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REVIEWS

T-Cadherin As a Receptor Regulating Angiogenesis and Blood Vessel Remodeling

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Abstract—The search for a membrane receptor responsible for hormone-like effects of low density lipoproteins (LDL) has revealed two proteins (Mol. wt. 105 and 130 kDa) in the membrane fraction of human aortic smooth muscle cells. These proteins were identified as mature T-cadherin and its unprocessed precursor. T-cadherin was originally cloned from chick embryo brain, where it was implicated in axon guidance in the developing nervous system. Our study on the T-cadherin distribution in human organs and tissues has indicated that T-cadherin is specifically expressed in nervous and cardiovascular system. However, physiological significance of T-cadherin expression in the vasculature, as well as intracellular signaling pathways mediating its effects remain obscure. This review summarizes our current knowledge about intracellular signaling utilized by T-cadherin and discusses possible functions of T-cadherin in the vasculature.

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Our search for the membrane receptor responsible for hormone-like effects of low density lipoproteins (LDL) has revealed two proteins (105 and 130 kDa) in the membrane fraction of human aortic smooth muscle cells (SMC). These proteins were identified as mature T-cadherin and its unprocessed precursor. T-cadherin (H-cadherin, cadherin-13) is a unique member of homophilic adhesion molecules family, which does not contain either transmembrane or cytoplasmic domains, but is anchored to plasma membrane via glycosilphosphoinositol (GPI) anchor [1]. In human organs and tissues T-cadherin is specifically expressed in nervous and cardiovascular system. In the nervous system this protein functions as a guidance receptor allowing the growing axon to avoid tissues expressing T-cadherin [2, 3]. Our data suggest that in cardiovascular system T-cadherin participates in the vessel wall remodeling. Also, this protein can suppress the angiogenesis by inhibiting the migration of endothelial cells.

STRUCTURE AND INTRACELLULAR LOCALIZATION OF T-CADHERIN

T-cadherin is a unique member of the cadherin superfamily of adhesion molecules mediating Ca^{2+}-dependent cell-cell adhesion and recognition [4]. T-cadherin is essential for establishing of cell polarity, sorting and differentiation during embryonic development and in the adult organism [4]. Classical cadherins consist of extracellular, transmembrane and cytoplasmic domains. The extracellular portion of cadherins contains conserved Ca^{2+}-binding domains, which mediate recognition and homophilic interaction with cadherins on neighboring cells. Intracellular domains of classical cadherins interact with actin cytoskeleton via catenins, ensuring the stability of cadherin-mediated adhesive junctions [5–7].

As classical cadherins, T-cadherin also has five Ca^{2+}-binding domains in its extracellular portion. Unlike other cadherins, T-cadherin is anchored to the cell surface membrane via a glycosilphosphoinositol (GPI) moiety, since it does not possess either transmembrane or cytoplasmic parts [8]. The lack of an intracellular domain and interaction with catenins suggests that T-cadherin does not mediate stable cell-cell adhesion (Fig. 1). This suggestion was supported by data regarding T-cadherin intracellular localization. Thus, in confluent cultures of vascular cells T-cadherin was distributed equally over the entire cell, in contrast to VE-cadherin, which is restricted to the cell junctions [9]. In cultures of transfected MDCK cells T-cadherin was also expressed apically, whereas N-cadherin resided basolaterally in the cell contact zone [10–12]. In vivo T-cadherin was detected on the apical cell surface of the chick interstinal epithelium. Such distribution suggests that T-cadherin functions as a recognition receptor (Fig. 2). Furthermore, confocal microscopy has revealed the accumulation of T-cadherin on the leading edge of migrating cells in scratch assays, demonstrating potential signaling and navigating functions of T-cadherin [13].

We have found that in plasma membrane of smooth muscle cells T-cadherin is restricted to caveolae, where it co-localizes with signal-transducing molecules, such as Src kinase and G-proteins [14, 15]. These findings also indicate that T-cadherin can initiate intracellular signaling cascades.

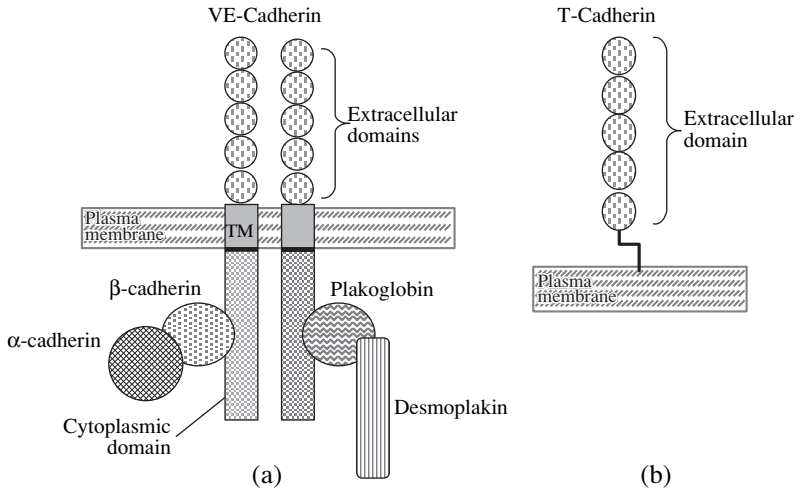

Fig. 1. Structure of the classical cadherin (VE-cadherin) and T-cadherin. (a) VE-cadherin homodimer, consisting of cytoplasmic, transmembrane (TM) and extracellular domains. (b) T-cadherin, which lacks cytoplasmic and transmembrane domains. Extracellular domains of cadherins are comprised of five Ca^{2+}-binding repeats (indicated by circles).

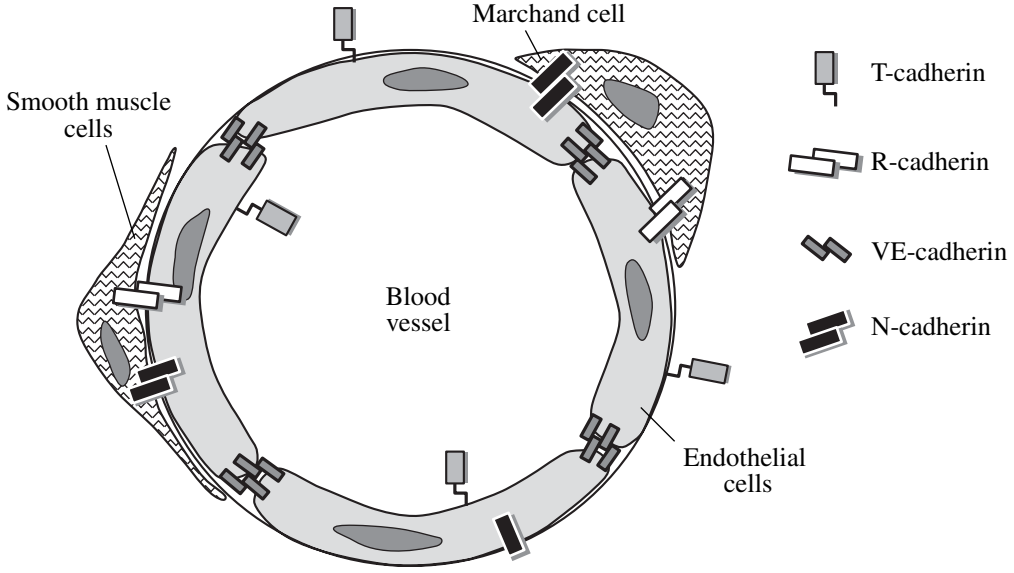

Fig. 2. Distribution of cadherins at the surface of vascular cells. T-cadherin is localized within the entire surface of endothelial cells, whereas classical cadherins are restricted to the cell contacts.

T-CADHERIN AS A SIGNALING RECEPTOR

In vascular cells T-cadherin was initially identified as LDL-binding receptor [1]. LDL interaction with T-cadherin at the surface of SMC and endothelial cells causes Ca^{2+}-mobilization, as well as activation of phosphoinositol turnover [17, 18]. Kinetics of such LDL action mediated by T-cadherin resembles the effect of angiotensin II, another Ca^{2+}-mobilizing hormone, but develops significantly faster than Ca^{2+} mobilization activated by PDGF-BB (platelet-derived growth factor-BB). LDLs exert such effects within the physiological range of their concentrations in blood and in vessel wall [18]. $[Ca^{2+}]_i$ elevation occurs due to mobilization of intracellular stores, as well as due to the inward flow from the extracellular medium. The same mechanisms are utilized by all Ca^{2+}-mobilizing hormones. Similarity with hormone action is enhanced by the ability of LDL to induce Ca^{2+} oscillations in single cells, as well as by the fact that such elevation of intracellular Ca^{2+} is inhibited by protein kinase C and by cAMP-dependent protein kinase activators [19]. Furthermore, LDLs, like other Ca^{2+}-mobilizing hormones, also activate phosphoinositol turnover in SMCs [19]. Thus, T-cadherin is a good candidate for a LDL signaling receptor.

To prove that T-cadherin is involved in intracellular signaling, we stably transfected HEK293 and L929

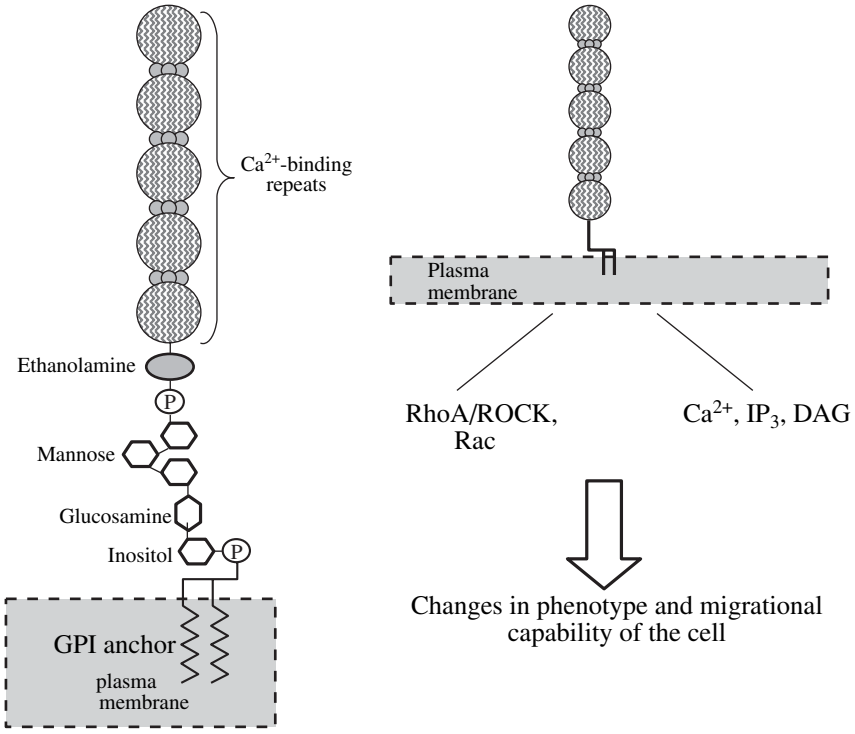

Fig. 3. T-cadherin structure (left) and its intracellular signaling pathways (right). IP_3—inositol-3-phosphate; DAG—diacylglycerol.

cells with cDNA of T-cadherin. LDL induces $[Ca^{2+}]_i$ elevation in cells expressing T-cadherin with the maximal amplitude 2–3.5 times higher compared to mock-transfected cells [20]. The effect of the LDL administration was totally abolished in the presence of a specific inhibitor of Ca^{2+}-ATPase of the sarcoplasmic reticulum. These data indicate that LDL binding to T-cadherin activates Ca^{2+}-mobilization by intracellular signaling similar to pathway(s) utilized by Ca^{2+}-mobilizing hormones. Following Ca^{2+}-mobilization, LDL binding to T-cadherin also leads to the activation of Erk 1/2 tyrosine kinase and the nuclear translocation of NF-κB [21].

T-cadherin is upregulated in vascular cells under pathological conditions. However, the physiological significance of the LDL-induced Ca^{2+}-signaling mediated by T-cadherin in the cardiovascular system remains unknown. Several important disease states, such as hypertension, ischemic heart disease, diabetes and others result from abnormal Ca^{2+}-signaling [22]. A broadening or increase in the amplitude of the Ca^{2+}-spikes enhances the extent of the Ca^{2+}-pulse, which over time could stimulate a distinct program of gene transcription and result in cardiac hypertrophy [23].

We have also demonstrated that LDL can induce T-cadherin-dependent cell migration. Thus, T-caherin expression in L929 cells facilitates spontaneous cell migration. Furthermore, the migration of T-cadherin expressing cells along the LDL gradient was significantly greater than the migration of the mock-transfected cells [20].

It is likely that T-cadherin regulates cell migration and phenotype via activation of small G-proteins and subsequent actin reorganization. The signaling effects of T-cadherin on cell adhesion and phenotype are mediated through activation of RhoA/ROCK and Rac. RhoA/ROCK is necessary for cell contraction, stress fiber assembly and inhibition of spreading, while Rac is required for the formation of membrane protrusions and actin-rich lamellipodia at the leading edge of migrating cells [24].

In cell culture T-cadherin mediates only week calcium-dependent cell-cell adhesion but is not concentrated in cell-cell contacts of transfected cells [25, 26]. T-cadherin-dependent adhesion is ablated by treatment with phosphatidylinositol-specific phospholipase C, which removes the GPI-anchored proteins. Furthermore, LDL inclusion in culture media inhibits cell-cell aggregation of HEK293 cells expressing T-cadherin [25]. Thus, T-cadherin is a physiologically relevant LDL receptor mediating LDL-induced cell signaling and cell migration (Fig. 3).

LDL is not the only ligand for T-cadherin. Recently, high-molecular weight (HMW) complexes of adiponectin were suggested to be a specific ligand for T-cadherin [27]. Adiponectin (adipocyte complement-related protein of 30 kDa) is a cytokine produced by adipose tissue. Adiponectin is a unique adipocyte-derived hormone that is considered to be an important

regulator of lipid and glucose metabolism [28]. Its plasma level is significantly decreased in patients with metabolic syndrome, obesity, type II diabetes and atherosclerosis. Furthermore, adiponectin suppresses vascular cell growth and therefore prevents vessel wall remodeling. Thus, depletion of adiponectin gene caused increased neointima formation in mice in the external vascular cuff injury model (cited in [29]). These data suggest the protective antiatherogenic function of adiponectin in the vascular wall. Adiponectin was shown to directly inhibit the LDL binding to proteoglycans and their accumulation in vascular wall [30]. In addition, adiponectin has been reported to protect apolipoprotein E-defficient mice from development of atherosclerotic lesions of vascular walls [31]. In vitro, adiponectin attenuates DNA synthesis, cell proliferation, and growth factor-induced migration in vascular SMC; and in endothelial cells, adiponectin inhibits proliferation [28, 29]. In chick chorioallantoic membrane and in mouse corneal angiogenesis model adiponectin suppresses blood vessel growth. This mechanism involves activation of 8-, 9-, and 3-caspase-mediated endothelial cell apoptosis [28]. Adiponectin binding to T-cadherin on vascular cells is associated with NF-κB activation, whereas in liver and muscle adiponectin stimulates AMP-activated protein kinase activation and fatty acid oxidation [27]. Two adiponectin receptors with distant homology to seven-transmembrane spanning G-protein-coupled receptors, namely AdipoRl and AdipoR2, were identified in several tissues [27]. Despite apparent physiological significance, intracellular signaling pathways mediating adiponectin effects remain largely elusive. Although T-cadherin was suggested to be a vascular-specific receptor for high molecular weight (HMW) isoforms of adiponectin, the mechanisms of the T-cadherin—adiponectin interaction and signaling are still obscure.

T-CADHERIN AS AN INHIBITOR OF APOPTOSIS AND CELL PROLIFERATION

T-cadherin can regulate of cell growth, survival and proliferation. Recently, T-cadherin expression increases in human umbilical vein endothelial cells (HUVEC) under the conditions of oxidative stress, and the increased production of reactive oxygen species (ROS) contributes to the T-cadherin elevation. Overexpression of T-cadherin in HUVEC results in higher phosphorylation of phosphatidylinositol 3-kinase (PIK3)—the target of Akt—and of mTOR—the target of $p70^{S6K}$ (survival pathway regulator). HUVEC overexpressing T-cadherin showed reduced levels of caspase activation and increased survival after exposure to oxidative stress. It was suggested that T-cadherin overexpression protects these cells against stress-induced apoptosis through activation of the PIK3/Akt/mTOR survival signal pathway and corresponding suppression of the p38 MAP pro-apoptotic pathway [32].

In cultured aortic SMCs, as well as in primary cultures of astrocytes, the expression of T-cadherin depends on proliferation status with maximum at confluence, suggesting the regulation of cell growth by contact inhibition [33, 34]. In contrast, data obtained in Dr. Resink's laboratory indicate that HUVEC overexpressing T-cadherin after adenovirus transfection enter S-phase more rapidly and exhibit increased proliferation potential [32]. Contrary to this data, known mitogens, such as platelet-derived growth factor (PDGF)-BB, epidermal growth factor (EGF) or insulin-like growth factor (IGF) elicit a reversible dose- and time-dependent decrease in T-cadherin expression in cultured aortic SMCs [33]. T-cadherin growth suppression in CHO cells is associated with increased expression of p21 (the cyclin-dependent kinase, cdk) [34, 35]. These data indicate that T-cadherin is involved in the regulation of the cell cycle and may act as a negative regulator of cell growth.

The in vitro data regarding the ability of T-cadherin to suppress cell growth were further supported by investigating several tumors. T-cadherin loss in tumor cells is associated with tumor malignancy, invasiveness and metastasis [36–43]. The suppression of T-cadherin gene expression was associated with allelic loss or hypermethylation of the T-cadherin promoter region [40, 42–44]. Recently it was demonstrated that tumor cells could regulate gene expression in growing vessels during tumor neovascularization [36, 38]. Thus, T-cadherin expression is decreased in tumor vessels [45]. In Lewis carcinoma lung metastasis the expression of T-cadherin is upregulated in blood vessels penetrating the tumor, while in the surrounding tumor tissue T-cadherin expression appeared to be downregulated [46]. In the model of T241 murine fibrosarcoma T-cadherin ligand adiponectin reduced tumor growth. Adiponectin itself did not influence the growth of tumor cells in vitro but reduced neovascularization of the tumor via caspase-activated apoptosis in endothelial cells [27]. Interestingly, FGF-2 appeared to play a crucial role in the induction of T-cadherin expression suggesting a cross-talk between adiponectin/T-cadherin and FGF-2 (a well-known stimulator of angiogenesis) signaling pathways [47]. These data suggest that T-cadherin functions as an inhibitor of tumor angiogenesis.

T-CADHERIN AS A REGULATOR OF VASCULAR WALL REMODELING AND ANGIOGENESIS

T-cadherin is predominantly expressed in nervous and cardiovascular system with maximal expression in aorta, arteries and in the heart [22]. In aorta wall, T-cadherin is expressed in endothelial cells, smooth muscle cells, and pericytes. Immunohistochemical staining of human organs and tissues has proved that T-cadherin is highly expressed in the heart, aortic wall, neurons of the brain cortex and spinal cord, and also in small blood vessels in spleen and other organs [48].

Expression of T-cadherin increases in atherosclerotic lesions and post-angioplasty restenosis—conditions associated with pathological angiogenesis [22, 48]. We have shown that T-cadherin expression is upregulated in endothelial cells, pericytes and SMCs within atherosclerotic lesions. Our data indicate also that upregulated T-cadherin expression in arterial wall after balloon angioplasty correlates with late stages of neointima formation and coincidently, with the peak in proliferation and differentiation of vascular cells. High expression of T-cadherin in adventitial *vasa vasorum* of injured arteries suggests that it is involved in the regulation of angiogenesis after vessel injury [22]. These data implicate T-cadherin to be a regulator of vascular functioning and remodeling.

In the chick embryo T-cadherin functions as a "repulsive molecule." Its expression in the caudal part of the sclerotome guides migration of a neural crest cells via rostral somites, which do not contain T-cadherin. Thus, in nervous system it suppresses axon growth and migration through tissues expressing T-cadherin [2, 3]. It is well known that there is a strong coordination between vascular and nervous system in embryogenesis, major vessels and peripheral nerves frequently align, and the same guiding molecules participate in neuronal and vascular growth and development. In contrast to nervous system, still little is known about molecular mechanisms of the vessel growth guidance. For example, Notch and ephrin-Eph signaling, which are important for differentiation and patterning of nervous system, also seems to be required for proper arterial-venous morphogenesis. Vascular endothelial growth factor (VEGF), a crucial factor for proliferation, differentiation and survival of endothelial cells, promotes glial cell survival and proliferation and axon outgrowth [49]. The dual involvement in nervous and vascular development has been shown for semaphorins and their plexin and neurophilin receptors, neutrins and their DCC/neogenin and their Unc5 receptors, slit ligands and their roundabout (Robo) receptors, and for some other proteins [49].

The mechanism of negative T-cadherin neuron guidance involves homophilic interaction followed by repulsion. These data suggest similar mechanism for the regulation of the blood vessel growth. Indeed, our recent studies have revealed that the growth of blood vessels is decreased in tissues, which abundantly express T-cadherin [50]. Inhibition of angiogenesis is associated with suppressed migration of T-cadherin-bearing endothelial cells. It is likely that T-cadherin mediates the integrity of vessel wall, inhibiting blood vessel growing into T-cadherin positive sites, as well as the migration of T-cadherin-bearing cells into vascular wall.

Taken together, these data suggest that T-cadherin in vascular cells functions as a GPI-anchored membrane receptor, activating Ca^{2+}- and small GTPase-dependent intracellular signaling cascades (Fig. 3). This in turn can lead to changes of vascular cell phenotype and migrating ability, implicating T-cadherin to the regulation of blood vessel remodeling and angiogenesis.

REFERENCES

1. Tkachuk, V.A., Bochkov, V.N., Philippova, M.P., Stambolsky, D.V., Kuzmenko, E.S., Sidorova, M.V., Molokoedov, A.S., Spirov, V.G., and Resink, T.J., Identification of an atypical lipoprotein-binding protein from human aortic smooth muscle as T-cadherin, *FEBS Lett.*, 1998, vol. 421, pp. 208–212.
2. Fredette, B.J. and Ranscht, B., T-cadherin expression delineates specific regions of the developing motor axon-hindlimb projection pathway, *J. Neurosci.*, 1994, vol. 14, no. 12, pp. 7331–7346.
3. Fredette, B.J., Miller, J., and Ranscht, B., Inhibition of motor axon growth by T-cadherin substrata, *Development*, 1996, vol. 122(10), pp. 3163–3171.
4. Perez-Moreno, M., Jamora, C., and Fuchs, E., Sticky business: orchestrating cellular signals at adherens junctions, *Cell*, 2003, vol. 112, pp. 535–548.
5. Angst, B.D., Marcozzi, C., and Magee, A.I., The cadherin superfamily: diversity in form and function, *J. Cell. Sci.*, 2001, vol. 114, pp. 629–641.
6. Ivanov, D.B., Philippova, M.P., and Tkachuk, V.A., Structure and functions of classical cadherins, *Biochemistry*, 2001, vol. 66, no. 10, pp. 1174–1186.
7. Yap, A.S. and Kovacs, E.M., Direct cadherin-activated cell signaling: a view from the plasma membrane, *J. Cell. Biol.*, 2003, vol. 160, pp. 11–16.
8. Ranscht, B. and Dours-Zimmermann, M.T., T-cadherin, a novel cadherin cell adhesion molecule in the nervous system lacks the conserved cytoplasmic region, *Neuron,* 1991, vol. 7, no. 3, pp. 391–402.
9. Philippova, M, Ivanov, D., Tkachuk, VA, Erne, P., and Resink, TJ., Polarization of T-cadherin to the leading edge of migrating vascular cells *in vitro*: a function in vascular cell motility, *Histochem. Cell Biol.*, 2003, vol. 120, pp. 353–360.
10. Sacristan, M.P., Vestal, D.J., Dours-Zimmermann, M.T., and Ranscht, B., T-cadherin 2: molecular characterization, function in cell adhesion, and coexpression with T-cadherin and N-cadherin, *J. Neuosci. Res.*, 1993, vol. 34, no. 6, pp. 664–680.
11. Koller, E. and Ranscht, B., Differential targeting of T- and N-cadherin in polarized epithelial cells, *J. Biol. Chem.*, 1996, vol. 271, pp. 30061–30067.
12. Goubaeva, F., Giardina, S., Yiu, K., Parfyonova, Ye., and Tkachuk, V.A., T-cadherin GPI-anchor is insufficient for apical targeting in MDCK cell, *Biochem. Biophys. Res. Comm.*, 2005, vol. 329, no. 2, pp. 624–631.
13. Ivanov D., Philippova, M., Tkachuk, V., Erne, P., and Resink, T., Cell adhesion molecule T-cadherin regulates vascular cell adhesion, phenotype and motility, *Exp. Cell Res.*, 2004, vol. 293, pp. 207–218.
14. Doyle, D.D., Goings, G.E., Upshaw-Earley, J., Page, E., Ranscht, B., and Palfrey, H.C., T-cadherin is a major glycophosphoinositol-anchored protein associated with noncaveolar detergent-insoluble domains of the cardiac sarcolemma, *J. Biol. Chem.*, 1998, vol. 273, no. 12, pp. 6937–6943.

15. Philippova, M.P., Bochkov, V.N., Stambolsky, D.V., Tkachuk, V.A., and Resink, T., T-cadherin and signal-transducing molecules co-localize in caveolin-rich membrane domain of vascular smooth muscle cells, *FEBS Lett.*, 1998, vol. 129, pp. 201–210.
16. Smirnov, V.N., Voyno-Yasenetskaya, T.A., Antonov, A.S., Lukashev, M.E., Shirinsky, V.P., Tertov, V.V., and Tkachuk, V.A., Vascular signal transduction and atherosclerosis, *Ann. N.Y. Acad. Sci.*, 1990, vol. 598, pp. 167–181.
17. Block, L.H, Knorr, M., Vogt, E., Locher, R., Vetter, W., Groscurth, P., Qiao, B.Y., Pometta, D., James, R., Regenass, M., et al., Low density lipoprotein causes general cellular activation with increased phosphatidylinositol turnover and lipoprotein catabolism, *Proc. Natl. Acad. Sci. USA*, 1988, vol. 85, no. 3, pp. 885–889.
18. Bochkov, V.N, Tkachuk, V.A., Hahn, A.W., Bernhardt, J., Buhler, F.R., and Resink, T.J., Concerted effects of lipoproteins and angiotensin II on signal transduction processes in vascular smooth muscle cells, *Arterioscler. Thromb.,* 1993, vol. 13, no. 9, pp. 1261–1269.
19. Bochkov, V., Tkachuk, V., Buhler, F., and Resink, T., Phosphoinositide and calcium signalling responses in smooth muscle cells: comparison between lipoproteins, Ang II, and PDGF, *Biochem. Biophys. Res. Commun.,* 1992, vol.188, no. 3, pp. 1295–1304.
20. Rubina, K., Talovskaya, E., Cherenkov, V., Ivanov, D., Stambolsky, D., Storozhevykh, T., Pinelis, V., Shevelev, A., Parfyonova, Ye., Resink, T., Erne, P., and Tkachuk, V., LDL induces intracellular signaling via atypical LDL-binding protein T-cadherin, *Mol. Cell. Biochem.*, 2005, vol. 273, pp. 33–41.
21. Kipmen-Korgun, D., Osibow, K., Zoratti, C., Schraml, E., Greilberger, J., Kostner, G.M., Jurgens, G., and Graier, W.F., T-cadherin mediates low-density lipoprotein-initiated cell proliferation via the Ca^{2+}-tyrosine kinase-Erk1/2 pathway, *J. Cardiovasc. Pharmacol.*, 2005, vol. 45, no. 5, pp. 418–430.
22. Kudrjashova, E., Bashtrikov, P., Bochkov, V., Parfyonova, Y., Tkachuk, V., Antropova, J., Iljinskaya, O., Tararak, E., Erne, P., Ivanov, D., Philippova, M., and Resink, T.J., Expression of adhesion molecule T-cadherin is increased during neointima formation in experimental restenosis, *Histochem. Cell. Biol.*, 2002, vol. 118, pp. 281–290.
23. Berridge, M.J., Bootman, M.D., and Roderick, H.L., Calcium signaling: Dynamics, homeostasis, and remodeling, *Nat. Rev Mol. Cell. Biol.*, 2003, vol. 4, pp. 517–529.
24. Philippova, M., Ivanov, D., Allenspach, R., Takuwa, Y., Erne, P., and Resink, T., RhoA and Rac mediate endothelial cell polarization and detachment induced by T-cadherin, *FASEB J.*, 2005, vol. 19, pp. 588–590.
25. Resink, T.J., Kuzmenko, Y.S., Kern, F, Stambosly, D., Bochkov, V.N., Tkachuk, V.A., Erne, P., and Niermann, T., LDL binds to surface expressed human T-cadherin in transfected HEK293 cells and influences homophilic adhesive interactions, *FEBS Lett.*, 1999, vol. 463, pp. 29–34.
26. Vestal, D.J. and Ranscht, B., Glycosyl phosphatidylinositol-anchored T-cadherin mediates calcium-dependent, homophilic cell adhesion, *J. Cell. Biol.*, 1992, vol. 119, pp. 451–461.
27. Hug, C., Wang, J., Ahmad, N.S., Bogan, J.S., and Tsao, T.-S., T-cadherin is a receptor for hexameric and high-molecular weight forms of Acrp30/adiponectin, *Proc. Natl. Acad. Sci. USA*, 2004, vol. 101, no. 28, pp. 10308–10313.
28. Brakenhielm, E., Veitonmaki, N., Cao, R., Kihara, S., Matsuzawa, Y., Zhivotovsky, B., and Funahashi C.Y., Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis, *Proc. Natl. Acad. Sci. USA*, 2004, vol. 101, no. 8, pp. 2476–2481.
29. Wang, Y., Lam, K.S.L. Xu, J.Y.X., Lu, G., Xu, L.Y., Cooper, G.J.S., and Xu, A., Adiponectin inhibits cell proliferation by interacting with several growth factors in an oligomerization-dependent manner, *J. Biol. Chem.,* 2005, vol. 280, no. 18, pp. 18341–18347.
30. Kobayashi, K., Inoguchi, T., Sonoda, N., Seiguchi, N., and Nawata, H., Adiponectin inhibits the binding of low-density lipoprotein to biglycan, a vascular proteoglycan, *Biochem. Biophys. Res. Commun.*, 2005, vol. 335, no. 1, pp. 66–70.
31. Okamoto, Y., Kihara, S., Ouchi, N., Nishida, M., Arite, Y., Kumada, M., Ohashi, K., Sakai, N., Shimomura, I., Kobayashi, K., Terasaka, N., Inaba, T., Funahashi, T., and Matsuzawa, Y., Adiponectin reduces atherosclerosis in apolipoprotein E-defficient mice, *Circulation*, 2002, vol. 106, pp. 2767–2770.
32. Joshi, M.B., Philippova, M., Ivanov, D., Allenspach, R., Erne, P., and Resink, T.J., T-cadherin protects endothelial cells from oxidative stress-induced apoptosis, *The FASEB J.*, 2005, vol. 19, no. 2, pp. 1737–1739.
33. Kuzmenko, Y.S, Kern, F., Bochkov, V.N., Tkachuk, V.A., and Resink, T.J., Density- and proliferation status-dependent expression of T-cadherin, a novel lipoprotein-binding glycoprotein: a function in negative regulation of smooth muscle cell growth? *FEBS Lett.*, 1998, vol. 434, pp. 183–187.
34. Zhi-Yong, H., Wu, Y., Hedrick, N., and Gutmann, D., T-cadherin mediated cell growth regulation invovles G_2 phase arrest and requires $p21^{CIP1/WAF1}$ expression, *Mol. Cell. Biol.*, 2003, vol. 23, no. 2, pp. 566–578.
35. Zhong, Y., Lopez Barcons, L., Haigentz, M., Ling, Y.H., and Perez-Soler, R., Exogenous expression of H-cadherin in CHO cells regulates contact inhibition of cell growth by inducing p21 expression, *Int. J. Oncol.,* 2004, vol. 24, pp. 1573–1579.
36. Takeuchi, T., Liang, S.-B., and Ohtsuki, Y., Downregulation of expression of a novel cadherin molecule, T-cadherin, in basal cell carcinoma of the skin, *Mol. Cancerogen*, 2000, vol. 35, pp. 173–179.
37. Takeuchi, T. and Ohtsuki, Y., Recent progress in T-cadherin (CDH13, H-cadherin) research, *Histol. Histopathol.*, 2002, vol. 16, pp. 1287–1293.
38. Wyder, L., Vitaliti, A., Schneider, H., Hebbrand, L.W., Moritz, D.R., Wittmer, M., Ajmo, M., and Klemenz, R., Increased expression of H/T-cadherin in tumor-penetrating vessels, *Cancer Res.*, 2000, vol. 60, pp. 4682–4688.
39. Kawakami, M., Staub, J., Clibi, W., Hartmann, L., Smith, D.I., and Shridhar, V., Involvement of H-cadherin (CDH13) on 16q in the region of frequent deletion in ovarian cancer, *Int. J. Oncol.,* 1999, vol. 15, pp. 715–720.

40. Takeuchi, T., Liang, S.-B., Matsuyoshi, N., Zhou, S., Miyachi, Y., Sonobe, H., and Ohtsuki, Y., Loss of T-cadherin CDH13 (H-cadherin) expression in cutaneous squamous cell carcinoma, *Lab. Invest.*, 2002, vol. 82, no. 8, pp. 1023–1029.

41. Hibi, K., Nakayama, H., Kodera, K., Ito, K., Akiyama, S., and Nakao, A., CDH13 promoter region is specifically methylated in poorly differentiated colorectal cancer, *Brit. J. Cancer,* 2004, vol. 90, pp. 1030–1033.

42. Kim, J.S., Han, J., Shim, Y.M., Park, J., and Kim, D.H., Abberant methylation of H-cadherin (CDH13) promoter is associated with tumor progression in primary non-small cell lung carcinoma, *Cancer*, 2005, vol. 104, no. 9, pp. 1825–1833.

43. Sakai, M., Hibi, K., Koshikawa, K., Inoue, S., Takeda, S., Kaneko, T., and Nakao, A., Frequent promoter methylation and gene silencing of CDH13 in pancreatic cancer, *Cancer Sci.*, 2004, vol. 95, no. 7, pp. 588–591.

44. Toyooka, K.O., Toyooka, S., Virmani, A.K., Sathyanarayana, U.G., Euhus, D.M., Gilcrease, M., Minna, J.D., and Gazdar, A.F., Loss of expression and abberant methylation of CDH13 (H-cadherin) gene in breast and lung carcinomas, *Cancer Res.*, 2001, vol. 61, pp. 4556–4560.

45. Cavallaro, U., Leibner, S., and Dejana, E., Endothelial cadherins and tumor angiogenesis, *Exp. Cell. Res.,* 2006, vol. 312, no. 5, pp. 659–667.

46. Lee, S.W., H-cadherin, a novel cadherin with growth inhibitory functions and diminished expression in human breast cancer, *Nat. Med.*, 1996, vol. 2, no. 7, pp. 776–782.

47. Adachi, Y., Takeuchi, T., Sonobe, H., and Ohtsuki, Y., An adiponectin receptor, T-cadherin, was selectively expressed in intratumoral capillary endothelial cells in hepatocellular carcinoma: possible cross talk between T-cadherin and FGF-2 pathways, *Virchows Arch.*, 2005, vol. 5, pp. 1–8.

48. Ivanov, D., Philippova, M., Antropova, J., Gubaeva, F., Iljinskaya, O., Tararak, E., Bochkov, V., Erne, P., Resink, T., and Tkachuk, V., Expression of cell adhesion molecule T-cadherin in the human vasculature, *Histochem. Cell. Biol.*, 2001, vol. 115, pp. 231–242.

49. Weinstein B.M. Vessels and nerves: marching to the same tune, *Cell*, 2005, vol. 120, pp. 299–302.

50. Rubina, K.A., Kalinina, N.I., Efimenko, A.Y., Potekhina, A.V., Talovskaya, E.V., Parfyonova, Y.V., and Tkachuk, V.A., T-cadherin suppresses angiogenesis *in vivo* by inhibiting migration of endothelial cells, *Circ. Res.*, 2007 (in press).