

March 18, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 8863-review.doc).

Title: Targeted migration of mesenchymal stem cells modified with CXCR4 to acute failing liver improves liver regeneration

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 8863

The manuscript has been improved according to the suggestions of reviewers:

1 Formats have been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Q: "Did the authors check the level of albumin in the treated mice vs the null mice? "

A: ALT and AST are the most common indexes for liver function. And liver function includes many indexes, such as ALT, AST, Albumin, Globulin, Bilirubin, Ammonia, ALP, LDH and so on. Different indexes represent different functions of liver. Among them, ALT and AST response to damage of hepatocytes. Albumin represents hepatic synthetic function. Bilirubin represents hepatic secretory function. Because we mainly assessed the damage of hepatocytes, we detected the level of ALT and AST, while albumin was not detected.

(2) Q: "no difference was observed cell viability between TAA+CXCR4-MSC and TAA-null-MSC, why is that?"

A: The viability of hepatocytes co-cultured with CXCR4-MSC was higher than that with Null-MSC, but there was no statistical difference. We speculate that because of either CXCR4-MSC or Null-MSC can secrete some trophic factors, such as VEGF, EGF, IGF, HGF, NO, EPO, et al, these factors can prevent the surrounding cells apoptosis (Rehman J, et al. Circulation 2004), so both CXCR4-MSC and Null-MSC can increase the cell viability. Though CXCR4 can upregulate ERK to improve cell survival, it was achieved through the ligand binding of CXCR4. In our study, CXCR4 located on the surface of MSC, not secreted to the medium, this may reduce the upregulation effect of CXCR4 on ERK. If we use recombinant CXCR4 protein instead of CXCR4-MSC to repeat this experiment, we may find the statistical difference.

(3) Q: "how long does MSC reside in the target tissue. Is MSC visible after 5 days? Also, when was the H&E staining done? Are you able to detect MSCs? If MSC are no longer detectable after 5 days, yet the authors are able to see recovery beyond that, does it mean the MSC has differentiated into hepatocytes? Or the improved recovery is due to paracrine signaling?"

A: Recent study reported that living mesenchymal stem cells disappear rapidly after intravenous infusion (Hoogduijn MJ, et al. 2011). We used fluorescence microscope to detect the MSC at week 2 and we couldn't find GFP+ MSCs (data not shown). So we considered that the therapeutic effect was achieved by paracrine effect. And the increase of VEGF and HGF confirmed our hypothesis.

3 References and typesetting were corrected

Thank you for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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