotype may exert antihypertensive effects by altering the vascular structure (56). *CDH13*-specific SNPs, such as rs12444338 and rs1048612, have been linked to variation in systolic blood pressure levels in hypertensive patients, accounting for ~1% of the phenotypic variance in blood pressure (60). Notably, these associations vary by population: In the South Korean population, carriers of the rs6565105 allele display elevated levels of LDL cholesterol compared with other genotypes (61), which may indirectly increase the risk of elevated blood pressure, whereas in African Americans, the effect of *CDH13* SNPs on systolic blood pressure has been identified in independent samples (60). These findings imply that *CDH13* polymorphism may regulate blood pressure differently in different ethnicities, and metabolic pathways may modulate its effects. A previous study showed that the *CDH13* rs11646213 polymorphism is associated with a lower risk of hypertension compared with other SNPs (62). These results suggest that certain *CDH13* polymorphisms may protect against hypertension. Notably, the greatest signal associated with blood pressure features, such as systolic and diastolic blood pressure, as well as hypertension, was the rs7500599 intron SNP of *CDH13*, which also interacts with particulate matter exposure (63). These findings suggest that variations in *CDH13* may affect the susceptibility of an individual to environmental stimuli, thereby affecting the likelihood of developing hypertension.

Animal models offer new perspectives on the pathophysiology of hypertension. Based on comparative studies of T-cadherin-knockout and wild-type mice, it has been reported that T-cadherin plays an important role in controlling blood pressure and endurance. Furthermore, T-cadherin knockout mice demonstrate a marked increase in systolic blood pressure and reduced endurance following exercise compared with wild-type mice, indicating that T-cadherin plays a notable role in regulating vascular reactivity and that T-cadherin deficiency reduces the compensatory capacity for cardiovascular functions (32). Furthermore, in a model of angiotensin II-mediated endothelial dysfunction, T-cadherin-deficient mice show markedly lower reactive oxygen species generation and NADPH oxidase 2 (Nox2) expression than their wild-type counterparts (53). These findings suggest that T-cadherin plays a role in controlling angiotensin II-induced vascular reactivity, which in turn influences blood pressure regulation.

Compared with rats with normal blood pressure, the levels of ceramide in the arterial tissue of spontaneously hypertensive rats have been demonstrated to be markedly elevated (64). A further study showed that ceramide is associated with thromboxane A2, a protein that may cause endothelial dysfunction in hypertension (64). Similar associations between ceramide levels and blood pressure have been reported in patients with hypertension. In patients with primary hypertension, plasma ceramide levels increase stepwise with the severity of hypertension. Ceramide levels in patients with stage 1 hypertension are between those in individuals with healthy blood pressure and stage 2-3 hypertension (65). A previous study has shown that ceramide/sphingosine-1-phosphate regulators play a role in blood pressure regulation in patients with hypertension (66). The adiponectin/T-cadherin system reduces intracellular ceramide levels via exosome secretion (34).

The interaction between T-cadherin and VE-cadherin was further supported by the observation that overexpression of T-cadherin in cultured human endothelial cells decreases VE-cadherin mRNA expression. This interaction may disrupt endothelial barrier function and affect vascular tone, which may have a stabilizing effect on vascularity and blood pressure regulation (53). According to previous studies, T-cadherin regulates blood pressure via several mechanisms, including oxidative stress, vascular remodeling and endothelial function modification (32,53,57). Although T-cadherin has been linked to hypertension in several studies, the generalizability of these results may be affected by confounding variables and population variations. A study conducted in Amish and European populations have validated statistically significant effects of *CDH13* SNPs on blood pressure (odds ratio, 1.2-2.0); however, phenotypic evaluations may be complicated due to the use of antihypertensive drugs (60). The study further showed that after controlling for confounders, the effect of certain *CDH13* SNPs on hypertension among African Americans was weakly significant (P=0.04) (60), indicating that contextual or epigenetic variables may alter the impact of genotype on hypertensive susceptibility. Cross-ethnic large-sample cohort studies and the integration of multi-omics data are needed to elucidate the precise role of *CDH13* polymorphisms in hypertension and thoroughly examine its molecular network to identify novel targets for the precise treatment of hypertension.

T-cadherin and heart failure. Heart failure, a common outcome in several cardiovascular disorders, is becoming a notable public health issue. Patients with heart failure typically have a low quality of life in addition to high hospitalization and mortality rates (67-69). According to estimates, 1-2% of all individuals in industrialized cultures have heart failure, while in those >70 years of age, the prevalence of heart failure is >10%. In Europe, the lifetime risk of the disease is ~33% for males and 28% for females aged >55 years (70), whereas in the US, the lifetime risk is 20% for those aged >40 years (71). Compared with Western populations, heart failure is more severe and develops at a younger age in

Asians and in low- and middle-income nations (69,72). When MSCs are used to treat pressure-overload heart failure, the adiponectin/T-cadherin system plays a key role in promoting myocardial regeneration and reducing oxidative stress by increasing exosome production and secretion. Experiments have demonstrated that mice lacking T-cadherin or adiponectin have much lower exosome counts and do not benefit from MSC therapy (30,73,74).

Heart failure frequently coexists with cardiac remodeling, which is defined as changes in the structure and function of the heart, and includes perivascular and interstitial fibrosis, ventricular arrhythmias (75) and structural remodeling. These changes alter the composition and structure of the heart, which in turn causes ventricular hypertrophy, cardiac fibrosis and heart failure (76,77). T-cadherin plays a key role in heart failure by regulating oxidative stress and inflammatory signaling implicated in cardiac fibrosis. The production of reactive oxygen species and Nox2 mRNA expression are markedly downregulated in T-cadherin-deficient mouse models of angiotensin II-induced endothelial dysfunction, indicating that T-cadherin may affect cardiac remodeling by regulating redox homeostasis. Furthermore, the absence of T-cadherin reduces bleomycin-induced lung fibrosis; however, further research is required to determine the precise mechanism by which T-cadherin affects myocardial fibrosis (53). Adiponectin may suppress fibrosis via the *CDH13*/p38 MAPKγ signaling axis, and reduced *CDH13* expression is linked to increased fibroblast activation in pulmonary fibrosis (78). Since cardiac fibrosis is a fundamental pathophysiological alteration in heart failure, *CDH13* may be a novel target for myocardial remodeling interventions.

Other calcineurin proteins, including N-cadherin and VE-cadherin, interact functionally with T-cadherin. Abnormal cardiomyocyte coupling in patients with end-stage heart failure may result from deregulation of the obscurin-kinase 1/N-cadherin axis (79). Further research is needed to determine whether a relationship exists between T-cadherin expression and the obscurin-kinase 1/N-cadherin axis in heart failure models. A previous study reported by Fukuda *et al* (73) identified three novel soluble isoforms of T-cadherin and reported that the 30 kDa isoform was associated with clinically important indicators of heart failure, such as B-type natriuretic peptide. Further studies are needed to determine whether other signaling pathways or molecular mechanisms are involved in heart failure pathology. T-cadherin overexpression can damage endothelial intercellular junction integrity and decrease VE-cadherin mRNA levels, affecting heart function and vascular permeability (53). An ovarian cancer study revealed a regulatory relationship between *CDH13* and DNA methyltransferase 1 (DNMT1) (80). Since DNMT1 is important in myocardial hypertrophy and fibrosis, *CDH13* may indirectly affect the development of heart failure through epigenetic networks. Future studies using data from various sources, including studies at the cellular level, animal models and clinical investigations, are needed to corroborate the association between T-cadherin and heart failure.

T-cadherin and diabetes. Although the underlying molecular mechanisms are unknown, several studies have linked the plasma levels of adiponectin and T-cadherin to an increased risk of diabetes (37,81,82). In obese individuals and patients with type 2 diabetes, plasma adiponectin levels are often reduced, a finding linked to insulin resistance and β-cell dysfunction (81). This suggests that low adiponectin levels are closely associated with diabetes. An animal study demonstrated that T-cadherin deficiency increases the risk of diabetes (37). Elevated levels of T-cadherin do not directly increase the risk of diabetes; rather, increased soluble T-cadherin levels serve primarily as a biochemical marker of insulin deficiency or impaired insulin signaling (82). Vascular endothelial cells, cardiac muscles, MSCs and skeletal muscles are the predominant cells that express T-cadherin, although pancreatic β-cells also rarely express T-cadherin (37,57,74,82). Although not expressed in β-cells, the endogenous humoral factor soluble T-cadherin notably promotes β-cell proliferation. Additionally, the Notch and IL-6/STAT3 pathways in pancreatic islets are regulated by T-cadherin (37). The Notch pathway contributes to the differentiation and proliferation of β-cells (83,84), which are promoted by soluble T-cadherin regulation. However, the absence of soluble T-cadherin suppresses the IL-6/STAT3 pathway and the activity of protein kinases involved in β-cell proliferation and apoptosis (37,85-87). Notably, the proliferative effects of T-cadherin are tissue specific; knocking out T-cadherin in the heart or skeletal muscles does not impact β-cell function (82). However, in mice with streptozotocin-induced diabetes, endothelial cell-specific T-cadherin knockout is associated with a 26% decrease in plasma soluble T-cadherin levels, which is accompanied by a marked increase in blood glucose (82). These findings imply that T-cadherin produced by endothelial cells may modulate β-cell activity or systemic insulin sensitivity, thereby regulating glucose metabolism.

A previous study demonstrated that diabetic mouse models, such as leptin receptor-deficient *db*/*db* model mice, have increased levels of plasma soluble T-cadherin (82), which could be an adaptive reaction to the compensatory requirement for β-cell activity. Furthermore, insulin can positively regulate the production of soluble T-cadherin from endothelial cells through the insulin receptor/Akt signaling pathway, and inadequate insulin secretion or insulin resistance may interfere with this regulatory mechanism (35,37). T-cadherin regulates insulin sensitivity via two different mechanisms: i) The effects of adiponectin on ceramide turnover are mediated via the T-cadherin/adiponectin signaling pathway, which improves endothelial function and suppresses inflammatory responses, resulting in increased insulin sensitivity (Fig. 1) (12,16,81); and ii) T-cadherin upregulation in vascular cells may interfere with insulin receptor signaling, resulting in endothelial insulin resistance (12,88).

GWASs have shown that the risk of diabetes is closely associated with *CDH13* polymorphism. The minor allele at the rs3865188 locus may have a protective effect against diabetes (OR, 0.71; 95% CI, 0.58-0.88; P=0.002), whereas the T-allele at the rs11646213 locus is associated with an elevated risk of T2D (OR, 1.11; 95% CI, 1.04-1.18; P=0.001) (41,89). Notably, the rs11646213 locus is also associated with elevated body mass index (P=0.03), indicating that *CDH13* polymorphisms may influence metabolic pathways associated with obesity, thereby indirectly increasing the risk of T2D (41). Although *CDH13* polymorphisms are markedly associated with T2D in white populations (42), in Han Chinese populations the

rs4783244 locus is not significantly associated with T2D (P=0.56), whereas the guanine-allele of rs4311394 may be associated with an increased risk of T2D (OR, 1.20; 95% CI, 1.01-1.41) (90). These differences may stem from the modifying effects of the genetic background or environmental factors. Similarly, the rs11646213 and rs3865188 variants are associated with the prevalence, incidence and progression of type 1 diabetic nephropathy and this association may depend on plasma adiponectin levels (89). The absence of T-cadherin in the vascular segments of T2D models leads to endothelial dysfunction, providing evidence that T-cadherin is involved in the pathogenesis of T2D complications (55).

There has been limited research directly linking T-cadherin to diabetes (12); additional research is needed to determine its precise role in the vascular endothelium, β-cells and insulin signaling. Future research should also concentrate on the molecular mechanism of T-cadherin/adiponectin interactions, variations in *CDH13* polymorphisms and the possibility of targeting this receptor for the treatment of diabetes. Furthermore, a bidirectional research strategy of validating mechanistic targets derived from model systems in well-phenotyped clinical cohorts, and conversely, using genetic or phenotypic associations discovered in cohorts to inform new mechanistic studies, will be essential to de-risk and accelerate the development of T-cadherin-targeted therapies.

Although T-cadherin has a notable impact on cardiovascular and metabolic health, it also plays a prominent role in cancer biology. Unlike conventional cadherins, which are typically associated with cancer progression, T-cadherin frequently functions as a tumor suppressor. The loss of T-cadherin expression, primarily due to *CDH13* promoter hypermethylation, represents a prevalent characteristic in several epithelial malignancies (91-94).

4. T-cadherin and tumors

Previously, classical cadherins, including E-, placental- and N-cadherins, have been the focus of the majority of studies on cancer. It has been speculated that tumor progression is linked to abnormal cadherin expression (92,95). The role of T-cadherin in signaling pathways implicated in tumor cell proliferation is discussed in the present section.

Tumorigenesis may activate various signaling pathways, and T-cadherin regulates tumors via several signaling mechanisms. *CDH13* overexpression prevents activation of the PI3K/Akt pathway, leading to decreased tumor cell survival and metastasis (95). Additionally, *CDH13* inhibits β-catenin nuclear translocation and decreases the expression of downstream genes such as *c-Myc* and *cyclin D1* to stop tumor cell growth (94). The degree of tumor immune infiltration in clear-cell renal cell carcinoma (ccRCC) is associated with *CDH13* expression, and patient prognosis is affected by *CDH13* methylation status and N6-methyladenosine alterations (96). Research has demonstrated that *CDH13* expression is positively associated with prognosis in patients with ccRCC. Specifically, high *CDH13* expression is notably associated with improved overall survival and progression-free survival, and associated with lower tumor stage and grade. Conversely, high DNA methylation in the *CDH13* promoter region is negatively associated with its mRNA expression and leads to poor patient prognosis. Furthermore, *CDH13* expression is regulated by N6-methyladenosine (m6A) RNA modifications, and its associations with multiple m6A regulatory factors collectively constitute a key epigenetic mechanism influencing patient prognosis (96).

Numerous tumors exhibit markedly reduced T-cadherin expression compared with healthy tissues (14,94,97,98). In gastric cancer, lower T-cadherin protein levels have been observed compared with normal tissues both *in vivo* and in cell lines, and these reduced levels have been notably associated with tumor aggressiveness and poor prognosis (99-102). T-cadherin expression is associated with the overall survival rate of patients with gastric cancer (99). Furthermore, in oral squamous cell carcinoma, the methylation status of *CDH13* is markedly associated with tumor and lymph node stages, lymph node metastasis and the risk of recurrence. Furthermore, patients with methylated *CHD13* have markedly lower overall and progression-free survival than patients without methylated *CHD13* (103,104). Reduced expression of T-cadherin in patients with triple-negative breast cancer is associated with lower postoperative survival, indicating its potential as an independent prognostic marker (105). Unlike other cancers, the expression of T-cadherin is increased in ccRCC, suggesting a unique expression pattern of this receptor. T-cadherin levels are markedly higher in low-grade than high-grade ccRCC, and this expression pattern can assist clinicians in diagnosis as well as tumor staging and grading. Further survival analysis has revealed that increased levels of T-cadherin are associated with improved overall and progression-free survival in patients with ccRCC, indicating that T-cadherin is a novel prognostic biomarker for ccRCC (96). However, the role of T-cadherin in specific tumor types remains controversial. For example, in prostate cancer, the expression of mRNA and protein levels of T-cadherin are not perfectly associated, with only the protein level being elevated. In prostate cancer, T-cadherin undergoes dynamic regulation and may exhibit stage-dependent effects, promoting differentiation and chemotherapy sensitivity in early stages but gradually diminishing during disease progression (97). This indicates that the relationship between the expression pattern and function of T-cadherin is highly context-dependent, rather than simply acting as a tumor suppressor or promoter. To further investigate the potential mechanism by which T-cadherin inhibits gastric cancer cell proliferation, a study by Lin *et al* (100) reported that the overexpression of T-cadherin downregulates the expression of CDK4 and cyclin D1, inducing G_0/G_1 phase cell cycle arrest. Additionally, T-cadherin overexpression upregulates E-cadherin and downregulates vimentin and MMP-2 expression, preventing the migration and invasion of gastric cancer cells (100). A molecular study has supported that T-cadherin inhibits gastric tumorigenesis by suppressing the Akt/mTOR signaling pathway (99). These findings suggest that T-cadherin may serve as a potential target for the treatment of gastric cancer and for predicting the prognosis of patients with gastric cancer.

Animal experiments have provided evidence that T-cadherin overexpression in pancreatic cancer reduces the volume of *in situ*-grafted tumors and the incidence of hepatic

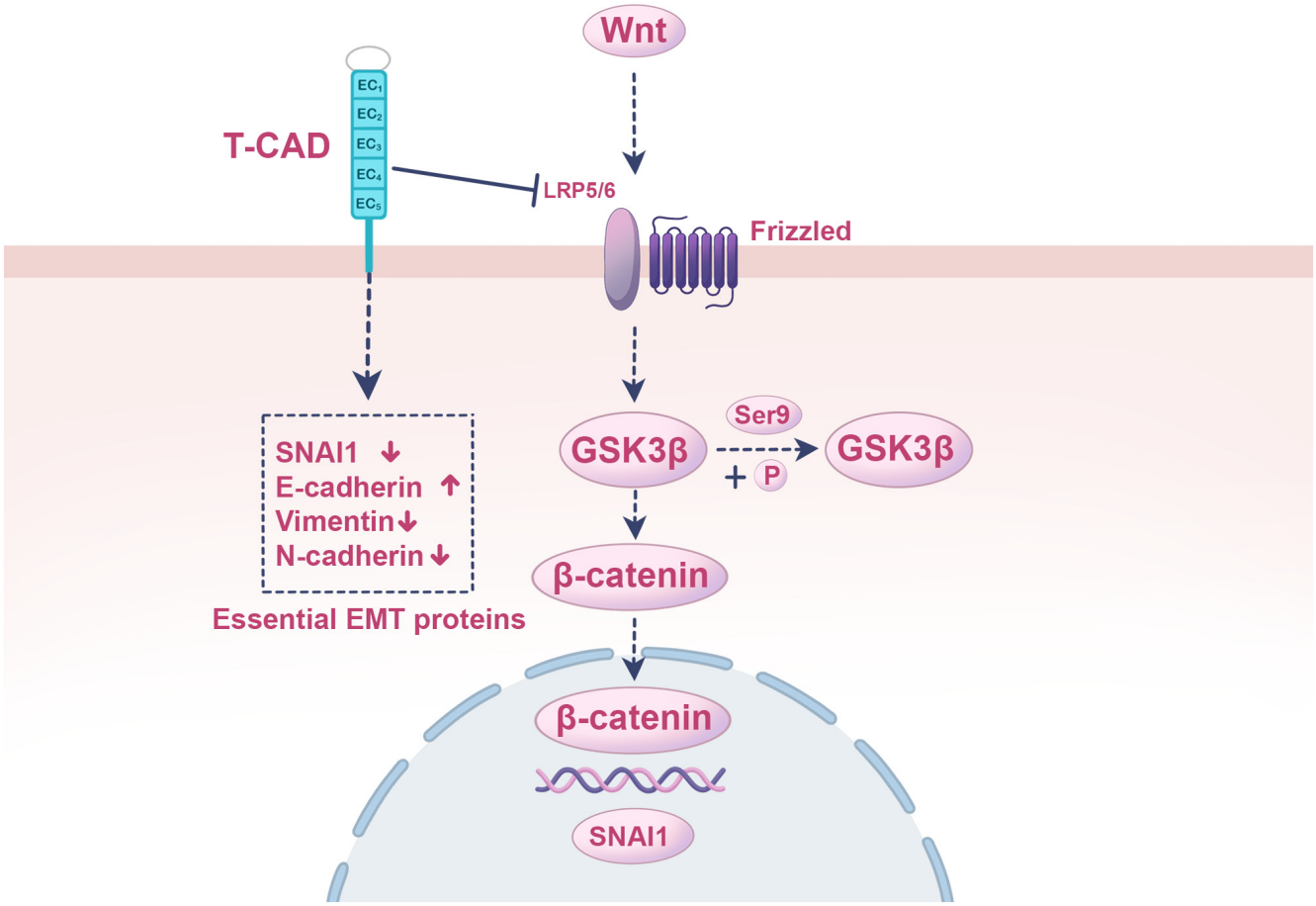

Figure 2. T-cadherin upregulation inhibits EMT by inactivating the Wnt/β-catenin pathway. The illustration depicts the mechanism through which T-cadherin suppresses core signaling that drives the EMT. Initiation of this suppression at the membrane requires T-cadherin upregulation that downregulates the Wnt co-receptor LRP5/6, impairing the canonical Wnt signaling pathway initiated by Wnt ligands binding to Frizzled receptors. The cytoplasmic signaling cascade is as follows: In the absence of the Wnt signal, GSK3β remains active, involving a lack of phosphorylation at Ser9. Active GSK3β then phosphorylates β-catenin, marking it for proteasomal degradation. This prevents β-catenin accumulation and its translocation into the nucleus. Nuclear transcriptional regulation is mediated by the loss of nuclear β-catenin, leading to reduced transcription of its target genes, including the key EMT transcription factor SNAI1. Reduced SNAI1 levels cause a reversal of EMT markers, manifested by the upregulation of the epithelial marker E-cadherin and the downregulation of the mesenchymal markers vimentin and N-cadherin, thereby counteracting the invasive and metastatic phenotype that accompanies EMT. T-CAD, T-cadherin; LRP5/6, low-density lipoprotein receptor-related protein 5/6; GSK3β, glycogen synthase kinase 3β; Ser9, serine 9; P, phosphate group; SNAI1, zinc finger protein SNAI1; EMT, epithelial-mesenchymal transition; E-cadherin, epithelial-cadherin; N-cadherin, neural-cadherin.

and mesenteric metastases. It also markedly inhibits the proliferation, migration and invasiveness of tumor cells (94). Furthermore, the carcinogenic effects of T-cadherin are dependent on the tumor microenvironment, which might impact tumor growth by blocking pathways linked to angiogenesis, such as the PI3K/Akt and Wnt/β-catenin pathways (94,96). The primary mechanism for inhibiting the expression of T-cadherin is hypermethylation of its promoter region, which is common in ovarian, breast, pancreatic and hepatocellular carcinomas. Studies have demonstrated that breast cancer molecular subtypes can be differentiated based on T-cadherin promoter methylation, with human epidermal growth factor receptor 2-positive and progesterone receptor-negative tumors exhibiting noticeably greater levels of promoter methylation than other types (106-108). miR-142-5p and the cyclic RNA hsa_circ_0000119 regulate *CDH13* promoter methylation in ovarian cancer, with notably greater levels observed in malignant tissues compared with those in adjacent normal tissues. By increasing the expression of DNMT1, hsa_circ_0000119 promotes hypermethylation of *CDH13*, thereby stimulating the production of T-cadherin, which in turn accelerates the development of ovarian cancer (80).

Furthermore, patients with hepatocellular carcinoma exhibit a much greater frequency of *CDH13* methylation than the general population, and this methylation is linked to environmental variables such as alcohol consumption and smoking (109,110). These findings suggest that *CDH13* promoter methylation levels may serve as a potential biomarker for predicting outcomes in patients with hepatocellular carcinoma. Notably, by controlling the demethylation of the *CDH13* promoter, the DNA repair enzyme DNA polymerase β can restore T-cadherin expression and prevent tumor spreading (111). Thus, restoring T-cadherin expression or focusing on its regulatory mechanisms represent possible treatment approaches. Demethylating medications such as 5-aza-2'-deoxycytidine have the potential to reverse cisplatin resistance in lung cancer cells (112) and to restore T-cadherin expression, which prevents tumor spreading (14,103). By upregulating T-cadherin expression and blocking the PI3K/Akt

pathway, the natural substance garcinol markedly inhibits the development of transplanted tumors and the proliferation of cervical cancer cells (95).

T-cadherin exerts tumor-suppressive effects in a range of epithelial-derived malignancies (112,113). Epithelial-mesenchymal transition (EMT) is an important step in morphogenesis that gives epithelial cells a mesenchymal appearance. EMT occurs during various stages of embryonic development, including placental creation, neural crest development and gastrulation. Researchers have speculated that epithelial malignancies must have mesenchymal characteristics to penetrate and spread, since EMT is an important signature of embryogenesis (112,113). A previous study demonstrated that T-cadherin overexpression suppresses the Wnt/β-catenin signaling pathway and prevents its activation by controlling the expression of markers linked to EMT (Fig. 2) (90).

The tumor-suppressive role of T-cadherin is supported by multiple studies. Future research should combine single-cell sequencing and spatial transcriptome technologies to fully understand the function of T-cadherin in regulating tumor heterogeneity and microenvironmental remodeling, as well as to explore its potential as a combination therapeutic target. The complex, context-dependent actions of T-cadherin in various disorders, including cardiovascular diseases, metabolic diseases and cancer, emphasize its unique status as a GPI-anchored atypical cadherin that mediates important extracellular signals. Thus, unraveling the complexities of relevant signaling processes is necessary.

5. Conclusions

Despite belonging to the cadherin superfamily, T-cadherin does not function as a classical cadherin due to the lack of transmembrane and cytoplasmic structural domains. This unique structure makes it challenging to understand how T-cadherin mediates intracellular signaling. Signal transduction by GPI-anchored proteins require interactions with bridging molecules within the lipid rafts of the plasma membrane (114,115). Both T-cadherin and integrin-linked kinase (ILK) are localized in plasma membrane lipid rafts (44,116). Studies have shown that ILK plays a role in strain-induced signal transduction (117,118), and it has been shown that ILK is a signaling regulator of GPI-anchored proteins (119). Another hypothesis for T-cadherin-mediated signal transduction is that T-cadherin co-localizes with caveolin, a marker of caveolae, within a smaller detergent-insoluble low-density membrane domain. This domain is rich in other GPI-anchored proteins, such as CD-59 and urokinase-type plasminogen activator receptors, and signaling molecules, such as the G protein αs subunit and Src family kinases; therefore, T-cadherin may interact with caveolae to mediate membrane signaling (44). Notably, caveolae and cell membrane lipid rafts are considered centers of signal transduction (117,118,120). Further research is needed to identify co-adaptor molecules for GPI-anchored proteins or specific signal transduction mediators of T-cadherin.

As a receptor for LDL and HMW adiponectin, T-cadherin often exerts opposing effects upon binding to these ligands. LDL and HMW adiponectin induce the formation of distinct T-cadherin clusters, leading to different cellular responses (25), which may explain their distinct physiological effects. A competitive relationship exists between LDL and HMW adiponectin for T-cadherin binding, as both are large complexes of similar diameters of ~25 nm (120). Adiponectin inhibits LDL-stimulated Ca^{2+} signaling in T-cadherin-overexpressing 293 cells (120,121). Furthermore, the expression of adiponectin is decreased in obesity, whereas LDL levels are increased. Changes in adiponectin-LDL ratio may drive different pathological responses (56).

Numerous studies have shown that T-cadherin primarily functions as a signaling molecule involved in cellular regulation, proliferation, apoptosis and migration. Serving as a receptor for both LDL and adiponectin, with genetic variations in the *CDH13* gene, T-cadherin plays notable roles in cardiovascular diseases, diabetes and cancer. Nevertheless, key questions regarding tissue specificity, signaling crosstalk and the precise mechanisms of T-cadherin activity in major intracellular signaling pathways remain to be fully elucidated.

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YS designed the review; YS and XW retrieved the relevant literature. YS and YB wrote and reviewed the article. XW wrote the figure legends and created the figures. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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