Ming *et al. J Cancer Metastasis Treat* 2023;9:33
DOI: 10.20517/2394-4722.2023.23

Journal of Cancer Metastasis and Treatment

Review

Open Access

The role of adiponectin in gastric cancer

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How to cite this article: Ming C, Orita H, Shangcheng Y, Yuan Q, Fedor CN, Yongyou W, Fukunaga T. The role of adiponectin in gastric cancer. *J Cancer Metastasis Treat* 2023;9:33. https://dx.doi.org/10.20517/2394-4722.2023.23

Received: 16 Mar 2023 **First Decision:** 4 Jul 2023 **Revised:** 26 Jul 2023 **Accepted:** 24 Aug 2023 **Published:** 8 Sep 2023

Academic Editor: Gary Li **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Adiponectin, an adipokine synthesized by adipose tissue, has garnered significant attention in biomedical investigations. Research on its implications suggests that reduced adiponectin levels in the bloodstream might serve as a potential predisposing factor for several types of cancers, including gastric cancer. Although many studies on adiponectin levels in gastric cancer patients have been reported, its predictive role as a biomarker remains controversial. Moreover, the significance of adiponectin receptor expression as a prognostic factor in gastric cancer tissues varies across different research studies, and the precise mechanism by which adiponectin influences the initiation and advancement of gastric cancer remains to be fully elucidated. Furthermore, the anti-inflammatory and postoperative anti-infective effects of adiponectin are worth further investigation. Based on existing studies, it is commonly suggested that in the presence of low adiponectin levels, the stomach might be vulnerable to stimulation or damage from certain carcinogens, promoting gastric cancer development and progression. Considering its complex systemic effects and high serum concentration, adiponectin might serve as a homeostasis regulator and not necessarily as an anti-cancer factor. In this review, we explore the current research available on adiponectin in relation to gastric cancer and discuss its role and corresponding receptors involved in gastric cancer.

Keywords: Adiponectin, adiponectin receptor, gastric cancer

INTRODUCTION

Gastric cancer (GC) stands as the fourth most prevalent malignancy in the human population, holding the distressing position of being the second highest contributor to global cancer-related mortality. Since the 1940s, the incidence of GC has increased worldwide and remains a significant health challenge[1]. Especially in East Asians, GC is commonly diagnosed, imposing an increasing disease burden. Although enormous efforts have been made to combat GC, there is still a long way to go before reducing the disease burden of GC. Currently, obesity has been found to be a risk factor for certain cancers, particularly endometrial, breast, esophageal, prostate, kidney, colorectal and gastric cancers[2]. Obesity leads to major changes in multiple hormones, adipokines, growth factors, glucose and lipid metabolism, inflammatory processes, and signaling pathways. From a biological perspective, the hormonal environment is altered in obese individuals, affecting insulin-like growth factor (IGF), resistin, endolipin, leptin, and adiponectin. Epidemiological studies have indicated that obese individuals tend to exhibit lower serum adiponectin levels in comparison to those with a normal body weight. There exists a negative correlation between adiponectin levels with body mass index (BMI) and increase following weight loss, suggesting the existence of certain feedback mechanisms[3]. Therefore, there may be correlations between obesity, adiponectin, and gastric cancer[4].

Two primary types of adipose tissue are present in the human body: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT primarily functions to store energy, and it is also an endocrine organ secreting more than 50 different adipokines including adiponectin, which are collectively known as adipokines[5]. Adiponectin possesses anti-diabetic, anti-atherosclerotic, and anti-inflammatory effects, as indicated by numerous reports, showing that it may play a key role in Metabolic Syndrome (MetS). Additionally, low serum levels of adiponectin are significantly associated with increased risk of various malignancies, such as colorectal cancer[6]. Adiponectin has been found to function as a potential anti-cancer factor for breast, endometrial, prostate, and other various cancers, both *in vivo* and *in vitro*[7-10]. These results suggested a noteworthy correlation between adiponectin and cancer. Here, we reviewed the role of adiponectin and its associated receptors in the development and progression of gastric cancer.

A BRIEF INTRODUCTION OF ADIPONECTIN AND ADIPONECTIN RECEPTORS

Adiponectin is a hormone derived from adipose tissue, expressed in differentiated adipocytes, and secreted into peripheral blood[11]. Identified as Acrp30, adipoQ, APM-1, and GBP28 by four research groups independently in the mid-1990s, adiponectin is an adipocyte complement-related 30 kDa protein encoded by a gene on chromosome 3. Full-length human adiponectin consists of 244 amino residues, with a collagen domain at the N-terminus and a globular domain at the C-terminus that has substantial homology with subunits of complement factor C1q[12-14]. *In vivo*, adiponectin acts through both endocrine and paracrine pathways[15]. Serum adiponectin concentrations are not influenced by circadian rhythm or feeding. However, there are significant gender differences, with females having significantly higher concentrations than males, suggesting that sex hormones can regulate adiponectin secretion[16]. Circulating levels of adiponectin are mainly associated with body weight and visceral fat accumulation. In normal individuals, circulating concentrations of adiponectin range from 3 to 30 ng/mL, while its expression is downregulated in obese individuals[17,18].

Adiponectin functions through binding to adiponectin receptors, of which three types have been identified: Adiponectin receptor 1 (AdipoR1), Adiponectin receptor 2 (AdipoR2) and T-cadherin, among which AdipoR1 and AdipoR2 serve as the principal receptors for adiponectin[19]. Yamauchi *et al.* first successfully cloned the human and mouse adiponectin receptors in 2003 and found that AdipoR1 and AdipoR2 share a strong structural resemblance, characterized by seven transmembrane structural domains[20]. AdipoR1 and

AdipoR2 activate downstream signaling molecules without G protein coupling, showing little structural or functional similarities with G protein-coupled receptors[21-23]. Adiponectin receptors are situated on the cell surface and are distributed in many tissues; AdipoR1 is primarily found in skeletal muscle cells, displaying a heightened affinity for the spherical domain of adiponectin but possessing a lower affinity for the full-length form, while AdipoR2 is mainly expressed in hepatocytes with moderate affinity for both spherical domain and full-length adiponectin. T-cadherin, discovered by Hug *et al.*, serves as a receptor for adiponectin capable of binding to hexamers and adiponectin with high molecular weigh[24]. However, it lacks intracellular domains and thus is not able to transduce downstream signals.

ADIPONECTIN AND SIGNAL PATHWAYS *IN VITRO*

Adiponectin has been reported to circulate in the blood in the form of high, medium, and low molecular weight isoforms and bind to corresponding receptors to activate a variety of intracellular signaling pathways, including the adenosine monophosphate (AMP)-activated protein kinase (AMPK), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), mammalian target of rapamycin (mTOR), c-Jun N-terminal kinase (JNK)/signal transducer and activator of transcription 3 (STAT3), and Wnt/β-catenin[25-27]. The first protein found to interact directly with adiponectin receptors was the adaptor protein containing domains such as pleckstrin homology, phosphotyrosine binding, and leucine zipper (APPL1). APPL1 plays critical roles in metabolism, anti-inflammation, and cytoprotection, while it also mediates other signaling pathways through direct interaction with membrane receptors and signaling proteins, affecting cell viability, proliferation, apoptosis, and chromosome remodeling[28]. Adiponectin has also been reported to activate AMPK, p38 mitogen-activated protein kinase (MAPK), peroxisome proliferator-activated receptor-α (PPAR-α), and Ras-related proteins by binding to APPL1, thereby enhancing glucose uptake, inducing fatty acid oxidation, inhibiting hepatic glycogen synthesis, increasing AMP/ ATP ratio, reducing triacylglycerol levels, and improving insulin sensitivity. Furthermore, activation of AMPK is mainly mediated by adiponectin receptor 1 (AdipoR1), whereas activation of PPAR-α promotes adiponectin binding to adiponectin receptor 2 (AdipoR2)[23].

When binding to its receptor, adiponectin induces the recruitment of the adaptor protein APPL1, thereby activating downstream signaling pathways that control cell viability, cell growth, and apoptosis, including AMPK, mTOR, PI3K/Akt, PPAR-α, and nuclear factor (NF)-kB, thus exerting its anti-cancer effects. Among them, activation of AMPK is considered to play a central role in it[29]. Although many studies on the signaling pathways of adiponectin in cancers have been reported, and the role of adiponectin in cancer cells is illustrated in Figure 1, its mechanism in gastric cancer cells is still unknown, leading to a need for further research.

FUNCTION OF ADIPONECTIN

Adiponectin in non-cancers

Currently, there are reports indicating that adiponectin is involved in the regulation of glucose and lipid metabolism and could also act as an insulin sensitizer[30]. In fact, it is now clear that the role of adiponectin in insulin resistance that occurs in obesity has become important. Reduced adiponectin expression in mRNA and serum levels has been related to insulin resistance and the heightened likelihood of diabetes onset in obese individuals and in Acrp30-knockout mice[31].

Regarding its role in the regulation of inflammation, adiponectin mainly acts as an anti-inflammatory factor in the immune system, although its ability to promote inflammatory actions has also been demonstrated[32-34]. As a member of the C1q tumor necrosis factor (TNF)-related protein superfamily, adiponectin promotes lipid opsonization through selective binding to phosphatidylserine, ceramide-1-

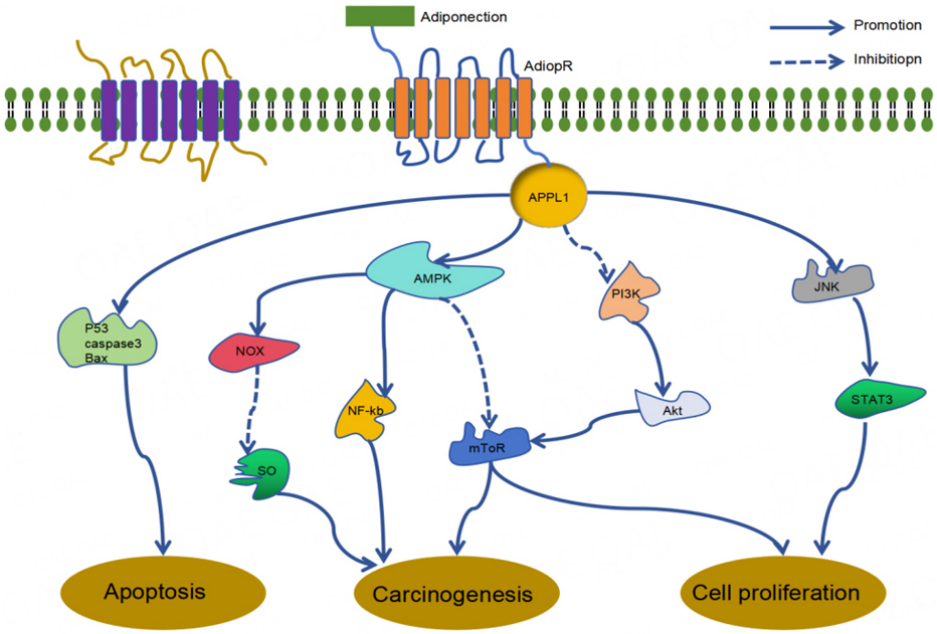

Figure 1. Intracellular signaling pathways of adiponectin within cancer cells. created by authors.

phosphate, glycosyl ceramide, and sulfatide via the C1q domain on liposomes, low-density lipoproteins (LDL), cell membranes, and serum[35]. In addition, adiponectin can inhibit TNF-α secretion in lipopolysaccharide (LPS)-stimulated human macrophages[36]. Adiponectin stimulates interleukin (IL)-10 secretion, which increases matrix metalloproteinase-1 inhibitor production in human macrophages, thereby alleviating tissue destruction[37]. Liu *et al.* found that adiponectin can reduce hepatocyte apoptosis to attenuate liver injury by activating the AMPK and mTOR pathway in septic rats, suggesting its important role in sepsis[38]. Adiponectin has anti-inflammatory activity both *in vivo* and *in vitro*; it neutralizes LPS activity and stimulates various anti-inflammatory factors, impairing the viability of macrophages to inhibit inflammatory cytokine production, thus playing a pivotal role in bolstering the immune defense.

Furthermore, in the process of thrombosis, adiponectin has been reported to act as an endogenous anti-thrombogenic factor, exerting anti-thrombotic and anti-platelet aggregation functions[39]. Adiponectin promotes AMPK phosphorylation of endothelial nitric oxide (NO) synthase in endothelial cells to produce NO, and promotes the proliferation of endothelial progenitor cells to repair vascular endothelium[40]. Moreover, adiponectin can decrease LDL-induced reactive oxygen species (ROS) production, and thus reduce vascular endothelium damage[41].

Adiponectin in cancers

Currently, the connection between low serum adiponectin levels and the development of several kinds of cancers has been found. In MC38 mouse colon cancer cells treated by IL-6, the anti-proliferative capability of adiponectin was observed, as it downregulated STAT3 phosphorylation/activation[42]. Nigro *et al.* found that adiponectin prompted the accumulation of ROS, resulting in increased colon cancer cell death[43]. In breast cancer, decreased adiponectin levels have been reported to increase IGF1 levels and its activity, which is known as a risk factor for breast cancer[44]. Furthermore, it has been suggested that adiponectin might have an independent effect on endometrial carcinogenesis by affecting estrogen and insulin resistance[45]. Adiponectin levels have also been associated with staging and pathological type for some tumors[46,47]. In addition, adiponectin has been used for differentiation between diseases such as pancreatic cancer and

chronic pancreatitis with elevated tumor markers[48].

However, despite observing a negative correlation found between circulating adiponectin levels and carcinogenesis and malignant degree, some studies have seen the opposite results[49,50]. For example, Arano *et al.* found a higher risk of liver cancer development in patients with chronic hepatitis C (CHC) who exhibited elevated serum adiponectin levels[49].

THE FUNCTION OF ADIPONECTIN IN GASTRIC CANCER

Adiponectin in the growth and proliferation of gastric cancer cells

Currently, research evidence demonstrates that adiponectin has the capacity to negatively regulate the growth and proliferation of gastric cancer cells *in vitro*. Ishikawa *et al.* found that adiponectin has the capability to exert inhibitory effects on the growth and proliferation of gastric cancer cells *in vitro*[51]. Using various *in vitro* cell lines of human gastric cancer, the research showed that adiponectin exerts a negative regulatory effect on cell functions, such as viability, proliferation, and migration. Interestingly, this negative regulatory ability was absent when AdipoR1 and AdipoR2 were knocked out. Meanwhile, adiponectin was found to negatively regulate tumor progression in tumor-bearing mice when injected intraperitoneally, demonstrating the function of adiponectin in inhibiting tumor growth *in vivo*.

Hamabe-Horiike *et al.* measured adiponectin levels in the greater omentum adjacent to gastric cancer and discovered that its expression was lower in patients with T3/T4 tumors compared to patients with T1 tumors[52]. They also co-cultured human gastric cancer cell lines with mature mouse 3T3-L1 adipocytes and found that the level of adiponectin expression decreased, while the proliferation and migration ability of the gastric cells increased. They concluded that gastric cancer cells affect the phenotype of adipocytes to reduce adiponectin secretion, creating a microenvironment for tumor growth, and suggesting that adiponectin has a negative regulatory effect on gastric cancer cells.

It has been reported that cancer-associated fibroblasts (CAFs) promote gastric cancer progression by secreting multiple soluble factors or interacting directly with cancer cells. Therefore, stromal fibrosis may be a novel strategy for the treatment of patients with various malignancies. Iwata *et al.* discovered that recombinant adiponectin paralog, C1q/TNF-related protein 6 (CTRP6), reduced α-smooth muscle actin (α-SMA) expression in human fibroblasts, induced by transforming growth factor-β (TGF-β), attenuating the enhancing ability of fibroblasts to tumor cell proliferation and metastasis, showing the potential therapeutic value of adiponectin through regulating gastric CAFs in diffuse gastric cancer[53].

Although many studies have shown adiponectin's potential to inhibit the growth *in vitro*, proliferation and migration of gastric cancer through binding to adiponectin receptors on cancer cells, it may also affect gastric cancer-associated cells. It is still questionable whether adiponectin exerts its inhibiting action on gastric cancer progression *in vivo* through direct binding with adiponectin receptors on cancer cells. In previous studies, the expression of adiponectin receptors was minimal or even absent in gastric cancer cells and normal gastric epithelium, compared to that in mesenchymal cells[54]. Therefore, we consider it possible that the anti-cancer effect of adiponectin *in vivo* might not be conducted by direct interaction with gastric cancer cells, while the actual mechanism needs to be further studied.

Adiponectin and inflammation in gastric cancer

Previous studies have suggested that adiponectin has the capability to increase the expression level of anti-inflammatory factors and inhibit gastric ulcer progression. Additionally, it has been reported that in patients with gastric cancer, adiponectin can be used as a predictor of postoperative infections. Zatorski *et al.* used

AdipoRon, the first oral adiponectin receptor agonist, to treat two gastric ulcer models in mice, and found that AdipoRon exerted anti-inflammatory functions through lowering myeloperoxidase activity and IL-1β expression in gastric tissues[55]. In addition, AdipoRon enhanced antioxidant defense by raising glutathione levels, superoxide dismutase, and glutathione peroxidase activity.

Yamamoto *et al.* studied clinical characteristics and surgery-related factors in 150 patients with gastric cancer, including preoperative adiponectin levels before surgery and on postoperative day one, and calculated the adiponectin ratio (preoperative/postoperative adiponectin levels)[56]. It was discovered that T2DM and the adiponectin ratio were independent predictors of postoperative infection. Particularly, the adiponectin ratio was the most valuable predictor for postoperative infection. Although adiponectin's anti-inflammatory effect has been demonstrated by various studies, its mechanism in gastric carcinogenesis and postoperative anti-infection is still unknown and needs further investigation.

Adiponectin as a biomarker in gastric cancer

Recent research findings have suggested that low serum adiponectin levels are correlated with an elevated susceptibility to gastric cancer. Ishikawa *et al.* determined fasting serum levels of adiponectin in 2005 using enzyme-linked immunosorbent assay (ELISA) and found it to be significantly lower in 75 patients with gastric cancer compared to 52 healthy controls ($P < 0.01$)[46]. Additionally, an extremely low level of adiponectin was found in patients with upper gastric cancers ($P = 0.012$), whereas the adiponectin level exhibited a tendency to decline with the progression of tumor stage. It has also been reported that there is an inverse relationship between adiponectin levels and parameters such as tumor size, depth of invasion, and tumor stage in undifferentiated cancers and that adiponectin levels are negatively correlated with tumor size, depth of invasion, and tumor stage in undifferentiated cancers. In 2020, Kordafshari *et al.* also confirmed that serum adiponectin levels were significantly lower in stomach cancer patients, which was consistent with previous studies[57].

Nakajima *et al.* found that the serum adiponectin, C-peptide, and BMI levels were significantly lower in stomach cancer patients, while the decrease of adiponectin levels in early gastric cancer patients was not statistically significant[58]. Thus, the use of adiponectin as a biomarker to diagnose early gastric cancer remains controversial and requires further study. Seker *et al.* carried out a case-control investigation and found that tumor stage was negatively correlated with serum adiponectin levels in undifferentiated gastric cancer[50], whereas there was no relation between gastric cancer and serum adiponectin levels in terms of stage, location, lymph node metastasis, and lymphatic and vascular invasion of the tumor, which was inconsistent with the study from Ishikawa *et al.*[46]. Additionally, a genome-wide association study on adiponectin in East Asians by Jiang *et al.* revealed that higher levels of adiponectin were linked to a reduced risk of gastric cancer[59].

Although most studies found a decreased serum adiponectin level in gastric cancer patients, some of them lacked statistical significance, and controversial results were reported on the correlation between serum adiponectin level and tumor size, depth of invasion, and tumor stage. In addition, previous studies were small in sample size and lacked standard techniques or reagents, urging the need for large-scale studies to confirm the value of adiponectin as a biomarker in gastric cancer diagnosis and staging.

THE FUNCTION OF ADIPONECTIN RECEPTOR AND CANCER

Previous studies have mainly focused on the relationship between gastric cancer and adiponectin receptors, since adiponectin exerts its effects through these receptor pathways. Barresi *et al.* discovered that the levels of AdipoR1 and AdipoR2 were significantly different in intestinal-type and diffuse-type gastric cancer

patients, with higher expression of AdipoR1 and AdipoR2 associated with a better prognosis[54]. They considered that the upregulation of these two adiponectin receptors in cancer tissues might be a response to the reduced levels of circulating adiponectin in gastric cancer patients. Furthermore, they found that adiponectin receptor staining was positive in the lamina propria stroma, the myocytes of muscularis propria and peritoneal adipose tissue, but not in cancer cells or normal gastric mucosa adjacent to the tumor, indicating that adiponectin might not stimulate its receptors through autocrine actions in cancer cells. This is consistent with the study by Otani *et al*., which showed that adiponectin receptor is expressed in human mesenchymal cells rather than tumor cells or normal gastric epithelium[60].

Lin *et al*. reported that in advanced gastric cancer, AdipoR1 and AdipoR2 were strongly expressed in non-tumor mesenchymal cells regardless of the visceral adipose (VAT)/subcutaneous adipose (SAT) ratio[61]. The survival rate was lower in patients with increased VAT/SAT ratio or decreased expression of adiponectin receptors, and vice versa. They concluded that the VAT/SAT ratio and the expression levels of adiponectin receptors are instructive in predicting prognosis and postoperative nutrition in patients with advanced gastric cancer. To assess risk factors in the pathogenesis of gastric cancer, we cannot ignore the relationship between adiponectin receptors and precancerous lesions. In 2021, Ayyildiz *et al.* performed immunohistochemical staining of adiponectin receptors in individuals with gastric cancer, patients with incomplete intestinal metaplasia (ICM), and patients with complete intestinal metaplasia (CM)[62]. They found that the expression of AdipoR1 and AdipoR2 was significantly reduced in the gastric cancer group compared to that in the CM and ICM groups, but no significant differences were found between the CM and ICM groups. Likewise, there was no association found between the expression of AdipoR1 and AdipoR2 and stages of cancer. Shin *et al.* found that in non-neoplastic gastric mucosa, gastric adenoma, intestinal-type gastric cancer, and metastatic gastric cancer, expression rates of adiponectin receptors increased stepwise, and they were associated with poorer overall survival (OS) and disease-free survival (DFS)[63]. Moreover, AdipoR2 expression was associated with poorer OS and DFS and was verified in multivariate analysis as an independent prognostic factor for intestinal-type gastric cancer. The adiponectin receptors decreased gradually in progress from precancerous lesions to gastric cancer, indicating the role of adiponectin receptors as a prognostic marker for patients with gastric cancer, especially those with intestinal-type ones[54].

On the other hand, Otani *et al*. reported a lower expression of AdipoR1 and AdipoR2 in gastric cancer tissue compared to normal gastric tissue, although this difference was not significantly correlated with clinicopathological features[60]. Furthermore, Tsukada *et al*. conducted an immunohistochemistry study in gastric cancer tissues and found that the survival rate of patients was higher in the AdipoR1-staining positive group as compared to those in the negative group, but multivariate analysis showed that AdipoR1 was not an independent prognostic factor[64]. Additionally, Ayyildiz *et al.* found that both receptors were expressed in early and advanced gastric cancers, but their expression was not associated with progression-free survival and OS, suggesting no prognostic value of dipoR1 and AdipoR2 for gastric cancer[65].

However, in the field of adiponectin receptor therapy, adiponectin receptor agonists have garnered significant attention as a burgeoning area of research with promising implications for various fields, particularly in oncology, metabolic disorders, and cardiovascular diseases. Zatorski *et al*. demonstrated the therapeutic effect of adiponectin receptor agonists in treating gastric ulcer mouse models by applying AdipoRon[55]. Recently, an adiponectin receptor agonist has been applied in cancer therapy. Ramzan *et al.* demonstrated the potential of AdipoRon to suppress ovarian tumor cell proliferation and induce apoptotic death, mediated through AMPK activation and mTOR inhibition[66]. In pancreatic ductal adenocarcinoma, AdipoRon showed enhanced anti-cancer effects in combination with gemcitabine. Moreover, it has the

potential to overcome chemotherapy drug resistance in PDAC treatment[67,68]. These findings show that AdipoRon holds promise as a potential therapeutic agent for cancer treatment.

According to the existing studies so far, we consider that the expression of adiponectin receptors is related to the occurrence and progression of gastric cancer, with a decreased expression in gastric cancer tissues. However, unfortunately, no sufficient evidence is available as to whether adiponectin receptors act as a biomarker for gastric cancer patients, especially in the aspect of clinical staging and postoperative survival prediction. Currently, adiponectin receptors might be used as a potential reference factor to estimate prognosis in gastric cancer, but their relationship needs to be confirmed in further studies. Meanwhile, current research suggests that adiponectin receptor agonists hold significant promise in the field of cancer therapy. Although several potential therapeutic effects have been shown, the research in this area is still in its early stages. Therefore, further research efforts will be necessary to shed more light on the potential value of adiponectin receptor agonists as a viable strategy in cancer treatment, offering new directions and hope for developing novel therapeutic approaches.

CONCLUSION

Despite increasing research data, the mechanisms underlying adiponectin's impact on gastric cancer remain elusive, especially concerning its anti-proliferative and inhibitory effects, and unfortunately, the results of present studies are contradictory. Furthermore, there are few studies regarding adiponectin's regulatory mechanism on gastric cancer *in vivo*, and how circulatory adiponectin regulates tumor progression still requires further investigation.

Low serum adiponectin levels might be a risk factor for gastric cancer, but whether it can be regarded as a biomarker for gastric cancer remains controversial. According to current studies, it appears that in the presence of low adiponectin levels, gastric cells might be vulnerable to being stimulated or damaged by certain carcinogens, which will further promote gastric cancer development and progression. Since adiponectin exerts multiple systemic effects and is highly concentrated in the serum, and while adiponectin receptor expression is low or absent in gastric epithelial cells and cancer cells, it is suggested that the anti-cancer effect of adiponectin acts through regulating homeostasis instead of directly acting on tumor cells. Meanwhile, the anti-inflammatory effect of adiponectin may be realized through regulating body hormones. In the future, more *in-vivo* studies with large-scale studies are necessary to figure out the exact role of adiponectin in the development and progression of gastric cancer.

DECLARATIONS

Acknowledgments

We acknowledge Yuan Q for his help in editing the manuscript. The author Ming C also thanks Prof. Yongyou W's project funds to support him in research at Juntendo University.

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Ming C, Orita H, Fukunaga T

Performing data acquisition, as well as providing administrative, technical, and material support: Shangcheng Y, Fedor CN, Yuan Q, Yongyou W

Writing the manuscript: Ming C

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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