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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 29948
Title: Melatonin, a novel selective ATF-6 inhibitor, induces human hepatoma cell apoptosis through COX-2 downregulation
Reviewer's code: 03350630
Reviewer's country: Belarus
Science editor: Jing Yu
Date sent for review: 2016-08-31 19:08
Date reviewed: 2016-09-15 03:25

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The article "Melatonin, a novel selective…" by L. Bu et al. deals with the mechanism(s) of melatonin-induced apoptosis in human hepatoma cells. Using a few modern methods, immunohistochemical analysis, flow cytometry, TUNEL assay, Western blotting, qRT-PCR, the authors showed a close relationships between the level of the expression of the activating transcription factor 6 (ATF6) and COX2. Using cell line Hep G2, it was shown that melatonin could selectively block ATF 6 and then inhibit COX2 expression, leading to enhanced liver cells apoptosis. These data provide a new mechanism by which melatonin downregulates COX2 expression and induces apoptosis by selectively targeting ATF6 in human HCC cells under endoplasmic reticulum stress. The article will be interesting for readers of this Journal. My minor comments: 1. The abbreviations in the Abstract should be explained. 2. It should be interesting to discuss the mechanism(s) of melatonin effect: antioxidant properties, an interaction with nuclear receptors, …. 3. The manuscript should be edited.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 29948
Title: Melatonin, a novel selective ATF-6 inhibitor, induces human hepatoma cell apoptosis through COX-2 downregulation
Reviewer's code: 03459580
Reviewer's country: Germany
Science editor: Jing Yu
Date sent for review: 2016-08-31 19:08
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript by Bu et al. describes the potent new capacity of melatonin playing the role in treatment of hepatocellular carcinoma patients. In general, enclosed set of data are very interesting nevertheless, major editorial corrections are strongly needed to improve the quality of this report. Small remarks that should be corrected in the text are listed below: 1. Please correct the mistake in the title: There is: Melatonin, a novel seletive..... Should be: Melatonin, a novel selective..... 2. Abstract: Please mention the full names followed by used abbreviations such as UPR, ATF-6, COX-2, CHOP, HCC. Please be consistent to use the same way of abbreviations throughout the whole manuscript. Sometimes it is written e.g. ATF6 and ATF-6 or COX2 and COX-2. Please change it accordingly. a. Line 7: There is: ....need to be carified. Should be: ....need to be clarified. b. Line 12: There is: ....(an ERinducer).... (missing space) Should be: ....(an ER inducer)... c. Line 16 and 17: There is: In conclusion, There....seletive.... Should be: In conclusion, there....selective.... 3. Introduction: a. Page 2, Line 5: There is: ....HepG-2.... Should be: ....HepG2.... 4. Materials and methods: a. Reagents (Line 11 and elsewhere): There

is: ....TRIZOL.... Should be: ....TRIzol? Reagent.... b. Hepatocellular carcinoma specimens Line 9 and 10: Please be consistent using the numbers pointing out the patients, not sometimes written with numbers and words. c. Immunohistochemical analysis Line 6: Please write in brackets the pH used for PBS. d. Cell culture ? Remove the sentence about the source of HepG2 cell line mentioning the Argentinian boy. It is simply redundant. ? DMEM was high or low glucose. Please specify and write it. Line 4: There is: The cell was cultured.... Should be: Cell culture was carried out in.... Line 7: There is: CO2 atmosphere. Should be: CO2 atmosphere. e. Flow cytometry Line 8: There is: A total of 1*106 cell/mL.... Should be: A total of 1×106 cell/mL.... f. qRT-PCR ? Please describe more precisely the conditions for performed PCR i.e. temperatures and times for denaturation, annealing, elongation etc. 5. Discussion: Page 3: Together with given citations of #19 and #20 add also essential references as follows: - Kleszczyński K, Zillikens D, Fischer TW. Melatonin enhances mitochondrial ATP synthesis, reduces reactive oxygen species formation, and mediates translocation of the nuclear erythroid 2-related factor 2 resulting in activation of phase-2 antioxidant enzymes (γ-GCS, HO-1, NQO1) in ultraviolet radiation-treated normal human epidermal keratinocytes (NHEK). J. Pineal Res. 61 (2016) 187–197. - Kleszczyński K, Tukaj S, Kruse N, et al. Melatonin prevents UVR-induced alterations in plasma membrane potential and intracellular pH in human keratinocytes. J. Pineal Res. 54 (2013) 89–99 - Fischer TW, Kleszczyński K, Hardkop LH, et al. Melatonin enhances antioxidative enzyme gene expression (CAT, GPx, SOD), prevents their UVR-induced depletion and protects against formation of DNA-damage (8-hydroxy-2′-deoxyguanosine) in ex vivo human skin. J. Pineal Res. 54 (2013) 303–312 - Fischer TW, Scholz G, Kn?ll B, et al. Melatonin suppresses reactive oxygen species induced by UV irradiation in leukocytes. J Pineal Res 2004; 37:107–112. - Slominski A, Pisarchik A, Zbytek B, et al. Functional activity of serotoninergic and melatoninergic systems expressed in the skin. J Cell Physiol 2003; 196:144–153. 6. Legends: Please adapt the statistics labeling appropriately. For instance in Fig. 2, there are **, # and ## but it is not consistent with the Legends. Please correct elsewhere accordingly! a. Fig. 2 - Please mention about incubation with TM what is seen in the graph but missing in the legend description. - In Line 3, please add 10-9 mol/L, it is simply missing! Is