—Review—

Multiple Functions of Cell Adhesion Molecule 1 (CADM1) and Its Role in the Pathogenesis of Cancer and Other Diseases

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Cell adhesion molecule 1 (CADM1) is an immunoglobulin superfamily cell adhesion molecule that was first identified as a tumor suppressor in non-small cell lung cancer because of its role in suppressing tumor formation in nude mice. CADM1 forms a homophilic dimer on the cell membrane and associates with actin-binding proteins (4.1s) and scaffold proteins (MAGuKs), which contain PDZ motifs. It forms a ternary protein complex involved in cell adhesion and the formation of epithelium-like structure. While CADM1 is expressed in epithelium, neuronal tissue, and testes, CADM1 expression is absent in many cancers of epithelial origin, including cancers of the lung, esophagus, stomach, liver, pancreas, breast, and prostate. In addition to its tumor-suppressive activity in epithelial cell adhesion, CADM1 acts as a tumor antigen, recognized by activated NK cells and CD8+ T cells through heterophilic interaction with CRTAM, thereby serving as a tumor suppressor in two ways. In contrast, CADM1 is overexpressed in adult T-cell leukemia/lymphoma (ATL) cells, making it a specific diagnostic marker of ATL on FACS analysis. CADM1 is also highly expressed in small cell lung cancer (SCLC) and other neuroendocrine tumors, and promotes metastasis, suggesting its potential as a target for diagnosis and treatment of SCLC. CADM1 also has a role in synapse formation and spermatogenesis, and deficient or abnormal CADM1 is linked to disorders such as male infertility in mice and autism spectrum disorder. Here, we summarize the multiple functions of CADM1 and its involvement in cancer and other diseases, focusing on disorders of aberrant cell adhesion. (J Nippon Med Sch 2025; 92: 122–131)

Key words: CADM1, immunoglobulin superfamily cell adhesion molecule (IgCAM), small cell lung cancer, tumor immunity, tumor suppressor gene

Using a Cell Adhesion Molecule, CADM1, as a Tumor Suppressor

Cell adhesion molecule 1 (CADM1) is a tumor suppressor gene that was identified by its suppressor activity in tumor formation in nude mice when a fragment of chromosome 11q23 was introduced into lung adenocarcinoma cells, which often exhibit loss of heterozygosity[1–3]. CADM1 is a cell adhesion molecule in the immunoglobulin superfamily (IgSF) and is highly expressed in epithelium, neuronal tissues, and testes. In contrast, its expression is often absent or decreased because of chromosomal loss or gene promoter methylation in non-small cell lung cancer (NSCLC) and other cancers, including esophageal, gastric, hepatic, pancreatic, breast, and prostate cancers[4]. In normal lung epithelium, CADM1 forms a homodimer and is expressed on the lateral membrane. It binds to CADM1 homodimers in adjacent cells through its three extracellular Ig loops, particularly the N-terminal loop[5]. The intracellular domain, relatively small at 46 amino acids, binds to 4.1 group proteins and MAGuK proteins through the 4.1-binding motif and PDZ-binding motif, respectively (**Fig. 1**)[6,7]. The 4.1 proteins, including 4.1B, 4.1 N, 4.1 G, and 4.1R, bind to actin and help organize the cytoskeleton, while MAGuKs are scaffold proteins with a

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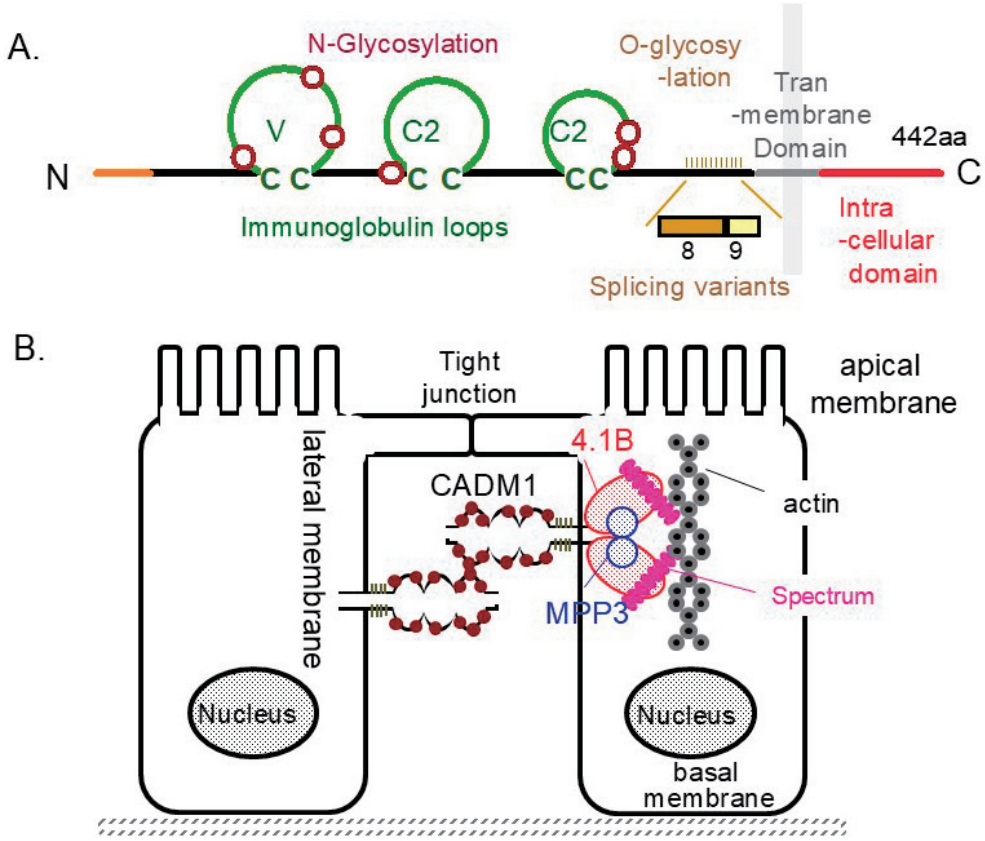

Fig. 1 Predicted structure of CADM1 protein (A) and its cascade in epithelium (B).

PDZ domain. In epithelium, MPP1, MPP2, MPP3, and CASK bind to CADM1 to form epithelium-like structures. CADM1, 4.1 proteins, and MAGuKs form a ternary protein complex beneath the cell membrane, contributing to epithelial structure and tumor suppression[8]. Similar to CADM1, expression of 4.1 proteins and MAGuKs is frequently diminished in some cancers[3,9,10]. When CADM1 expression is downregulated by siRNA in cultured cells, epithelial morphology is drastically compromised, indicating that the CADM1 complex is crucial for maintaining epithelial cell structure. Its loss leads to malignant cancer through disruption of this structure[10].

Another mechanism of tumor suppression by CADM1 involves its interference with growth factor signaling through associations with growth factor receptors on the cell membrane. CADM1 has been shown to suppress the epithelial-mesenchymal transition *in vitro*, induced by hepatocyte growth factor (HGF) in MDCK canine kidney cells, helping to maintain epithelial-like morphology[11]. This suppression of the HGF-MET pathway appears to result from formation of a CADM1-MET protein complex on the cell membrane. Similarly, CADM1 binds to ErbB3 to inhibit the EGFR pathway[12] or associates with Csk-binding protein, an SRC activator, in lipid rafts on the cell membrane to suppress SRC activity[13]. The formation of these complexes between CADM1 and growth factor receptors is a unique tumor suppression mechanism that is distinct from its role in cell adhesion (**Fig. 2A, B, C**). CADM1 homologues such as CADM2, CADM3, and CADM4 often exhibit similar activity by binding to 4.1 and MAGuK family proteins, thus functioning as organ-specific tumor suppressor genes[14–16].

Consistent with these findings, no CADM1 expression was observed in various advanced cancers[3,17], making it a potential marker of malignant progression. Additionally, CADM1 expression is sometimes absent in precancerous lesions, including late-stage pancreatic intraepithelial neoplasia[18] and late-stage cervical intraepithelial neoplasia[19,20], and in multi-stage carcinogenesis in the pancreas and uterine cervix. In the latter, absence of CADM1 expression in cervical smear specimens is an established diagnostic marker that is useful for early detection of cervical cancer (**Table 1**).

Tumor Suppressor Activity of CADM1 by Involvement in Immunological Surveillance

Most IgSF molecules bind to identical or other IgSF members, and some act as receptors and ligands for im-

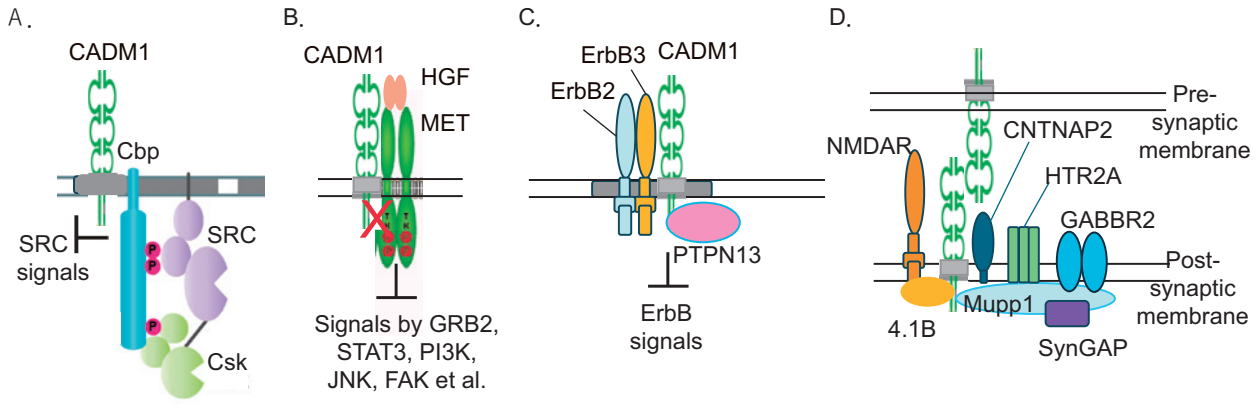

Fig. 2 Intervention of growth factor signals by CADM1 through associating with growth factor receptors within the lipid raft on the cell membrane in epithelium and synapses. A. Suppression of SRC signaling by binding with CSK-binding protein. B. Suppression of HGF-MET signaling by associating with MET. C. Suppression of ErbB3 signaling by recruiting a phosphatase, PTPN13. D. Complex formation of CADM1 with NMDAR through 4.1B or with GARBBR2 through Muppl at the post-synaptic membrane.

Table 1 Promoter methylation of the *CADM1* gene in primary cancer and precancerous lesions*

Tumor	Promoter methylation (%)
Primary tumors	
Non-small cell lung cancer	21/48 (44)
Nasopharyngeal cancer	13/38 (43)
Esophageal cancer	28/56 (50) *
Gastric cancer	15/97 (16)
Hepatocellular carcinoma	4/14 (29)
Pancreatic cancer	25/91 (27)
Breast cancer	10/30 (33)
Uterine cervical cancer	30/52 (58)
Prostate cancer	7/22 (32)
Meningioma	26/41 (63) **
Medulloblastoma	0/30 (0)
Precancerous lesions	
Pancreatic intraepithelial neoplasia***	
PanIN-1/2	0/39 (0)
PanIN-3	2/7 (29)
Pancreatic cancer	25/91 (27)
Cervical intraepithelial neoplasia****	
Normal epithelium	0/10 (0)
CIN2	6/10 (60)
CIN3	32/42 (76)
Cervical cancer	18/24 (75)

* Ref. 3, 4
** Incidence of loss of CADM1 expression by IHC
*** Ref. 18
**** Ref. 20

mune checkpoints, such as PD1 and PD-L1. CADM1, expressed in epithelial cells, also plays a role in triggering antitumor immunity. Class I-restricted T-cell-associated molecule (CRTAM) was identified as an IgSF whose expression increases on the cell membrane of activated NK or CD8+ T cells. CADM1 was then recognized as a specific binding partner of CRTAM in epithelial cells. When a trans-heterophilic interaction occurs between CRTAM on NK or CD8+ T cells and CADM1 on epithelial cells with abnormal adhesion, NK cell cytotoxicity is trig-

gered, and cytokines like γ-interferon are secreted from CD8+ T cells to immunologically eliminate CADM1-expressing epithelial cells. When CADM1 expression is induced in cancer cells and these cells are transplanted into the peritoneal cavity of mice, they are effectively eliminated by NK cells. This suggests that CADM1 expressed in cancer cells acts as a tumor antigen specifically recognized by NK or CD8+ T cells, while advanced cancer cells lacking CADM1 may evade immune surveillance, gaining a survival advantage[21–24]. The reason why activated NK cells or CD8+ T cells do not target normal epithelial cells expressing CADM1 is unknown. Because they form cis-homodimers and trans-heterodimers, CADM1 proteins are structurally densely packed between adjacent epithelial cells, which may make it difficult for circulating NK and CD8+ T cells to recognize and target CADM1 protein on the lateral membrane of epithelial cells. In contrast, CADM1 in malignant epithelial cells would be aberrantly exposed by disrupted tissue architecture and would be targeted easily by infiltrating NK or CD8+ T cells. In summary, CADM1 functions as a unique tumor suppressor, both by maintaining epithelial structure through cell adhesion and by triggering antitumor immune responses as a tumor antigen recognized by NK and CD8+ T cells (**Fig. 3, 4**).

High Expression of CADM1 in ATL

CADM1 is expressed in most epithelial tissues but not in peripheral blood cells under normal conditions. Interestingly, CADM1 is overexpressed in adult T-cell leukemia (ATL) cells[25]. ATL is an intractable leukemia/lymphoma that affects approximately 1,000 people annually in Japan; it affects 3-5% of individuals carrying HTLV-1 antibodies after a latent period of over 40 years after infection with the retrovirus HTLV-1. CADM1 is expressed in all ATL cell types and in some cutaneous T-cell lymphomas, such as mycosis fungoides and Sezary syndrome, but not in other leukemias, lymphomas, or normal CD4+ T cells[3,26,27]. The presence of CADM1 expression in HTLV-1-infected cells suggests its early involvement in ATL leukemogenesis. The TAX protein, a transcriptional factor encoded by HTLV-1, is thought to play a key role in inducing CADM1 expression[28]. After the asymptomatic carrier stage, ATL cells gradually increase in number, with reduced clonal heterogeneity, and the disease progresses from the smoldering type to the chronic, lymphoma, or acute types, which are associated with poor outcomes. Early detection in HTLV-1 carriers is thus crucial for effective management and treatment. Currently, fluorescence-activated cell sorting (FACS) analysis of peripheral blood cells using CADM1 and CD7 as surface markers (HAS-Flow), which was established in Japan, is used worldwide as a specific diagnostic tool for ATL[29,30].

Investigation of the oncogenic mechanism of CADM1 has identified a unique binding protein, Tiam-1, which binds to CADM1 through a PDZ-binding motif and constitutively activates RAC, enhancing cell motility[31]. CADM1 also promotes polyubiquitination of TAX and activates NFKB, driving infiltration into the skin and other organs, a hallmark of ATL[28–31]. Studies show that trans-homophilic interaction of CADM1 on T-cell lymphoma cells and endothelial cells is critical for liver infiltration in mice[32]. These molecular pathways offer promising therapeutic targets, in addition to established treatments such as molecularly targeted therapy using antiCCR4 antibodies[33].

Overexpression of CADM1 in SCLC

SCLC accounts for 15% of lung cancers and is highly resistant to treatment, often exhibiting hematogenous metastasis at an early stage. Similar to ATL, CADM1 is overexpressed in approximately 80% of SCLC cases. Notably, SCLC expresses a unique splicing variant of CADM1 specific to the testis. CADM1 has three splicing variants: the neuronal variant (v[−]), the epithelial variant (v8), and the testicular variant (v8/9), which depend on the presence or absence of exon 8 and/or 9 sequences. These sequences encode the extracellular but juxtamembrane portion of the CADM1 protein. In SCLC, the v8 variant (with exon 8) and the v8/9 variant (with exons 8 and 9) are expressed in nearly equal amounts[34]. The extracellular domains of CADM1v8 and v8/9 in SCLC are cleaved by different proteases, ADAM10 and ADAM 17, respectively, releasing distinct extracellular fragments into the culture medium or patient serum[35]. A diagnostic antibody was developed by using serum from SCLC patients to detect SCLC by targeting these cleaved CADM1 v8/9 fragments[36]. CADM1v8/9 could detect a subset of SCLC cases not identified by current markers, ProGRP and NSE, making it a promising new serum marker. CADM1 also shows potential as a therapeutic target, as its loss or downregulation reduces tumorigenicity in SCLC cells in nude mice[37]. Interestingly, CADM1 expression is particularly high in highly infiltrative leukemia (ATL) and highly metastatic cancer (SCLC). The mechanism by which CADM1 regulates opposing functions of suppressing and promoting cancer is a matter of considerable interest. The presence of tissue-specific binding

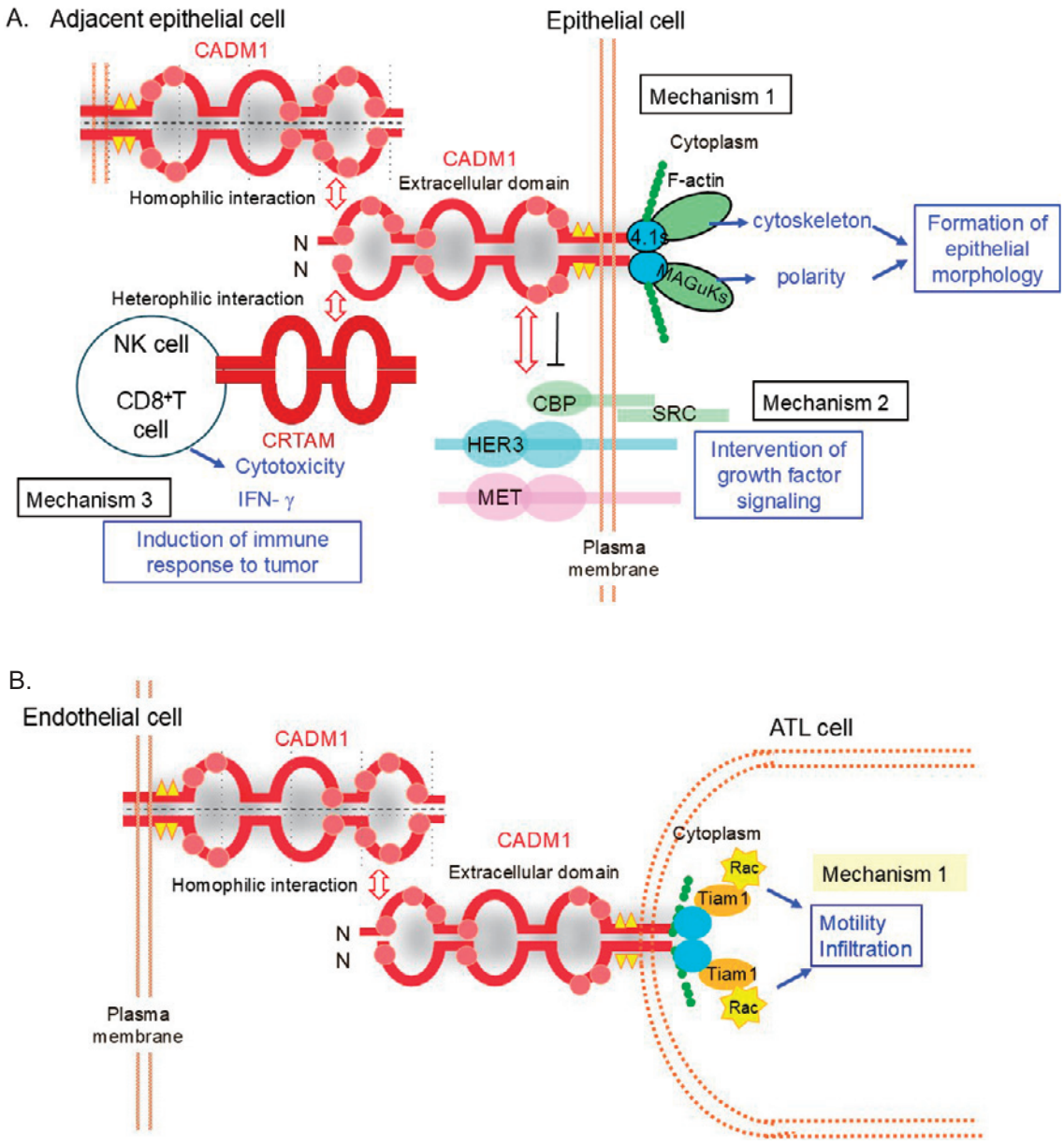

Fig. 3 Conceptual mechanisms of tumor suppressor activity in epithelium (A) and infiltrative activity in ATL cells (B). A. CADM1 acts as a tumor suppressor through three mechanisms: formation of epithelial morphology through a unique downstream cascade, intervention of growth factor signaling by associating with growth factor receptors on the cell membrane, and induction of immune response to tumor through trans-heterophilic interaction with CRTAM on NK cells or CD8+ T cells. B. CADM1 promotes infiltrative activity of ATL cells into various organs through trans-homophilic interaction with CADM1 on vascular endothelial cells.

proteins on the cell membrane or in downstream cascades might be a mechanism by which CADM1 exerts these contrasting functions in oncogenesis. Moreover, CADM1 expression was abnormally high in a small subset of cancer cells, in addition to ATL and SCLC[3], suggesting that CADM1 may exert opposing functions, depending on the cellular context or the stage of epithelial-mesenchymal transition.

A Synaptic Adhesion Molecule Associated with Autism Spectrum Disorder

CADM1, also known as synaptic adhesion molecule SynCAM1, is expressed on presynaptic and postsynaptic membranes and plays a role in synapse formation through trans-homophilic interactions[38]. Interestingly, *Cadm1* gene-deficient mice exhibit behaviors associated with autism spectrum disorder (ASD), and rare variant sequences of the CADM1 gene have been identified in

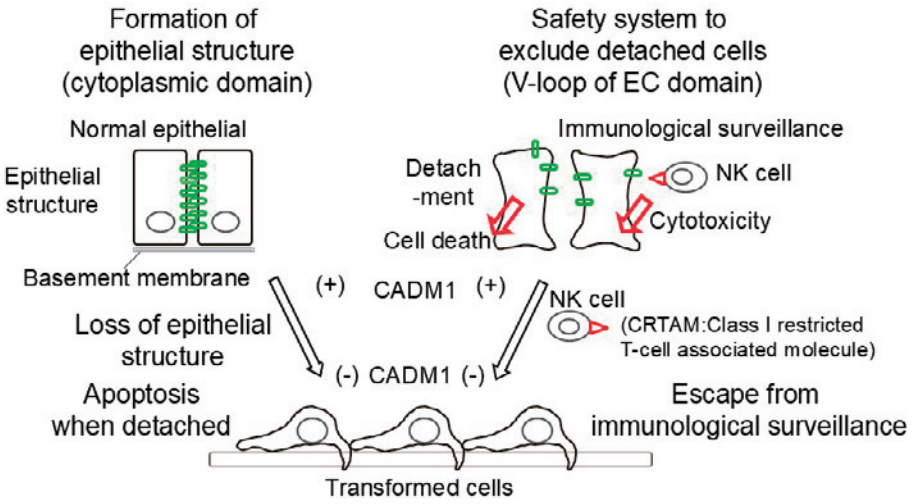

Fig. 4 CADM1 acts as an epithelial guardian and a tumor suppressor in two ways. Biphasic regulation of repair and death is a sophisticated self-guarding system of organisms, while its disruption could lead to cancer.

humans with ASD[39]. CADM1 has also been linked to suicide risk[40] and other neurodevelopmental disorders[41]. Forced CADM1 expression increases the number of excitatory synapses, suggesting its involvement in the formation and maintenance of these synapses. Mechanistically, it was proposed that synaptic CADM1 recruits NMDA receptors via 4.1B and GABBR2 via Mupp1[42](**Fig. 2D**).

Furthermore, genome-wide association studies have revealed links between CADM1 and conditions such as obesity[43], anorexia nervosa[44], and bipolar disorder. CADM1 overexpression in hypothalamic and hippocampal neurons has been shown to induce obesity and decrease energy expenditure, indicating that CADM1, along with CADM2 and CADM3, may be involved in human psychiatric and neurological disorders[43].

Function as a Sperm Cell Adhesion Molecule Essential for Spermatogenesis

Conventional *Cadm1* gene-deficient male mice are infertile and exhibit azoospermia, with a mature sperm count of about 1 in 10,000 and a motility rate of less than 1%. Sperm precursor cells, identified by positive PAS staining, are sloughed off into the seminiferous tubules and undergo apoptosis[45–47]. CADM1 is highly expressed in the testes and exhibits bimodal expression during spermatogenesis: once in the early phase in spermatogonia and spermatocytes in the seminiferous tubule epithelium, and again in the intermediate phase in differentiated spermatids during sperm maturation. In *Cadm1* gene-deficient mice, spermatids are sloughed off from Sertoli cells during the intermediate phase, suggesting that CADM1 is essential for the adhesion of spermatocytes and spermatids to Sertoli cells and for their normal differentiation into mature spermatozoa. However, the specific binding molecules on Sertoli cells remain unidentified, and no direct link between CADM1 and human male infertility has been reported.

Additional Functions of CADM1 and Associated Pathogenesis

CADM1 is expressed in mast cells and is involved in releasing histamine granules through trans-homophilic interactions with CADM1 on nerve cells, thus triggering allergic reactions, neuritis, and peritonitis in mouse models[48]. Recently, somatic mutations in the *CADM1* gene have been identified in a small subset of aldosterone-producing adenomas resected from patients with reversible hypertension. Amino acid substitutions in CADM1 at intramembranous positions p379 or p380, found in these tumors, affect gap junction permeability, regulating aldosterone levels. This suggests a role for CADM1 in suppressing aldosterone production via gap junction communication[49,50].

The physiological functions of CADM1 and its dysfunction in various diseases are summarized in **Table 2**. CADM1 aberrations contribute to tumor formation, tumor immunity, ATL infiltration, SCLC metastasis, synapse formation, spermatogenesis, mast cell activation, and aldosterone production. Although *Cadm1* gene-deficient mice develop normally, showing no embryonic lethality or severe malformations[45], CADM1 clearly plays important roles in disease development and progression

Table 2 Multiple functions of CADM1, based on cell to cell interaction, and pathological importance of CADM1 dysfunction and aberrant expression

Tissue	CADM1 expressing cell/CADM1 (alias) (Styles of expression)		Binding protein/Interacting cell (Styles of expression)		Downstream molecules	Physiological functions	Diseases by aberrant function
Epithelia	Epithelial cell	CADM1/Necl2 (Constitutive)	CADM1/Necl2 (Constitutive)	Epithelial cell	4.1B, 4.1N MPP1-3, Pals2, CASK etc.	Epithelium-like morphology	Tumor formation Invasion
Tumor immunity	Cancer cell /Antigen presenting cell (Constitutive)	CADM1 (Constitutive)	CRTAM (Inducible)	NK cell /CD8+ T cell	4.1B, 4.1N MPP1-3, Pals2, CASK etc.	Immunological surveillance Cytotoxic reaction Interferon γ secretion	Tumor growth
Synapse	Pre-synaptic membrane (Constitutive)	CADM1/SynCAM1 (Constitutive)	CADM1/SynCAM1 (Constitutive)	Post-synaptic membrane	4.1B, 4.1N, 4.1 G CASK Syntenin, Mupp1 etc.	Synapse formation	Autism spectrum disorder Suicide Obesity, anorexia nervosa
Testis	Spermatogonia Spermatocyte (Constitutive)	CADM1/SgIGSF (Constitutive)	ND	Sertoli cells	ND	Spermatogenesis	Male infertility
ATL	ATL cell	CADM1 (Overexpression)	CADM1 (Inducible)	Endothelial cells	4.1s Tiam-1 etc.	Cell mobility	Infiltration of ATL into organs
Small-cell lung cancer	SCLC cell	CADM1 variant 8/9 (Overexpression)	ND	Endothelial cells	4.1R	Anchorage-independent cell growth	Metastasis (s/o)
Mast cell	Mast cell	CADM1 (Constitutive)	CADM1	Smooth muscle cell Fibroblast Nerve cell	ND	Histamine release Homeostasis	Peritonitis, bronchial asthma Neuritis Atopic dermatitis
Aldosterone producing adenoma	Aldosterone-producing cells	CADM1 mutant (somatic) (Constitutive)	CADM1 mutant (somatic) (Constitutive)	Aldosterone-producing cells (Constitutive)	ND	Secretion through gap junction	Hypertension

in phenotypically healthy adults, as outlined in **Table 2**.

IgCAMs, which include over 400 proteins, such as CADM1, rarely cause embryonic lethality when functionally deficient. However, growing evidence indicates that IgCAMs have unique physiological roles in the epithelial, nervous, and immune systems, and IgCAM dysfunction contributes to cancer and psychiatric, neurological, and immunological disorders. Highly specific temporally and spatially regulated interactions between cells, driven by the structural diversity of IgCAMs, underlie these diverse biological and pathological phenomena. Research on CADM1 has revealed the broad functional range of IgCAMs. We propose that diseases and pathological states caused by or associated with disrupted cell adhesion be categorized as "diseases of aberrant cell adhesion," to provide a framework for understanding, managing, and treating these disorders.

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Conflict of Interest: The authors declare no conflicts of interest.

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