

Short Communication

Investigating Local Delivery of Mesenchymal Stromal Cell Extracellular Vesicles for Treatment-resistant Periodontitis: A Hypothesis

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system**ABSTRACT**

Background: One of the main reasons for tooth loss and functional incompatibility of dentition is periodontitis which is a multi-factorial disease. Among the main reasons for periodontitis is inflammation.

Hypothesis: Some keystone bacteria, such as *Prophyromonas gingivalis* with a notable number of virulence factors could activate and modify inflammatory pathways in gingiva. A well-established therapy for this disease is topical antibiotics; however, these treatments have side effects and could promote antibiotic-resistant infections as well. Such antibiotic-resistant infections are a group of periodontitis with a severely complicated treatment approach that could fail. Thus, new strategies need to be developed for treatment-resistant (antibiotic-resistant) periodontitis. In the past decades, many randomized controlled clinical trials have shown that mesenchymal stromal cells (MSCs) could treat inflammatory-dependent diseases or disorders. In addition to MSCs, the anti-inflammatory effects of their extracellular vesicles (EVs) have also been studied in the clinic.

Results: Considering the anti-inflammatory potential of MSCs-derived EVs, it could be hypothesized that local delivery of these EVs could be an effective method for periodontal treatment due to the accessible location of the periodontium.

Conclusion: This study suggests further in vivo studies and randomized clinical trials on the potential effects of MSCs-derived EVs on periodontal disease treatment.

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Introduction

Periodontitis is the sixth most prevalent disease in humans [1]. Between 2011 and 2020, periodontitis and severe periodontitis in dentate adults were estimated to be around 62% and 23.6%, respectively [2]. Periodontitis is the major cause of periodontium and periodontal ligament breakdown around teeth [3]. Poor treatment or no treatment of this disease often leads to tooth loss [4]. Periodontitis is a multifactorial disease and the host-bacteria relation/interaction is the main background factor behind this condition. A normal person with a competent immune system responds properly to bacterial-induced inflammation caused by this disease. This inflammation may result in tissue response and tissue destruction around teeth and the complete periodontal ligament structure, including cementum, alveolar bone, dentin, and fibers could be affected [4]. On the other hand, antibiotic-resistant bacteria are a concerning challenge faced by many medical doctors and dentists now. Adjunctive local and systemic antibiotic treatment temporarily increases the antibiotic resistance of subgingival microorganisms [5]. Without a proper response to the antibacterial agents, some serious untreatable diseases could appear. To prevent this situation, antibiotic consumption should be strictly monitored. Also, a randomized controlled trial shows limited effect of systemic antibiotics on most periodontal problems. However, they also report that the local delivery of some of these medications showed promising results. On the other hand, some of these local delivery drugs have serious side effects and, in some cases, antibiotic allergy. Therefore, new approaches to periodontal treatment could be crucial [6]. Accordingly, this study introduces a possible new treatment strategy for local treatment of periodontitis with topical mesenchymal stromal cells (MSCs)-derived-extracellular vesicles (EVs) or MSCs-derived EVs.

Hypothesis

Local delivery gels and biodegradable chips containing MSCs-derived EVs could be useful in the treatment of periodontitis through the prohibition of overresponse of inflammatory pathways. Also, they could prevent antibiotic-resistant infections.

Discussion

MSCs have potent anti-inflammation and immune system modulation qualities. Their potent therapeutic properties have been studied in different clinical trials. According to a recent systematic review and meta-analysis, it has been shown that MSCs are safe to be used in the

clinic [7]. One of the cell secretions which recently has attracted much attention is EVs [8]. The MSC-derived EVs have been used for the treatment of chronic inflammatory diseases, such as graft-versus-host disease which clinically improved the patient's condition through reducing the skin lesions [9]. Also, in an unpublished clinical trial, these EVs have been used for the treatment of COVID-19 patients in an inflammatory state (under review data for publication (IRCT Code: RCT20200418047121N2).

Lipopolysaccharide is a major virulence factor in perio-pathogen bacteria, such as *Prophyromonas gingivalis* which could induce a pro-inflammatory reaction [10]. Human MSCs-derived exosomes exert an anti-inflammatory effect by targeting the ROCK1/PTEN pathway which could decrease lipopolysaccharide-induced inflammation [11]. A recent study showed that 3D-exos (exosomes cultured with a 3D system) exhibited enhanced anti-inflammatory effects in a ligature-induced model of periodontitis by restoring the reactive T helper 17 (Th17) cell/Treg balance in inflamed periodontal tissues [12]. A recent animal study showed treatment by exosomes secreted by periodontal stem cells (PDLSCs) led to an increase in the formation of mineralized nodules and the expression of osteogenic genes and proteins in the inflammatory periodontal ligament of periodontitis patients. These exosomes suppressed the over-activation of canonical Wnt signaling to recover the osteogenic differentiation capacity of I-periodontal stem cells [13]. MSCs-derived exosomes could decrease different inflammatory markers, such as C-reactive protein which has an accepted role in the destruction pathway of periodontal ligament and alveolar bone [14]. Studies have shown that MSCs-derived EVs could be a useful treatment option for microbial diseases, such as pneumonia, sepsis-associated liver and kidney injuries, and periodontitis, due to their anti-microbial roles [15].

As mentioned, a systemic review and meta-analysis showed that intravenous MSC injection appears to be safe in humans [7]; therefore, using MSC exosomes in colloid in gels or on local delivery chips could also be safe and applicable. Although a recent systematic review and meta-analysis concluded that MSC therapy is safe [7], some concerns are still existing as well. Thus, EVs originating from the already-used-in-clinic MSCs could have similar and even better clinical responses in comparison to MSCs. They could be less immunogenic, have faster tissue penetration, and be the soul of cell-free therapies based on MSCs [16].

Conclusion

Inflammation and infections of bacterial origins are the major causes of periodontal structure breakdown and the keystones of periodontitis. MSCs-derived EVs show promising results in inflammation resolution and have a potent anti-inflammatory effect. Also, studies suggest that these agents have antimicrobial potential as well. Moreover, these exosomes are safe and also could be used in local delivery ways; however, further in vivo and human studies are required.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and supervision: Maryam Norooz-zhad; Investigation: Koosha Farshadianpour, Kiarash Kiani, and Mona Salighe Rad; Writing the original draft: Koosha Farshadianpour, Kiarash Kiani, and Mona Salighe Rad; Review, editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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