

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 61530

**Title:** Identification of the circRNA-miRNA-mRNA regulatory network and its prognostic effect in colorectal cancer

**Reviewer's code:** 02583459

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Director, Doctor

**Reviewer's Country/Territory:** Greece

**Author's Country/Territory:** China

**Manuscript submission date:** 2020-12-11

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-12-25 03:45

**Reviewer performed review:** 2021-01-08 18:00

**Review time:** 14 Days and 14 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## **SPECIFIC COMMENTS TO AUTHORS**

Identification of the circRNA-miRNA-mRNA regulatory network and its prognostic effect in colorectal cancer The paper of Yin TF et al describes the role of circRNA-miRNA-mRNA regulatory network and its potential prognosis in colorectal cancer CRC. They have used databases taken from Group on Earth Observations (GEO) and the Cancer Genome Atlas (TCGA) and they have identified a competitive regulatory model among circRNAs, miRNAs and mRNAs. Moreover they have found promising indicators that drive several processes involved in initiation and the progression of CRC cancer and affect the prognosis of CRC. For that reason, they downloaded three datasets (GSE126095, GSE41655 and GSE41657) of large-scale CRC samples in the GEO database, checked differentially expressed (DE) circRNAs, DE miRNAs and DE mRNAs in CRC tissues compared to normal controls, and predicted the downstream target molecules of circRNAs and miRNAs. Moreover, several functional analyses were conducted to identify the underlying mechanism involved in the pathogenesis of CRC. To verify the prognostic effect of the mRNAs found above, they performed survival analysis using the gene profiles and clinical information in the TCGA database. Finally, survival-related genes were determined, and a prognostic subnetwork was developed. The novelty and significance of this manuscript are that it deals with a large scale of several circRNAs, miRNAs and mRNAs, their differential expression and their competitive interplay using sophisticated methodology. Interestingly, the authors predict that this network affects several biological processes such as the retinol metabolic process, leukocyte chemotaxis, extracellular matrix remodeling, endoplasmic reticulum stress, ADH activity, gastric acid secretion, nitrogen metabolism and NOD-like receptor signaling pathway which might represent essential signaling pathways involved in the pathogenesis of CRC. In addition, the authors have identified three mRNA (CA2, ITLN1, and LRRC19) which are

downstream effectors of this network and are significantly correlated with the clinical outcome of CRC patients. In fact, upregulation of these mRNAs might be related to better clinical outcome in CRC patients. However, their hypothesis about the role of the circRNAs, miRNAs and mRNAs network in CRC is partially supported by a series of observations based strictly on theoretical and computational approaches and statistics.

Therefore, one crucial weak point of this study is that it is based only on predictions and it lacks any functional biological assays to clarify the mechanism that drives these biological processes executed by circRNAs, miRNAs and mRNAs network. It is very important in the future, the authors to perform several biological assays to confirm their present findings at the molecular cellular level. Practically, the authors can conduct experiments using several colorectal cell lines and try to clarify the molecular mechanisms that drives the competitive regulation of the circRNA-miRNA-mRNA network which affects these biological processes. These studies will provide useful tools in the understanding of the pathogenesis of CRC at the molecular level having an impact on its prognosis. At last they have to address the percentage of enrichment of differential expression of circRNAs, miRNAs and mRNAs identified and how they are cross regulated among the normal tissue, colorectal adenoma and carcinoma in the results? It will also be necessary for the authors to add some more sentences in the discussion about the specific targets of the network during those biological processes described and involved in the pathogenesis of CRC. Which steps of these processes are affected by this network?