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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 72109

Title: Gut homeostasis, injury, and healing: new therapeutic targets

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03252330
Position: Editorial Board
Academic degree: MD, MSc

Professional title: Associate Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2021-10-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-10-21 07:40

Reviewer performed review: 2021-11-03 17:49

Review time: 13 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The submitted review focuses on the mechanisms involved in gut healing after injury, and on the possible new therapeutic approaches. Although the review includes several aspects of the mechanisms responsible for injury and/or healing, only some of the molecular data that became available in the last years are reported or discussed. A wider coverage of the molecular mechanisms involved in the differentiation, for example, is not trivial, since the authors state, on page 12, that: "Although some authors describe the initial steps of this process as dedifferentiation, it is the firm opinion of the senior author that this should rather be considered a redifferentiation toward a migratory phenotype". This sentence has to be supported by data that go beyond pure morphology. The sentence on page 17 "A specific TFF receptor has not been described. Rather, the TFFs mediate epithelial restitution via the EGFR[146,147], CXC chemokine receptors (CXCR)[148,149], or other receptors." should be further detailed, since TFFs are identified as possible therapeutic agents. Figure 3 should also include a panel showing the passages involved in FAK activation. A figure summarizing all the more promising new therapeutic approaches should be added. The sentence:" Thus, even though PPIs are still recommended to treat upper GI ulcers, their prophylactic use with NSAIDs to prevent upper GI injury is no longer recommended[42]." Should be modified, since guidelines recommend the use of PPI in patients with risk of peptic ulcer disease (DOI: 10.1136/gutjnl-2019-319300 and FDA guidelines).

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Peer-review model: Single blind

Reviewer's code: 05260944
Position: Peer Reviewer
Academic degree: MD

Professional title: Academic Fellow

Reviewer's Country/Territory: Russia

Author's Country/Territory: United States

Manuscript submission date: 2021-10-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-08 17:37

Reviewer performed review: 2021-11-12 07:51

Review time: 3 Days and 14 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The article describes the pathophysiological and molecular mechanisms of protection, surface damage and healing of the gastrointestinal mucosa. The title of the article does not fully correspond to the content of the article. instead of "Gut" I recommend to use "gastrointestinal mucosa". The first 10 pages describe in great detail the physiological and pathophysiological mechanisms of damage and protection of gastrointestinal mucosa, which are well known and do not require such detail, it is better to shorten this part and add more information about the molecular mechanisms. It is recommended to elaborate more your reasoning about this problem. "However, if the wound extends into deeper layers such as the submucosa and muscularis, these must also be reconstructed for healing by processes beyond the scope of this review" - p.14, it is suggested to expand the review , or highlight that it is mainly about superficial defects of the gastrointestinal mucosa. It is necessary to update the literature review with recent studies of up to last 5 years.

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Title: Gut homeostasis, injury, and healing: new therapeutic targets

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02440884
Position: Editorial Board
Academic degree: MD

Professional title: Chief Doctor, Full Professor, Professor, Senior Lecturer

Reviewer's Country/Territory: Germany

Author's Country/Territory: United States

Manuscript submission date: 2021-10-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-05 09:53

Reviewer performed review: 2021-11-15 10:07

Review time: 10 Days

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In the review new therapeutic targets for treatment of mucosal injuries in the intestine are addressed. A pathophysiologial overview is given and important targets and molecules are discussed. A focus is given on focal adhesions and the focal adhesion kinase (FAK). The topic of the manuscript is of broad importance and in the scope of the journal. Comments 1. In some parts of the review the facts and data are given as accepted truth representative for the whole gastro-intestinal system. The authors should make the attempt to give the data more precise to illustrate the loco-regional high diversity of molecular/ cellular wound-healing and the underlying mechanisms along the GI-tract. 2. NSAIDs are discussed as important substances for mucosal injury. In a short paragraph the morphological overlap of NSAID induced injuries with ischemic triggered tissue damage should be addressed and loco-regional differences of molecular mechanisms should be introduced to the reader. 3. Bile acids are addressed as molecules with tissue damage capacity. Additional information is necessary concerning the heterogeneity of bile acids and their divers tissue effects in the GI-tract. 4. Figure 1: the scheme addresses mucosal healing in the stomach. The information “gut” is misleading. Alternative an additional scheme is necessary addressing mucosal healing in the small/ large gut.