Am J Cancer Res 2021;11(7):3406-3424
www.ajcr.us /ISSN:2156-6976/ajcr0133367

Review Article

Targeting claudins in cancer: diagnosis, prognosis and therapy

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Received March 22, 2021; Accepted June 18, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Increasing evidence has linked claudins to signal transduction and tumorigenesis. The expression of claudins is frequently dysregulated in the context of neoplastic transformation, suggesting their promise as biomarkers for diagnosis and prognosis or targets for treatment. Claudin binders (Clostridium perfringens enterotoxin and monoclonal antibody) have been tested in preclinical experiments, and some of them have progressed into clinical trials involving patients with certain cancers. However, the clinical development of many of these agents has not advanced to clinical applications. Herein, I review the current status of preclinical and clinical investigations of agents targeting claudins for diagnosis, prognosis and therapy. I also discuss the potential of combining claudin binders with other currently approved therapeutic agents.

Keywords: Claudins, cancer, diagnosis, prognosis, targeted therapy

Introduction

The paracellular space between neighboring epithelial cells was found to be sealed by several types of cell-cell junctions, one of which is tight junctions (TJs). Claudins were identified in 1998 as the major integral membrane proteins essential for TJ assembly [1]. Our contemporary understanding of this protein family was based on their canonical barrier function, which is to discriminate solutes on the basis of size and charge as a semipermeable gate. In recent decades, increasing evidence has suggested that claudins may be involved in signal transduction and may be causally important in nearly all aspects of tumorigenesis, including inflammation, growth, survival, proliferation, epithelial-mesenchymal transition (EMT), metastasis, therapy resistance and cancer stem cell (CSC) renewal [2]. Except for their various expression patterns and contradictory roles in different cancer types and stages, the expression of claudins has tissue specificity, and some claudins are only expressed in very few normal or cancer tissue types. In addition, it has been observed that most claudins are buried in the TJ complex in normal tissues, and perturbations in TJs during malignant transformation cause epitopes of claudins to be exposed on the surface of tumor cells [3]. Therefore, claudins have been a focus of the biotechnology and pharmaceutical industries as potential therapeutic targets. The purpose of this review is to provide a biological context for claudins as diagnostic and prognostic biomarkers and therapeutic targets in human cancer, to highlight claudin binders that have shown benefit in patients or promise in preclinical studies and to discuss ongoing efforts to develop new claudin-targeted approaches and potential combination strategies with other antitumor therapies.

Claudins and its physiological functions

Claudins are a family of integral membrane proteins that make up TJs, which are the chief intercellular junctions that act as permeability barriers and confer polarity to epithelial cells by demarcating the membrane upper and lower regions. Currently, the mammalian claudin family comprises 27 proteins, and many alternative splicing claudin proteins are expressed in various tissues. In the past decade, the crystal structures of this protein family have been grad-

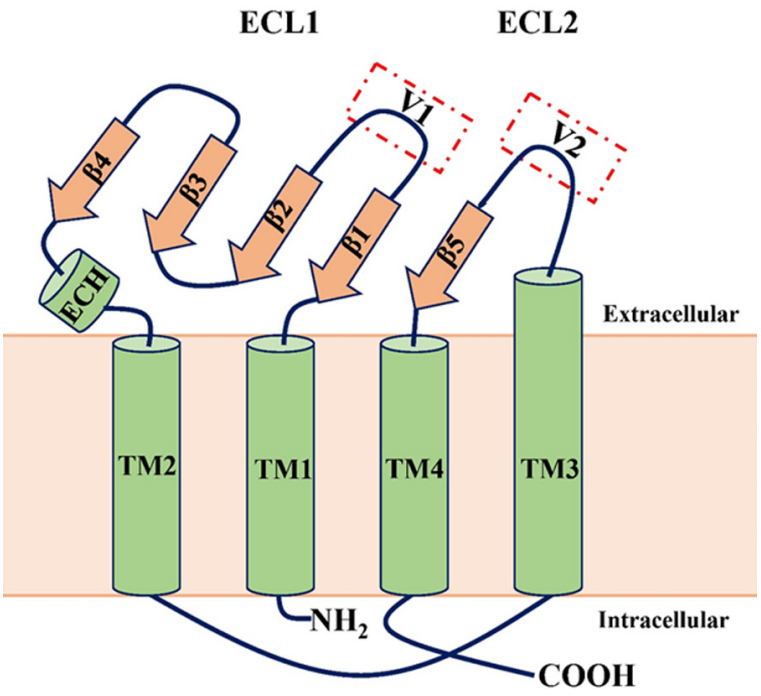

Figure 1. Representative structures of a claudin. Claudins are tetratransmembrane proteins, including four transmembrane domains (TM1-4) and two extracellular loops (ECL1 and ECL2). The ECL1 contains four β-strands and an extracellular helix (ECH), and ECL2 contains a β-strand and a cell surface-exposed transmembrane 3 domain. Each ECL also contains a variable region (V1 and V2).

ually elucidated [4]. Claudins are tetratransmembrane proteins, including four transmembrane domains (TM1-4), the intracellular N and C termini, and two extracellular loops (ECL1 and ECL2). ECL1 contains four β-strands and an extracellular helix (ECH), and ECL2 contains a β-strand and cell surface-exposed transmembrane 3 domain. The ECLs are involved in the formation of interactions between claudin strands and determine the gate function of claudin-based TJs by two variable regions (**Figure 1**) [4]. According to physiological studies, two mechanisms have been proposed for gate function: the "pore" mechanism, in which solutes or ions pass through a paracellular channel formed by the TJ strands (enabling transport of molecules with an estimated diameter of ~4 Å), and the "leak" mechanism, in which solutes supposedly pass through breaks in the TJ strands (permitting permeation of molecules up to a size limit of ~60 Å) [5]. Claudins are also organized as a membrane fence in epithelial cells, causing the asymmetric localization of membrane proteins and lipids in the exoplasmic leaflet [5]. Additionally, through interaction with many other signaling molecules, claudins mainly function as inhibitory factors and retain such signaling molecules in the submembrane compartment, to influence cell growth, survival, proliferation, and differentiation [6]. Some claudins are found to be outside the TJ complex, such as in the basolateral membrane, cytoplasm and nucleus, and these claudins always associate with other molecules to engage in cell-extracellular matrix (ECM) interactions and signal transduction. However, the specific functions of claudins in the cytoplasm and nucleus are not known [7]. ECLs are also specific binding sites for *Clostridium perfringens* enterotoxin (CPE) and monoclonal antibodies (mAbs), which have been utilized for imaging and treatment in pathological conditions [8].

Dysregulated expression and the roles of claudins in cancer

In line with their aforementioned important functions, dysregulation of claudin-mediated barrier function and signaling is a precursor for the pathogenesis of cancer [9]. The claudin expression profile of many different normal and tumor tissues was assessed at the mRNA and protein levels. These studies revealed a range of outcomes that reflect the complexity of claudins in terms of spatial localization, tumor types and stages of disease. A large body of evidence highlights a tissue-specific manner of claudin expression, and the expression of claudins appears to be reversed with carcinogenesis; that is, the expression of claudin is downregulated in cancers arising from its specific highly expressed tissues, while the expression of claudin is upregulated in cancers arising from its less expressed tissues [10, 11]. Consistent with the various expression patterns of claudins, pro and antitumorigenic roles of claudins have been reported. The precise mechanisms through which claudins suppress or promote tumorigenesis have not been well established. The potential mechanisms by which claudins suppress carcinogenesis may involve the aforementioned paracellular barrier and signal

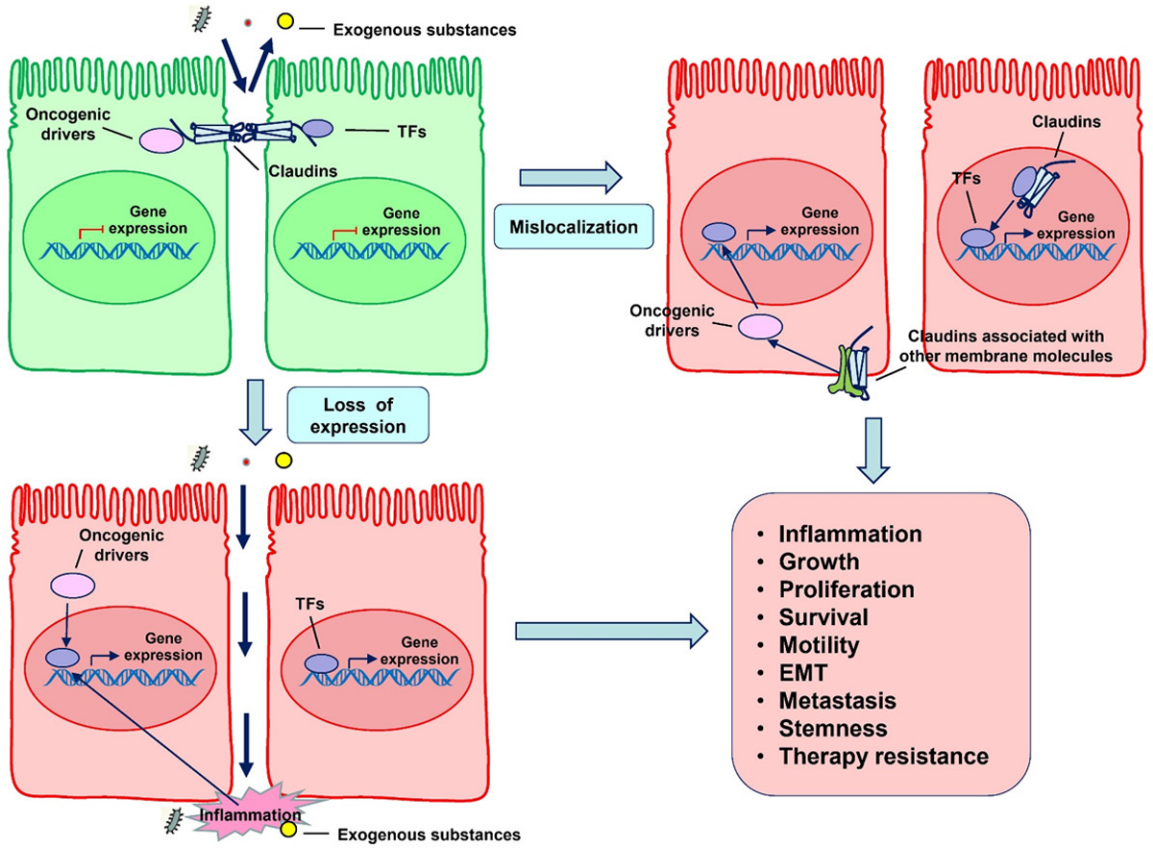

Figure 2. Schematic model of the pro and antitumorigenic roles of claudins. The potential mechanisms by which claudins suppress carcinogenesis may involve the paracellular barrier and signal transduction functions, and loss of the expression of claudins leads to inflammation and activation of oncogenic pathways. In regard to its protumorigenic role, studies mainly support the hypothesis that mislocalized claudins activate various signaling pathways or transcription factors (TFs) to promote tumorigenesis.

transduction functions claudins play under physiological conditions. Through the gate function, claudins prevent the passing of exogenous substances (foreign molecules and microorganisms) through the paracellular space; otherwise, inflammation will occur, which is the most common predisposition for cancer. Additionally, loss of the epithelial barrier allows growth factor infiltration into the mucosa to promote neoplastic transformation and growth [12]. In TJ complexes, claudins bind and retain oncogenic drivers, such as YAP/TAZ, β-catenin, and PDK1, in the submembrane compartment to inhibit their activation directly or indirectly [6]. In addition, specific claudin maintains epithelial cell attachment and suppresses cell proliferation by colocalizing and forming a protein complex with integrin β1 on the basolateral membrane [13]. In regard to its protumorigenic role, studies mainly support the hypothesis that claudins activate various signaling pathways or proteases to promote tumorigenesis. Outside TJs, claudins participate in signal transduction, ECM degradation and receptor cleavage through association with other molecules, such as epithelial cell adhesion molecule (EpCAM), membrane type-matrix metalloproteinases (MT-MMPs), disintegrin and metalloproteinase 10 (ADAM10) and integrins, leading to the activation of many oncogenic pathways [14-16]. Claudins also form complexes with transcription factors (TFs), such as YAP/TAZ and β-catenin, to induce the nuclear accumulation of these TFs, although the exact mechanisms through which claudins induce gene transcription are not clear [17, 18]. Through these mechanisms, claudins are believed to play a role in nearly all aspects of tumor biology and all steps of tumor development, including inflammation, growth, survival, proliferation, epithelial-mesenchymal transition (EMT), metastasis, therapy resistance and cancer stem cell (CSC) renewal [2] (**Figure 2**).

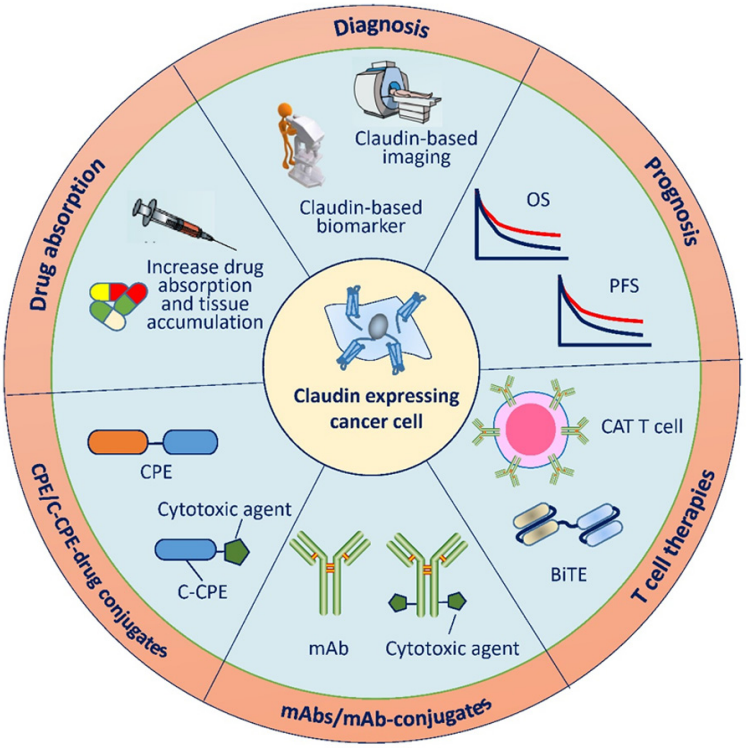

Figure 3. Clinical applications of claudin-targeting agents in the diagnosis, prognosis and treatment of cancer. Detection methods include immunohistochemistry (IHC) and radiolabeled or nonradiolabeled imaging approaches. Therapeutic agents for targeting claudins in patients with cancer include Clostridium perfringens enterotoxin (CPE), monoclonal antibodies (mAbs), C-terminal of CPE (C-CPE), mAb-drug/material conjugates, bispecific T cell engagers (BiTEs) and chimeric antigen receptor (CAR) T cells.

As their importance in cancer initiation and progression has been well established and they have obvious expression patterns, claudins can be targeted or used as biomarkers for determining diagnosis, prognosis, and treatment (**Figure 3**).

Clinical application in diagnosis

Biomarkers for diagnosis: With few exceptions, claudins are markers of epithelial differentiation and are expressed in nearly all carcinomas with tissue type and cancer type specificity; thus, they can be utilized for differential diagnosis. For example, claudins 4, 7 and 8 are useful markers in the differentiation of carcinomas from sarcomas [19-22]. Claudin-4 was found to be a useful marker to distinguish undifferentiated carcinomas from sarcomas with epithelioid morphology [23]. Claudin-based markers are also utilized in the diagnosis of tumors arising from other epithelial cell types; for example, claudin-5 can be used to distinguish mesothelioma from angiosarcoma [24]. The specific altered expression profiles of claudins can be used as biomarkers for identifying cancer cells and for identifying the stomach and pancreatobiliary tract as the primary sites of metastatic adenocarcinoma [25, 26]. In addition, one study used the localization of claudin-7 on circulating extracellular vesicles (EVs) as a robust and reliable tool for early breast cancer diagnosis in a low-cost, specific, versatile, and user-friendly strategy [27].

Molecular classification based on claudins: The heterogeneous molecular nature of cancer is a significant obstacle in treatment planning; therefore, subclassification may help make precision treatment decisions. In terms of molecular classifications based on claudins, one of the most notable is the claudin-low subtype of breast cancer, which is characterized by decreased expression of cell-cell adhesion proteins (claudins 3, 4 and 7 and E-cadherin), increased expression of genes associated with EMT, and CSC features [28, 29]. Another example is the subtype of gastric cancer that is associated with the *CLDN18-ARHGAP26* gene fusion; this subtype is most common in younger patients with genomically stable tumors and is associated with high stage and poor prognosis [30-32]. Immunophenotype analyses in other cancers, including endocervical adenocarcinoma, have employed claudins to improve the diagnostic accuracy of histopathological classifications [33]. In addition, it was reported that claudin-3 expression was correlated with breast cancer type 1 (BRCA1) mutation and could help determine whether BRCA testing was necessary in triple-negative breast cancer (TNBC) [34].

Claudin-targeted imaging: Claudins and their tumor-specific expression have also been utilized in the field of cancer imaging. Multiple

approaches for improving the imaging of claudin-positive tumors using claudin-targeted contrast-enhanced technologies have been investigated. For example, radiolabeled (^{111}In-labeled) anti-claudin-4 mAb and C-terminal of CPE (C-CPE) have been reported to allow noninvasive detection of claudin-4 upregulation during the development of pancreatic or breast cancer and could potentially be helpful in the early detection and characterization of these malignancies using single-photon emission computed tomography (SPECT) imaging [35, 36]. Recently, the authors of these studies generated a series of smaller-sized C-CPE mutants with improved binding affinity for claudin-4, which showed great promise in imaging claudin-4-overexpressing pancreatic cancer in vivo [37]. However, the clinical application of these contrast agents has yet to be evaluated.

Nonradiolabeled approaches, such as fluorescent probes linked with C-CPE, are also under investigation. A fluorescein isothiocyanate (FITC)-conjugated C-CPE peptide has been developed and was shown to specifically bind to multiple ovarian cancer cell lines that express claudins 3 and 4 in vitro and in vivo [38]. Similarly, a C-CPE coupled with the fluorophore Cy5.5 has been studied using pancreatic cancer cell lines and xenograft models. Good retention was observed in claudin-4-positive tumors, resulting in an increased fluorochrome concentration compared with that in normal pancreatic tissues [39]. This approach has also been utilized as a visualization tool for identifying micrometastatic chemotherapy-resistant lesions in ovarian cancer patient-derived xenograft (PDX) mouse models [40]. Targeted approaches for advanced endoscopic techniques based on the differential expression of claudins have also been developed for early colorectal lesion screening and treatment; some of these lesions are especially difficult to detect, such as flat dysplasia or serrated polyps. A promising approach for the real-time endoscopic imaging of colonic tumors overexpressing claudin-1 has been proposed, in which claudin-1 can be detected endoscopically in vivo by binding with a near-infrared-labeled peptide or antibody [41-43]. These studies suggest the possibility of using claudins as a tool for endoscopic imaging and fluorescence-guided surgery for tumors in future clinical applications.

Clinical application in prognosis

Numerous studies have reported purported associations between the expression of specific claudins (mRNA and/or protein levels) and the extent of tumor progression and patient survival (**Table 1**). However, most of the observed clinical data are correlative; moreover, some of these studies provide contradictory data both within the same cancer type and in different cancers for the same claudin molecules; such contradictory results suggest that claudin expression and functions are highly dependent on the tumor type and the state of the disease, complicating the applicability of these molecules as prognostic markers and underlying the need for patient stratification on the basis of claudin profiles in future studies. For example, patients with the claudin-low molecular subtype of breast cancer (low expression of claudins 3, 4 and 7 and E-cadherin) have poor prognosis, whereas low claudin-3 and claudin-4 expression is correlated with longer overall survival (OS) than high claudin-3 and claudin-4 expression in clear renal cell carcinomas [29, 44]. In gastric cancer, high claudin-7 expression correlates with shorter OS, while high claudin-18 expression correlates with longer OS [45].

Despite these contradictory results, we can still make some general conclusions about the prognosis associated with some specific claudins in cancer. That is, in cancer types in which one claudin is highly expressed in the corresponding normal tissues, a decrease in or loss of its expression always predicts poor survival. In contrast, ectopic expression of a claudin in a tumor arising from a tissue that does not normally express this claudin also predicts poor prognosis. These relationships are most prominent for claudin-6 and claudin-18; one is nearly completely silenced in adult tissues, and the other is strictly expressed in normal lung and gastric tissues. Claudin-6 has been found to be reactivated in some cancer types, such as gastric, endometrial and lung cancer, and this reactivation was positively correlated with poor patient survival [67-69]. For claudin-18, loss of expression is an independent indicator of poor prognosis in patients with gastric cancer, while positive expression is associated with poor survival in intrahepatic cholangiocarcinoma and CRC [78-80].

Table 1. Claudins as prognostic factors in human cancer

Claudin	Decreased expression correlating with poor prognosis	Increased expression correlating with poor prognosis	No correlation
Claudin-1	Lung cancer [46], CRC [47, 48], Prostate cancer [49]	Lung cancer [50], RCC [51], Cervical cancer [52], Ovarian cancer [53]	CRC [54]
Claudin-3	Breast cancer [55], Colon cancer [56]	Breast cancer [57], Ovarian cancer [58]	Endometrial cancer [59]
Claudin-4	Gastric cancer [60], Pancreatic cancer [61]	Breast cancer [55], Ovarian cancer [62], Gastric cancer [63]	Endometrial cancer [59], Ovarian cancer [58], Gastric cancer [64, 65]
Claudin-6	Lung cancer [66]	Endometrial cancer [67], Gastric cancer [68], Lung cancer [69]	Atypical teratoid rhabdoid tumors [70]
Claudin-7	CRC [71], OSCC [72], HCC [73], Lung cancer [74]	Gastric cancer [75], Breast cancer [76], Ovarian cancer [77]	NA
Claudin-18	Gastric cancer [75, 78]	Intrahepatic cholangiocarcinoma [79], CRC [80]	Gastric and esophageal adenocarcinomas [81], Gastric cancer [82]

The table is not an exhaustive list and is used only to highlight the relevance of claudins in many cancers. CRC, colorectal cancer; HCC, hepatocellular carcinoma; NA, not applicable; OSCC, oral squamous cell carcinoma; RCC, renal cell cancer.

In addition, other changes in claudins have also been used to predict prognosis in cancers. The abnormal localization of some claudins, such as claudin-3 expression in the cytoplasm, was shown to be an indicator of survival in cancer patients [34]. Epigenetic modifications such as methylation of claudins are reported to be promising prognostic markers in various cancers [45, 83]. Furthermore, the serum levels of some claudins are promising biomarkers for predicting the development, proliferative ability, and prognosis of cancer because blood is easy to obtain and can be obtained repeatedly.

Targeting claudins for cancer therapy

Rationale for targeting claudins: Although claudins may contribute to various hallmarks of cancer, to what extent cancers depend on signaling from claudins is not clear; therefore, blocking claudins in cancer cells may not be as effective as blocking other pathways, such as HER-2, PI3K/Akt and MAPK. However, conventional signaling pathway-targeted therapy has many limitations. It has become evident that blocking a single pathway may lead to disappointing results due to the feedback upregulation of targeted pathways, simultaneous activation of other interactive and/or redundant pathways, and resistance to targeted drugs through mutations or oncogene switching [84, 85]. One way to overcome these challenges is to find and inhibit all the activated pathways in each tumor, and another way is to deliver other effective tumor killers to tumor tissues precisely and effectively. Targeting claudins falls into the latter strategy, consistent with targeting folate receptor in ovarian cancer and carcinoembryonic antigen (CEA) in CRC [86, 87].

An ideal molecule for targeted therapy in cancer should meet two criteria: first, its expression should be restricted in certain tissues, with no expression or inaccessibility to targeting strategies in other normal tissues to avoid adverse effects; second, its expression should be positive, and its epitopes should be exposed in corresponding malignant tissues, rendering them targeted. Claudins have been identified to meet the two criteria and as promising targets for the treatment of cancer. Although normal epithelial cells also express claudins, as mentioned above, claudin expression has tissue specificity, and some claudins are only expressed in very few tissue types. For example, claudin-18 expression is normally restricted to the lung and stomach; although its expression is decreased in malignant tissues, its expression is still can detected in some gastric cancer tissues [10]. Claudin-6 is a strictly oncofoetal cell surface antigen whose expression is completely absent in normal human tissues but reactivated in germline tumors such as testicular, ovarian and uterine cancer [88]. In addition, it has been observed that most claudins, if not all, are buried in the TJ complex in normal tissues, while in malignant tissues, higher accessibility of claudins is caused by extrajunctional mislocalization of the molecules [3]. Owing to this specific expression profile and difference between normal and tumor cells, claudins are attractive targets that can theoretically enable selective drug delivery with minimal adverse events. Many potential approaches for targeting claudins in patients with cancer are available, including CPE, mAbs, C-CPE or mAb-drug/material conjugates, bispecific T cell engagers (BiTEs) and chimeric antigen receptor (CAR) T cells (**Figure 3**). Several phase I to phase III clinical studies involving claudin-targeted agents are currently ongoing (**Table 2**).

CPE: Claudins are known to be targets for various pathogenic viruses and bacteria that hijack claudins to enter and infect cells or target signaling mechanisms to loosen junctions to cross tissue barriers, and this phenomenon has been exploited in therapeutic strategies. The two best elucidated examples are hepatitis C virus (HCV) and CPE, with CPE being the most investigated and promising in terms of therapeutic applications [89]. The C-terminal domain of CPE binds both ECL-1 and ECL-2 of claudins; this causes the formation of a pore near the N-terminal domain and leads to calcium influx, resulting in host cell death [3]. CPE strongly binds to claudins 3 and 4, but it also binds to claudins 6, 9, 14, and 19 with less affinity [8]. The ability of CPE to bind claudins presents an opportunity for targeting cancers overexpressing claudins. In preclinical experiments, the binding of CPE to claudins was documented to have a cytotoxic effect on ovarian, breast, colon, prostate and gastric cancer cells that were positive for claudin-3 and/or claudin-4 [90-94]. CPE is a cost-effective bacterial prod-

Table 2. Clinical trials with agents targeting claudins

Agent	Subject	Design	Outcome	Phase	NCT identifier
Monoclonal antibody (Claudin-6)					
ASP1650	Incurable platinum refractory GCTs	Single arm, lead-in phase: dose escalation; phase II: ASP1650 alone	Completed, NA	II	NCT03760081
IMAB027	Advanced ovarian cancer	Single arm, dose escalation	Completed, NA	I	NCT02054351
Monoclonal antibody (Claudin-18.2)					
IMAB362 (Zolbetuximab)	Treatment-refractory metastatic GEA	Single arm, dose escalation	All dose levels were generally well tolerated	I	NCT00909025 [115]
IMAB362 (Zolbetuximab)	Advanced GEA	Single arm, IMAB362 alone or plus ZA and/or IL-2	Disease control: 55%; OS: 40 weeks; Median PFS: 12.7 weeks	I	NCT01671774 [109]
IMAB362 (Zolbetuximab)	Advanced GEA	Single arm, IMAB362 alone	Response rate: 10%; Disease control: 30%; Median PFS: 14.5 weeks	IIA	NCT01197885 [116]
IMAB362 (Zolbetuximab)	Advanced GEA	Randomized: IMAB362 plus EOX versus EOX	ORR: 25% vs 39%; OS: 8.4 vs 13.4 months; Median PFS: 4.8 vs 7.9 months	IIB	NCT016300831 [109]
IMAB362 (Zolbetuximab)	Unresectable or metastatic GC/GEJC	Single arm, Part 1: Safety; and Part 2: Expansion	Completed, NA	I	NCT03528629
IMAB362 (Zolbetuximab)	Metastatic PC	Randomized: IMAB362 plus Nab-P + GEM versus Nab-P + GEM	Recruiting	II	NCT03816163
IMAB362 (Zolbetuximab)	Unresectable or metastatic solid tumors	Randomized: IMAB362 versus IMAB362 plus mFOLFOX6 versus IMAB362 plus pembrolizumab	Recruiting	II	NCT03505320
IMAB362 (Zolbetuximab)	Unresectable or metastatic GC/GEJC	Randomized: IMAB362 plus CAPOX versus placebo plus CAPOX	Recruiting	III	NCT03653507
IMAB362 (Zolbetuximab)	Unresectable or metastatic GC or GEJC	Randomized: IMAB362 plus mFOLFOX6 versus placebo plus mFOLFOX6	Recruiting	III	NCT03504397
TST001	Unresectable or metastatic solid tumors	Single arm, dose escalation stage and expansion stage (first line: TST001 + CAPOX second-line +: TST001 + paclitaxel)	Recruiting	I	NCT04495296
TST001	Unresectable or metastatic solid tumors	Single arm, dose finding portion and a recommended dose expansion portion	Recruiting	I	NCT04396821
AB011	Advanced solid tumors	Single arm, a dose escalation stage and an expansion stage	Recruiting	I	NCT04400383
CAR T cell *(Claudin-18.2)*					
CAR T cells	Advanced GC and PC	Single arm, dose escalation	ORR: 42.8; Median PFS: 130 days	I	NCT03159819 [125]
CAR T cells	Advanced solid tumor subjects	Single arm, dose escalation	Recruiting	I	NCT03874897
CT041	Advanced GC and PC	Single arm, a dose escalation part and a recommended dose expansion part	Recruiting	I	NCT04404595
CAR T cells	Advanced cancers	Single arm, 3 or more cycles	Recruiting	I	NCT03198052
LCAR-C18S cells	Advanced GC	Single arm	Recruiting	I	NCT04467853
CT041 Autologous CAR T cells	Advanced GC/GEJC and PC	Single arm, phase Ib: dose exploration phase and dose extension phase; phase II: effectiveness and safety confirmation phase	Recruiting	Ib/II	NCT04581473
Bispecific T-cell engager *(Claudin-18.2)*					
AMG 910	Metastatic or unresectable GC/GEJC	Single arm, a dose escalation part and a recommended dose expansion part	Recruiting	I	NCT04260191

CAR, chimeric antigen receptor; GC, gastric cancer; GCTs, germ cell tumors; GEA, gastroesophageal adenocarcinomas; GEJC, gastroesophageal junction cancer; IL, interleukin; NA, not applicable; ORR, objective response rate; OS, overall survival; PC, pancreatic cancer; PFS, progression-free survival; ZA, zoledronic acid.

uct, and its claudin-targeting and toxic domains are already natively combined, which indicates that it is a feasible antitumor agent. However, native CPE binds to only limited claudins, and the potential immune response against and side effects involving normal claudin-expressing cells limit the clinical applications of CPE. Several approaches have been utilized to address these disadvantages. Structure-guided mutagenesis of CPE has been performed to enable cytotoxic targeting of tumors expressing other claudins. Currently, one such CPE mutant with high affinity for claudin-1 was shown to induce necrosis and reduce growth in thyroid and lung cancer xenograft models [95]. Moreover, CPE can be expressed in target cells by nonviral in vivo gene transfer, causing direct cell killing, which is further enhanced by a toxin-mediated bystander effect [92, 95]. Intratumoral application of CPE has been reported to have great therapeutic potential without general toxin-associated side effects in xenograft-bearing mouse models [95, 96]. In addition, CPE fragments conjugated or fused with other antitumor materials have also been developed. A dual photodynamic and photothermal system was designed by linking CPE to a photodynamic agent, and this system showed increased uptake by claudin-4-expressing glioblastoma cells and potent anticancer effects [97]. A fusion protein containing the 30 amino acids at the C-terminal end of CPE and TNF was efficiently delivered into target ovarian cancer cells and showed more cytotoxicity than free TNF [98]. Gold nanoparticles (AuNPs) conjugated to C-CPE bind to claudin-expressing tumor cells and kill the cells via gold nanoparticle-mediated laser perforation (GNOME-LP) and represent another interesting approach [99, 100]. However, the effects of these approaches in humans have not yet been validated.

Monoclonal antibodies: In an oncology setting, in addition to affecting signaling pathways, mAbs can mediate antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against cancer cells [101]. As classic cell surface molecules, claudins may be ideal targets for mAbs. In addition to their successes in preventing and curing HCV, in 2005, Offner et al. investigated the potential of claudins as targets in antibody-based therapies for cancers [102, 103]. Since then, mAbs against the extracellular domains of some claudins (claudins 1 [104], 2 [105], 3 [106], 4 [107], 5 [108], and 18.2 [109]) have been generated, and their pharmaceutical activities as cancer therapies are being investigated. A murine mAb against human claudin-1 (6 F6 mAb) was able to combat colony formation, xenograft growth and metastasis of claudin-1-positive colorectal cancer (CRC) cells, suggesting its utility as a therapeutic [110]. An anti-claudin-4 antibody was also tested in CRC, and the efficacy was promising; the antibody was observed to synergize with 5-fluorouracil (5-FU) and anti-EGFR antibodies [111]. Several other studies have found that anti-claudin-4 mAbs are effective for combating various cancers and specifically accumulate in tumors but not normal tissues [112, 113]. Antibody-drug conjugates (ADCs) have also been generated and shown to inhibit the growth of pancreatic and gastric PDX tumors [114]. These promising proof of concept experiments have advanced some mAbs against claudins, including anti-claudin-18.2 (IMAB362) and anti-claudin-6 (IMAB027) antibodies, into clinical trials (**Table 2**).

IMAB362 (claudiximab or zolbetuximab) is a chimeric IgG1 antibody highly specific for claudin 18.2 and exerts its activity against claudin 18.2-positive cancer cells via multiple modes of action. It binds to claudin-18.2 on the tumor cell surface to promote cell death via ADCC and CDC, to induce apoptosis and to inhibit cell proliferation [109]. IMAB362 has been evaluated as a single agent in a phase I clinical trial for the treatment of patients with advanced gastroesophageal cancer. All dose levels of IMAB362 were generally well tolerated, and the most common adverse effects were nausea and vomiting without dose-limiting toxicity [115]. In another phase I trial in which patients with claudin-18.2-positive gastroesophageal adenocarcinomas received IMAB362 in combination with zoledronic acid (ZA) and interleukin-2 (IL2), the safety and efficacy were good [109]. Subsequently, two phase II trials involving patients with advanced/recurrent gastric and gastroesophageal junction (GEJ) cancer revealed a promising objective response rate (ORR) and promising OS in patients receiving IMAB362 monotherapy or IMAB362 in combination with epirubicin, oxaliplatin and capecitabine (EOX) [109, 116]. These results led to the initiation of a number of phase I to phase III

trials involving patients with advanced solid tumors (mainly gastric, GEJ and/or pancreatic adenocarcinoma) treated with anti-claudin 18.2 antibody monotherapy or anti-claudin 18.2 antibody in combination with conventional chemotherapeutic agents (**Table 2**). Trials of the other two recombinant humanized anti-claudin 18.2 IgG1 mAbs (AB011 and TST001) are currently recruiting patients, while two phase I clinical trials testing anti-claudin 6 mAbs (ASP1650 and IMAB027) in patients with incurable platinum-refractory germ cell tumors and advanced ovarian cancer have already been completed. Evaluating the clinical prospects of these mAbs and combinations is currently difficult; final conclusions will be possible upon the completion of adequately powered randomized trials.

T cell therapy: CAR T cells have been clinically successful in patients with B cell malignancies, but they have encountered challenges and been much less effective in patients with solid tumors [117, 118]. One key hurdle is the lack of cell surface antigens with high cancer-specific expression, which, if present, would allow for efficient tumor eradication. Owing to the differential expression of some claudins, such as claudin-6 and claudin-18.2, on the membranes of cells of various solid tumors of high medical need, interest in the development of CAR T cells targeting these claudins is not surprising. Engineered CAR T cells containing a single-chain variable fragment (scFv) with exquisite specificity for and high binding affinity to claudin-6 and claudin-18.2 and a T cell receptor chain in combination with a 4-1BB costimulatory domain were successful in inducing tumor regression with minimal adverse effects in preclinical models [11]. Jiang et al. also combined a humanized claudin-18.2-specific scFv with the CD28 costimulatory domain to construct claudin-18.2-CAR T cells and showed that these cells not only potently suppressed tumor growth in a cancer cell line xenograft mouse model but also had no obvious deleterious effects on normal organs [119]. However, in solid tumors, the clinical effect of CAR T cells is also hindered by their rapid decline in frequency, which occurs due to the inability of CAR T cells to reach tumor cells and the absence of proliferation signals [120-122]. Several approaches designed to further improve the efficacy of anti-claudin CAR T cells have been developed, including a CAR T cell-amplifying RNA vaccine (CARVac) capable of producing antigen-processing cells (APCs) with native claudin antigens (claudin-6 and claudin-18.2) expressed on the cell surface, which improves the engraftment of transferred CAR T cells and therapeutic tumor control [11].

Another clinical tool that can be used clinically to target claudin-18.2 is BiTEs, which retarget autologous activated T cells to cancer cells by crosslinking the T cell CD3 molecule and claudin-18.2, thereby improving ADCC with little toxicity. In an efficacy and preliminary toxicity study, these BiTEs exhibited a significant tumor cell lysis effect in vitro, inhibited the growth of pancreatic and gastric tumors, and did not produce obvious signs of toxicity in the stomachs of experimental mice [114]. A novel tetravalent bispecific (TetraBi) platform targeting claudin-18.2 was tested and showed impressive antitumor activity, providing a potentially better therapeutic index than bispecific formats [123]. BiTEs targeting claudin-6 have also been developed, and their tumor cell killing and T cell activation effects have been verified [124]. However, explorations of these strategies for clinical therapy are limited.

Such CAR T cells and BiTEs are being tested in several phase I trials that are currently recruiting patients with advanced tumors that are positive for claudin-18.2, one of which has already been completed with promising results. This phase I study explored the clinical characteristics of claudin-18.2-specific CAR T cells, including safety, tolerability and cytokinetics, in 12 patients with claudin-18.2-positive solid tumors. Among the 11 evaluable subjects, the ORR reached 33.3%, with an mPFS of 130 days; 1 patient achieved a CR, 3 patients had PR, 5 patients had SD, and 2 patients had progressive disease (PD) [125].

Drug absorption: Claudins help control the diffusion of ions, solutes, and water across epithelial and endothelial cell sheets to maintain homeostasis, which also prevents mucosal and epidermal absorption of drugs and the delivery of drugs from the systemic circulation to tissues. Modulation to loosen the paracellular space can increase mucosal and epidermal drug absorption, as well as drug delivery to tissues; this effect is currently mainly achieved by using sodium caprate and mannitol, which have some limitations [126, 127]. A series of proofs-

of-concept studies attempting to develop claudin-directed drugs to reversibly open TJs have been reported. The results of these studies demonstrate that targeting claudins with C-CPE, claudin peptidomimetics, or mAbs could be a useful strategy for the development of noninvasive systems to improve paracellular drug delivery across the mucosa, epidermis and BBB [128, 129]. In addition, intercellular junctions in cancer cells retain some function, which may reduce the efficacy of solute penetration, and modifying these barriers is a useful strategy to induce the accumulation of anticancer drugs in cancer tissues. In this regard, C-CPE induced morphologic changes in spheroids of ovarian cancer cells, and combined therapy with C-CPE and paclitaxel achieved significant synergic antitumor effects in vivo [130]. Short peptides that mimic the ECL of claudins were also found to increase antitumor drug accumulation in tumors [131]. PMTPV, a short peptidomimetic of claudin-1, elevated the accumulation and cytotoxicity of DXR in the spheroids by decreasing the expression and increasing the endocytosis and lysosome-dependent degradation of claudin-1 in lung cancer cells [132]. Treatment with an anti-claudin-4 antibody abolished the barrier functions in monolayers of T24 and RT4 bladder cancer cells. Treatment with an anti-claudin-4 antibody in combination with cisplatin showed more efficacious tumor growth inhibition than treatment with cisplatin alone or control group treatment [133]. However, claudins buried in junctional complexes are thought to be poorly accessible to large-molecule binders, such as antibodies, in physical conditions, and whether they are effective in clinical use needs careful verification.

Future perspectives and conclusion

From a translational perspective, claudin-targeting strategies seem to hold substantial promise, and this idea has been validated by clinical applications using specific claudin-targeting therapies (targeting claudin-6 and claudin-18.2). Although proof-of-concept experiments have verified the antitumor effect of many other claudin-targeting therapies, most of them remain in the laboratory stage, and their translation into clinical practice is eagerly awaited. What delays their clinical implications may be relevant to safety concerns. Although no apparent adverse effects were observed in these studies, the expression of these claudins was more global than that of claudin-18.2 and claudin-6, and these claudins play roles in the formation of the intercellular seal between epithelial cells and endothelial cells. Knockout mouse models of the genes encoding claudins have shown that there are risks associated with claudin-targeted therapeutics [134]. Efficacy and toxicity in humans are two main considerations for future research. Another need is to further develop the technology for creating human mAbs against claudins with more specificity and tumor tissue accumulation. In terms of medical economics and accessibility of claudins, chemical-type claudin binders are another promising approach. Therapeutic screens through molecular docking and relative dynamics analyses to identify agents targeting claudin-4 have been reported [135]. Such systems will be a novel method of screening for claudin binders, which could lead to the design of efficacious claudin-targeted drugs. Additionally, alternative strategies by which claudins can be exploited as a target for improving therapy outcomes should be proposed. Most conventional cancer cytotoxic therapies, including radiotherapy and chemotherapy, eliminate cells by inducing cell death, which is effective for removing highly proliferative cells but not quiescent CSCs, and this shortcoming leads to disease relapse [136]. Moreover, dying cells might secrete mitogens to elicit compensatory proliferation of these CSCs [137]. Thus, targeting and eliminating subsets of cells with stem and progenitor characteristics in cancer is essential for improving outcomes. Because specific claudins are important for and expressed in CSCs, they offer attractive targets for cancer therapy targeting CSCs. A pioneering study tested three strategies, including antibodies, cytotoxin-conjugated antibodies and CPE, all of which efficiently killed claudin-6-positive undifferentiated cells, thus eliminating the tumorigenic potential of human pluripotent stem cell-containing cultures [88].

The combination of several agents against different cancer pathological processes is currently the main strategy used to improve the outcomes of patients with cancer who can tolerate such treatment. Combination strategies including claudin-targeting agents are in clinical trials; the majority of combinations include

claudin-targeting agents and conventional chemotherapy regimens. Combining claudin-targeted therapies with cytotoxic chemotherapy might be feasible and effective owing to the targeted nature and lack of side effects of the combination. Although claudins are not oncogenic drivers, numerous studies have demonstrated crosstalk between claudins and many other signaling pathways, such as PI3K/Akt, MAPK, Hippo/YAP and Wnt/β-catenin, indicating that combinations with drugs targeting these pathways should be approached with caution because the effects of such combinations are uncertain owing to the diverse roles of claudins in regulating these signaling pathways. In addition, claudin-targeting therapies can deliver cytotoxic agents specifically to tumor cells, and in combination with DNA damage repair (DDR) inhibitors or apoptosis-targeting therapies, claudin-targeting therapies might circumvent the synergistic effects on normal tissues and significantly improve outcomes in patients with claudin-positive cancer. As mentioned above, the mutation frequency of claudins is low in cancer, and whether endogenous claudins can be processed and presented by MHC molecules to become the target of $CD8^+$ T lymphocytes is not clear. Finally, the degree of immunogenic cell death caused by claudin-targeting agents is not known. Therefore, the effect of combination therapy with immune checkpoint inhibitors (ICIs) requires further investigation, which will provide further therapeutic options for patients with claudin-overexpressing cancers.

In summary, alteration of claudins is a common phenotype associated with many different cancer types. Although a large body of evidence highlights that claudins can act as both protooncogenes and tumor promotors in different cancer types, stages and microenvironments, as molecules located on the cell surface, they are ideal molecules for targeted therapy. Unfortunately, however, except for in certain malignancies, the clinical applications of targeting claudins have progressed slowly. To strengthen the therapeutic window of claudins, a more translational view of claudins by researchers and exploration of new rational combinations are warranted.

Acknowledgements

The author thanks the Health Commission of Mianyang City and the Science and Education Department of the Third Hospital of Mianyang for their support.

Disclosure of conflict of interest

None.

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