Author's response to reviews

Title: Weak Up-regulation of Serum Response Factor in Gastric Ulcers in Patients with Co-morbidities is Associated with Increased Risk of Recurrent Bleeding

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Author's response to reviews: see over
Dear Editor-in-chief, Prof. Melissa Norton:

At first, all the author appreciate the constructive comments to provide us an opportunity to revise our article, entitled with “Weak Up-regulation of Serum Response Factor in Gastric Ulcers in Patients with Co-morbidities is Associated with Increased Risk of Recurrent Bleeding”. We here provide our point-to-point response of revision and sincerely hope the article could be satisfactory and accepted for publication as "Original article" in your excellent journal “BMC Gastroenterology”. We hereby certify that this manuscript consists of original unpublished work that is not being considered for publication elsewhere.

All authors also have read the manuscript and conflict of interest statement and approved their submission for publication; the work is original and has not been published and is not being considered for publication elsewhere, in whole or in part, in any language. To speed the review, we have marked the revised part of article in blue color. Further comments concerning this manuscript should be addressed to the corresponding author: Professor Bor-Shyang Sheu, MD., Department of Internal Medicine, Medical College, National Cheng Kung University, 138 Sheng Li Road, Tainan, Taiwan, 70428. E-mail: sheubs@mail.ncku.edu.tw

Sincerely yours

Bor-Shyang Sheu, MD.
Response to Reviewer #1:

Query 1: Both NSAIDs and *H. pylori*, the most important damaging factors of gastric mucosa had no effect on SRF expression. Since SRF plays a central role in ulcer healing, how this phenomenon could be explained? The authors should discuss this issue in context of literature.

Response: The study does not mean there is no effect of SRF by *H. pylori* or NSAIDs. In Figure 2, our result just illustrate there were no differences between the SRF expressions of gastric ulcer related with *H. pylori* infection and NSAID in etiology. We also try to explain why there are no differences between the ulcers with different major etiologies. SRF is activated by extracellular stimulations such as serum and mitogens through a ternary complex factors-dependent pathway involving the ras-raf- MAPK-ERK cascade and other pathways. *H. pylori* infection activates the SRE-driven *c-fos* transcription in epithelial cells through the activation of ERK/MAPK cascade. It is well known that NSAID suppresses the ERK signaling pathway via block of Ras/cRaf interaction, however, little is known about the effect of NSAID on SRE-driven genes transcription. The possible reasons may be whatever the etiology of gastric ulcers is, SRF shall have been triggered and activated by wounding, despite of the etiological causes. Following the suggestion, we add some statements in discussion (Page 14, 2nd paragraph, lines 1-6).

Query 2: What was the positive control for immunohistochemical staining for SRF? Authors should include the positive SRF-immunostaining control in the manuscript.

Response: The colon ulcer tissue was used for positive control (Page 7, lines 8). We add the picture of the positive control as Figure 1E.

Query 3: SRF is an important component of ulcer healing which promotes migration and proliferation of gastric epithelial and smooth muscle cells. Authors should analyze the changes in proliferation index (PCNA or Ki-67) at the ulcer edge in dependence of SRF expression.

Response: We agree that it is important to analyze the change in proliferation index at the ulcer edge. However, we did not analyze such change. Accordingly, we describe such novel point as limits of our study and implicate the potential study is anticipating in the discussion (Page 14, line 1-3).

Query 4: Decrease in SRF expression inhibition angiogenesis driven by VEGF, which plays a crucial role in ulcer healing. It would be of importance to investigate this aspect of ulcer healing. Did patients with low SRF-expression had decreased VEGF expression?

Response: SRF deficiency inhibits VEGF-stimulated endothelial cell migration and proliferation and inhibits angiogenesis. However, this study did not examine VEGF expression. Further study should validate whether patients with weak SRF up-regulation have decreased VEGF expression and poor angiogenesis (Page 13, last paragraph).
**Response to Reviewer #2:**

**Query 1:** In the last sentence of the discussion, authors hope in the future study SRF can be measured in the serum instead of tissue staining. Unfortunately, that is impossible. SRF is a transcription factor. It cannot be measured by serum check-up.

**Response:** We totally agree the reviewer’s point and we delete the sentence.

**Query 2:** In multiple places of the text, authors say “SRF expression on gastric ulcer tissues”, it should be “in gastric tissues”.

**Response:** We have revised “SRF expression on gastric ulcer tissues” to be “SRF expression in gastric ulcer tissues”.