Levels of miRNA miR200b-5p (miR200b*) in the minor salivary glands (MSG) of patients with Sjögren’s syndrome: Possible prognostic value for future lymphoma development?

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ABSTRACT

Sjögren’s syndrome (SS) is a chronic autoimmune disease with a broad clinical spectrum extending from organ-specific exocrinopathy to various systemic manifestations. Approximately 6-10% of SS patients develop B-cell non-Hodgkin lymphoma, which is the main cause of increased mortality in SS. The development of lymphoma has been associated with the expression of several clinical, laboratory and histopathological markers. The pathogenetic mechanisms underlying syndrome development and lymphomagenesis are unknown. Most likely, the heterogeneity of clinical phenotypes and the broad outcome of SS patients reflect discrete and complex pathogenetic pathways in patient subgroups.

The expression pattern of certain microRNAs (miRNAs) has been linked to reduced salivary gland (SG) function, as well as Ro/SSA and La/SSB autoantigens expression. Furthermore, reduced levels of miR200b-5p miRNA in the SG tissues were associated with MALT-lymphoma, suggesting that they may participate in SS lymphomagenesis. Indeed, miR200b miRNAs are critical regulators of oncogenes and their suppressors. In this context, the down-regulated expression of miR200b-5p in the SG tissues of SS patients with MALT-lymphoma may represent a pathogenetic pathway and a promising prognostic biomarker for development of lymphoma. In the current study, the levels of miR200b-5p expression will be evaluated in SGs from SS patients that: a) do not have adverse prognostic factors for lymphoma development; b) had developed lymphoma in the future (prelymphoma); and c) had SS-associated lymphoma. Their association with SS-related lymphoma and value as prognostic biomarkers will be validated with anticipated significant effect in lymphoma prediction and understanding of SS lymphomagenesis.

Ethical Approval: Ethics Committee of the School of Medicine, National University of Athens, Greece (Protocol No.: 1516023992)

Keywords: Sjögren’s syndrome, miRNA miR200b-5p, lymphoma, risk factors.

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INTRODUCTION
Sjögren’s syndrome (SS) is a prototype autoimmune disease with broad clinical expression ranging from organ-specific exocrinopathy (predominantly of salivary and lachrymal glands) to various systemic extraglandular manifestations. The extraglandular systemic manifestations are a common finding and can be classified into those characterized by periepithelial inflammation (involvement of the lung, liver, interstitial nephritis) or immune-complex mediated vasculitis (peripheral neuropathy, glomerulonephritis, purpura). Approximately 6-10% of SS patients develop B-cell non-Hodgkin lymphoma. Lymphoma is an important outcome, since it is the main cause of increased mortality in SS. Sjögren’s syndrome patients at risk of developing lymphoma can be distinguished by certain clinical and laboratory markers, which are evident at diagnosis. Several such prognostic factors have been reported. Salivary gland (SG) enlargement, cryoglobulinemia and low serum levels of the C4 complement protein are the most widely accepted adverse prognostic factors for future lymphoma development in SS. In addition, various histopathological parameters, such as the organization of SG infiltrates of SS patients into ectopic germinal centers, the increased infiltration of SGs by macrophages or the production of IL18 by macrophages have been associated with the future development of lymphoma, thereby connecting the local inflammatory reactions with lymphomagenesis. Most likely, local glandular inflammatory reactions associate with the systemic manifestations of the syndrome, as supported by the fact that patients with extensive lymphocytic infiltrates exhibit severe systemic disease. The pathogenetic mechanisms that lead to the development of the syndrome and lymphomagenesis are unknown. However, the heterogeneity of clinical phenotypes and the broad outcome of patients with Sjögren’s syndrome probably reflect the action of discrete and complex pathogenetic pathways. The epithelial cells, which are the targets of autoimmune responses, are key regulators of SS inflammatory responses. The salivary gland epithelial cells (SGEC) are capable to respond to innate immunity signals and to participate in the recruitment, activation and differentiation of lymphocytes. Recent studies implicate certain microRNAs (miRNAs) in SS pathogenesis. The miRNAs are small RNA molecules (18-22nt) that suppress gene expression at the post-transcriptional level by inhibiting the translation of mature miRNAs. They regulate almost all biological processes, including the proliferation and differentiation of cells, apoptosis and organ development. Due to their central role in the activation, proliferation and differentiation of immune cells, research interest was focused in their involvement in the development of autoimmune diseases. Deregulated expression of several miRNAs has been implicated in several autoimmune diseases. In Sjögren’s syndrome, the expression pattern of miRNAs has been associated with reduced SG function. Recently, we have shown that the expression of miR16, miR200b-3p, let7b and miR483-5p is deregulated, whereas let7b, miR16, miR181a and miR200b-3p miRNAs may be involved in the regulation of the expression of Ro/SSA and La/SSB autoantigens, the increased expression of which in the SGs is thought to participate in the development of SS autoimmune responses. Furthermore, reduced levels of miR200b-3p and miR200b-5p miRNAs in the SG tissues of SS patients were associated with the formation of germinal centers in autoimmune lesions and MALT-lymphoma. The distinct pattern of expression of miR200b-3p and miR200b-5p miRNAs most likely suggests that they may participate in the underlying mechanisms of lymphomagenesis in SS. Indeed, the miR200b family miRNAs are critical regulators of the expression of oncogenes and their suppressors. Furthermore, they have been suggested as markers of metastasis and poor disease prognosis. In this context, the downregulated expression of miR200b-5p in the SG tissues of SS patients with MALT-lymphoma may represent a pathogenetic pathway and a promising prognostic biomarker for development of lymphoma.

PATIENTS AND METHODS
Therefore, the levels of miR200b-5p expression will be studied in SGs from SS patients that a) do not have adverse prognostic factors for lymphoma development; b) developed lymphoma in the future (prelymphoma); and c) had SS-associated lymphoma. Their deregulation in SS-associated lymphoma and their value as prognostic biomarkers for lymphoma will be validated in a sufficient cohort. If their deregulation is confirmed, the expression of miR200b-5p will be examined histologically by in situ hybridization to reveal expressing types of cells and functional cell to identify pathogenetic pathways.

ANTICIPATED BENEFITS
This study is expected to have great impact on both the prediction and understanding of the mechanisms involved in SS lymphomagenesis.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.
REFERENCES


