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**ESPS Peer-review Report**
**Name of Journal:** World Journal of Gastroenterology
**ESPS Manuscript NO:** 6174
**Title:** The Hedgehog signaling pathway as a new therapeutic target in pancreatic cancer
**Reviewer code:** 00289642
**Science editor:** Wen, Ling-Ling
**Date sent for review:** 2013-10-08 09:51
**Date reviewed:** 2013-11-18 13:55

| CLASSIFICATION | LANGUAGE EVALUATION | RECOMMENDATION | CONCLUSION |
|---|---|---|---|
| [ Y] Grade A (Excellent) | [ Y] Grade A: Priority Publishing | Google Search: | [ ] Accept |
| [ ] Grade B (Very good) | [ ] Grade B: minor language polishing | [ ] Existed | [ ] High priority for publication |
| [ ] Grade C (Good) | [ ] Grade C: a great deal of language polishing | [ ] No records | [ ]Rejection |
| [ ] Grade D (Fair) | [ ] Grade D: rejected | BPG Search: | [ Y] Minor revision |
| [ ] Grade E (Poor) | | [ ] Existed | [ ] Major revision |
| | | [ ] No records | |

**COMMENTS TO AUTHORS**

In this brief review article, Drs. Onishi and Katano discussed the current strategies to treat pancreatic cancer, highlighting the therapeutic potential of inhibiting the Hedgehog signaling cascades in targeting pancreatic cancer stem cells. Specifically, after a brief introduction of the Hh signaling pathway and its roles in cancer, they overviewed studies showing that the activation of Hh signaling, through either autocrine or paracrine mechanisms, can serve as an indicator of pancreatic cancer malignancy in clinical settings. Hh signaling cascade is active in the pancreatic cancer stem cells, and hypoxia condition, commonly observed in pancreatic cancer environment, leads to Hh signaling activation. Taken together, they argued that targeting the Hh signaling cascades can be a novel therapeutic strategy to treat pancreatic cancer. The manuscript is well-written, with up-to-date informative and persuasive arguments on the importance of targeting Hh signaling in pancreatic cancer treatment. Some minor suggestions: are studies with animal models consistent with the role of Hh signaling in pancreatic CSCs or Hh up-regulation under hypoxia conditions? A discussion of results from animal studies will strengthen the arguments in the essay.

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**COMMENTS TO AUTHORS**
In their review "The Hedgehog signaling pathway as a new therapeutic target in pancreatic cancer" the authors points out the relevance of the Hedgehog signaling pathway and its role as a novel therapeutic target in pancreatic cancer treatment.

In their submitted review the authors show the physiological role of the Hedgehog pathway during embryogenesis, the dysregulation in pancreatic cancer cells and underline the therapeutic option by inhibiting this pathway in pancreatic cancer.

The authors describe the physiological function of the Hedgehog pathway and point out different steps of this pathway and their role during activation. Nevertheless, to get a better insight in the importance of the Hedgehog pathway it would be helpful to present some target genes of this signaling, which are affected by activation of the Hedgehog pathway and play a crucial role in carcinogenesis.

Furthermore, the authors describe the different activation paths of the Hedgehog signaling and their influence in tumor disease. However, also here the authors are encouraged to present target genes of this pathway which are typically dysregulated in cancer cells.

Furthermore, in the introduction part the author underline that Hedgehog signaling contributes to tumor aggressiveness by taking influence on proliferation, invasion and progression of cancer cells. Nevertheless, the majority of this review deals with the activation mechanism of this

pathways in cancer cells and less with the exact influence of Hedgehog activation in tumor cell characteristics. For these reasons the authors are encouraged to provide more information concerning the influence of the Hedgehog pathway on the cellular/molecular level and its effect on proliferation and invasion?

However, besides using the Hedgehog pathway in tumor therapy it would be very interesting to know, in how far this signaling could also be used as a prognostic tool. Are there any data indicating that the activity of Hedgehog signaling correlates with patients' outcome? How feasible will be the incorporation of the Hh signaling in every day clinical routine? The authors are encouraged to discus these matter.

A more detailed prospective how and when Hh signaling can be used in future clinical life should be discussed more in detail.

**Confidential comment to the editor:**

Taken together, the authors provided an interesting overview about the actual role of the hedgehog signaling pathway and the status of inhibiting this pathway in tumor therapy. Although some details are missing, the author could provide a good insight in this topic. Therefore my final decision would be major revision of this paper.