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Flat C, 23/F., Lucky Plaza,  
315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 5895

**Title:** Inflammatory pathways in the early steps of colorectal cancer development

**Reviewer code:** 00058121

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

**Date sent for review:** 2013-09-29 15:52

**Date reviewed:** 2013-11-03 23:52

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)	<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

This is a comprehensive review concerning inflammatory pathways in the early steps of colorectal cancer development. I have a few comments to the authors: ? In my opinion the manuscript needs to be a little shorter – some information is redundant considering especially the role of macrophages and neutrophils. The way this manuscript is written focuses only to a limited percentage of readers dedicated to the issue. Please try to give some of the information on tables. ? Please comment on: IL-22BP has a crucial role in controlling tumorigenesis and epithelial cell proliferation in the colon. Please comment on the IL-22-IL-22BP axis that critically regulates intestinal tissue repair and tumorigenesis in the colon. [Nature. 2012 Nov 8;491(7423):259-63] ? In the last 3 lines of “Cyclooxygenase and Resolvins section” authors comment on the hypothesis about “the balance struck by linoleic and arachidonic acid metabolisms in the LOX pathway activity shifts from the antitumorigenic 15-LOX-1 and 15-LOX-2 pathways to the protumorigenic 5-LOX and 12-LOX pathways during tumorigenesis “. There is a potential explanation and please comment: The acyl-CoA synthetase 4 (ACSL4), which esterify mainly arachidonic acid (AA) into acyl-CoA, is increased in breast, colon and hepatocellular carcinoma. The transfection of MCF-7 cells with ACSL4 cDNA transforms the cells into a highly aggressive phenotype and controls both lipooxygenase-5 (LOX-5) and cyclooxygenase-2 (COX-2) metabolism of AA, suggesting a causal role of ACSL4 in tumorigenesis. PLoS One. 2012;7(7):e40794. doi: 10.1371. ? Anaerobic metabolism: please give reference and comment on the following: Mitochondrial transcription factor A (TFAM) is required for expression and maintenance of mtDNA. [Am J Pathol. 2012 Jan;180(1):24-31]. Ability of pathophysiological concentrations of insulin to induce DNA damage in colon cells and human peripheral lymphocytes through the overproduction of reactive oxygen species (ROS). [Mutat Res.



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2013 May-Jun;745-746:34-9] ? Please comment on Hypoxia inducible factor 1 and its role in apoptosis: Cancer cells die through apoptotic pathway either being biphasic caspase-3-dependent (HCT116) or independent (HT29). Multipathway analysis reveals that CBF-induced apoptosis is likely modulated by the hypoxia-inducing factor-1 alpha subunit (HIF-1  $\alpha$ ) as its inhibition was evident in vitro and in vivo. [Evid Based Complement Alternat Med. 2013;2013:849054. doi: 10.1155/2013/849054. Epub 2013 May 30] ? Please explain the mechanism that the inflammation results in hypoxia: e.g. the role of hypoxia-inducible factor and epithelial integrins as mediators of epithelial repair following inflammatory injury at the mucosal surface [Front Immunol. 2013 Sep 11;4:272.] ? Section "Nuclear factor..... Nrf2" authors state: "The involvement of Nrf2 in cancer pathogenesis is a controversial topic, provided a number of reports that still assign Nrf2 a role in cancer chemoprevention from genotoxic agents or inflammation". Please consider: At the later stages, the hypoxic microenvironment around the malignant tumors has a profound influence on the character of Nrf2. Under the hypoxic microenvironment, expression of certain downstream genes of Nrf2 involved in angiogenesis are obviously elevated; other transcription factors derived from hypoxic microenvironment interact with Nrf2 and in that way promote or inhibit the invasion and metastasis. [Crit Rev Eukaryot Gene Expr. 2013;23(1):37-47.] ? Some additional information as to the Role of Sirtuins in IBD-Please consider: Autophagy and sirtuin activities are linked through 5'AMP-activated protein kinase (AMPK) activation, which switches on autophagy and increases sirtuin. The effect of melatonin on AMPK and the impact of this effect on IBD and colon cancer remains an open question. [J Pineal Res. 2011 Aug;51(1):44-60] ? Finally a short reference to studies translating each pathway's perspective to clinical practice would be to the read



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### ESPS Peer-review Report

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

**ESPS Manuscript NO:** 5895

**Title:** Inflammatory pathways in the early steps of colorectal cancer development

**Reviewer code:** 00058381

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

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**Date reviewed:** 2013-11-08 04:56

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

### COMMENTS TO AUTHORS

**Major comment:** This manuscript provides an interesting description of inflammatory pathways in the early steps of colorectal cancer development. However, from the clinical point of view, a more concise presentation of the crucial facts would be desirable. **Minor comments:** Stylistic/linguistic improvement required (e.g. problems with singular and plural like "...several points remains obscure", "A continuous ROS production contribute...", "The major players of these changes is..." etc.) NB: Have the figures been made by the authors?



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## ESPS Peer-review Report

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

**ESPS Manuscript NO:** 5895

**Title:** Inflammatory pathways in the early steps of colorectal cancer development

**Reviewer code:** 00068472

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

**Date sent for review:** 2013-09-29 15:52

**Date reviewed:** 2013-11-10 21:32

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"/> Rejection
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

**General** The authors address the important area of inflammation in colorectal cancer development. At first sight the manuscript seems impressive. However, overall, the presentation of the topic is a little confused. In my view, the manuscript should be shortened. The English language should be improved.

**Specific comments** Overall, the presentation of the topic is a little confused. The English language should be improved. In my view, the manuscript should be shortened. (i.e. sections: Inflammatory cells and proteins, Macrophages, Neutrophils; Oxidative microenvironment; Nuclear factor E2-related factor 2 (Nrf2). In "Inflammation and remodelling" section the authors discuss briefly the role of proteolytic enzymes in inflammation and cancer. They should spend time to describe in more detail what role MMPs and TIMPs play in inflammation, inflammatory diseases, cancer-associated inflammation and colorectal cancer progression. Please also see some recent reviews in this respect (Herszenyi L. et al. Dig Dis. 2012;30(3):249-54.; Lakatos G. et al. Dig Dis 2012; 30: 289-295; or Herszenyi L. et al. Int J Mol Sci 2012; 13(10): 13240-13263.). In this section, the role of other proteolytic enzymes, such as cysteine proteases /cathepsins/, urokinase plasminogen activator/inhibitor system should also be addressed in more detail. The authors should describe the various therapeutic options and potential target therapy regarding inflammation, including some chemoprevention strategies for colorectal cancer. A clear-cut table including the main players in inflammatory pathways in colorectal cancer development should be added. As previously suggested, the list of References should be completed.