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August 1st, 2018

Dr. Jin-Lei Wang
Editor-in-Chief,

RE: Submission of REVISED '**Editorial' (40637**)

Dear Dr. Wang, **The upgraded role of autophagy in colorectal carcinomas**

Please find enclosed our REVISED Research Editorial entitled "**The upgraded role of autophagy in colorectal carcinomas**" to be considered for publication in ***World Journal of Gastrointestinal Oncology***

We would like to thank you and the reviewers for your thoughtful evaluation of our manuscript and for your most welcome comments/suggestions. Accordingly, we have now revised thoroughly our manuscript to reflect these comments.

Please find below a point-by-point **response** to ALL the issues raised by the Reviewers:

Reviewer Comments
Reviewer: 1

SPECIFIC COMMENTS TO AUTHORS
This is a poorly written editorial that lacks substance and will be of no use to readers of WJGO.

AUTHOR RESPONSE: We thank the reviewer.

Reviewer: 2

SPECIFIC COMMENTS TO AUTHORS
In the current study, the authors provide an Editorial to the role of autophagy in colorectal cancer. They suggested that combination therapy of several

chemotherapeutic agents and autophagy inhibitors such as hydroxychloroquine would represent a major step that could be evaluated as a putative therapeutic strategy in mCRC patients. Overall, the manuscript is well performed and worthy to be published.

AUTHOR RESPONSE: We thank the reviewer.

Reviewer: 3

SPECIFIC COMMENTS TO AUTHORS

SPECIFIC COMMENTS TO AUTHORS
The authors present recent updated brief summary on autophagy in coloretal cancer. The manuscript is well organized from basic knowledge to clinical application. Minor typo: 1. line 9, page 4: ... that m(?) mutatnt RAS.... 2. line 8, page 5: ... anti- antineoplamatic .... → anti-neoplastic.

AUTHOR RESPONSE: We thank the reviewer for bringing this to our attention.

1. line 9, page 4: m(?) mutatnt RAS should be mutant RAS
2. line 8, page 5: ... anti- antineoplamatic should be anti-neoplastic

Reviewer: 4

SPECIFIC COMMENTS TO AUTHORS

This paper mainly introduced the upgraded role of autophagy in colorectal carcinomas. The author discusses three parts respectively, namely, the role of oncogenes in autophagy initiation, the controversial role of autophagy in CRC and the autophagy in clinical practice. I think this editorial is interesting. However, there are some questions below: 1. The mechanism of autophagy on signaling pathways should be more clearly elucidated. 2. Author should tell us the role of autophagy between increasing and decreasing in CRC, which is more important. 3. There are some writing errors in the paper. Please check them out carefully.

1. **AUTHOR RESPONSE: We thank the reviewer for bringing this to our attention**

Line 2, page 3: "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 [6]. Moreover, several studies support the idea that BRAFV600E mutation induces the expression of autophagic markers; LC3 and Beclin-1 in CRC cells"
edit as
"PI3K/AKT/mTOR and BRAF/MEK/ERK signaling pathways regulate the mechanism of autophagy. AKT and mTORC1 inhibit autophagy via phosphorylation (on serine residues) of Beclin-1, and decrease the activity of VPS34. On the other hand, activation of ULK1 initiates autophagy through the

formation of Beclin-1-VPS34 complex. Both these mechanisms are responsible for the suppressor or induction respectively of nucleation and elongation steps of autophagy machinery. In addition, the nucleation of phagophore requires the formation of class III- Beclin-1 complex, and in turn, the induction of protective mechanism of autophagy [5]. Furthermore, the second signaling pathway, RAS/RAF/MEK/ERK is characterized as an autophagic inducer. Many evidences support that BRAF oncogene and it signaling pathway increase the expression of autophagic markers, LC3 and Beclin-1 in colorectal tumor cells [6]. In conclusion, PI3K/AKT/mTOR and BRAF/MEK/ERK signaling pathways inhibit and induce the autophagy respectively."

2. AUTHOR RESPONSE: We thank the reviewer.
The controversial role of autophagy remains a field of increasing debate. It is well know that during the first steps of cancer, autophagy may act as a suppressor mechanism. On the other hand, during advanced stages of cancer autophagy, alternatively, act as tumor promoter. It is necessary to determine how these dual roles of autophagy in CRC are regulated and identify the signals, molecules, and mechanisms that enable autophagy to play a dominant pro-malignant role in one situation and the opposite role in another.

1. Marinković M, Šprung M, Buljubašić M, Novak I. Autophagy Modulation in Cancer:Current Knowledge on Action and Therapy. Oxid Med Cell Longev. 2018 Jan 31;2018:8023821.
2. F. Burada, E.R. Nicoli, M.E. Ciurea, D.C. Uscatu, M. Ioana, D.I. Gheonea, Autophagy in colorectal cancer: an important switch from physiology to pathology, World J. Gastrointest. Oncol. 7 (2015) 271e284.
3. S. Jin, E. White, Role of autophagy in cancer: management of metabolic stress, Autophagy 3 (2007) 28e31.

3. AUTHOR RESPONSE: We thank the reviewer. We have made the appropriate editing

Trusting that we have adequately **addressed** the Reviewers' concerns, we would like to thank you for your help in improving significantly our work.

Kind regards,

Associate Prof. Michalis V. Karamouzis
Corresponding author