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

AIMIN ZHANG[1], MOWEI KONG[2], XIUYUN ZHANG[1] and ZHENYING PEI[2]

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

Received June 27, 2022; Accepted September 6, 2022

DOI: 10.3892/ol.2022.13511

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.

Contents

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, C1q, 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

Correspondence to: Mr. Mowei Kong, Department of Cardiology, Guiqian International General Hospital, 1 Dongfeng Avenue, Wudang, Guiyang, Guizhou 550018, P.R. China
E-mail: 1600181272@qq.com

Key words: C1qTNF-related protein 6, colon cancer, gastric cancer, protein kinase B

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

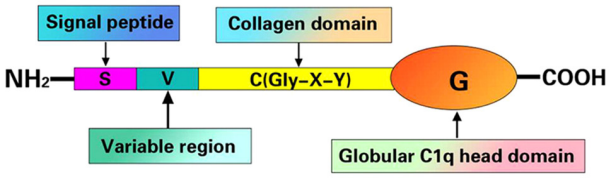

Figure 1. Schematic structure of complement Clq/TNF proteins.

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).

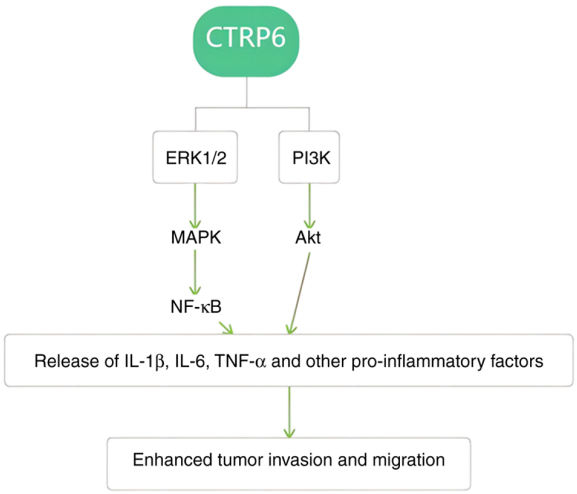

Figure 2. CTRP6 enhances tumor invasion and migration through the activation of the MAPK and Akt pathways. CTRP6, C1qTNF-related protein 6.

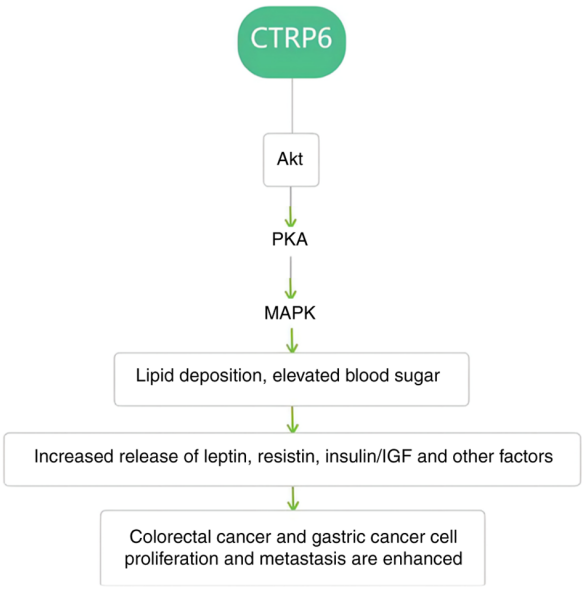

Figure 3. CTRP6 enhances tumor cell proliferation and metastasis by regulating glycolipid metabolism through the activation of the Akt/PKA/MAPK pathway. PKA, protein kinase A; IGF, insulin-like growth factor; C1qTNF-related protein 6.

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 chemoattractant 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.

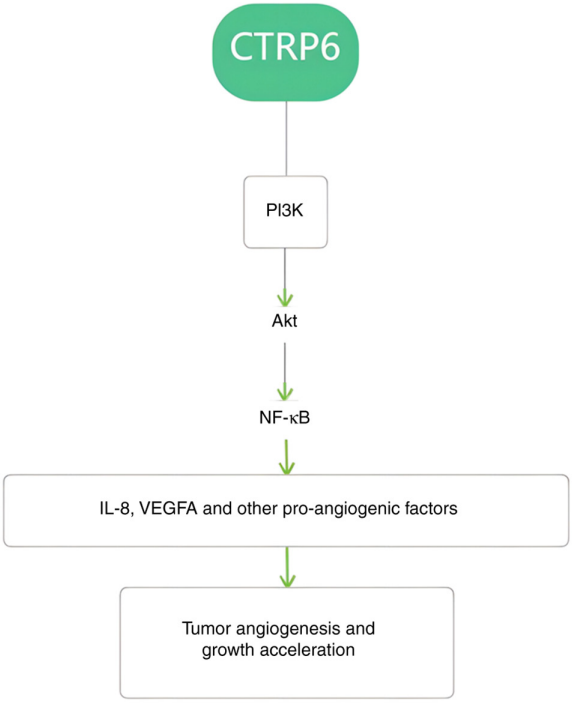

Figure 4. CTRP6 regulates tumor angiogenesis through the activation of the PI3K/Akt pathway. C1qTNF-related protein 6.

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-1α/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/Ak/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).

Table I. Review of the underlying mechanisms of C1qTNF-related protein 6 in digestive tract tumors.

Cancer type	Related signaling pathways	Proinflammatory function	Glycolipid metabolism	Angiogenesis	(Refs.)
Colorectal	PI3K/Akt, MAPK/ERK1/2/NF-κB, AMPK	Activation of the PI3K/Akt and MAPK/ERK1/2/NF-κB pathways releases inflammatory factors such as IL-1β, IL-6 and TNF-α	Activation of Akt/PKA/MAPK to release lepokines such as leptin, estrogen and resistin	Activation of the PI3K/Ak/NF-κB pro-angiogenic factor, IL-8 and VEGFA	(26,33,37-39,47,49,55,58,59)
Gastric	PI3K/Akt, Raf/MAPK, Akt/IL-6/STAT3 or MAPK/IL-6/STAT3/AMPK	PI3K/Akt mediates fibroblast invasion in gastric cancer and is enhanced by IL-8. Mediation of the MAPK pathway to promote IL-6 and IL-1β release	Activation of Akt/PKA/MAPK to release chemokines such as SDF-1	Activation of Akt/IL-6/STAT3 or MAPK/IL-6/STAT3 promotes angiogenesis	(27,28,34-36,46,48,54)
Liver	PI3K/Akt/NF-κB, MAPK/ERK1/2/NF-κB, AMPK	Activation of the MAPK pathway promotes IL-1β, IL-6 and TNF-α release	-	Activation of the PI3K/Ak/NF-κB pro-angiogenic factor, IL-8 and VEGFA	(6,29,39,56,61)

AMPK, AMP-activated protein kinase; PKA, protein kinase A; SDF-1, stromal cell-derived factor 1.

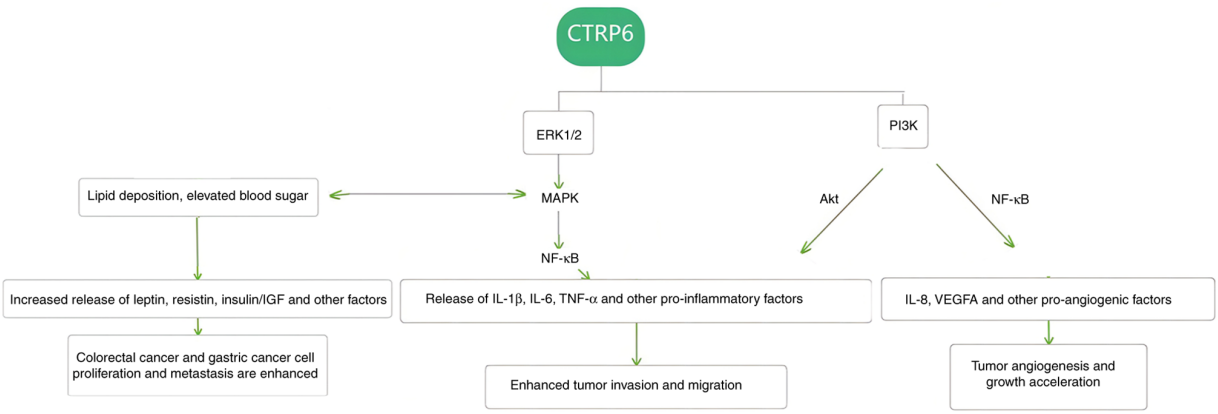

Figure 5. Summary of CTRP6 pathways regulating digestive system tumors. IGF, insulin-like growth factor; C1qTNF-related protein 6.

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.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

MK wrote the manuscript, and AZ, XZ and ZP reviewed and revised the manuscript. All authors approved the final version of this manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang CL, Wu LL and Li L: Research progress of complement-C1q/tumor necrosis factor-related protein 3. Sheng Li Xue Bao 69: 666-676, 2017.
2. Schäffler A and Buechler C: CTRP family: Linking immunity to metabolism. Trends Endocrinol Metab 23: 194-204, 2012.
3. Han M, Wang B, Zhu M and Zhang Y: C1QTNF6 as a novel biomarker regulates cellular behaviors in A549 cells and exacerbates the outcome of lung adenocarcinoma patients. In Vitro Cell Dev Biol Anim 55: 614-621, 2019.
4. Lin W, Chen X, Chen T, Liu J, Ye Y, Chen L, Qiu X, Chia-Hsien Cheng J, Zhang L, Wu J and Qiu S: C1QTNF6 as a novel diagnostic and prognostic biomarker for clear cell renal cell carcinoma. DNA Cell Biol 39: 1000-1011, 2020.
5. Wang L, Liu Z, Duan L, Ma B and Sun Z: C1q tumor necrosis factor-related protein 6 (CTRP6) inhibits the proliferation and migration of ovarian cancer cells. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 31: 1664-1668, 2015 (In Chinese).
6. Wan X, Zheng C and Dong L: Inhibition of CTRP6 prevented survival and migration in hepatocellular carcinoma through inactivating the AKT signaling pathway. J Cell Biochem 120: 17059-17066, 2019.
7. Qu HX, Cui L, Meng XY, Wang ZJ, Cui YX, Yu YP, Wang D and Jiang XJ: C1QTNF6 is overexpressed in gastric carcinoma and contributes to the proliferation and migration of gastric carcinoma cells. Int J Mol Med 43: 621-629, 2019.
8. Takeuchi T, Adachi Y and Nagayama T: Expression of a secretory protein C1qTNF6, a C1qTNF family member, in hepatocellular carcinoma. Anal Cell Pathol (Amst) 34: 113-121, 2011.
9. Kishore U, Gaboriaud C, Waters P, Shrive AK, Greenhough TJ, Reid KB, Sim RB and Arlaud GJ: C1q and tumor necrosis factor superfamily: Modularity and versatility. Trends Immunol 25: 551-561, 2004.
10. Wong GW, Krawczyk SA, Kitidis-Mitrokostas C, Revett T, Gimeno R and Lodish HF: Molecular, biochemical and functional characterizations of C1q/TNF family members: Adipose-tissue-selective expression patterns, regulation by PPAR-gamma agonist, cysteine-mediated oligomerizations, combinatorial associations and metabolic functions. Biochem J 416: 161-177, 2008.
11. Kim MJ, Lee W, Park EJ and Park SY: C1qTNF-related protein-6 increases the expression of interleukin-10 in macrophages. Mol Cells 30: 59-64, 2010.
12. Wong GW, Wang J, Hug C, Tsao TS and Lodish HF: A family of Acrp30/adiponectin structural and functional paralogs. Proc Natl Acad Sci USA 101: 10302-10307, 2004.
13. Kong M, Gao Y, Guo X, Xie Y and Yu Y: Role of the CTRP family in tumor development and progression. Oncol Lett 22: 723, 2021.
14. Chen L and Su G: Identification of CTRP1 as a prognostic biomarker and oncogene in human glioblastoma. Biomed Res Int 2019: 2582416, 2019.
15. Maeda T, Jikko A, Abe M, Yokohama-Tamaki T, Akiyama H, Furukawa S, Takigawa M and Wakisaka S: Cartducin, a paralog of Acrp30/adiponectin, is induced during chondrogenic differentiation and promotes proliferation of chondrogenic precursors and chondrocytes. J Cell Physiol 206: 537-544, 2006.
16. Akiyama H, Furukawa S, Wakisaka S and Maeda T: CTRP3/cartducin promotes proliferation and migration of endothelial cells. Mol Cell Biochem 304: 243-248, 2007.
17. Gao J, Gu G, Lu L and Wang X: Research progress of C1q tumor necrosis factor-related protein 4. International Journal of Cardiovascular Diseases 99-101, 2016.
18. Thanasupawat T, Glogowska A, Burg M, Wong GW, Hoang-Vu C, Hombach-Klonisch S and Klonisch T: RXFP1 is targeted by complement C1q tumor necrosis factor-related factor 8 in brain cancer. Front Endocrinol (Lausanne) 6: 127, 2015.
19. Hano K, Hatano K, Saigo C, Kito Y, Shibata T and Takeuchi T: An adiponectin paralog protein, CTRP6 decreased the proliferation and invasion activity of oral squamous cell carcinoma cells: Possible interaction with laminin receptor pathway. Mol Biol Rep 46: 4967-4973, 2019.
20. Gou J, Kang S, Qu H and Cui Y: Expression of complement C1q/tumor necrosis factor-related protein 6 in colon cancer. Journal of Gastroenterology and Hepatology 28: 313-316, 2019.
21. Kirketerp-Møller N, Bayarri-Olmos R, Krogfelt KA and Garred P: C1q/TNF-Related protein 6 is a pattern recognition molecule that recruits collectin-11 from the complement system to ligands. J Immunol 204: 1598-1606, 2020.
22. Lei X, Seldin MM, Little HC, Choy N, Klonisch T and Wong GW: C1q/TNF-related protein 6 (CTRP6) links obesity to adipose tissue inflammation and insulin resistance. J Biol Chem 292: 14836-14850, 2017.
23. Xu E, Yin C, Yi X and Liu Y: Knockdown of CTRP6 inhibits high glucose-induced oxidative stress, inflammation and extracellular matrix accumulation in mesangial cells through regulating the Akt/NF-kB pathway. Clin Exp Pharmacol Physiol 47: 1203-1211, 2020.

24. Li Y, Sun J, Gu L and Gao X: Protective effect of CTRP6 on cerebral ischemia/reperfusion injury by attenuating inflammation, oxidative stress and apoptosis in PC12 cells. Mol Med Rep 22: 344-352, 2020.
25. Altomare DA and Testa JR: Perturbations of the AKT signaling pathway in human cancer. Oncogene 24: 7455-7464, 2005.
26. Pintha K, Chaiwangyen W, Yodkeeree S, Suttajit M and Tantipaiboonwong P: Suppressive effects of rosmarinic acid rich fraction from perilla on oxidative stress, inflammation and metastasis ability in A549 cells exposed to PM via C-Jun, P-65-Nf-kb and Akt signaling pathways. Biomolecules 11: 1090, 2021.
27. Bou Malhab LJ and Abdel-Rahman WM: Obesity and inflammation: Colorectal cancer engines. Curr Mol Pharmacol 15: 620-646, 2022.
28. Liu X, Yao L, Qu J, Liu L, Lu N, Wang J and Zhang J: Cancer-associated fibroblast infiltration in gastric cancer: The discrepancy in subtypes pathways and immunosuppression. J Transl Med 19: 325, 2021.
29. Zhai J, Shen J, Xie G, Wu J, He M, Gao L, Zhang Y, Yao X and Shen L: Cancer-associated fibroblasts-derived IL-8 mediates resistance to cisplatin in human gastric cancer. Cancer Lett 454: 37-43, 2019.
30. Chi X, Liu Z, Wei W, Hu X, Wang Y, Wang H and Xu B: Selenium-rich royal jelly inhibits hepatocellular carcinoma through PI3K/AKT and VEGF pathways in H22 tumor-bearing mice. Food Funct 12: 9111-9127, 2021.
31. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y and Li Y: Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 6: 263, 2021.
32. Li Z, Chi H, Zhu W, Yang G, Song J, Mo L, Zhang Y, Deng Y, Xu F, Yang J, *et al*: Cadmium induces renal inflammation by activating the NLRP3 inflammasome through ROS/MAPK/NF-kB pathway in vitro and in vivo. Arch Toxicol 95: 3497-3513, 2021.
33. Eyre S, Hinks A, Bowes J, Flynn E, Martin P, Wilson AG, Morgan AW, Emery P, Steer S, Hocking LJ, *et al*: Overlapping genetic susceptibility variants between three autoimmune disorders: Rheumatoid arthritis, type 1 diabetes and coeliac disease. Arthritis Res Ther 12: R175, 2010.
34. Ray AL, Berggren KL, Restrepo Cruz S, Gan GN and Beswick EJ: Inhibition of MK2 suppresses IL-1β, IL-6, and TNF-α-dependent colorectal cancer growth. Int J Cancer 142: 1702-1711, 2018.
35. Yang T, Zhang J, Zhou J, Zhu M, Wang L and Yan L: Resveratrol inhibits Interleukin-6 induced invasion of human gastric cancer cells. Biomed Pharmacother 99: 766-773, 2018.
36. Xia Y, Khoi PN, Yoon HJ, Lian S, Joo YE, Chay KO, Kim KK and Jung YD: Piperine inhibits IL-1β-induced IL-6 expression by suppressing p38 MAPK and STAT3 activation in gastric cancer cells. Mol Cell Biochem 398: 147-156, 2015.
37. Shokrzadeh M, Mohammadpour A, Hoseini V, Abediankenari S, Ghassemi-Barghi N and Tabari YS: Serum cytokine OF IL-2, IL-10 and IL-12 levels in patients with stomach adenocarcinoma. Arq Gastroenterol 55: 385-389, 2018.
38. Mohamed EA, Bassiouny K, Alshambky AA and Khalil H: Anticancer properties of N,N-dibenzylasparagine as an Asparagine (Asp) analog, using colon cancer caco-2 cell line. Asian Pac J Cancer Prev 23: 2531-2540, 2022.
39. Neurath MF: IL-23 in inflammatory bowel diseases and colon cancer. Cytokine Growth Factor Rev 45: 1-8, 2019.
40. Kern L, Mittenbühler MJ, Vesting AJ, Ostermann AL, Wunderlich CM and Wunderlich FT: Obesity-Induced TNFα and IL-6 signaling: The missing link between obesity and inflammation-driven liver and colorectal cancers. Cancers (Basel) 11: 24, 2018.
41. Pu X and Chen D: Targeting adipokines in obesity-related tumors. Front Oncol 11: 685923, 2021.
42. Sadeghi A, Fadaei R, Moradi N, Fouani FZ, Roozbehkia M, Zandieh Z, Ansaripour S, Vatannejad A and Doustimotlagh AH: Circulating levels of C1q/TNF-α-related protein 6 (CTRP6) in polycystic ovary syndrome. IUBMB Life 72: 1449-1459, 2020.
43. Wu W, Xu K, Li M, Zhang J and Wang Y: MicroRNA-29b/29c targeting CTRP6 influences porcine adipogenesis via the AKT/PKA/MAPK Signalling pathway. Adipocyte 10: 264-274, 2021.
44. Wu W, Ji M, Xu K, Zhang D, Yin Y, Huang X, Peng Y and Zhang J: Knockdown of CTRP6 reduces the deposition of intramuscular and subcutaneous fat in pigs via different signaling pathways. Biochim Biophys Acta Mol Cell Biol Lipids 1865: 158729, 2020.
45. Wu WJ, Mo DL, Zhao CZ, Zhao C, Chen YS, Pang WJ and Yang GS: Knockdown of CTRP6 inhibits adipogenesis via lipogenic marker genes and Erk1/2 signalling pathway. Cell Biol Int 39: 554-562, 2015.
46. Wang M, Tang X, Li L, Liu D, Liu H, Zheng H, Deng W, Zhao X and Yang G: C1q/TNF-related protein-6 is associated with insulin resistance and the development of diabetes in Chinese population. Acta Diabetol 55: 1221-1229, 2018.
47. Chen HY, Yang MD, Chou YC, Ma YS, Peng SF, Liao CL, Chen PY, Hsia TC, Lien JC and Chen CH: Ouabain Suppresses Cell Migration and Invasion in Human Gastric Cancer AGS Cells Through the Inhibition of MMP Signaling Pathways. Anticancer Res 41: 4365-4375, 2021.
48. Kasprzak A: Insulin-Like Growth Factor 1 (IGF-1) Signaling in Glucose Metabolism in Colorectal Cancer. Int J Mol Sci 22: 6434, 2021.
49. Kruszyna Ł, Murawa D, Jagodziński PP, Oszkinis G and Krasiński Z: The expression and prognostic significance of VEGF and CXCR4 in gastric cancer: Correlation with Angiogenesis, Lymphangiogenesis and Progression. Curr Issues Mol Biol 44: 3075-3088, 2022.
50. Batzorig U, Wei PL, Wang W, Huang CY and Chang YJ: Glucose-Regulated Protein 94 Mediates the Proliferation and Metastasis through the Regulation of ETV1 and MAPK Pathway in Colorectal Cancer. Int J Med Sci 18: 2251-2261, 2021.
51. Wiśniewska W, Kopka M, Siemiątkowska K, Fudalej MM, Sobiborowicz A and Badowska-Kozakiewicz AM: The complexity of tumour angiogenesis based on recently described molecules. Contemp Oncol (Pozn) 25: 33-44, 2021.
52. Phung TL, Ziv K, Dabydeen D, Eyiah-Mensah G, Riveros M, Perruzzi C, Sun J, Monahan-Earley RA, Shiojima I, Nagy JA, *et al*: Pathological angiogenesis is induced by sustained Akt signaling and inhibited by rapamycin. Cancer Cell 10: 159-170, 2006.
53. Si Y, Fan W and Sun L: A review of the relationship between CTRP family and coronary artery disease. Curr Atheroscler Rep 22: 22, 2020.
54. Yamaguchi S, Shibata R, Ohashi K, Enomoto T, Ogawa H, Otaka N, Hiramatsu-Ito M, Masutomi T, Kawanishi H, Murohara T and Ouchi N: C1q/TNF-Related protein 9 promotes revascularization in response to ischemia via an eNOS-Dependent manner. Front Pharmacol 11: 1313, 2020.
55. He L, Wang W, Shi H, Jiang C, Yao H, Zhang Y, Qian W and Lin R: THBS4/integrin α2 axis mediates BM-MSCs to promote angiogenesis in gastric cancer associated with chronic Helicobacter pylori infection. Aging (Albany NY) 13: 19375-19396, 2021.
56. Auyeung KK and Ko JK: Angiogenesis and oxidative stress in metastatic tumor progression: Pathogenesis and novel therapeutic approach of colon cancer. Curr Pharm Des 23: 3952-3961, 2017.
57. Zhao Z, Gao J, Li C, Xu X, Hu Y and Huang S: Reactive oxygen species induce endothelial differentiation of liver cancer stem-like sphere cells through the activation of Akt/IKK signaling pathway. Oxid Med Cell Longev 2020: 1621687, 2020.
58. Lin JX, Weng XF, Xie XS, Lian NZ, Qiu SL, Wang JB, Lu J, Chen QY, Cao LL, Lin M, *et al*: CDK5RAP3 inhibits angiogenesis in gastric neuroendocrine carcinoma by modulating AKT/HIF-1α/VEGFA signaling. Cancer Cell Int 19: 282, 2019.
59. Chung SY, Chao TC and Su Y: The stemness-high human colorectal cancer cells promote angiogenesis by producing higher amounts of angiogenic cytokines via activation of the Egfr/Akt/Nf-kB pathway. Int J Mol Sci 22: 1355, 2021.
60. Li HY, Li M, Luo CC, Wang JQ and Zheng N: Lactoferrin exerts antitumor effects by inhibiting angiogenesis in a HT29 human colon tumor model. J Agric Food Chem 65: 10464-10472, 2017.
61. Wang L, Yi T, Kortylewski M, Pardoll DM, Zeng D and Yu H: IL-17 can promote tumor growth through an IL-6-Stat3 signaling pathway. J Exp Med 206: 1457-1464, 2009.
62. Carling D: AMPK. Curr Biol 14: R220, 2004.
63. Huang H, Wang L, Qian F, Chen X, Zhu H, Yang M, Zhang C, Chu M, Wang X and Huang X: Liraglutide via activation of AMP-Activated protein kinase-hypoxia inducible factor-1α-Heme Oxygenase-1 signaling promotes wound healing by preventing endothelial dysfunction in diabetic mice. Front Physiol 12: 660263, 2021.
64. Zulato E, Bergamo F, De Paoli A, Griguolo G, Esposito G, De Salvo GL, Mescoli C, Rugge M, Nardin M, Di Grazia L, *et al*: Prognostic significance of AMPK activation in advanced stage colorectal cancer treated with chemotherapy plus bevacizumab. Br J Cancer 111: 25-32, 2014.
65. Dai W, Wang Y, Yang T, Wang J, Wu W and Gu J: Downregulation of exosomal CLEC3B in hepatocellular carcinoma promotes metastasis and angiogenesis via AMPK and VEGF signals. Cell Commun Signal 17: 113, 2019.

66. Wang Y, Wang B, Guerram M, Sun L, Shi W, Tian C, Zhu X, Jiang Z and Zhang L: Deoxypodophyllotoxin suppresses tumor vasculature in HUVECs by promoting cytoskeleton remodeling through LKB1-AMPK dependent Rho A activatio. Oncotarget 6: 29497-29512, 2015.
67. Sen K, Banerjee S and Mandal M: Dual drug loaded liposome bearing apigenin and 5-Fluorouracil for synergistic therapeutic efficacy in colorectal cancer. Colloids Surf B Biointerfaces 180: 9-22, 2019.
68. Qu LH, Hong X, Zhang Y, Cong X, Xiang RL, Mei M, Su JZ, Wu LL and Yu GY: C1q/tumor necrosis factor-related protein-6 attenuates TNF-α-induced apoptosis in salivary acinar cells via AMPK/SIRT1-modulated miR-34a-5p expression. J Cell Physiol 236: 5785-5800, 2021.
69. Xie YH, Xiao Y, Huang Q, Hu XF, Gong ZC and Du J: Role of the CTRP6/AMPK pathway in kidney fibrosis through the promotion of fatty acid oxidation. Eur J Pharmacol 892: 173755, 2021.
70. Moon HS, Liu X, Nagel JM, Chamberland JP, Diakopoulos KN, Brinkoetter MT, Hatziapostolou M, Wu Y, Robson SC, Iliopoulos D and Mantzoros CS: Salutary effects of adiponectin on colon cancer: In vivo and in vitro studies in mice. Gut 62: 561-570, 2013.
71. Iwata Y, Yasufuku I, Saigo C, Kito Y, Takeuchi T and Yoshida K: Anti-fibrotic properties of an adiponectin paralog protein, C1q/TNF-related protein 6 (CTRP6), in diffuse gastric adenocarcinoma. J Cancer 12: 1161-1168, 2021.
72. Murayama MA, Kakuta S, Inoue A, Umeda N, Yonezawa T, Maruhashi T, Tateishi K, Ishigame H, Yabe R, Ikeda S, *et al*: CTRP6 is an endogenous complement regulator that can effectively treat induced arthritis. Nat Commun 6: 8483, 2015.
73. Lei H, Wu D, Wang JY, Li L, Zhang CL, Feng H, Fu FY and Wu LL: C1q/tumor necrosis factor-related protein-6 attenuates post-infarct cardiac fibrosis by targeting RhoA/MRTF-A pathway and inhibiting myofibroblast differentiation. Basic Res Cardiol 110: 35, 2015.
74. Dong X, Hu H, Fang Z, Cui J and Liu F: CTRP6 inhibits PDGF-BB-induced vascular smooth muscle cell proliferation and migration. Biomed Pharmacother 103: 844-850, 2018.
75. Li R, Du J, Yao Y, Yao G and Wang X: Adiponectin inhibits high glucose-induced angiogenesis via inhibiting autophagy in RF/6A cells. J Cell Physiol 234: 20566-20576, 2019.
76. Shah D, Sandhu K, Das P and Bhandari V: Adiponectin ameliorates hyperoxia-induced lung endothelial dysfunction and promotes angiogenesis in neonatal mice. Pediatr Res 91: 545-555, 2022.
77. Zhang N, Zhou J, Zhou Y and Guan F: MicroRNA-148a inhibits hepatocellular carcinoma cell growth via epithelial-to-mesenchymal transition and PI3K/AKT signaling pathways by targeting death receptor-5. Appl Biochem Biotechnol 194: 2731-2746, 2022.
78. Sp N, Kang DY, Jo ES, Lee JM and Jang KJ: Iron metabolism as a potential mechanism for inducing TRAIL-Mediated extrinsic apoptosis using methylsulfonylmethane in embryonic cancer stem cells. Cells 10: 2847, 2021.