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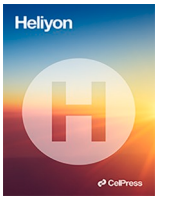

Review article

Expression patterns of claudins in cancer

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ABSTRACT

Claudins are four-transmembrane proteins, which were found in tight junctions. They maintain cell barriers and regulate cell differentiation and proliferation. They are involved in maintaining cellular polarity and normal functions. Different claudins show different expression patterns. The expression level and localization of claudins are altered in various cancers. They promote or inhibit proliferation, invasion, and migration of cancer cells through multiple signaling pathways. Therefore, claudins may serve as diagnostic markers, novel therapeutic targets, and prognostic risk factors. The important roles of claudins in cancer aroused our great interest. In the present review, we provide a summary of insights into expression patterns of claudins in cancer, which is more comprehensive and provides new ideas for further research.

1. Introduction

Tight junctions (TJs) are a type of intercellular junctions. They are widely distributed at the apical regions of epithelial cells and endothelial cells. TJs act as mechanical junctions and selective barriers. As a result, TJs are essential for the maintenance of cellular polarity [1]. TJs are formed of the intricate combinations of multiple proteins. In 1998, Furuse et al. successfully identified and designated the claudin (CLDN) protein within the complex structure of TJs [2]. The CLDN family is a major component of TJs (Fig. 1). At least 24 members have been identified. CLDNs are important to cell barriers, cell differentiation, and proliferation [1]. The expression profile of CLDNs is tissue-specific. For example, CLDN18.1 was mainly expressed in the lung, whereas CLDN18.2 was mainly found in the stomach [3,4].

Previous studies have shown apparent changes in the expression level and localization of CLDNs in several pathological conditions [5–10]. Depending on the different types of cancer, CLDNs can exert either tumor suppressor or tumor promoting effects through different pathways. For example, CLDN1 could promote cancer cell proliferation or invasion in colorectal cancer [11], thyroid cancer [12], estrogen receptor (ER)-negative breast cancer [13], gastric cancer [14], pancreatic cancer [15]. In contrast, it could inhibit cancer cell proliferation in prostate cancer [16], lung adenocarcinoma [17], and ER-positive breast cancer [13]. Therefore, CLDNs may provide new insights into pathological diagnosis and perhaps new targets for therapy. Compared with previous reviews, this paper summarized CLDNs-related studies and progress more comprehensively, which would provide new ideas for subsequent intensive research.

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1.1. Classification, expression and function of claudins

Mammalian CLDNs are divided into classic and non-classic CLDNs. Classic CLDNs include 1–10, 14, 15, 17, and 19. Non-classic CLDNs comprise 11–13, 16, 18, and 20–24 (Fig. 2). The C-terminus of classic CLDNs is short. Nonclassic CLDNs have a longer C-terminus, which interacts with cytoplasmic scaffolding proteins [18]. They can also be divided into two types according to the main functions: pore-forming and sealing CLDNs. The pore-forming CLDNs could form paracellular channels, such as CLDN2, 10, and 15. The sealing CLDNs could limit paracellular permeability, like CLDN1, 3, 4, 5, 7, and 11 [18]. CLDNs are expressed in a variety of normal human tissues. We summarized the expression patterns (Table 1) and functions (Table 2) of CLDNs in normal tissues.

1.2. Claudins in cancer

Alterations of the expression or localization of CLDNs have been observed in various tumors. Their expression profiles can be regulated by different mechanisms. Furthermore, these changes could result in alterations of cancer cell functions through various pathways.

Epithelial-mesenchymal transition (EMT) is the process by which epithelial cells transform into cells with a mesenchymal phenotype, allowing epithelial cells to acquire mesenchymal characteristics such as increased migration rate [40]. EMT is therefore one of the keys to cancer cell metastasis. High expression of CLDN1 in colorectal cancer [41], hepatocellular carcinoma [42], and lung cancer [43] might enhance cancer cell aggressiveness through promotion of EMT. CLDN3 could inhibit EMT in hepatocellular carcinoma [44] and lung cancer [45]. Whether CLDN6 promotes EMT depends on the tumor type. CLDN6 promoted EMT in gastric cancer [46], but suppressed EMT in breast cancer [47].

Cell proliferation and apoptosis can also be affected by changes of CLDNs expression. In colorectal cancer, high expression of CLDN1 could promote proliferation and resist apoptosis [48]. However, in pancreatic cancer, increased CLDN1 might suppress cancer cell proliferation and promote apoptosis [15]. In lung cancer, CLDN18.1 expression was down-regulated, which promoted cancer cell proliferation and inhibited apoptosis [49].

Furthermore, CLDNs are associated with cancer chemoresistance. In pancreatic cancer cells, CLDN7 promoted cell resistance to cisplatin [50]. High expression of CLDN1 and CLDN2 could also confer resistance to cisplatin in lung cancer cells [51,52].

1.3. Claudins in gastric cancer

CLDNs play vital roles in gastric cancer (Table 3). Different CLDNs can affect the occurrence and development of gastric cancer through multiple pathways.

CLDN1's role in gastric cancer is debated. Recent research suggested that CLDN1 was the direct target of the tumor suppressor RUNX3. RUNX3 could up-regulate CLDN1 expression and reduce tumorigenicity by binding to its promoter region. Meanwhile, transforming growth factor beta (TGF-β) might promote the combination of the two [54]. Besides, some research showed that β-catenin which was increased in gastric cancer could up-regulate CLDN1. High CLDN1 expression was associated with lymph node involvement, higher TNM stage, poor overall survival (OS) [14], and poor postoperative survival in gastric cancer patients [53], suggesting that CLDN1 may promote gastric cancer development.

Researches on CLDN6 in gastric cancer are controversial. Several studies showed that CLDN6 expression was increased in gastric cancer which might promote cell migration [55]. By interacting with large tumor suppressor 1/2 (LATS1/2), CLDN6 reduced the phosphorylation level of Yes-associated protein 1 (YAP1) and promoted YAP1 entry into the nucleus, thereby increasing the transcriptional activity of the EMT-associated transcription factor Snail1, which promoted EMT and increased cancer cell invasion [46]. Other works showed that CLDN6 might be a tumor suppressor in gastric cancer. Overexpression of CLDN6 in gastric cancer cells could inhibit the c-Jun N-terminal kinase (JNK) pathway, promote the differentiation of tumor cells which would make them more similar to

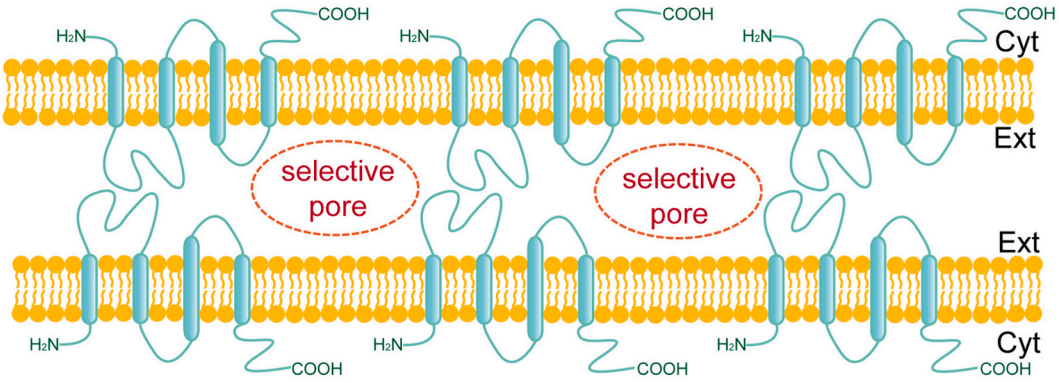

Fig. 1. Claudins are essential components of intercellular tight junctions. Claudins are four-transmembrane proteins that act as mechanical barriers by interconnecting and are involved in forming intercellular selective pores.

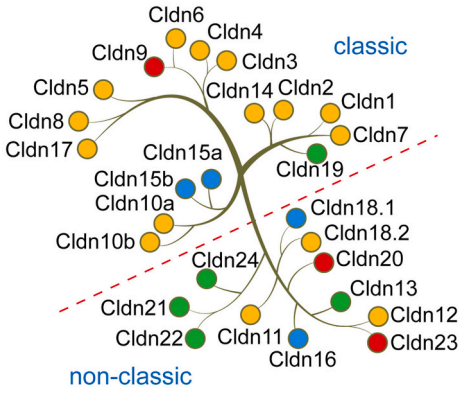

Fig. 2. Mammalian claudins are mainly divided into two categories. One is classic, and the other is non-classic. The blue dots indicate that the claudin may mostly play a tumor suppressor role in tumors. The red dots indicate that the claudin may mainly play a role in promoting tumors. Yellow dots mean that the claudin plays a tumor-promoting or tumor-suppressing role in different tumors. Green dots indicate that the specific role of claudin in tumors has not been reported yet.

Table 1
Expression patterns of claudins in normal tissues.

Claudins	Expression patterns	Reference
CLDN1	Intestine, brain, kidney, liver, testis, fetal lung alveolar epithelial (HFL) cells, bronchiolar epitheliums, and pancreatic ducts and exocrine glands	[19–21]
CLDN2	Pancreatic ducts and exocrine glands	[21]
CLDN3	Colorectal, thyroid, salivary gland, pancreas, prostate cancer, liver, kidney, HFL cells, bronchiolar epitheliums, pancreatic ducts and exocrine glands, and pancreatic islet endocrine glands	[19–21]
CLDN4	Breast, ovary, prostate, bladder, gastrointestinal mucosa, bile duct, HFL cells, type II alveolar epitheliums, bronchiolar epitheliums, and pancreatic ducts and exocrine glands	[19–21]
CLDN5	HFL cells, type II alveolar epitheliums, and vascular endothelial cells	[20,22,23]
CLDN6	Normal tissues during embryonic development	[24,25]
CLDN7	Bronchiolar epitheliums, pancreatic ducts and exocrine glands, and pancreatic islet endocrine glands	[20,21]
CLDN10a	Kidney	[26]
CLDN14	Thick ascending limb of Henle	[27,28]
CLDN18.1	HFL cells and type II alveolar epitheliums	[19]
CLDN18.2	Gastric mucosal epithelial cells	[4]

Table 2
Function of claudins in normal tissues.

Claudins	Function	Reference
CLDN2	Formation of cation channels	[29]
	Promotes the permeability of Na^+ and water through solvent dragging	[30]
CLDN5	Formation of blood-brain barrier	[22]
CLDN10a	Formation of anion channels	[29,31]
CLDN10b	Formation of cation channels	[29,31]
CLDN14	Regulated the permeability of Ca^{2+} in the thick ascending limb of Henle (TAL)	[27,28]
CLDN15	Formation of cation channels	[29]
	Decoupled the solvent dragging effect of CLDN2	[32]
CLDN16	Regulated the permeability of Mg^{2+} in the TAL	[33,34]
CLDN17	Formation of anion channels	[29]
CLDN18.1	Maturation and differentiation of the alveolar epithelium	[3,35–37]
CLDN18.2	Regulated the permeability of H^+ between gastric mucosal epithelial cells	[38]
	Formation of gastric mucosal barrier	[39]
CLDN19	Regulated the permeability of Mg2+ in the TAL	[34]

normal gastric epithelial cells, and reduce the degree of malignancy of gastric cancer cells [57].

Furthermore, the clinicopathological analysis showed that low expression of CLDN6 in gastric cancer was associated with lymph node metastasis, late stage, distant metastasis and poor prognosis [63]. Although its function is disputed, it has been developed as a therapeutic target. The potential of CLDN6 as a tumor immunotherapy target was demonstrated by a virus-like particle (VLP) vaccine against CLDN6, which induced a complement-dependent cytotoxic (CDC) response in mice [64]. In addition, a chimeric antigen receptor (CAR) T-cell therapy targeting CLDN6 in combination with RNA lipoplex (LPX) is in phase I/II clinical trials for solid tumors

Table 3
Roles of claudins in gastric cancer.

Claudins	Activity	Findings	Reference
CLDN1	Tumor promoter	Associated with lymph node metastasis, higher TNM stage, worse overall survival (OS), and postoperative survival	[14,53]
	Tumor suppressor	Reduced the tumorigenic effect of GC cells	[54]
CLDN2	Tumor promoter	Promoted the invasion and growth of GC cells	[55]
CLDN4	Tumor suppressor	Inhibited the invasiveness of gastric cancer cells	[56]
CLDN6	Tumor promoter	Promoted EMT through the LAST1/2-YAP1 pathway	[46]
	Tumor suppressor	Promoted GC cell differentiation by inhibiting the JNK pathway	[57]
CLDN7	Tumor promoter	Promoted the invasiveness of GC	[55]
CLDN9	Tumor promoter	Promoted the migration of GC	[55]
CLDN10	Tumor promoter	Low expression of CLDN10 correlated with better OS	[58]
CLDN11	Tumor suppressor	Low expression of CLDN11 was associated with increased cancer cell invasion, migration, and proliferation	[59]
CLDN18.2	Tumor promoter	CLDN18-ARHGAP26 gene fusion reduced the adhesion of cancer cells and makes cancer cells more invasive	[60]
	Tumor suppressor	Deletion of *Cldn18.2* could cause gastric inflammation and create conditions for GC	[61]
CLDN23	Tumor promoter	Patients expressing CLDN23 had a worse prognosis and were associated with vessel cancer embolus	[62]

expressing CLDN6 (NCT04503278), which has shown high efficacy [65].

CLDN11 expression was decreased in gastric cancer. Decreased lncRNA PCAT18 in gastric adenocarcinoma would increase the miR-135b, thereby inhibiting the transcription of *CLDN11* and promoting the invasion, migration, and proliferation of cancer cells [59]. Meanwhile, miR-421 could also inhibit CLDN11 and arrest the G1/S cell cycle [66]. Furthermore, CLDN11 expression was regulated by epigenetic mechanisms as well. Hypermethylation of the *CLDN11* promoter leads to its silencing [67,68]. However, CLDN11 was increased in gastric cancer metastases [69], suggesting that CLDN11 has different functions at different stages in the occurrence and development of gastric cancer.

Infection with Helicobacter pylori (*H. pylori*) causes persistent inflammation and damage to the gastric mucosa, eventually resulting in gastric cancer. However, *Cldn18.2*-KO mice could develop refractory gastritis in the absence of *H. pylori* infection, leading to spasmolytic polypeptide expressing metaplasia (SPEM) and ultimately gastric cancer. When incubated with *H. pylori*, deleting *CLDN18.2* could cause permeability defects [70,61]. These studies show that *CLDN18.2* deletion can cause gastritis and increased gastric cancer susceptibility.

The clinicopathological analysis of CLDN18.2 in gastric cancer is disputed. Some studies showed that CLDN18.2 had no significant relationship with gender [71,72], age [73], primary tumor location [73], TNM stage [72], Lauren classification, and prognosis [5,71, 74–78]. However, other studies showed that high CLDN18.2 expression was correlated with age (<70 years old) [77], higher initial stage [77], lymph node and distant metastasis, diffuse gastric cancer in Lauren classification, and better prognosis [72,79–81].

In normal gastric mucosa, CLDN18.2 is located in the cell membrane. In contrast, gastric cancer cells showed diffuse CLDN18.2 positivity in the membrane, cytoplasm, and even nucleus [10]. Meanwhile, CLDN18.2 expression in gastric cancer cells was correlated with mucin-5AC (MUC5AC) expression and mucin-2 (MUC2) deletion [79,82]. In the invasive front of gastric cancer, higher CLDN18.2 expression was associated with lower Ki67 expression [83]. CLDN18.2 was also linked to the human epidermal growth factor receptor 2 (HER2) expression [71,78] and Epstein-Barr virus (EBV) infection [5,73,77].

It is interesting to note that CLDN18.2 has become an emerging gastric cancer therapeutic target. A phase I clinical trial of CAR T-cell therapy targeting CLDN18.2 is currently underway (NCT03874897) and has shown promising efficacy in patients with advanced or refractory gastric cancer [84]. IMAB362 is a newly developed chimeric monoclonal antibody capable of killing CLDN18.2-positive tumor cells by antibody-dependent cell-mediated cytotoxicity (ADCC) and CDC [85]. In addition, in some gastric cancers, mainly diffuse gastric cancer and signet ring cell carcinoma, the CLDN18-ARHGAP26 gene fusion can be observed. It was associated with patient age, stage, metastasis, prognosis, and genomically stable (GS) gastric cancer subtype and exclusively with RHOA and cadherin 1 (CDH1) mutations. CLDN18.2 is diffusely positive in gastric cancer cells with the gene fusion. The fusion protein could disrupt the post-synaptic density-95, disks-large, and zonula occludens-1 (PDZ)-binding domain of wild-type CLDN18.2, reduce cancer cell adhesion, and promote cancer cell invasion [60,86,87].

CagA is a virulence-related factor of *H. pylori*. After *H. pylori* infection, cagA could up-regulate the expression of caudal-related homeobox transcription factor 2 (CDX2) and promote the binding of CDX2 to the promoter region of *CLDN2*, which increased the CLDN2 expression. Upregulated CLDN2 may promote the invasion of gastric cancer cells [88]. These studies indicate CLDN2 primarily plays a promoting role in gastric cancer progression. Instead, CLDN4 mainly acted as a tumor suppressor in gastric cancer by inhibiting the invasion and migration of gastric cancer cells. CLDN4 could be regulated by epigenetic mechanisms of methylation and histone modifications [56]. Furthermore, CLDN7 promoted cancer cell invasion, and CLDN9 enhanced cell migration [55]. Reduced CLDN10 was associated with better OS and had a negative correlation with immune cell infiltration [58]. CLDN23 was decreased in gastric cancer, but patients with higher CLDN23 expression had worse prognosis and more vascular tumor thrombus [62].

1.4. Claudins in colorectal cancer

CDX2 is up-regulated in most colorectal cancer cases. By cooperating with CDX1 and GATA binding protein 4 (GATA4), it increased the expression of β-catenin, which then raised the transcriptional activity of T-cell factor (Tcf) and initiated the transcription of *CLDN1* [89,90]. As a tumor suppressor, SMAD family member 4 (SMAD4) was down-regulated in colorectal cancer and lost its inhibitory effect on CLDN1 expression [91]. Tumor necrosis factor-α (TNFα), one of the critical cytokines in colitis-associated colorectal cancer (CAC) development, could also up-regulate CLDN1 expression [41]. CLDN1 up-regulated the EMT-related transcription factors Snail and Slug by the activation of the c-Abl-Ras-Raf-1-ERK1/2 pathway, thereby promoting EMT and increasing cell invasion and migration [41]. Another EMT-related transcription factor is zinc finger E-box binding homeobox 1 (ZEB1). CLDN1 could up-regulate the activity of ZEB1 through the Wnt and PI3K/AKT pathways, which down-regulated E-cadherin and promoted EMT. In a feedback loop, down-regulation of E-cadherin activated the Wnt pathway. Simultaneously, the PI3K/AKT pathway could activate Snail and Slug transcriptional activity [92]. In addition, CLDN1 could also activate the Notch pathway by upregulating ERK and matrix metalloproteinase 9 (MMP9), which increased inflammation and cancer cell proliferation [93].

Anoikis is a type of programmed cell death induced by separating cells from the extracellular matrix, which is one of the essential mechanisms of tumor metastasis. In colorectal cancer, CLDN1 bound to Src protein, activated Akt, and up-regulated Bcl-2, allowing cancer cells to acquire the anti-anoikis ability and enhanced metastasis [48].

High expression of CLDN1 in colorectal cancer was associated with poor prognosis [92]. In conclusion, CLDN1 plays a promoting role in the progression of colorectal cancer by enhancing the invasion, migration, and proliferation of cancer cells. However, some studies indicated that high CLDN1 expression was associated with a better prognosis [94]. Differences in the length of follow-up may explain the discrepancy with previous studies. The former was followed for over 10 years, while the latter was followed for 3 and 5 years. This suggests that high CLDN1 expression might have a negative correlation with long-term prognosis. Moreover, CLDN1 was a novel target for colorectal cancer [95].

CLDN2 is up-regulated in colorectal cancer and mainly plays a promoting role. The microenvironment of colorectal cancer activated the ERK1/2 and PI3K pathways in an epidermal growth factor receptor (EGFR)-dependent manner and up-regulated CLDN2 [96]. Inhibition of CLDN2 expression could dissociate the CLDN2/zonula occludens 1 (ZO1)/ZO-1-associated Y-box factor (ZONAB) complex. ZONAB translocated to the nucleus which promoted the transcription of n-myc downstream-regulated gene 1 (NDRG1). NDRG1 could increase cyclin-dependent kinase inhibitor activity, thereby arresting the cell cycle. At the same time, NDRG1 could ubiquitinate caveolin-1 and inhibit EMT. In addition, CLDN2 stabilized the CLDN2/ZO1/ZONAB complex and prevented ZONAB from entering the nucleus, thereby inhibiting NDRG1 expression and promoting cancer cell proliferation, invasion, and migration [97,98]. Highly expressed CLDN2 could also promote liver and lung metastasis, which was linked to its PDZ-binding motif [99].

In colorectal cancer cells, EGF bound to EGFR and activated the ERK1/2 and PI3K/AKT pathways, thereby upregulating CLDN3 expression [100]. However, another study showed that CLDN3 expression was down-regulated by epigenetic mechanisms in colorectal cancer. Low expression of CLDN3 promoted EMT through activation of the Wnt/β-catenin pathway and enhanced cell migration ability. Low CLDN3 expression could also activate the IL-6/IL-23/STAT3 pathway and further activate the Wnt pathway. Accordingly, patients with higher CLDN3 expression showed improved outcomes [101].

The role of CLDN7 in colorectal cancer is still controversial. The Wnt/Tcf4 pathway inhibited CLDN7 expression via SRY box transcription factor 9 (SOX9) in colorectal epithelial cells. In colorectal cancer, this inhibitory effect was relieved, and high CLDN7 expression disrupted cell polarity and promoted proliferation [102]. However, another study suggested that low expression of CLDN7 increased Snail1 activity and promoted EMT [103]. Meantime, low expression of CLDN7 was associated with poor differentiation, vein invasion, and liver metastasis [103,104]. CLDN8 mainly plays a promoting role in colorectal cancer progression. The LncRNA LINC00662 was up-regulated in colorectal cancer and competed with miR-340-5p for binding, thereby increasing the co-expression of CLDN8/IL22. CLDN8 then activated the MAPK/ERK pathway and up-regulated the expression of MMP-9, promoting cell proliferation, invasion, and migration [105,106]. CLDN11 expression was under epigenetic regulation, which was reduced by promoter hypermethylation. Low level of CLDN11 was associated with metastasis and poor prognosis [107]. In vitro, CLDN12 induced cell proliferation which could be inhibited by anti-CLDN12 antibody [108]. This suggests that anti-CLDN12 may be one of the targeted therapies for colorectal cancer. The expression of CLDN14 was increased, which promoted cancer cell proliferation, invasion, and migration by activating the PI3K/AKT/mTOR pathway [109]. CLDN23 could also enhance the proliferation and migration of colorectal cancer cells [110].

Table 4
Roles of claudins in pancreatic cancer.

Claudins	Activity	Findings	Reference
CLDN1	Tumor suppressor	Promoted apoptosis and inhibited proliferation	[15]
CLDN4	Tumor suppressor	Inhibited the invasiveness of cancer cells	[113]
CLDN7	Tumor promoter	Improved the invasion and metastasis, and promoted the resistance to cisplatin	[50]
CLDN12	Tumor promoter	Promoted EMT	[115]
CLDN18.2	Tumor suppressor	High expression of CLDN18.2 correlated with a better prognosis	[116]

1.5. Claudins in pancreatic cancer

CLDNs play key roles in the pathogenesis of pancreatic cancer (Table 4). Pancreatic cancer usually originates from precancerous lesions, including pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasia (MCN), and intraductal papillary mucinous neoplasia (IPMN), of which PanIN is the most common [111]. CLDN4 was highly expressed in pre-cancerous pancreatic lesions, and its expression was increased with the histological grade of MCN and IPMN, especially in pancreaticobiliary IPMN [112]. K-ras mutations were found in pancreatic cancer, and activating K-ras could up-regulate CLDN4 [113]. TGFβ could promote cancer cell invasion by inhibiting CLDN4 expression. Meanwhile, patients with higher CLDN4 expression had a better prognosis [113]. CLDN3 and CLDN4 were specific receptors for Clostridium perfringens enterotoxin (CPE). CPE could reduce cell permeability and induce cell apoptosis by binding to CLDN3 and CLDN4 [114]. As a result, CPE can be used for the treatment of CLDN4-positive pancreatic cancer.

CLDN18.2 was also highly expressed in high-grade pancreatic intraepithelial neoplasia (PanIN-2, 3), IPMN, MCN, well-differentiated pancreatic cancer, and pancreatic cancer metastases [112,117,118]. The expression level of CLDN18.2 increased with the degree of malignancy of pancreatic cancer. It could be used as a diagnostic marker for early pancreatic cancer, and patients with higher CLDN18.2 expression had a better outcome [119,116]. CLDN18.2 was mainly regulated by the PKC pathway and could be epigenetically regulated by DNA methylation [120,121]. Previous studies showed that IMAB362 for CLDN18.2-positive gastric and pancreatic cancer patients could achieve significant curative effects with fewer side effects [122]. Furthermore, the chemotherapeutic drugs gemcitabine or 5-fluorouracil were able to increase CLDN18.2 expression in vitro [123,124].

CLDN1 was expressed in the membranes of normal pancreatic ducts and well-differentiated pancreatic cancer cells. CLDN1 has the potential to be used as a diagnostic marker for pancreatic cancer. TNFα could promote cell apoptosis and inhibit proliferation by up-regulating CLDN1 [15]. Therefore, CLDN1 mainly plays a tumor suppressor role. CLDN2 was mainly expressed on benign pancreatic lesions and decreased in MCN and IPMN [112]. CLDN7 decreased with pancreatic ductal adenocarcinoma differentiation but was not associated with patients' prognosis [119]. Besides, CLDN7 could form a complex with EpCAM, improving cell invasion, metastasis, and resistance to cisplatin [50]. Zinc finger protein 460 (ZNF460) promoted the expression of LINC00857 which competed with miR-150-5p to promote CLDN12 expression. LINC00857 could also enhance the binding of SRSF1 to pre-CLDN12, increase alternative splicing and promote the expression of CLDN12. High CLDN12 expression could promote EMT, cell invasion, and migration [115].

1.6. Claudins in hepatocellular carcinoma

In hepatocellular carcinoma (HCC), miR-29a expression was decreased and the inhibitory effect on CLDN1 was lost [125]. CLDN1 activated the Ras-Raf-1-ERK pathway through c-Abl, up-regulating the transcriptional activities of Slug and ZEB1 to promote EMT [42]. CLDN1 could also activate PKCδ through c-Abl and up-regulate MMP-2 to promote cancer cell invasion [126]. Hypermethylation of its promoter led to the downregulation of CLDN3 in HCC and the loss of its inhibitory effect on the Wnt/β-catenin pathway, which promoted EMT and enhanced cell metastasis and proliferation [44]. CLDN6 was up-regulated in HCC, promoting cell proliferation, invasion, and migration by activating EGFR/AKT/mTOR pathway [127]. CLDN9 was also increased and promoted cell migration through the Tyk2/STAT3 pathway [128].

The expression of miR-486 was decreased in HCC, while CLDN10 was increased. CLDN10 was able to promote EMT, migration, and angiogenesis [129]. High level of CLDN10 expression were associated with disease recurrence after radical hepatectomy [130,131]. miR-99b was up-regulated in HCC which inhibited the transcription of *CLDN11*, thereby promoting cancer cell migration [132]. EZH2 was an enhancer of transcriptional regulators. In HCC, EZH2 could silence CLDN14 via H3K27me3. Low CLDN14 expression activated the Wnt/β-catenin pathway, which promoted EMT and cancer cell invasion [133]. CLDN17 was also increased, which activated the

Table 5
Roles of claudins in lung cancer.

Claudins	Activity	Findings	Reference
CLDN1	Tumor promoter	Promoted EMT in NSCLC	[43]
		Initiated autophagy and induced resistance to CDDP in NSCLC	[51]
		High expression of CLDN1 in lung adenocarcinoma was associated with poor prognosis	[135]
	Tumor suppressor	Loss of CLDN1 expression in lung adenocarcinoma correlated with disease progression and cancer cell invasiveness	[17]
		High expression of CLDN1 was associated with better prognosis in lung SCC	[136]
CLDN2	Tumor promoter	Up-regulated MMP9 and promoted the migration of lung adenocarcinoma cells	[137]
		Increased drug resistance to CDDP	[52]
CLDN3	Tumor promoter	High expression of CLDN3 was associated with poor prognosis in lung SCC	[136]
	Tumor suppressor	Decreased expression in lung SCC promoted EMT through the Wnt/β-catenin signaling pathway	[45]
CLDN6	Tumor suppressor	Low expression of CLDN6 was associated with poor prognosis in NSCLC	[138]
CLDN7	Tumor suppressor	Improved the adhesion of lung cancer cells, inhibited cell proliferation, invasion, and migration	[139, 140]
CLDN9	Tumor promoter	Promoted the movement of lung cancer cells	[141]
CLDN12	Tumor promoter	Promoted EMT in SCC cells via Tyk2/Stat1 pathway	[142]
CLDN18.1	Tumor suppressor	Inhibited proliferation and invasion by inhibiting YAP1/PI3K/PDK1/AKT pathway	[49]

STAT3 pathway via Tyk2 and enhanced cell migration capacity. Simultaneously, patients with higher CLDN17 expression had a poorer prognosis [134].

1.7. Claudins in lung cancer

Lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. CLDNs exert vital funtions both in SCLC and NSCLC (Table 5).

In NSCLC cells, TNFα could promote EMT by up-regulating CLDN1 [43]. Increased CLDN1 initiated autophagy by increasing the phosphorylation level of unc-51 like autophagy activating kinase 1 (ULK1), resulting in the resistance of NSCLC to cisplatin [51]. High expression of CLDN1 in lung adenocarcinoma was correlated with poor prognosis (Sun et al., 2016). In summary, CLDN1 may have an oncogenic role in NSCLC. However, another study suggests that loss of CLDN1 was linked to disease progression and cancer cell invasion [17]. Higher CLDN1 expression was associated with a better prognosis in lung squamous cell carcinoma (SCC) [136]. In invasive lepidic predominant adenocarcinoma (LPA), CLDN1 expression was lower than adenocarcinoma in situ (AIS), and the survival rate was better in patients with higher CLDN1 expression [143]. In the process from AIS to LPA, CLDN1 is thought to play a key role. These studies suggest that CLDN1 may be involved in suppressing tumor growth in lung SCC.

MMP9 cleaved EGF to activate the EGFR/MEK/ERK pathway and up-regulated c-Fos expression in lung adenocarcinoma cells. C-Fos interacted with c-Jun to form the AP-1 dimer complex, which bound to the AP-1 site in CLDN2 promoter region to promote CLDN2 expression [144]. CLDN2 could increase the nuclear distribution of Sp1 to up-regulate MMP9 expression which would promote cancer cell migration [137]. These works suggest a possible crosstalk between CLDN2 and MMP9. ATP-binding cassette transporters were able to transport substrates across the cell membrane. In lung cancer, CLDN2 stimulated the expression and function of ATP-binding cassette subfamily C member 2 (ABCC2) by upregulating Sp1. ABCC2 increased chemotherapy resistance by reducing chemotherapy drug accumulation in cancer cells [52]. Chemotherapy resistance may therefore be more common in patients with high CLDN2 expression. Kaempferol and luteolin are natural flavonoids found in various plants. They could reduce the interaction between STAT3 and CLDN2 promoter to down-regulate the expression of CLDN2 which would inhibit the proliferation of lung adenocarcinoma cells [145]. Therefore, CLDN2 could be developed as a therapeutic target for lung cancer, and flavonoids exert an anti-tumor effect by inhibiting CLDN2.

The expression of CLDN7 was reduced in lung cancer. Low expression of CLDN7 decreased the expression of integrin beta1, resulting in poor adhesion between tumor cells and the stroma [139]. It could also promote cancer cell proliferation. In NSCLC, hepatocyte growth factor (HGF) could bind to its receptor c-Met to activate the ERK/MAPK pathway which would promote cell invasion and migration. CLDN7 could be an inhibitor of HGF activation of the ERK/MAPK pathway. However, decreased expression of CLDN7 led to the loss of this inhibitory ability, resulting in increased invasion and migration [140]. In addition, low expression of CLDN7 was found to be related to poor prognosis in lung SCC [146]. CLDN7 has been shown to be an important tumor suppressor for lung cancer.

CLDN18.1 was essential for alveolar epithelial maturation and differentiation. Immunohistochemistry showed that CLDN18.1 expression was down-regulated in lung cancer. Lung adenocarcinoma could spontaneously develop in *Cldn18.1*-KO mice. In vitro, assays indicated that CLDN18.1 was able to inhibit cell proliferation and invasion and promote cell death. CLDN18.1 inhibited the

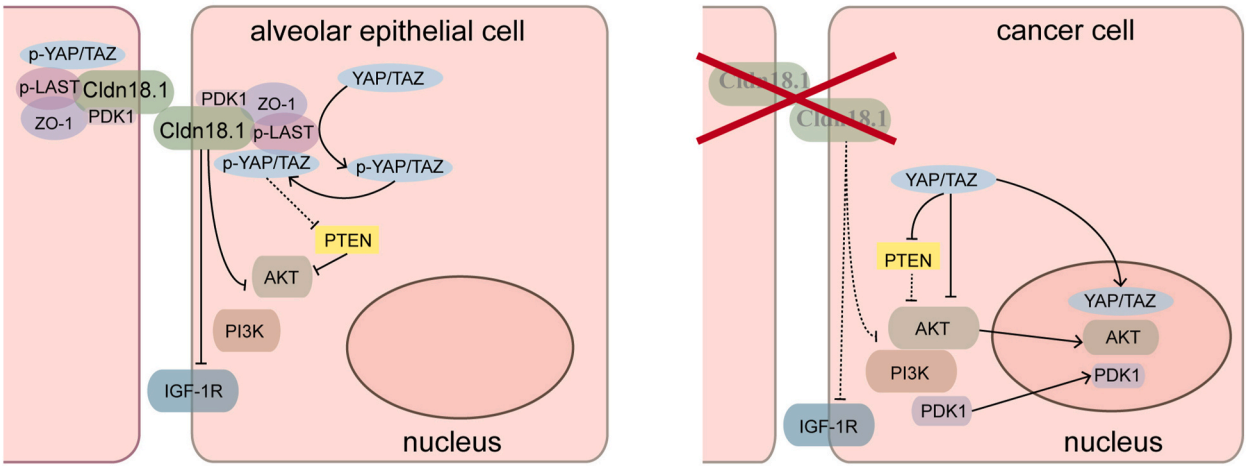

Fig. 3. Claudin 18.1 (CLDN18.1) is a tumor suppressor in alveolar epithelial cells. In normal alveolar epithelial cells, CLDN18.1 binds to Zonula Occludens-1 (ZO-1) and Hippo kinases (*p*-LATS) in normal alveolar epithelial cells to form a complex. Yes-associated protein (YAP) is phosphorylated by p-LAST and anchored at this complex, inhibiting YAP translocation to the nucleus. Meanwhile, inhibition of YAP can preserve the activity of phosphatase and tensin homolog (PTEN), thereby inhibiting phosphatidylinositol 3-kinase/phosphoinositide-dependent kinase 1 (PI3K/PDK1)/AKT signaling pathway. CLDN18.1 can also directly inhibit PDK1, AKT, and insulin-like growth factor-1 receptor (IGF-1R). In lung cancer cells, deletion of *Cldn18.1* causes YAP activation and translocation to the nucleus to promote cancer cell proliferation. Meanwhile, activated YAP can inhibit the activity of PTEN and activate the PI3K/PDK1/AKT signaling pathway, which further promotes cancer cell proliferation.

translocation of Yes-associated protein (YAP) to the nucleus, thereby inhibiting the PI3K/PDK1/AKT pathway (Fig. 3). Taken together, these results suggest that CLDN18.1 functions primarily as a tumor suppressor in lung cancer [49].

Reduced expression of CLDN3 in lung SCC activated the Wnt/β-catenin pathway to promote EMT which would increase the ability of cancer cells to invade and migrate [45]. However, there was literature suggesting that high CLDN3 expression in pulmonary SCC was associated with poor prognosis [136]. In lung SCC, CLDN5, 7, and 18 could reduce the phosphorylation level of AKT by inhibiting the interaction between AKT and PDK1, which could reduce cyclin D1 to suppress G1-S cell cycle progression [147]. CLDN6 was down-regulated in NSCLC. Low CLDN6 expression was associated with poor prognosis and was an independent risk factor for predicting NSCLC prognosis [138]. CLDN18.2 could also be expressed in NSCLC and can be used as one of the therapeutic targets [148]. CLDN9 was overexpressed in lung cancer, promoted tumor cell motility, and might be associated with metastasis [141]. Similar to CLDN1, the expression of CLDN10 was decreased in LPA compared to AIS, and the survival rate of CLDN10-positive patients was higher, suggesting that CLDN10 may also play a role in the progression from AIS to LPA [143]. By activating the Tyk2/Stat1 pathway, increased CLDN12 in lung SCC reduced E-cadherin expression and promoted EMT. Meanwhile, high CLDN12 expression was associated with lymph node metastasis and poor prognosis [142]. As in the case of colorectal cancer, an anti-CLDN12 antibody also inhibited the proliferation of lung cancer cells in vitro [108]. This makes CLDN12 a promising target for cancer therapy.

Sulforaphane (SFN) is one of the best anti-cancer substances from plants as it inhibits the carcinogenesis of cells and induces the apoptosis of cells. SFN-Cys is an intermediate metabolite with a longer retention time in the body and higher concentrations in lung. SFN-Cys could down-regulate CLDN5 and up-regulate CLDN7 through ERK1/2 in lung cancer cells. The type of lung cancer determined the effect of SFN-Cys on CLDN1. SFN-Cys increased the expression of CLDN1 in lung adenocarcinoma but decreased the expression of CLDN1 in SCC. At the same time, SFN-Cys reduced the interaction of CLDN1, 5, and 7 with α-tubulin to disrupt microtubule dynamics and induce cancer cell apoptosis [149]. Chrysin is also a type of flavonoid. CLDN1 and 11 were up-regulated in SCC. Chrysin could down-regulate the expression of CLDN1 and 11 by reducing the phosphorylation level of AKT and inhibiting the interaction between AKT and PDK1. Ultimately, this increased the toxicity of doxorubicin (DXR) to lung SCC [150].

1.8. Claudins in breast cancer

CLDN6 was reduced in breast cancer and functioned primarily as a tumor suppressor. Epigenetic modifications might affect the expression of CLDN6. Abnormal hypermethylation of CpG islands in the promoter region led to a decrease in the expression of CLDN6 [151]. Meanwhile, MeCP2 was capable of binding to CpG islands in the aberrantly methylated promoter region of CLDN6. It recruited histone deacetylase (HDAC) to deacetylate H3Ac and H4Ac, thereby inhibiting transcription and leading to a reduction in CLDN6 expression [152]. SMAD2 also down-regulated CLDN6 by DNA methyltransferase 1 (DNMT1)-mediated promoter methylation [47].

The low levels of CLDN6 could trigger the activation of the p38 MAPK pathway, leading to an increase in the expression of MMP2. This, in turn, enhanced cell proliferation and migration capabilities [153]. Conversely, CLDN6 downregulation could reduce the transcriptional activity of apoptosis signal-regulating kinase 1 (ASK1) and inhibited JNK and p38 pathway activation. This led to an increased Bcl2/Bax ratio, a decreased caspase3 expression, and an inhibition of the mitochondrial apoptosis pathway [154,155]. Additionally, in breast cancer cells, the activation of ERβ with estradiol could boost the transcription of CLDN6. High levels of CLDN6 promoted autophagy through the autophagy regulator beclin1 while inhibiting cell invasion and migration [156]. To summarize, CLDN6 acts as a tumor suppressor in breast cancer by reducing cell invasion and migration, promoting cell apoptosis, and inducing autophagy.

However, the expression of CLDN6 was linked to resistance to chemotherapy. Over-expressed CLDN6 interacted with p53 and caused the translocation of p53 from the nucleus to the cytoplasm. This led to increased expression of glutathione S-transferase-p1 (GSTP1), which rendered cancer cells resistant to drugs such as adriamycin, 5-fluorouracil, and cisplatin [157]. In triple-negative breast cancer, overexpression of CLDN6 resulted in increased expression of afadin (AF-6) and decreased phosphorylation of ERK, which in turn increased cancer cell resistance to adriamycin (ADM) [158].

Snail and Slug could bind to the E-box in the promoter region of CLDN1 and decrease its expression [159]. In ER-negative breast cancer, CLDN1 had a pro-cancer effect with anti-apoptotic properties and promoted the migration of cancer cells [13]. However, in ER-positive breast cancer, CLDN1 promoted apoptosis of cancer cells and acted as a tumor suppressor [13].

The level of CLDN2 expression was decreased in breast cancer, and this reduction had been found to be associated with advanced stage and lymph node metastasis [160]. This suggests that CLDN2 may play a role as a tumor suppressor. However, in cases of liver metastases from breast cancer, there was an increase in CLDN2 expression. The elevated CLDN2 in this context promoted the metastasis of cancer cells by facilitating the formation of complexes between integrin receptors α2β1 and α5β1, which led to increased adhesion between cancer cells and the extracellular matrix [161].

The level of CLDN3 expression was positively correlated with the occurrence of lymph node metastasis in triple-negative breast cancer [162]. CLDN4 expression was negatively correlated with tumor size and positively correlated with disease-free survival (DFS) [162]. Elevated expression of CLDN5 was linked to a poor prognosis. This increased expression of CLDN5 could facilitate cell movement and migration through the neural Wiskott-Aldrich syndrome protein (N-WASP) and Rho-associated coiled-coil containing protein kinase (ROCK) pathways [163]. CLDN8 expression was down-regulated and correlated with androgen receptor (AR) expression levels. Co-expression of CLDN8 and AR in breast cancer was correlated with a better prognosis [164]. CLDN10 was decreased in breast cancer, and the CLDN10 rs1325774 polymorphism was related to an increased breast cancer risk [165]. Reduced miR-205 resulted in the loss of its inhibitory effect on CLDN11, leading to increased CLDN11 expression. CLDN11 promoted cancer cell proliferation and inhibited apoptosis [166]. A higher level of CLDN11 in invasive breast ductal carcinoma was associated with a worse overall survival rate [167].

In breast cancer, IL-18 was elevated, leading to the inhibition of CLDN12. Low CLDN12 expression enhanced cell migration by activating the p38 MAPK pathway [168]. However, in ER-negative breast cancer, high expression of CLDN12 was associated with a poor overall survival rate [169]. In triple-negative breast cancer, twist1 inhibited CLDN15 expression by binding to its promoter region, resulting in enhanced cell invasion, migration, and angiogenic mimicry formation [170]. CLDN16 could reduce cancer cell invasiveness and proliferation, and patients with low CLDN16 expression had a poor prognosis [171]. On the other hand, over-expression of CLDN20 in breast cancer cells promoted cell invasiveness, and high expression of CLDN20 was associated with a poor prognosis [172].

1.9. Claudins in tumors of genital organs and urinary system

The lipolysis stimulated receptor (LSR) is a critical component of the tricellular junction. Downregulation of LSR could enhance nscriptional activity of Sp1, which would lead to increased expression of CLDN1 in endometrial cancer. High level of CLDN1 could then increase the expression of MMP2, 9, 10, and MT1-MMP, which ultimately increased the invasiveness of cancer cells [173]. CLDN2, 3, and 4 were also elevated, and the heightened CLDN3 and 4 were correlated with myometrial invasion [174,175]. Additionally, CLDN6 expression was increased and linked to poor prognosis, serving as an independent prognostic marker for this type of cancer [176]. On the other hand, CLDN7 was decreased in endometrial cancer. Low level of CLDN7 could promote cell proliferation and invasion [177].

CLDN6 expression was reduced in cervical cancer. As in breast cancer, reduced CLDN6 expression inhibited the activity of ASK1, which in turn suppressed the programmed cell death of cancer cells [178,179]. Cervical intraepithelial neoplasia (CIN) is a precursor of cervical cancer. The expression of CLDN12 was increased in CIN and cervical cancer. However, low CLDN12 expression in cervical cancer was correlated with poor prognosis [180].

The expression of miR-155 was reduced in ovarian cancer, resulting in a loss of its ability to inhibit CLDN1. CLDN1 could then increase the expression of MMP2 and 9 while reducing the expression of E-cadherin and β-catenin. These changes promoted cancer cell invasion and migration [181]. CLDN3 and 4 were elevated in ovarian cancer [182], which might increase cancer cell aggressiveness, possibly by increasing MMP2 activity [183]. However, in contrast to colorectal cancer, EGF actually reduced the expression of CLDN3 and 4. This was due to the activation of the MEK/ERK and PI3K/AKT pathways [184]. The low expression of them led to activation of the PI3K/AKT pathway and increased transcriptional activity of twist, which promoted EMT [185]. Low CLDN3 and 4 in ovarian cancer were linked to chemotherapy resistance. The decreased expression could lead to decreased mRNA levels of Copper Transporter 1 (CTR1), which would reduce cellular copper absorption and disrupt copper homeostasis. This, in turn, increased the resistance of cancer cells to cisplatin, a commonly used chemotherapy drug [186]. However, it is still unclear why CLDN3 and 4 are highly expressed in ovarian cancer, despite the ability of EGF to down-regulate these CLDNs and the presence of high EGFR expression in these tumors [187]. In addition, some studies suggested that chemotherapy-resistant or recurrent ovarian cancers actually exhibited high levels of CLDN3 and 4 [188,189]. There was also research suggesting that CLDN4 expression did not have a significant correlation with cisplatin resistance [190].

CLDN6 had been found to be up-egulated in ovarian cancer and was inversely associated with the infiltration of immune cells [191]. In addition, CLDN6 was one of the receptors for CPE, which induced cytotoxicity and increases the sensitivity of ovarian cancer cells to CPE [192]. A phase I clinical trial (NCT02054351) was conducted with IMAB027, an immune-activating monoclonal antibody targeting CLDN6. Furthermore, BNT142, a drug that specifically targeted CLDN6 was currently in Phase I/II clinical trials (NCT05262530). These studies highlight the potential of CLDN6 as a promising therapeutic target for ovarian cancer. Elevated CLDN7 expression in epithelial ovarian cancer (EOC) was linked to shorter progression-free survival. CLDN7 could also decrease the sensitivity of EOC cells to cisplatin, but treatment with CLDN7 siRNA could improve the situation [193]. Therefore, combination therapy targeting CLDN7 can effectively overcome chemoresistance to cisplatin. CLDN10 expression was elevated and positively correlated with immune cell infiltration. Higher CLDN10 expression was related to improved overall survival [191]. The role of CLDN10 might be associated with the TGFβ and Wnt/β-catenin pathways in ovarian cancer [194].

CLDN1 had been implicated as a tumor suppressor in prostate cancer. Loss of CLDN1 was linked to disease progression and cancer cell invasion [16]. CLDN4 was associated with a poor prognosis [195]. Another important factor in prostate cancer was AR, which could increase the expression of CLDN8. CLDN8 in turn activated the AKT/MAPK pathway, leading to an increase in cell proliferation and migration [196].

The expression of CLDN1 was increased in papillary renal cell carcinoma and could be used as a diagnostic marker. However, loss of CLDN1 was associated with tumor dedifferentiation and aggressiveness. In clear cell renal cell carcinoma (ccRCC), CLDN1 was associated with the occurrence of cancer and metastasis [197]. CLDN8 expression was reduced in ccRCC and patients with low expression had a poor prognosis. CLDN8 might be an independent prognostic factor for ccRCC. Besides, CLDN8 could inhibit cell invasion, migration, and proliferation through the AKT and EMT pathways [198]. Promoter hypermethylation in renal cell carcinoma led to reduced expression of CLDN10 which would reduce expression and acetylation of ATP synthase subunit O (ATP5O) [199]. This led to reduced expression of NADH dehydrogenase [ubiquinone] iron-sulfur protein 2 (NDUFS2), which in turn affected reactive oxygen species (ROS) production, succinate dehydrogenase subunit B (SDHB) expression, and caspase3 expression. Ultimately, this inhibited the mitochondrial apoptosis pathway and promoted cell proliferation, migration, and invasion [200]. As for CLDN14 and 16, although they were associated with renal ion transport, their role in renal cancer needs to be further investigated.

1.10. Claudins in other tumors

In oral SCC, the expression of CLDN1 was increased. Increased CLDN1 led to cleavage of the laminin-5 gamma 2 chain by promoting

the expression of MMP2, MMP9, and MT1-MMP. Lysate promoted the invasion of cancer cells by binding with EGFR [201]. Besides, high expression of CLDN1 was associated with high grade, late stage, nerve and vascular invasion, and lymph node invasion [202]. On the other hand, lacking CLDN7 in the center of oral SCC could be used as a marker to predict regional recurrence [203]. The expression of CLDN8 was reduced, but a higher expression of CLDN8 was linked to a lower overall survival rate [204]. In addition, the expression of CLDN17 was also down-regulated in oral cancer, which in turn increased the transcriptional activity of Snail and twist to promote EMT and enhance cell invasion and migration [205].

The expression of CLDN1 was increased in hypopharyngeal SCC. Elevated CLDN1 might stimulate the growth of new lymphatic vessels within the tumor, leading to an increased likelihood of lymph node metastasis [206,207]. In laryngeal carcinoma, CLDN1 and 7 were reduced, while CLDN3 and 8 were increased. These changes in expression levels can be used as molecular markers for the diagnosis [208].

In esophageal squamous cell carcinoma (ESCC), the transcription factor twist could prevent CLDN4 expression by binding to E-box site in the promoter region of CLDN4 [209]. Hypermethylation of its promoter region could also reduce the expression. Low expression of CLDN4, an independent risk factor for overall survival and recurrence, was linked to lymph node metastasis, the depth of invasion, the degree of differentiate, and the T stage of cancer [210,211]. CLDN6 could also be silenced by methylation in ESCC [212]. Loss of CLDN7 in ESCC would promote EMT to increase the invasion of cancer cells [213].

In melanoma, PKC increased CLDN1 expression and translocated it from the cell membrane to the cytoplasm. The high level of CLDN1 could then increase the expression of MMP2 and facilitate the invasion of tumor cells [214]. B-1 lymphocytes could secrete IL-10, which promoted CLDN10 expression. CLDN10 then activated the ERK pathway to facilitate the tumor cells metastasis [215]. Dysplastic nevus is an intermediate stage between common nevus and melanoma. Melanoma showed methylation in the promoter region of CLDN11 compared to dysplastic nevus. This suggests that loss of CLDN11 in melanoma is accompanied by an increased ability of tumor cells to invade surrounding tissues [216].

CLDN1 was increased in papillary thyroid disease (PTC) and its lymph node metastases [217]. In metastatic follicular thyroid carcinoma (FTC), PKC increased the nuclear expression of CLDN1. Elevated CLDN1 might facilitate cancer cell invasion and migration [12]. In thyroid cancer, CLDN10 was highly expressed in PTC but not in FTC, making it a potential discriminator between the two types of cancer [218]. Increased CLDN10 could promote proliferation, invasion, and migration of thyroid cells. Furthermore, the expression of CLDN10 was also related to lymph node metastasis in thyroid carcinoma [219].

In nasopharyngeal carcinoma (NPC), hypermethylation of the CLDN11 promoter prevents GATA1 from binding to the transcription start site. This led to CLDN11 being down-regulated which would reduce the interaction of CLDN11 with tubulin alpha-1b and beta-3. As a result, cell invasion and migration were enhanced. Using tubulin polymerization inhibitors could block the invasion and migration of NPC cells with low CLDN11 expression, suggesting their potential as therapeutic drugs [220].

In retinoblastoma (RB), miR-361-5p was reduced, preventing it from binding to the 3′ untranslated region of CLDN8. This resulted in increased expression of CLDN8, which would promote cell proliferation and inhibit cell apoptosis [221].

In pituitary oncocytoma, CLDN9 was increased. Furthermore, aggressive oncocytomas have higher expression of CLDN9 compared to non-invasive ones [222]. This suggests that CLDN9 may be involved in enhancing the invasiveness of cancer cells.

In glioblastoma, polycomb repressor complex 2-mediated H3K27me3 silenced the expression of miRNA-1275, which would up-regulate CLDN11. High expression of CLDN11 could inhibit cell proliferation [223].

In osteosarcoma, CLDN2 was reduced. This reduction resulted in the silencing of afadin. This activated the Ras/Raf/MEK/ERK pathway to promote the migration of cancer cells [224]. In addition, silencing CLDN8 could promote apoptosis. It could also reduce the level of CDK2, induce cell cycle arrest in G0/G1 phase, and inhibit cell proliferation [225]. Furthermore, CLDN12 could increase cancer cell invasion through PI3K/AKT pathway. High CLDN12 expression was associated with TNM stage, lung metastasis, and shorter survival time [226].

CLDN15 was less commonly altered in tumors. However, it could be expressed with high sensitivity and specificity in malignant pleural mesothelioma. This makes it a potential diagnostic marker for this particular cancer [227].

2. Discussion

CLDNs are the major constituents of tight junctions. CLDNs maintain cell polarity and regulate paracellular permeability under normal physiological conditions. However, when tissues are damaged, changes in the cellular microenvironment can affect the expression of CLDNs through various pathways. These changes in CLDNs can disrupt paracellular permeability, cell polarity, and overall cell function in different ways. Different tissues will be affected by different types of CLDN alterations. Some changes may help to repair tissues, while others may exacerbate tissue damage. Therefore, investigating the role of CLDNs in both normal and pathological conditions is crucial for understanding the development and occurrence of cancer. These findings may provide new insights into cancer diagnosis and therapy.

The potential of CLDNs as prognostic factors has been suggested by extensive analysis of clinicopathological data. By examing the expression of CLDNs, patients can be divided into positive and negative groups, which facilitates prognosis prediction and the formulation of appropriate treatment and follow-up plans. However, it is important to note that there may be conflicting results when analyzing certain clinicopathological data due to possible racial and regional differences in CLDNs expression. In addition, the final results may be significantly affected by the fact that some anti-CLDN antibodies may react with other subtypes of CLDNs. Therefore, in order to make the experimental results more accurate, it is necessary to validate the effectiveness and cross-reactivity of the antibodies based on specific circumstances before conducting the experiment.

CLDNs are essential in the regulation of cellular functions through multiple signaling pathways. Some of them are particularly

involved in promoting cancer development. For example, they contribute to the induction of EMT through the Wnt/β-catenin pathway, as well as cancer cell proliferation, migration, and invasion through the MAPK and PI3K/AKT pathways. Targeted therapy can inhibit these tumor-promoting pathways and demonstrate anti-tumor efficacy. However, it is important to be cautious about potential side effects, as CLDNs are also expressed in normal cells.

Chimeric monoclonal antibodies specifically recognize highly expressed CLDNs on the surface of tumor cells, leading to the activation of ADCC and CDC mechanisms that effectively eliminate tumor cells. Although CLDNs are also present in normal tissues, they are predominantly localized at cellular junctions, where they are tightly connected and less accessible to binding by antibodies. This characteristic of CLDNs in normal cells contributes to the significant therapeutic effects and reduced side effects of chimeric monoclonal antibodies against CLDNs, making them highly promising in the field of tumor-targeted therapy.

Cisplatin is a commonly used anti-cancer drug, but its effectiveness is limited by the development of drug resistance. CLDNs have been found to be linked to cisplatin resistance. Combining anti-CLDN therapy may help reduce drug resistance in cancer cells. Therefore, further research into the relationship between CLDNs and drug resistance may potentially improve the effectiveness of chemotherapy for cancer patients.

Tumor immunotherapy has brought about a significant revolution in the field of tumor treatment, and the infiltration of immune cells is closely tied to prognosis and response to immunotherapy. A potential role for CLDNs in tumor immunotherapy has been indicated by their association with immune cell infiltration in the tumor stroma.

Extracting anti-tumor compounds from natural plants offers the benefits of reduced side effects and readily available resources. CLDNs have the potential to be targeted by a range of naturally derived compounds from plants, making them useful in the development of anti-tumor drugs.

However, the specific roles of various CLDN subtypes in tumorigenesis and development are not well understood and there is a lack of clinicopathological data. Nevertheless, CLDNs hold great promise for various applications in cancer research. Further investigation of CLDNs may lead to new approaches to cancer diagnosis, treatment, and prevention.

Data availability statement

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CRediT authorship contribution statement

Daoyu Tao: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft. **Bingxin Guan:** Conceptualization, Data curation, Formal analysis, Methodology. **Hui Li:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Chengjun Zhou:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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