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Dr. Thomas Y. Ma
Editor-in-Chief
World Journal of Gastrointestinal Pathophysiology

Dear Dr. Ma,

Thank you very much for inviting me to write the review article “The elusive liver factor that causes pancreatic alpha cell hyperplasia” (ID 00077678). I now submit it to you.

Reviewer 1.

The work is very interesting and innovative. The search for markers is very important in assessing the risk of pancreatic neuroendocrine tumors (PNETs). The title should include the information that this is a manuscript of a review character. The abstract and introduction are clear for the reader. Chapter: Materials and methods was not presented. Due to the fact that the article is of review character after the introduction it should include information on the method used, such as databases, data, material analysis period, the criteria for inclusion and exclusion.

Author response: We appreciate the positive comments. We now add “a review of literature” in the title to indicate it is a review article (Page 1). We also add a section on how data are collected (page 5).

Reviewer 2.

The major concern i have with this manuscript is that though the title reads 'the elusive liver factor', giving the feel that the authors have discovered it, htere is no proven factor. Thus the entire is review is purely hypothetical. Hence, i am unsure that World Journal of Gastrointestinal Pathophysiology would be the appropriate journal for this manuscript. A more appropriate journal would be, "Medical Hypothesis".

Author response: Elusive means “hard to find or capture” by Merriam-Webster dictionary. We clearly present data to strongly demonstrate the existence of a liver factor. We still do not know the identity of the liver factor (thus “elusive”). Therefore our review is based on strong experimental grounds and not hypothetical.

Reviewer 3.

Yu et al. present a review on Alpha cell hyperplasia and Focus on the reactive ACH and on the Mahvash disease. The review article is well-written and summarizes in vitro and in

vivo mouse experiments. The review would benefit from an additional drawing of the cellular mechanisms and pathways involved in reactive ACH.

Author response: We appreciate the positive comments. We add such a drawing (new Fig 2).

Thank you very much for your consideration.

Sincerely yours,

A handwritten signature in black ink, appearing to be 'Run Yu', written in a cursive style.

Run Yu, MD, PhD