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315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 5921

**Title:** The natural history of hepatic metastases from colorectal cancer; pathobiological pathways with clinical significance

**Reviewer code:** 02544402

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2013-09-30 10:51

**Date reviewed:** 2013-10-06 21:59

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 checked="" 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)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

This is a very important and substantial piece of work which will provide stimulating interest to the reader wanting to have a comprehensive overview of the molecular mechanisms involved in cell transformation from normal colonic epithelial cell to colorectal liver metastases. My concerns relate a) to the overall length of the work- this very much reads like the introduction to a thesis or a book rather than a review in a journal and the reference list of 194 is far higher than I would expect for such a review. If this is the brief that the editor seeks then fair enough, but a casual reader would certainly be put off by the length of the article. b) there are numerous grammatical errors in the text which is a minor point that could be corrected by proof reading. I think the figures in particular are excellent and the authors are to be congratulated on providing such high quality images.



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 5921

**Title:** The natural history of hepatic metastases from colorectal cancer; pathobiological pathways with clinical significance

**Reviewer code:** 00037998

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2013-09-30 10:51

**Date reviewed:** 2013-10-14 09:09

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" 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)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

In this review, the authors have described in detail the cellular and molecular events, interactions and pathways involved in colorectal cancer (CRC) initiation, progression and liver metastasis. Started with genetic alteration that initiated CRC, step by step, the authors described how CRC cells grew in the primary large intestine site, promoted local angiogenesis and lymphangiogenesis and reached to the stage of intravascular survival in the lymphatic and the blood vessels. They then described how CRC cells interacted with various types of cells in liver, which facilitated the colonization of CRC cells in liver. This is a thorough review of CRC liver metastasis at cellular and molecular levels, where the involvements and interactions of multiple pathways and numerous cell types have been revealed and summarized. It has demonstrated the enormous amount of work, knowledge and efforts from the authors in writing this review. More importantly, it has brought the updated knowledge in the field, which should prove to be interesting to basic biomedicine scientists, oncologist and clinicians in related disciplines. Minor concerns: 1. The page number is not labelled clearly. 2. Page 6, last paragraph, first line, should be "may generate CRC."



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 5921

**Title:** The natural history of hepatic metastases from colorectal cancer; pathobiological pathways with clinical significance

**Reviewer code:** 00181023

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2013-09-30 10:51

**Date reviewed:** 2013-10-22 04:08

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 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 checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Although this appears to be an invited review, I have to admit that I have serious problems with it. The language is "slangy" and "imprecise", there are many, many errors, and it is in my eyes impossible that the manuscript can be amended, i.e. corrected by performing a revision. Let us start from the beginning: 1. It is a bit unusual to have a semicolon in a title of scientific manuscript - please amend (this is of course only a matter of style) 2. Please do not use abbreviations in the abstract - it is not necessary to introduce CRC here (again only a matter of style) 3. Introduction, second paragraph: The transformation of normal cells at their initial sites includes multiple genetic events (correct!), but this does not occur "during multiple metastatic stages". 4. Introduction, third paragraph, first line "cellular mutations": where if not in cells, particularly in the cell nuclei, will mutations occur? This is a typical example of the poor ("slangy" and imprecise) language quality. 5. Next page, third paragraph: colorectal liver metastasis = slang (should not be used in scientific writing). 6. The part "initial genetic alterations of epithelial cells in colorectal carcinogenesis" is wrong in most parts, I will focus on the problems in detail: 6a. "CRC's initial indication is certain cellular mutations" - this is no sentence that makes sense. 6b. hMLH1 (not hMSLH1) 6c. Line seven of this paragraph: early adenoma formation occurs via the aberrant crypt focus, this is by far not a "polypoid structure" 6d. Line nine of this paragraph: The cancer cells do not "detach from the intestinal epithelium" - the metastatic process includes the detachment of single cells or small clusters of cells (EMT, migrating cancer stem cell concept) from the tumor itself, i.e. from neoplastic glands. 6e. Line 12 of this part: 80% of cancers follow the CIN pathway, this is wrong. Currently, we believe that approximately 60% of tumors follow this pathway. 6f. Next page, lines 1-2: "FAP is the most



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common disease attributed to CIN pathway" - this is totally incorrect, and you should know! 6g. Lines 6-7 on the same page: "Neoplastic cells in which genetic material has been mutated through MIN have aberrant DNA mismatch". No! MIN (I would prefer MSI) is the consequence of mismatch repair deficiency, it is the other way round (hen and egg situation). 6h. Line 11: "The main genetic disorder caused by MIN is a sequence of mutations in DNA mismatch repair genes" - the same error, it is the other way round. First, mismatch repair deficiency, then MSI (MIN). 6i. The CIMP type leads to promoter methylation of MLH1 (serrated route to cancer), it is responsible for the MSI tumors that are not Lynch. In your text, they appear as something independent from MSI... 7. "Interactions of neoplastic cells with the stroma..." , second line of this part: "colorectal tissue stroma" - a structure like that does anatomically not exist. 8. Macrophages (next page). "the development of tumour causes an inflammatory reaction to the intestinal tissue". No! It may, to varying extent induce tumor-associated inflammation, but not inflammation to the non-neoplastic bowel wall... You must be anatomically accurate and precise. In fact, here I stopped reading: The text is of extremely poor quality, has multiple errors and I do not see any chance for revision - I am sorry, I (doing reviews for more than 40 journals for years, particularly in the field of molecular pathology of colorectal cancer) have never seen an invited manuscript as poor as this one.