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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 39281

Title: Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways - A review

Reviewer's code: 00227487

Reviewer's country: Japan

Science editor: Fang-Fang Ji

Date sent for review: 2018-04-16

Date reviewed: 2018-04-17

Review time: 13 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I think this review article is well written and comprehensive. However, following two reviews can be cited. 1) Tanaka T. Colorectal carcinogenesis: Review of human and experimental animal studies. J Carcinog. 2009;8:5. PubMed PMID: 19332896 2) Rosenberg

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DW, Giardina C, Tanaka T. Mouse models for the study of colon carcinogenesis. Carcinogenesis. 2009 Feb;30(2):183-96. PubMed PMID: 19037092

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

[ ] The same title

[ ] Duplicate publication

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 39281

Title: Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways - A review

Reviewer's code: 02440884

Reviewer's country: Germany

Science editor: Fang-Fang Ji

Date sent for review: 2018-04-16

Date reviewed: 2018-04-18

Review time: 2 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The review is focussed on pathways driving colorectal carcinogenesis. In the manuscript important pathways are mentioned and some networks are addressed. Comments 1. Important pathways should be illustrated with detailed schemes. 2. The molecular

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network of the different pathways should be addressed in detail. 3. miRNAs are important players in CRC. They should be introduced to the reader. 4. The serrated pathway and MSI pathway should be given

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 39281

Title: Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways - A review

Reviewer's code: 00073640

Reviewer's country: Slovenia

Science editor: Fang-Fang Ji

Date sent for review: 2018-04-16

Date reviewed: 2018-04-19

Review time: 3 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The title is topical and the abstract is promising. The manuscript is well written and structured. However, there are some major drawbackes that need to be corrected: 1. Section Colon polyps – gate keeper in CRC: the whole section needs to be properly

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corrected, including the title. Gate keeper in CRC???? In this section data and definitions are oversimplified and do not represent the actual pathological knowledge. Colon polyps are macroscopically visible pathological formation, protruding above the mucosa surface into colon lumen. Histologicaly, polyp can represent a mucosal fold, inflammatory formation, benign (hyperplastic, dysplatic lesion, adenoma) and malignant tumor (carcinoma). Cautiously, the term polyp denotes also other formations!!! Colon polyps are not the lesions with aberrant growth that appear on the colon. There are also various forms of flat lesions and dysplatic crypts (they are not polyps) that can progress in CRC. CRC can also arise from carcinoma in situ, which is not polyp. When there is a talk about polyps, hyperplatic, adenomatous or malignant lesions, which are terms that denote precise pathology, there is a need to be correct and not to mislead. Therefore, I strongly suggest including correct pathological definitions and classification in this section. 2. Section- Symptoms and risk factors: Authors wrote: "The risk due to environmental factors include consuming diet rich in red meat and fat, etc...". It was found that the composition of the fat in more important than the amount of ingested fat. For instance, diets high in n-3 polyunsaturated fatty acids (PUFA), olive oil or n-9 monosaturated fatty acids have shown a protective or no effect on the colon carcinogenesis in animal models, while diet high in saturated fatty acids, such as lard or beef tallow, and n-6 PUFA, such as corn or sunflower oil, has been associated with an increased risk of colon cancer. 3. Section - Stages of colon cancer: Figure 1 is misleading and does not show all stages correctly – stage III and IV includes the whole organism. It is also interesting that authors did not picture polyp structure (described in the previous section), but only small lesion inside the mucosa. 4. Murine models of colorectal cancer: murine models are briefly introduced, therefore I strongly suggest refering the readers to some good review articles of particular model for more information about characteristics of a model. 5. Section Epithelial cells: Authors wrote: "The abnormal accumulation of

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epithelial cells can cause mutation in oncogenes and tumour suppressor genes that result in polyp, the neoplastic growth." Delete the word polyp from the sentence (as explained under point 1). "Thus formed adenomatous polyps in the colon and rectum, which is a benign lesion, have the potential to further develop into cancer and metastasize to other organs" Replace the word polyp with the term lesion (see point 1). 6. Currently, there are different signaling pathways known in CRC – for instance, hereditary CRC (FAP, hereditary nonpolyposis), sporadic CRC (serrated, non-serrated), CRC associated with ulcerative colitis. In the article not all pathways are mentioned. Thus, I suggest introducing all currently known pathways otherwise the authors should reform the title (sporadic CRC for instance). 7. Schematic presentations of signaling pathways would additionaly improve the manuscript.

INITIAL REVIEW OF THE MANUSCRIPT

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[ ] The same title

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[ ] Plagiarism

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 39281

Title: Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways - A review

Reviewer's code: 00183445

Reviewer's country: Poland

Science editor: Fang-Fang Ji

Date sent for review: 2018-04-16

Date reviewed: 2018-04-23

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript meets the main criteria for publication. The work contains important epidemiological data on the prevalence of colorectal carcinogenesis. It classifies polyps and indicates the possibility of their transformation and focuses on the role of

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inflammatory response in colorectal carcinogenesis. Describes symptoms, risk factors and stages of colon cancer. A significant advantage of the work is the presentation of the best experimental models of colorectal cancer. The Authors discuss the role of epithelial cells as target cells in colorectal cancer. Emphasizes the importance of various types of cell death to search for new therapeutic tools. Finally, signaling pathways in colon cancer are well described as a tools for new terapeutic options. The article is well constructed. It requires only a few language corrections, especially in the use of commas. Figure 2 needs to clarify the abbreviations. I am not convinced about the pictures inside Figure 3. It is better to make a table. In general it is a good proposition among medical review articles.

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