**RESPONSE TO REVIWER 1**

Thank you for your comments regarding our manuscript. These comments have been valuable in ensuring we produce a high-quality manuscript and have also been constructive in guiding our research. We have reviewed the comments carefully and have made corrections and responses with the hope that they meet your standards. We have answered the comments carefully and step by step as follows. The revised parts will be labeled with red and presented within the Response. These changes have substantially improved the quality our manuscript while preserving the content and general framework.

1. An introduction into FAPs is missing. There needs to be a paragraph describing the functions of FAPs in general (not with a focus on aging), this part also needs to include the canonical markers for FAPs as well as the role of FAPs in resting muscle as well as in regenerating muscle. Otherwise it is not possible for the reader to understand the alterations in FAPs during aging which the authors refer to.

**Response:** Thanks for your kind suggestion, we have added an introduction to FAPs, including the general function of FAPs, typical markers of FAPs, and the role of FAPs in resting and regenerating muscles.

**After Revision:**

Over the past decade, FAPs have been recognized as important regulators of muscle homeostasis and regeneration in healthy muscle, but also in acutely injured skeletal muscle and pathologically degenerated muscle. FAPs were first identified in 2010 as muscle-resident progenitor cells that express PDGFR and primarily produce myofibroblasts and adipocytes(15, 16). Under normal muscle regeneration circumstances, activated FAPs eventually succumb to apoptosis through mechanisms that are dependent on macrophage-secreted tumour necrosis factor(17). However, if apoptosis does not take place in a timely manner, FAPs can differentiate into pro-fibrotic fibroblasts and white adipose tissue in the presence of prolonged inflammatory signals in injured muscle. (14, 18, 19).

2. The whole article needs more structuring. The roles of FAPs in resting muscle and regenerating muscle need to be discussed in either separate paragraphs or there needs to be a clear cut between the two states. An introduction into regeneration of skeletal muscle is missing. A reader who is not an expert in skeletal muscle is not able to understand the article without such an introduction. Please include.

**Response:** Thanks for your valuable suggestions on this detailed deficiency of our manuscript. We have added this important detail to article.

3. A small note on changes in FAPs in diseases would be nice. This would allow the reader to put the changes which occur in FAPs during aging to a disease context (what are the similarities, what are the differences etc.).

**Response:** Thanks for your constructive suggestions on this detail, we have added the changes of FAPs.

4. In the abstract the authors state that FAPs are a subset of muscle progenitor cells> this is not correct, FAPs are FAPs multi-potent progenitors, having the ability to differentiate into fibroblasts, adipocytes, and possibly into osteoblasts and chondrocytes, although not into myoblasts (Joe et al., 2010; Uezumi et al., 2010). FAPs are rather mesenchymal progenitor cells!

**Response:** Thank you for your kind comments, we have carefully revised the original sentence. We are so sorry for our unprofessional mistakes.

**After Revision:**

Fibro-adipogenic progenitor cells (FAPs) are muscle-resident progenitor cells that are essential for the maintenance of skeletal muscle fiber size and muscle regeneration.

5. In line 50 (In addition, decreased muscle regeneration, increased fibrosis, and adipose infiltrations were also associated with age(3). Is the related to humans? Please specify.

**Response:** Thanks for your kind suggestion. We added references to age-related reduction in muscle regeneration, increased fibrosis and fat infiltration mentioned in several studies. This phenomenon has been reported in both animal models and humans.

6. Line 50-52: Aging also leads to an imbalance in muscle homeostasis, and skeletal muscle homeostasis is maintained by a balance of physical and functional interactions of different cell types in the muscle ecotone(4-7). Which “different cell types” are meant? The word ecotone is not appropriate to describe the cellular context of skeletal muscle, it is rather used in ecology!

**Response:** **Thanks for your kind suggestion. The different cell types were mentioned in the following. And we have corrected the “ecotone” to “niche”, which is mentioned in the reference.**

7. Line 58: what do the authors mean by “disrupted”?

**Response:** Thank you for your kind comments, the “disrupted” means that the skeletal muscle homeostasis can be disrupted by various pathological factors.

8. Line 62: pathologically degenerated muscle. Which diseases are meant?

**Response:** We thank you for asking this question of our manuscript. For example, muscle degeneration due to type 2 diabetes, muscle degeneration due to amyotrophic lateral sclerosis, etc.

9. Line 65: FAPs exhibit injury context-dependent pluripotent behavior. This sentence suggests that FAPs are indeed pluripotent stem cells (which they are not), please rephrase.

**Response:** Thanks for your suggestion, we have rewritten this paragraph, as described in the revised manuscript.

10. The article would benefit from a thorough read-through for sentence construction.

**Response:** Thank you for your kind comments, we have carefully revised sentence construction throughout the manuscript. We are so sorry for our poor writing.

11. Line 82: Age-related sarcopenia constitutes an important health problem, leading to impaired regeneration, impaired adaptive response to exercise training, and disrupted metabolic regulation(20). Sarcopenia is not leading to impaired regeneration, it coincides with it. This needs to be stated correctly.

**Response:** Thanks for your valuable suggestions on this detailed deficiency of our manuscript. We have modified the sentence that sarcopenia is interconnected with impaired regenerative capacity of muscles, impaired adaptive response to exercise training, and disturbances in metabolic regulation of muscles.

**After Revision:**

Aging is characterized by declining multiple physiological functions. The regenerative potential of muscle decreases with age and the progressive decrease in skeletal muscle mass is also known as sarcopenia(24). Age-related sarcopenia constitutes an important health problem that is closely associated with impaired muscle regeneration, impaired adaptive response to exercise training, and disorders of muscle metabolic regulation (25).

12. Line 88: the reporter mouse line PDGFRalpha needs to be explained, e.g. that PDGFR alpha is the canonical marker for FAPs.

**Response:** We have described the characteristic markers of FAPs in the modified above.

13. Lines 92-95: The exact mechanisms that allow FAPs to gravitate toward lipogenesis and fibrogenesis are currently unknown but may include alterations in local signaling, gene expression, and stem cell epigenetics, as well as the presence of baseline differences in subpopulations of FAPs.

This is highly speculative! Can the authors provide some evidence for their suggestions, especially the statement that there might be subpopulations of FAPs.

**Response:** Thanks for your kind suggestion. Many studies have proved this statement. “Human skeletal muscle CD90+ fibro-adipogenic progenitors are associated with muscle degeneration in type 2 diabetic patients”, “Emerging skeletal muscle stromal cell diversity: Functional divergence in fibro/adipogenic progenitor and mural cell populations” and “Single-cell RNA sequencing and lipidomics reveal cell and lipid dynamics of fat infiltration in skeletal muscle” were suggested for reviewer.

14. Line 96: the wording “ecological niche” is not appropriate for cell biological findings. Plesase rephrase.

**Response:** As you suggested, we have deleted the ecological.

After Revision:

For example, Moratal et al. found that aging leads to changes in the niche in which FAPs are exposed, creating a more favorable environment for FAPs fibrotic or adipogenic differentiation(8).

15. Line 97: what is meant by “fibrillation”?

**Response:** Thanks for your comments, we have converted “fibrillation” to “fibrotic”.

**After Revision:**

For example, Moratal et al. found that aging leads to changes in the niche in which FAPs are exposed, creating a more favorable environment for FAPs fibrotic or adipogenic differentiation(8).

16. Line 98: in which species does increased fibrotic tissue occur with increasing age?

**Response:** Thanks for your question, it was human species.

17. Line 106-116: this paragraph needs to be re-written: which factors are causing differentiation into fibrotic cells and which one into adipogenic cells? How does that change with age? The paragraph as it is right now, is too short and does not include all important inflammatory signals. It is also not clear which factors are causing which phenotype.

**Response:** Thanks for your suggestion, we have added the subtitles to this paragraph to make the manuscript more coherent.

18. Line 117-119: the authors use the word myosteatosis which is correct and then muscle steatosis. Please use myosteatosis in both cases.

**Response:** Thanks for your valuable suggestions on this detailed deficiency of our manuscript. We have corrected this mistake.

After Revision:

Due to their adipogenic potential, FAPs play a central role in myosteatosis.

19. Line 126: which myogenic cells are meant?

**Response:** Thanks for your comments, it was Myogenic progenitors cells. We have added Myogenic progenitors cells to the manuscript.

After revision:

Furthermore, one study found that conditioned medium from myogenic progenitors isolated from young individuals increased FAPs proliferation and inhibited adipogenic differentiation, whereas conditioned medium from myogenic progenitors isolated from aged donors failed to improve FAPs proliferation and prevented adipogenic differentiation(8).

20. Line 131: citation is missing

**Response:** Thank you for pointing out this missing in our manuscript. We have added the reference.

21. Line 144: please define the abbreviation MuSCs and explain their function and characteristics (brief description is sufficient).

**Response:** Thanks for your kind suggestion, we have defined the abbreviation MuSCs in introduction.

22. Lien 155: which paracrine substances are meant?

**Response:** Thank you for your kind comments, it means IL-33.

23. Figure 1: fibrosis is not necessarily causing increased aging, please correct this in the schematic. In the schematic it should be specified which factors cause adipogenic and which ones fibrogenic differentiation of FAPs.

**Response:** We thank you very much for pointing out this shortcoming of our manuscript. We have corrected the mistake in the figure and clarified which factors lead to adipogenesis and which factors lead to fibrogenic differentiation of FAPs.

24. Are there also factors in aging skeletal muscle which are increased during aging of FAPs and alter muscle or muscle stem cell function? It is hard to believe that during aging only a reduction in factors secreted by FAPs is occurring. Please check the literature carefully.

**Response:** Thanks for your comments, we did not show in our review the idea that only the factors secreted by FAPs are decreasing in aging skeletal muscle, only that the literature reports more attention to this phenomenon during aging.

25. Often the abbreviations are not explained when they are used for the first time. Please go through the text carefully and add the missing descriptions.

**Response:** Thank you very much for your constructive suggestions. It is really a mistake that we failed to explain the abbreviations. We have added comments to the abbreviations the first time they are used.

26. Line 169-173: Lemos et al. discovered that whereas the use of nilotinib, a tyrosine kinase inhibitor targeting the TGF signaling pathway, increased FAP apoptosis and consequently decreased fibrosis, blocking TNF signaling prevented the apoptosis of FAPs, resulting in a doubling of FAPs and a twofold increase in fibrosis after muscle injury(31). Please rephrase the sentence since it is not understandable to the reviewer what is meant.

**Response:** Thanks for your valuable suggestions on this detailed deficiency of our manuscript. We have rephrased the sentence.

**After Revision:**

FAPs activity and number regulation may have an impact on how much fibrosis and adipose infiltration occur following muscle aging because FAPs have the ability to develop into fibroblasts and adipocytes. Numerous studies have actually examined this theory. Lemos et al discovered that blocking TNF signalling stopped FAPs apoptosis, resulting in double the amount of FAPs and twice the amount of fibrosis after muscle injury. They also showed that nilotinib, a tyrosine kinase inhibitor that targets the TGF signalling pathway, increased FAPs apoptosis and decreased fibrosis(17). Imatinib, a related small molecule inhibitor that inhibits PDGFR α signaling and has been shown in studies to increase grip strength in mice with dystrophic limbs, significantly reduced muscle fibrosis(34).

27. Line 173-175: is it really shown that imatinib is reducing fibrosis via FAPs as suggested by the authors here?

**Response:** Thank you for your kind comments, it is true that there are such reports in the references.

28. Figure 2: please include in the figure legend what the different inhibitors (like imatinib) are inhibiting.

**Response:** Thanks for your valuable suggestions on this detailed deficiency of our manuscript. We have modified the figure.

29. Line 231: the authors discuss here the importance of senescence for the first time in the review. Either include a paragraph on senescence before the conclusion section or rephrase the conclusion section. It rather reads that it is added to the rest of the manuscript and is not a conclusion of the facts presented before.

**Response:** Thanks for your kind suggestion, we have rephrased the sentence.

**After Revision:**

For skeletal muscle to remain healthy, it is crucial to comprehend the mechanisms underlying tissue regeneration and degeneration caused by cellular aging. The numerous functions of skeletal muscle cell aging in muscle regeneration and degeneration are being increasingly supported by research. In this review, we discuss the fundamental relationships between FAPs and aging as well as how FAPs affect the aging-related degeneration and regeneration of muscle. The regulatory function of FAPs in preserving muscle growth and function serves as an example of recent developments in our understanding of these proteins.

30. Line 245: it reads like FAPs are only spatiotemporally controlled during aging and degeneration of skeletal muscle. Please rephrase since FAPs are spatiotemporally controlled during development and in the adult as well.

**Response:** As you suggested, we have rephrased the sentence.

**After Revision:**

Skeletal muscle research will develop with a better understanding of the connection between FAPs and the pathophysiology and physiology of muscle aging. However, there are still a few problems that need to be resolved. First, the phenotypes and roles of FAPs that are spatiotemporally modulated during skeletal muscle ageing and degeneration are yet unclear; Second, what is the role of FAPs in controlling the initiation and development of muscle senescence degeneration;

31. Line 255-257: the conclusion does not fit to the context of the manuscript. Please rephrase.

**Response:** We thank you for pointing out this shortcoming of our manuscript. We have rephrased the conslusion.

**After Revision:**

To summarise, there is no question that understanding how to improve skeletal muscle damage recovery and minimise muscle loss in older people is critical. Moreover, while FAPs cells remain mostly unknown, a fuller knowledge of the intricate role of muscle aging with FAPs is essential for the creation of really effective targeted therapeutics for aging.

32. Author contributions: if all authors contributed equally, why are there differences in author sequences then and not all are shared first or last authors? Please check the authors’ contributions carefully.

**Response:** We are sorry for our carelessness. We have modified the author contributions.

**Review #2**

1. Subtitles may be added to the "Contribution and mechanism of FAPs in aging" section. The paragraph "Lukjanenko et al. showed that..." could be moved forward. Because it still talks about the formation and function of FAPs.

**Response:** Thanks for your professional suggestion. We have added the subtitles to the "Contribution and mechanism of FAPs in aging" section. However, we did not move forward the paragraph "Lukjanenko et al. showed that...". Because it talks about a new segmentation of mechanism of FAPs in aging.

2. Subtitles may be added to the "Potential therapeutic role of FAPs in aging" section. Segmentation should be done according to the different targets of the drug.

**Response:** Thanks for your insightful suggestion. According to the different targets of the drug, we have added to the "Potential therapeutic role of FAPs in aging" section.

3. The text in Figure 1 and Figure 2 is too small.

**Response:** Thank you for your kind comments. We have enriched the text in Figure 1 and Figure 2.

4. English could be improved by native speakers.

**Response:** We are so sorry that we failed to revise our grammar and language throughout the manuscript correctly. This time, we sent the manuscript to native English experts for revision. We hope this embarrassing problem would not prevent the manuscript from publishing.