Name of journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 13920

Dear Editor,

Thank you very much for considering this article for publication. According to the recommendations of the reviewers, the following changes have been made

The answers and comments to reviewers sugestions are included in red):

- Post code details have been added
- Corresponding author and other details have ben added
- References have been changed in the text and bibliography

Reviewer: 2446054

There were a number of language spelling issues that need to be fixed.

"Embryogenic, cytoquines, tissular"

This has been extensively reviewed

also a glossary would help: decorine scleraxis are not defined

Decorin and scleraxis have been defined

The review of basic research findings does not identify the experimental animal in which the studies are done. This needs correction. (section 2)

Animal type is included in table 1

I think the paper would be strengthened by addition of a figure outlining the anatomy of a tendon (perhaps with arrows pointing to sc and growth factors operative in the respective area

AN image and diagram has been added

Reviewer:

Specific comments:

Specific comments: 1. Page 3, Abstract: "Promising results have been reported with the use of MSC of different origins in animal studies: they have been shown to have better healing properties, increasing the amount of fibrocartilage formation and improving the orientation of fibrocartilage fibers with less immunologic response and reduced lymphocyte infiltration." Do you mean autologous MSCs?

Autologous has been added as pointed out.

2. Page 3, Abstract: "The study of the molecular environment during embryogenesis and during normal healing after injury is key in devising strategies to get a successful repair." Can you elaborate what molecular environment?

The molecular environment of the healing process has been developed in the text thoroughly in parts 2 and 3.

3. Page 6: "Thus, the focus in research has changed from mechanical improvement of the repair techniques to finding ways to improve the biological environment around that repair.15-22" The authors should say a little more

about these eight references: What specifically each of these eight papers talk about – what biological environment around that repair?

Information has been updated in the text. During the past decade, numerous techniques have been used in order to improve healing of the rotator cuff based on a change in anchor materials, number of sutures and type of suture. However, re-tears are still frequent. Since the healing process of the enthesis is complex, numerous different biological treatments have been applied in order to improve the properties of the repair. The articles mentioned are developed in the subsequent category, but they could be also explained in the introduction if desired

4. Page 6: "Stem cells have demonstrated great potential in enhancing the biologic healing process.26:" Again, they should have detailed what biologic healing process here.

This has been extended and updated in the text

5. Page 7: "The enthesis has been divided into four zones: tendon, non-mineralized fibrocartilage, mineralized fibrocartilage and bone.'' Here, they should draw a schematic diagram for these four zones in combining with molecular interaction on page 9 to enhance the readability.

AN image and diagram have been added

6. Page 7: "The reparative process can be divided into 3 phases (inflammatory, reparative and remodelling).'' If inflammatory is in phase one, they should talk

about how non-autologous MSC-based may trigger inflammatory response in repair.

In this part of the text, attention is focused in the biochemical environment. In the stem cell section attention is srawn on the low immunogenicity of allogenic stem cells.

7. Page 7: “Diaz-Heredia? et al.’’ – a typo.

Corrected

8. Page 11: “they used BMP-2 to 7, TGF?1, TGF?2, TGF-?3 and FGF. They detected better histologic and biomechanical properties.16 Other investigators have obtained similar results with BMP-12,42 BMP-13,17 BMP-14,43 FGF,40,44 IGF-145 and PDGF-b.15‘’ How do these GFs work for biomechanical properties? Some factors may contradict this purpose – how do they reconcile?

As the structure of the enthesis is complex and has four zones, different factors may play a different role depending on which area of healing are we trying to stimulate. Timing of exposure to different factors has also been pointed out as determinant. A sentece has been added

9. Page 12: Lim et al. used mesenchymal stem cells (MSCs) – they should keep consistent using abbreviation MSCs thorough the paper – so annoying to see these repeats.

Corrected. Sorry to annoy the reviewer.

10. Page 12: in a rabbit model and found a significant increase in maximum load to failure at 8 weeks of sacrifice.58 Not meaningful here, please clarify.

Corrected and shortened.

11. Page 18: A combination of stem cells, modified before implantation, using exposure to different growth factors or modifications to the culture conditions to generate a desired phenotype is one of the most investigated pathways.26 A combination of stem cells? - Do you mean mixing different types of stem cells?

A combination of stem cells is what the author of reference 26 suggests as a possible option for the future

2. Page 19 - the use of stem cell therapy in rotator cuff should still be considered and experimental technique. That's not a logic sentence.

Corrected

13. Page 20 - Mesenchimal stem cells(MSC). A typo.

Corrected

14. Overall, how does stem cell mediated repair may offer a new way to understand the molecular mechanisms and molecular environment?

As explained in part 2 and 3, what is thought is that stem cell therapy can modify the healing process due to its anti-inflammatory properties. This fact is important because it can resemble the healing process in prenatal life that occurs without scar tissue.

Stem cells do not help in understanding these processes but as more and more is understood about these, MSC seem to be good tools to enhance healing.

Reviewer: 2446101

1. The abstract should be rewritten. The background should be explained with one or two sentences, while the current and future situation of SCT on RCD could be emphasized. And the abstract had better be integrated into one paragraph.

Abstract has been modified and integrated into one paragraph.

2. In fact, although the authors referred to other stem cells fetal stem cells, most of discussion focused on mesenchymal stem cells. I suggest the authors add some discussion on other kind of stem cells used for treating RCD.

To our knowledge, only MSCs have been applied to rotator cuff models.

3. The part of choice of scaffold for MSCs deployment should be more detailed, which is better to be discussed based on its classification.

Some more information has been added at this point.

4. If it is possible to add some figures to review the reparative process with SCT.

AN image and diagram have been added

5. There are some minor language problems which should be checked carefully It has been modified.

Corrected

Reviewer: 2709820

The introduction strays from the topic and spends too much time on anatomy. This should be condensed

Introduction has been shortened, especially the part explaining anatomy as asked by reviewer.

Recommend a major revision prior to publication with tables summarizing both animal and human data.

Table 1 contains data regarding animal studies and human studies have been explained in the text in a different paragraph.