The mechanism of CTRP6 in promoting cancer in digestive system tumors

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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 cells and plays a biological role in many aspects such as glucose and lipid metabolism and inflammation. Function. Recent studies have revealed the tumor-promoting effect of CTRP6 in gastric cancer, liver cancer, colorectal cancer and other gastrointestinal tumors, but there is no systematic discussion on the tumor-promoting mechanism of CTRP6. This article will review the role of CTRP6 in tumors of the digestive system and its possible mechanisms.

Introduction

Complement Clq/TNF-related protein 6 (CTRP6) is one of the CTRP family members homologous to adiponectin discovered in recent years. All CTRP members are secreted proteins, which are widely expressed in various tissues and cell types[1].In recent years, many studies have found that CTRP6 plays a role in fat metabolism, glucose metabolism, cardiovascular, inflammatory response, and autoimmunity [2]research of the role in cancer is an emerging area.Previous studies have revealed that overexpressed CTRP6 is associated with a poor prognosis in lung adenocarcinoma[3]and CTRP6 is able to serve as a marker for the prognosis and diagnosis of renal clear cell carcinoma[4].In contrast, studies have also revealed a protective role of CTRP6 in inhibiting cancer cell metastasis in ovarian cancer[5].From this we can argue that CTRP6 has both oncogenic and antitumor effects, which may be related to the type of cancer.But little is still known about the role of CTRP6 in digestive tumors.It was not until recent years with increasing attention that the relationship between CTRP6 and gastric cancer, liver cancer and colon cancer was gradually revealed[6,7,8].This paper reviews the pathophysiological role of CTRP6 in the development of tumorigenesis in the digestive system and explores possible mechanisms.

Ctrp6: General Characteristics

CTRP6 is found in serum and is a member of the CTRP protein family.CTRP6 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-like domain, and a carboxyl-terminal spherical domain homologous to the complement protein C1q, where the spherical domain is an important domain for its biological functions that stimulate p42/44MAPK phosphorylation[9-10].CTRP6 in humans 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].Alternatively, the study found that the globular domain of human CTRP6 shares up to 33% of the amino acids with adiponectin, suggesting that CTRP6 may have some similarities to the physiological effects of adiponectin[12].

Many of the proteins in the CTRP family are involved in tumor regulation.Previous studies have suggested that CTRP1 may promote human glioblastoma progression and predict a poor prognosis of GBM[13]CRPT3 reduces glucose levels by reducing hepatic gluconeogenesis and induces hepatic Akt activation, which subsequently stimulates the proliferation of chondrogenic cells[14-15]CTRP4 can act as a regulator of tumor-promoting inflammation[16]CTRP8 is involved in brain cancer formation[17].The regulatory role of CTRP6 in tumor biology is associated with multiple mechanisms and has different roles depending on tumor type.CTRP6 inhibits the proliferation and migration of epithelial ovarian cancer cells by blocking the IL-8/VEGF pathway[18].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 is capable of serving as a novel cancer diagnostic and prognostic biomarker for clear cell renal cell carcinoma[20].

The study of CTRP6 in digestive tumors is currently focused on, liver, colon and gastric cancer.Previous studies have shown that CTRP6 is significantly highly expressed in liver and colon cancer tissues compared to normal liver and colon tissues and may be used as early markers of the above two tumors for their diagnosis[8,21].CTRP6 is overexpressed in gastric cancer and is involved in the appreciation and migration of gastric cancer cells[7].The regulatory mechanisms of CTRP6 will be detailed in the following sections.

The Regulation Of Immunization-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[22-23].CTRP6 has a role in regulating the secretion of inflammatory factors and may have proinflammatory or inhibitory inflammatory effects depending on the site of action.It was shown that knockdown of CTRP6 resulted in a significant reduction in the production levels of tumor necrosis factor(TNF)-α, interleukin (IL) -1, and IL-6 in high glucose-induced glomerular mesilial cells[24].Overexpression of CTRP6 can activate PI3K/Akt signaling by inhibiting the rhoa/rock/PTen pathway and improve the inflammatory damage caused by cerebral ischemia / reperfusion[25].

Activation of the PI3K/Akt pathway is one of the common molecular mechanisms in human tumor development.PI3K/Akt signaling negatively regulates processes like cell growth, proliferation, glucose metabolism, and migration, and is thought to play a key regulatory role in tumor invasiveness[26].One of the specific mechanisms by which the PI3K/Akt pathway promotes tumorigenesis is the dysregulation of inflammatory mediators and immunity.It has been shown that rosemary acid subsequently prevents lung tumor invasion by reducing the production of inflammatory factors, such as IL-6, IL-8, TNF-α and COX-2, by inhibiting Akt phosphorylation[27].We speculate that this mechanism of action of the PI3K/Akt pathway is equally applicable during the pathogenesis of digestive tumors.Recent studies show 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[28].The PI3K/Akt

pathway also mediates the aggressive role of cancer-associated fibroblasts in gastric cancer, while IL-8 enhanced expression of PI3K/Akt pathway expression and increased chemoresistance to gastric cancer[29-30].In the study of hepatoma, royal plasma produced increased IL-2 levels and TNF-αcontent in serum by inhibiting PI3K expression and phosphorylation of AKT, thereby preventing and controlling hepatocarcinogenesis in mice[31].From the above studies, we can speculate that CTRP6 may promote tumorigenesis and progression in the digestive system by releasing inflammatory factors by activating the PI3K/Akt pathway.Results provide strong evidence for the above speculation in Wan et al[6] by inhibiting CTRP6 to block AKT signaling and in turn preventing the survival and migration of hepatocellular carcinoma.

It was previously shown that overexpressed CTRP6 enhances the proliferation, migration and invasion of lung adenocarcinoma cells by regulating the signaling pathway in which MAPK lies[3].The MAPK/NF-kB pathway is one of the common intersection pathways of various cellular signaling pathways, such as inflammation, stress, and is involved in cellular activity, including carcinogenesis[32].Activation of MAPK/NF-kB signaling enhances the secretion of IL-1β and IL-18 and leading to the development of renal inflammation[33].The study by Eyre et al[34] found that the globular domain of CTRP6 can stimulate the phosphorylation of MAPK/ERK1/2, and when treated with selective MAPK/ERK1/2 inhibitors, it will eliminate CTRP6-mediated IL-10 expression.The latest study reveal the fact 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, can effectively delay the progression in colorectal cancer[35].In gastric cancer, IL-6 promotes the growth and metastasis of gastric cancer, and resveratrol can prevent IL-6-induced gastric cancer metastasis by blocking Raf/MAPK signaling[36].Pepperine in turn inhibits IL-1β -induced IL-6 expression by inhibiting the MAPK and STAT3 pathways in gastric cancer cells[37].Other recent studies have also demonstrated the oncogenic role of inflammatory factors such as IL-1β and IL-6 in gastric cancer, colorectal cancer, and liver cancer[38，39，40，41].We believe that CTRP6 activation of the MAPK/ERK1/2/NF-kB 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 and development through the activation of the Akt pathway and regulating inflammatory factors in the MAPK pathway (Figure 1).

The Regulation Of Glycolipid Metabolism

Disorganized glucose and lipid metabolism are the two main processes that increase tumor risk and severity.Abnormal lipid metabolism leads to disturbances of adipokine secretion that are strongly associated with tumorigenesis and progression[42].Obesity due to abnormal lipid metabolism is an independent risk factor for tumorigenesis and development in a variety of breast, pancreatic, ovarian, and colorectal cancer[42].The role of CTRP6 in glycolipid metabolism has been extensively studied[43].Animal experiments show that CTRP6 can affect pig adipogenesis by AKT/PKA/MAPK signaling, while

knockdown of CTRP6 reduces muscle and subcutaneous fat deposition through different signaling pathways[44-45].Cellular experiments showed that knockdown of CTRP6 inhibited adipocytes' adipogenesis by adipogenesis marker genes and the MAPK/ERK1/2 signaling pathway[46].The above 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 glycouria[47].

MAPK is a key molecule in the regulation of bioenergy metabolism and is expressed in various metabolically related organs.In digestive system tumors, human gastric cancer cells and colorectal cancer are all regulated by the pathway where MAPK is located[48-49].In the process of adipose metabolism, one of the mechanisms by which obesity becomes a risk factor for rectal cancer is the metabolic disorders of adipokines, obesity increases the expression of leptin, estrogen, resistin, MIF, MCP-1 and insulin / IGF, decreased adiponectin expression levels will promote the progression of obesity-related tumors (e. g., breast cancer, pancreatic cancer, ovarian cancer and colorectal cancer), promote the proliferation, invasion and metastasis of tumor cells[28].And obesity-induced gastric cancer stimulates the chemotactic protein SDF-1 to specific receptors CXCR4 and CXCR7 to regulate cancer cell motility and angiogenic regeneration, a process mediated by the p38 MAPK pathway[50].The MAPK pathway remains important in the glucose metabolism of tumors.It was shown that knockdown of glucose regulatory protein 94 inhibited the ability of cancer cell proliferation and metastasis in colorectal cancer cells by inhibiting the levels of the MAPK pathway, including ERK/p-ERK, JNK/p-JNK and p38/p-p38 signaling[51].It can be speculated from the above 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 pathway (Figure 2), but direct evidence of CTRP6 tumor promotion through MAPK pathway activation is currently lacking.The following study may examine the effect of CTRP6 on cell metabolism by activating / blocking the pathway between colorectal cancer and gastric cancer cells.And the study of Xia et al [23] demonstrated that CTRP6 induces inflammatory factors by regulating glycan and lipid metabolism, which also provides a reference to the above view.

Promote New Blood Vessels

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[52].PI3K/Akt signaling is one of the classical pathways leading to increased vascular number and increased vascular permeability, achieving the purpose of revascularization by enabling the transformation of the vascular smooth muscle phenotype[53].In the CTRP family, various factors such as CTRP1, CTRP3, CTRPP5 can regulate inflammatory factors and glycolipid metabolism by activating pathways such as PI3K/Akt/eNOS, p38MAPK/NF-kB, and in turn regulate vascularization due to chronic inflammation[54].Recent studies have found that the ability of CTRP9 is correlated with AKT and AMPK pathway activation by promoting endothelial cell function and ischemia-induced revascularization[55].And we believe that the above development process is equally suitable for the role of CTRP6 in digestive tract tumors.Digestive tumors

such as gastric cancer, liver cancer and colorectal cancer are all regulated by the signaling pathway where Akt lies[56、57、58].The latest study confirms that the CDK5RAP3 gene improves patient prognosis by inhibiting tumor angiogenesis through downregulation of gastric neuroendocrine cancer AKT/HIF-1α/VEGFA signaling[59].In colorectal cancer, highly dry human colorectal cancer cells promote angiogenesis through activation of the angiogenic cytokines IL-8 and VEGFA produced by the Egfr/Akt/NF-kB pathway,and lactoferrinsuppresses colon cancer angiogenesis by regulating the PI3K/Erk1/2/Akt pathway[60-61].Moreover，Wang et al [62] found that IL-6 activates STAT3 to achieve the role of stimulating angiogenesis in gastric cancer, and in a previous discussion we have discussed the expression mechanism of CTRP6 promoting pro-inflammatory factors such as IL-6 through the PI3K/Akt pathway and the pathway where MAPK is located [29、30、36、37].Thus in gastric cancer, CTRP6 most likely achieves a role in promoting gastric cancer angiogenesis by activating the Akt/IL-6/STAT3 or MAPK/IL-6/STAT3 pathway.Currently, it has been demonstrated that CTRP6 promotes hepatoma angiogenesis and subsequently reduces HepG2 cell necrosis by regulating Akt signaling in HCC cells[63].It is reasonable to believe that CTRP6 regulates colorectal, liver cancer and other tumors by activation of proangiogenic substances such as PI3K/Ak/NF-kB (Figure 3).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[64-65].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[66、67、68].In colon cancer, the double-loaded liposomes of apigenin and 5-fluorouracil inhibit tumor angiogenesis by inhibiting AMPK phosphorylation in colorectal cancer [69].CTRP6 can activate the pathway of AMPK in various tissues and play different roles such as promoting cellular differentiation and antifibrosis[70-71].In colon cancer, CTRP6 was shown to be highly expressed, and its expression content was not correlated with patient age, sex, pathological type, etc[21].However, these evidence is not sufficient to derive the role of CTRP6 in colon cancer to promote tumor angiogenesis associated with activation of the AMPK pathway.In contrast, it has been suggested that adiponectin inhibits tumor angiogenesis by regulating the AMPK pathway in the colon cancer[72].Due to the similarity of CTRP6 to adiponectin structure, we can even speculate that CTRP6 may have an effect on inhibiting tumor angiogenesis[12].Regarding the above speculation, more research is needed to confirm it.

Other Views

Yoshinori [73] showed that overexpression of CTRP6 has an inhibitory effect on tumor stromal fibrosis in gastric cancer, whose development is thought to promote cancer progression and confer chemoresistant properties in malignant tissues.This suggests that CTRP6 may also function as an inhibitor of gastric cancer.However, after the addition of recombinant CTRP6 protein, the study did not change the proliferation rate and invasiveness of gastric cancer cells.Therefore, without the evidence of more research, we still tend to believe that CTRP6 plays a major tumor-promoting role in gastric cancer.

Murayama et al [74] found that the recombinant human CTRP6 protein was able to increase the expression of the anti-inflammatory factor IL-10 and inhibited CTRP6-mediated IL-10 expression after pretreatment with the selective ERK1/2 inhibitor U0126.It is thus inferred that CTRP6 may play an anti-inflammatory effect in the induction of IL-10 expression through the ERK1/2 pathway.It studies 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[75].This seems to contradict the speculation that CTRP6 promotes inflammatory factor release through the activation of the Akt pathway, and the MAPK pathway.But the current evidence is insufficient to prove which mechanism is dominant or coexisting in digestive tumors.

It was also found that the secretion levels of IL-8 in ovarian cancer were opposite to 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[18].CTRP6 inhibits PDGF-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[76].The above studies contradict studies where CTRP6 promotes tumor angiogenesis in HCC[63].We speculate that this contradiction may result from a different regulatory role of CTRP6 on blood vessels in different tissues because adiponectin similar to CTRP6 showed similar properties in recent studies[77-78].

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 normal tissues, and may influence the development of colon cancer by regulating glycolipid metabolism, inflammatory response and may serve as a marker for early screening of colon cancer[21,35,39].In HCC, CTRP6 is highly expressed and promotes the survival and migration of HCC cells through mechanisms such as promoting tumor angiogenesis[6,7].The production of the above mechanism is mainly realized by the activation of the Akt pathway and the MAPK pathway, summarized as (Table 1).Although CTRP6 may also regulate the above tumors by activation of the AMPK pathway[70-71]But there is not enough evidence to prove it.

The biological function of CTRP6 is complex and has received attention as a regulator of metabolism in past studies, while current studies remain less frequent in tumors.Continuing research into CTRP6 will deepen our understanding of its biological function and help increase its understanding of the tumor regulatory role.These current findings suggest that CTRP6 and its downstream pathways may become drug targets for tumor therapy, which brings a glimmer of dawn for the conquest of digestive tumors.

Tables

Table 1. Review of the underlying mechanisms of CTRP6 in digestive tract tumors

r	Related pathways	Proinflammatory function	Sugar and fat metabolism	Angiogenesis	Reference
ctal	PI3K/Akt MAPK/ERK1/2/NF-kB AMPK	Activation of the PI3K/Akt, MAPK/ERK1/2/NF-kB pathway 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-kB pro-angiogenic factor, Il-8, VEGFA, is release	28 35 39 40 41 49 51 57 60 61
c	PI3K/Akt Raf/MAPK Akt/IL-6/STAT3 or MAPK/IL-6/STAT3/AMPK	Regulation of PI3K/Akt mediated the invasive role of fibroblasts in gastric cancer, enhanced by IL-8; and mediating the MAPK pathway to promote IL-6, IL-1β release	Activate Akt/PKA/MAPK to release chemokines such as SDF-1	Activation of Akt/IL-6/STAT3 or MAPK/IL-6/STAT3 promotes angiogenesis	29 30 36 37 38 48 50 56
	PI3K/Ak/NF-kB MAPK/ERK1/2/NF-kB AMPK	Activation of the MAPK pathway promotes IL-1β, IL-6 and TNF-α release	-	Activation of the PI3K/Ak/NF-kB pro-angiogenic factor, Il-8, VEGFA, is release	6 31 41 58 63

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Ethical approval and consent to participate

This is an review research.The Research Ethics Committee has confirmed that no ethical approval is required.

Patient consent for publication

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Informed consent

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Figures

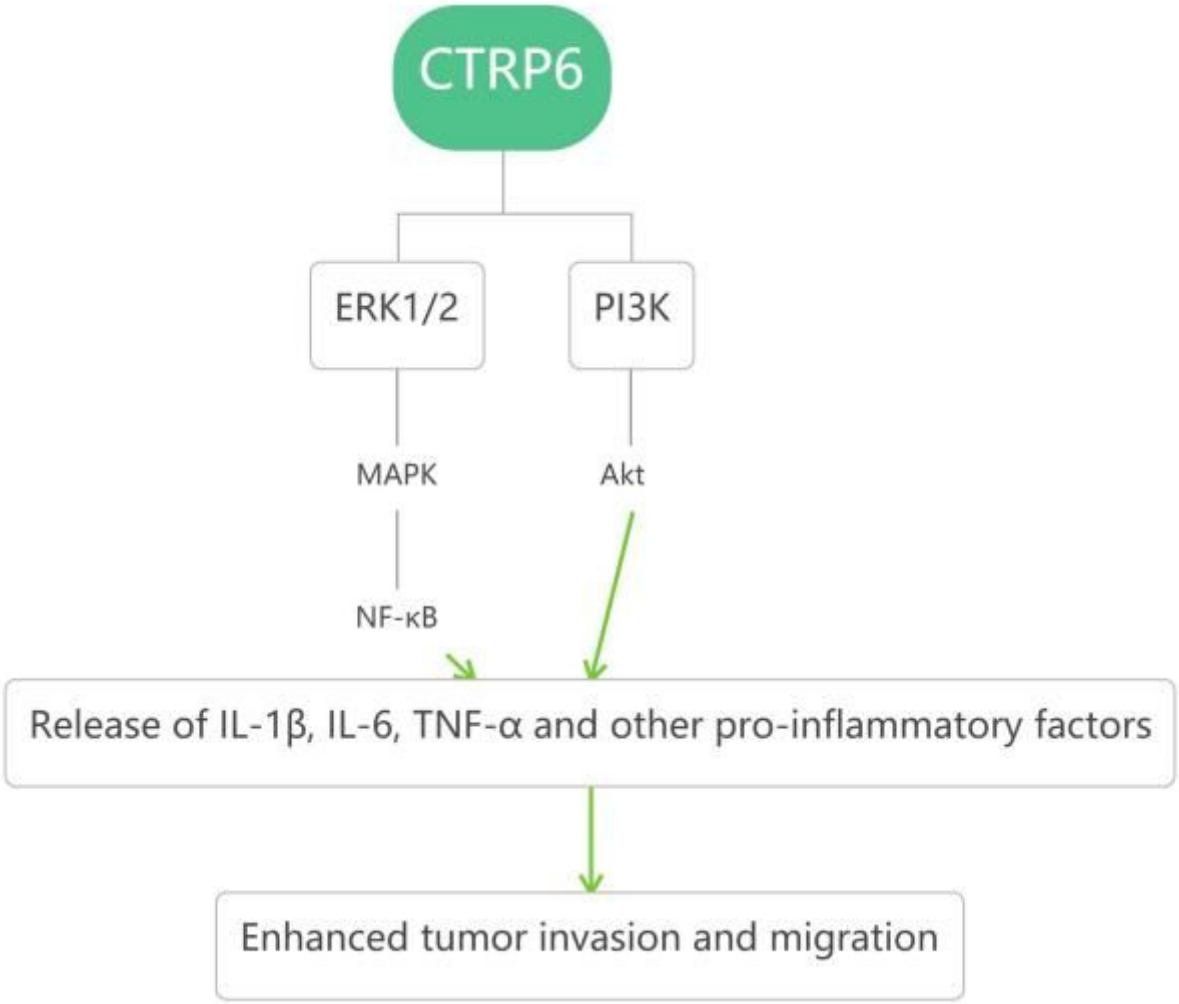

Figure 1

CTRP6 enhances tumor invasion and migration enhancement through the activation of the pathway where MAPK and Akt are located

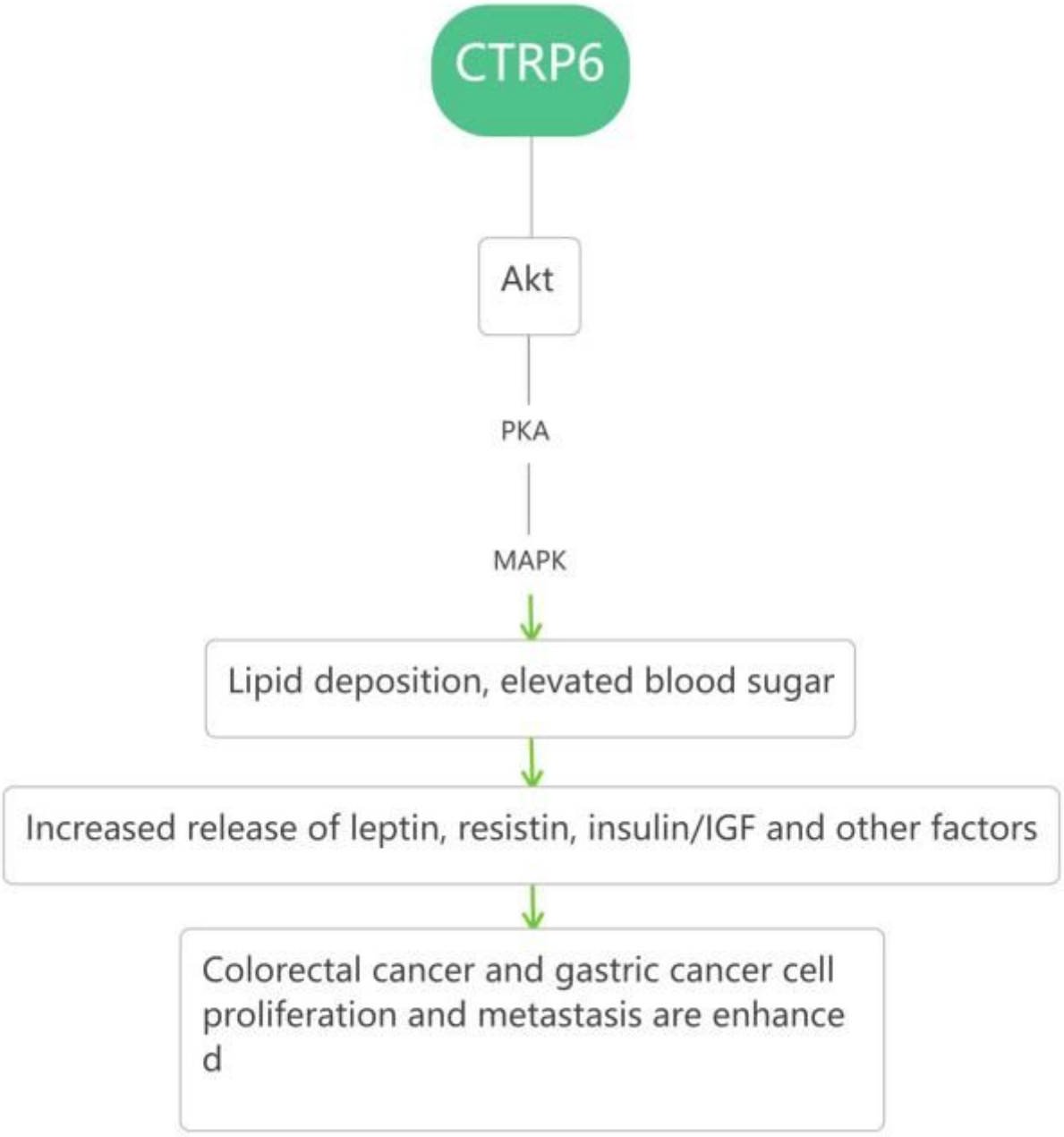

Figure 2

CTRP6 enhances tumor cell proliferation and metastasis by regulating glycoladipid metabolism by activating the AKT/PKA/MAPK pathway

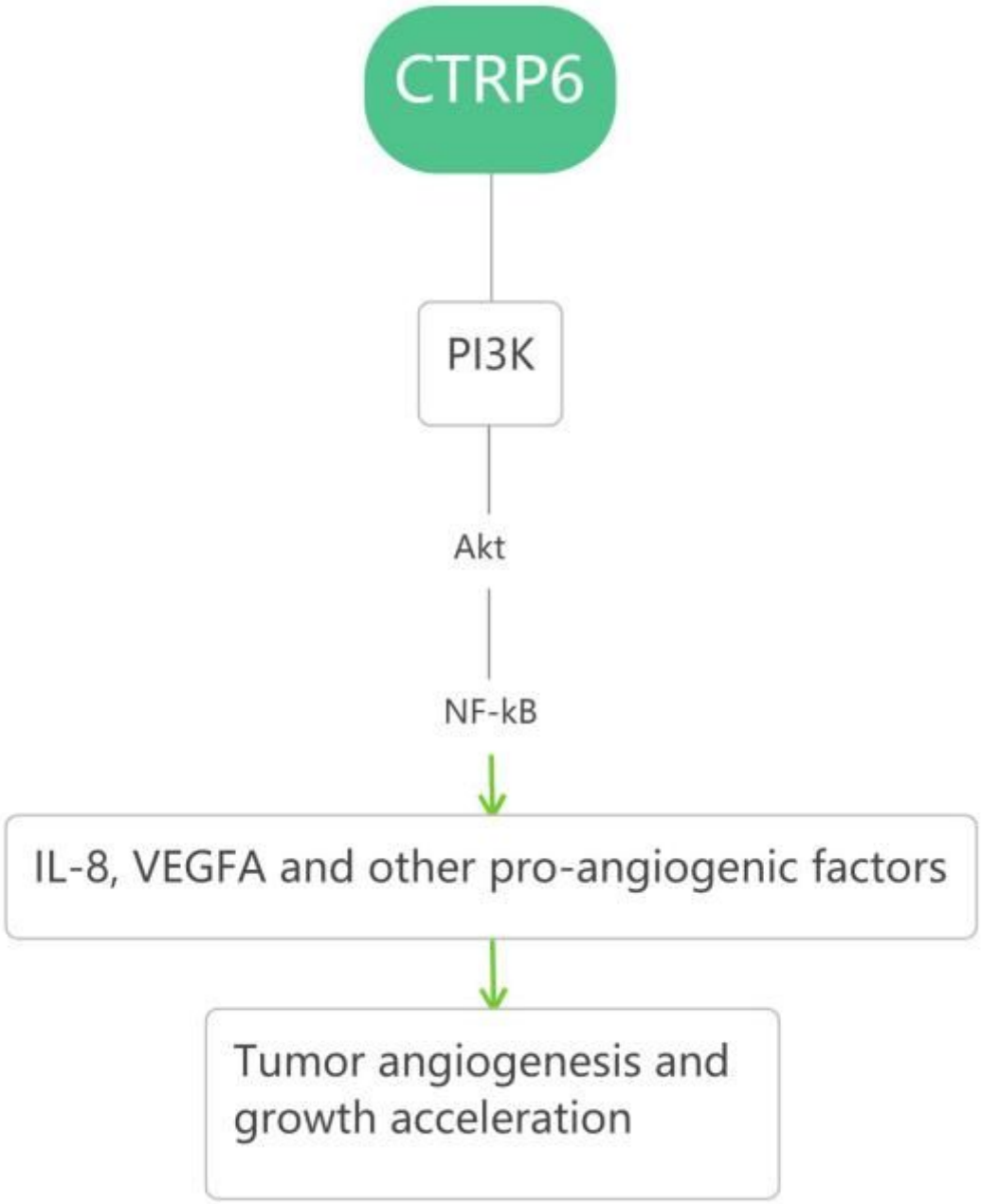

Figure 3

CTRP6 regulates tumor angiogenesis through the activation of the PI3K/Akt pathway