

Human and Viral microRNA Expression in Sjögren Syndrome



Sjögren syndrome (SS) is one of the most common autoimmune diseases, and mainly affects women. It is characterized by features of systemic autoimmunity and dysfunction and inflammation in the exocrine glands. The dysfunction of the salivary glands often causes significant morbidity and has social implications. In a significant percentage of affected patients, extraglandular manifestations lead to systemic diseases with serious medical implications as more major organs are affected. Non-Hodgkin lymphoma is another major complication of SS, occurring in 5% of patients. The pathogenesis of SS has not been delineated, but it is believed that both immunologic and non-immune mechanisms are involved.

In this issue of *The Journal*, Peng, *et al*, report their findings of microRNA profiling of peripheral mononuclear cells of primary SS (pSS) in a Chinese patient cohort¹. Four patients with pSS and 3 healthy controls were profiled with microarrays and some of the most differentially expressed microRNA were validated with quantitative real-time PCR in a total of 33 pSS patient and 10 healthy control samples, including the samples used for microarrays. After all analyses, miRNA-146a, miRNA-155, and miRNA-181a were found to be the most differentially expressed. Not surprisingly, those microRNA have previously been associated with autoimmune diseases and immune microRNA studies.

miRNA-146a is a very interesting microRNA involved in several biological functions and diseases, from acquired immunity² to cancer^{3,4}. miRNA-146a has been shown to be a negative regulator of nuclear factor- κ B activation through regulation of IRAK1/TRAF6 of the MyD88-dependent pathway⁵. In autoimmune diseases, it has been shown to be downregulated in the peripheral mononuclear cells of patients with systemic lupus erythematosus but upregulated in patients with rheumatoid arthritis^{5,6}. miRNA-146a has also previously been associated with SS and was shown to be upregulated in peripheral mononuclear cells⁷. Similarly to miRNA-146a, miRNA-155 has also been implicated in a variety of

pathologies^{8,9,10}. However, in the case of SS and in relation to the viral differentially expressed microRNA reported in this article, the relation of miRNA-155 to Epstein-Barr virus infection (EBV)^{11,12} and the association of this microRNA to lymphomas deserve further evaluation^{13,14,15}.

The finding that the overexpression of miRNA-181a is attributed to the B cells and not the T cells of patients with pSS, yet there was no clinical correlation of the level of expression of this microRNA except for antinuclear antibody, is intriguing for a number of reasons. First, it shows that overexpression of this microRNA does not correlate with disease activity and chronicity and thus it might be one of the first and constant molecular alterations that occurs in pSS B cells. Second, measures of the relative level of miRNA-181a in B and T cells might prove to be a biomarker for pSS. Finally, knowing the exact cell type of a dysregulated microRNA greatly facilitates the study of its role in disease, because the functional effect of a microRNA is in many cases tissue dependent. This has already been shown to be the case for miRNA-181a in hematopoiesis. In one of the seminal articles examining the role of microRNA in hematopoiesis¹⁶, mouse bone marrow cells were infected with a retrovirus expressing miRNA-181a and were then transplanted into lethally irradiated mice, allowing the infected cells to reconstitute all blood lineages. Examination of the lineage composition of peripheral blood cells originating from the infected cells showed that miRNA-181a expression increased the number of B lymphoid cells, with a concurrent decrease in T lymphoid cells, especially CD8+. Because the differentiation of B and T cells is developmentally independent, the functional role of miRNA-181a in those cells is vastly different. Another finding from that study is that in murine bone marrow cells, miRNA-181a expression was low in pre-B progenitor cells and upregulated in differentiated mature B lymphocytes. Identifying the molecular trigger of this upregulation only in B cells will contribute to our limited understanding of disease

See Elevated miRNA-181a levels in pSS PBMC, page 2208

pathogenesis in SS and help in the development of targeted therapies.

Another very interesting finding from this microRNA profiling is the simultaneous overexpression of viral microRNA in blood mononuclear cells. This finding is in accordance with a previous study that identified many of the same viral microRNA unregulated in the salivary glands of pSS¹⁷.

Viral microRNA function in host cells, their interaction with cellular microRNA, and the relation of viral microRNA to stage of the viral life cycle have not been studied for the majority of viral microRNA. In the present article¹, the presence of EBV microRNA and the upregulation of miRNA-181a in B cells, which are the only lymphatic cells known to be infected by EBV, generate interesting questions about the possibility of a viral microRNA driving the expression of a cellular microRNA in a specific cell type promoting a disease phenotype.

The interplay between viral infections and viral and cellular microRNA in the pathogenesis of autoimmune diseases is difficult to delineate, but the presence and differential expression of the viral microRNA in a number of pathologies suggest that they might play crucial roles in complex diseases, especially ones in which environmental factors have been shown to be contributing factors.

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