

Peer Review File

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Reviewer A

Good topic

Reply: Thank you for your feedback and for reading our work.

Changes in the text: None.

Reviewer B

The Authors performed a literature review on current advances and future directions of Tissue Engineering strategies for breast reconstruction. The review is interesting to a global audience. Since legislative aspects have also some importance, the following reference is missing: "Raposio E, Ciliberti RG. Clinical use of adipose-derived stem cells: European legislative issues. *Ann Med Surg (Lond)*. 2017;24:61-4".

Reply: Thank you very much for these comments on our work, and for your relevant remark. We added a new paragraph at the end of the fat grafting section, highlighting the need to take regulations into account and to help legislative evolutions through robust studies.

Changes in the text: We added a paragraph at the end of Section 3.2 (see page 12, lines 322-330).

Reviewer C

The article is interesting and well-written. It is necessary to discuss better the different methods of fat enrichment and fat processing, describing the methods of Adipose-derived Mesenchymal Stem Cells (AD-MSCs) and Stromal Vascular Fraction Cells (SVFs) isolation (enzymatic or mechanic), and related methods of fat purification (filtration, centrifugation, both, washing, etc). Additionally, the use of titanium mesh in breast reconstruction as new biotechnology applied to breast surgery should be discussed.

For the above-mentioned reason, it is necessary to improve the section "Improving fat grafting trophicity" by analyzing the following references: (the authors are free to analyze also other references):

Breast fat oncological safety

doi: 10.1016/j.bjps.2022.08.026

doi: 10.3390/cancers11071021

doi: 10.17219/acem/31673

Breast fat grafting (SVF, PRP, centrifugation, Filtration):

doi: 10.1007/s00266-022-03089-x

doi: 10.3390/jcm8040504

doi: 10.4103/JCAS.JCAS_24_18

doi: 10.1097/GOX.0000000000000285

doi: 10.1097/PRS.0b013e3182a00e57

doi: 10.5966/sctm.2011-0065

-Enzymatic vs Mechanical digestion of fat graft-

doi: 10.3390/ijms20215471

doi: 10.1007/s00266-023-03364-5.

-biomolecular basis of AD-MSCs

doi: 10.3390/ijms15046517

doi: 10.3390/cells8030282

-Breast comparison with prosthesis-

doi: 10.1007/s00266-005-0178-x

-Breast fat augmentation, and fat vs prosthesis-

doi: 10.3390/jcm10153310

doi: 10.1093/as/sjz292

-Breast biomaterial titanium mesh

doi: 10.1016/j.bioactmat.2021.05.002

Reply: Thank you very much for your thorough review of our paper. We totally agree that these references are of great value for our topic. We proceeded to substantial improvements of sections 3.1 and 3.2 accordingly to the content of these new citations. We hope our edits will reach your satisfaction, and we thank you for these relevant points helping greatly improving our manuscript.

Changes in the text:

- We added two sentences about titanium-coated mesh in section 3.1, pages 6-7, lines 177-180.

- We developed section 3.2 (page 8, lines 228-231) with the suggested references on implant based versus fat grafting in breast reconstruction and breast augmentation.

- We added all suggested and relevant references and corresponding ideas on pages 9-10 (lines 255; 259-263) regarding different techniques for SVF isolation.

- We highlighted the suggested references providing more evidence of ASC and SVF

safety on pages 10-11 (lines 286-294). Moreover, we discussed the outcomes from the study comparing SVF and PRP enhanced fat grafting (page 11, lines 296-299).

- We found relevant to add a sentence and citation about gentle manipulation of the fat (79, page 11, line 308-309).