Peer Review File

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Review Comments

High purity oxygen therapy has good clinical efficacy in the treatment of diabetic foot, but the mechanism of its promotion of wound healing is not clear. In the manuscript "Research on the Mechanism of Local Oxygen Therapy Promoting Wound Healing of Diabetic Foot Based on RNA-seq Technology", the authors evaluated the clinical effect of local oxygen therapy on diabetic foot and conducted a transcriptome analysis of DF pathological samples before and after treatment.

Comment 1: A number of improvements need to be made before the manuscript can be accepted. There are many examples of grammatical errors or irregular writing throughout the text. The language of this paper needs to be polished by a native English speaker.

Reply 1: Thank you for your kind suggestions; we fully agree with your opinion. Based on your suggestions, we have sent the manuscript to a professional editing company for language polishing, and have uploaded the corresponding certificate as an attachment.

Changes in the text: We have already corrected the corresponding contents in the manuscript.

Comment 2: The content of the introduction is too simple. Relevant content (such as the progress that has been made with the treatment of DF) should be added to further enrich this part.

Reply 2: Based on your suggestions, we have included diabetic foot (DF) treatment–related content in the Introduction section.

Changes in the text: We have already corrected the corresponding contents in the manuscript (page 3-page 4) and highlighted the content by yellow.

Comment 3: For the treatment group, was the decision to undergo treatment made by the doctors or the patients themselves?

Reply3: The patients enrolled in the treatment (LOT, i.e. treatment) group had the following three features: 1. All patients in the two groups met the inclusion criteria. 2. All patients had full understanding of high-purity oxygen therapy, and were suitable for micro-oxygen therapy; the patients in the treatment group were willing to adopt the new treatment for DF, and could afford the treatment costs. 3. There was no significant difference in age, sex and disease course between the local oxygen therapy (LOT, i.e. treatment) and control groups ($P > 0.05$).

Changes in the text: None

Comment 4: The figures do not correspond to the figure legends. In Figure 4, the images were labeled (A-H). Please describe these in detail in the Figure 4 legend.

Reply 4: Thank you for the kind suggestions. Figure 4 illustrates the KEGG function of the differentially expressed genes (DEGs) screened, which had been conducted using the WebGestalt platform. Based on the KEGG common database, we identified the biological function of the DEGs with FDR of <0.05, thereby obtaining the GO function and KEGG pathway related to the DEGs selected. As per your suggestion to describe these results in detail, we have listed the biological function enrichment results, including that for GO function and KEGG pathway, in Table S2.

Changes in the text: The correction including 2 parts. 1st , we added the GO and KEGG analysis methods in the methods section (page.7), and highlighted the content by yellow. 2nd, we listed the GO and KEGG results in Table.S2.

Comment 5: Please list the 577 DEGs in a supplementary table.

Reply 5: Thank you for the kind suggestions; we have corrected it according to your advice. We have listed the DEGs, including the gene name, ratio, *t*-test p-value and genes' up- or downregulation, in Table S1.

Changes in the text: We listed the DEGs results in Table.S1

Comment 6: Why were the most significantly downregulated genes and the most significantly upregulated genes not tested? Please add a test experiment of representative genes from the most significantly downregulated genes and the most significantly upregulated genes.

Reply 6: Thank you for the kind suggestions. First, the main aim of the study was to evaluate the clinical effect of LOT on DF, and the research on the mRNA regulation landscape was conducted to explain the biological function network of LOT in DF. Considering that a series of biomarkers participate in the tissue repair process, we concentrated on the systemic mechanism of the therapy rather than on a single biomarker or phenotype. Second, although we screened some valuable biomarkers, and more in-depth research is needed to identify their biological function in the process of LOT, as a clinical mechanism study, the aim of this research was to explain the biological effect of LOT on DF, and not that of a specific biomarker or related phenotype. Considering your meaningful suggestions, however, we will in further studies conduct biomolecular experiments, such as PCR and western blotting, on the biomarkers screened, and confirm their regulatory characteristics, and determine the role of different biomarkers and signalling pathways involved in the process of LOT for treating DF.

Changes in the text: None