Review

Title: The Role of Adiponectin in Gastric Cancer

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Abstract

Adiponectin is an adipokine produced by adipose tissue, which has been widely studied in biomedical research. Epidemiological evidence shows that a low serum adiponectin level may be a risk factor for various malignancies, including gastric cancer. Although many studies on adiponectin level in gastric cancer patients have been reported, its predictive role as a biomarker remains controversial. Moreover, the prognostic role of adiponectin receptor expression in gastric cancer tissues differs between studies, and the mechanism of how adiponectin affects the development and progression of gastric cancer remains unclear. 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 information available on adiponectin in...
relation to gastric cancer and discussed its role and corresponding receptors involved in gastric cancer.

**Keywords:** Adiponectin, Adiponectin receptor, Gastric cancer

**INTRODUCTION**

Gastric cancer (GC) is the fourth most common cancer in humans and ranks as the second leading cause of death among all forms of cancer worldwide. The incidence of GC has increased worldwide since the 1940s and remains as an important health issue. 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. 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 shown that serum adiponectin levels are lower in obese individuals compared to those with a normal body weight. Adiponectin levels correlate negatively with body mass index (BMI) and increase following weight loss, suggesting the existence of certain feedback mechanisms. Therefore, there may be correlations between obesity, adiponectin, and gastric cancer.

There are two primary types of adipose tissue in the human body: brown adipose tissue (BAT) and white adipose tissue (WAT). 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. Adiponectin has been shown to have anti-diabetic, anti-atherosclerotic, and anti-inflammatory effects by many reports, suggesting that it may play a key role in Metabolic Syndrome (MetS). Additionally, low serum adiponectin levels have been significantly associated with an increased risk of various malignancies, such as colorectal cancer. Adiponectin has been found to act as an anti-cancer factor for breast, endometrial, prostate, and other various cancers, both in vivo and in vitro. These results suggested a significant association between adiponectin...
and cancer. Here, we reviewed the role of adiponectin and its associated receptors in the development and progression of gastric cancer.

1. 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\(^1\). 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: AdipoR1, AdipoR2 and T-cadherin, among which AdipoR1 and AdipoR2 are the main receptors for adiponectin\(^{19}\). Yamauchi et al.\(^{20}\) first successfully cloned the human and mouse adiponectin receptors in 2003 and found that AdipoR1 and AdipoR2 are highly structurally related, with seven transmembrane structural domains. 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 expressed on the cell surface and are distributed in many tissues. AdipoR1 is predominantly expressed on skeletal muscle cells with high affinity for spherical domain but low affinity for full-length adiponectin, while AdipoR2 is mainly expressed in hepatocytes with moderate affinity for both spherical domain and full-length adiponectin. T-cadherin, discovered by Lodish et al, is a receptor for adiponectin that can bind to
hexamers and high molecular weight adiponectin\textsuperscript{24}. However, it lacks intracellular domains and thus is not able to transduce downstream signals.

2. 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\textsuperscript{25-27}. The first protein found to interact directly with adiponectin receptors was the adaptor protein containing a pleckstrin homology domain, phosphotyrosine binding domain, and leucine zipper motif (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\textsuperscript{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, and thereby enhancing glucose uptake, inducing fatty acid oxidation, inhibiting hepatic glycogen synthesis, increasing intracellular AMP/adenosine triphosphate (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)\textsuperscript{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)-κB, thus exerting its anti-cancer effects. Among them, activation of AMPK is considered to play a central role in it\textsuperscript{29}. Although many studies on the signaling pathways of adiponectin in cancers have been reported, its mechanism in gastric cancer cells is still unknown leading to a need for further research.

Figure-1 Signaling pathways of adiponectin in cancer cells.
3. FUNCTION OF ADIPONECTIN

3.1 Adiponectin in non-cancers

In human, it has been reported that adiponectin in 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 adiponectin plays an important role in insulin resistance that occurs in obesity. Reduced adiponectin expression in mRNA and serum levels has been associated with insulin resistance and susceptibility to diabetes developing 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 pro-inflammatory effects have 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-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. Adiponectin stimulates interleukin (IL)-10 secretion, which increases matrix metalloproteinase-1 inhibitor production in human macrophages, thereby alleviating tissue destruction. 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. Adiponectin has anti-inflammatory activity both in vivo and in vitro, it neutralizes LPS activity, stimulates various anti-inflammatory factors, impairs the viability of macrophages to inhibit inflammatory cytokine production, thus playing a crucial role in 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. Adiponectin promotes AMPK phosphorylation of endothelial nitric oxide (NO) synthase in endothelial cells to produce NO, as well as promotes proliferation of endothelial progenitor cells to repair vascular endothelium. Moreover, adiponectin can decrease LDL-induced reactive oxygen species (ROS) production, and thus reduces vascular endothelium damage.

### 3.2 Adiponectin in cancers

Currently, the development of several kind of cancers has been found to be associated with low serum adiponectin levels. In IL-6-treated MC38 mouse colon cancer cells, anti-proliferative potential of adiponectin was observed through downregulating STAT3 phosphorylation/activation. Nigro et al. found that adiponectin induced the accumulation of ROS in colon cancer cells, leading to increased cell death. In breast cancer, decreased adiponectin levels has been reported to increase IGF1 levels and its activity, which is known as a risk factor for breast cancer. Furthermore, it has been suggested that adiponectin might have an independent effect on endometrial carcinogenesis by affecting estrogen and insulin resistance. Adiponectin levels have also been associated with staging and pathological type for some tumors. In addition, adiponectin has been used for differentiation between diseases such as pancreatic cancer and chronic pancreatitis with elevated tumor markers.

However, despite observing a negative correlation found between circulating adiponectin levels and carcinogenesis and malignant degree, some studies have seen the opposite results. For example, Toru et al. found that patients with chronic hepatitis C (CHC) and high serum...
adiponectin levels had a higher risk of liver cancer developing.

4. THE FUNCTION OF ADIPONECTIN IN GASTRIC CANCER

4.1 Adiponectin in the growth and proliferation of gastric cancer cells

Currently, research evidence demonstrates that adiponectin has the ability to negatively regulate the growth and proliferation of gastric cancer cells in vitro. Ishikawa et al.\(^5\) demonstrated that adiponectin plays an inhibitory role in regulating growth and proliferation of gastric cancer cell lines in vitro. Using various cell lines of human gastric cancer, the research showed that adiponectin negatively regulates cell viability, proliferation, and migration in vitro. 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.

Toshihide et al.\(^5\) 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. 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 through secreting multiple soluble factors or interacting directly with cancer cells. Therefore, stromal fibrosis may be a new target for the treatment of patients with various malignancies. Iwata et al.\(^5\) discovered that recombinant adiponectin paralog, C1q/TNF-related protein 6 (CTRP6), reduced transforming growth factor-β (TGF-β) induced α-smooth muscle actin (α-SMA) expression in human fibroblasts, attenuating the enhancing ability of fibroblasts to gastric cancer cell proliferation and invasion, suggesting the potential therapeutic value of adiponectin through regulating gastric CAFs in diffuse gastric cancer.

Although in vitro studies have shown that adiponectin may inhibit the growth, 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. Therefore, we consider it is 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.

4.2 Adiponectin and inflammation in gastric cancer

Previous studies have indicated that adiponectin can 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. 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 as well as calculating the adiponectin ratio (preoperative/postoperative adiponectin levels). 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.

4.3 Adiponectin as a biomarker in gastric cancer

Recent studies have shown that low serum adiponectin levels are associated with an increased risk of 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 when compared to 52 healthy controls (P < 0.01). Additionally, an extremely
low level of adiponectin was found in patients with upper gastric cancers (P = 0.012), whereas the adiponectin level tended to decrease as tumor stage increased. It has also been reported that adiponectin levels were negatively correlated with tumor size, depth of invasion and tumor stage in undifferentiated cancers. In 2020, a case-control study conducted by Kordafshari et al. 57 also confirmed that serum adiponectin levels were significantly lower in patients with gastric cancer, which was consistent with previous studies.

Nakajima et al. 58 found that the serum adiponectin, C-peptide, and BMI levels were significantly lower in patients with gastric cancer, while the decrease of adiponectin levels in patients with early gastric cancer was not statistically significant. Thus, the use of adiponectin as a biomarker to diagnose early gastric cancer remains controversial and requires further study. Seker et al. 50 conducted a case-control study and found that tumor stage was negatively correlated with serum adiponectin levels in undifferentiated gastric cancer, whereas there were 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 studies on adiponectin in East Asians by Jiang et al. 59 revealed that an elevated adiponectin level was associated with a reduced risk of gastric cancer.

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.

5. THE FUNCTION OF ADIPONECTIN RECEPTOR AND CANCER

Previous studies have mainly focused on the relationship between gastric cancer and adiponectin receptors, AdipoR1, and AdipoR2, since adiponectin acts via these receptors. Barresi et al. 54 discovered that the expression of AdipoR1 and AdipoR2 was significantly different in patients with intestinal-type and diffuse-type gastric cancer, with higher expression of AdipoR1 and AdipoR2 associated with a better prognosis. They considered that the upregulation of these two adiponectin receptors in cancer tissues might be a response to low circulating adiponectin
concentrations in patients with gastric cancer. Furthermore, they found that adiponectin receptor staining was positive in the stroma of lamina propria, 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 Ishikawa et al.\textsuperscript{60} which showed that adiponectin receptor is expressed in human mesenchymal cells rather than tumor cells or normal gastric epithelium.

Lin et al.\textsuperscript{61} 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. The survival rate was lower in patients with increased VAT/SAT ratio or decreased expression of AdipoR1 and AdipoR2, and vice versa. They concluded that the VAT/SAT ratio and the expression levels of AdipoR1 and AdipoR2 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.\textsuperscript{62} performed immunohistochemical staining of AdipoR1 and AdipoR2 in patients with gastric cancer, patients with incomplete intestinal metaplasia (ICM) and patients with complete intestinal metaplasia (CM). They found that AdipoR1 and AdipoR2 expression was significantly lower in gastric cancer group when compared with that in the CM and ICM group but no significant differences were found between the CM and ICM group. Likewise, there was no correlation found between AdipoR1 and AdipoR2 expression and stages of cancer. Shin et al.\textsuperscript{63} 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). 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 expression of adiponectin receptors decreased gradually in the 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\textsuperscript{54}.

On the other hand, Otani et al.\textsuperscript{60} reported that AdipoR1 and AdipoR2 expression was lower in gastric cancer tissue compared to normal gastric tissue but was not significantly correlated with
clinicopathological features. Furthermore, Tsukada et al.\textsuperscript{64} 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. Additionally, Ayyildiz et al.\textsuperscript{65} 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 AdipoR1 and AdipoR2 for gastric cancer.

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.\textsuperscript{55} demonstrated the therapeutic effect of adiponectin receptor agonists in treating gastric ulcer mouse models by applying AdipoRon. Recently, an adiponectin receptor agonist has been applied in cancer therapy. Ramzan et al.\textsuperscript{66} demonstrated the potential of AdipoRon to suppress proliferation and induce apoptotic death in human high-grade serous ovarian tumor cell lines and primary tumors, mediated through AMPK activation and mTOR inhibition. 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.\textsuperscript{67, 68} These findings suggest that AdipoRon could serve as a promising therapeutic agent for cancer treatment.

According to the existing studies so far, we consider that expression of adiponectin receptors is related to the development 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 of anti-proliferative and inhibitory effects of adiponectin on gastric cancer cells remain unclear, 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 has multiple systemic effects and is present as a high concentrated serum protein, 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 hormone. 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 gastric cancer.

DECLARATIONS

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Authors’ contributions
Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Cheng M, Hajime O, Tetsu F;
Performed data acquisition, as well as provided administrative, technical, and material support: Yan S, Yuan Q and Wu Y; CM wrote the manuscript.

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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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locomally advanced gastric cancer—— highlighting the role of adiponectin receptors and PPARα, β/


Dear Reviewer,

I hope this email finds you well. Thank you for taking the time to review my manuscript and for providing valuable feedback. I sincerely appreciate your comments and suggestions, which have been instrumental in improving the quality of the article.

I have made the necessary revisions accordingly, according to the current research on adiponectin in cancer cells, and made a figure to clearly illustrate the signaling pathway of adiponectin in cancer cells. I have also made efforts to update some references, particularly focusing on the aspect of adiponectin receptor agonists that you mentioned, which holds great potential for future research.

Once again, thank you for your valuable insights and guidance. I hope the revised manuscript meets the high standards of the journal.

Please do not hesitate to reach out if you require any further information or have additional queries. I look forward to your feedback on the revised submission.

Best regards

Cheng Ming