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REVIEW

The Role of Deregulated MicroRNAs in Immune Cells of Sjögren's Disease

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Abstract: The 2024 Nobel Prize in Physiology or Medicine, awarded for the discovery of microRNAs (miRNAs) as essential regulators of gene expression, has spotlighted their pivotal roles in disease processes, including autoimmune conditions such as Sjögren's disease (SD). SD is a chronic autoimmune disease marked by lymphocytic infiltration of exocrine glands, resulting in significant glandular dysfunction and diverse systemic effects. Recent research has revealed that miRNAs play crucial roles in SD pathogenesis, orchestrating immune cell activity, epithelial cell integrity, and the regulation of inflammatory pathways. Dysregulation of specific miRNAs is associated with exacerbated immune responses, glandular damage, epithelial cell dysfunction, and sustained inflammation, positioning these small RNA molecules as central players in disease progression. This review synthesizes current findings on the roles of miRNAs in SD, highlighting how certain miRNAs contribute to immune dysregulation, epithelial dysfunction, and disease chronicity. Additionally, we explore the potential of miRNAs as biomarkers for disease activity, reflecting both immune and epithelial health, and as novel therapeutic targets. By consolidating recent advancements, we aim to offer a comprehensive perspective on the involvement of miRNAs in SD and to underscore the potential for miRNA-based strategies to transform the diagnosis, management, and treatment of SD.

Keywords: Sjögren's disease, MicroRNA, immune dysregulation, epithelial integrity

Introduction

Sjögren's disease (SD) is a chronic autoimmune disease primarily characterized by lymphocytic infiltration of exocrine glands, leading to a hallmark triad of symptoms: xerostomia (dry mouth), keratoconjunctivitis sicca (dry eyes), and systemic manifestations that may involve the joints, skin, and internal organs.[1] The exact etiology of SD remains elusive, but it is understood to involve a complex interplay of genetic predisposition, environmental factors, and dysregulated immune responses, resulting in the loss of tolerance to self-antigens.[2]

Recent advancements in molecular biology have uncovered the critical role of microRNAs (miRNAs), which are small, non-coding RNA molecules approximately 21–25 nucleotides in length.[3] MiRNAs function as key post-transcriptional regulators of gene expression by binding to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or repression of translation.[4] This regulatory mechanism allows miRNAs to orchestrate numerous biological processes, including cell proliferation, differentiation, apoptosis, and immune response modulation.[5,6]

The groundbreaking discoveries made by Victor Ambros and Gary Ruvkun in the field of miRNA biology have provided invaluable insights into the functional roles of these molecules across various biological systems.[7] Their work has demonstrated how miRNAs can act as critical regulators in numerous diseases, including cancer, cardiovascular disorders, and autoimmune conditions.

In SD, an increasing body of evidence suggests that miRNAs play pivotal roles in the disease's pathogenesis.[8] For instance, specific miRNAs have been implicated in the modulation of immune cell functions, including the activation of autoreactive T and B cells, the regulation of pro-inflammatory cytokines, and the maintenance of epithelial integrity within exocrine glands.[9,10] Dysregulation of miRNAs has been associated with altered immune responses, contributing to

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the chronic inflammation and tissue damage observed in SD. Moreover, the expression profiles of miRNAs in the serum and salivary glands of SD patients have been shown to differ significantly from those of healthy individuals, suggesting their potential as biomarkers for disease diagnosis and progression.[11] Furthermore, targeting specific miRNAs offers a promising therapeutic avenue, as modulation of miRNA expression could restore normal immune function and ameliorate glandular damage.

This review aims to provide a comprehensive overview of the role of miRNAs in the pathophysiology of SD. By synthesizing current knowledge on the interactions between miRNAs and immune system dynamics, we hope to illuminate the potential of miRNAs as biomarkers and therapeutic targets, ultimately enhancing our understanding and management of this multifaceted autoimmune disorder.

Biogenesis of MicroRNAs and Their Role in Sjögren's Disease

MiRNAs are a class of important non-coding RNA molecules, typically consisting of 21 to 25 nucleotides, that play a crucial role in gene regulation.[12] The biogenesis of miRNAs begins with the transcription of primary miRNA transcripts (pri-miRNAs), which are synthesized by RNA polymerase II and form a hairpin structure known as precursor miRNA (pre-miRNA).[13] In the nucleus, the enzyme Drosha, in association with the cofactor DGCR8, processes pri-miRNA into pre-miRNA.[14] Subsequently, pre-miRNAs are exported to the cytoplasm via Exportin-5, where they are further cleaved by the enzyme Dicer into mature miRNAs.[15] These mature miRNAs are then incorporated into the RNA-induced silencing complex (RISC), where they guide the complex to target mRNAs based on sequence complementarity, leading to either mRNA degradation or the inhibition of translation, thus regulating gene expression[16] Figure 1.

In SD, dysregulation of miRNAs has been closely linked to the pathogenesis and progression of the disease.[17] Specific miRNAs play pivotal roles in the activation of immune cells, where they influence immune responses by modulating the expression of cytokines.[18]

Epithelial Cells

Epithelial cells play a crucial role in the pathogenesis of SD. These cells, particularly in exocrine glands like salivary and lacrimal glands, contribute significantly to glandular dysfunction, which is a hallmark of SD. Dysregulation of miRNAs in epithelial cells can exacerbate inflammation, impair cell-cell communication, and disrupt epithelial integrity, leading to the chronic inflammation and glandular damage observed in SD. Several miRNAs have been implicated in epithelial dysfunction in SD. For example, miR-155 is upregulated in epithelial cells in the context of SD and has been shown to modulate inflammation by regulating the expression of cytokines like TNF-α and IL-6. Additionally, miR-146a, which is widely studied for its role in immune regulation, also affects epithelial cells. It targets genes such as TRAF6 and IRAK1, which are involved in inflammatory signaling pathways like NF-κB, contributing to epithelial dysfunction and promoting inflammation. Furthermore, miR-21 is another key regulator in epithelial cells that has been associated with fibrosis and tissue remodeling, both of which are common in SD. miR-21 acts by regulating PTEN and other pathways involved in cell survival and apoptosis, which can lead to tissue damage when dysregulated.

These miRNAs not only contribute to epithelial dysfunction but also present potential as biomarkers for disease activity, reflecting the extent of epithelial injury and inflammation in SD. Dysregulated miRNAs in epithelial cells thus serve as promising targets for therapeutic intervention, with the potential to restore epithelial homeostasis and limit the inflammatory response that drives disease progression in SD.

T Cells

T cells are critical mediators of the adaptive immune response and are implicated in the pathogenesis of SD. In SD, the balance between different T cell subsets is disrupted. $CD4^+$ T helper (Th) cells, particularly Th17 cells, have been shown to be prominent in the salivary glands of SD patients.[19] MiR-155 is crucial in promoting Th17 differentiation, enhancing the production of pro-inflammatory cytokines such as IL-17, which contributes to tissue inflammation and damage.[20] Additionally, miR-146a helps regulate T cell activation and limits excessive inflammatory responses, suggesting a dual role of miRNAs in maintaining immune homeostasis and promoting autoimmunity.[21] Specifically, miR-146a targets several key genes involved in immune responses, including TNF receptor-associated factor 6 (TRAF6) and interleukin-1

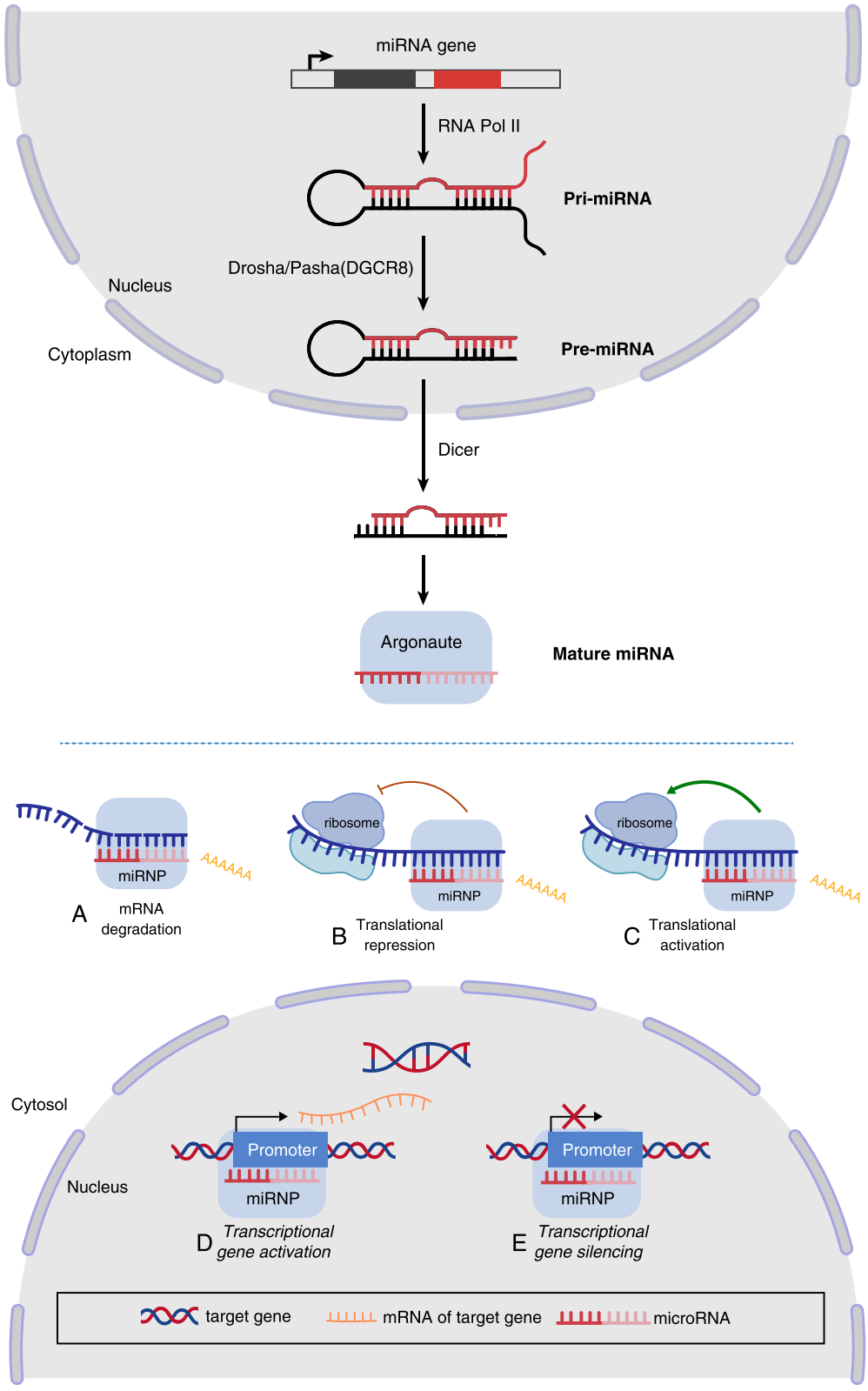

Figure 1 Mechanisms of miRNA-mediated regulation of gene expression. The process of miRNA maturation begins in the nucleus and is first transcribed by RNA polymerase II to generate longer pri-miRNAs. Such initial transcripts usually contain one or more stem-loop structures. Subsequently, Drosha/Pasha in the nucleus recognizes and cleaves pri-miRNAs to process them into pre-miRNAs. After further processing and transport, pre-miRNAs are transported into the cytoplasm. In the cytoplasm, Dicer enzyme will further cleave the pre-miRNA, removing its stem-loop structure and producing a mature miRNA duplex of approximately 21 to 25 base pairs, which is then loaded into miRNP. Binding of miRNP to target mRNA sequences that can lead to mRNA degradation (**A**) or/and inhibition of mRNA translation into protein (**B**) are two typical mechanisms of miRNA action. The binding of some miRNAs to certain targets has been shown to increase translation (**C**) rather than inhibit it. In addition, several miRNA species have been shown to bind to gene promoter sequences in the nucleus, acting as transcriptional activators (**D**) or silencers (**E**).

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receptor-associated kinase 1 (IRAK1), which are critical for the NF-κB signaling pathway. By downregulating these genes, miR-146a modulates the activation of pro-inflammatory cytokines and contributes to the resolution of inflammation. This regulatory mechanism underscores the complex role of miR-146a in controlling immune responses, preventing excessive inflammation, and potentially limiting the development of autoimmune conditions like SD.

B Cells

B cells are central to the autoimmune process in SD due to their role in producing autoantibodies against self-antigens, such as Ro/SSA and La/SSB.[22] The dysregulation of miRNAs like miR-21 and the miR-17-92 cluster enhances B cell survival and proliferation.[23,24] miR-21 promotes the activation of B cells and inhibits their apoptosis, allowing autoreactive B cells to persist.[25] Additionally, the expression of these miRNAs leads to increased secretion of autoantibodies, perpetuating the autoimmune response and contributing to the symptoms of SD.

Dendritic Cells

Dendritic cells (DCs) function as antigen-presenting cells that activate T cells and initiate immune responses.[26,27] In SD, DCs exhibit abnormal activation, which can be influenced by miRNAs such as miR-125b and miR-155.[28,29] MiR-155 enhances the production of pro-inflammatory cytokines (such as IL-6 and TNF-α) and promotes the activation of naive T cells into autoreactive T cell populations.[30] Dysregulated DC function can lead to enhanced presentation of self-antigens, driving the autoimmune process in SD.

Macrophages

Macrophages play a crucial role in the inflammatory milieu of SD. They can polarize into either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, significantly influencing the immune landscape.[31] In SD, the imbalance between these phenotypes is often observed. MiR-155 has been implicated in promoting the M1 phenotype, leading to increased production of inflammatory cytokines.[32] Conversely, miR-146a can favor the M2 phenotype, which is associated with tissue repair.[33] However, the persistent activation of M1 macrophages contributes to tissue damage and chronic inflammation in SD.

Natural Killer Cells

Natural killer (NK) cells are part of the innate immune system and contribute to the immune surveillance of autoreactive cells.[34] In SD, NK cells can exert both protective and pathogenic roles. They produce cytokines such as IFN-γ that can enhance the inflammatory response. MiRNAs like miR-15a and miR-16 are involved in regulating NK cell activation and proliferation.[35–37] Dysregulated NK cell activity may lead to increased tissue damage and exacerbate autoimmune processes in SD.

Regulatory T Cells

Tregs are essential for maintaining immune tolerance and preventing autoimmune responses regulatory T cells (Tregs).[38] In SD, the function of Tregs is often impaired, leading to a breakdown of tolerance to self-antigens. MiR-146a is critical for Treg function, and its dysregulation can impair the suppressive capacity of Tregs.[39,40] As a result, the lack of effective Treg-mediated control allows for the expansion of autoreactive T and B cells, contributing to the pathogenesis of SD.

Neutrophils

Neutrophils are key players in the innate immune response and are involved in the initial stages of inflammation in SD.[41] They release various pro-inflammatory mediators and can contribute to tissue damage. MiRNAs regulate neutrophil activation, survival, and chemotaxis. For instance, specific miRNAs can modulate the production of chemokines that attract other immune cells to the site of inflammation.[42] In SD, the persistent activation of neutrophils can contribute to the chronic inflammatory state characteristic of the disease.

Mast Cells

Mast cells are implicated in various inflammatory and allergic responses.[43] They release histamine and a range of cytokines and chemokines that can exacerbate inflammation in SD.[44] The regulation of mast cells by miRNAs can influence their activation and the subsequent inflammatory response.[45,46] Dysregulated mast cell activity may contribute to the exacerbation of symptoms in SD, particularly in the context of glandular dysfunction. Table 1 summarized the role of miRNA in those immune cell regulation and Sjogren syndrome.

Table 1 Role of MicroRNAs in Immune Cell Function and Their Implications in Sjogren Syndrome

Cell Type	miRNA	Function	Relation to Sjögren's Disease
T Cells	MiR-155	Promotes Th17 cell differentiation and enhances the production of pro-inflammatory cytokines (IL-17, IL-6, TNF-α), leading to tissue inflammation.	Increased Th17 cells in SD contribute to glandular inflammation, leading to dry symptoms and tissue damage.
	MiR-146a	Regulates T cell activation and limits excessive inflammatory responses by targeting TRAF6 and IRAK1 pathways.	Dysregulated T cell activity may exacerbate autoimmune responses in SD, contributing to disease progression.
B Cells	MiR-21	Promotes B cell activation and inhibits apoptosis, allowing autoreactive B cells to persist by targeting PTEN and Bcl-2 pathways.	Autoantibodies (eg, Ro/SSA and La/SSB) produced by B cells are critical to disease progression in SS.
	miR-17-92 cluster	Enhances B cell survival and proliferation by regulating genes involved in cell cycle and apoptosis (eg, E2F1, BIM).	Increased autoreactive B cell numbers worsen autoimmune responses, contributing to SD pathogenesis.
Dendritic Cells	MiR-155	Enhances production of pro-inflammatory cytokines (IL-6, TNF-α) and promotes autoreactive T cell activation.	Drives the autoimmune process in SD by promoting the presentation of self-antigens.
	MiR-125b	Affects abnormal activation of dendritic cells, regulating genes involved in immune activation (eg, IL-12, CCR7).	Abnormally activated dendritic cells contribute to the exacerbation of immune responses and symptoms of SS.
Macrophages	MiR-155	Promotes the M1 macrophage phenotype, leading to increased pro-inflammatory cytokine production (eg, IL-1β, IL-6, TNF-α).	M1 macrophages play a significant role in inflammation, tissue damage, and the chronic inflammatory state in SS.
	MiR-146a	Promotes the M2 macrophage phenotype, which aids tissue repair, by targeting NF-κB signaling and MAPK pathways.	An imbalance between M1 and M2 macrophages results in chronic inflammation, further driving tissue damage in SD.
Natural Killer (NK) Cells	MiR-15a/ MiR-16	Regulates NK cell activation and proliferation, modulating apoptosis through pathways like Bcl-2 and caspase activation.	Dysregulated NK cell activity enhances chronic inflammation and tissue damage in SD, leading to further disease progression.
Regulatory T Cells (Tregs)	MiR-146a	Critical for Treg function; regulates immune tolerance by targeting genes such as FoxP3 and NF-κB.	Impaired Treg function promotes the expansion of autoreactive T and B cells, contributing to the autoimmune nature of SD.
Neutrophils	–	Releases pro-inflammatory mediators (eg, IL-8, MPO) during the initial inflammation stages.	Activated neutrophils contribute to the tissue damage and chronic inflammation characteristic of SD.
Mast Cells	–	Involved in allergic and inflammatory responses, releasing histamine and cytokines such as IL-4 and IL-6.	Dysregulated mast cell activity may exacerbate glandular dysfunction and contribute to inflammation in SD.

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Clinical Implications and Therapeutic Potential of MicroRNAs in Sjögren's Disease

The distinctive expression profiles of miRNAs in patients with SD offer promising avenues for clinical applications. Given the critical roles that miRNAs play in the disease's pathophysiology, they hold the potential to serve as non-invasive biomarkers for several key aspects of SD.

Diagnostic and Prognostic Biomarkers

Recent studies have indicated that specific miRNA signatures can be detected in the saliva and serum of SD patients, distinguishing them from healthy individuals.[47] For example, elevated levels of certain miRNAs, such as miR-21 and miR-155, correlate with disease activity and severity.[8] These miRNAs can reflect the inflammatory state and immune dysregulation characteristic of SD.[48] Consequently, identifying these unique miRNA profiles may facilitate earlier diagnosis, allowing for timely interventions. Additionally, monitoring changes in miRNA levels over time can provide valuable insights into disease progression, making them potential biomarkers for tracking disease activity and evaluating therapeutic responses.[48]

Personalized Treatment Strategies

The identification of miRNA signatures in SD patients also paves the way for personalized treatment strategies. By understanding the specific miRNAs associated with an individual's disease profile, clinicians may tailor therapeutic approaches to target these molecules. For instance, patients exhibiting high levels of pro-inflammatory miRNAs could benefit from treatments aimed at inhibiting these specific miRNAs, thus potentially alleviating inflammation and tissue damage.[49] Conversely, patients with downregulated miRNAs that play protective roles may benefit from therapies designed to restore their levels, thereby enhancing immune regulation and promoting glandular function.[50]

Therapeutic Interventions Targeting miRNAs

The therapeutic potential of miRNAs in SD is an emerging area of research. Several innovative approaches are being explored, including the use of miRNA mimics and inhibitors. miRNA mimics are designed to replicate the function of downregulated miRNAs, restoring their expression and, consequently, their regulatory roles in the immune response. For example, delivering mimics of miR-146a could help enhance the regulatory pathways that control immune responses and mitigate excessive inflammation in SD.[51] On the other hand, miRNA inhibitors, also known as antagomirs or anti-miRs, are utilized to suppress the activity of overexpressed miRNAs that contribute to the pathogenesis of SD. For instance, inhibiting miR-155, which is linked to the activation of autoreactive T and B cells, could reduce inflammatory cytokine production and diminish the autoimmune response.[52]

Preclinical studies have shown promising results with these approaches, demonstrating that modulating miRNA levels can positively impact immune function and inflammation in models of autoimmune disease. These findings lay the groundwork for future clinical trials aimed at assessing the safety and efficacy of miRNA-based therapies in SD.

Discussion

The investigation of miRNAs in SD sheds light on their crucial roles in immune regulation and disease progression.[53] Recent studies have shown that specific miRNAs can serve as indicators of the disease, helping to distinguish SD patients from healthy individuals. For example, elevated levels of miR-21 and miR-155 have been detected in the saliva and serum of those with SD, correlating with the severity of inflammation and immune dysfunction.[54] This suggests that miRNAs could play a significant role in diagnosing SD non-invasively, which would allow for earlier intervention and more tailored treatment approaches. By monitoring changes in miRNA levels, clinicians might gain valuable insights into disease activity, leading to better management strategies for patients.

Moreover, the therapeutic potential of targeting miRNAs in SD is becoming increasingly apparent. Techniques such as miRNA mimics and inhibitors present innovative ways to restore normal immune function. For instance, increasing the levels of miR-146a could help dampen the inflammation that characterizes SD by enhancing immune regulation. On

the other hand, inhibiting miR-155 may reduce the activation of autoreactive T and B cells, ultimately lessening the autoimmune response. Preliminary studies in animal models have shown that these interventions can positively impact immune function and tissue integrity, setting the stage for future clinical trials.[55]

Additionally, integrating miRNA research with emerging technologies could further our understanding of SD. Techniques like single-cell RNA sequencing and CRISPR gene editing offer exciting opportunities to explore the specific roles of miRNAs in different immune cell types. This could help reveal the complex regulatory networks at play in SD and identify additional therapeutic targets.[56] As we continue to learn more about the functions of miRNAs and their interactions with the immune system, we open up new avenues for developing targeted therapies that could significantly change how we approach the treatment of SD.[18]

In summary, the growing interest in miRNAs within the context of SD highlights their importance not only in understanding the disease but also in improving diagnostic and therapeutic strategies. By leveraging the unique properties of miRNAs, we can potentially enhance our approaches to managing this complex autoimmune condition, ultimately benefiting patients through more effective care and treatment options.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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