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Review Article

Non-Coding RNA in Systemic Sclerosis

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Abstract

Systemic Sclerosis (SSc) is a multifaceted autoimmune disease marked by extensive fibrosis, vascular irregularities, and immune system dysfunction. The etiology of SSc is influenced by a complex interplay of genetic predispositions, environmental factors, and immune abnormalities. Recent research has highlighted the significant roles of non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in regulating gene expression and contributing to SSc pathogenesis. miRNA-133, a muscle-specific miRNA, is notably downregulated in SSc, correlating with increased fibroblast activation and profibrotic marker expression, such as TGF-β. This downregulation impedes the TGF-β/SMAD pathway, suggesting that restoring miRNA-133 could attenuate fibrosis. Conversely, lncRNA-H19 is upregulated in SSc, enhancing TGF-β and PKM2 levels, and acts as a molecular sponge for miRNAs, including miRNA-133, exacerbating fibroblast proliferation and extracellular matrix deposition. The expression levels of miRNA-133 and lncRNA-H19, along with serum PKM2 and TGF-β, hold potential as biomarkers for SSc, providing insights into disease severity and progression. Advances in non-coding RNA research and multi-omics technologies are unveiling intricate regulatory networks, offering promising therapeutic avenues and personalized treatment strategies for SSc.

Keywords: Systemic sclerosis; MiRNA-133; lncRNA H19; PKM2; TGF-β

Introduction

Systemic Sclerosis (SSc) is a complex autoimmune disorder characterized by widespread fibrosis, vascular abnormalities, and immune dysregulation. The pathogenesis of SSc involves a sophisticated interplay between genetic predisposition, environmental triggers, and immune system dysfunction. Recent advancements have underscored the critical roles of non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), in modulating gene expression and contributing to the pathophysiological mechanisms underlying SSc [1].

MiRNA-133 and lncRNA-H19 in SSc Pathogenesis

MiRNA-133 is a muscle-specific miRNA with a well-documented role in cardiac and skeletal muscle development. In SSc, miRNA-133 is significantly downregulated, which correlates with enhanced fibroblast activation and increased expression of profibrotic markers, including TGF-β. This downregulation may contribute to the pathological fibrosis observed in SSc patients [1-3]. Mechanistically, miRNA-133 inhibits the TGF-β/SMAD signaling pathway, which is crucial for the regulation of extracellular matrix production and fibrosis [1,2]. Recent studies have also suggested that restoring miRNA-133 levels can attenuate fibrosis in experimental models, making it a promising therapeutic target in mitigating fibrosis in SSc [1,3,4]. LncRNA-H19 is a pivotal regulator in various biological processes, including growth and development. Its upregulation in SSc patients is associated with increased TGF-β and PKM2 levels, both of which are key mediators in fibrogenesis and metabolic reprogramming. H19 can act as a molecular sponge for miRNAs, thereby modulating their availability and activity [1,5]. Specifically, H19's interaction with miRNA-133 affects the latter's ability to regulate target genes involved in fibrosis [1]. Elevated H19 expression has been shown to exacerbate fibroblast proliferation and extracellular matrix deposition, further driving the fibrotic process in SSc [1,5,6].

Clinical Implications and Biomarker Potential

The study by Khedr et al. highlights the potential of miRNA-133 and lncRNA-H19 as biomarkers for SSc. The expression levels of these non-coding RNAs, along with serum levels of PKM2 and TGF-β, provide valuable insights into disease sever-

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ity and progression [1]. Elevated PKM2 and TGF-β levels are indicative of metabolic reprogramming and fibrotic activity, respectively, which are hallmarks of SSc pathology [1]. Monitoring these biomarkers could aid in early diagnosis, assessing disease activity, and tailoring personalized therapeutic strategies for SSc patients [1].

Recent Advances and Future Directions

The field of non-coding RNA research is rapidly evolving, with new findings continuously emerging. Recent studies have demonstrated that miRNA-133 mimics or agonists can effectively reduce fibrosis in preclinical models of SSc, suggesting a potential therapeutic approach [1,4,7]. Similarly, targeting lncRNA-H19 with specific inhibitors or antisense oligonucleotides has shown promise in mitigating fibrotic responses and restoring normal cellular functions [1,6].

Moreover, advancements in multi-omics technologies, such as single-cell RNA sequencing and proteomics, are providing deeper insights into the complex regulatory networks involving miRNAs and lncRNAs in SSc. These approaches are helping to unravel the dynamic interactions between non-coding RNAs and their target genes, paving the way for novel therapeutic interventions [8].

Conclusion

The intricate roles of miRNA-133 and lncRNA-H19 in the pathogenesis of systemic sclerosis highlight their significance as both biomarkers and therapeutic targets. Continued research into their molecular mechanisms and interactions will be crucial for developing effective treatments for SSc. Leveraging the latest technological advancements and expanding our understanding of non-coding RNA biology hold promise for improving patient outcomes and managing this debilitating disease.

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