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Autophagy inhibitors in the treatment of colorectal cancer: a brief review

Martina Ceci[1,2,*], Manuela Iezzi[1,2], Marco Trerotola[1,3]

[1] *Center for Advanced Studies and Technology (CAST), University "G. d'Annunzio", 66100 Chieti, Italy*
[2] *Department of Neurosciences, Imaging and Clinical Sciences, University "G. d' Annunzio", 66100 Chieti, Italy*
[3] *Department of Medical, Oral and Biotechnological Sciences, University "G. d' Annunzio", 66100 Chieti, Italy*
*Corresponding author. E-mail: martina.ceci@unich.it

Abstract. Colorectal cancer (CRC) is the third most frequent cancer. The first-line adjuvant or neoadjuvant chemotherapy is represented by 5-fluorouracil (5-FU) but its application is limited due to induction of chemoresistance. Recent studies showed that the 5-FU resistance in CRC is closely related to the activation of autophagy. During human carcinogenesis, autophagy has been demonstrated to play opposite roles of inhibitor or promoter of malignant progression depending on initial or advanced stages of growth. Currently, the autophagy inhibitor chloroquine (CQ) and its derivate, hydroxychloroquine (HCQ), are the only Food and Drug Administration (FDA)-approved drugs for clinical use. This review summarizes recent findings on the possible employment of autophagy inhibitors to overcome chemoresistance engaged in the CRC.

Keywords: colorectal cancer, chemotherapy, chemoresistance, autophagy, chloroquine.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequent cancer and the second most common cause of cancer-related deaths worldwide (Sung *et al.*, 2021). In the clinical practice, surgery is the primary option followed by chemotherapy. 5-fluorouracil (5-FU) is utilized for treatment of patients with stage II/III CRC (Blondy *et al.,* 2020), thus representing the best first-line adjuvant or neoadjuvant chemotherapeutic choice.

The clinical applications of 5-FU have been significantly limited due to the development of innate or acquired chemoresistance in most patients with metastatic CRC. To enhance the efficacy and reduce the adverse effects of 5-FU, novel combination treatments are being currently employed, such as FOLFOX (5-FU, Leucovorin with Oxaliplatin) or FOLFIRI (5-FU, Leucovorin with Irinotecan), which improved both efficacy and survival rate in CRC patients (Alnuqaydan *et al.*, 2020).

Despite the impact of the chemoresistance on CRC patients survival, the mechanisms underlying chemoresistance to 5-FU remain poorly understood. Recent studies have shown that the 5-fluorouracil resistance in CRC is closely related to the activation of cancer cell autophagy (Alnuqaydan *et al.,* 2020; Mulcahy Levy *et al.,* 2017).

Finding effective chemotherapeutic drugs for CRC remains one of the greatest challenges in long-term management of metastatic CRC patients. This review describes the most recent findings that demonstrated the complex mechanisms underlying chemoresistance in CRC patients. Among these mechanisms, several studies have shown that autophagy plays a vital role in the resistance to tumor chemotherapeutic treatments.

THE DUAL ROLE OF AUTOPHAGY IN CRC

Autophagy protects cancer cells from stress-induced damage, promoting resistance and reducing the efficiency of anti-cancer drugs. Therefore, identifying the mechanisms underlying autophagy modulation during malignant progression might provide new approaches in the pharmacological treatment of CRC (Yang *et al.,* 2015)

Autophagy is an evolutionarily conserved catabolic process by which the cells degrade and recycle their internal components. Autophagy is accomplished through the formation of autophagosomes, double-membraned vesicles that engulf cellular proteins and organelles for delivery to the lysosomes and following degradation. The formation and turnover of the autophagosomes is divided into five stages: initiation, nucleation of the autophagosome, elongation of the autophagosome membrane, fusion with the lysosome for cargo degradation (Boya *et al.*, 2013).

A large number of studies have demonstrated that autophagy plays a dual role in cancer progression. In early stages of tumorigenesis autophagy maintains cellular homeostasis by degrading damaged and toxic cellular components. On the other hand, autophagy facilitates malignant progression at later stages by promoting cancer cell growth under stressful stimuli such as hypoxia and nutrient deprivation (Singh *et al.,* 2017).

Despite the complex interplay between the tumor suppressive and promoting role in cancer, autophagy is a novel and promising target for CRC therapy. The use of various autophagy inhibitors has been recently proposed as a novel strategy to sensitize CRC cells to chemotherapy and overcome drug resistance.

AUTOPHAGY IN CLINICAL PRACTICE

Recently, several extensive studies on autophagy clarified the possible molecular mechanisms engaged in the CRC progression, in order to hypothesize and develop novel targeted drugs. Currently, chloroquine (CQ) and its derivate, hydroxychloroquine (HCQ), are the only Food and Drug Administration (FDA)-approved drugs for clinical use. These drugs inhibit the last step of the autophagic flux, by deacidifying the lysosomes and compromising the activity of most lysosomal proteases (Mulcahy Levy *et al.,* 2017). This results in the accumulation of late endosomes and redirection of their content to the extracellular space.

The SOX2/β-catenin/Beclin1/autophagy signaling axis has been shown to be able to regulate chemo-resistance, cancer stem cells properties, and epithelial–mesenchymal transition in CRC (Zhu *et al.,* 2021). This is particularly important in clinical contexts, as inhibition of cancer autophagy could lead to strong reduction of metastatic spreading.

Another study reported that targeting ERK leads to the production of high concentrations of reactive oxygen species (ROS) which turn on autophagy by activating ROS/p53. The combination of autophagy and ERK inhibition was shown to have a strong additive antitumor effect in CRC treatment (Mi *et al.,* 2021).

Wang *et al.* recently suggested a novel potential therapeutic strategy for CRC by combined inhibition of PI3K/Akt/mTOR signaling and autophagy. This combination therapy was demonstrated to lead to a significant increase of apoptosis (Wang *et al.,* 2021).

Several experimental evidence is now accumulating that provides insight in the molecular mechanisms underlying autophagy and chemoresistance in CRC. One of these studies conducted by Chen and colleagues identified serine hydroxymethyltransferase-2 (SHMT2) as a critical regulator of 5-FU chemoresistance in CRC. The authors showed that patients with CRC that expressed low levels of SHMT2 exhibited resistance to 5-FU and suffered of worse prognosis compared with patients with CRC expressing high levels of SHMT2 (Chen *et al.,* 2021). Under 5-FU treatment, SHMT2 depletion promotes autophagy and inhibits apoptosis, thus suggesting that the lethality of 5-FU treatment to CRC cells was enhanced by treatment with CQ *in vitro* and *in vivo* (Chen *et al.,* 2021).

Other mechanisms involved in 5-FU resistance of CRC have been described. Among them, Sun and colleagues performed a series of *in vitro* and *in vivo* experiments and found that ubiquitin-specific protease 11 could induce resistance to 5-FU activating autophagy

through AMPK/Akt/mTOR pathway via stabilization of valosin-containing protein (Sun *et al.,* 2021). Although the clinical outcome of using autophagy inhibitors for treatment of CRC patients is still under assessment (Mohsen *et al.,* 2022) and clinical trials are now in progress (https://clinicaltrials.gov/ct2/results?cond=Colorectal+Cancer&term=Autophagy), there is strong experimental evidence that these agents should be employed in combination with specific signaling modulators in order to maximize their potential.

CONCLUSIONS

We summarized here the most recent findings of the involvement of autophagy in the chemoresistance in CRC. CQ and HCQ appear to represent efficient inhibitors of autophagy both *in vitro* and *in vivo*, making them potential targets for future cancer therapies.

Taken together, these findings contribute to improving our understanding of the molecular mechanisms of chemotherapy resistance in CRC. The signaling targets described here may contribute to the development of novel combined therapeutic strategies for treatment of CRC based on modulation of cell autophagy, providing a potentially novel window of intervention to reduce chemoresistance.

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