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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 25923
Title: The GUCY2C signaling axis and colon cancer prevention
Reviewer's code: 02445096
Reviewer's country: United States
Science editor: Ya-Juan Ma
Date sent for review: 2016-03-26 21:13
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] 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	
		[ ] No	

COMMENTS TO AUTHORS

Strengths

Review from the lab of Dr. Waldman, who has published frequently on the role of GUCY2C in CRC, so this group is eminently qualified to prepare a review. Their last review was in 2013. So, now three years later it is time for an update.

Overall, the review covers much of what is known about GUCY2C, and compared with their previous review adds more speculation about pathways influenced by loss of GUCY2C signaling, e.g., changes in metabolism.

Concerns

Reviews need to be both comprehensive and precisely accurate. For this review there are some deficiencies in both areas that should be addressed.

Comprehensiveness

1.It would be helpful to know more about the two hormone ligands (guanylin, uroguanylin) that activate GUCY2C? How are they normally regulated, what is their known role in GI tract diseases and is there much known about why their levels decrease in early stages of CRC. Two recent papers from the Gustafsson lab in Trondheim might be included in the review, see Brenna et al, 2015 and Brenna et al., 2016. The 2016 paper describes the use of ISH to localize guanylin and uroguanylin to specific cell types in the intestinal tract. The 2015 paper describes the down-regulation of both genes in IBD.

2.There should be more information about GUCY2C and its signaling cascade in human CRC. Are there any somatic mutations in GUCY2C reported (e.g., in TCGA data)? Any evidence of epigenetic regulation? Is loss of GUCY2C signaling more prevalent in certain subtypes of CRC, e.g., MSS vs MSI, left side vs right side, serrated, flat or tubulovillus adenomas, etc? A statement in the review indicates that down-regulation of the hormone ligands "often times accompanies APC loss" – so, is there evidence that hormone down-regulation is more prevalent in APC-dependent, CIN, MSS CRC vs MMR-dependent, MSI CRC? Further, in Fig. 1 genomic instability is shown to be a consequence of loss of hormone ligands, leading to tumorigenesis. Is this genomic instability strictly chromosomal? Finally, is there clinical data on the loss of the hormone ligands? For example, is loss of this signaling cascade associated with worse prognosis?

Precision & Accuracy

1.There are numerous instances of statements where the intent is fairly clear but the wording is not precise. It is suggested that the authors go through the wording of every sentence very carefully and revise the text where necessary.

Some examples:

Second paragraph of introduction starts out " Colorectal tumorigenesis is widely accepted as a disease of both sporadic and inherited genomic instability…and chromosomal instability". Customarily, we refer to CRC as having sporadic and inherited forms of the disease, and that genomic instability of some kind is characteristic of all CRC, and certainly not just chromosomal instability.

Another example is referring to mutant APC as "stabilizing beta catenin" – generally, the most common APC mutations do not produce proteins that physically interact with beta catenin protein,

thus causing a failure of beta catenin protein degradation, resulting in excess nuclear localization etc. Therefore, it is somewhat inaccurate to imply a function of the mutant APC protein that it does not possess, it is more accurate to say that the absence of wildtype APC protein stabilizes beta catenin levels or leads to excess beta catenin levels.

At several points the statement is made that GUCY2C is "inactivated" – yet, it is also claimed that levels of GUCY2C do not change in CRC, only levels of their hormone ligands. Now, it is understood that what is meant is that the GUCY2C signaling cascade is inactivated in the absence of hormone ligands, but that is not what is stated at several junctures – which can lead to confusion.

Another, "for several years, CRC has been implicated as the gold standard for investigating…". Indeed, this has been true for more than two decades, not several years.

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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

1. The main idea of the third part, "Genetic pathways for colorectal cancer", has not been shown very clear. The relationship between genetic factors and GUCY2C signaling axis should be clarified and those well known genetic pathways could be written more briefly. It is better to discuss the mechanism of hormone loss in the development of CRC in detail. 2. Information in the forth part, "GUCY2C signaling axis and colorectal cancer", is put together without a good logical order. It is better to use a few more subheadings to show the mechanism of GUCY2C related colorectal tumorigenesis more clearly, e.g., GUCY2C signaling axis and metabolism, GUCY2C signaling axis and proliferation, GUCY2C signaling axis and stem-like properties, etc. 3. There are some typos in this manuscript. E.g., "Intestinal homeostasis maintenance by the GUCY2C signaling axis"; "... cGMP-dependent protein kinase II (PKGII) leading to PKGII-dependent phosphorylation ..."; "... leads to consequent microsatellite instability ..."; "... including cyclin D1, pRb and B-catenin ...".