

Reviewer concerns

1. They should also discuss the fifth kind of DSCs.

Reply: The fifth kind of DSCs mentioned above is stem cells from human exfoliated deciduous teeth (SHEDs). There were five studies on SHEDs which met our review criteria and have been discussed under relevant sections.

Reference Article No. 15, 16, 20 & 23 have discussed under the comparative proteomic profiles of SHEDs with DPSCs

Article 15: Pivoriuūnas A, Surovas A, Borutinskaite V, Matuzevicius D, Treigyte G, Savickiene J, Tunaitis V, Aldonyte R, Jarmalaviciuūte A, Suriakaite K, Liutkevicius E, Venalis A, Navakas D, Navakauskiene R, Magnusson KE. Proteomic analysis of stromal cells derived from the dental pulp of human exfoliated deciduous teeth. *Stem Cells Dev* 2010; **19**: 1081-1093 [PMID: 19824824 DOI: 10.1089/scd.2009.0315]

Article 16: Taraslia V, Lympieri S, Pantazopoulou V, Anagnostopoulos AK, Papassideri IS, Basdra EK, Bei M, Kontakiotis EG, Tsangaris GT, Stravopodis DJ, Anastasiadou E. A High-Resolution Proteomic Landscaping of Primary Human Dental Stem Cells: Identification of SHED- and PDLSC-Specific Biomarkers. *Int J Mol Sci* 2018; **19**: 158 [PMID: 29304003 doi: 10.3390/ijms19010158]

Article 20: Akpınar G, Kasap M, Aksoy A, Duruksu G, Gacar G, Karaoz E. Phenotypic and proteomic characteristics of human dental pulp derived mesenchymal stem cells from a natal, an exfoliated deciduous, and an impacted third molar tooth. *Stem Cells Int* 2014; **2014**: 457059 [PMID: 25379041 DOI: 10.1155/2014/457059]

Article 23: Wang H, Zhong Q, Yang T, Qi Y, Fu M, Yang X, Qiao L, Ling Q, Liu S, Zhao Y. Comparative characterization of SHED and DPSCs during extended cultivation in vitro. *Mol Med Rep* 2018; **17**: 6551-6559 [PMID: 29532869 DOI: 10.3892/mmr.2018.8725]

Reference Article 25 has discussed the comparative proteomic profiles of SHEDs with PDLSCs

Article 25: Xiong J, Menicanin D, Zilm PS, Marino V, Bartold PM, Gronthos S. Investigation of the Cell Surface Proteome of Human Periodontal Ligament Stem Cells. *Stem Cells Int* 2016; **2016: 1947157 [PMID: 27579043 DOI: 10.1155/2016/1947157]**

Separate section of SHEDs was not presented to avoid repetition.

2. What is the conclusion of the review? What kind of DSC is the ideal way to approach cell-based tissue design?

Reply: Dental stem cells are heterogeneous population of ectomesenchymal origin and to choose an ideal stem cell of DSCs origin is challenging. Factors such as number of passages, time of stem cell cultivation, media, and microenvironment and donor characterization determine the stemness and phenotypic behaviour of stem cells. Further to add initially we have to determine whether there is variation in physiological sensitivity of paracrine signals between these stem cells owing to its anatomical niche.

We concluded that: “Dental stem cells were unique and different from the other MSCs present in the body. The uniqueness of dental stem cells could be attributed to their origin and development through the interplay of epithelial-mesenchymal interactions. The presence and localization of the various dental stem cells (DPSCs, PDLSCs, DFSCs, APSCs & SHEDS) also had an impact on their final differentiation, which was reflected in the proteomic analysis. The microenvironment, niche and preconditioning factors had a substantial impact on the final outcome of the differentiation of dental stem cells. These factors either enhanced or suppressed the desired final differentiation outcome. Factors such as the source of dental stem cells (single/multiple donors), the culturing techniques, and the systemic condition of the donor have a bearing on the proteomes. The

majority of the proteins secreted by the various dental stem cells were mainly involved in the regulation of differentiation. The field of proteomics has recently greatly developed, considering the distinguishing proof and quantitation of proteins, even in small samples. Since there is a developing enthusiasm for the remedial impacts of autocrine/paracrine factors from MSCs, future investigations should assess all parts of the secretome and its related extracellular vesicles with regard to dental stem cells.”

3. The language need to be polished.

Reply: The manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at AJE. The certificate is attached for your reference.