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Review Article

Claudin18.2-targeted cancer theranostics

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Abstract: Claudin 18.2 (CLDN18.2) is an emerging target for the treatment of CLDN18.2-expressing cancers such as gastric and pancreatic cancers. Cell and antibody therapies targeting CLDN18.2 are under intensive clinical trials. In this setting, how to efficiently and specifically detect CLDN18.2 expression before and after the therapies is a clinical challenge. In recent years, molecular imaging with radiolabeled antibodies or antibody fragments have shown promise in noninvasively annotating antigen expression across the body. In this *Perspective*, we will bring together the most recent progress on CLDN18.2-targeted imaging and therapy of solid tumors.

Keywords: CLDN18.2, antibody therapeutics, CAR-T, BiTE, immunoPET

Introduction

Gastrointestinal (GI) tumors represent the most common form of malignant neoplasm, with the majority of patients receiving a diagnosis in intermediate to late stages. Despite being the cornerstone of treatment for advanced GI tumors, traditional chemotherapy is subject to considerable limitations in terms of therapeutic outcomes. The advent of individualized and precise therapies has sparked a renewed interest in targeted therapy and immunotherapy, which have emerged as hotspots of comprehensive treatment for this malignancy, offering new avenues of hope for patients with advanced gastric cancer and other GI tumors. The tight junction protein claudin 18.2 (CLDN18.2) has demonstrated significant potential in the field of tumor-targeted therapy, with promising outcomes observed for solid tumors like pancreatic and gastric cancer [1]. The CLDN protein family is composed of no less than 27 transmembrane proteins, which are categorized into classical and non-classical types based on their sequence characteristics. CLDN18 belongs to the non-classical type. Following post-translational modifications, the expression of CLDN18 has two isoforms: CLDN18.1 and CLDN18.2 [2]. CLDN18.2 is exclusively expressed in the tight junctions of gastric mucosal cells, remaining inaccessible to intravenously administered antibodies [3]. With the malignant transformation of gastric mucosal cells, CLDN18.2 is exposed and becomes available by therapeutic antibodies.

CLDN18.2-targeted cancer therapeutics: all flowers bloom together

Presently, individualized immunotherapy forms the crux of targeted therapy for CLDN18.2-positive tumors. Various approaches such as monoclonal antibodies (mAb), chimeric antigen receptor T (CAR-T) cells, bispecific antibodies (BsAb), and antibody-drug conjugates (ADC) have been developed and shown promising results. As a result, numerous studies are now underway to assess the clinical efficacy of these therapies. Jia and colleagues investigated the immune microenvironmental profile of CLDN18.2-positive gastric cancer by multiplex immunohistochemistry, and the results suggested that positive CLDN18.2 expression is associated with poor prognosis and CLDN18.2-positive gastric cancer is unlikely to benefit from programmed cell death protein 1 (PD-1) and its ligand (PD-L1) inhibitors, while CLDN18.2-targeted CAR-T cell therapy may be a promising treatment strategy [4]. Indeed, the CAR-T technology is undergoing continuous refinement and development. Recently, Harris

and colleagues utilized the Receptor Targeting Chimeras (ReceptorTAC) technology to degrade the T cell antigen receptor and create CLDN18.2-specific CAR-T cells, which can prevent allogeneic T cell reactivity. This innovative approach presents a novel strategy for the generation of allogeneic T cells with encouraging clinical implications [5]. The interim findings from a phase I clinical trial (NCT03874897) conducted at the Peking University Cancer Hospital demonstrated encouraging results for patients with CLDN18.2-positive digestive cancers treated with CAR-T therapy targeting CLDN18.2. The overall efficacy rate was 48.6%, the disease control rate was 73.0%, and the 6-month efficacy rate was 44.8%. Notably, patients with gastric cancer exhibited a higher overall efficacy rate and disease control rate of 57.1% and 75.0%, respectively, and a 6-month overall survival rate of 81.2%, with an acceptable safety profile [6]. BsAb contain two specific antigen binding sites that redirect T cells to tumor target antigens, inducing T cell-mediated cell killing. Liang et al. developed and synthesized anti-CLDN18.2-CD28 BsAb. Both *in vivo* and *ex vivo* experiments demonstrated that treatment with anti-CLDN18.2-CD28 reduced tumor load and increased infiltration of T cells into the tumor, while also reducing immunosuppressive cells. Furthermore, the treatment did not exhibit any systemic adverse effects [7]. Belmontes et al. developed bispecific T cell engager (BiTE) molecules and showed that the quadruple combination of CLDN18.2 BiTE + anti-4-1BB + anti-PD-1 + anti-CTLA-4 exhibited enhanced antitumor efficacy [8]. BsAbs have promising results in inducing T cell-mediated cell killing by redirecting T cells towards tumor target antigens, but face several challenges. One challenge is the complex manufacturing process, requiring precise engineering to avoid issues such as stability, solubility, and aggregation. Another challenge is the potential for off-target effects and toxicity. Additionally, the production of BsAbs can be costly, limiting accessibility to patients. Overcoming these challenges requires ongoing research and development efforts to improve the efficacy and safety of BsAbs for cancer treatment [9].

Zolbetuximab (IMAB362) is a chimeric mAb and mediates specific killing of CLDN18.2-positive cells through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity [10]. Following initial studies reporting the manageable safety profiles and anti-tumor activity of zolbetuximab in patients with gastric or gastro-oesophageal junction patients [11, 12], a randomized phase II study reported that the addition of zolbetuximab to the first-line EOX (epirubicin + oxaliplatin + capecitabine) significantly improved the progression-free survival (PFS) and overall survival (OS) than that obtained in the EOX treatment group [13]. The novel treatment option also improved the quality of life of the included patients [14]. Ongoing phase III studies are investigating the therapeutic efficacy of zolbetuximab 600-800 mg/m^2 in patients with moderate-to-strong CLDN18.2 expression (>70% of tumor cells). CLDN18.2 is among the most promising targets that can be leveraged to improve the theranostic landscape of gastric cancers. As far as we know, immunohistochemistry (IHC) staining with CLAUDETECT™ 18.2 is the only available option to determine CLDN18.2 expression. However, IHC is limited to examine the surgically resected or the biopsied tissue, failing to provide the heterogenous expression of CLDN18.2 across the whole tumor tissue or in the metastases. Novel techniques that can determine the expression level of CLDN18.2 and further diagnose CLDN18.2-expressiong tumors are needed.

Immuno-positron emission tomography (immunoPET) imaging of CLDN18.2

ImmunoPET is a rapidly expanding direction in the field of molecular imaging [15]. ImmunoPET has a well-recognized role in guiding the early development of antibody therapeutics and is increasingly used in clinical practice to select patients for molecularly targeted therapies and immunotherapies. It can also help assess the therapeutic responses after administration of the antibody therapeutics. By labeling mAbs with radiometals (e.g., ^{64}Cu or ^{89}Zr) [16-20], we have developed several novel immunoPET probes and characterized the diagnostic efficacies in preclinical settings. Admittedly, the clinical translational way of these probes is arduous and long. Hurdles impeding the clinical translation include high expenditure in producing humanized mAbs, scarcity of long-lived radiometals or radiohalogens, multiple cycles of imaging, and the resultant high radiation exposure. To alleviate these concerns and facilitate same-day imaging, antibody derivatives

and protein scaffold mimicking antibodies have been leveraged to develop next-generation molecular imaging probes [15, 21]. Nanobodies are naturally occurring antigen recognition domains found in alpacas, llamas, and camels [22]. They are 12-15 kDa in size, highly stable in various conditions, display strong binding affinities, and can be expressed in bacterial, yeast, and mammalian expression systems with high yields. Nanobodies are the most promising candidates to substitute their full-size counterparts for diagnostic applications [23]. Nanobody-derived immunoPET probes targeting human epidermal growth factor receptor 2 and programmed death ligand-1 have been successfully translated to the bedside [24-26].

The CLDN18.2 protein plays a significant role in tumor cell proliferation, differentiation, and migration. Its distinct expression pattern has made it a unique molecular target for immunoPET imaging. There are several immunoPET probes currently under investigation in preclinical models for targeting CLDN18.2. Wei et al. developed a series of nanobody-derived tracers ([^{68}Ga]Ga-NOTA-hu19V3, [^{64}Cu]Cu-NOTA-hu19V3, and [^{18}F]F-hu19V3) and evaluated the diagnostic value of the tracers in several preclinical models [27]. While [^{68}Ga]Ga-NOTA-hu19V3 showed high kidney accumulation, [^{64}Cu]Cu-NOTA-hu19V3 and [^{18}F]F-hu19V3 had relatively lower kidney accumulation, indicating the complementary roles of the tracers in annotating CLDN18.2. Zhao et al. developed a molecular imaging approach based on CLDN18.2 for precise tumor detection and surgical guidance. The team prepared a monoclonal antibody 5C9 targeting CLDN18.2 and constructed the ^{124}I-C59 probe for imaging and a near-infrared fluorescence-II probe (FD1080-5C9) for guiding surgical removal of lesions. These probes demonstrated high specificity and accuracy, highlighting their potential as effective clinical tools for cancer diagnosis and treatment [28]. Zhong et al. developed the variable region of the heavy chain of the heavy chain-only antibodies (VHHs), named hu7v3, targeting CLDN18.2 as a vector for diagnostic and therapeutic applications. The humanized hu7v3-Fc, which was fused with human IgG1 Fc, was labeled with ^{89}Zr, and ^{89}Zr-hu7v3-Fc exhibited higher tumor uptake and better tumor penetration compared to the ^{89}Zr-labeled mAb probe ^{89}Zr-Zolbetuximab [29]. Hu et al. developed three ^{89}Zr-labeled anti-CLDN18.2 antibody probes for non-invasive dynamic visualization of CLDN18.2 expression on the surface of gastric cancer cells. These probes include ^{89}Zr-VHH, ^{89}Zr-VHH-ABD (serum albumin-binding), and ^{89}Zr-VHH-Fc [30]. The development of antibodies and their derivatives has significantly enhanced the precision of CLDN18.2 diagnostics, thus propelling the field forward. Availability of antibody forms suitable for various radionuclides also aids in expanding the clinical use of immunoPET. The advent of immunoPET has ushered in a new era of patient care for those with tumors.

Since the expression of CLDN18.2 protein is highly conserved, an ideal CLDN18.2-targeted molecular imaging approach may identify CLDN18.2 expression across a variety of species including mouse, rat, rabbit, dog, monkey, and human [3, 31]. Gastric and gastroesophageal junction adenocarcinomas are on the top list for CLDN18-targeted theranostics. However, accumulating evidence indicates that several other types of cancers may also express CLDN18.2. Previous studies reported CLDN18 expression in 60-90% of pancreatic ductal adenocarcinoma (PDAC). A more recent study reported that over 50% of primary and metastatic PDACs highly express CLDN18.2 [32], adding to the validity of the previous evidence. Given that CLDN18.2 expression persists during tumor metastasis, therapeutic strategies aimed at targeting CLDN18.2 could offer a viable treatment approach for a significant population of pancreatic cancer patients. Zhang et al. conducted a study to examine the expression and clinical significance of CLDN18.2 in PDAC using immunohistochemistry. The findings revealed that 56.52% of PDAC patients demonstrated CLDN18.2 positivity, which correlated with certain clinicopathological characteristics such as sex, smoking, and pathological differentiation. Moreover, CLDN18.2 positivity was associated with improved survival but not PFS. Therefore, the study suggests that CLDN18.2 could potentially serve as a therapeutic target for PDAC and provides compelling pathological evidence for CLDN18.2-targeted therapy in PDAC patients [33]. The findings of Pellino and colleagues revealed that CLDN18.2 expression was correlated with younger age (below 70 years), advanced tumor stage, and reduced occurrence of peritoneal and liver

metastases [34]. Aberrantly activation or expression of Claudin18.2 was also found in non-small-cell lung cancer and colitis-associated colorectal adenocarcinomas [35, 36]. These results indicate that CLDN18.2-targeted diagnostic or therapeutic agents would be in principle eligible for a considerable number of tumors [1].

Perspectives of CLDN18.2-targeted theranostics

There are several practical factors limiting the development and characterization of CLDN18.2-targeted theranostic agents. First of all, cancer cell lines naturally and stably expressing CLDN18.2 are lacking. Most of the gastric cancer cell lines express CLDN18.2 at low levels. Therefore, cancer cell lines transfected with CLDN18.2 or patient-derived xenograft models were used in most of the previous studies. Since the natural expression of CLDN18.2 in gastric mucosal cells, CLDN18.2-targeted tracers may have diagnostic value in patients with total or subtotal gastrectomy to detect local and/or distant metastases. In patients with partial gastrectomy or endoscopic submucosal dissection, CLDN18.2 expression in gastric mucosal cells may act as antigen sink and further migrate the tracers from binding to the mestasatic lesions. Lastly, nanobody-derived radiopharmaceuticals are rapidly cleared from kidneys to the bladder. Although the rapid renal clearance results in high tumor-to-background ratio, it will compromise the diagnostic value for tumor lesions located near kidneys and cause undesirable nephrotoxicity when a therapeutic dose is given [37]. To develop next-generation theranostic platforms, strategies that can improve the pharmacokinetics of radiopharmaceuticals need to be adapted [38-40].

Diffuse gastric cancer is known to be highly aggressive, with high rates of recurrence and metastasis, and a poor prognosis. Targeting CLDN18.2 presents a promising therapeutic approach [41]. Development and clinical translation of CLDN18.2-targeted theranostric agents may help improve the management of CLDN18.2-expressing cancers such as gastric and pancreatic cancers. The potential for targeted CLDN18.2 treatment is promising, however, there remains a vast landscape of exploration before reaching the pinnacle of precision treatment.

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Disclosure of conflict of interest

None.

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