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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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MINIREVIEWS

Latest therapeutic target for gastric cancer: Anthrax toxin receptor 1

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Abstract

Anthrax toxin receptor 1 (ANTXR1), also known as tumor endothelial marker 8, is a highly conserved cell surface protein overexpressed in tumor-infiltrating vessels. It was first found in vascular endothelial cells of human colorectal cancer. Although our understanding of its physiological function is limited, it has been found that ANTXR1 binds collagen and promotes migration of endothelial cells *in vitro*. ANTXR1 is upregulated in vessels of different tumor types in mice and humans, and is also expressed by tumor cells themselves in some tumors, such as gastric, lung, intestinal and breast cancer. Developmental angiogenesis and wound healing were not disturbed in ANTXR1 knockout mice, but compared with wild-type mice, growth of melanoma was impaired after ANTXR1 knockout, indicating that host-derived ANTXR1 can promote tumor growth on the basis of immune activity. Previous studies have shown that ANTXR1 vaccines or sublethal doses of anthrax toxin can inhibit angiogenesis, slow tumor growth and prolong survival. These studies suggest that ANTXR1 is necessary for tumor rather than physiological angiogenesis. It has been found that ANTXR1 plays an important role in tumor angiogenesisas well as in the growth and metastasis of many kinds of tumors. This article reviews the physiological function of ANTXR1 and its role in different kinds of cancer.

Key Words: Gastric cancer; Therapeutic target; Biomarker; Anthrax toxin receptor 1; Tumor endothelial marker 8; Immunotherapy

Core Tip: Anthrax toxin receptor 1, also known as tumor endothelial marker 8, is a highly conserved cell surface protein overexpressed in tumor infiltrating vessels.

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INTRODUCTION

Malignant tumors are still a major threat to human health, because most patients are diagnosed at the late stage and have lost the opportunity for radical surgery. For advanced cancers, the traditional methods of radiotherapy and chemotherapy cannot effectively prolong survival time and improve quality of life. However, with the development of precision therapy, immunotherapy and targeted therapy have become prominent. Immunotherapy was initially suitable for malignant tumors with high levels of somatic mutations, such as melanoma[1], Hodgkin's lymphoma[2] and non-small cell lung cancer[3]. It has subsequently been proved that it has a good curative effect in gastric, colorectal and other common cancers[4]. As a result, more potential biomarkers and therapeutic targets have been found, and the treatment of malignant tumors has entered a new era. Previous studies have found that anthrax toxin receptor 1 (ANTXR1) plays an important role in the occurrence and development of malignant tumors and can be used as a new prognostic biomarker and potential therapeutic target for gastric cancer (GC)[5].

BIOLOGICAL FUNCTION OF ANTXR1

ANTXR1 was discovered nearly 20 years ago, although few studies have investigated its physiological function beyond its role as a receptor for anthrax toxin[6]. In the past few years, insights into its endogenous role have come from a rare disease: Growth retardation, alopecia, false missing teeth and optic nerve atrophy syndrome caused by ANTXR1 functional deletion mutations. Symptoms show that ANTXR1 mainly regulates extracellular matrix homeostasis[7], angiogenesis[8], cell migration and skin elasticity. Some studies have found that ANTXR1 is the target of Runx2, regulating the proliferation and apoptosis of chondrocytes[9]. However, the most important biological function is to regulate extracellular matrix homeostasis, angiogenesis and cell migration, which may be closely related to tumor occurrence and development of metastasis[10] (Table 1).

ANTXR1 REGULATES TUMOR GROWTH AND METASTASIS

Early studies[11] have found that high expression of ANTXR1 can be detected in paracancerous tissues of a variety of malignant tumors, suggesting that ANTXR1 is involved in regulating tumor growth and metastasis. Evans *et al*[12] in 2018 found that Seneca Valley virus (SVV) uses ANTXR1 to enter cells, which is the same as the surface receptors pirated by anthrax toxins from bacteria. This observation is particularly important because SVV is a known oncolytic virus that selectively infects and kills tumor cells, especially those of neuroendocrine origin. This suggests that ANTXR1 is a collagen receptor related to tumor growth. In the same year, Zhang *et al*[13] found that urokinase plasminogen activator (uPA) is the interaction partner of ANTXR1. Binding of uPA stimulates the phosphorylation of ANTXR1 and augments phosphorylation of epidermal growth factor receptor (EGFR) and extracellular signal-regulated kinase (ERK) 1/2. Finally, ANTXR1-Fc, a recombinant fusion protein comprising the extracellular domain of human ANTXR1 linked to the Fc portion of human IgG1, inhibited interaction between uPA and ANTXR1, uPA-induced migration of HepG2 cells *in vitro*, and growth and metastasis of human MCF-7 xenografts *in vivo*. uPA, ANTXR1 and EGFR overexpression and ERK1/2 phosphorylation were colocated on frozen cancer tissue sections. This experiment confirmed once again that ANTXR1 may play a significant role in the regulation of tumor growth and metastasis (Table 1).

Table 1 Biological function of anthrax toxin receptor 1

Biological function of ANTXR1	Summary of findings	Ref.
Non-tumor related biological function	Regulates extracellular matrix homeostasis	Sergeeva *et al*[6] and Hu *et al*[7]
	Regulates angiogenesis	Sergeeva *et al*[6] and Besschetnova *et al*[8]
	Regulates cell migration, and skin elasticity.	Sergeeva *et al*[6]
	Regulates the proliferation and apoptosis of chondrocytes	Jiang *et al*[9]
Tumor related biological function	Regulates tumor growth and Metastasis	Høye *et al*[10] and Evans *et al*[12]
	Overexpress in gastric adenocarcinoma	Sotoudeh *et al*[11]
	Active the PI3K/AKT/mTOR signaling pathway	Cai *et al*[19]
	Mediates uPA-stimulated EGFR phosphorylation	Zhang *et al*[13]
	Promotes tumor angiogenesis	Nanda *et al*[16] and Chaudhary *et al*[17]

uPA: Urokinase plasminogen activator.

TUMOR PATHOLOGICAL ANGIOGENESIS INDUCED BY ANTXR1

Solid tumors have a hidden ability to nourish their swelling and growth by stimulating neovascularization or angiogenesis of blood vessels adjacent to nonmalignant tissues. After tumor vascularization, tumor blood vessels provide vital oxygen and nutrients for tumor cells to maintain their sustainable growth, and provide an important escape pathway for tumor metastasis. Because of its key role in promoting tumor growth and metastasis, the treatment of tumor blood vessels has become the main target of anticancer therapy[14]. Vascular endothelial growth factor (VEGF) and its receptor VEGFR2 are the most advanced targets for antiangiogenesis therapy. However, the drugs targeting ANTXR1 an block the formation of pathological as well as normal physiological blood vessels. ANTXR1 is a highly conserved cell surface protein that is overexpressed in tumor-infiltrating vessels and in many tumor-associated endothelial cells[15,16]. It was found that developmental angiogenesis and wound healing were not disturbed in ANTXR1 knockout mice, but compared with wild-type mice, the growth of melanoma in mice was impaired after ANTXR1 knockout, indicating that host-derived ANTXR1 can promote tumor growth on the basis of immune activity[17]. Previous studies have shown that ANTXR1 vaccines or sublethal doses of anthrax toxin can inhibit angiogenesis, slow tumor growth and prolong survival. These studies suggest that ANTXR1 is necessary for tumor rather than physiological angiogenesis. ANTXR-1 can selectively inhibit tumor-induced pathological angiogenesis, showing a wide range of antitumor activities, and can enhance the activity of anticancer drugs without increasing toxicity (Table 1).

ROLE OF ANTXR1 IN DIFFERENT KINDS OF CANCER

GC

Although the prospect of immunotherapy for gastric adenocarcinoma is promising, the choice of effective antigen targets is limited. In 2019, Sotoudeh *et al*[11] found that ANTXR1 was a potential target, which was expressed in both malignant tumor cells and tumor endothelial cells. Immunohistochemistry was used to detect the percentage of ANTXR1-positive cells in tumor cells and endothelial cells of primary, nontumor and metastatic lesions of gastric adenocarcinoma. The relationship between expression of ANTXR1 and Lauren histological classification of primary tumor, neoadjuvant chemotherapy, radiotherapy history and overall survival of patients was also evaluated. Above-median expression of ANTXR1 in tumor cells was associated with significantly lower overall patient survival. The results show that ANTXR1 is an important target for preclinical and clinical evaluation of immunotherapy for gastric adenocarcinoma. In the same year, Sotoudeh *et al*[18] found that ANTXR1 was a possible target for CAR-T cells in the treatment of gastric adenocarcinoma. In 2020, Cai *et al*[19] conducted a study to explore the role of ANTXR1 in GC. They found that expression of ANTXR1 was significantly upregulated in GC, and its overexpression was related to poor prognosis of patients with GC. High protein expression level of

ANTXR1 was positively correlated with many clinicopathological parameters of GC patients. The results showed that ANTXR1 induced GC cell proliferation, cell cycle progression, invasion and migration, and induced inhibition of apoptosis. Mechanistic studies have shown that ANTXR1 promotes GC by activating the PI3K/AKT/mTOR signaling pathway. ANTXR1 plays an important role in the occurrence and development of GC and can be used as a new prognostic biomarker and potential therapeutic target for GC (Table 2).

Colorectal cancer

In 2009, Fernando *et al*[20] established a mouse model of rectal cancer to study the role of ANTXR1 in rectal cancer. It has been confirmed that tumor endothelial cells express ANTXR1 fusion protein located in tumor blood vessels, and have decreased vascular density, accompanied by local thrombosis. This suggests that ANTXR1 can affect tumor development by affecting the blood vessels of colorectal cancer[21] (Table 2).

Lung cancer

In 2018, Gong *et al*[22] explored the effects of ANTXR1 on the proliferation, apoptosis, migration and invasion of XWLC-05 Lung cancer cells. The expression of ANTXR1 in human lung cancer and paracancerous tissues was detected by quantitative reverse transcriptase polymerase chain reaction and western blotting. The interference vector encoding RNA (shRNA) against ANTXR1 was designed and transfected into XWLC-05 lung cancer cells. Expression of ANTXR1 in lung cancer tissues was significantly higher than that in paracancerous tissues. After silencing ANTXR1 by shRNA interference, the cell proliferation was inhibited and the apoptosis rate increased. The cell cycle was blocked in G1 phase, and the migration and invasion ability of cancer cells decreased. Silencing ANTXR1 can inhibit the proliferation of XWLC-05 lung cancer cells, promote apoptosis, block the cell cycle in G1 phase, and reduce cell migration and invasion. Therefore, ANTXR1 may become a potential target for the treatment of lung cancer. Current domestic clinical studies have explored the expression of ANTXR1 in patients with lung cancer and its relationship with clinicopathology and prognosis[23]. Through analysis of the clinical characteristics of 407 patients with lung cancer, it has been found that ANTXR1 has a good diagnostic effect and is expected to become a good index for early clinical diagnosis and prognosis of lung cancer (Table 2).

Breast cancer

As early as 2007, Felicetti *et al*[24] suggested that expression of ANTXR1 may be more like an adjuvant than an immune target. However, the opposite view was put forward by Gutwein *et al*[25] in 2011. They showed that expression of ANTXR1 in tumor tissues was higher than that in noncancerous breast tissues. ANTXR1 was highly expressed in the stroma of adjacent triple-negative breast cancer cells, and there was a focal immunoreactive area in the tumor. ANTXR1 was not expressed in normal lymphoid tissue, but expressed in the site of lymph node metastasis. This suggests that ANTXR1 may be a new diagnostic marker and biological target for triple-negative breast cancer. In the same year, Opoku-Darko *et al*[26] confirmed this view through a mouse breast cancer model. In 2018, Byrd *et al*[27] developed an ANTXR1-specific CAR-T cell immunotherapy strategy for triple-negative breast cancer. CAR-T cells secrete immunostimulatory cytokines after ANTXR1-specific recognition, killing tumor endothelial cells and ANTXR1-positive, triple-negative breast cancer cells. It is worth noting that ANTXR1-CAR-T cells target breast cancer stem cells. Adoptive metastatic ANTXR1-CAR-T cells block tumor neovascularization by killing ANTXR1 triple-negative breast cancer cells and tumor endothelial cells, thus inducing xenograft regression. This method provides preclinical evidence for ANTXR1 as an immunotherapy target for triple-negative breast cancer (Table 2).

ANTXR1 PROVIDES A NEW METHOD OF DRUG DELIVERY

Szot *et al*[28] in 2018 found that nonmalignant stromal cells can promote tumor growth, accounting for 90% of the mass of solid tumors, but they can also be used to improve cancer treatment. This study identified the monomethyl auristatin E (MMAE)-linked antibody–drug conjugate (ADC) of ANTXR1. Anti-ANTXR1 ADC stimulates strong anticancer activity through an unexpected killing mechanism (DAaRTS; drug activation and matrix release), that is, the tumor microenvironment locates the active drug at the tumor site. After ADC prodrugs are removed from circulation, tumor-

Table 2 Role of anthrax toxin receptor 1 in different kinds of cancer

Different kinds of cancer	Summary of findings	Ref.
Gastric cancer	Overexpress in gastric adenocarcinoma	Sotoudeh *et al*[11]
	Active the PI3K/AKT/mTOR signaling pathway	Cai *et al*[19]
	It is the potent antigenic targets for CAR T cell therapy	Sotoudeh *et al*[18]
Colorectal cancer	Influence tumor development by disrupting tumor vasculature.	Fernando *et al*[20]
	It possible use as biomarkers for screening, diagnosis, and therapy	Pietrzyk *et al*[21]
Lung cancer	It regulates the proliferation, apoptosis, migration and invasion of lung cancer cells.	Gong *et al*[22]
	It is an excellent indicator for early clinical diagnosis and prognosis of lung cancer.	Sun *et al*[23]
Breast cancer	It enhances tumor immunity in conjunction with immunization against differentiation ag.	Felicetti *et al*[24]
	It expression in triple-negative breast cancer.	Gutwein *et al*[25]
	It enhances tumor growth and metastasis in breast cancer cells.	Opoku-Darko *et al*[26]
	ANTXR1-Specific CAR T cells as a targeted therapy for breast cancer.	Byrd *et al*[27]

associated stromal cells release active MMAE-free drugs, killing nearby proliferating tumor cells in a nontargeted way. In preclinical studies, ADC therapy is well tolerated, which can induce regression and often eradication of many types of solid tumors, prevent metastatic growth and prolong overall survival. McCann *et al*[29] also verified this claim. By using ANTXR1-positive tumor matrix for targeted drug activation, these studies revealed a potential drug delivery pathway that can enhance the treatment of many types of cancer.

CONCLUSION

The arrival of targeted immunotherapy has resulted in treatment of malignant tumors entering a new era. The discovery of multiple therapeutic targets brings multiple treatments. Keynote059, Keynote061, Keynote 062, attraction02 and other studies have repeatedly verified the effectiveness of programmed death (PD)-1 therapy. In addition indoleamine 2, 3-dioxygenase, T cell immunoglobulin-and mucin-domain-containing molecule-3 and lymphocyte-activation gene 3 have been found as functional biomarkers similar to PD-1, and their expression was related to the overall survival. ANTXR1 is one of the best potential therapeutic targets, which not only plays an important role in gastric, lung, bowel and breast cancer, but also brings new methods of drug delivery. However, our understanding of ANTXR1 is still in its infancy, and more research is needed to explore its role. Challenges should be resolved, such as: Whether ANTXR1-CAR-T cells can be used in more cancers; whether inhibition of ANTXR1 can inhibit tumor pathological angiogenesis, and whether there is a deeper relationship between ANTXR1 and VEGF and HER2; and whether there is a deeper relationship between ANTXR1 and PD-1. How to bring research to the clinic and achieve survival benefit for patients are the real value and ultimate goals of research.

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