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EDITORIAL

Tumor-related factor complement Clq/TNF-related protein 6 affects the development of digestive system tumors through the phosphatidylinositol 3-kinase pathway

Mo-Wei Kong, Xin-Rui Li, Yu Gao, Ting-Fang Yang

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Abstract

In this editorial, we review the work of Razali *et al* published in *World J Gastroenterology*, with a particular focus on the effect of rs10889677 variation in the phosphatidylinositol 3-kinase (PI3K) pathway and buparlisib on colitis-associated cancer. The role of PI3K in promoting cancer progression has been widely recognized, as it is involved in regulating the survival, differentiation, and proliferation of cancer cells. The complement Clq/TNF-related protein 6 (CTRP6) is a newer tumor-associated factor. Recent studies have revealed the pro-tumor effect of CTRP6 in gastric cancer, hepatocellular carcinoma, colorectal cancer, and other gastrointestinal tumors through the PI3K pathway. This article attempts to reveal the mechanism through which the CTRP6 affects the development of digestive system tumors through the PI3K pathway by summarizing recent research.

Key Words: Phosphatidylinositol 3-kinase; Complement Clq/TNF-related protein 6; Gastric cancer; Colorectal cancer; Tumor-related factor

Core Tip: The complement Clq/TNF-related protein 6 (CTRP6), a member of the CTRP family, is increasingly recognized for its role in the development of digestive system tumors, particularly through its interaction with the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. This pathway is a key regulator of cell growth, survival, and metabolism, and its dysregulation is a common feature in various cancers. In gastric, colorectal, and liver cancers, CTRP6 has been shown to promote tumor progression by activating the PI3K/Akt pathway, leading to increased cell proliferation, migration, and angiogenesis. Targeting CTRP6 or its downstream signaling components could offer a novel therapeutic strategy for these malignancies. Further research is essential to fully understand the role of CTRP6 in tumorigenesis and to develop targeted therapies that exploit its influence on the PI3K/Akt pathway.

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INTRODUCTION

The complement C1q/TNF-related protein 6 (CTRP6) is a multifunctional protein that has been increasingly implicated in the pathogenesis of various digestive system tumors, including gastric, colorectal, and liver cancers[1]. The development of these tumors is a complex process influenced by genetic, environmental, and metabolic factors, with the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway emerging as a central regulator in this context[2].

The PI3K/Akt pathway is a critical signaling cascade that controls cell growth, survival, and metabolism[3]. Its dysregulation is a hallmark of many cancers, leading to uncontrolled cell proliferation and resistance to apoptosis[4,5]. CTRP6, through its ability to modulate this pathway, has been identified as a potential mediator of tumorigenesis in the digestive system.

In gastric cancer, CTRP6 has been associated with tumor growth, migration, and invasion, with its overexpression linked to the activation of the PI3K/Akt pathway[6]. This activation results in the release of pro-inflammatory cytokines, which further promote tumor progression. Similarly, in colorectal cancer, CTRP6's role in glycolipid metabolism and inflammation is intricately linked to the PI3K/Akt pathway, influencing angiogenesis and tumor growth[7]. In liver cancer, CTRP6's association with tumor angiogenesis and cell survival is also mediated by this pathway[8]. This review aims to provide an overview of the current understanding of CTRP6's role in digestive system tumors, with a particular focus on its interaction with the PI3K/Akt pathway.

CTRP6 AND THE PI3K PATHWAY

CTRP6's role in tumorigenesis is multifaceted, with evidence suggesting that it can both promote and inhibit tumor growth, depending on the cancer type[9]. In the context of digestive system tumors, such as gastric and liver cancers, CTRP6 has been shown to be overexpressed and is implicated in tumor cell proliferation, migration, and angiogenesis [10]. The mechanistic link between CTRP6 and the PI3K pathway involves several key processes. CTRP6 can activate the PI3K/Akt pathway by binding to specific receptors on tumor cells, leading to the phosphorylation of Akt, a pivotal downstream effector[11]. This activation promotes cell survival signals, inhibits apoptosis, and enhances cell proliferation, all of which contribute to tumor growth and progression[11]. Furthermore, CTRP6's influence on the PI3K pathway is also seen in its ability to regulate inflammation and glycolipid metabolism, both of which are closely associated with tumor development. Inflammatory cytokines, such as IL-6, can activate the PI3K/Akt pathway, and CTRP6 may facilitate this process by promoting the secretion of these cytokines[12]. Additionally, CTRP6's role in glycolipid metabolism can indirectly affect the availability of substrates for the PI3K pathway, further fueling tumor growth[2]. In the realm of angiogenesis, a critical process for tumor growth and metastasis, CTRP6 has been shown to promote the formation of new blood vessels through the activation of proangiogenic factors, such as VEGF, *via* the PI3K/Akt pathway[13].

In conclusion, CTRP6's impact on the PI3K pathway is a complex and multifaceted process that contributes to the progression of digestive system tumors. Its ability to activate the PI3K/Akt pathway, regulate inflammation and glycolipid metabolism, and promote angiogenesis underscores its potential as a therapeutic target. Targeting the CTRP6-PI3K axis could offer a novel approach to inhibit tumor growth and metastasis, offering new hope for the treatment of these aggressive malignancies.

CTRP6 IN GASTRIC CANCER

In gastric cancer, CTRP6 overexpression has been associated with increased PI3K/Akt signaling, which is a hallmark of cancer progression[14]. The activation of this pathway by CTRP6 Leads to the phosphorylation of Akt, a key mediator of

cell survival and proliferation[15]. This, in turn, promotes cell cycle progression, inhibits apoptosis, and enhances the survival of gastric cancer cells, contributing to tumor growth.

CTRP6's role in gastric cancer is further complicated by its ability to modulate the tumor microenvironment. It has been shown to influence the secretion of pro-inflammatory cytokines, such as IL-6, which can activate the PI3K/Akt pathway. This inflammatory milieu not only supports the survival of cancer cells but also facilitates angiogenesis, the formation of new blood vessels that supply nutrients to the tumor, thus promoting its growth and metastasis[15,16]. Moreover, CTRP6's interaction with the PI3K pathway may also affect the epithelial-to-mesenchymal transition, a process that enables cancer cells to acquire a more invasive and migratory phenotype[17]. This transition is crucial for the spread of cancer cells from the primary tumor site to distant organs, a key step in the metastatic process. The PI3K/Akt pathway's role in gastric cancer is further highlighted by its involvement in chemoresistance. CTRP6-mediated activation of this pathway can lead to increased resistance to chemotherapy, making treatment more challenging and reducing the effectiveness of current cancer therapies[18].

In conclusion, CTRP6's influence on the PI3K pathway in gastric cancer is a multifaceted mechanism that promotes tumor growth, invasion, and chemoresistance. Targeting the CTRP6-PI3K axis could provide a novel therapeutic strategy for gastric cancer, potentially leading to more effective treatments and improved patient outcomes.

CTRP6 IN COLORECTAL CANCER

The role of CTRP6 in colorectal cancer is similar to its role in gastric cancer. CTRP6's role in colorectal cancer is further amplified by its ability to regulate glycolipid metabolism, a process that is often deregulated in cancer cells[19]. The PI3K/Akt pathway is known to influence glucose and lipid metabolism, providing the necessary energy and building blocks for tumor cells[10]. CTRP6's modulation of these metabolic pathways can indirectly enhance the activity of the PI3K pathway, further fueling colorectal cancer development[20]. In addition, CTRP6's influence on the PI3K pathway may also contribute to the tumor's inflammatory microenvironment. Inflammatory cytokines, such as IL-6 and TNF-α, can activate the PI3K/Akt pathway, and CTRP6 may facilitate this process by promoting the secretion of these cytokines[12]. This inflammatory milieu can further enhance PI3K/Akt signaling, creating a positive feedback loop that supports colorectal cancer progression[21].

In conclusion, CTRP6's role in colorectal cancer is intricately linked to the PI3K pathway, influencing cell survival, metabolism, inflammation, and angiogenesis. Targeting the CTRP6-PI3K axis could offer a novel therapeutic strategy for colorectal cancer, potentially leading to more effective treatments and improved patient outcomes. Further research is warranted to elucidate the precise mechanisms by which CTRP6 modulates the PI3K pathway in colorectal cancer and to develop targeted therapies that can exploit these interactions.

CONCLUSION

CTRP6's role in the development of digestive system tumors, particularly through its interaction with the PI3K pathway, underscores its potential as a novel therapeutic target. Targeting CTRP6 or its downstream signaling pathways could provide a new avenue for the treatment of these malignancies. Further research is needed to fully understand the mechanisms by which CTRP6 contributes to tumorigenesis and to develop targeted therapies that exploit its role in the PI3K pathway.

FOOTNOTES

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