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REVIEW

Expression and Targeted Application of Claudins Family in Hepatobiliary and Pancreatic Diseases

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Abstract: Hepatobiliary and pancreatic diseases are becoming increasingly common worldwide and associated cancers are prone to recurrence and metastasis. For a more accurate treatment, new therapeutic strategies are urgently needed. The claudins (CLDN) family comprises a class of membrane proteins that are the main components of tight junctions, and are essential for forming intercellular barriers and maintaining cellular polarity. In mammals, the claudin family contains at least 27 transmembrane proteins and plays a major role in mediating cell adhesion and paracellular permeability. Multiple claudin proteins are altered in various cancers, including gastric cancer (GC), esophageal cancer (EC), hepatocellular carcinoma (HCC), pancreatic cancer (PC), colorectal cancer (CRC) and breast cancer (BC). An increasing number of studies have shown that claudins are closely associated with the occurrence and development of hepatobiliary and pancreatic diseases. Interestingly, claudin proteins exhibit different effects on cancer progression in different tumor tissues, including tumor suppression and promotion. In addition, various claudin proteins are currently being studied as potential diagnostic and therapeutic targets, including claudin-3, claudin-4, claudin-18.2, etc. In this article, the functional phenotype, molecular mechanism, and targeted application of the claudin family in hepatobiliary and pancreatic diseases are reviewed, with an emphasis on claudin-1, claudin-4, claudin-7 and claudin-18.2, and the current situation and future prospects are proposed.

Keywords: claudins, hepatocellular carcinoma, cholangiocarcinoma, pancreatic cancer, targeted therapy

Introduction

Hepatobiliary pancreas-related diseases are becoming more common in modern societies and the associated tumors are highly malignant. Most patients are at an advanced stage when diagnosed, and the 5-year survival rate is low, which seriously threatens quality of life.[1] The main causes of death in patients with hepatobiliary and pancreatic tumors are recurrence and metastasis, and epithelial-mesenchymal transition (EMT) is crucial for the migration and metastasis of cancer cells.[2] Specifically, EMT is a process of transformation of epithelial cells into mesenchymal cells, in which epithelial cells lose apical cell polarity, lose adhesion, and acquire the mesenchymal cell phenotype, thus gaining cell migration abilities, which promotes metastasis and drug resistance.[3] This process is largely dependent on the breakdown and loss of tight junctions (TJs) between cells.

TJs are intercellular connection device that provides barrier and/or channel functions in the paracellular cleft and facilitates the maintenance of cell polarity.[4–7] TJs are composed of four transmembrane proteins, including occludin, tricellulin, marvelD3 and claudins, which belong to TJ-associated marvel protein (TAMP) family.[8–12] Claudins are the main components of tight junctions and function in mediating cell adhesion and paracellular permeability.[13–17] The claudin family contains at least 27 transmembrane proteins,[16,18] and the molecular weight of human claudin proteins range from 21–34 kDa.[17]

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Structurally, claudins are composed of four transmembrane segments, two extracellular segments (ECS) and one intracellular loop (Figure 1).[19] Among these structures, the ECS of claudins plays an important role in determining claudin function.[20,21]

Claudin family members not only form pores to regulate extracellular fluid and ions in epithelial cells, but also maintain epithelial homeostasis. Dysregulation of claudin proteins has been identified as an important mechanism for the loss of cell adhesion and metastasis, which leads to structural destruction and impaired function of epithelial and endothelial cells. Dysregulation of claudin expression has been shown to be associated with a variety of human diseases, among which it is most common in tumors, and changes in claudin expression are associated with specific pathogenic events (Table 1). In terms of carcinogenesis, different dysregulated claudin isoforms have different effects on different target cells (Table 2).[22–27] In recent years, claudin-18.2 has been increasingly used as a therapeutic target in solid tumors. This article summarizes the role of claudin family of proteins in hepatobiliary and pancreatic tumors and their potential as therapeutic targets.

Claudin-1

Claudin-1 Benign Disease

Claudin-1 (CLDN1) is the first member of the claudin family and has a molecular weight of 22 kDa.[14] It is crucial for epithelial barrier function[68] and plays a role in inflammation and tumor progression in various organs.

Claudin-1 is closely associated with hepatitis C and liver cancers and plays a role in the entry of the HCV virus into hepatocytes.[69,70] Specifically, the complex formed by claudin-1 and CD81 plays an important role in regulating the entry of HCV virus into cells.[71–73] Antibodies targeting claudin-1 can neutralize HCV infectivity by reducing E2 binding to the cell surface and disrupting the CD81-claudin-1 interaction.[72] These proteins provide a new targets for the treatment of

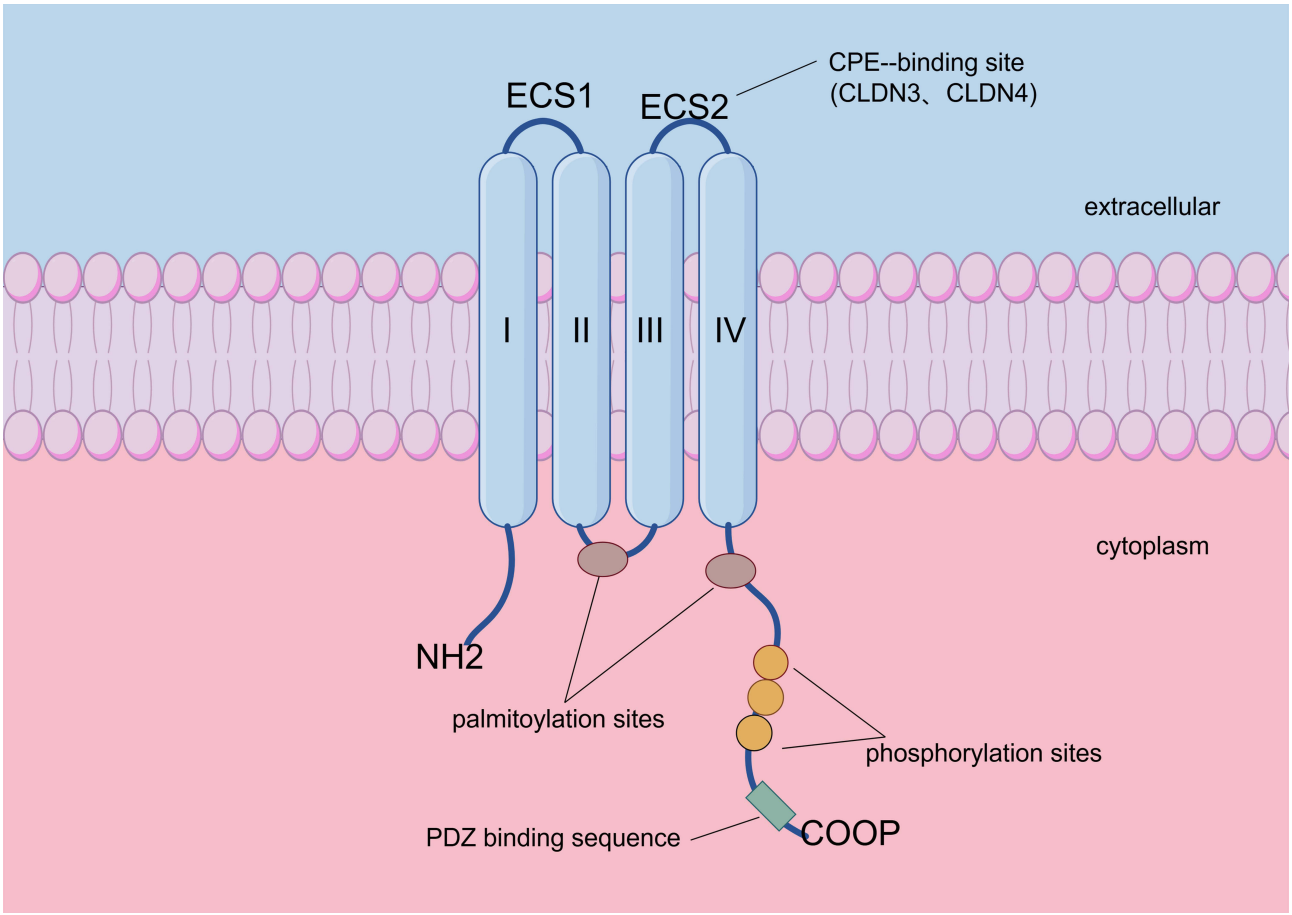

Figure 1 Structure of Claudin protein. (By Figdraw).

Table 1 Claudins in Non-Neoplastic Disease

Non-Neoplastic Disease	CLDN Subtype	Tissue Expression	Supplementary Statement
Demyelinating peripheral neuropathies	CLDN1	Upregulation[28]	The expression of claudin-1 can affect the demyelination process by altering the permeability of the blood nerve barrier.[28]
Xerostomia	CLDN10	Downregulation[29]	Assembly of claudin-10 is necessary for salivary secretion, and downregulation of claudin-10 induces hyposecretion.[29]
Multiple sclerosis (MS)	CLDN11	Upregulation[30]	The expression of Claudin-11 gene in white blood cells was significantly higher than that in normal group.[30]
Actinic keratosis (AK)	CLDN1	Downregulation[31]	Claudin-1 may be a useful marker of pathological severity of AK.[31]
Psoriatic	CLDN7	Upregulation[32]	Claudin-7 expression is regulated by HMG-CoA reductase in the epidermis.[32]
Atopic Dermatitis	CLDN3	Downregulation[33]	Loss of Claudin-3 leads to sweat leakage from sweat glands.[33]
Asthma	CLDN18.1	Downregulation[34]	Claudin-18 defects lead to increased sensitization of temperament antigen and airway hyperreactivity.[34]
Functional Dyspepsia (FD)	CLDN12	Downregulation[35]	Regulatory miRNA up-regulate CLDN12, which leads to increased duodenal permeability in FD.[35]
Diabetes	CLDN2	Upregulation[36]	CLDN2 can be used as a novel biomarker for prediabetes.[36]
Testicular intraepithelial neoplasia (TIN)	CLDN11	Upregulation[37]	The destruction of blood-testis barrier (BTB) is related to the dysfunction of claudin-11.[37]

Table 2 Claudins in Neoplastic Disease

Neoplastic Disease	CLDN Subtype	Tissue Expression	Supplementary Statement
Gliomas	CLDN1	Downregulation[38]	Down-regulated expression is potentially associated with the progression of glioblastoma multiforme (GBM)[38]
	CLDN3	Upregulation[39]	Promote the growth and metastasis of GBM and mediate the tumorigenic effect of TGF-β.[39]
	CLDN4	Upregulation[40]	CLDN4 can enhance the malignancy of glioma cells through the NNAT/Wnt signaling pathway.[40]
	CLDN5	Downregulation[38]	Down-regulated expression is potentially associated with the progression of GBM.[38]
Thyroid carcinoma	CLDN1	Upregulation[41,42]	Claudin-1 may help distinguish follicular adenoma from follicular thyroid carcinoma and typical variant thyroid-form carcinoma.[41]
	CLDN6	Upregulation[43]	
	CLDN10	Upregulation[44]	CLDN10 is a functional gene that promotes tumorigenesis in papillary thyroid cancer (PTC), acting as an oncogene in PTC.[44]
Lung adenocarcinoma	CLDN1	Downregulation[45]	CLDN1 is an inhibitor of cancer invasion and metastasis.[45]
	CLDN2	Upregulation[46]	Enhances the proliferation of lung adenocarcinoma cells[46]
	CLDN3	Upregulation[47]	CLDN3 overexpression promotes the malignant potential of lung adenocarcinoma, which may be regulated by EGF-activated MEK/ERK and PI3K-Akt pathways.[47]
Pancreatic cancer (PC)	CLDN1	Downregulation[48]	Claudin-1 acts as a tumor suppressor in PC.[48]
	CLDN4	Upregulation[49]	High expression of claudin 1 was significantly associated with the aggressive phenotype of pancreatic ductal mucinous tumors[49]
	CLDN5	Upregulation[50]	Association between high claudin 5 expression and poor survival.[50]
	CLDN7	Upregulation[51]	There was a statistically significant relationship between reduced Claudin 7 expression and reduced survival.[51]
	CLDN18.2	Upregulation[52]	High CLDN18.2 expression was associated with longer overall survival.[53]
	CLDN23		Claudin-23 is involved in the regulation of pancreatic cancer cell dissociation through changes in gene expression and intracellular localization.[54]
Prostate cancer	CLDN1	Upregulation[55]	Elevated Claudin-1 expression levels predict a good prognosis for ERG-positive cancers.[55]
	CLDN3	Downregulation[56]	Loss of Claudin-3 expression is a prognostic marker for castration-resistant prostate cancer (CRPC).[56]
	CLDN4	Upregulation[57]	High claudin-4 expression was associated with high tumor grade, lymphocyte invasion, positive lymph node metastasis, and high mean peritumoral lymphatic vessel density.[57]
	CLDN8	Upregulation[58]	CLDN8 promotes the proliferation and migration of prostate cancer cells.[58]

(*Continued*)

Table 2 (Continued).

Neoplastic Disease	CLDN Subtype	Tissue Expression	Supplementary Statement
Renal cell carcinoma (RCC)	CLDN2	Downregulation[59]	CLDN2 inhibits RCC progression by inhibiting YAP activation.[59]
	CLDN7	Upregulation[60]	CLDN7 can be used as a useful diagnostic marker for the diagnosis of chromophobe RCC and eosinophil cytoma.[60]
	CLDN8	Downregulation[61]	Potential tumor suppressor.[61]
	CLDN10	Downregulation[62,63]	Overexpression of Claudin-10 inhibits the growth and metastasis of human clear cell renal cell carcinoma by regulating ATP5O and causing mitochondrial dysfunction.[62]
Urothelial carcinoma (UC)	CLDN1	Upregulation[64]	Decreased Claudin-1 and Claudin-4 expression indicates the progression of urothelial carcinoma.[64]
	CLDN4	Upregulation[64]	Decreased Claudin-1 and Claudin-4 expression indicates the progression of urothelial carcinoma.[64]
	CLDN11	Downregulation[65]	CLDN11 reduce the aggressiveness of bladder cancer cells.[65]
Osteosarcoma (OS)	CLDN10	Upregulation[66]	CLDN10 promotes malignant phenotype of osteosarcoma cells through JAK1/Stat1 signaling.[66]
	CLDN12	Upregulation[67]	CLDN12 promotes cell proliferation and migration through the PI3K/Akt signaling pathway in osteosarcoma cells.[67]

HCV infection. Compared with common benign hepatobiliary diseases, pancreatic inflammation and other benign diseases have little correlation with claudin-1.

Claudin-1 Malignant Disease

Claudin-1 Functional Phenotype

Claudin-1 is involved in cancer invasion and metastasis and closely relates to hepatobiliary and pancreatic tumors. Furthermore, Claudin-1 is involved in the occurrence and metastasis of HCC,[74–76] and claudin-1 also regulates cholangiocarcinoma (CCA) cell invasiveness.[77] Simultaneously, the claudin-1 expression level correlates with the prognosis of patients with gallbladder cancer.[78,79] Claudin-1 acts as a tumor suppressor in PC in pancreatic cancer.[48] Mechanistically, claudin-1 affects tumor progression by regulating epithelial mesenchymal transition (EMT). Claudin-1 overexpression induces EMT by activating the c-Abl/ERK signaling pathway to regulate the expression of the transcription factors Slug and Zeb1, thereby promoting the invasiveness of HCC cells.[80] miR-193b expression inhibits pancreatic ductal adenocarcinoma (PDAC) cell proliferation, migration, invasion and EMT by inhibiting the eEF2K/MAPK-ERK oncogenic axis while upregulating the expression of E-cadherin and claudin-1.[81] Downregulation of 5-HT1B and 5-HT1D receptors,[82] synthetic 8-hydroxydeoxyguanosine (synthetic 8-OHdG),[83] or knockdown of LONP1[84] can inhibit the EMT of pancreatic cancer cells by upregulating claudin-1.

The Claudin-1 Molecular Pathway

Claudin-1 regulates multiple pathways and is involved in cancer progression. The c-Abl-protein kinase Cδ (PKCδ) signaling pathway and the c-Abl/Raf/Ras/ERK signaling pathway function with claudin-1 to enhance HCC invasion.[80,85,86] Furthermore, claudin-1 participates in the cell dissociation process of PC cells by activating mitogen-activated protein kinase 2 (MEK2).[87] The expression of claudin-1 is regulated by multiple factors. As its upstream molecule, hgH inhibits claudin-1 expression and promotes the stem cell properties of HCC.[88] Interestingly, TMPRSS4 promotes tumor sphere formation ability and cancer stem cell (CSC) traits by upregulating claudin-1.[89] In addition, mitochondrial defects, heat shock factor 1(HSF1), lactate dehydrogenase B(LDHB), and miR-29a affect the role of claudin-1 in mediating HCC invasiveness.[90–92] As a key molecule, claudin-1 is involved in regulating CCA invasiveness by multiple molecules and pathways, such as the P38 MAPK signaling pathway, polypeptide N-acetylgalactosaminotransferase-5 (GALNT5), etc.[77,93] Furthermore, claudin-1 expression in human pancreatic cancer cells is induced by tumor necrosis factor–α (TNF-α).[94] In pancreatic cancer tissue, ZIP4[95] as well as the distribution-deficient protein Par3-Tiam1 downregulate the tight junction marker proteins ZO-1 and claudin-1, thereby promoting pancreatic cancer invasion and metastasis.[96] PKCα downregulates claudin-1 through Snail and mitogen-activated protein kinase/ERK-dependent pathways.[97]

Claudin-1-Targeted Applications

Recent research has found that claudin-1 antibodies may provide therapeutic opportunities for HCC.[80] Among which, targeting claudin-1 can treat HCC by affecting tumor stemness, metabolism, oncogenic signaling and disrupting the tumor immune microenvironment.[80] Currently, Alentis Therapeutics had developed two Claudin-1 monoclonal antibodies, ALE-F02 and ALE-C04.

Claudin-4

Claudin-4 Benign Disease

Claudin-4 (CLDN4) is composed of 209 amino acids, with four transmembrane segments, and is an integral component of tight junctions. Few studies have investigated the role of claudin-4 in benign hepatobiliary and pancreatic diseases. However, a few studies have found that the core genes CDH1 and claudin-4, which may be regulated by FOXP3 or USF2, play important roles in acute pancreatitis (AP).[98]

Claudin-4 Malignant Disease

Claudin-4 Functional Phenotype

Claudin-4 is differentially expressed in various cancers including HCC and CCA tissues, and can be used as a marker to distinguish HCC from CCA.[99,100] A study conducted multiple linear regression analysis of standardized gene expression data for differential expression between CCA and HCC, and used claudin-4 to develop a "CCA diagnostic equation", which was used to improve the accuracy of CCA diagnosis.[101] Compared with hepatobiliary tumors, there are relatively more studies on claudin-4 in pancreatic tumors. Claudin-4 is closely associated with PC occurrence and progression, and different types of pancreatic cancer have different claudin-4 expression levels.[102] Claudin-4 can be used to differentiate pancreatic ductal adenocarcinoma (PDAC) from benign epithelium (BE) surrounding tumor tissue.[103] Furthermore, the expression of claudin-4 is associated with pancreatic tumor progression, especially with unique pathways of intestinal differentiation.[49,104] Claudin-4 can be used as a prognostic marker for liver cancer and pancreatic ductal adenocarcinoma.[105]

The Claudin-4 Molecular Pathway

Claudin-4, a downstream molecule of zinc finger protein 703 (ZNF703), mediates EMT of HCC.[106] In pancreatic cancer tissue, claudin-4, as a downstream molecule, is regulated by a variety of factors and pathways in pancreatic cancer tissues. Claudin-4 is a target of the transforming growth factor beta and Ras/Raf/extracellular signal-regulated kinase pathways.[107] Inhibiting MEK-ERK signaling in PC cells has been found to increase the expression of E-cadherin and claudin-4, thereby inhibiting the invasive activity of pancreatic cancer cells.[108] During EMT in human PC cells, PKCα activation downregulates TJ barrier function and the clostridium perfringens enterotoxin (CPE) receptor by modifying claudin-1 and claudin-4.[109] The transcription factors DEC1 and BACH1 regulate claudin-4 expression in PC, thereby affecting EMT.[110,111]

Claudin-4 Targeted Application

Currently, many studies have evaluated clinical applications of claudin-4; however, the scope of its application is limited to the pancreas. Residues inside and outside the ECS2 structural domain of the claudin-4 protein are used for subtype-specific targeting by the c-terminal fragment of CPE (C-CPE),[112–116] thereby achieving the effects of targeted claudin-4 radiography and cancer therapy. As a target of radiographic imaging, claudin-4 can detect pancreatic cancer and precancerous lesions, which contributes to the early detection of pancreatic cancer.[107,117–121] In addition, claudin-4 is also an effective target for cancer therapy.[122] Targeting claudin-4 may improve the effectiveness and safety of anticancer drug treatments for pancreatic ductal carcinoma (PDC).[123] Interestingly, the effect of CPE targeting claudin-4 in normal HPDE cells differs from that in PC, which may relate to the different localization of claudin-4 in normal HPDE cells and PC cells.[124] Based on the spatial structure of claudin-4, a recent study developed a synthetic antibody fragment (sFab) that binds to human claudin-4 —— COP-1.[125] Taken together, claudin-4 may serve as a target for radiological imaging and pancreatic cancer therapy.

Claudin-7

Claudin-7 Benign Disease

Claudin-7 (CLDN7) consists of 211 amino acid residues and is mainly distributed in the intestine, stomach, lungs, bladder, skin and kidneys.[126] The expression levels of claudin-7 vary in tumor tissues, and claudin-7 expression in malignant tumor tissues may be relate to tumor grade and prognosis.[127–130] Current research on benign hepatobiliary and pancreatic diseases has not found a correlation between claudin-7 and these diseases.

Claudin-7 Malignant Disease

Claudin-7 Functional Phenotype

Compared with normal liver tissue, the expression of claudin-1 and claudin-7 is increased in cirrhosis and hepatocellular carcinoma.[76,131] The downregulated or abnormal expression of claudin-7 is associated with liver metastasis of malignant tumors.[132] A prior survival analysis showed that patients with high claudin-7 expression in HCC tissues had better prognosis than those without.[131] Furthermore, other studies have reported that downregulation of claudin-7 is a positive prognostic marker in HCC.[105] Similar to claudin-4, claudin-7 may be a useful marker for distinguishing HCC from CCA in humans,[100] and this conclusion has also been verified in canine specimen studies.[133] Notably, the expression of claudin-7 has helped distinguish different types of pancreatic tumors,[134] and claudin-7 expression has been found to differ in pancreatic adenocarcinoma, with different degrees of differentiation.[135] In PC cells, claudin-7 knockdown induces significant proliferation inhibition.[136] Furthermore, studies on tumors in PC have found that the TJ protein claudin-7 binds to the tumor marker EpCAM to inhibit EpCAM-mediated cell-cell adhesion and promote migration, proliferation, apoptosis resistance and tumorigenicity.[137–139] Claudin-7-dependent tumor exosomes promote non-metastatic tumor cells to restore cancer-initiating cell (CIC) activity.[140] It was further proposed that LDN7 can serve as a CIC biomarker,[139] however, the prerequisites for claudin-7 as a CIC marker involve glycolipid-rich membrane microdomain (GEM) localization and palmitoylation. In addition, claudin-7 not only affects the assembly of tumor exosomes, but palmitoylated claudin-7 also helps transmit information through exosomes.[141]

Other Claudins

Other claudin molecules associated with hepatobiliary and pancreatic diseases include claudin-2, 3, 5, 6, 9, 10, 11, 12, 14, 17, and 23 isoforms. Among them, barrier-forming claudin-3, −5, −6, −9, −11, and-14 mainly form tightly closed paracellular barriers, pore-forming claudin −2, −10a/b, and-17 can selectively pass ions and solutes, while the barrier or channel-forming functions of claudins −12, −23 has not yet been determined.[17,142–144]

Benign Disease

Plasma claudin-3 is a marker of intestinal permeability(IP) in patients with liver disease.[145] In the liver, claudin-3 is vital to maintain metabolic homeostasis, retention of bile acids, and optimal hepatocyte proliferation during liver regeneration.[146] claudin-2 and claudin-3 relate to cholesterol stones, and in mouse experiments, knockdown of claudin-2 and claudin-3 was found to increase susceptibility to cholesterol gallstone disease.[147,148] As mentioned previously, claudin-1 plays a role in HCV entry, and claudin-6 and claudin-9 can also mediate HCV entry into target cells.[149]

Malignant Disease

Functional Phenotype

Multiple claudin isoforms are involved in the occurrence, invasion, and metastasis of hepatobiliary and pancreatic tumors, and the expression level of claudin-5 relates to HCC prognosis.[105,150] Fibrolamellar liver cancer is a subtype of HCC, and claudin-5 is specifically expressed in fibrolamellar liver cancer.[151] Claudin-6 is upregulated in HCC tissues and promotes HCC progression.[152,153] Claudin-9[154] and claudin-17[155] are related to the aggressiveness of hepatocytes. Claudin-10 is highly expressed in HCC[154] and is functionally involved in HCC invasion.[155] Claudin-10 is a molecular marker for poor prognosis after liver resection in patients with HCC.[154,156] It is worth noting that claudin-1, claudin-2 and claudin-4 are up-regulated in an HCC cell line with claudin-10 overexpression, which indicates that claudin-10

expression in cancer cells may affect the expression levels of its family members.[155] Claudin-14 is a direct target of EZH2-mediated H3K27ME3,[157] and in HCC tissues, EZH2-H3K27ME3 overexpression enhances HCC migration and invasion by downregulating the claudin-14 expression.[157] Low expression of claudin-14 is an independent prognostic factor for decreased survival rate of patients with HCC.[157] Furthermore, reduced claudin-3[158] and claudin-14[157] expression leads to an increase in Wnt/β-catenin signaling, which is a critical driver of EMT.[159] The expression of claudin-3 differs in HCC and CCA,[158,160] and claudin-3 in bile-derived external vesicles (EVs) is a useful CCA biomarker.[160] In pancreatic diseases, claudin-2 provides a useful molecular marker for precancerous PDAC lesions.[161] Furthermore, claudin-3 is highly upregulated in PC,[115] and claudin-3 upregulation promotes PC cell migration and invasion.[162] Similar to claudin-4 expression, different types of PC have different expression levels of claudin-3, among which claudin-3 is highly expressed in pancreatic endocrine tumors.[163] Furthermore, claudin-3 expression closely related to PC differentiation.[164] Claudin-5 is present in endothelial cells of normal pancreatic tissue,[50] and claudin-5 can be used to distinguish different types of PC.[134,165] An immunohistochemical study in dogs found that loss of claudin-5 expression may contribute to carcinogenesis in exocrine pancreatic cells.[166] Furthermore, some studies have shown that increased claudin-5 expression is associated with poor prognosis of pancreatic adenocarcinoma, which may relate to increased locomotion and A more aggressive carcinomas spread.[50]

Molecular Pathway

In liver cancer tissues, claudin-3 can significantly inhibit metastasis by inhibiting the Wnt/β-catenin-EMT axis in HCC cells.[158] Claudin-6 silencing significantly inhibits the EGFR/AKT/mTOR signaling pathway in HCC, thereby inhibiting cell proliferation, migration, and invasion.[152] Claudin-9[167] and claudin-17[168] affect the Stat3 signaling pathway through Tyk2, which ultimately enhances the metastatic ability of HCC. Claudin-11, a downstream molecule of miR-99b, mediates the inhibitory effect of miR-99b knockdown on HCC cell metastasis in vitro (Figure 2).[169] miR-324-3p targets and downregulates claudin-3 to reduce PC cell migration, invasion, tumor formation, microvessel density, and lymph node metastasis.[162] In pancreatic adenocarcinoma (PAAD) tissue, claudin-12 serves as a downstream molecule of LINC00857, which is regulated by the transcription factor ZNF460. The upregulation of claudin-12 expression can facilitate the progression of PAAD.[170] As a TJ proteins, claudin-23 is involved in the regulation of PC cell dissociation through changes in gene expression and intracellular localization, thus affecting PC progression. Its expression is possibly correlated with the activation of the MEK signaling pathway during PC cell dissociation.[54]

Targeted Application

A human-rat chimeric IgG1 form of the monoclonal antibody (xi-1A2) may serve as a leading candidate rat monoclonal antibody (mAb) for safe claudin-2-targeted cancer therapy.[171] With the in-depth research on claudin-3 and hepatobiliary and pancreatic diseases, it was found that Hizikia fusiforme (EHF) can inhibit the main components of TJ such as claudin-1, claudin-3 and claudin-4, thereby tightening TJs to inhibit cancer cell invasion.[172] In addition, the receptor for Clostridium perfringens enterotoxin (CPE) happens to be the same as claudin-3 and claudin-4, which provides a natural material for the targeted application of claudin-3.[173] Abion developed ABN501, the world's first monoclonal antibody targeting Claudin-3, for the treatment of breast and ovarian cancer. Notably, a Phase I/II first human clinical trial has been initiated for claudin-6, to evaluate the safety and initial efficacy of human claudin-6 RNA-encoded T cell binding bisspecific antibody BNT142 RNA-LNP in patients with claudin-6-positive advanced solid tumors (NCT05262530).[174]

Claudin-18.2

Claudin-18 (CLDN18) is divided into two subtypes, of which claudin-18.1 is highly expressed in lung epithelial type I cells, while claudin-18.2 is specifically expressed in gastric tissue.[175,176] In normal gastric tissue, claudin-18.2 is buried in the tight junctions of gastric mucosal cells.[175,177] Due to malignant transformation and loss of cell polarity, claudin-18.2 is exposed on the surface of tumor cells, making it accessible to antibodies.[178]

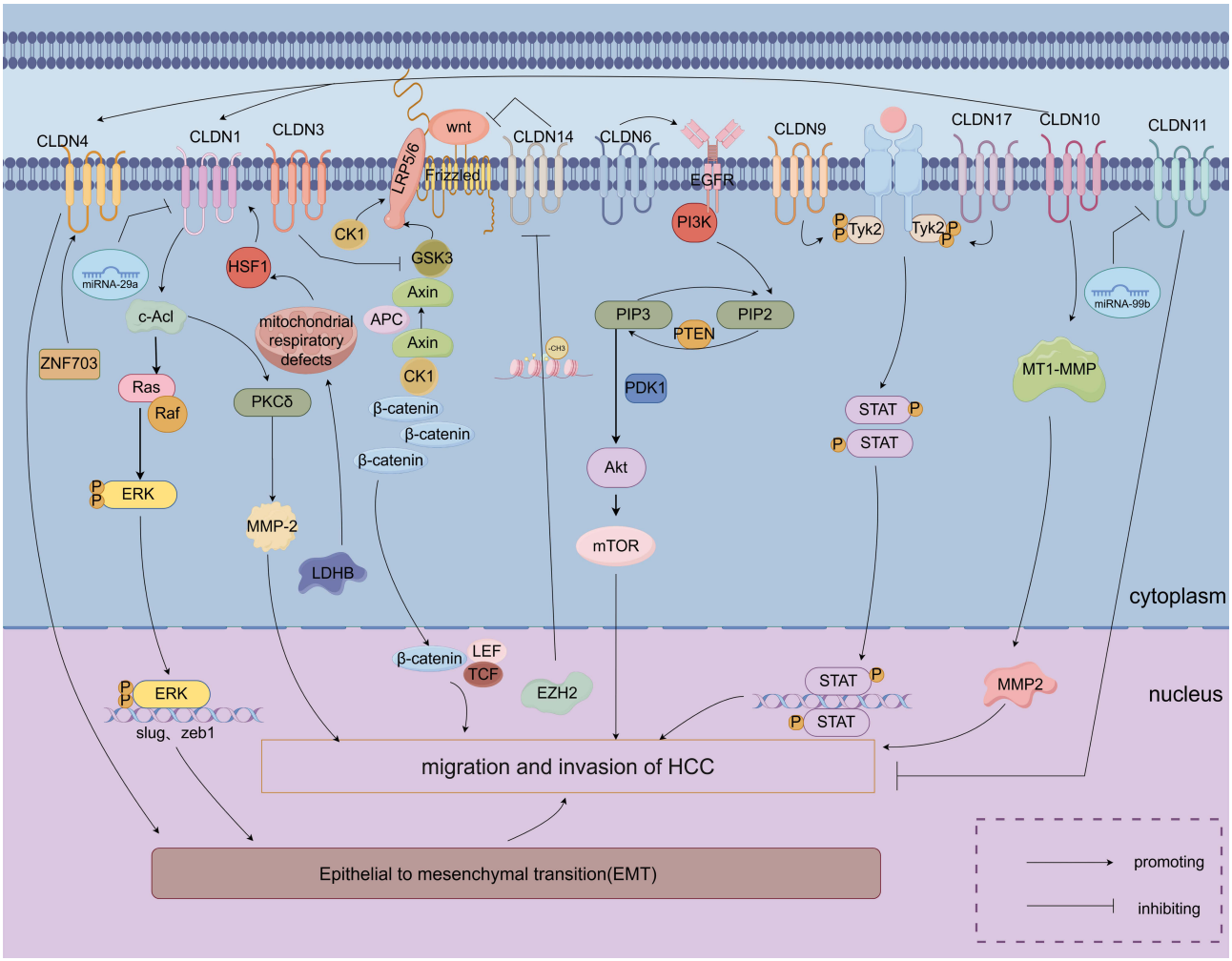

Figure 2 Regulatory mechanisms of HCC migration and invasion of different CLDN subtypes. (By Figdraw).
Abbreviations: HCC, hepatocellular carcinoma; EMT, epithelial-mesenchymal transition; LDHB, lactate dehydrogenase B; HSF 1, Heat Shock Factor 1; ZNF703, zinc finger protein 703; EZH2, enhancer of zeste homolog 2; PKCα, protein kinase C-α; ERK, extracellular signal-regulated kinase; Zeb1, zinc finger E-box binding homeobox 1; EGFR, epidermal growth factor receptor; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; Tyk2, tyrosine kinase 2; Stat3, signal transducer and activator of transcription 3; MT1-MMP, maturation of membrane type 1-matrix metalloproteinase; MMP2, matrix metalloproteinase 2.

Claudin-18.2 and Gastric Cancer

Functional Phenotype

Prior studies have found that claudin-18.2 protein levels are down-regulated in gastric cancer cells[179–181] and increased in gastric adenocarcinomas.[182] Notably, claudin-18 is generally maintained in peritoneally disseminated (PD) gastric cancer,[183] where claudin-18.2 positivity is associated with more frequent peritoneal metastasis.[184] Experiments in mice found that deletion of claudin-18.2 promoted the progression of gastric cancer.[177,185] The reason why claudin-18.2 deletion promotes gastric cancer progression may not only relate to TJ dysfunction, but also inflammation mediated by changes in paracellular permeability.[186,187] Claudin-18.2 plays a key role in mediating the adhesion between gastric cancer cells and cancer-associated fibroblasts (CAFs), thereby promoting gastric cancer progression and embolization.[188] In addition, the claudin-18-ARHGAP fusion gene was found in gastric cancer tissues, which may relate to the aggressive characteristics of gastric cancer.[189,190] The fusion gene can cause RHOA activation in diffuse gastric cancer (DGC) and activation of FAK and YAP signaling.[191] In gastric cancer tissues, the positive expression of claudin-18.2 closely relates to the tumor immune microenvironment.[181,190,192]

Molecular Pathway

The claudin-18 protein is divided into two isoforms. As a downstream target gene, claudin-18 is regulated by the T/EBP/NKX2.1 homology domain transcription factor, thereby selectively splicing and encoding the gastric-specific isoform claudin-18.2.[175] Regarding the mechanism by which claudin-18.2 deletion promotes the occurrence and progression of gastric cancer, prior research has found that the claudin-18.2 gene serves as a direct downstream target of miR-1303 and mediates miR-1303 regulation during on the proliferation and invasion of gastric cancer cells.[179] At the same time, claudin-18.2 protein regulates multiple signaling pathways, thereby affecting the occurrence and progression of gastric cancer, such as p53 and STAT signaling,[177] Notch and Wnt signaling pathways,[186] YAP/TAZ signaling,[193] etc.

Targeted Application

In view of the specific expression characteristics of claudin-18.2 in gastric cancer tissues, molecular imaging[194] and claudin-18.2-targeted therapy have become new options for the diagnosis and treatment of gastric cancer.[195–199] According to the search results of the ClinicalTrials.gov database, there are currently more than one hundred clinical trials targeting claudin-18.2. Among these, Zolbetuximab is currently the most widely studied and recognized claudin-18.2-targeted therapy.[200,201] Zolbetuximab targets binding to claudin-18.2 on the surface of tumor cells. Under normal conditions, cells are tightly connected structures, and Zolbetuximab is difficult to bind to claudin-18.2; in carcinoma, tumor cells overexpress claudin-18.2 and claudin-18.2 is exposed to the outer side of the basement membrane, which makes it easier for Zolbetuximab to bind to claudin-18.2 and play a role (Figure 3).[202] Zolbetuximab combined with the anti-programmed cell death 1 antibody inhibited tumor growth more effectively than either drug alone.[203]

Furthermore, zolbetuximab combined with CAPOX has been tested as a potential first-line therapy (NCT03653507).[204] Several early clinical trials presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting explored other targeted approaches to claudin-18.2 in difficult-to-treat advanced solid tumors, including claudin-18.2-targeting antibody-drug conjugate LM-302 and IBI343, bispecific antibody IBI38 against claudin-18.2/CD3, and chimeric antigen receptor T-cell therapy satricabtagene autoleucel.[205] Besides IBI38, bispecific antibodies targeting both HER2 and claudin-18.2 can enhance immune effector function to kill gastric cancer cells that express both antigens.[206] A novel tri-specific T-cell engager DR303 has recently emerged for claudin-18.2-positive cancer immunotherapy, which can bind to claudin-18.2, human serum albumin (HSA), and CD3, showing significant tumor suppression effects.[207] Satricabtagene autoleucel (satri-cel)/CT041, a self-engineered chimeric antigen receptor (CAR) T cell targeting claudin-18.2, has shown potential for treatment with manageable safety in patients with advanced gastric or gastrointestinal stromal tumors expressing claudin-18.2 (NCT03874897).[208] The latest research has found that [177Lu]Lu-labeled anti-claudin-18.2 antibody [177Lu]Lu-TST001 shows the potential for radio immunotherapy in a mouse heterologous transplantation model of gastric cancer, which can serve as a potential new targeted therapeutic drug.[209] Claudin-18.2 targeted therapy has achieved better results in gastric cancer, although few studies have investigated such therapies in patients with hepatobiliary and pancreatic diseases.

Claudin-18.2 and Hepatobiliary and Pancreatic Diseases

At present, no link between claudin-18 and benign hepatobiliary and pancreatic diseases has been identified; however, claudin-18 affects their occurrence and development. Compared to gastric cancer, claudin-18.2 has been less studied in hepatobiliary and pancreatic diseases. The expression of claudin-18.2 in normal tissues is limited to gastric epithelium,[210,211] but claudin-18.2 is also expressed in a variety of gastrointestinal tumors, including gastric cancer, pancreatic cancer, cholangiocarcinoma, etc.[212] Claudin-18 is upregulated in tumor tissues of patients with HCC,[213] and in pancreatic cancer, claudin-18 is a marker of early oncogenic processes[214] and is commonly expressed in precursor PDAC lesions.[161,214,215] In addition, claudin-18.2 is highly expressed in PDAC,[52,210,211,216,217] and most PDAC specimens show high claudin-18.2 expression, especially well-differentiated PDAC.[217] Membrane-bound claudin-18 is a useful marker for the diagnosis of PC,[135] and in pancreatic tissue, the expression of claudin-18 and annexin A8 can be used to differentiate between benign reactive glands and pancreatic invasive ductal adenocarcinoma.[218] Claudin-18.2 can also be used to distinguish different subtypes of PDAC,[219] as it is specifically expressed in the intestinal-type component of intraductal papillary mucinous carcinoma(IPMC).[220] The rate of claudin-18.2 positivity is high in pancreatic neoplasms,

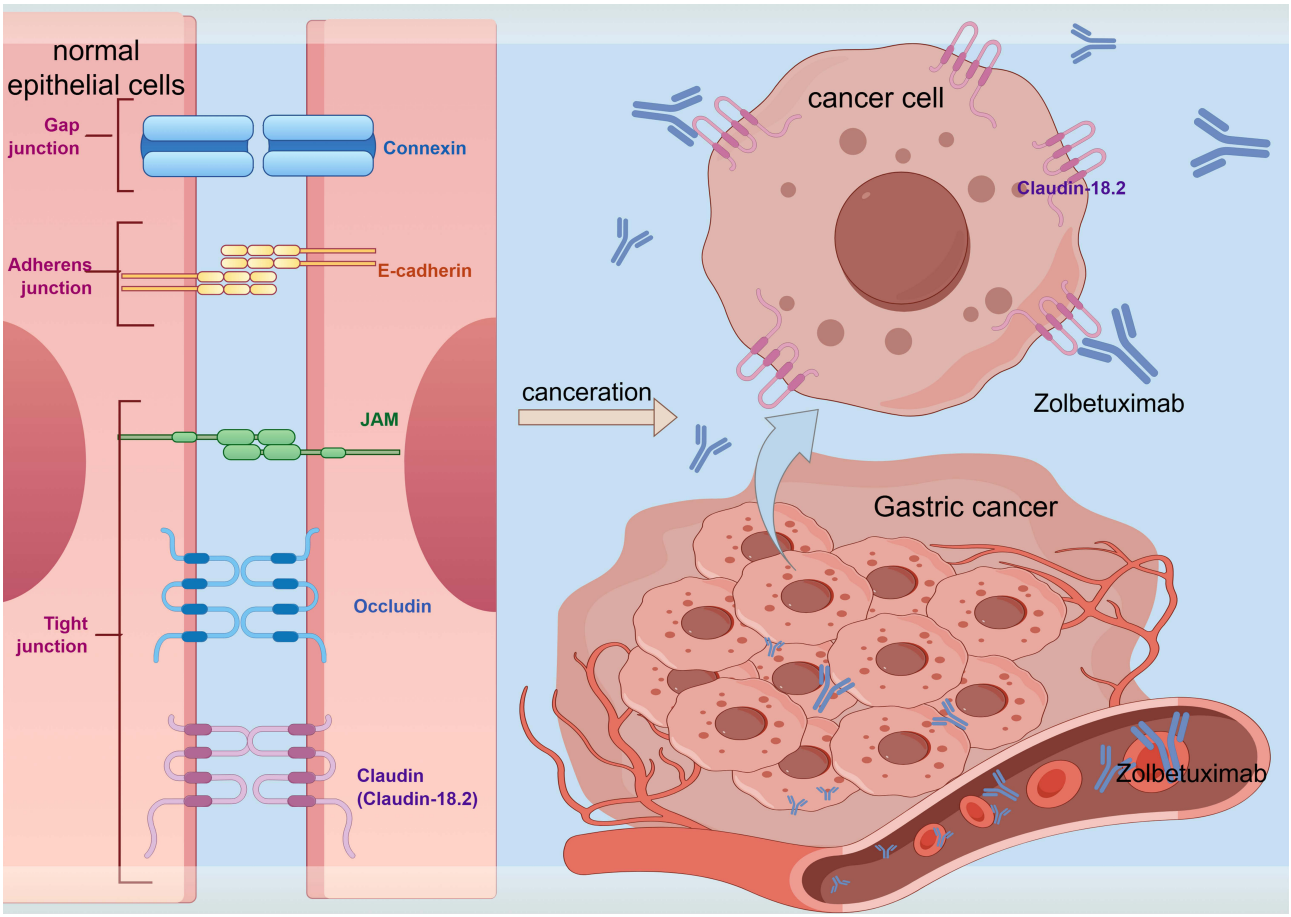

Figure 3 The principle of Zolbetuximab targeting CLDN18.2+ tumor cells. (By Figdraw).

and it is worth noting that its expression is not limited to the primary tumor but is also maintained in metastases.[52] Therefore, claudin-18 represents a marker for identifying the stomach and pancreatobiliary tract as the primary sites of metastatic adenocarcinoma.[221,222] Furthermore, claudin-18 can be used to improve the accuracy of diagnosis of pancreatobiliary malignancies.[223] The expression of claudin-18.2 correlates with various clinicopathological characteristics, such as lymph node metastasis, distant metastasis, nerve invasion, stage, and survival rate of patients with PDAC.[216,217] Among patients, claudin-18 expression positively associates with more differentiated histology and better prognosis.[53,217,224] This may relate to the expression of claudin-18 on cancer cells, which promotes the invasion of PC T lymphocytes and anti-tumor immunity.[224] Furthermore, activation of the PKC pathway significantly induces the expression of claudin-18 in normal HPDE cells and PC cells.[214,225,226]

The expression characteristics of claudin-18.2 make it a new and attractive target for antibody therapy in epithelial tumors (Table 3).[178] Claudin-18.2 also provides a target for the treatment of gastric cancer and PC.[211] The monoclonal antibody zolbetuximab, which targets claudin-18.2, is used to treat pancreatic ductal adenocarcinoma.[210,216,227] For the targeted treatment of human claudin-18.2-positive cancers, prior studies have developed a recombinant antibody hu7v3-Fc based on a humanized VHH. In a mouse xenograft model, the anti-tumor efficacy of hu7v3-Fc was significantly higher than that of the zolbetuximab monoclonal antibody.[228] In recent years, claudin-18.2-targeted chimeric antigen receptor (CAR) T cell therapy (CAR-T) has become a hot topic in the treatment of gastric cancer and PC.[229,230] In addition, targeting claudin-18.2 can be used as a computerized imaging tracer to assist in disease diagnosis.[231]

Table 3 Clinical Trials Targeting Claudin-18.2 for the Treatment of Solid Tumors. (Date Source: Classical.clinicaltrials.gov)

study	NCT Number	Status	Study Results	Interventions	Phases	Enrollment	Study Type
1	NCT06038396	Recruiting	No Results Available	Drug: RC118 Drug: Toripalimab	Phase 1/2	64	Interventional
2	NCT05367635	Recruiting	No Results Available	Drug: SKB315 for injection	Phase 1	206	Interventional
3	NCT05980416	Recruiting	No Results Available	Drug: EO-3021	Phase 1	120	Interventional
4	NCT06219941	Recruiting	No Results Available	Drug: AZD0901 Drug: 5-Fluorouracil Drug: Leucovorin Drug: l-leucovorin Drug: Irinotecan Drug: Nanoliposomal Irinotecan Drug: Gemcitabine	Phase 2	123	Interventional
5	NCT05161390	Recruiting	No Results Available	Drug:LM-302 Injection	Phase 1/2	206	Interventional
6	NCT05009966	Recruiting	No Results Available	Drug: SYSA1801 for injection	Phase 1	272	Interventional
7	NCT05001516	Active, not recruiting	No Results Available	Drug: LM-302	Phase 1	42	Interventional
8	NCT04805307	Recruiting	No Results Available	Drug: CMG901	Phase 1	162	Interventional
9	NCT05156866	Recruiting	No Results Available	Drug: TORL-2-307-ADC	Phase 1	70	Interventional
10	NCT04914117	Completed	No Results Available	Drug: RC118 for injection	Phase 1	7	Interventional
11	NCT05205850	Recruiting	No Results Available	Drug: RC118-ADC	Phase 1/2	135	Interventional
12	NCT05867563	Recruiting	No Results Available	Drug: TQB2103 for injection	Phase 1	71	Interventional
13	NCT05065710	Recruiting	No Results Available	Drug: ZL-1211	Phase 1/2	162	Interventional
14	NCT05837299	Recruiting	No Results Available	Drug: IMC008	Phase 1	18	Interventional
15	NCT03874897	Recruiting	No Results Available	Drug: CAR-CLDN18.2 T-Cells Drug: PD-1 Monoclonal Antibody Drug: Chemotherapy	Phase 1	123	Interventional
16	NCT05583201	Recruiting	No Results Available	Biological: KD-496	Early Phase 1	18	Interventional
17	NCT05472857	Recruiting	No Results Available	Biological: Claudin 18.2 CAR-T	Phase 1	30	Interventional
18	NCT05199519	Completed	No Results Available	Drug: IBI345	Phase 1	7	Interventional
19	NCT05393986	Recruiting	No Results Available	Drug: CT048 Autologous Injection (CT048)	Phase 1	63	Interventional
20	NCT05620732	Recruiting	No Results Available	Biological: Claudin 18.2 CAR-T cells	Not Applicable	20	Interventional
21	NCT05981235	Recruiting	No Results Available	Biological: AZD6422 CLDN18.2 CAR-T product	Phase 1	96	Interventional
22	NCT05952375	Recruiting	No Results Available	Drug: Chimeric antigen receptor T cell preparation targeting Claudin 18.2	Not Applicable	9	Interventional
23	NCT04581473	Recruiting	No Results Available	Drug: CT041 autologous CAR T-cell injection Drug: Paclitaxel or Irinotecan or Apatinib or Anti-PD-1 antibody	Phase 1/2	192	Interventional

(*Continued*)

https://doi.org/10.2147/JHC.S483861

Table 3 (Continued).

study	NCT Number	Status	Study Results	Interventions	Phases	Enrollment	Study Type
24	NCT04842812	Recruiting	No Results Available	Biological: TILs and CAR-TILs targeting HER2, Mesothelin, PSCA, MUC1, Lewis-Y, GPC3, AXL, EGFR, Claudin 18.2/6, ROR1, GD1, or B7-H3	Phase 1	40	Interventional
25	NCT05946226	Recruiting	No Results Available	Biological: IMC002 injection	Phase 1	18	Interventional
26	NCT04404595	Active, not recruiting	No Results Available	Biological: CT041	Phase 1/2	110	Interventional
27	NCT05539430	Recruiting	No Results Available	Biological: LB1908	Phase 1	56	Interventional
28	NCT05862324	Recruiting	No Results Available	Biological: TAC01-CLDN18.2	Phase 1/2	113	Interventional
29	NCT04400383	Active, not recruiting	No Results Available	Drug: AB011 Injection	Phase 1	62	Interventional
30	NCT04495296	Recruiting	No Results Available	Drug: TST001 Drug: Oxaliplatin Drug: Capecitabine Drug: Paclitaxel Drug: Gemcitabine Drug: Cisplatin Drug: Nivolumab	Phase 1/2	320	Interventional
31	NCT06027346	Recruiting	No Results Available	Biological: Bio-008	Phase 1	60	Interventional
32	NCT04671875	Recruiting	No Results Available	Drug: Recombinant Humanized Monoclonal Antibody MIL93	Phase 1	228	Interventional
33	NCT04396821	Recruiting	No Results Available	Drug: TST001 Drug: Nivolumab Injection [Opdivo] Drug: mFOLFOX6 Drug: Gemcitabine Drug: Albumin-Bound Paclitaxel	Phase 1/2	150	Interventional
34	NCT05639153	Recruiting	No Results Available	Drug: DR30303	Phase 1	94	Interventional
35	NCT05159440	Recruiting	No Results Available	Drug: TORL-2-307-MAB	Phase 1	70	Interventional
36	NCT05707676	Recruiting	No Results Available	Drug: LB4330	Phase 1	66	Interventional
37	NCT05857332	Recruiting	No Results Available	Drug: SG1906	Phase 1	60	Interventional
38	NCT06005493	Recruiting	No Results Available	Drug: AZD5863	Phase 1/2	200	Interventional
39	NCT05278832	Recruiting	No Results Available	Drug: QLS31905	Phase 1	104	Interventional
40	NCT04856150	Recruiting	No Results Available	Drug: Q-1802	Phase 1	66	Interventional
41	NCT05839106	Recruiting	No Results Available	Drug: PM1032 injection	Phase 1/2	200	Interventional
42	NCT05482893	Recruiting	No Results Available	Drug: PT886 Drug: Paclitaxel Drug: Gemcitabine Drug: Abraxane	Phase 1/2	72	Interventional
43	NCT05365581	Recruiting	No Results Available	Drug: ASP2138	Phase 1	240	Interventional
44	NCT05719558	Recruiting	No Results Available	Drug: ASP1002	Phase 1	210	Interventional

Conclusion

According to existing research, multiple claudin proteins are closely associated with hepatobiliary and pancreatic diseases. In liver diseases, the mechanism and impact of claudin-1 are more significant. Claudin-2, −6, −9, −10, and −17 may act as adverse factors in the progression of liver cancer. In contrast, claudin-3, −4, −5, −7, −11, and −14 may be favorable factors for the development and prognosis of liver cancer, and claudins expression is often used to distinguish cholangiocarcinoma from liver cancer. Among these, claudin-4[99,100] and claudin-7[100,133] may serve as valuable markers for distinguishing between HCC and CCA. Compared to hepatobiliary diseases, pancreatic tumors and claudin proteins have been studied extensively. Among these, claudin-1, −4, and −23 have tumor suppressor effects, whereas claudin-2, −3, −5, −7, and −12 may have adversely affects the prognosis of patients with pancreatic tumors. In addition, claudin-3,[163] claudin-4,[102] claudin-5,[134,165] claudin-7,[134] claudin-18.2[219] can be used to distinguish between different types of pancreatic cancer. Regarding claudins targeting drugs, targeting antibodies for claudin-1, claudin-3, and claudin-6 have been developed and entered into preclinical studies. In hepatobiliary and pancreatic diseases, it has been proposed that claudin-4[122] and claudin-7 can be used as new molecular targets for the treatment of pancreatic cancer.[136] At present, it is known that claudin-18.2 has a good effect in the targeted therapy of gastric cancer. The prospects of targeted therapy for claudin-18 in PC have also been reported; however, the expression and mechanism of action of claudin-18 in hepatobiliary diseases remain unclear. Therefore, strengthening the research on the mechanism of action of claudin-18 and hepatobiliary and pancreatic tumors will be helpful for providing new plans for targeted therapy and immunotherapy of hepatobiliary and pancreatic tumors and carrying out related clinical trials to improve the precision treatment of such diseases. These approaches have the potential to ultimately improve the prognosis of patients with hepatobiliary and pancreatic tumors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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