

Dear Fang-Fang Ji,

Science Editor, Editorial Office

Attached please find the revised version of our Manuscript No.23393 entitled "Update on the treatment of focal segmental glomerulosclerosis in renal transplantation". We thank the reviewers for their comments and we hope that corrections and point-by-point replies to the Reviewers' comments will be considered adequate.

Reviewer 1.

1.The section of abstract should be modified and more concise.

Reply. Abstract has been reevaluated and corrected considering reviewers indications.

2.In this review, the pathogenesis of FSGS has not been fully elucidated. The authors mentioned only circulating factors, urokinase type plasminogen activator receptor (suPAR) and permeability factor. However, some other pathogenesis are not discussed.

Reply. We reviewed our chapter about pathogenetic mechanisms including other crucial factors (page 7, line 4-29).

3.Besides mesenchymal stem cells (HuMSCs), other cells, e.g. podocyte progenitor cells, have the ability to switch to the podocyte phenotype and migrate to the glomerular tuft, and reduce the kidney damage after transplantation. It is encouraged to add this discussion.

Reply. We added a comment about podocyte progenitor cells in our discussion (from page 18, line 25 to page 19, line 2).

4.It has been reported that stem cell transplantation may result in some dangerous disadvantages, such as teratomas formation by stem cells. In this review, the authors discussed the application of adult stem/progenitor cells rationally for improving kidney fibrosis and modulating the inflammatory response, but the possible side effects are not mentioned.

Reply. In the previous version of the manuscript we have only reported that safety of BM-MSCs remains an open question; according to reviewer's comment, we include adverse events referring to the BM-MSCs use (page 18, line 17-24)

Reviewer 2. Grammatical concerns 1) It would be better to replace the word "nonblack" by "nonAfrican" from the standpoint of anti-discrimination. 2) Page 4, line 8. The word "poorely" should be corrected as "poorly". 3) Page 4, line 12. The phrase "In renal transplanted patients both ..." should be corrected as "In renal transplanted patients, both ...". 4) Page 4, line 20. It would be better to replace the number "2,03" by "2.03". 5) Page 5, line 5. The word "ex vivo" should be written in italics. 6) Page 5, line 8. The word "stricking" should be corrected as "striking". 7) Page 5, lines 15-18. The sentence "Nevertheless, this disease-specificity was not confirmed in other studies that showed increased suPAR levels also in other

conditions (bacterial and viral infections, sepsis, cancer)[16] but primarily in patients with altered glomerular filtration rate (GFR), suggesting an inverse relation between suPAR levels and GFR[17]." seems rather illegible. It would be better to rewrite this sentence as, for example, "Nevertheless, the specific involvement of suPAR in glomerulonephritis was not confirmed by other studies, which showed increased (plasma) suPAR levels in other pathological situations (bacterial and viral infections, sepsis, cancer)[16]. Rather, increased suPAR levels were primarily observed in patients with reduced glomerular filtration rate (GFR), suggesting that an elevation of suPAR levels is just an indicator of reduced GFR[17]". 8) Page 5, lines 19-21. It would be better to rewrite the sentence "Also the ability of suPAR to differentiate between FSGS and non-FSGS glomerulonephritis has been questioned by Bock et al[18], who showed similar suPAR levels in FSGS patients, non-FSGS controls and healthy volunteers" as "Moreover, the usefulness of suPAR to distinguish between FSGS and non-FSGS glomerulonephritis has been questioned by Bock et al[18], who showed similar (plasma) suPAR levels among FSGS patients, non-FSGS controls and healthy volunteers." and so on. 9) Page 5, line 22. It would be better to rewrite the phrase "Some different circulating factors, as" as "Other circulating factors such as ...". 10) Page 6, line 2. It would be better to rewrite the word "microRNAs-miRNAs" as "microRNAs" for simplification. 11) Page 7, line 19. The word "follow-up;" should be corrected as "follow-up." 12) Page 8, line 13. The word "despite" should be replaced by "although" because "despite" is a preposition, but not a conjunction. 13) Page 11, lines 8 and 12. The word "anti-TNF alfa" should be corrected as "anti-TNF alpha". 14) Page 11, line 30. The word "unlabeled" should be corrected as "unlabelled". 15) Page 13, line 20. The word "Authors" should be corrected as "authors". 16) Page 13, line 26. The phrase "in a well establish murine model" should be corrected as "in a well-established murine model" 17) Page 15, line 1. The word "Cya" should be corrected as "CyA". 18) Page 16, line 15. The phrase "Protocol biopsies are an helping strategy...." should be corrected as "Protocol biopsy is a helping strategy....".

Reply. We included all the suggested revisions in the manuscript.

Reviewer 3. If the new mechanism literatures on FSGS were added, it will be more interesting.

Reply. As expressed before for reviewer 1, we reviewed our chapter about pathogenetic mechanisms in new mechanisms reported in Literature (page 7, line 4-29).

Best regards,

Luigi Biancone