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Anti-Inflammatory Effect of Specialized Proresolving Lipid Mediators on Mesenchymal Stem Cells and Hard Tissue Formation: An In-Vitro Study

Abstract:

Introduction: Inflammation is a sophisticated biological reaction designed to protect the body from detrimental stimuli and facilitate tissue healing. Nonetheless, dysregulated or unresolved inflammation can result in chronic illnesses and tissue injury. Specialized pro-resolving mediators (SPMs) are natural lipid-based molecules that play vital roles in the resolution of inflammation. Among SPMs, Resolvin E1 (RvE1) and maresin 1 (MaR1) play a protective biological role in eliminating the unfavorable inflammatory effects of insulting influxes and stimulating the reparative tissue process. A relatively new concept was established, in which SPMs actively enhance the inflammatory resolution and tissue regeneration that leads to inflammation resolution by providing "stop signals" that contribute to pro-inflammatory cytokines clearance, preventing damage in inflammatory diseases. To date, there is no available evidence evaluating the effects of a combined mixture of RvE1 and MaR1 on bone remodeling and inflammatory lesion healing processes.

Objectives:

- To compare the effects of RvE1 and MaR1 on human bone marrow-derived mesenchymal stem cell (hBMMSC) viability, proliferation, migration, survival capacity, and expression of inflammation-related cytokines in an inflammatory microenvironment.
- To evaluate the individual and combined effects of RvE1 and MaR1 on osteogenesis-related protein expression in hBMMSCs in an inflammatory microenvironment.

Materials and Methods:

Part I: The effects of RvE1 and MaR1 in lipopolysaccharide (LPS) stimulated hBMMSCs were determined. The hBMMSCs were divided into five different groups, each of which was treated with or without SPMs. Group-1: negative control (no LPS stimulation), Group-2: positive control (LPS-stimulated), Group-3: RvE1 100 nM + 1 µg/mL LPS, Group-4: MaR1 100 nM + 1 µg/mL LPS, and Group-5: RvE1 100 nM + MaR1100 nM + 1 µg/mL LPS. Cell proliferation, apoptosis, migration, colony formation, Western blotting, cytokine array, and LC/MS analysis were all performed on each group to determine the impact of SPMs on inflamed hBMMSCs. p-value ≤ 0.05 was considered as significant.

Part II: The influence of applying RvE1 and MaR1, either individually or in combination, on the osteogenic differentiation of hBMMSCs under inflammatory conditions was investigated. The hBMMSCs were treated with SPMs in the presence of LPS to mimic an inflammatory environment. Osteogenic differentiation was evaluated using Alkaline Phosphatase activity (ALP) and Alizarin Red staining. Additionally, we conducted proteomic analysis to characterize changes in the protein expression profile, focusing on proteins associated with osteogenesis and osteoclastogenesis across the three experimental groups and at 7- and 14-days' time points. p-value ≤ 0.05 was considered as significant.

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Results:

Part I: RvE1 plus MaR1 effectively reduced inflammation in hBMMSCs. Specifically, there was observed upregulation of Interleukin-4 (IL-4), Interleukin-10 (IL-10), and Transforming Growth Factor-β1 (TGF-β1), along with downregulation of Receptor Activator of Nuclear factor kappa-B Ligand (RANKL), Tumor Necrosis Factor-α (TNF-α), and Interferon-γ (IFN-γ). These changes demonstrated significant differences compared to groups receiving single treatment approach (A p-value of ≤ 0.05). Furthermore, the LC/MS analysis identified the distinctive role of differentially regulated peptides in immunological pathways that characterize the cellular response to inflammation. Inflamed hBMMSCs treated with a combination of RvE1 and MaR1 promoted the highest inflammatory resolution compared to the other groups (>2-fold change, and $p \leq 0.05$); this finding suggests a potential new approach of treating inflammation caused by dental infections.

Part II: Treatment with RvE1 and MaR1, both individually and in combination, significantly enhanced calcified deposit formation (A p-value of ≤ 0.05). Proteomic analysis revealed differential expression of proteins associated with osteogenesis and osteoclastogenesis, highlighting the modulatory impact of SPMs on bone metabolism (>2-fold change, and $p \leq 0.05$). RvE1 and MaR1 promote osteogenic differentiation of hBMMSCs in an inflammatory environment, with their combined application yielding synergistic effects. This study provides insights into the therapeutic potential of SPMs in enhancing bone regeneration, suggesting a promising avenue for developing regenerative therapies for periodontal disease and other conditions characterized by inflammation-induced bone loss.

Conclusions: RvE1 and MaR1 inhibited excessive inflammation and enhanced bone mineralization while causing no significant cellular damage. Therefore, the simultaneous use of RvE1 and MaR1 may offer advantages for treatment and represent a promising therapeutic strategy to support the integrity of hBMMSCs in inflammatory environments.

Biography: Dr. Shahd Alzahrani is an Endodontist at the Ministry of Interior Medical Services. She holds both a Bachelor of Dental Surgery (BDS) and a Doctor of Science in Dentistry (DScD) in Endodontics from King Saud University (KSU), Saudi Arabia. Alongside her clinical practice, Dr. Alzahrani has been involved in postgraduate dental education at KSU and was previously granted research support for a two-year project at King Faisal Specialist Hospital and Research Center.

Her clinical and research interests center on regenerative endodontics and the advancement of endodontic materials and techniques. She has authored several publications in peer-reviewed journals, including work on regenerative approaches and rotary instrumentation. Dr. Alzahrani is a member of the American Association of Endodontists (AAE) and the Saudi Endodontic Society (SES).

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