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## Upgraded role of autophagy in colorectal carcinomas

Evangelos Koustas, Panagiotis Sarantis, Athanassios G Papavassiliou, Michalis V Karamouzis

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### Abstract

Autophagy is a basic catabolic process closely associated with degradation of cellular components. The role of autophagy in colorectal cancer (CRC) remains controversial. The mechanism of autophagy has been identified as protecting mechanism against tumorigenesis by isolation of damaged organelles or as cytoprotective provides energy in hypoxic regions of CRC tumors. Mutations in proto-oncogenes, such as *RAS* and *BRAF*, have been associated with autophagy initiation through signaling pathways of BRAF/MEK/ERK and PI3K/AKT/mTOR. A combination therapy of chemotherapeutic agents and autophagy inhibitors such as hydroxychloroquine or immunotherapy might represent a major step that could be evaluated as a putative novel therapeutic strategy in CRC patients.

**Key words:** Autophagy; Tumorigenesis; Clinical trials; Autophagy inhibitors; Colorectal cancer

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**Core tip:** The significant role of autophagy in maintaining the balance of tumorigenesis and cancer cell death remains controversial. The last decade grown body of evidence support the notion that autophagy is a promising target for many malignant tumors, including colorectal cancer (CRC). A novel therapeutic approach which could involve autophagy inhibitors or immunotherapy plus chemotherapeutic drugs could open a new field for treating patients with CRC.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed malignancies leading to many cancer-related deaths worldwide. Some patients are initially diagnosed with metastatic CRC (mCRC), while 20% of CRC patients will eventually develop metastases, thus emphasizing the importance of novel effective treatment options<sup>[1]</sup>.

Many studies have shown that CRC is closely associated with the cytoprotective mechanism of autophagy, a self-digesting process in cells. The last decade, many studies have identified and characterized autophagy as an important mechanism in mammalian systems, in healthy state and during carcinogenesis<sup>[2]</sup>. Cancer cells have the ability to use autophagy mechanism in trafficking of many oncogenic factors, such as chemotactic, pro-invasive or pro-inflammatory molecules and/or angiogenic molecules. Malignant tumors that use autophagy have the ability to change their micro-environment through the regulation of crosstalk between cancerous and stromal cells. This is a significant property which has been described in many chemotherapeutic treatment approaches<sup>[3]</sup>. Three different types of autophagy have been so far identified; macroautophagy, microautophagy, and chaperone-mediated autophagy. Macroautophagy has been closely associated with the formation of phagophore which engulfs cytosolic proteins for degradation in lysosomes<sup>[4]</sup>.

## ROLE OF ONCOGENES IN AUTOPHAGY INITIATION

It is well experienced that the majority of mCRC patients eventually develop acquired resistance during their chemotherapy-based treatment. Oncogenes such as *EGFR*, *RAS* and *BRAF* have been characterized as key elements in the modulation of resistance mechanisms in mCRC. Additionally, these oncogenes regulate the cytoprotective mechanism of autophagy. *EGFR* is responsible for activation of signaling pathways that affect autophagy, among them PI3K-AKT-mTOR<sup>[5]</sup>. This pathway inhibits autophagy through the formation of PI3K-Beclin-1 homodimers. On the other hand, *BRAF*-depend signaling pathway (*BRAF*/MEK/ERK) has been shown to trigger autophagy *via* up-regulation of Beclin-1<sup>[6]</sup>. Moreover, several studies support the idea that *BRAFV600E* mutation induces the expression of autophagic markers; light chain 3 and Beclin-1 in CRC cells. Additionally, anti-EGFR MoAbs (such as cetuximab and panitumumab) induce autophagy which acts as a protective response in CRC cells. Several studies have described that mutant *RAS* can prevent the formation of autophagophore in autophagy machinery through the reduction of *BECN1* expression<sup>[7]</sup>.

## CONTROVERSIAL ROLE OF AUTOPHAGY IN CRC

The controversial role of autophagy in CRC development has been supported by a plethora of data. Cancer cells have been found to require high basal levels of autophagy for cell proliferation<sup>[8]</sup>. In already established tumors, autophagy has been associated with the hypoxic tumor regions where the metabolic demands are increased. The increasing levels of autophagy in hypoxic regions of tumors have also been associated with the modulation of immunosurveillance and immunosuppression in tumor microenvironment<sup>[9]</sup>. In addition, advanced tumors appear to be addicted in autophagy to maintain their energy balance. Through autophagy, cancer cells recycle intracellular components and build pro-tumorigenic factors. *KRAS*-dependent tumors also use autophagy machinery to maintain basic components to support cancer cells' growth under stressful condition<sup>[10]</sup>.

## AUTOPHAGY IN CLINICAL PRACTICE

The mechanism of autophagy has been suggested as a crucial modulator that can be targeted to improve the effect of anti-neoplastic drugs in several tumors, including mCRC. This notion has led to the development of agents that inhibit autophagy, thereby improving treatment outcome. The last decade many molecules that inhibit autophagy have been developed. Autophagy inhibitors, such as chloroquine and its analog hydroxychloroquine (HCQ), have been shown to decrease autophagy through the disruption of lysosomal function<sup>[6]</sup>. The anti-antitumoral effect of these agents has been assessed in the clinical setting. Phase I and II clinical trials have already evaluated the efficacy of the combination of HCQ and chemotherapy (e.g., oxaliplatin, fluorouracil) and anti-angiogenic agents (e.g., bevacizumab) in mCRC patients. Furthermore, mCRC patients have achieved disease stabilization after combining HCQ with vorinostat<sup>[11]</sup>. Further elucidation of the effect of the currently existed as well as developing autophagy inhibitors in CRC patients is of paramount importance due to the dual role of autophagy in CRC.

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