Mechanism of action of CTRP6 in the regulation of tumorigenesis in the digestive system (Review)

AIMIN ZHANG1, MOWEI KONG2, XIUYUN ZHANG1 and ZHENYING PEI2

1Department of Nutriology, Shijiazhuang Second Hospital, Shijiazhuang, Hebei 050000; 2Department of Cardiology, Guiqian International General Hospital, Guiyang, Guizhou 550018, P.R. China

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Abstract. Tumors of the digestive system have always received attention, and their occurrence and development are regulated by various mechanisms such as inflammation and immunity, glucose and lipid metabolism, and tumor angiogenesis. Complement Clq/TNF-related protein 6 (CTRP6) is a member of the CTRP family; it is widely expressed in various tissues and cell types, and plays a biological role in a number of mechanisms, such as glucose and lipid metabolism and inflammation. Recent studies have revealed the tumor-promoting effect of CTRP6 in gastric cancer, liver cancer, colorectal cancer and other gastrointestinal tumors, but, to the best of our knowledge, there has been no systematic discussion on the tumor-promoting mechanism of CTRP6. The present study reviews the role of CTRP6 in tumors of the digestive system and its possible mechanisms.

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1. Introduction

Complement Clq/TNF-related protein 6 (CTRP6) is one of the CTRP family members homologous to adiponectin discovered in recent years (1-3). All CTRP members are secreted proteins, which are widely expressed in various tissues and cell types (1). Previous studies have found that CTRP6 plays a role in fat metabolism, glucose metabolism, cardiometabolism, inflammatory response and autoimmunity (2,3); however, research on the role of CTRP6 in cancer is an emerging area. Previous studies have revealed that the overexpression of CTRP6 is associated with a poor prognosis in lung adenocarcinoma (1,3), and CTRP6 is also able to serve as a marker for the diagnosis and prognosis of renal clear cell carcinoma (4). By contrast, a previous study also revealed a role of CTRP6 in the inhibition of cancer cell metastasis in ovarian cancer (5). From this, it can be argued that CTRP6 has both oncogenic and antitumor effects, which may be related to the cancer type. However, little is known about the role of CTRP6 in digestive tumors. It was not until recently that the relationship between CTRP6 and gastric, liver and colon cancer was gradually revealed (6-8). The present study reviews the pathophysiological role of CTRP6 in the development of tumorigenesis in the digestive system and explores the possible mechanisms.

2. CTRP6: General characteristics

CTRP6 is found in serum and is widely expressed in the human uterus, skin, placenta, lung, fat and other tissues (1). CTRP6 contains an amino-terminal signal peptide, a short variable domain, a collagen domain and a carboxyl-terminal spherical domain homologous to the complement protein, Clq, where the spherical domain is important for the stimulation of p42/44MAPK phosphorylation pathways (9,10) (Fig. 1). In humans, CTRP6 induces IL-10 mRNA and protein expression in monocytes, and when blocking phosphorylation by cotreating cells with selective p42/44MAPK inhibitors, CTRP6-mediated IL-10 expression is abolished (11). Another study found that the globular domain of human CTRP6 shares up to 33% amino acid identity with adiponectin, suggesting that the actions of CTRP6 may share some similarities to the physiological effects of adiponectin; for example, they both participate in the regulation of a number of physiological and pathophysiological processes such as glucose and lipid metabolism, and inflammation (12). Fig. 1 shows the schematic structure of the CTRP family (13).

A number of the proteins in the CTRP family are involved in tumor regulation. A recent study suggested that CTRP1...
may promote human glioblastoma progression and predict a poor prognosis (14). CTRP3 reduces glucose levels by reducing hepatic gluconeogenesis and induces hepatic Akt activation, which subsequently stimulates the proliferation of chondrogenic cells (15,16). CTRP4 can act as a regulator of tumor-promoting inflammation (17), while CTRP8 is involved in brain cancer formation (18).

The regulatory role of CTRP6 in tumor biology is associated with multiple mechanisms and has different roles depending on the tumor type. CTRP6 inhibits the proliferation and migration of epithelial ovarian cancer cells by blocking the IL-8/VEGF pathway (5). CTRP6 can also inhibit the progression of oral squamous cell cancer cells by disrupting the lamin-laminin receptor axis (19). CTRP6 also has a potential role in promoting tumor growth, invasion and metastasis, and can serve as a novel cancer diagnostic and prognostic biomarker for clear cell renal cell carcinoma (4).

The study of CTRP6 in digestive tumors is currently focused on, liver, colon and gastric cancer. Previous studies have shown that CTRP6 is highly expressed in liver and colon cancer tissues compared with non-cancerous tissues, and may be used as an early marker for the diagnosis of these diseases (8,20). CTRP6 is overexpressed in gastric cancer and is involved in the division and migration of gastric cancer cells (7). The regulatory mechanisms of CTRP6 will be detailed in the following sections.

3. Regulation of inflammation

CTRP6, a novel metabolic immunomodulator that binds to multiple endogenous ligands, is an intermediate link in obesity with adipose tissue inflammation and insulin resistance (21,22). CTRP6 serves a role in regulating the secretion of inflammatory factors and may have a proinflammatory or inhibitory inflammatory effect depending on the site of action. In a previous study, the knockdown of CTRP6 resulted in a significant reduction in the expression of TNF-α, IL-1 and IL-6 in high glucose-induced glomerular mesilial cells (23). Overexpression of CTRP6 can activate PI3K/Akt signaling by inhibiting the Ras homologue family A/Rho associated kinase/PTEN pathway and improve the inflammatory damage caused by cerebral ischemia/reperfusion (24).

Activation of the PI3K/Akt pathway is one of the common molecular mechanisms in human tumor development. PI3K/Akt signaling negatively regulates processes such as cell growth and proliferation, glucose metabolism and cell migration, and is considered to play a key regulatory role in tumor invasiveness (25). One of the specific mechanisms by which the PI3K/Akt pathway promotes tumorigenesis is through the dysregulation of inflammatory mediators and immunity. It has been shown that rosmarinic acid subsequently prevents lung tumor invasion by reducing the production of inflammatory factors, such as IL-6, IL-8, TNF-α and cyclooxygenase-2, by inhibiting Akt phosphorylation (26). We speculate that this mechanism of action of the PI3K/Akt pathway is equally applicable during the pathogenesis of digestive tumors. A recent study has shown that the chronic inflammatory status due to obesity is a risk factor for the development of colorectal cancer, and that the PI3K/Akt pathway is one of the important pathways to mediate this process (27). The PI3K/Akt pathway also mediates the aggressive role of cancer-associated fibroblasts in gastric cancer, while IL-8 enhances expression of PI3K/Akt pathway expression and increases chemoresistance to gastric cancer (28,29). In a recent study on hepatoma, royal jelly increased IL-2 and TNF-α levels in serum by inhibiting PI3K expression and phosphorylating Akt, thereby preventing and controlling hepatocarcinogenesis in mice (30). From the aforementioned studies, we can speculate that CTRP6 may promote tumorigenesis in the digestive system by releasing inflammatory factors and activating the PI3K/Akt pathway. This speculation is supported by the study by Wan et al (6), where it was shown that the inhibition of CTRP6 blocked Akt signaling and in turn prevented the survival and migration of hepatocellular carcinoma (HCC).

It has recently been shown that overexpression of CTRP6 enhances the proliferation, migration and invasion of lung adenocarcinoma cells by regulating the MAPK signaling pathway (3). The MAPK/NF-κB pathway is one of the common intersection pathways of various cellular signaling pathways, such as inflammation and stress, and is involved in cellular activity, including carcinogenesis (31). Activation of MAPK/NF-κB signaling enhances the secretion of IL-1β and IL-18, and leads to the development of renal inflammation (32). In a study by Eyre et al (33), it was found that the globular domain of CTRP6 could stimulate the phosphorylation of MAPK/ERK1/2, and when human serum were treated with selective MAPK/ERK1/2 inhibitors, CTRP6-mediated IL-10 expression was eliminated (24). In an additional study, it was revealed that digestive tract tumors are regulated by inflammatory factor secretion by the MAPK signaling pathway. IL-1β, IL-6 and TNF-α, the inflammatory factors produced by inhibiting the MAPK pathway, could effectively delay the progression of colorectal cancer (34). In gastric cancer, IL-6 promotes tumor growth and metastasis, and resveratrol can prevent this by blocking Raf/MAPK signaling (35). Piperine in turn inhibits IL-1β-induced IL-6 expression by inhibiting the MAPK and STAT3 pathways in gastric cancer cells (36). Additional studies have also demonstrated the oncogenic role of inflammatory factors such as IL-1β and IL-6 in gastric, colorectal and liver cancer (37-40). We hypothesize that CTRP6 activation of the MAPK/ERK1/2/NF-κB pathway promotes the secretion of inflammatory factors such as IL-1β, IL-6 and TNF-α, and in turn accelerates tumor progression.

In conclusion, it can be speculated that one role of CTRP6 in digestive system tumors is to regulate tumor development through the activation of the Akt pathway and the regulation of inflammatory factors in the MAPK pathway (Fig. 2).

![Figure 1. Schematic structure of complement Clq/TNF proteins.](image-url)
4. Regulation of glycolipid metabolism

Disordered glucose and lipid metabolism are the two main processes that increase tumor risk and severity. Abnormal lipid metabolism leads to disturbances in adipokine secretion, which is strongly associated with tumorigenesis and tumor progression (41). Obesity due to abnormal lipid metabolism is an independent risk factor for tumorigenesis and tumor development in a variety of liver, pancreatic, ovarian and colorectal cancer types (26,40,42). The role of CTRP6 in glycolipid metabolism has been extensively studied (43). Animal experiments showed that CTRP6 could affect pig adipogenesis by activating Akt/PKA/MAPK signaling, while knockdown of CTRP6 reduced muscle and subcutaneous fat deposition through alternative signaling pathways (43,44). Cellular experiments showed that knockdown of CTRP6 inhibited adipogenesis by inhibiting the expression of adipogenesis-related genes and the MAPK/ERK1/2 signaling pathway (45). The aforementioned studies revealed the role of CTRP6 in promoting fat deposition. Clinical experiments related to glucose metabolism have demonstrated that CTRP6 may be associated with insulin resistance and type 2 diabetes (46).

MAPK is a key molecule in the regulation of bioenergy metabolism and is expressed in various metabolically related organs (47,48). In adipose metabolism, one of the mechanisms by which obesity becomes a risk factor for rectal cancer is due to the metabolic disturbance of adipokines (48). Obesity increases the expression of leptin, estrogen, resistin, macrophage migration inhibitor factor, monocyte chemotactic protein 1 and insulin/insulin-like growth factor, and reduces the expression of adiponectin, which promotes obesity-related tumors (e.g., breast, pancreatic, ovarian and colorectal cancer) proliferation, invasion and metastasis (41). Obesity-induced gastric cancer stimulates the binding of chemotactic protein and stromal cell-derived factor 1 to CXC chemokine receptor 4 (CXCR4) and CXCR7 to regulate cancer cell motility and angiogenic regeneration, a process mediated by the p38 MAPK pathway (49). The MAPK pathway remains important in the glucose metabolism of tumors. In a previous study, the knockdown of glucose-regulated protein 94 inhibited the ability of cancer cell proliferation and metastasis in colorectal cancer cells by inhibiting the expression of the MAPK pathway, including ERK/p-ERK, JNK/p-JNK and p38/p-p38 signaling (50). It can be speculated from the aforementioned studies that the effect of CTRP6 on colorectal and gastric cancer is at least partly due to the regulation of glycolipid metabolism through the MAPK-PKA pathway (Fig. 3), but direct evidence of CTRP6 tumor promotion through MAPK pathway activation is currently lacking. The study by Lei et al (22) examined the effect of CTRP6 on cell metabolism by activating/blocking the pathway between colorectal cancer and gastric cancer cells. It was demonstrated that CTRP6 induces inflammatory factors by regulating glycan and lipid metabolism (22), which is in agreement with the aforementioned speculation.

5. Angiogenesis

Tumor angiogenesis is a key factor in tumor growth, progression and metastasis, and inhibiting tumor angiogenesis can be used as an effective means to treat tumors (51). PI3K/Akt signaling is one of the classical pathways leading to increased vessel number and vascular permeability, achieving the purpose of revascularization by enabling the transformation of the vascular smooth muscle cell (VSMC) phenotype (52). In the CTRP family, various factors such as CTRP1, CTRP3 and CTRP5 can regulate inflammatory factors and glycolipid metabolism by activating pathways such as the PI3K/Akt/endothelial NO synthase and p38/MAPK/NF-κB pathways, and in turn regulate vascularization due to chronic inflammation (53). A recent study found that CTRP9 is correlated with Akt and AMP-activated protein kinase (AMPK) pathway activation by promoting endothelial cell function and ischemia-induced revascularization (54). We consider that the aforementioned development process is equally suitable for the role of CTRP6 in digestive tract tumors.
Figure 4. CTRP6 regulates tumor angiogenesis through the activation of the PI3K/Akt pathway. C1qTNF-related protein 6.

Digestive tumors such as those of gastric, liver and colorectal cancer are all regulated by the Akt signaling pathway (55-57). A recent study confirmed that the CDK5 regulatory subunit-associated protein 3 gene improves patient prognosis by inhibiting tumor angiogenesis through the downregulation of gastric neuroendocrine cancer Akt/hypoxia-inducible factor-α/VEGFA signaling (58). In colorectal cancer, highly dry human colorectal cancer cells promote angiogenesis through the activation of the angiogenic cytokines, IL-8 and VEGFA, produced by the EGFR/Akt/NF-κB pathway, and lactoferrin suppresses colon cancer angiogenesis by regulating the PI3K/ERK1/2/Akt pathway (59,60). Moreover, Wang et al (61) found that IL-6 activates STAT3 to stimulate angiogenesis in gastric cancer and, as discussed previously, CTRP6 promotes pro-inflammatory factors such as IL-6 through the PI3K/Akt and MAPK pathways (27,28,34,35). Thus, in gastric cancer, CTRP6 most likely serves a role in promoting gastric cancer angiogenesis by activating the Akt/IL-6/STAT3 or MAPK/IL-6/STAT3 pathway. It has previously been demonstrated that CTRP6 promotes hepatoma angiogenesis and subsequently reduces HepG2 cell necrosis by regulating Akt signaling in HCC cells (8). It is reasonable to speculate that CTRP6 regulates colorectal and liver cancer, and other tumors, by the activation of proangiogenic factors such as PI3K/Akt/NF-κB (Fig. 4). However, there is no direct basis for CTRP6 to activate the Akt pathway to promote vascular effects in other digestive tumors outside HCC.

AMPK is a major regulator of glycolipid metabolism and protein synthesis, and also functions in regulating angiogenesis (62,63). Activation of AMPK-related pathways can serve as a prognostic marker for colon tumors and can also play a role in regulating angiogenesis in gastric cancer and HCC (64-66). It was recently demonstrated that dual-loaded liposomes containing apigenin and 5-fluorouracil inhibited tumor angiogenesis by inhibiting AMPK phosphorylation in colorectal cancer (67). CTRP6 can activate the AMPK pathway in various tissues and thus plays different roles in mechanisms such as the promotion of cellular differentiation and antifibrosis (68,69). In colon cancer, CTRP6 was shown to be highly expressed, and its expression level was not correlated with patient age, sex or pathological type, among others (4). However, this evidence is insufficient to deduce whether the role of CTRP6 in colon cancer is related to tumor angiogenesis associated with AMPK pathway activation. By contrast, it has been suggested that adiponectin inhibits tumor angiogenesis by regulating the AMPK pathway in colon cancer (70). Due to the proposed structural similarity of CTRP6 and adiponectin, we can even speculate that CTRP6 may have an effect on inhibiting tumor angiogenesis (12). More research should be conducted to confirm this speculation.

6. Alternative views

Iwata et al (71) observed that the overexpression of CTRP6 had an inhibitory effect on tumor stromal fibrosis in gastric cancer, the development of which is considered to promote cancer progression and confer chemoresistant properties in malignant tissues. This suggests that CTRP6 may also function as an inhibitor of gastric cancer progression. However, after the addition of recombinant CTRP6 protein, the study did not record changes in the proliferation rate and invasiveness of the gastric cancer cells (71). Therefore, without additional research, we still tend to consider that CTRP6 plays a major tumor-promoting role in gastric cancer.

Murayama et al (72) found that the recombinant human CTRP6 protein increased the expression of the anti-inflammatory factor IL-10 in mice and inhibited CTRP6-mediated IL-10 expression after pretreatment with the selective ERK1/2 inhibitor U0126 and then resolved the symptoms of arthritis. It is thus inferred that CTRP6 may play an anti-inflammatory effect in the induction of IL-10 expression through the ERK1/2 pathway. An additional study also found that CTRP6 overexpression decreased the expression of inflammatory factors IL-1β, IL-6 and TNF-α, and increased the expression of anti-inflammatory factor IL-10 (73). This seems to contradict the speculation that CTRP6 promotes inflammatory factor release through the activation of the Akt and MAPK pathways. However, the current evidence is insufficient to prove which mechanism is dominant or coexisting in digestive tumors.

A previous study also found that the secretion levels of IL-8 in ovarian cancer were opposite to those of CTRP6 and were dose-dependent, so it was hypothesized that CTRP6 may be involved in inhibiting the proliferation and metastasis of ovarian cancer cells by inhibiting IL-8 and vascular endothelial growth factors (5). CTRP6 inhibits platelet-derived growth factor-BB-induced VSMC proliferation and migration, at least in part by the inhibition of PI3K/Akt/mTOR signaling, and thus may be a potential target for the treatment of atherosclerosis (74). The aforementioned studies contradict the observation that CTRP6 promotes tumor angiogenesis in HCC. We speculate that this contradiction may result from a different regulatory role of CTRP6 in blood vessels and in different tissues, as the structurally similar adiponectin showed similar properties in recent studies (75,76).
Additionally, in a recent study, Zhang et al. (77) proposed that microRNA (miR)-148a inhibited HCC cell growth by targeting death receptors and downregulating epithelial-to-mesenchymal transition and PI3K/Akt signaling pathways. Moreover, methylsulfonylmethane inhibits iron metabolism and modulates p38/p53/ERK signaling and miR expression targeted to inhibit the proliferation of embryonic cancer stem cells (78). These studies suggest that miRs are likely to be involved in the regulation of CTRPs in gastrointestinal tumors, miRs may be involved in the regulation of CTRPs on gastrointestinal tumors by activating the PI3K/Akt pathway. More research needs to be conducted to confirm this conclusion.

7. Conclusion

CTRP6 plays a role in promoting tumorigenesis and development in digestive system tumors through multiple mechanisms. In gastric cancer tissues and cells, the overexpression of CTRP6...
affects the proliferation, migration, invasion and apoptosis of tumor cells through the release of pro-inflammatory factors (8). In colon cancer, CTRP6 expression is significantly higher than in non-cancerous tissues and may influence the development of colon cancer by regulating glycolipid metabolism and inflammatory response, and thus may serve as a marker for the early screening of colon cancer (4,33,37). In HCC, CTRP6 is highly expressed and promotes the survival and migration of HCC cells through mechanisms such as the promotion of tumor angiogenesis (6,7). The induction of the aforementioned mechanism is mainly realized by the activation of the Akt and MAPK pathways, as summarized in Table I and Fig. 5. CTRP6 may also regulate the aforementioned tumors via activation of the AMPK pathway (67,68) but there is insufficient evidence to prove this.

The biological function of CTRP6 is complex and has received attention as a regulator of metabolism in previous studies, although there are less current studies analyzing CTRP6 in cancer. Continuing research into CTRP6 will deepen our understanding of its biological function and help increase the understanding of its role in tumor regulation. Current findings suggest that CTRP6 and its downstream pathways may become drug targets for tumor therapy.

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Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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