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Review article

THE ROLE OF MICRORNA IN PERIODONTITIS AND HYPERTENSION

Theodora Bolyarova
Department of Periodontology, Faculty of Dental Medicine, Medical University - Sofia, Bulgaria. .

ABSTRACT

Periodontitis is a socially significant disease due to its potential to locally cause tooth loss and impaired function, and systemically, due to its influence on the onset and progression of various chronic diseases. Hypertension is socially significant because of its widespread prevalence and its potential to cause damage to various organs.

MicroRNAs (miRNA) are involved in various immune and inflammatory response processes as post-transcriptional blockers that bind to mRNA and silence specific target genes. One of the mechanisms by which periodontitis may affect other systemic diseases, such as cardiovascular diseases, including hypertension, is believed to be due to changes in serum miRNA levels caused by periodontal infection. Such aberrant miRNA expression can impact signaling cascades related to immune mechanisms, potentially triggering chronic diseases involving inflammatory processes in their pathogenesis.

Contemporary research focuses on identifying changes in miRNA expression associated with these pathologies, exploring their potential as next-generation biomarkers for early diagnosis, confirming shared signaling pathways between periodontal diseases and hypertension, and guiding the development of novel molecular therapeutic strategies. The significance of such scientific studies lies in their expected contribution to addressing public health challenges such as hypertension and periodontitis.

Keywords: MicroRNAs, Periodontitis, Hypertension, Next-generation sequencing,

INTRODUCTION

Periodontitis is defined as a chronic multifactorial inflammatory disease associated with a dysbiotic plaque biofilm, characterized by the progressive destruction of the tooth-supporting apparatus [1]. Bacteria are considered necessary but not sufficient for the development of the disease. The recognition of periodontitis as an inflammatory condition driven by the host immune response opens new avenues for diagnosis, treatment, and long-term management based on the identification of disease biomarkers [2]. The interplay between periodontitis and other systemic diseases, such as cardiovascular diseases and diabetes, leads to changes in the expression patterns of biomarkers.

Hypertension is a complex, multifactorial, and multisystem disorder influenced by both intrinsic and environmental factors [3]. Two key molecular and cellular events underlying its pathogenesis in various organs are the production of reactive oxygen species and inflammation. Identifying biomarkers involved in its pathogenesis and useful for early diagnosis is of critical importance [4].

MicroRNAs (miRNAs), ranging from 20 to 23 nucleotides in length, are short non-coding RNAs that act as post-transcriptional regulators by binding to messenger RNA (mRNA) and silencing specific target genes. MicroRNAs participate in various immune response processes by regulating the expression of immune-related genes [5]. Unlike proteins or mRNAs, miRNAs have been shown to be highly stable across different types of biological samples and can be isolated from tissues and biofluids. Dysregulated miRNA expression is associated with various pathologies, making them viable candidates for biomarker research and therapeutic strategies.

For instance, miR-146 and miR-155 are linked to key immune system regulators by inducing the expression of specific cytokines such as TNFα, IL-1β, type I and II interferons (IFNs), or RANKL. Therefore, the expression of these two miRNAs is associated with processes involving chronic inflammation [6]. MicroRNAs are part of epigenetic mechanisms playing critical roles in chronic inflammatory condi-

tions present in diseases such as cardiovascular diseases, Alzheimer's disease, rheumatoid arthritis, and periodontitis. Their expression has been analyzed in various samples, including gingival biopsies, periodontal ligament stem cells, serum, plasma, saliva, gingival crevicular fluid, and supragingival biofilm.

Most studies have examined the wide and distinctive expression of miRNAs using various techniques, such as RT-PCR, microarrays, and next-generation sequencing (NGS). NGS technologies are transforming biomedical research by providing increased data volume, efficiency, and applications. Platforms like Illumina or Ion Torrent employ "short-read" technologies that include massively parallel sequencing of short sequences, allowing millions of individual sequencing reactions to occur simultaneously. The NGS workflow involves library preparation, sequencing, and bioinformatics data analysis. Advances in characterizing cellular RNA species using RNA-seq technologies are expected to enhance our understanding of gene expression, its role in cell physiology, and intercellular interactions, leading to groundbreaking scientific discoveries and applications with significant economic and health impacts [7].

MicroRNA and Periodontitis

Studies have demonstrated a connection between elevated levels of miR-146a, miR-146b, miR-142-3p, miR-155, and miR-203 in saliva and the progression of periodontal disease [8]. Increased levels of miR-145-5p in saliva have been associated with higher mean pocket depth and bleeding on probing index, while elevated levels of miR-140-3p in plasma have been observed among patients with periodontitis. Furthermore, independent associations between miR-140-3p, miR-145-5p, and miR-125a-3p levels in gingival tissues and the presence and severity of periodontitis have been identified [9].

Significant increases in relative levels of miR-223 and miR-200b in serum and gingival crevicular fluid were found in patients with periodontitis, showing a positive correlation with TNF-á. Conversely, a significant decrease in miR-203 was associated with a negative correlation with TNF-á [10].

Multiple levels of control over periodontal disease mediated by miRNAs have been highlighted: their role in periodontal inflammation and dysregulation of homeostasis; acting as regulatory targets of long non-coding RNAs (lncRNAs); contributing to susceptibility to periodontal disease through miRNA polymorphisms; mdulating the periodontal microbiome via viral miRNAs [11]. Dysregulated non-coding RNAs (ncRNAs) play a dual role—either protective or destructive—in the development of periodontitis, primarily influencing cellular proliferation, differentiation, and apoptosis through interactions with various molecules or signaling pathways [12].

MicroRNA and Hypertension

Aberrant expression of non-coding RNAs (ncRNAs) can trigger cellular dysfunction and promote pathological events associated with hypertension. The discovery of miRNA dysregulation in hypertension and their expression may be linked to genes and biological pathways, identifying them as potential biomarkers. Various miRNAs can participate in processes such as inflammation, endothelial dysfunction, and others involved in the development of cardiovascular diseases.

Studies using experiments on human cell lines, isolated peripheral blood mononuclear cells, animal models, and human subjects have identified concentrations of specific miRNAs as potential markers for cardiovascular diseases, including hypertension. Identifying miRNAs specifically deregulated in hypertension offers the possibility of considering new therapeutic approaches for treating vascular damage and hypertension [13].

The immune system plays a role in hypertension and target organ damage. Activation of T-cells in hypertensive patients is associated with the action of miRNAs as post-transcriptional regulators of immune cells. Deregulated miRNAs (DE miRNAs) are thought to be involved in cytosolic transport and protein kinase B signaling. Vascular damage is an early manifestation of hypertension. MiR-431 and its target, Ehf (a gene responsible for synthesizing the ETS transcription factor), may act as key regulators in the pathophysiology of vascular damage in hypertension [4].

Results from bibliometric studies indicate that research on miRNAs in the field of hypertension is rapidly developing and focuses mainly on several key areas, including circulating miRNAs, SNP-driven miRNA profiles, miRNA-regulated target genes, the relationship between miRNAs and hypertension-related diseases, and miRNA-mediated signaling pathways. Notable miRNAs associated with hypertension, such as miR-126-3p, miR-182-5p, and miR-30a-5p, suggest their potential as diagnostic biomarkers or therapeutic targets.

Network analysis reveals the involvement of these miRNAs in critical signaling pathways, including oxidative stress, apoptosis, and inflammatory responses. These findings highlight circulating miRNAs as a focal point in hypertension research [14].

The Link Between Periodontitis and Hypertension

There is epidemiological evidence that hypertension and periodontitis are closely linked, though data on the nature of this relationship remain limited. Most studies included in systematic reviews and meta-analyses show that a larger

proportion of patients with significant tooth loss (a criterion for severe periodontitis) have hypertension and higher systolic blood pressure compared to those with less tooth loss. A significant association between the two conditions has been observed [15].

The connection between periodontitis and hypertension is further supported by experimental and interventional studies worldwide. A causative role for low-grade inflammation is emphasized, providing biological evidence for the significance of inflammation in the adrenergic system, the clinical hypertensive phenotype, and the elevation of circulating systemic inflammation markers. Periodontal treatment has been shown to favorably influence blood pressure profiles and control in prehypertensive and hypertensive individuals [16, 17].

One area of investigation into the link between these conditions is the potential epigenetic influence mediated by non-coding RNAs, such as miRNAs. A review identified 13 shared miRNAs between periodontitis and hypertension, which are predicted to interact with numerous genes involved in various signaling pathways linked to the pathophysiology of both diseases, inflammation, and immune responses. According to predictions by the DIANA-mirPath program, these miRNAs may regulate genes involved in 52 signaling pathways [17].

CONCLUSION

Research results on changes in miRNA expression in tissues and biological fluids studied separately for periodontitis and hypertension remain heterogeneous. Ongoing studies aim to identify a panel of miRNAs as biomarkers for both conditions, to clarify the relationship between the diseases, to determine molecular biomarkers from the miRNA group, and to guide new therapeutic approaches.

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Address for correspondence:
Theodora Nikolaeva Bolyarova
Department of Periodontology, Faculty of Dental Medicine, Medical University – Sofia;
1, St. G. Sofiiski Blvd., 1431 Sofia, Bulgaria
E-mail: t.bolyarova@fdm.mu-sofia.bg,