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Review

Recent progress in T-cadherin (CDH13, H-cadherin) research

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Summary. T-cadherin is a unique cadherin cell adhesion molecule that is anchored to the cell surface membrane through a glycosyl phosphatidyl inositol (GPI) moiety. The cytoplasmic domain, which T-cadherin lacks, is believed to be critical for homophilic binding through interaction with submembrane cytoskeletal proteins. Does this mean that T-cadherin is an unimportant molecule? However, the T-cadherin amino acid motif has been well conserved through evolution in vertebrates, suggesting that T-cadherin may have biological significance in higher animals. Consistent with this hypothesis, recent studies have thrown light on the relevance of T-cadherin in the fields of oncology, neurology, respirology and cardiovascular physiology. In this manuscript, we review current advances in T-cadherin research.

Key words: T-cadherin, Cancer, Angiogenesis, Neuron, Alveolar proteinosis

Nomenclature

T-cadherin was first identified in chicken as a unique glycosyl phosphatidyl inositol (GPI)-linked membrane cadherin (Ranscht and Dours-Zimmermann, 1991). Human CDH13, cadherin13, was subsequently reported by Tanihara et al. (1994). Independently, Lee (1996) identified a candidate gene, expression of which is altered in human breast cancer. This candidate gene, which was strongly expressed in heart, was termed H-cadherin and appeared to be identical to CDH13. As shown in Table 1, molecular homology between these species clearly indicated that CDH13 (H-cadherin) is a human homologue of chicken T-cadherin. The cadherins have been divided into more than 10 subclasses, depending on their tissue distribution; these include E- (epithelial), N- (neuronal) and P- (placental) cadherins. Although the classical cadherins were designated by the tissue or organ in which they are strongly exppressed, it seems reasonable to use "T-cadherin" instead of CDH13 or H-cadherin given the history outlined above.

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Molecular structure of T-cadherin

Classical cadherins are composed of a highly conserved cytoplasmic domain of approximately 160 amino acids, a single transmembrane domain, and a large extracellular portion that is organized in a series of five structurally-related tandem repeats (Ranscht, 1994). The conserved intracellular domain of classical cadherins is believed to bind to a group of cytoplasmic proteins, termed catenins, which serve as a link between cadherins and the cytoskeleton (Nagafuchi and Takeichi, 1988; Ozawa et al., 1989). T-cadherin has a strikingly diverse structure, as illustrated in Figure 1. T-cadherin has five tandem repeats in its extracellular portion; however, it is attached to the plasma membrane through a GPI anchor without a cytoplasmic domain (Ranscht and Dours-Zimmermann, 1991; Tanihara et al., 1994; Lee, 1996). HPT-1, Ksp-cadherin, and LI-cadherin also each have a short cytoplasmic domain that consists of only about 20 amino acids exhibiting no homology with this highly conserved region of classical cadherins (Berndorff et al., 1994; Dantzig et al., 1994; Thomson et al., 1995). Although LI-cadherin lacks a typical cytoplasmic domain which induces reorganization of the actin cytoskeleton, LI-cadherin was still able to mediate Ca^{2+}- dependent cell-cell adhesion. A recent study further revealed that an artificially constructed GPI-anchored form of LI-cadherin still can induce Ca^{2+}-dependent, homophilic cell-cell adhesion in transfected cells (Kreft et al., 1997). T-cadherin also induced homophilic adhesion between transfected cells (Vestal and Ranscht, 1992). These findings indicated that a cytoplasmic domain may not be necessary for homophilic binding of several cadherin molecules.

T-cadherin homology among species

Human, gorilla, mouse, chicken, frog, and zebrafish T-cadherin cDNAs including partial sequences have

been cloned. As shown in Table 1, the T-cadherin molecule is highly conserved between these species. The degree of identity of it among is much higher than for E-cadherin. This suggests that the T-cadherin amino acid motif has been well conserved through evolution in vertebrates. The availability of the euchromatic genomic sequences of *Drosophila melanogaster* (Adams et al., 2000; Rubin et al., 2000) makes it possible to examine how cadherin molecules developed through evolution. Hynes and Zhao (2000) described the cadherin superfamily in *D. melanogaster*. Three cadherins of *D. melanogaster* exhibit homology with the catenin-binding cytoplasmic domains of vertebrate cadherins. These three molecules may have developed into classical vertebrate cadherins through evolution. However, no T-cadherin homologue, or GPI-anchored cadherin, has been found in *D. melanogaster*. It is thus likely that T-cadherins newly developed in vertebrates. The high degree of homology among T-cadherins in vertebrates suggests that these molecules play critical roles in biological processes of higher animals.

Distribution of T-cadherin molecule in various human tissues and cells

Lee (1996), using Northern blotting, found that T-cadherin is highly expressed in human heart, expressed to a lesser extent in brain, lung, muscle and kidney, and hardly detectable in the pancreas and liver. We also examined T-cadherin expression in developing and adult human brain by Northern blotting, in situ hybridization, and immunohistochemical staining (Takeuchi et al., 2000a). T-cadherin was expressed in neural cell surface membrane and neurites in adult cerebral cortex, medulla, oblongata, and nucleus olivaris. Interestingly, T-cadherin was less expressed in developing brain and adult spinal cord. In lung tissue, T-cadherin molecule was expressed not only in the pulmonary vasculature but also in bronchioloalveolar type II cells (Takeuchi et al., 2001). Very recently, T-cadherin expression in the human vasculature was reported (Ivanov et al., 2001). Ivanov et al. found that T-cadherin is present in both the aortic intima and media and was expressed in endothelial cells, smooth muscle cells, and pericytes. In the adventitia, T-cadherin is present in the walls of the vasa vasorum. Lee (1996) reported that T-cadherin is predominatly expressed in normal cells, but not in the majority of human cancer cells. He detected T-cadherin mRNA expression in two human oseteosarcoma cell lines, HOS and SaOS cells, but not in other cancer cell lines examined. Sato et al. (1998b) examined T-cadherin expression in human lung cancer cell lines and found that 3 out of 7 lung cancer cell lines expressed T-cadherin. We also examined T-cadherin mRNA expression in various human cultured cells, and found that most osteosarcoma cell lines strongly expressed T-cadherin. Most cultured sarcoma cell lines, including those from patients with rhabdomyosarcoma, or leiomyosarcoma but not neuroblastoma, expressed T-cadherin mRNA (unpublished data). In conclusion, this broad expression in various human tissues and cells suggests that T-cadherin may play multiple roles in biological processes, since it seems unlikely that T-cadherin plays only a single role in these polymorphorous cell types.

Table 1. Homology of T-cadherin and E-cadherin in various species. Deduced amino acid sequence of cadherins of various species was compared with human cadherins.

	T-CADHERIN	E-CADHERIN	N-CADHERIN	P-CADHERIN
Human	100%	100%	100%	100%
Mouse	92%	69%	84%	74%
Chicken	74%	62%	77%	58%
Zebrafish	74%	51%	68%	not found

T-cadherin in cancer research

T-cadherin as a tumor suppressor factor

As shown in Table 2, T-cadherin has been mapped to human chromosome 16q24, for which loss of heterozygosity in patients with sporadic breast, prostate, liver, ovary and lung cancer has been reported (Carter et al., 1990; Tsuda et al., 1990; Sato et al., 1991, 1998a; Tsuda et al., 1994). Lee (1996) first mapped the T-cadherin (H-cadherin) gene to16q24 by FISH, and reported that T-cadherin acts as a tumor suppressor factor in breast cancer. Miki et al. (1997) examined 48 primary breast cancers in which loss of 16q24 had been detected. They found no mutaions other than in a single

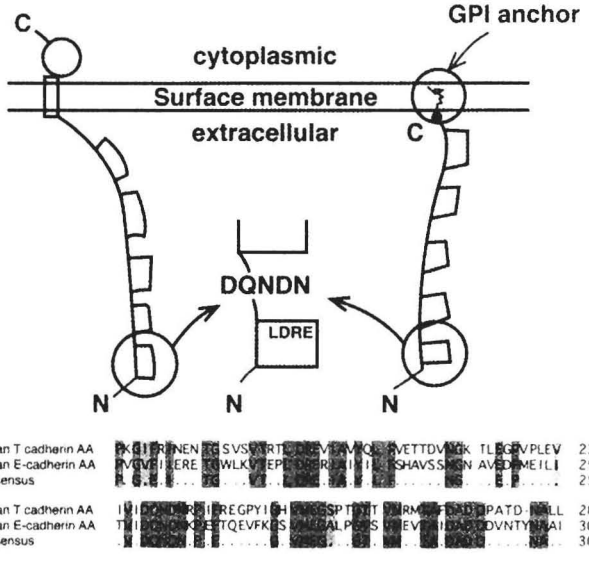

Fig. 1. Protein structures of E-cadherin (left) and T-cadherin (right) are schematically shown. Five cadherin repeats are indicated by the box. Homology of the first cadherin repeat is representatively aligned. The LDRE cluster and the putative calcium-binding site, DQNDN, characteristic of cadherin cell-adhesion molecules, are well conserved.

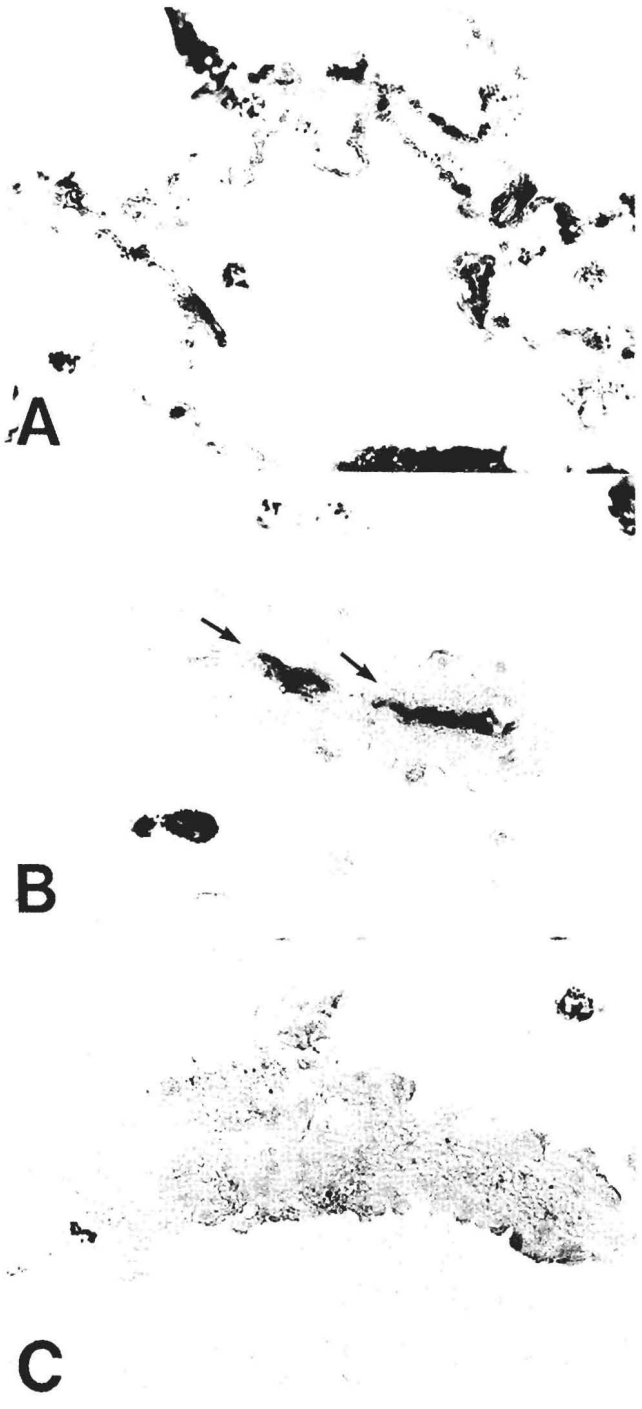

Fig. 2. *In situ* hybridization with human T-cadherin antisense cRNA probe. Bronchioloalveolar cells exhibit positive signals in non-cancerous regions of lung tissues from a patient with primary bronchioloalveolar carcinoma **(A)**. In contrast, adenocarcinoma cells from the same patient demonstrate lack of staining whereas, tumor endothium exhibited staining (arrow, **B**). No significant reactivity is observed with sense cRNA probe **(C)**. The procedure used, including the generation of cRNA probes, was previously described in detail (Takeuchi et al. 2000a). A, x 200; B, x 400; C, x 400

breast cancer; however, they also reported that T-cadherin mRNA expression was reduced in 5 out of 10 breast cancers compared with that in normal mammary epithelial cells. They suggested that the decreased expression of T-cadherin in breast cancers is probably caused by repression of transcription and/or translation of T-cadherin. Subsequently, Sato et al. (1998b) found that the T-cadherin gene was inactivated in a considerable number of human lung cancer specimens. They reported that hypermethylation related to inactivation of the T-cadherin molecule was found in 45% of primary lung cancers. Methylation of DNA is an epigenetic modification that can play an important role in the control of gene expression in mammalian cells. The presence of hyper-methylated CpG islands in the promoter region of various genes can suppress their expression and is involved in tumorigenesis (Jones, 1996). Recently, we confirmed by in situ hybridization technique that T-cadherin mRNA level was significantly reduced in a considerable number of lung cancer specimens (Fig. 2). To address the question as to whether T-cadherin expression in lung cancers correlated with histological classification or metastatic activity, we immunostained primary lung cancer specimens and found that lack of T-cadherin expression was neither related to histopathological classification nor metastasis to lymph nodes. Specifically, 57% (16 out of 28 cases) and 50% (19 out of 38 cases) of squamous cell carcinoma and adnocarcinoma specimens, respectively, did not express T-cadherin. Respectively, 12 out of 25 and 15 out of 27 lung cancer specimens with and without lymph node metastasis expressed T-cadherin (unpublished data). In contrast, T-cadherin expression in osteosarcoma cells appears to be correlated with lung metastasis, as determined by immunohistochemical staining (Takeuchi et al., 2000b). In a study of ovarian cancer, Kawakami et al. (1999) reported that loss of heterozygosity (LOH) in the *T-cadherin* gene region was observed in 6 of 17 specimens examined. They also reported that hypermethylation of the T-cadherin gene was observed in 4 out of 6 ovarian tumors. No reports are available describing the involvement of T-cadherin in hepatocellular carcinoma or prostatic cancer. Recently, we examined whether noncancerous human hepatocytes or prostatic gland expressed *T-cadherin*. Preliminary immunohistochemical staining demonstrated that neither noncancerous hepatocytes nor prostatic gland cells expressed T-cadherin.

Table 2. Location of various cadherins in a short arm of human chromosome 16.

CDH 8	16q22.1
CDH11	16q22.1
VE-cadherin (CDH5)	16q22.1
E-cadherin (CDH1)	16q22.1
P-cadherin (CDH3)	16q22
T-cadherin (CDH13/H-cadherin)	16q24.2-24.3
M-cadherin (CDH15)	16q24.3

Lack of staining of hyperplastic prostatic glands with T-cadherin antibody is demonstrated in Figure 3. Moreover, several prostatic carcinoma specimens were not stained with anti-T-cadherin antibody. It is thus unlikely that T-cadherin acts as a tumor suppressor factor in either hepatocellular carcinoma or prostatic carcinoma.

In summary, it is possible that T-cadherin acts as a tumor suppressor factor in breast, lung, and ovarian cancers. Hypermethylation of CpG islands in the promoter region may decrease T-cadherin expression and affect the tumorigenicity of these cancers.

T-cadherin is overexpressed in tumor endothelium

Recent advances in targeting therapy against tumor neovascularization have highlighted a molecule which was selectively expressed in tumor endothelial cells but

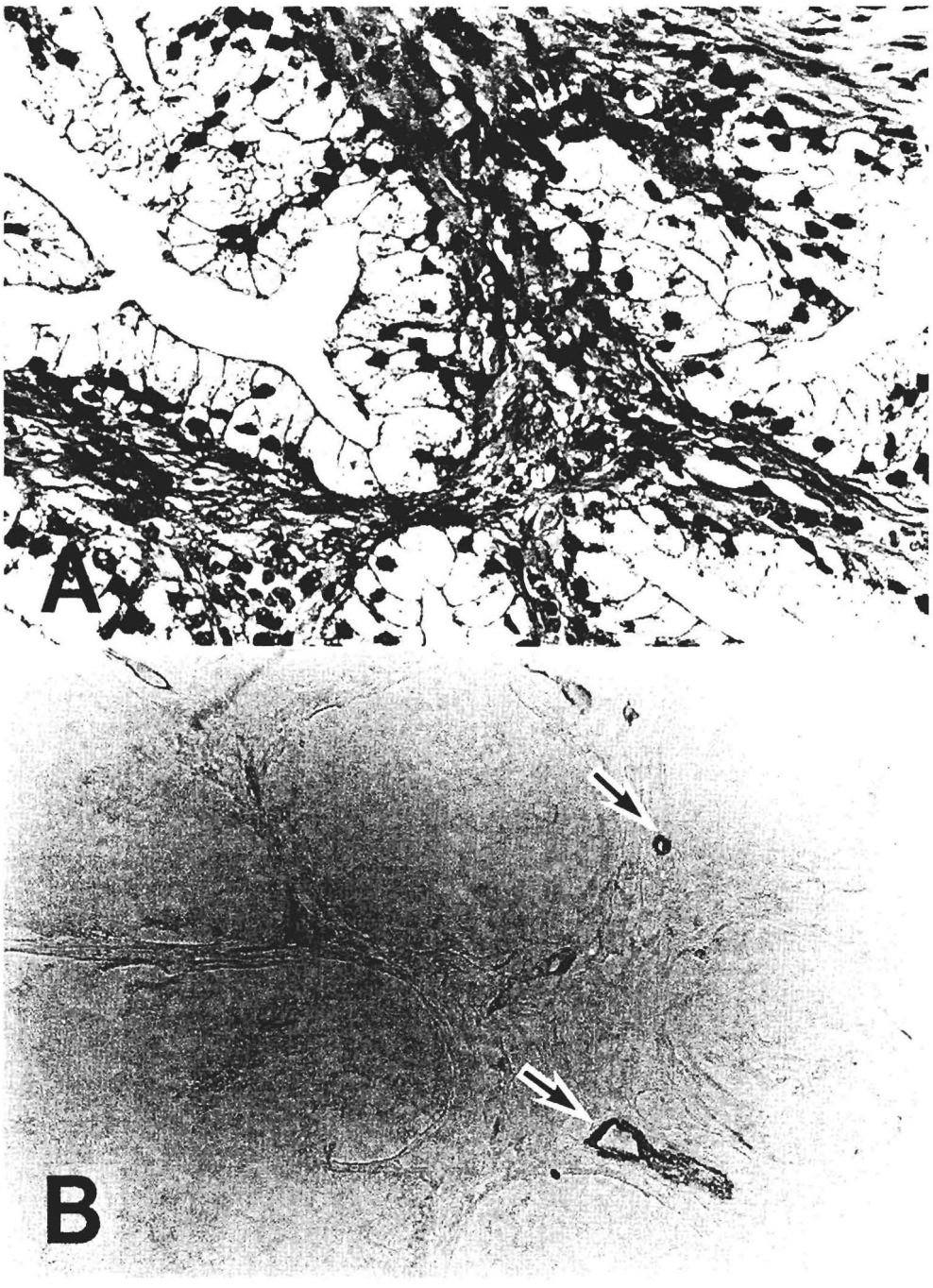

Fig. 3. Immunohistochemical staining of nodular hyperplastic prostatic glands with affinity-purified rabbit antibody to human T-cadherin peptide **(B)**. Generation and characterization of antibody was described previously (Takeuchi et al. 2000a). Note the lack of staining in prostatic glands but endothelial cells in small vessels are strongly stained with anti-T-cadherin antibody (**B**, arrow). Hematoxylin-eosin (HE) staining is shown in **A**. A,

barely found in intact vascular endothelial cells (Schlingemann et al., 1991; Folkman, 1992; Burrows and Thorpe, 1994). Wyder and Klemenz et al. (2000) first reported that T-cadherin was overexpressed in murine tumor penetrating blood vessels. They used the substractive hybridization method to identify proteins that are specifically expressed on the surface of endothelial cells in tumors and successfully isolated T-cadherin cDNAs from tumor vessels of murine Lewis lung carcinoma lung metastases. They reported that T-cadherin was ubiquitously expressed on endothelial cells in several, but not all, transplanted tumors examined. Murine T-cadherin was expressed in only a subset of vessels within certain organs such as lung, liver, spleen, brain, heart, and kidney. Very recently, we also observed that human T-cadherin was overexpressed in tumor sinusoidal endothelial cells in hepatocellular carcinoma (manuscript in preparation). Studies to determine whether T-cadherin is a good candidate for antiangiogenic therapy are now in progress.

T-cadherin in vasculocirculology

Recent studies have revealed that T-cadherin may play a significant role in angiogenesis. Tkachuk et al. (1998) identified T-cadherin as an atypical lipoprotein-binding protein in membranes of vascular smooth muscle cells that is distinct from currently known lipoprotein receptors. Subsequently, Kuzmenko et al. (1998) characterized T-cadherin as a negative regulator in rat aortic smooth muscle cells. In a series of experiments, Resink et al. obtained results suggesting that low-density lipoprotein is a physiologically relevant ligand for T-cadherin and GPI moiety of T-cadherin is necessary and sufficient for mediation of lipoprotein binding (Resink et al., 1999; Stambolsky et al., 1999; Niermann et al., 2000). Hyperlipidemia inhibits proliferation of endothelial cells in culture and angiogenesis in vivo and in arterial explants (Chen et al., 2000). These findings, together with the finding that T-cadherin is overexpressed in tumor vessels, suggest that T-cadherin may be a positive regulator of angiogenesis. It is likely that T-cadherin adsorbs lipoprotein and that it is involved in angiogenesis.

T-cadherin in neurology

T-cadherin was first cloned from chick embryo brain. Fredette et al. (1996) reported that T-cadherin is a negative guidance cue for motor axon projections. We also reported that T-cadherin acts as a negative growth regulator of epidermal growth factor in human neuroblastoma cells (Takeuchi et al., 2000a). Notably, T-cadherin expression in developing brain is much weaker than in adult brain. These findings indicate that T-cadherin is a negative growth regulator of neural growth. However, it must be recalled that the effect of a molecule on neural growth or development always depends on the experimental conditions used. For example, myelin-associated glycoprotein promotes neurite growth in one set of culture conditions, and inhibits neurite outgrowth in other conditions. (McKerracher et al., 1994: Matsuda et al., 1996) N-cadherin can stimulate migratory processes such as axonal growth and cell migration (Doherty and Walsh, 1996). Notably, T-cadherin exhibits a homology with N-cadherin (deduced amino acid homology of approximately 43%). Further studies including generation of gene-targeting mice are needed to determine that T-cadherin represses neural growth *in vivo*.

T-cadherin in respiratory sciences

Recently, we found that T cadherin could regulate surfactant protein (SP)-D gene expression in human bronchioloalveolar type-II cells (Takeuchi et al., 2001). We transfected T-cadherin expression vector into A549 cells. Cultured A549 cells with alveolar type-II cell characteristics lacked T-cadherin; however, human alveolar type-II cells were found to express T-cadherin on immunohistochemical staining. Interestingly, A549 cells transfected with expression vector containing T-cadherin cDNA lost production of surfactant protein SP-D. (As expected the transfected A549 cells expressed T-cadherin). In contrast, original and control vector-trasfected A549 cells produced SP-D. SP-D is a member of the family of collagenous host defense lectins, designated collectins (Crouch et al., 2000). SP-D is believed to be an important component of the innate immune response to microbial challenge (Clements et al., 1998). We found that alveolar type-II cells in proteinosis specimens lacked T-cadherin expression. Pulmonary alveolar proteinosis is a chronic intersititial pneumonia with filling of alveoli by dense, granular, eosinophilic material. Recent studies have implicated granulocyte-macrophage colony-stimulating factor (GM-CSF) in the pathogenesis of human pulmonary alveolar

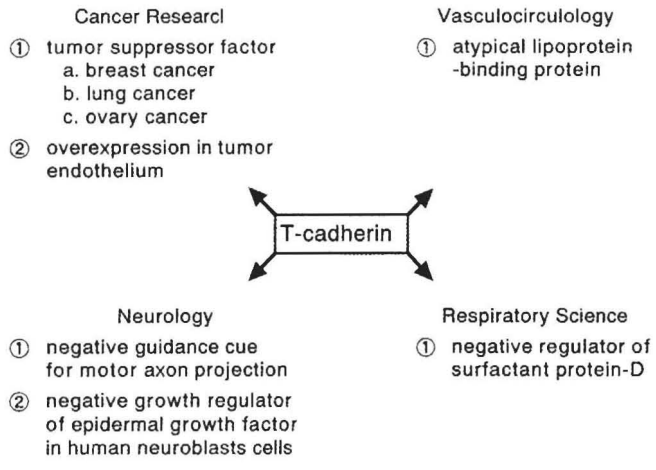

Fig. 4. Expanding world of T-cadherin research.

proteinosis (Dranoff et al., 1994; Huffman et al., 1996; Reed and Whitsett, 1998). Therefore, downregulation of T-cadherin may not be a primary event in the pathogenesis of alveolar proteinosis, but may be correlated with SP-D overexpression in alveolar type-II cells. High levels of SP-D in bronchoalveolar lavage fluid of patients with pulmonary alveolar proteinosis has been reported (Kuroki et al., 1998). In summary, T-cadherin may regulate surfactant protein production in bronchioalveolar cells.

Concluding comments

Cadherin molecules have long been thought to be simple sticky molecules. However, in recent years cadherins have emerged as a growing superfamily of molecules. T-cadherin has an interesting structure, and has recently attracted many researchers in various biologies and pathologies as summarized in Fig. 4. As described in this review, T-cadherin may participate in many biological processes in various tissues, including intercellular adhesion, cell communication, morphogenesis, angiogenesis, tumorigenicity, and even regulation of surfactant protein production.

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