Dear Professor Lian-Sheng Ma, Professor Jia-Qi Zhu, Professor Jia-Ping Yan, and Reviewers:
I would like to express my gratitude for your letter and comments concerning our manuscript. The comments are all valuable and were very helpful for revising and improving our paper as well as for providing important guiding significance to our research. Please find the itemized responses below. All changes are highlighted in yellow in the manuscript and revision note. Once again, thank you very much for your review.

Title of the Manuscript: The role of high mobility group box protein 1 (HMGB1) in depression: A mechanistic and therapeutic perspective
Manuscript Number: 74779
Invited Manuscript ID: 05627010
Changes Marked in Manuscript: Highlighted in Yellow

Reviewer 1

Dear Professor: Thank you very much for taking the time to review this manuscript. We truly appreciate your important and constructive comments and suggestions. Thank you for your efforts in helping us improve our manuscript. We have studied the comments carefully and have made corrections, which we hope meet with your final approval. Please find the itemized responses below and the revisions in the resubmitted files. Once again, thank you very much for your important comments and suggestions.

Comment 1: The review is excellent and has relevant content that contributes to basic science around depression. Other reviews on this topic have already been reviewed (Rana T, Behl T, Mehta V, Uddin MS, Bungau S. Molecular insights into the therapeutic promise of targeting HMGB1 in depression. Pharmacol Rep. 2021 Feb;73(1):31-42).

Authors' Response: We are very encouraged to receive your preliminary approval. As the reviewer said, "The review is excellent and has relevant content that contributes to basic science around depression". We hope that this study based on our view and experience as a multidisciplinary team consisting of both clinical and basic science experts can be helpful for further understanding the role of high mobility group box protein 1 (HMGB1) in depression, from mechanism to therapeutic perspective. With your important comments and suggestions, the quality of our article received significantly improvement. Thanks for your great efforts. In addition, the review by Rana T et al. is really important and excellent in this field. We have further studied this review and added a useful introduction to this article in the revised manuscript to provide readers with more information. Thanks for your important suggestion.

Change to Text: 1. Page 3, Paragraph 1, Introduction, "High mobility group box 1 (HMGB1), a chromosomal protein, has been found to perform an essential job in the neuroinflammation of several central nervous system diseases, which might also be a potential therapeutic target(11-15). Rana et al. proposed that HMGB1-mediated neuroinflammation in depression could have insights into the pathogenesis understanding and therapeutic promise(11). Herein, with recent studies concerning this topic, we review the role of HMGB1 in depression and propose several potential key mechanistic and future therapeutic perspectives." was added to provide readers with more information.

2. Page 3, Paragraph 1, Introduction, "However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods." was added with two references (8 and 9) to provide readers with more information.

3. Two references were added to provide readers with more information.

8. do Prado-Lima PAS, Costa-Ferro ZSM, Souza BSF, da Cruz IBM, Lab B. Is there a place for cellular therapy in depression? World J Psychiatry. 2021 Sep 19;11(9):553-67. PubMed PMID: 34631460. PMCID: PMC8474995. Epub 20210919. eng.

9. Onaolapo AY, Onaolapo OJ. Glutamate and depression: Reflecting a deepening knowledge of the gut and brain effects of a ubiquitous molecule. World J Psychiatry. 2021 Jul 19;11(7):297-315. PubMed PMID: 34327123. PMCID: PMC8311508. Epub 20210719. eng.

4. Several references were renumbered as the requirements of the journal.

11. Rana T, Behl T, Mehta V, Uddin MS, Bungau S. Molecular insights into the therapeutic promise of targeting HMGB1 in depression. Pharmacol Rep. 2021 Feb;73(1):31-42. PubMed PMID: 33015736. Epub 2020/10/06. eng.

12. Paudel YN, Shaikh MF, Chakraborti A, Kumari Y, Aledo-Serrano Á, Aleksovska K, et al. HMGB1: A Common Biomarker and Potential Target for TBI, Neuroinflammation, Epilepsy, and Cognitive Dysfunction. Front Neurosci. 2018;12:628. PubMed PMID: 30271319. PMCID: PMC6142787. Epub 2018/10/03. eng.

13. Vijayakumar EC, Bhatt LK, Prabhavalkar KS. High Mobility Group Box-1 (HMGB1): A Potential Target in Therapeutics. Curr Drug Targets. 2019;20(14):1474-85. PubMed PMID: 31215389. Epub 2019/06/20. eng.

14. Nishibori M, Mori S, Takahashi HK. Anti-HMGB1 monoclonal antibody therapy for a wide range of CNS and PNS diseases. J Pharmacol Sci. 2019 May;140(1):94-101. PubMed PMID: 31105025. Epub 2019/05/21. eng.
15. Wang S, Guan Y, Li T. The Potential Therapeutic Role of the HMGB1-TLR Pathway in Epilepsy. Curr Drug Targets. 2021;22(2):171-82. PubMed PMID: 32729417. Epub 2020/07/31. eng.

Comment 2: 1. It would be interesting to explore more about the signaling pathways and include self-explanatory figures that summarize the idea of the article.

Authors' Response: Thank you very much for your helpful suggestion. Reviewing on HMGB1-related signaling pathways is really important in this manuscript, which we made it too brief. We are so sorry for that and have added more information on this part in the revised manuscript. Furthermore, we added a self-explanatory figure to summarize the idea of the manuscript as the reviewer suggested, which we believe can provide more useful information to readers in a concise visual way. Thanks for your insightful comment.

Change to Text: 1. Page 4, Paragraph 1, "For the HMGB1-TLRs pathway (mainly including TLR2 and TLR4), MyD88 dependent and independent pathways were activated, resulting in the simulation of NF-κB and induction of pro-inflammatory response(19). For MyD88-dependent pathway, MyD88 serves as a domain-containing adaptor for the cytoplasmic Toll/IL-1 receptor (TIR)(20). Stimulated by ligands, MyD88 recruits IL-1 receptor-associated kinase-4 (IRAK-4) to TLRs; and IRAK-1 is phosphorylated and then associates with TRAF6, thereby activating the IKK complex and leading to activation of MAP kinases (JNK, p38 MAPK) and NF-κB(21, 22). The MyD88-independent pathway also mediates the immune response *via* TRIF and TRAF3, leading to recruitment of IKKε/TBK1, phosphorylation of IRF3, and expression of interferon-β(23, 24)." was added.

2. Page 4, Paragraph 1, "Fully reduced HMGB1 (fr-HMGB1), which is a kind of three redox states (fr-HMGB1, disulfide HMGB1, and sulfonyl HMGB1), can act as a chemoattractant through connections with RAGE(28). Furthermore, binding with chemokine receptor type 4 (CXCR4), promotes chemotactic activity (stimulates leukocyte recruitment)(29)." was added.

3. A new figure, "Fig.1 Illustration of mechanistic and therapeutic perspective of HMGB1 in depression" was added to provide readers with more information. **[TO THE EDITOR: The requirement of figures reads "please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file". However, our figure is generated by Pathway Builder Tool (PBT 2.0), which cannot export decomposable figures. Only a finished figure can be provided in the PowerPoint. We can provide the original file of PBT. Or you can ask us to modify types of components as your requirement. We are so sorry for potential inconvenience caused.]**

4. Eight references were added to provide readers with more information.

19. Zuo T, Yue Y, Wang X, Li H, Yan S. Luteolin Relieved DSS-Induced Colitis in Mice via HMGB1-TLR-NF-κB Signaling Pathway. Inflammation. 2021 Apr;44(2):570-9. PubMed PMID: 33015735. Epub 2020/10/06. eng.
20. Barton GM, Kagan JC. A cell biological view of Toll-like receptor function: regulation through compartmentalization. Nat Rev Immunol. 2009 Aug;9(8):535-42. PubMed PMID: 19556980. PMCID: PMC3934928. Epub 20090626. eng.
21. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol. 2010 May;11(5):373-84. PubMed PMID: 20404851. Epub 20100420. eng.
22. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018 Jan;281(1):8-27. PubMed PMID: 29247995. PMCID: PMC5756628. eng.
23. Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, et al. Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. Science. 2003 Aug 1;301(5633):640-3. PubMed PMID: 12855817. Epub 20030710. eng.
24. Fitzgerald KA, Kagan JC. Toll-like Receptors and the Control of Immunity. Cell. 2020 Mar 19;180(6):1044-66. PubMed PMID: 32164908. Epub 20200311. eng.
28. Venereau E, Casalgrandi M, Schiraldi M, Antoine DJ, Cattaneo A, De Marchis F, et al. Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. J Exp Med. 2012 Aug 27;209(9):1519-28. PubMed PMID: 22869893. PMCID: PMC3428943. Epub 20120806. eng.
29. Tirone M, Tran NL, Ceriotti C, Gorzanelli A, Canepari M, Bottinelli R, et al. High mobility group box 1 orchestrates tissue regeneration via CXCR4. J Exp Med. 2018 Jan 2;215(1):303-18. PubMed PMID: 29203538. PMCID: PMC5748844. Epub 20171204. eng.

Comment 3: 2. The authors describe neuroinflammation but do not explore the role of glia cells, especially astrocytes and microglia, crucial cells in the neuroinflammation process. What occurs in HMGB1-astrocytes and HMGB1-microglia interaction ?

Authors' Response: Thank you for your important and crucial suggestion. A detailed discussion on the role of glia cells, especially astrocytes and microglia, crucial cells in the neuroinflammation process is really important, which we did not make it clear. We are so sorry for that and have added it in the revised manuscript. Thanks for your useful comments.

Change to Text: 1. Page 5, Paragraph 1, "More recently, neuroinflammation has been proposed to play a significant role in several diseases including depression, epilepsy, stroke, traumatic brain injury, Parkinson's disease, and Alzheimer's disease(11-15). HMGB1 is considered as an essential neuroinflammatory facilitator, which is released by glial cells and neurons upon inflammasome activation and acts as a pro-inflammatory cytokine(15). Neurons are considered as a primary and necessary driver of neuroinflammation through release of HMGB1, with the subsequent amplification via recruitment of immunocompetent cells, including microglia and astrocytes(31). HMGB1 has been proved that it releases from neurons in many CNS diseases and then triggeres neuroinflammation as an upstream inflammatory mediator(15, 32). Activated by HMGB1, microglia functions as key contributor of the inflammatory processes sequentially influences neural cells, following by the activation of microglial NF-κB pathway and production of pro-inflammatory cytokines(33). The study of Cao et al. using a Parkinson's disease model revealed that HMGB1 released from inflamed microglia and/or degenerating neurons, bound to microglial Mac1 and activated NF-κB pathway and NADPH oxidase to stimulate production of multiple inflammatory and neurotoxic factors(34). Astrocytes are also a population of CNS cells with distinctive morphology and functions. Xiao et al. suggested that HMGB1 promoted the release of sonic hedgehog from astrocytes through signal pathway JNK, p38 and stat3 mediated by receptor RAGE in an animal model of multiple sclerosis, suggesting the important role of HMGB1-astrocytes medicated neuroinflammation(35). Also, some types of reactive astrocytes can also be induced by activated neuroinflammatory microglia and take parts in various human neurodegenerative diseases, formulating a complex immune network(36)." was added.

4. Six references were added to provide readers with more information.

31. Yang H, Andersson U, Brines M. Neurons Are a Primary Driver of Inflammation via Release of HMGB1. Cells. 2021 Oct 18;10(10). PubMed PMID: 34685772. PMCID: PMC8535016. Epub 20211018. eng.

32. Sun Q, Wu W, Hu YC, Li H, Zhang D, Li S, et al. Early release of high-mobility group box 1 (HMGB1) from neurons in experimental subarachnoid hemorrhage in vivo and in vitro. J Neuroinflammation. 2014 Jun 12;11:106. PubMed PMID: 24924349. PMCID: PMC4107626. Epub 20140612. eng.

33. Brevet M, Kojima H, Asakawa A, Atsuchi K, Ushikai M, Ataka K, et al. Chronic foot-shock stress potentiates the influx of bone marrow-derived microglia into hippocampus. J Neurosci Res. 2010 Jul;88(9):1890-7. PubMed PMID: 20155811. eng.

34. Gao HM, Zhou H, Zhang F, Wilson BC, Kam W, Hong JS. HMGB1 acts on microglia Mac1 to mediate chronic neuroinflammation that drives progressive neurodegeneration. J Neurosci. 2011 Jan 19;31(3):1081-92. PubMed PMID: 21248133. PMCID: PMC3046932. eng.

35. Xiao Y, Sun Y, Liu W, Zeng F, Shi J, Li J, et al. HMGB1 Promotes the Release of Sonic Hedgehog From Astrocytes. Front Immunol. 2021;12:584097. PubMed PMID: 33868221. PMCID: PMC8047406. Epub 20210401. eng.

36. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017 Jan 26;541(7638):481-7. PubMed PMID: 28099414. PMCID: PMC5404890. Epub 20170118. eng.

Comment 4: 3. Adding a topic on neuroinflammation linking with depression would be interesting.

Authors' Response: Thank you for your important suggestion. As the reviewer suggested, adding a topic on neuroinflammation linking with depression would be interesting. Thus, we added more information on neuroinflammation linking with depression in the revised manuscript to provide readers with more information. Once again, thanks for your helpful suggestion.

Change to Text: 1. Page 5, Paragraph 2, "Depression is also found to closely link with neuroinflammation, which is mainly characterized by the increased mediators of inflammation and neurodegeneration(37). Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules, including IL-1β, IL-6, TNF- α and CRP(38, 39). Preclinical study based on animals also exhibited the activation of microglia together with enhanced inflammatory mediators. In a chronic mild stress (CMS) mouse model of depression, NLRP3-inflammasome/caspase-1/IL-1β axis microglia-mediated neuroinflammation was found

being activated(40). Another study suggested rats exposed to CMS exhibited a significant increase in inflammatory mediators, including TNF-α and IL-1β, activation of NF-κB signaling pathway in the hippocampus. Icariin, a flavonoid inhibiting neuroinflammation, could negatively regulated the activation of the NLRP3 inflammasome/caspase-1/IL-1β(41). Chronic treatment with corticosterone and intraperitoneally administration of lipopolysaccharide depressed models also showed a higher expression level of pro-inflammatory phenotype characterized by IL-1β, IL-6, TNF-α and IκB-α(42, 43). These findings provide a powerful connection of neuroinflammation and depression." was added.

4. Seven references were added to provide the readers with more information

37. Beumer W, Gibney SM, Drexhage RC, Pont-Lezica L, Doorduin J, Klein HC, et al. The immune theory of psychiatric diseases: a key role for activated microglia and circulating monocytes. J Leukoc Biol. 2012 Nov;92(5):959-75. PubMed PMID: 22875882. Epub 2012/08/10. eng.

38. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006 Jan;27(1):24-31. PubMed PMID: 16316783. PMCID: PMC3392963. Epub 20051128. eng.

39. Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, et al. IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep. 2018 Aug 13;8(1):12050. PubMed PMID: 30104698. PMCID: PMC6089986. Epub 20180813. eng.

40. Lu M, Yang JZ, Geng F, Ding JH, Hu G. Iptakalim confers an antidepressant effect in a chronic mild stress model of depression through regulating neuro-inflammation and neurogenesis. Int J Neuropsychopharmacol. 2014 Sep;17(9):1501-10. PubMed PMID: 24621884. Epub 20140313. eng.

41. Liu B, Xu C, Wu X, Liu F, Du Y, Sun J, et al. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. Neuroscience. 2015 May 21;294:193-205. PubMed PMID: 25791226. Epub 20150317. eng.

42. Chabry J, Nicolas S, Cazareth J, Murris E, Guyon A, Glaichenhaus N, et al. Enriched environment decreases microglia and brain macrophages inflammatory phenotypes through adiponectin-dependent mechanisms: Relevance to depressive-like behavior. Brain Behav Immun. 2015 Nov;50:275-87. PubMed PMID: 26209808. Epub 20150722. eng.

43. Bay-Richter C, Janelidze S, Hallberg L, Brundin L. Changes in behaviour and cytokine expression upon a peripheral immune challenge. Behav Brain Res. 2011 Sep 12;222(1):193-9. PubMed PMID: 21466824. Epub 20110402. eng.

Comment 5: Finally, the article is interesting, but can easily be improved.

Authors' Response: Thank you for your recognition of our manuscript. We hope that this study based on our view and experience as a multidisciplinary team consisting of both clinical and basic science experts can be helpful for further understanding the role of high mobility group box protein 1 (HMGB1) in depression, from mechanism to therapeutic perspective. With your important comments and suggestions, the quality of our article received significantly improvement. Thanks for your great efforts. Moreover, we recognize that high-quality international publications need to be provided in accurate English and rigorous content. We apologize for the grammatical and language errors, as English is not our native language. We carefully rechecked the full text of the manuscript following the comments of the reviewers and used a language-editing service to further improve the grammar and language of the manuscript; the editing certificate is provided in the Appendix. Additionally, the contents were rechecked to ensure their correctness and accuracy. Once again, thank you for your helpful efforts in the revision procedure.

Change to Text: 1. Language corrections were made with the help of a language editing service.

Reviewer 2

Dear Professor: Thank you very much for taking the time to review this manuscript and provide important comments and suggestions. We are very glad and encouraged to receive your approval. Once again, thank you very much for your great efforts in reviewing our manuscript.

Comment 1: The manuscript is unique, and it is critical to comprehend the current scientific evidence regarding the role of the HMGB1 protein in depression. It will be useful input in the future for the development of antidepressant drugs.

Authors' Response: Thank you very much for your recognition and approval of our manuscript. We hope that this study based on our view and experience as a multidisciplinary team consisting of both clinical and basic science experts can be helpful for further understanding the role of high mobility group box protein 1 (HMGB1) in depression, from mechanism to therapeutic perspective. With your important comments and suggestions, the quality of our article received significantly improvement. Thanks for your great efforts. Furthermore, we added a self-explanatory figure to

summarize the idea of the manuscript as the reviewer suggested, which we believe can provide more useful information to readers in a concise visual way. Moreover, we recognize that high-quality international publications need to be provided in accurate English and rigorous content. We apologize for the grammatical and language errors, as English is not our native language. We carefully rechecked the full text of the manuscript following the comments of the reviewers and used a language-editing service to further improve the grammar and language of the manuscript; the editing certificate is provided in the Appendix. Additionally, the contents were rechecked to ensure their correctness and accuracy. Once again, thank you for your helpful efforts in the revision procedure.

Change to Text: 1. A new figure, "Fig.1 Illustration of mechanistic and therapeutic perspective of HMGB1 in depression" was added to provide readers with more information. **[TO THE EDITOR: The requirement of figures reads "please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file". However, our figure is generated by Pathway Builder Tool (PBT 2.0), which cannot export decomposable figures. Only a finished figure can be provided in the PowerPoint. We can provide the original file of PBT. Or you can ask us to modify types of components as your requirement. We are so sorry for potential inconvenience caused.]**

2. Language corrections were made with the help of a language editing service.

Science editor

Dear Professor Jia-Qi Zhu: Thank you for your remarkable response letter and the reviewers' comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our paper as well as providing important guiding significance to our research. We have studied the comments carefully and have made corrections that we hope meet with approval. Once again, thank you very much for your precise scientific spirit. Your first-rate, high-level journal gives us a wonderful platform for psychiatry communication and promoting mental health.

Comment 1: Thank you for accepting the invitation to submit your manuscript to the World Journal of Psychiatry (WJP). This minireview is critical to understanding the current scientific evidence on the role of HMGB1 protein in depression, providing useful information for future antidepressant drug development, which will lead to the development of multidisciplinary basic and clinical research on psychiatry. Other reviews have been published on this topic. The author can further improve the article to make it more complete.

Authors' Response: Thank you very much. We revised the manuscript, marked the changes, and finished the revision cover letter as required. We hope that this study based on our view and experience as a multidisciplinary team consisting of both clinical and basic science experts can be helpful for further understanding the role of high mobility group box protein 1 (HMGB1) in depression, from mechanism to therapeutic perspective. With your important comments and suggestions, the quality of our article received significantly improvement. Thanks for your great efforts. Furthermore, we added a self-explanatory figure to summarize the idea of the manuscript as the reviewer suggested, which we believe can provide more useful information to readers in a concise visual way. Moreover, we recognize that high-quality international publications need to be provided in accurate English and rigorous content. We apologize for the grammatical and language errors, as English is not our native language. We carefully rechecked the full text of the manuscript following the comments of the reviewers and used a language-editing service to further improve the grammar and language of the manuscript; the editing certificate is provided in the Appendix. Additionally, the contents were rechecked to ensure their correctness and accuracy. Once again, thank you for your helpful efforts in the revision procedure. Thanks for your precise scientific spirit. We appreciate your great efforts.

Change to Text: 1. We uploaded the revised manuscript, revision cover letter, revision note, and other materials as required.

2. A new figure, "Fig.1 Illustration of mechanistic and therapeutic perspective of HMGB1 in depression" was added to provide readers with more information. **[TO THE EDITOR: The requirement of figures reads "please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file". However, our figure is generated by Pathway Builder Tool (PBT 2.0), which cannot export decomposable figures. Only a finished figure can be provided in the PowerPoint. We can provide the original file of PBT. Or you can ask us to modify types of components as your requirement. We are so sorry for potential inconvenience caused.]**

3. Language corrections were made with the help of a language editing service.

Company editor-in-chief

Dear Professor Lian-Sheng Ma: Thank you for your remarkable response letter and the reviewers' comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our paper as well as providing important guiding significance to our research. We have studied the comments carefully and have made corrections that we hope meet with approval. Once again, thank you very much for your great effort in addressing our manuscript. Your first-rate, high-level journal gives us a wonderful platform for psychiatry communication and promoting mental health.

Comment 1: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a table/figure (medical imaging) to the manuscript. There are no restrictions on the figures (color, B/W).

Authors' Response: Thank you very much. We revised the manuscript, marked the changes, and finished the revision cover letter as required. We hope that this study based on our view and experience as a multidisciplinary team consisting of both clinical and basic science experts can be helpful for further understanding the role of high mobility group box protein 1 (HMGB1) in depression, from mechanism to therapeutic perspective. With your important comments and suggestions, the quality of our article received significantly improvement. Thanks for your great efforts. Furthermore, we added a self-explanatory figure to summarize the idea of the manuscript as the reviewer suggested, which we believe can provide more useful information to readers in a concise visual way. Moreover, we recognize that high-quality international publications need to be provided in accurate English and rigorous content. We apologize for the grammatical and language errors, as English is not our native language. We carefully rechecked the full text of the manuscript following the comments of the reviewers and used a language-editing service to further improve the grammar and language of the manuscript; the editing certificate is provided in the Appendix. Additionally, the contents were rechecked to ensure their correctness and accuracy. Once again, thank you for your helpful efforts in the revision procedure. Thanks for your precise scientific spirit. We appreciate your great efforts.

Change to Text: 1. We uploaded the revised manuscript, revision cover letter, revision note, and other materials as required.

2. A new figure, "Fig.1 Illustration of mechanistic and therapeutic perspective of HMGB1 in depression" was added to provide readers with more information. **[TO THE EDITOR: The requirement of figures reads "please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file". However, our figure is generated by Pathway Builder Tool (PBT 2.0), which cannot export decomposable figures. Only a finished figure can be provided in the PowerPoint. We can provide the original file of PBT. Or you can ask us to modify types of components as your requirement. We are so sorry for potential inconvenience caused.]**

3. Language corrections were made with the help of a language editing service.