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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6260
Title: Tumor stem cells and colorectal cancer
Reviewer code: 02446041
Science editor: Cui, Xue-Mei
Date sent for review: 2013-10-12 13:45
Date reviewed: 2013-11-05 03:09

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

COMMENTS TO AUTHORS

Comment: Cancer stem cell theory and stem cell therapy may conjure up images of a potential cure for cancer based on animal models. However, the results from clinical trials are disappointing. Stem cell identity and heterogeneity are among the major concern. Having derived from their own studies, the authors drafted a comprehensive review on implementing colorectal cancer (CRC) to address these issues. CRC is a fascinating example of a larger cancer stem cell concept and the manuscript is precisely focused and well written. The author, however, can enhance the clarity, cohesiveness, and logic flow by addressing the following specific comments. Specific comment: In "Core Tip": The authors state "CRC stem cells remain attractive targets for anti-tumor therapy." They also state "The coexistence of two epithelial stem cell types (normal SC, CRC-SC) questions whether intestinal cells are singularly-derived." If they cannot distinguish them, how can they target CRC-SC? They should reconcile and modify the logic flow with clarity. In "Introduction", page 6 - Paragraph 2, the authors state, "Growing evidence suggests that individual CRC cells differ in functional and proliferative capacity to the point that separate cells may serve unique roles.[5, 6]" However, their citations are not specific for CRC and they should have specified the CRC-related evidence as the sentence stands. Here, "separate cells" – what do they refer to? - Paragraph 3, "The aim this review is primarily to reappraise current evidence" should be "The aim for this..." Page 8, "Theories on CRC population dynamics—which are not explored in Fearon and Vogelstein's model—have also subsequently been proposed." It needs reference. Page 10, "that Bmi1+ cells restored the intestinal epithelium following radiation injury sufficient to eliminate Lgr5+ stem cells." How do Bmi1+ cells eliminate Lgr5+ stem cells? Human relevant? Lgr5+, Bmi1? Page 10, "An evolving model of normal intestinal stem cell behavior" – Can the authors integrate these three options into one in a summary sentence or

paragraph? For example, they said, "the composite behavior of various semi-mutable cells contained within the intestinal crypt" – what timeline in what space does such an event exists? What is the sequential event for "various semi-mutable cells?"How does it relate to the Wnt signaling pathway with Bmp agonist on page 13 (Ref. 19, 32)? Page 14, Can they clarify the difference between CRC-supporting ISEMFs and normal stem cell-supporting ISEMFs? Page 14, if "Paneth cells are only found in the small intestine," what is the equivalent in other segments? Do they share the same biomarkers if they serve the same function? Page 15, "Uncertainty remains as to whether all intestinal epithelial cells are equally prone to developing cancer." Is there any single cell study? It's hard to believe all intestinal epithelial cells are equal for any given function or status. Page 16, "Wnt-constitutive non-stem cells in the intestine can de-differentiate and re-acquire stem cell properties in a NF-?B dependent manner, ultimately leading to tumorigenesis". In the context of Wnt is essential for normal stem cells, can the authors elaborate Wnt is a switch? In what conditions does Wnt go to cancer instead to maintain normal stem cell stage. Page 17, They state: "Very few, if any, markers are both specific to CRC stem cells and ubiquitous among all CRCs.[8]" They state Dclk1; however, it'll be helpful to have a table to list these biomarkers. Page 19, Among CRC SC biomarkers, like "Lgr5+-high CRC cell fraction", " low to no Lgr5", "DCLK1+", CD133+, CD133- cell fraction, did anybody check if all these biomarkers exist in human CRC? The authors cite, "Nakanishi et al.[71] did not find DCLK1 among all tumors in their mouse experiments," however; it's well known that human is different from mouse. Page 21, "Given that colorectal cancer is of monoclonal origin," what is the evidence to support this

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COMMENTS TO AUTHORS
I love this article. Is it possible to add a table on potential stem cell markers proposed so far in colorectal cancer; or the scheme of the concept of colorectal cancer stem cells.

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COMMENTS TO AUTHORS

The authors summarized the current knowledge in the field of colorectal stem cells with the focus on normal intestinal stem cells and different potential cancer stem cells (Lgr5+ stem cells, quiescent label-retaining cells). Further, they discussed the difficulties regarding the identification of cancer stem cells. The manuscript contains some flaws which need to be addressed before publication: General remarks ? The title doesn't attract enough attention to this important research field Introduction ? The first paragraph needs to be entirely rewritten, because the case numbers from the different continents are confusing. ? "the past 25 years": in five years this number refers to another period, better: Since e.g. 1985 Fearon and Vogelstein's Model for Colorectal Carcinogenesis ? The listed genetic aberrations are not CRC-specific. It's unclear whether Fearon and Vogelstein first discovered this aberrations in CRC or whether these mutations have already been identified and then also found in CRC. ? "Some aspects of Fearon and Vogelstein's stepwise model…": This paragraph is not easy to understand. Normal Intestinal Stem Cells ? Nearly eight pages about normal intestinal stem cells are too much in a review titled "Tumor Stem Cells and Colorectal Cancer" ? please be shorter and be more concise Intestinal Stem Cell Niche ? The term "bacteria and epithelial cell-derived chemicals" is ambiguous, better: natural enteric flora and epithelial cell-derived soluble factors The second part of this review "Intestinal Tumor/Cancer Stem Cells" is by far better written as the first part, very well structured and easy to follow, especially the part "Epithelial Mesenchymal Transition: Prevailing Metastatic Program?". Even the second part would benefit a lot of a shortening.

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COMMENTS TO AUTHORS
The article is really interesting and well written. The discussion is consistent, although it could be semplified. I suggest minor language polishing.