Literature Review: Comparison of the Effects of Cigarette Smoke on Mesenchymal Stem Cells and Dental Stem Cells

Brandon Nguyen[1], Tamer Alpagot[2], Heesoo Oh[3], David Ojcius[4], Nan Xiao[4#]

[1] Candidate of Doctor of Dental Surgery Program, [2] Department of Periodontics, [3] Department of Orthodontics, and [4] Department of Biomedical Sciences, Arthur A. Dugoni School of Dentistry, University of the Pacific, California, USA

Abstract

With the advent and widespread use of e-cigarettes, exposure to nicotine is arguably higher and more accessible than ever. Although much is known about the systemic effects of nicotine, some clinically-relevant areas still remain unclear, such as the effect of nicotine on stem cells and its implications in regenerative medicine. This poster reviews recent studies on the mesenchymal stem cells, with a focus on the effect of cigarette smoke on dental stem cells.

Background

Stem cells are distinguished from other cell types due to two important defining characteristics. First, stem cells must exhibit self-renewal potential, which is the ability to produce identical copies of themselves through mitotic divisions over time. Second, stem cells must exhibit multilineage differentiation potential – pluripotency, which is the ability to give rise to various specialized cell types and serves as the driving concept behind stem cell regeneration. They also possess migration potential in order to reach sites of injury. These abilities allow stem cells to participate in the body's natural processes of wound healing and tissue generation and raise the potential of using stem cells in various applications in regenerative medicine.

However, certain environmental predisposing conditions such as cigarette smoke can negatively impact these abilities and stem cell viability for transplantation and regeneration. Most of the research conducted on stem cells involves mesenchymal stem cells (MSCs), typically from the bone marrow. The substantial growth in this research has allowed further understanding of the deleterious effects of cigarette smoke on MSCs, as well as improved our knowledge on the therapeutic usage of MSCs for smoking patients.

As of now, there is a considerable lack of research focused on dental stem cells. Given that the first exposure to smoke occurs in the oral cavity, and that the content of nicotine is estimated to be nearly 8 times higher in saliva than in blood plasma (8 hours following application of nicotine patch; saliva: 76.8 ng/ml, plasma: 10.0 ng/ml)[1], the potentially more susceptible stem cell populations in the oral cavity deserve more attention. Dental stem cells share many properties with MSCs, and a disruption in their function by higher concentrations of a known inhibitor of stem cell function would create significant problems in the repair process.

Materials & Methods

References were sourced on Google Scholar and PubMed using the keywords "dental stem cell nicotine," "dental stem cell cigarette smoke," "mesenchymal stem cells," and "dental stem cells". References included were within 10 years of publication.

Summary

Effect of cigarette smoke on mesenchymal stem cells (MSCs)

It has been shown that cigarette smoke extract (CSE) exhibits dose-dependent inhibitory effects in MSC viability and migration. High concentrations of CSE (5 and 10%) had lethal effects on MSCs. Lower concentrations (1%), however, showed no significant difference in cell viability, but impaired cell migration[2]. In vivo experiments have also shown that exposure to low-moderate human exposure of cigarette smoke to mice decreased recruitment and differentiation of MSCs to sites of injury[3].

Another study showed that MSC exposure to nicotine, an active compound in cigarette smoke, produced similar dose-dependent effects on osteoblastic differentiation. Exposure to 2mM of nicotine significantly decreased measures of osteoblastic differentiation such as calcium accumulation, alkaline phosphatase activity, and bone sialoprotein[4]. Other nicotine-containing products such as e-cigarettes have also shown to suppress proliferation and osteoblastic differentiation of MSCs[5].

Effect of cigarette smoke on dental stem cells

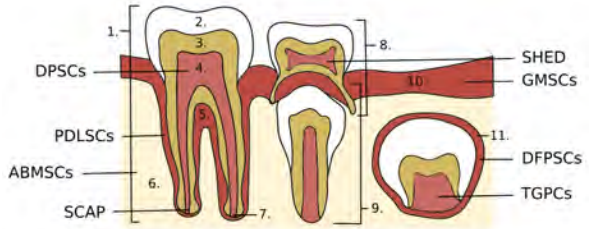

Figure 1. Illustration of origins of various dental stem cells: postnatal dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), dental follicle progenitor cells (DFPCs), alveolar bone-derived MSCs (ABMSCs), stem cell from apical papilla (SCAP), tooth germ progenitor cells (TGPCs), and gingival MSCs (GMSCs). 1. Postnatal/permanent tooth, 2. Enamel, 3. Dentin, 4. Pulp chamber, 5. Periodontal ligament, 6. Alveolar bone, 7. Apical papilla, 8. Deciduous tooth, 9. Erupting permanent tooth, 10. Gingiva, 11. Dental follicle

It has been shown that dental pulp stem cells (DPSCs) cultured from third molars of smokers exhibited significantly less expression of osteogenic differentiation markers and decreased proliferation rates compared to DPSCs cultured from non-smokers[6].

These results mirror those of a similar study with periodontal ligament stem cells (PDLSCs) isolated from smokers, which showed a 2.53-fold decrease in proliferation rates, reduced calcium deposition levels following osteogenic differentiation *in vitro*, and a 12% slower migration rate compared to PDLSCs from non-smokers[7]. It has been proposed that nicotine induces osteogenic differentiation deficiency of PDLSCs via activation of α7 nicotinic acetylcholine receptor (α7 nAChR) and the wnt/β-catenin signaling pathway. This impairment of osteogenic differentiation of PDLSCs by nicotine may contribute to smoking related periodontitis[8].

Nicotine has been shown to have a dose-dependent effect on PDLSCs. Higher doses (10^{-3} mol/L) induced vacuolar degeneration and a significant decrease in cell proliferation. Lower doses (10-4 to 10-6 mol/L) produced a less significant difference in cell morphology and a reduced effect on cell proliferation[8].

The mechanism by which nicotine affects dental stem cells remains largely uncertain. It has been proposed that this could be the result of miRNA downregulation of genes responsible for cell migration (protein tyrosine kinase 2) and osteogenic differentiation (RUNX family transcription factor 2)[9]. It has been suggested that nicotine stimulates the upregulation of miR-1305, which binds directly to the 3' UTR of the downstream pluripotency factor POLR3G in stem cells thereby hindering stem cell differentiation[10]. Still, much of this mechanism remains unclear and more research is needed to understand the full scope to which nicotine affects stem cell function.

Conclusion

The similarities between the responses of mesenchymal stem cells and dental stem cells to cigarette smoke offers a unique opportunity to apply previous MSC research to future dental stem cell studies. The incorporation of continued research, *in vivo* studies, and clinical trials may elucidate the effects cigarette smoke and nicotine on dental stem cells as well as broaden our understanding of regenerative medicine and its implications for the oral cavity.

References

1. Lindell G, Lunell E, Graffner H. Transdermally administered nicotine accumulates in gastric juice. *Eur J Clin Pharmacol*. 1996;51(3-4):315-318. doi:10.1007/s002280050204
2. Wahl EA, Schenck TL, Machens H-G, Egaña JT. Acute stimulation of mesenchymal stem cells with cigarette smoke extract affects their migration, differentiation, and paracrine potential. *Sci Rep*. 2016;6. doi:10.1038/srep22957
3. Zhou Y, Gan Y, Taylor HS. Cigarette smoke inhibits recruitment of bone-marrow-derived stem cells to the uterus. *Reprod Toxicol*. 2011;31(2):123-127. doi:10.1016/j.reprotox.2010.10.007
4. Kim B-S, Kim S-J, Kim H-J, et al. Effects of nicotine on proliferation and osteoblast differentiation in human alveolar bone marrow-derived mesenchymal stem cells. *Life Sciences*. 2012;90(3):109-115. doi:10.1016/j.lfs.2011.10.019
5. Shaito A, Saliba J, Husari A, et al. Electronic Cigarette Smoke Impairs Normal Mesenchymal Stem Cell Differentiation. *Sci Rep*. 2017;7. doi:10.1038/s41598-017-14634-z
6. Kamel A, Kamal S, AbuBakr N. Effect of smoking on the proliferation capacity and osteogenic potential of human dental pulp stem cells (DPSCs). *Dent Med Probl*. 2020;57(1):0-0. doi:10.17219/dmp/113179
7. Ng TK, Huang L, Cao D, et al. Cigarette smoking hinders human periodontal ligament-derived stem cell proliferation, migration and differentiation potentials. *Sci Rep*. 2015;5(1):1-7. doi:10.1038/srep07828
8. Zhou Z, Li B, Dong Z, et al. Nicotine Deteriorates the Osteogenic Differentiation of Periodontal Ligament Stem Cells through α7 Nicotinic Acetylcholine Receptor Regulating wnt Pathway. *PLOS ONE*. 2013;8(12):e83102. doi:10.1371/journal.pone.0083102
9. Ng TK, Carballosa CM, Pelaez D, et al. Nicotine Alters MicroRNA Expression and Hinders Human Adult Stem Cell Regenerative Potential. *Stem Cells and Development*. 2012;22(5):781-790. doi:10.1089/scd.2012.0434
10. Jin S, Collin J, Zhu L, et al. A Novel Role for miR-1305 in Regulation of Pluripotency-Differentiation Balance, Cell Cycle, and Apoptosis in Human Pluripotent Stem Cells. *STEM CELLS*. 2016;34(9):2306-2317. doi:10.1002/stem.244

Acknowledgement

This work was supported by Tobacco-Related Diseases Research Program Grant T30IP0917 from Regents of the University of California, and Interdisciplinary Pilot Research Grant Award DRES03-129 from the Arthur A. Dugoni School of Dentistry, University of the Pacific.