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Wan Chai, Hong Kong, China

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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 00003619

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-08-22 05:58

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input checked="" type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

None



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 00227592

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-09-01 23:35

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> [ Y] Accept
<input type="checkbox"/> [ Y] Grade B (Very good)	<input type="checkbox"/> [ Y] Grade B: minor language polishing	<input type="checkbox"/> [ ] Existed	<input type="checkbox"/> [ ] High priority for publication
<input type="checkbox"/> [ ] Grade C (Good)	<input type="checkbox"/> [ ] Grade C: a great deal of language polishing	<input type="checkbox"/> [ ] No records	<input type="checkbox"/> [ ] Rejection
<input type="checkbox"/> [ ] Grade D (Fair)	<input type="checkbox"/> [ ] Grade D: rejected	BPG Search:	<input type="checkbox"/> [ ] Minor revision
<input type="checkbox"/> [ ] Grade E (Poor)		<input type="checkbox"/> [ ] Existed	<input type="checkbox"/> [ ] Major revision
		<input type="checkbox"/> [ ] No records	

## COMMENTS TO AUTHORS

It is a very interesting review of CLOCK genes and their role in colorectal cancer. The topics are covered very well and thoroughly. However, there are so many long sentences throughout the manuscript. It is very difficult to read, and sometimes I find it very hard to understand. For example, the second sentence of page 7 has 6 lines. I strongly recommend the author to shorten these long sentences. In addition, I have a few suggestions: 1) Based on Cancer statistics 2013, colorectal cancer is the third leading cause of cancer death in the United States. Please change “second” to “third” and also cite the reference. 2) Please introduce abbreviation “SCN” after “suprachiasmatic nucleus” in the second paragraph of page 3. 3) The author states that degradation of Beta-catenin induces the expression of several mediators of cell proliferation, but I think that nuclear accumulation of beta-catenin caused by decreased degradation in the cytoplasm induces expression of these mediators. 4) There are several minor grammar errors throughout the manuscript, please correct.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 02446403

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-09-03 20:24

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

The authors address the role of CLOCK genes in CRC progression. The evidence that these genes are really relevant in cancer progression is quite weak and based mainly on indirect evidence. The review starts with a discussion of the molecular determinants of the circadian rhythm which is very difficult to read: a cartoon and a critical discussion of the results suggesting a hierarchy of relevance of the involved genes might help. Similar consideration for the next paragraphs. In particular the chapter on DNA damage presents studies without a logical sequence or a critical discussion. The chapter on clinical correlation simply describes some up and down regulation of genes whose relevance is amply debatable. Finally the conclusions reiterate some concepts already presented whereas one would expect a personal interpretation of the results and some suggestions to move forward. Several misspellings and some inappropriate references



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 00068625

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-11-27 02:24

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

The problem presented in the paper has been discussed for several years, but it still remains actual topic. Literature citations are appropriate and adequate. The paper is organized in a clear and easy to understand manner.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 00054948

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-11-28 19:41

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

It is an interesting review, timely summarizing the roles of clock genes in colorectal cancer initiation and treatment outcomes. My suggestions are provided as below:

- The authors may include several key references published recently.
  - Karantanos T J Surg Oncol. 2013 Sep 13. doi: 10.1002/jso.23434. [Epub ahead of print] The article showed that CLOCK1 gene polymorphism is associated CRC incidence but not treatment outcome.
  - Yu H PLoS One. 2013 Apr 23;8(4):e61679. doi: 10.1371/journal.pone.0061679. Print 2013. Yu et al found circadian regulator Cryptochrome 1 is associated with CRC.
  - Soták M et al. Int J Cancer. 2013 Mar 1;132(5):1032-41. doi: 10.1002/ijc.27760. Epub 2012 Aug 24. The roles of clock genes and clock-controlled cell cycle genes were studied in murine colorectal tumors.
- The title “c-MYC/p21 SIGNALING AND CELL CYCLE AS TARGETS OF CIRCADIAN CIRCLE” may need to be modified as c-MYC and p21 are regulators of cell cycle.
- The authors may include a figure for this section so that the involvement of clock in cell cycle can be explained clearly.
- The authors may explain the genes regulated by beta-catenin in much more details and include a figure as well.
- The authors may need to provide their own opinions about the problems and future directions in this research field.



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 02486710

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-12-07 00:41

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

It is an interesting paper, summarizing the roles of clock genes in colorectal cancer initiation and treatment outcomes. 1-Please add your limitations and endpoints clearly. 2- Please explore the role of CLOCK genes in CRC pathogenesis clearly and please make a few comments if these pathways can be used in the CRC treatment. 3- Please make grammatical revision with the help of a native English speaker. 4- The conclusion needs some revisions. Start with a summary of the important findings in the literature. Please re organize the sentences based on a plan.



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5185

**Title:** CLOCK genes: Their role in colorectal cancer

**Reviewer code:** 02552296

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-08-21 16:19

**Date reviewed:** 2013-12-18 01:26

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

### COMMENTS TO AUTHORS

This is a review manuscript which is well written. From the manuscript missed a scheme to showing and explaining all the interactions of these genes. Also, in page 6th , 1st paragraph, 3rd range: In particular it is know that the BMAL1/CLOCK1 heterodimer promote the acetylation: the authors must descript which acetylation?