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## PEER-REVIEW REPORT

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

**Manuscript NO:** 35659

**Title:** Fusobacterium’s Link To Colorectal Neoplasia Placed Under The Microscope: A Systematic Review

**Reviewer’s code:** 00070509

**Reviewer’s country:** South Korea

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2017-07-30

**Date reviewed:** 2017-08-02

**Review time:** 2 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	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"/> The same title	<input checked="" 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"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

### COMMENTS TO AUTHORS

I think this manuscript is valuable to understand the association of Fusobacterium and colorectal cancer. The authors reviewed 90 articles systematically and comprehensively and found some reliable associations between Fusobacterium and colorectal cancer. This manuscript is well designed and written.



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## PEER-REVIEW REPORT

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

**Manuscript NO:** 35659

**Title:** Fusobacterium's Link To Colorectal Neoplasia Placed Under The Microscope: A Systematic Review

**Reviewer's code:** 01512187

**Reviewer's country:** Germany

**Science editor:** Ya-Juan Ma

**Date sent for review:** 2017-08-10

**Date reviewed:** 2017-08-21

**Review time:** 11 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	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"/> The same title	<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"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

### COMMENTS TO AUTHORS

This is a broad review of literature dedicated to fusobacterium sequences found in colonic samples from patients with colonic cancer. The review will be definitively helpful for all interested in the topic, surely often cited and should be published. However the presentation is very subjective, the terminology blurring and the interpretation overextended. The presentation would be improved, if some especially marked overstatements will be corrected. 1. The title "FUSOBACTERIUM'S LINK TO COLORECTAL NEOPLASIA PLACED UNDER THE MICROSCOPE:" should be changed. I do understand that the authors are using the word "microscope" literarily. However, the metaphor is definitively wrong in the context of the manuscript. No data on microscopic appearance of the microbe-mucosa interactions are presented or discussed in the review. The only reference , which was using FISH with unspecific



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Fusobacteria probe[57] completely avoids the description of the observed histopathology of bacterial involvement and is not discussed by author in context. 2. The authors are pretty reluctant in using medical terms. Also this bad habit is getting more and more spread as pure biologic studies are published in medical journals, the WJG is clinically oriented. The correct use of clinical terminology should be aimed at. The word pathogen was mentioned in the following sentences: Fusobacterium is one of the most cited bacterial pathogens Oral Fusobacterium consist mainly of the species Fusobacterium nucleatum (Fn), an adherent [12], invasive [13], and proinflammatory [14, 15] pathogen Fn is classified into subsp. animalis, fusiforme, nucleatum, polymorphum, and vincentii [20]. F. Varium is another pathogenic Fusobacterium Fusobacterium and other pathogens with CRC. studies linking pathogens such as Fusobacterium to survival through peripheral immune modulation Compared to PCR, loop-mediated isothermal amplification (LAMP) is a simple, non-costly and accurate method for pathogens testing that was shown to be more sensitive than PCR for Fn detection [108]. In all these cases applying the word "pathogen" is incorrect. Most fusobacteria, including Fusobacterium nucleatum, are indigenous for healthy mouth microbiota. Although some fusobacteria species can be involved in pathogenesis. Declaring a bacterium to be a pathogen can not be done at will. I recommend to replace the word "pathogen" through bacteria in all cited sentences, or exactly the author should define what he means. 3. The presentation is often to affirmative and misleading at the same time For example: "... Fn is the most detected species of Fusobacterium in CRC tissue [40-52]. Furthermore, Fn ssp Animalis is the most abundant subspecies of Fn in CRC tissue in two out of three studies that had more indepth analysis....." Using "was" instead of "is", is probably more appropriate. "Most abundant" should be "frequent". Otherwise the concentrations of microorganism should be mentioned. The above statement is misleading. What the authors avoid to say in the above sentence is the fact, that in each person (CRC tissue sample) sequences of multiple different fusobacteria species were detected in different composition with some Fusobacteria predominant (most detected, abundant, frequent.... whatever), which makes the possibility of infection through a single pathogen unlikely and Fusobacteria using some kind of changes in environment occurring around carcinogenesis more probable. The authors should discuss this point and bring their explanation of this fact instead of hiding it behind "most". 4. I do understand the enthusiasm of the authors, however the overstatements and blurred terminology devalue the manuscript. This is especially noticeable in conclusions starting with the first and very strong sentence: "Fn enrichment in colorectal mucosa seems to be an early event occurring during colon carcinogenesis, even prior to the formation of adenoma or serrated lesions but not sufficient on its own to initiate CRC." What do the authors mean with enrichment? Adherence? Invasion? Adsorption?



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What do the authors mean with colorectal mucosa: epithelial cells, mucus, stroma? What do they want to express with even in “early event of carcinogenesis”, even prior to carcinogenesis? Do the authors mean that Fn is primary to cancer? As what? Infection? Colonization? Phagocytosis? How multiple individually composed Fusobacteria sequences found in each sample can be primarily? I would start the conclusions with: Sequences of Fusobacteria and especially *Fusobacterium nucleatum* are significantly more often detected in colorectal tissues and stools of patients with CRC than in healthy controls. The histopathology of this findings is unclear: no relevant data exist to whether the bacteria are adherent, invasive, taken up by macrophages, polluting the crypts, or simply stick to vulnerable and not protected mucosal areas. The lack of this information makes the interpretation of the data difficult. Fusobacteria are indigenous for healthy mouth microbiota, highly adherent to teeth and oro- pharyngeal epithelium in the presence of low viscous saliva environment, but unspecialized for viscous environment and therefor normally only transient in the intestine, the mucosa is covered with a mucus layer, which is impenetrable for bacteria. In case of a disturbed mucus barrier (locally over carcinoma or generally in the colon due to conditions preceding carcinoma formation like ulcerative colitis and other), oral Fusobacteria may get advantages in attaching to the denuded regions of colonic epithelium, leading to all described peculiarities in occurrence of Fusobacteria sequences in colonic cancer and making Fusobacteria to an interesting indicator of condition. Although the mechanism and sequels of this attachment (invasion, colonization, phagocytosis) are presently unclear, a strong correlation between colonic mucosa associated Fusobacteria and cancer, make the possibility of Fusobacteria coinvolvement in colonic carcinogenesis to an intriguing concept, which still has to be unraveled in details. 5. English is not my native language. For my opinion many of the sentences are grammatically wrong or at least difficult to understand: For example: “Fn is demonstrated to have cancer promoting properties in several rodent models support a role in the human colon cancer cascade.” Either the thoughts are jumping or something is lacking. I recommend an English native editor to go through the text.