

# CLDN7: Epithelial gatekeeper from physiology to pathology-roles in cancer and epithelial-related diseases (Review)

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**Abstract.** Claudin-7 (CLDN7) is a key component of epithelial tight junctions. It plays a vital role in maintaining cell polarity, barrier integrity and paracellular transport. Abnormal CLDN7 expression is closely related to the onset and progression of various diseases. It is especially markedly associated with the growth and metastasis of multiple cancers. Additionally, dysregulated CLDN7 expression contributes to the progression of intestinal, skin and respiratory system diseases. The present review summarized the structure, expression, physiological functions, stability and regulatory mechanisms of CLDN7, emphasizing its role in tumors. The expression patterns, regulatory mechanisms, effect on malignant phenotypes and clinical significance of CLDN7 were also discussed.

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## 1. Introduction

Claudin-7 (CLDN7), a critical member of the claudin family, was first cloned and identified in mice by Morita *et al* in 1999 (1). Its encoding gene maps to human chromosome 17p13.1 (2). The CLDN7 protein structure comprises four transmembrane domains, two extracellular loops and a cytoplasmic tail region (3). CLDN7 exhibits a specific expression pattern in human tissues. It is highly expressed in epithelial tissues such as the gastrointestinal tract, mammary glands, lungs and kidneys, while showing very low expression in neural and hematopoietic tissues, suggesting its close involvement in epithelial tissue differentiation and barrier maintenance (4). Abnormal CLDN7 expression is strongly linked to tumorigenesis, proliferation and metastasis in cancers including colorectal cancer (CRC), lung cancer and breast cancer (5-7). Additionally, CLDN7 plays a crucial role in several non-neoplastic diseases, such as respiratory disorders, intestinal diseases and skin conditions. For instance, CLDN7 is essential for intestinal epithelial cell function and self-renewal and its absence leads to spontaneous colitis (8,9). Reduced CLDN7 expression levels may trigger excessive keratinocytes proliferation and impaired barrier function, contributing to psoriasis development (10,11). CLDN7 is widely distributed in the respiratory barrier and is involved in respiratory diseases including allergic rhinitis, chronic obstructive pulmonary disease and asthma (12-14). However, there is currently a lack of comprehensive reviews on the role and mechanisms of CLDN7 in both neoplastic and non-neoplastic diseases. The present review first introduced the structure, expression, regulation, physiological functions and stability of CLDN7. Subsequently, its expression, mechanisms of action and clinical significance in tumors were outlined. Moreover, the role of CLDN7 in respiratory, intestinal and skin diseases were discussed. The present review provided a theoretical basis for developing CLDN7-targeted therapies for both neoplastic and non-neoplastic diseases.

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## 2. Methods

To comprehensively review research progress on CLDN7, a search strategy combining Medical Subject Headings (MeSH) and free-text keywords centered on 'CLDN7' or 'claudin-7' was utilized. To enhance comprehensiveness, search terms also included synonyms and narrower terms related to its functions (e.g., 'tight junction', 'cell adhesion') and associated diseases (e.g., 'cancer', 'carcinoma', 'colitis'). Online databases searched included PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webof-science.com/>), and Google Scholar (<https://scholar.google.com/>), with searches conducted up to October 31, 2025; the Human Protein Atlas (HPA and Consensus datasets, version 25.0), the iPTMnet database (<https://research.bioinformatics.udel.edu/iptmnet/>, accessed September 15, 2025) and the Gene Expression Profiling Interactive Analysis (GEPIA) database (<http://gepia.cancer-pku.cn/>, accessed August 28, 2025). The literature search included all relevant publications from each database's inception up to October 31, 2025. Inclusion criteria primarily encompassed English-language original research articles (both preclinical and clinical), reviews and meta-analyses explicitly examining the expression, function, or regulatory mechanisms of CLDN7 in human diseases, particularly cancers and inflammatory diseases.

## 3. Structure

The CLDN7 gene maps to chromosome 17p13.1, comprising four exons and three introns. Transcription generates three alternatively spliced mRNA variants encoding two distinct protein subtypes (variants 1 and 2 encode the same subtype) (<https://atlasgeneticsoncology.org>). Amino acid composition, molecular formula, molecular weight and isoelectric point of the two CLDN7 subtypes were analyzed using ProtParam online software (<http://au.expasy.org/tools/>). CLDN7 subtype 1 is a classic sequence of 211 amino acids, primarily containing 25 Ala, 23 Gly and 21 Leu, residues. Its molecular formula is  $C_{1007}H_{1588}N_{256}O_{279}S_{21}$ , with a molecular weight of 22,418.49 Da, a theoretical isoelectric point (pI) of 8.91, an estimated *in vitro* half-life of 30 h and an instability index of 49.60. CLDN7 subtype 2 comprises 145 amino acids and possesses a shorter C-terminal region, lacking amino acids 159-211 compared with subtype 1. Its composition includes 19 Ala, 19 Leu and 17 Gly residues. Its molecular formula is  $C_{671}H_{1094}N_{172}O_{186}S_{19}$ , with a molecular weight of 15,156.25 Da, theoretical pI of 8.93 and instability index of 57.57. All claudin family members are quadrimembrane proteins of 20-34 kDa with highly conserved topology: An intracellular  $NH_2$ -terminus, a longer intracellular  $COOH$ -terminus, two extracellular loops (larger ECL1, smaller ECL2) and a short intracellular loop (15). CLDN7 is a complete membrane protein with four hydrophobic transmembrane domains, two extracellular loops (ECL1 and ECL2), an amino terminus and a carboxyl terminus (3). The schematic structure of CLDN7 is illustrated in Fig. 1. ECL1 contains conserved cysteine residues forming disulfide bonds and multiple positively charged lysine and arginine residues. These confer high permeability to anions (e.g.,  $Cl^-$ ), establishing CLDN7 as a key protein constituent of the anion channels (16). CLDN2, CLDN15

and CLDN22 are primarily involved in cation channel formation (17). Several claudins (including CLDN1, CLDN3, CLDN5, CLDN11 and CLDN19) possess an uncharged first extracellular loop and thus lack ion selectivity, functioning primarily to seal intercellular connections (18). Studies indicate that some claudins form functional pores only through specific interactions with other claudin molecules. For instance, the combination of CLDN16 and CLDN19 constitutes a cation channel, whereas the pairing of CLDN4 and CLDN8 forms an anion channel (19,20). The C-terminal tails of claudins exhibit diversity in sequence and length and contain PDZ domain-binding motifs (18). These motifs anchor CLDN7 to scaffolding proteins such as ZO-1, thereby stabilizing tight junctions (TJs) (21).

## 4. Expression and regulation of CLDN7

According to the HPA and Consensus datasets, CLDN7 shows high expression in most tissues, with tissue-specific enhancement observed in the esophagus and intestines. Beyond the gastrointestinal tract, CLDN7 expression is detected in epithelial tissues including the breast, lung and prostate, but is very low or nearly absent in muscle and neural tissues (<https://www.proteinatlas.org/>). Abnormal changes in CLDN7 expression frequently occur during tumorigenesis. For example, in CRC, CLDN7 mRNA and protein expression levels are markedly lower than those in adjacent normal mucosa (22,23). In breast cancer, analysis of numerous clinical samples indicates that ~50% of primary tumor tissues show loss of CLDN7 expression (24). In ovarian cancer, CLDN7 mRNA is highly upregulated in all four major subtypes (serous, mucinous, clear cell and endometrioid) compared with normal ovarian tissues (25). In non-neoplastic diseases such as inflammatory bowel disease (IBD), reduced CLDN7 expression in the gut results in impaired barrier function (26). Psoriasis patients exhibit elevated expression of CLDN7 in keratinocytes, which correlates with alterations in skin barrier function (27).

The expression of CLDN7 is regulated by multiple factors, including primarily epigenetic mechanisms, transcription factors, post-translational modifications and signaling pathways (Fig. 2).

**Epigenetic regulation.** Epigenetic regulation of CLDN7 expression primarily involves microRNA (miRNA)-mediated mechanisms, DNA methylation and histone modifications.

**microRNAs (miRNAs/miRs).** miRNAs are small endogenous RNA molecules, typically 18-25 nucleotides in length. They mediate gene silencing by binding to the 3'-untranslated region (3'-UTR) of target mRNAs, leading to either RNA cleavage or translational repression (28). Studies have demonstrated that miRNAs regulate CLDN7 expression.

**miR-155:** In eosinophilic esophagitis (EoE), miR-155 expression is markedly elevated and directly targets the 3'-UTR of CLDN7. This reduces CLDN7 mRNA and protein expression, ultimately impairing epithelial barrier function (29).

**miR-1193:** In cervical cancer, miR-1193 is markedly down-regulated, negatively regulating CLDN7 expression through direct binding to its 3'-UTR. This suppresses the proliferation, invasion and migration of cervical cancer cells (30).

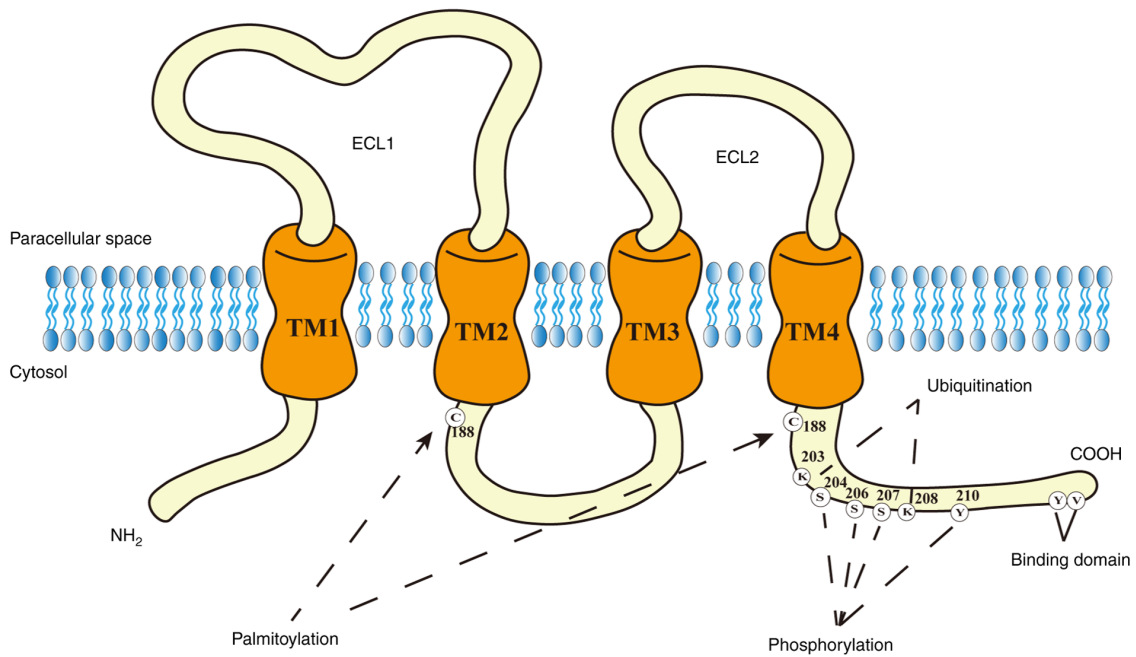


Figure 1. Schematic diagram of CLDN7 structure. CLDN7 is a complete membrane protein with four hydrophobic TM, two extracellular loops (ECL1, ECL2), an amino terminus and a carboxyl terminus. CLDN7, claudin-7; TM, transmembrane domains.

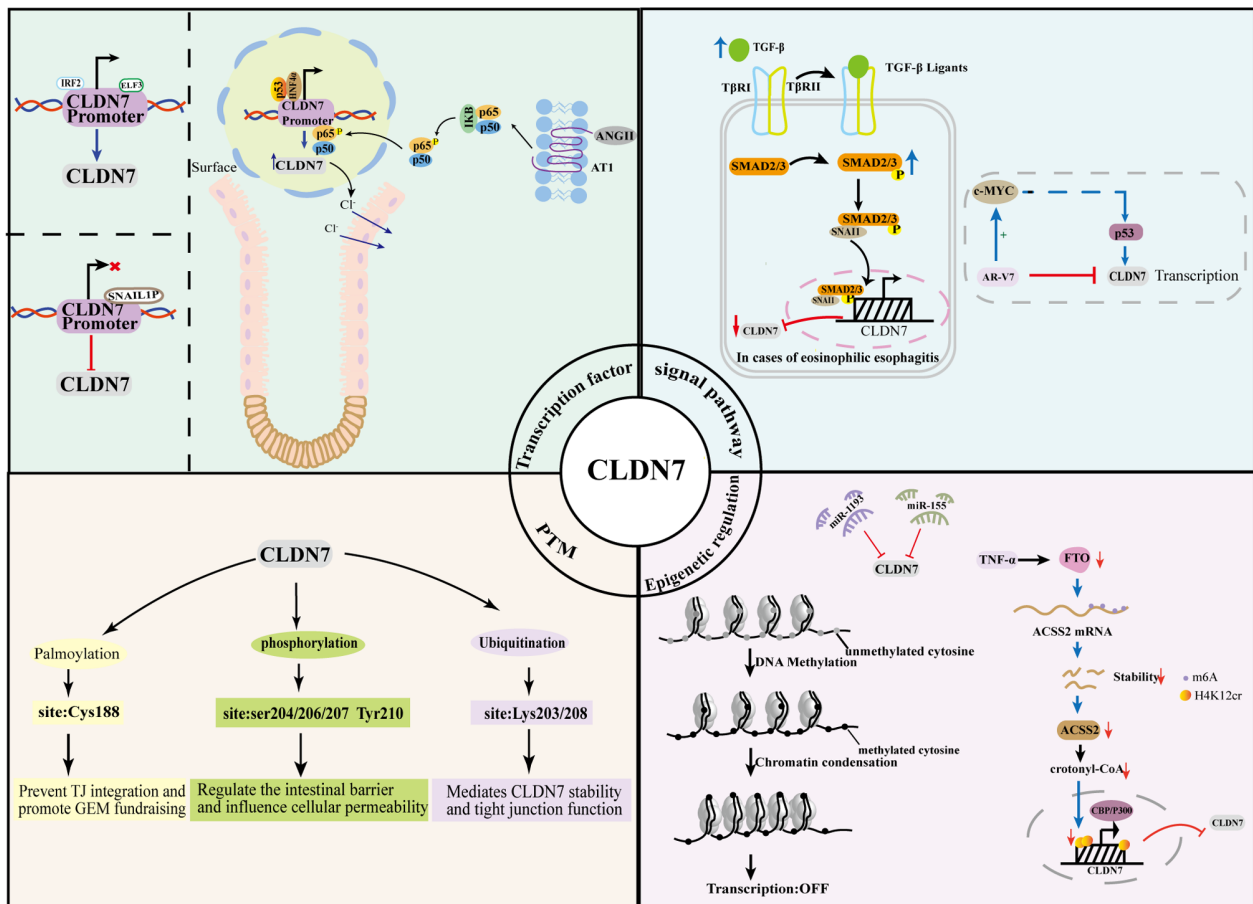


Figure 2. Schematic diagram of CLDN7 expression and regulatory mechanism. CLDN7, claudin-7; PTM, post-translational modification; ELF3, E74-like factor 3; IRF2, interferon regulatory factor 2; HNF4α, hepatocyte nuclear factor 4α; p65, nuclear factor-kappa B subunit p65; p50, nuclear factor-kappa B1; p53, tumor protein p53; SNAIL1P, SNAIL family transcriptional repressor; IκB, inhibitor of nuclear factor-kappa B; ANGII, angiotensin II; AT1, angiotensin II type 1 receptor; TGF-β, transforming growth factor-beta; TβRI and II, transforming growth factor-beta receptor type I and type II; SMAD2/3, SMAD family member 2 and SMAD family member 3; c-MYC, MYC proto-oncogene; AR-V7, androgen receptor variant 7; ACSS2, acyl-CoA synthase short-chain family member 2; crotonyl-CoA, crotonyl coenzyme A; FTO, fat mass and obesity-associated protein; CBP/p300, CREB-binding protein/E1A-binding protein p300; m6A, N6-methyladenosine; H4K12cr, histone H4 lysine 12 crotonylation; miR-155, microRNA 155; miR-1193, microRNA 1193.

**DNA methylation.** Promoter methylation induces transcriptional silencing by preventing transcription factors from binding to their target sites. Hypermethylation of CpG islands in the CLDN7 promoter by DNMT3A/DNMT3B and DNMT1 causes chromatin condensation and transcriptional repression. This disruption of the epithelial barrier promotes tumor progression (22,31,32). Hypermethylation-induced silencing of CLDN7 and subsequent reduced expression play a critical role in tumor development (32). Hypermethylation of CLDN7 occurs at the invasive front of esophageal squamous cell carcinoma, potentially leading to CLDN7 heterogeneity and reduced expression (33). Additionally, hypermethylation of the CLDN7 promoter region results in reduced mRNA expression, positively correlating with deeper tumor invasion, higher histological grade and advanced clinical stage. It is also associated with metastasis and poor prognosis in cancers including CRC and clear cell renal cell carcinoma (32,34).

**Histone modification.** Research has revealed that in IBD, TNF- $\alpha$  signaling downregulates the demethylase fat mass and obesity-associated protein, enhancing N6-methyladenosine modification and suppressing AR-V7 androgen receptor variant 7 expression. This deficiency impairs crotonyl-CoA synthesis, leading to reduced CBP/p300-catalyzed histone mark H4K12cr modification at the CLDN7 promoter. Ultimately, this suppresses CLDN7 transcription by altering the chromatin state (35).

**Transcription factors.** E74-like Factor 3 (ELF3): ELF3, also known as ESE-1 or ESX, is a transcription factor belonging to the E Twenty-Six (ETS) family, encoded by the ELF3 gene on chromosome 1q32.1. It is highly expressed in epithelial cells (36). ELF3 directly activates CLDN7 transcription by recognizing the Ets-binding site located 150 bp upstream of the CLDN7 promoter, thereby maintaining TJs and the epithelial phenotype (37).

**Hepatocyte Nuclear Factor 4 $\alpha$  (HNF4 $\alpha$ ):** HNF4 $\alpha$  is a prototypical nuclear receptor transcription factor. Its expression increases markedly along with p53 during colonic epithelial differentiation. Together, these factors synergistically activate CLDN7 transcription. Subsequently, CLDN7 protein localizes at the apical TJs to form a Cl<sup>-</sup> selective channel, shifting ion transport from basal secretion to apical absorption, thus maintaining electrolyte homeostasis (38).

**p65:** p65 (RelA) is a key subunit of the nuclear factor  $\kappa$ B transcription factor family. In colonic epithelium, Ang II activates the IKK signaling pathway via the AT1 receptor, promoting nuclear translocation of p65. This translocation enables p65 to bind the  $\kappa$ B site in the CLDN7 promoter and recruit the p300/CBP coactivator, forming an enhancement complex. This complex upregulates CLDN7 expression and enhances the paracellular permeability of TJs to Cl<sup>-</sup> (39).

**Interferon regulatory factor 2 (IRF2):** IRF2 is a member of the IRF transcription factor family, which activates transcription of multiple direct target genes and regulates immune responses and immune cell development (40,41). In oral squamous cell carcinoma (OSCC), IRF2 binds the promoter region of CLDN7 and induces CLDN7 expression, thereby inhibiting proliferation, invasion and migration of OSCC cells (42).

**SNAIL:** SNAIL1 (Snail) and SNAIL2 (Slug) belong to the Snail family of zinc-finger transcriptional repressors (43).

In esophageal squamous cell carcinoma and breast cancer cell lines, Snail and its homolog SNAILP suppress CLDN7 transcription by binding to the E-box of its promoter (44,45). Additionally, Slug may regulate CLDN7 expression in squamous cell carcinoma and adenocarcinoma of the lung by binding to the E-box on the CLDN7 promoter; however, further validation is required (46).

**Post-translational modifications (PTMs).** PTM refers to covalent, enzymatic, or non-enzymatic addition of specific chemical groups to amino acid side chains. Such modifications include phosphorylation, palmitoylation, ubiquitination, glycosylation and acetylation, profoundly affecting protein conformation, stability, trafficking and function (47). PTM sites of CLDN7 are shown in Fig. 1.

**Palmitoylation.** Palmitoylation occurs at Cys188, preventing CLDN7 incorporation into TJs. Instead, it redirects CLDN7 to glycolipid-enriched membrane microdomains, influencing membrane microdomain localization and downstream signaling (48).

**Phosphorylation.** Phosphorylation is the most extensively studied PTM of CLDN7. Phosphorylation at Ser206 mediated by WNK4 reduces CLDN7 integration into TJs and enhances paracellular permeability to Cl<sup>-</sup> (49). Conversely, phosphorylation at Ser204/S207 and Tyr210 promotes CLDN7 assembly at TJs, strengthening epithelial barrier function (50,51).

**Ubiquitination.** Research on CLDN7 ubiquitination remains relatively limited. According to annotations from the iPTMnet database, ubiquitination of CLDN7 occurs primarily at lysine 203 and lysine 208 (<https://research.bioinformatics.udel.edu/iptmnet/>, accessed September 15, 2025). Existing studies suggest that this modification process may be dynamically regulated by E3 ubiquitin ligases (such as LNX1) and deubiquitinating enzymes (such as USP28), thereby influencing CLDN7 protein stability and tight-junction (TJ) function (52,53).

**Signaling pathway.** In hepatocellular carcinoma, the androgen receptor variant 7 (AR-V7) collaborates with c-MYC to counteract downstream transcriptional activation of CLDN7 by p53. This markedly suppresses CLDN7 expression, disrupting epithelial barrier integrity and accelerating c-MYC-driven tumor progression (54). Activation of the transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling pathway results in SMAD2/3 phosphorylation. Phosphorylated SMAD2/3 forms a transcriptional repression complex with SNAIL1, which directly binds to the CLDN7 promoter. This interaction inhibits CLDN7 transcription, leading to reduced expression and impaired epithelial barrier integrity (55).

**Stability of CLDN7.** Multiple factors influence CLDN7 stability, including its oligomerization properties, degradation processes and interactions with other proteins. Purified CLDN7 forms multiple oligomeric structures (monomers, dimers, trimers and higher-order oligomers) in detergents. These oligomers may contribute to CLDN7 stability and function within the cell membrane (56). CLDN7 degradation also affects its stability. CLDN7 undergoes degradation not only by MMP7 hydrolysis (57), but also through the ubiquitin-proteasome pathway mediated by E3 ubiquitin

ligases (58,59). Additionally, CLDN7 protein degradation involves lysosomal pathway: Lysosomes serve as major intracellular degradation sites, encapsulating and degrading proteins through endocytosis and autophagy (60). Epithelial cell adhesion molecule (EpCAM) interacts with CLDN7, stabilizing it on epithelial cells surfaces (61,62). Further research demonstrates that EpCAM and trophoblast cell surface antigen 2 (Trop2) share regulatory functions for CLDN7, allowing partial compensation. Dual-knockout mice lacking both proteins exhibit severe impairment in CLDN7 expression and localization (63). The absence of EpCAM leads to CLDN7 loss in mouse intestinal epithelial cells, causing TJ defects. Interestingly, this deletion does not reduce CLDN7 mRNA levels, suggesting that EpCAM regulates CLDN7 expression via post-transcriptional mechanisms (64). Moreover, EpCAM protects CLDN7 from endocytosis and lysosomal degradation (61,62). These findings indicate that EpCAM stabilizes CLDN7 proteins at the cell surface and that the direct interaction between these two proteins is essential for CLDN7 stability.

### 5. The physiological functions of CLDN7

**Barrier function.** CLDN7 localizes not only to apical regions of intestinal epithelial cells but also strongly distributes along basolateral membranes in the intestine (65). Intestinal epithelial integrity is essential for nutrient absorption and defense against pathogens. CLDN7 forms a physical barrier in intestinal epithelial cells, isolating harmful substances (such as bacteria, toxins and antigens) from the internal environment (34). Intestinal-specific CLDN7 knockout mice exhibit severe intestinal defects, including mucosal ulceration, epithelial cell shedding, inflammation and elevated matrix metalloproteinase expression (8,66). In normal intestine, integrin  $\alpha 2$  forms a stable protein complex with CLDN7 and CLDN1. This complex is disrupted in CLDN7-deficient mice. Furthermore, the expression and localization of integrin  $\alpha 2$  are also altered, highlighting CLDN7's role in cell-matrix interactions (66). Additionally, CLDN7 maintains intestinal homeostasis and prevents IBD and colorectal cancer (CRC) progression. In intestinal-specific CLDN7 knockout mice, CLDN7 deficiency promotes colitis and subsequent CRC progression by disrupting TJ integrity and amplifying inflammation (8).

**Stem cell fate regulation.** CLDN7 regulates small intestinal stem cell (ISC) functions, influencing ISC survival, self-renewal and epithelial differentiation (9,67). The balance between stem cell homeostasis and cell fate determination in the intestine depends upon interactions between Wnt and Notch signaling pathways (68,69). CLDN7 precisely regulates the Wnt/ $\beta$ -catenin signaling pathway through direct interaction with  $\beta$ -catenin. This ensures moderate activation, maintaining stable expansion and stemness of Lgr5<sup>+</sup>/Olfm4<sup>+</sup> intestinal stem cells. Concurrently, CLDN7 synergizes with Notch signaling, suppressing excessive differentiation toward the secretory cell lineage and promoting steady-state renewal and differentiation of absorptive epithelial cells (9). A recent study revealed that CLDN7 regulates colonic stem cell behavior by modulating the Notch and Hippo signaling

pathways. Activation of Notch signaling or inhibition of Hippo signaling rescues defects caused by CLDN7 deficiency (70). Under CLDN7 deficiency,  $\beta$ -catenin stability decreases, becoming susceptible to degradation. This weakens Wnt signaling pathway activity, leading to stem cell depletion and differentiation toward secretory lineages (9). Exogenous activation of Wnt signaling or restoration of CLDN7 expression effectively reverses this pathological process, restores intestinal epithelial homeostasis and promote regenerative repair after injury (67).

**Renal ion transport.** CLDN7 is crucial for renal ion transport and localizes primarily to the distal tubules, collecting ducts and the thick ascending limb of Henle's loop in the kidney (71). Renal phenotypes indicate that CLDN7 is essential for maintaining salt homeostasis in the distal nephron. CLDN7 forms non-selective paracellular channels that facilitate Cl<sup>-</sup> and Na<sup>+</sup> reabsorption in the collecting duct. When overexpressed, CLDN7 reduces Cl<sup>-</sup> conductance and increases Na<sup>+</sup> conductance, indicating it promotes NaCl reabsorption through charge-selective channels (72). Negatively charged amino acids (D38, E53) within the first extracellular domain (ED1) of CLDN7 are critical for the paracellular Cl<sup>-</sup> barrier. Mutating these residues to positive charges markedly increases Cl<sup>-</sup> permeability without affecting Na<sup>+</sup> permeability or TJ ultrastructure. Thus, ED1 determines charge selectivity, while ED2 has minimal impact (16). CLDN7 knockout mice die shortly after birth, partly due to severe renal salt depletion and dehydration (73). In the renal collecting duct, CLDN7 is phosphorylated by WNK4 kinase, with Ser206 of the COOH-terminus region being the phosphorylation site (49). WNK4-mediated phosphorylation of CLDN7 regulates paracellular chloride permeability, maintaining salt balance. Gain-of-function mutations in WNK4 lead to CLDN7 hyperphosphorylation, increased chloride leakage, impaired sodium chloride reabsorption and abnormal potassium handling (74). The WNK4-CLDN7 phosphorylation mechanism is a key regulator of salt-sensitive hypertension (75).

### 6. CLDN7 and diseases

#### *CLDN7 and tumors*

**Expression of CLDN7 in tumors.** CLDN7 expression is widely dysregulated in numerous malignant tumors, including lung, colorectal, ovarian, breast, gastric, esophageal and prostate cancers and is closely associated with tumor progression and metastasis (34,76,77). Expression profiles of CLDN7 across different cancer types are systematically summarized in Table I. Research indicates that abnormal CLDN7 expression and disrupted localization affect tumorigenesis through dual mechanisms. On one hand, compromised epithelial barrier integrity occurs. On the other hand, it interferes with fundamental cellular regulatory networks (proliferation, differentiation, apoptosis), disrupting homeostasis and potentially inducing cellular transformation and tumor development (78). Notably, loss of CLDN7 expression often correlates with impaired cell adhesion and malignant progression (79). However, some studies suggest that elevated CLDN7 expression may enhance tumor cell migration, invasion and

Table I. The changes in the expression pattern of CLDN7 in tissues.

Cancer	Methodology	Sample size	Positive rate, %	CLDN7 expression level	(Refs.)
Colorectal cancer	IHC	11	28	Downregulation	(82)
Lung cancer	RT-qPCR, WB	-	-	Downregulation	(5,78)
Ovarian cancer	IHC, WB	29	66	Upregulation	(25)
Breast cancer	RT-qPCR	65	29.23	Downregulation	(83)
Nasopharyngeal carcinoma	IHC	18	55.5	Upregulation	(84)
Oral squamous cell carcinoma	IHC	66	93.3	Upregulation	(34)
Liver cancer	IHC	67	91.04	Upregulation	(85)
Gastric cancer	IHC	134	29.9	Upregulation	(86)
Prostate cancer	IHC	141	-	Upregulation	(87)
Thyroid cancer	IHC	107	94	Downregulation	(88)
Triple-negative breast cancer	IHC	222	32.4	Upregulation	(89)
Cervical adenocarcinoma	IHC	55	-	Upregulation	(90,91)
Pancreatic cancer	IHC	141	-	Downregulation	(92)
Endometrial cancer	IHC	31	54.8	Downregulation	(93)
Esophageal adenocarcinoma	IHC	227	70	Upregulation	(94)
Esophageal squamous cell carcinoma	IHC,WB	40	30	Downregulation	(51,95)
Lung adenocarcinoma	IHC	86	-	Upregulation	(96)
Cervical adenocarcinoma	IHC	55	-	Upregulation	(90)
Superficial (non-muscle-invasive) urothelial bladder carcinoma	IHC	111	22	Downregulation	(97)
Adenoid cystic carcinoma of the salivary gland	IHC	50	38	Downregulation	(98)
Human throat cancer	IHC	80	22.5	Downregulation	(99)

CLDN7, claudin-7; IHC, immunohistochemistry; WB, western blotting; RT-qPCR, reverse transcription-quantitative PCR.

metastasis (80). These findings indicate that CLDN7 may have bidirectional roles in tumorigenesis, acting either as a tumor suppressor or a pro-oncogenic factor.

#### *Regulation of tumor phenotypes by CLDN7*

**Tumor proliferation.** CLDN7 exhibits variable expression levels across different tumors, influencing cancer cell proliferation (81,82). Furthermore, CLDN7 regulates tumor cell migration and invasion through barrier function and signaling pathways (7,8). Regulatory mechanisms of CLDN7 in cancer are illustrated in Fig. 3.

Cell proliferation is closely associated with the cell cycle and CLDN7 inhibit tumor cell cycle progression. Its tumor-suppressive role in CRC depends on p53. In p53 wild-type cells, CLDN7 induces G<sub>0</sub>/G<sub>1</sub> phase arrest and apoptosis (6). In squamous lung cancer cells, CLDN7 accelerates the interaction between PDK1 and AKT, inhibits sustained AKT phosphorylation, upregulates p21, decreases Cyclin D1 levels and suppresses the G<sub>1</sub>-S transition, thus inhibiting cell proliferation (5). Through immunofluorescence co-localization and immunoprecipitation, Lu *et al* demonstrated that CLDN7 co-localizes with integrin  $\beta$ 1, forming a protein complex in human lung cancer cells, contributing to its anti-proliferative effects (83). Moreover, in CRC tissues, CLDN7 knockout

mouse models and CRC cell lines have shown that its loss suppresses tumor growth, migration and apoptosis via a SOX-9-mediated Wnt/ $\beta$ -catenin pathway (7). Therefore, CLDN7 can suppress tumor proliferation by regulating the cell cycle and modulating signaling pathways.

**Tumor migration and invasion.** CLDN7 regulates tumor migration and invasion mainly by controlling barrier function and epithelial-mesenchymal transition (EMT) (76,84). CLDN7 also modulates signaling pathways (such as Wnt/ $\beta$ -catenin), suppressing tumor metastasis (81).

The intestinal epithelial barrier protects against infection and injury. Chronic inflammation is a critical factor in tumorigenesis (85). In normal epithelium, CLDN7 localizes at the apical TJs, forming a high-resistance barrier that prevents tumor cells from penetrating the basement membrane and infiltrating into the stroma (86). In an AOM/DSS-induced colitis-carcinoma model, CLDN7 deficiency disrupts TJ integrity, increases mucosal permeability and disrupts linear E-cadherin staining (8). Additionally, CLDN7 knockout mice exhibit severe enteritis, disrupted epithelium, necrotic glands and markedly loosened basement membrane junctions (87).

EMT promotes tumor dissemination by causing loss of epithelial markers and gain of mesenchymal markers. EMT

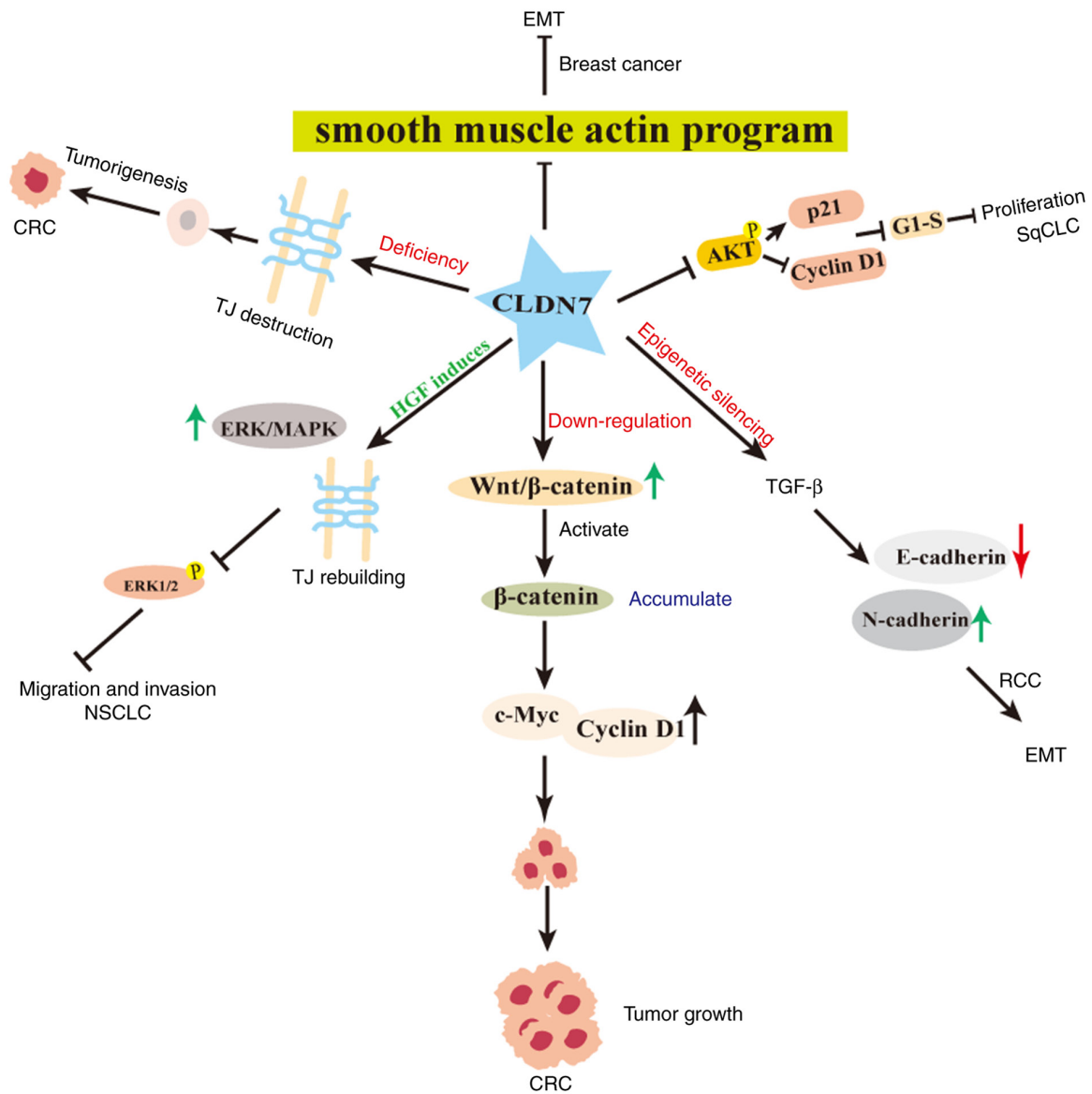


Figure 3. Regulatory mechanisms of CLDN7 in cancer. CLDN7, claudin-7; EMT, epithelial-mesenchymal transition; AKT, AKT serine/threonine kinase; p21, cyclin-dependent kinase inhibitor 1A; Cyclin D1, G1/Specific Cyclin-D1; Wnt/β-catenin, wingless/integrated/β-catenin; c-Myc, MYC proto-oncogene; TGF-β, transforming growth factor-beta; SqCLC, squamous-cell lung cancer; RCC, renal cell carcinoma; CRC, colorectal cancer; NSCLC, non-small-cell lung cancer.

disrupts intercellular adhesion, detaching epithelial cells from the basal layer, thus enhancing motility (76). CLDN7 is an epithelial marker in multiple tumors and its expression regulates EMT, influencing tumor metastasis (32,88). In CRC, reduced CLDN7 expression correlates with lower histological grade, facilitating invasion and metastasis through EMT regulation (76). Moreover, APC loss or β-catenin mutation activates Wnt signaling, downregulating CLDN7 and E-cadherin, while upregulating Snail/ZEB1/Vimentin, disrupting TJs and initiating EMT (89). In renal cell carcinoma, epigenetic silencing of CLDN7 promotes TGF-β-driven EMT (E-cadherin↓, N-cadherin↑) and restoring CLDN7 expression can reverse EMT, suppressing local invasion and distant metastasis (32). In salivary adenoid cystic carcinoma (SACC), CLDN7 knockdown enhances metastasis, decreases E-cadherin expression and increases N-cadherin and vimentin expression (81). Furthermore, West *et al* (84) used mouse models, human organoids and multi-omics

data to demonstrate that CLDN7 blocks EMT by inhibiting SMA-actin, thereby reducing breast cancer invasion and metastasis.

In the canonical Wnt/β-catenin pathway, β-catenin accumulates in the cytoplasm, enters the nucleus and promotes tumor progression by activating downstream genes (90). CLDN7 silencing activates Wnt/β-catenin signaling, promoting proliferation and metastasis in SACC and CRC. In SACC, nuclear β-catenin accumulation accompanies EMT, whereas in CRC, β-catenin drives transcription of c-Myc and Cyclin D1, promoting CRC cell proliferation and metastasis (7,84). Additionally, hepatocyte growth factor induction enables CLDN7 to re-establish TJs and suppress ERK/MAPK signaling in human lung cancer cells, markedly reducing ERK1/2 phosphorylation and thereby inhibiting non-small cell lung cancer cell migration and invasion (77).

*Clinical significance of CLDN7 in tumors.* Analysis using the GEPIA database indicates that CLDN7 expression

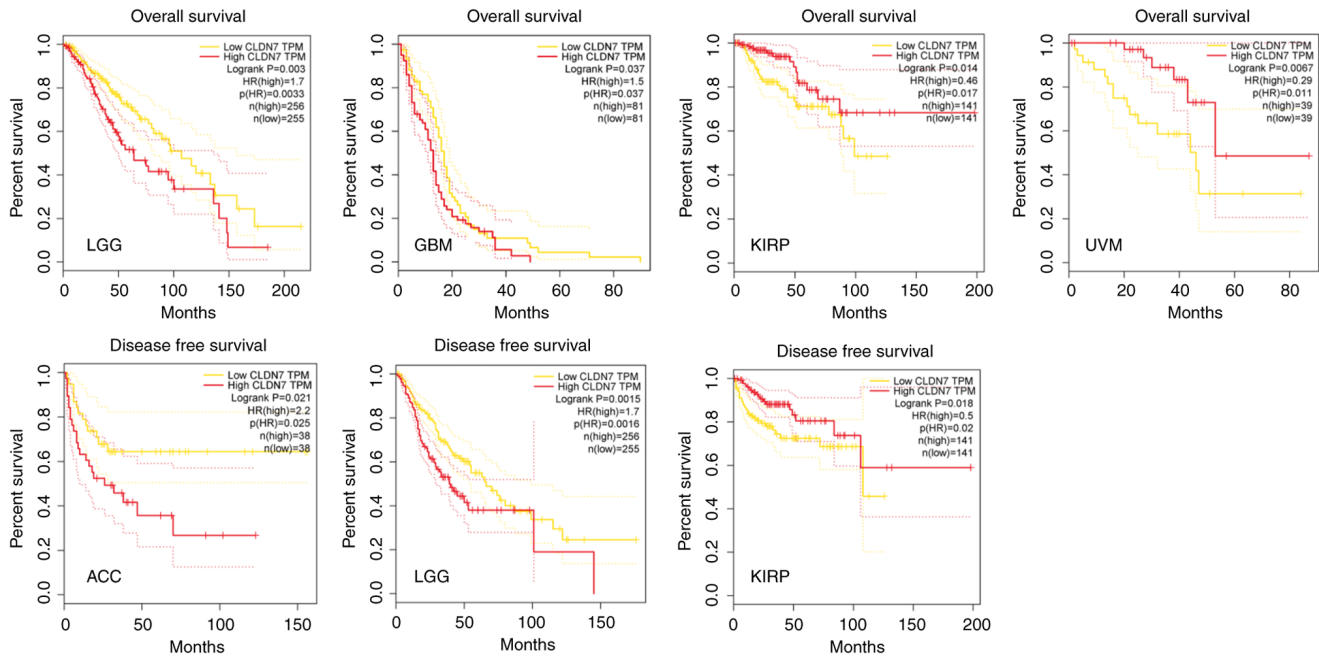


Figure 4. Correlation between CLDN7 levels and OS or DFS in different tumor tissues. Data were retrieved from the Gene Expression Profiling Interactive Analysis (GEPIA) public database (<http://gepia.cancer-pku.cn>). CLDN7, claudin-7; OS, overall survival; DFS, disease-free survival; TPM, transcripts per million; HR, hazard ratio; LGG, low-grade glioma; GBM, glioblastoma multiforme; KIRP, clear cell renal cell carcinoma; UVM, uveal melanoma; ACC, adrenal cortical carcinoma.

correlates with overall survival (OS) and disease-free survival (DFS) (Fig. 4). In low-grade glioma (LGG) and glioblastoma multiforme, high CLDN7 expression is associated with poorer OS. In clear cell renal cell carcinoma and uveal melanoma, low CLDN7 expression predicts poorer OS. High CLDN7 expression correlates with reduced DFS in adrenal cortical carcinoma and LGG, whereas the opposite occurs in clear cell renal cell carcinoma. Histopathological analysis of pancreatic and nasopharyngeal carcinoma tissues shows a statistically significant association between reduced CLDN7 expression and lower survival rates (91). In gastric cancer, high CLDN7 expression correlates with shorter survival (92). Overexpression of CLDN7 in breast cancer is associated with poorer DFS (88). In colon cancer, low CLDN7 expression and positive perineural infiltration are independent predictors of poor DFS (93). Thus, CLDN7 may serve as a prognostic biomarker in various cancers.

CLDN7 downregulation is closely associated with aggressive phenotypes and poor prognosis across multiple tumor types. Knockdown of CLDN7 markedly increases ERK1/2 phosphorylation, promoting cell proliferation and invasion, whereas restoration of CLDN7 expression markedly attenuates these malignant phenotypes (83). Clinicopathological analyses demonstrate markedly reduced CLDN7 expression in peritumoral tissues and metastatic lymph nodes of esophageal cancer. Its loss correlates positively with deeper tumor invasion, lymphatic vessel invasion and nodal metastasis, suggesting that CLDN7 may predict lymph-node metastasis (33). At the invasive front of esophageal squamous-cell carcinoma, CLDN7 is frequently hypermethylated, causing heterogeneous downregulation. Its deletion decreases E-cadherin expression, promoting tumor growth and invasion, while abnormal localization contributes to transformation

and E-cadherin dysregulation (94). Similarly, loss of CLDN7 in oral squamous-cell carcinoma correlates with high tumor grade, advanced TNM stage, vascular invasion and regional lymph-node involvement (95). Low CLDN7 expression in breast and endometrial cancers correlates with higher histological grade and distant metastasis, representing an independent prognostic factor (96,97). In non-small-cell lung cancer, ectopic CLDN7 expression enhances cisplatin-induced apoptosis via caspase activation, thereby increasing drug sensitivity (98).

Overexpression of CLDN7 may promote malignant tumor behavior (34). Microarray analysis of esophageal adenocarcinoma reveals markedly higher CLDN7 transcription levels compared with adjacent normal mucosa, suggesting that its activation may represent an early event in tumorigenesis (95). Palmitoylated CLDN7 forms complexes with MMP-family proteins and CD147, potentially promoting tumor metastasis (48). Gastric cancer also exhibits sustained CLDN7 upregulation, which progressively increases with disease stage (99). Adenocarcinomas of the prostate (100), pancreas (100), cervix (101) and ovary (25) frequently display CLDN7 overexpression, associated with poor prognosis. Conversely, silencing CLDN7 via RNA interference markedly reduces invasive and migratory capabilities of cancer cells (82,102). In ovarian cancer cells, high CLDN7 expression is associated with platinum resistance, whereas its knockdown restores cisplatin sensitivity (103).

Currently, research on CLDN7-targeted anti-cancer drugs remains at the preclinical stage and no specific CLDN7 agents have received clinical approval. However, several compounds modulate CLDN7 expression or function to exert anti-tumor effects. In CRC, the methylation inhibitor 5-aza-2'-deoxycytidine reverses promoter methylation, markedly increasing

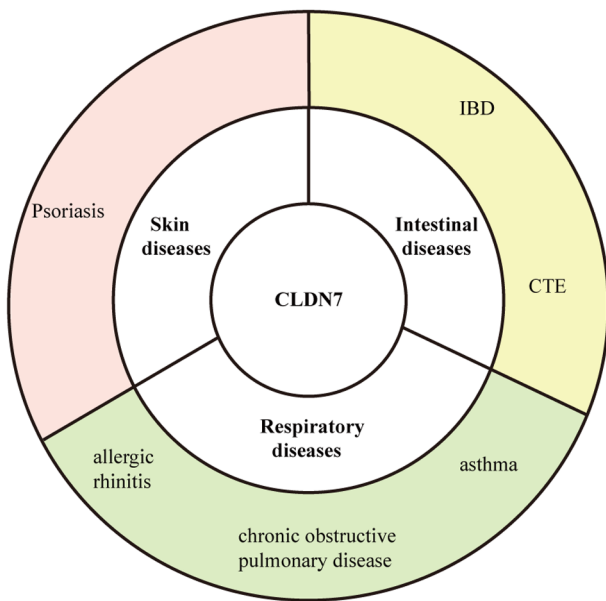


Figure 5. The role of CLDN7 in non-cancer diseases. CLDN7, claudin-7; IBD, inflammatory bowel disease; CTE, congenital tufting enteropathy.

CLDN7 expression (31,104). Additionally, 2-deoxy-D-glucose (2-DG) inhibits glycolysis, blocking tumor-derived CLDN7-mediated metabolic reprogramming and immunosuppressive effects of tumor-associated neutrophils, thus indirectly reducing the tumor-promoting role of CLDN7 (82).

**Role of CLDN7 in non-cancer diseases.** CLDN7 also contributes to the development of intestinal, skin and respiratory diseases (Fig. 5).

#### CLDN7 and intestinal diseases

**IBD.** IBD represents a group of disorders characterized by intestinal epithelial barrier damage and chronic inflammation (105). CLDN7 expression is markedly reduced in IBD and patients exhibit persistent epithelial hyperpermeability and microbial invasion (106). CLDN7 deficiency correlates with impaired gut epithelial integrity, exacerbated intestinal inflammation and increased matrix metalloproteinase expression (57). Furthermore, CLDN7 deficiency selectively increases paracellular permeability to small-molecule organic solutes, enhancing bacterial product infiltration and exacerbating intestinal inflammation (107). Analysis of gut microbiota in CLDN7-deficient mice demonstrates reduced microbial diversity, intensifying DSS-induced inflammation (108). When therapeutic interventions mitigate intestinal injury, CLDN7 expression is restored, promoting intestinal epithelial recovery (109).

**Congenital tufting enteropathy (CTE).** CTE is a rare intestinal disorder characterized by intractable neonatal diarrhea and intestinal epithelial tufting (110). CTE primarily results from loss-of-function mutations in the EpCAM gene. A subset of cases involves mutations in SPINT2, which normally protects EpCAM from matriptase-mediated degradation; SPINT2 mutations also result in near-complete EpCAM loss (111,112). Studies show that loss-of-function mutations in EpCAM or SPINT2 cause excessive degradation of CLDN7,

severely impairing or abolishing its stability (111,112). Despite distinct genetic origins, both mutations ultimately lead to significant CLDN7 dysfunction, disrupting TJ structure and intestinal epithelial barrier function. This breakdown is a major contributor to severe diarrhea characteristic of CTE.

**CLDN7 and skin diseases.** Psoriasis is an inflammatory skin disease characterized by excessive keratinocyte proliferation, impaired barrier function and marked inflammatory cell infiltration (113). CLDN7 expression is dysregulated in psoriasis. Kirschner *et al* (11) detected markedly reduced CLDN7 expression in early-stage psoriasis using immunofluorescence and real-time PCR. Additionally, CLDN7 localization at the cell membrane is diminished in the basal and granular layers, indicating compromised barrier integrity. Another study demonstrated that pro-inflammatory cytokines, such as IL-36 $\gamma$ , downregulate CLDN7 expression in keratinocytes, exacerbating epidermal barrier defects and driving inflammatory responses (10). Conversely, elevated CLDN7 expression occurs in the granular epidermal layer of psoriasis patients and inhibition of HMG-CoA reductase reduces this elevation (27). Thus, CLDN7 likely contributes to psoriasis pathogenesis.

**CLDN7 and respiratory diseases.** CLDN7 is broadly expressed in the respiratory barrier and is implicated in respiratory diseases, including allergic rhinitis (AR), chronic obstructive pulmonary disease (COPD), and asthma.

**AR.** AR is a common condition affecting ~400 million individuals worldwide (114). Although AR is not life-threatening, it markedly disrupts daily activities. Reports indicate that damage to the nasal epithelium is crucial in AR pathogenesis (115,116). Nasal epithelium from AR patients exhibits markedly lower CLDN7 transcript levels compared with non-allergic controls. This reduction strongly associates with secondhand smoke exposure, where oxidative stress disrupts the CLDN7-mediated TJ barrier, increasing susceptibility to AR (14).

**COPD.** Long-term exposure to tobacco smoke and particulate matter (PM) disrupts TJs in airway epithelium, increasing barrier permeability, mucus secretion and bacterial translocation in COPD (12). Studies indicate markedly reduced mRNA expression levels of TJ proteins (CLDN1, CLDN3, CLDN7, CLDN15) in COPD, suggesting their potential as novel biomarkers for early COPD diagnosis (117).

**Asthma.** Dysfunction of airway epithelial cells in asthma is associated with impaired wound healing, compromised TJs and excessive cell proliferation. These factors contribute to abnormal airway responses to external pathogens (118-120). Asthmatic patients exhibit lower plasma CLDN7 levels, positively correlating with lung function (FEV1/FVC). Additionally, CLDN7 expression is suppressed by titanium dioxide exposure, suggesting that PM exposure may induce airway epithelial barrier dysfunction, inflammation and hyperresponsiveness (13). Exposure to diesel exhaust particles similarly alters CLDN4, CLDN5 and CLDN17 expression in mouse nasal passages and lungs (121). Such consistent regulation across respiratory barriers offers potential therapeutic targets for airway diseases.

In summary, CLDN7 markedly influences multiple non-tumor diseases, including intestinal disorders, skin conditions and respiratory diseases. Additionally, CLDN7 plays a

critical role in salt homeostasis in renal collecting duct cells through modulation by WNK4 and regulation of NaCl transport (75). These findings highlight the broad involvement of CLDN7 in regulating various non-neoplastic conditions.

Several agents modulate CLDN7 expression and function. Compounds aiming to restore barrier integrity typically upregulate CLDN7 expression. Metformin reverses TNF- $\alpha$ -induced reductions in CLDN7 transcription and protein levels in intestinal organoids by activating AMPK (122). Nobiletin restores CLDN7 expression and TJ integrity by recruiting HNF4 $\alpha$  to directly bind the CLDN7 promoter (109). Polysaccharides from *Atractylodes macrocephala* Koidz upregulates CLDN7 by simultaneously inhibiting MAPK-mediated MMP-7/8 activity (reducing protein degradation) and activating the JAK-STAT-IRF1 pathway (enhancing transcription), thus restoring TJ function (123). Conversely, prolonged treatment with the MAPK agonist anisomycin selectively activates p38, causing removal of CLDN7 from TJs, reducing transepithelial electrical resistance and increasing paracellular permeability (124). Furthermore, vitamin D upregulates CLDN7 expression in active ulcerative colitis, enhancing barrier recovery and reducing inflammatory infiltration (125). These agents remain in preclinical stages, primarily tested in colitis or cancer models. If clinical trials confirm their efficacy and safety, their application may extend to other inflammatory or epithelial barrier-related diseases beyond the gastrointestinal tract.

## 7. Conclusions and perspectives

CLDN7, a crucial member of the claudin family, comprises four transmembrane domains, two extracellular loops and N- and C-terminal regions. It shows high expression in various epithelial tissues and is regulated by transcription factors, post-translational modifications and epigenetic mechanisms. Beyond its classical barrier function, CLDN7 also regulates stem cell fate and ion transport, maintaining epithelial tissue homeostasis.

CLDN7 exhibits functional dysregulation in both cancer and non-cancer diseases, displaying bidirectional roles and distinct pathological outcomes. In tumors, CLDN7 expression loss correlates with EMT and elevated metastatic risk. Conversely, its overexpression promotes malignant progression through mechanisms such as palmitoylation and MMP-CD147 complex formation, correlating with poor prognosis in multiple malignancies. In non-cancer diseases, CLDN7 expression is typically downregulated, leading to increased epithelial/mucosal barrier permeability and contributing to chronic inflammation. Mechanistically, both disease categories involve CLDN7-mediated disruption of barrier integrity and related signaling pathway alterations. Overall, the pathological roles of CLDN7 depend on expression levels, post-translational modifications and subcellular localization, reflecting context-dependent functionality across diverse diseases. Although no CLDN7-selective targeted drugs have entered clinical use, preclinical studies demonstrate that agents, including epigenetic modulators, glycolysis inhibitors, AMPK activators and natural products, effectively influence epithelial barrier function, EMT and tumor cell chemosensitivity by modulating CLDN7 expression.

However, clinical translation of CLDN7 still faces several challenges: i) Current understanding of CLDN7's mechanisms in tumors and non-neoplastic diseases remains insufficient, necessitating further research to support drug development and clinical application. ii) As CLDN7 is expressed in most normal tissues, potential side effects require careful consideration in targeted therapy design. iii) CLDN7 exhibits bidirectional prognostic significance, high in some cancers and low in others, even among different cancer subtypes, creating uncertainty in indication selection and risk assessment. Additionally, several unknowns and future research directions remain: Clarifying the reasons underlying differential CLDN7 expression across tumors and determining if CLDN7 regulatory signaling pathways are tissue- or cell-type-specific in neoplastic and non-neoplastic diseases.

In summary, future studies should elucidate the tissue-specific expression patterns of CLDN7 and regulatory mechanisms underlying its bidirectional diseases roles, further refining its pathological regulatory network. CLDN7 has the potential to serve as a novel biomarker for tumor and non-tumor inflammatory diseases, facilitating early diagnosis and prognosis. Meanwhile, targeted drug development based on CLDN7's regulatory mechanisms, combined with tissue-specific delivery technologies to minimize off-target effects, may offer promising therapeutic strategies, demonstrating considerable potential for clinical translation.

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## Availability of data and materials

Not applicable.

## Authors' contributions

XL and YY collected literatures, created the figures and wrote the first draft of the manuscript. LS collected literatures. ZL and YHY conceived the review, analyzed the relevant literatures and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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