

Reviewer 01

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

The manuscript is a comprehensive overview on Notch signaling pathways and the implication related for developing innovative therapies against cholangiocarcinoma. The manuscript is well written in English and deserves to be published in World Journal of Gastrointestinal Oncology after minor revisions. 1 the authors should explain if the manuscript is a systematic review or a narrative review and the procedure adopted in articles' selection. In case of systematic review authors should follow PRISMA guidelines. 2 Keyword: modify "Cholangiocarcinma" in cholangiocarcinoma 3 In the introduction authors describe an increase in the incidence and mortality rate of cholangiocarcinoma. They should add few lines on the uncertain benefit concerning adjuvant therapy highlighting the aggressive behavior of CCA after radical surgery. Please cite the reference: Messina C, Merz V, Frisinghelli M, et al. Adjuvant chemotherapy in resected bile duct cancer: A systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol. 2019;143:124-129.

Answers:

1 The authors should explain if the manuscript is a systematic review or a narrative review and the procedure adopted in articles' selection. In case of systematic review authors should follow PRISMA guidelines.

This is not a systematic review, therefore, PRISMA guidelines have not been followed. It's a narrative review and the entire search has been done via Pubmed.

2 Keyword: modify "Cholangiocarcinma" in cholangiocarcinoma

It has been corrected. Kindly review.

3 In the introduction authors describe an increase in the incidence and mortality rate of cholangiocarcinoma. They should add few lines on the uncertain benefit concerning adjuvant therapy highlighting the aggressive behavior of CCA after radical surgery. Please cite the reference: Messina C, Merz V, Frisinghelli M, et al. Adjuvant chemotherapy in resected bile duct cancer: A systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol. 2019;143:124-129.

The recommended reference has been mentioned and added on page No: 04.

Reviewer 02

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Bisma R. and co-authors in the current review gave an update on the contribution of Notch signaling in the development of cholangiocarcinoma (CCA). Overall this review is adequate, however, the originality seems biased by the publication in 2017 (Cigliano et al.) of a very similar paper. In this perspective the authors should privilege the description of most recent findings (after 2017) with regard to Notch and CCA. Some other points, in my opinion, need attention: 1) The relationship between miR-200 and Notch signaling in tumor development should be included. 2) I would suggest to organize the review in sub paragraphs (such for instance: Notch 1, Notch 2; Notch 3 and so on, also for paragraphs regarding ligands and therapeutic agents) in order to improve clarity. 3) I would include a table summarizing main data (with references) regarding Notch signaling and CCA in human and animal models. 4) Another table should summarize main experimental results obtained modulating Notch signaling in CCA. 5) The conclusion paragraph should be shortened as it includes information already reported in the previous parts of the review. 6) There are some type errors that need to be fixed.

Answers:

Bisma R. and co-authors in the current review gave an update on the contribution of Notch signaling in the development of cholangiocarcinoma (CCA). Overall this review is adequate, however, the originality seems biased by the publication in 2017 (Cigliano et al.) of a very similar paper. In this perspective the authors should privilege the description of most recent findings (after 2017) with regard to Notch and CCA.

All the references regarding the role of Notch Signalling pathway in cholangiocarcinoma (CCA) and current therapeutic innovations have been updated in main contents and texts of article and could be found/confirmed in reference section. Choosing 'last 5 years search option' in Pubmed search engine has preferably performed for the search for references after 2017.

1) The relationship between miR-200 and Notch signaling in tumor development should be included.

It has been included on the page No: 32.

2) I would suggest to organize the review in sub paragraphs (such for instance: Notch 1, Notch 2; Notch 3 and so on, also for paragraphs regarding ligands and therapeutic agents) in order to improve clarity.

It has been done. Kindly review the main body of article. All recommended headings have been added.

3) I would include a table summarizing main data (with references) regarding Notch signaling and CCA in human and animal models.

Table 01 entitled ‘**Table 01: List of main representative of Notch Signalling pathway and their current findings in development of Cholangiocarcinoma (CCA)**’ has been made and provided with the revised manuscript. Kindly review.

4) Another table should summarize main experimental results obtained modulating Notch signaling in CCA.

Table 02 entitled ‘Table 02: Anti-Notch therapeutic targets examined in vivo and/or in vitro for the treatment of CCA’ has been made and provided with the revised manuscript. Kindly review.

5) The conclusion paragraph should be shortened as it includes information already reported in the previous parts of the review.

The conclusion paragraph has been shortened and information already reported in the previous parts has been removed. Kindly review.

6) There are some type errors that need to be fixed.

All type errors have been removed and checked several time in revised manuscript. Kindly review.

Reviewer 03

Thanks to Reviewer for nice comments and recommendation for publication in WJGO.