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LETTER TO THE EDITOR

Crosslink among cyclin-dependent kinase 9, ATP binding cassette transporter G2 and Beclin 1 in colorectal cancer

Zhong-Bao Shao, Ke He, Yu-Bin Su, Zhi Shi

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Abstract

Colorectal cancer (CRC) ranks third in the number of cancers mainly because of the inability to diagnose it at an early stage. The pathogenesis of CRC is complicated, which is the result of the complex interaction of multiple genetic and environmental factors. Currently, one of the main treatments for CRC is chemotherapy. But the primary cause of CRC treatment failure is drug resistance. The expression of cyclin-dependent kinase 9 (CDK9) was correlated with elevated autophagy levels in colon cancer, and high expression of CDK9 indicates a poor prognosis in CRC. The incidence of autophagy and the expressions of Beclin 1 and ATP binding cassette transporter G2 are different in left and right colon cancer, and autophagy may be involved in the occurrence of chemotherapy resistance. In this article, the roles of CDK9, ATP binding cassette transporter G2 and Beclin 1 in CRC were elucidated, emphasizing the linkages among them and providing potential therapeutic targets of CRC.

Key Words: Cyclin-dependent kinase 9; ATP binding cassette transporter G2; Beclin 1; Colorectal cancer; Chemotherapy

Core Tip: The expression of cyclin-dependent kinase 9 (CDK9) was correlated with elevated autophagy levels in colon cancer, and high expression of CDK9 indicates a poor prognosis in colorectal cancer (CRC). The incidence of autophagy and the expressions of Beclin 1 and ATP binding cassette transporter G2 were different between left and right colon cancer. The roles of CDK9, ATP binding cassette transporter G2 and Beclin 1 in CRC were clarified, underlining the linkages among them and providing potential therapeutic targets of CRC.

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TO THE EDITOR

A clinical and translational study by Zheng *et al*[1], reported that the rate of autophagy and the expressions of Beclin 1 (BECN1) and ATP binding cassette transporter G2 (ABCG2) differed between left and right colon cancer tissues. Autophagy may be associated with chemotherapy resistance in colorectal cancer (CRC) patients. And cyclin dependent kinase 9 (CDK9) is highly expressed in CRC that can be used as a prognostic marker in CRC patients. This research could provide a theoretical basis for the exploration of CDK9 and autophagy inhibitors in combination therapy to enhance tumor cell sensitivity to chemotherapy.

CRC ranks third in the number of cancers mainly owing to the inability to diagnose it at an early stage[2]. The pathogenesis of CRC is complexed, which is the result of the complex interaction of a lot of genetic and environmental factors[3]. At present, one of the main treatments for CRC is chemotherapy. But the primary cause of CRC treatment failure is drug resistance[4]. Consequently, elucidating research into molecular mechanisms of drug resistance can be beneficial to develop new diagnostic or therapeutic strategies to overcome the challenges in the treatment of CRC.

THE CROSSLINK AMONG CDK9, ABCG2 AND BECN1 IN CRC

ABCG2, as an important member of the ATP-binding cassette transmembrane transporter superfamily, plays a significant role in cancer multidrug resistance[5]. Several agents have been reported to be able to reverse ABCG2-mediated multidrug resistance in CRC cells by inhibiting the transporter activity of ABCG2[6,7]. Now, we are interested in the authors' new finding that the expression level of ABCG2 in right colon cancer was higher than that in paracarcinoma tissue, but the expression level of ABCG2 was not significantly different between left colon cancer and paracarcinoma tissue. These findings might be useful for gaining insight into the pathogenesis of left and right colon cancer and improving treatment strategies for CRC therapy.

Autophagy refers to a catabolic process in which macromolecular substances such as misfolded proteins and damaged organelles are transported to lysosomes for degradation[8]. It can prevent genome damage and induce cancer cell death. And on the other hand, autophagy is a pro-oncogenic mechanism that provides drug resistance to cancer cells and promotes cancer cell growth[9]. The sensitivity of cancer cells to chemotherapeutic drugs can be restored by the use of autophagy inhibitors, such as chloroquine, or by the knockdown of autophagy-related proteins, including BECN1, autophagy-related gene 7, and autophagy-related gene 10[10]. Currently, autophagy inhibitors are promising for cancer treatment. Some small molecule autophagy inhibitors have been discovered according to the autophagy process[10]. Recent research has revealed FDW028 (a novel FUT8 inhibitor) exhibits potent anti CRC effects by facilitating lysosomal degradation of CD276 through the chaperone-mediated autophagy pathway[11]. Erianin (a natural product) can induce autophagy-dependent ferroptosis and inhibit tumor growth and metastasis in $KRAS^{G13D}$ CRC[12]. Strigolactones are endogenous plant hormones that can act as a potential autophagy inhibitor by blocking autophagosome-lysosome fusion in HCT116 CRC cells[13]. BECN1, a key autophagy regulator, serves as a potential therapeutic target and is associated with chemotherapeutic resistance in cancers[14]. Previous studies have demonstrated that JAK2-depended BECN1 phosphorylation may confer chemotherapy resistance in CRC[15]. Based on Zheng *et al*'s research, the expression of BECN1 may be different between left and right colon cancer[1]. This research provided new ideas for further investigation on the drug resistance in CRC.

CDK family, a large class of serine/threonine protein kinases, plays a vital role in cell cycle progression and gene transcription regulation. There have been some reports on CDK inhibitors in the treatment of CRC. Zeng *et al*[16] proposed that CDK1 serves as a potential target for oxaliplatin-resistant CRC treatment. Lee *et al*[17] reported that the combination of palbociclib (CDK 4/6 inhibitor) and gedatolisib (phosphatidylinositol 3-kinase/mammalian target of

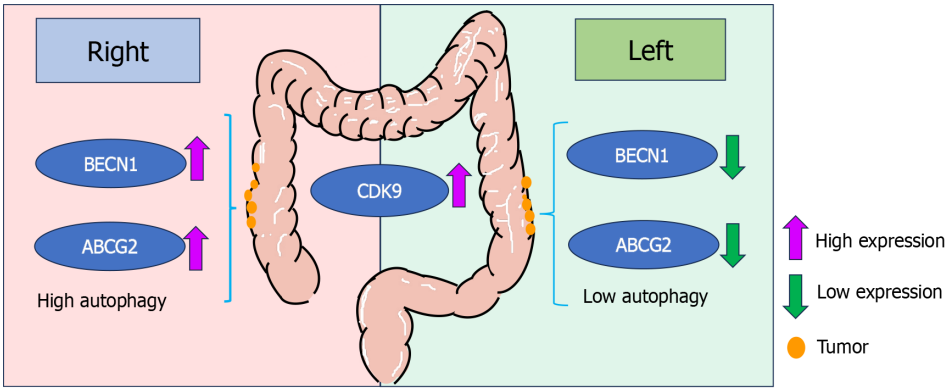

Figure 1 The relationships between cyclin-dependent kinase 9, ATP binding cassette transporter G2, Beclin 1 and autophagy in colorectal cancers. CDK9: Cyclin-dependent kinase 9; BECN1: Beclin 1; ABCG2: ATP binding cassette transporter G2.

rapamycin dual inhibitor) has synergistic anti-proliferative effects in both wild-type and mutated CRC cell lines. In a recent study, Wang *et al*[18] revealed that CDK3, CDK5 and CDK8 functioned as potential diagnostic markers for CRC. These findings give rationale for the application of CDK inhibitors in CRC treatment. CDK9 is an important member of the CDK family that regulates the transcription of genes such as chemoresistant genes in tumors, and some CDK9 inhibitors have entered clinical trials in combination with other drugs[19]. According to Zheng *et al*[1], the expression of CDK9 is positively correlated with autophagy in colon cancer. This finding may provide valuable information for further research on targeting CDK9 as a therapeutic strategy for CRC. The relationships between CDK9, BECN1, ABCG2 and autophagy are show in Figure 1.

CONCLUSION

The expression of CDK9 was correlated with elevated autophagy levels in colon cancer. Additionally, the expressions of ABCG2 and BECN1 were different between left and right colon cancer patients. Targeting CDK9, ABCG2 and BECN1 might be potential therapeutic strategies for CRC.

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FOOTNOTES

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