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miR-370 and miR-493: Potential Biomarkers in the Pathophysiology of COVID-19

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ABSTRACT

MicroRNAs (miRs) are key post-transcriptional regulators of gene expression and have emerged as important modulators of host responses during viral infections, including coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Growing evidence indicates that *miR-370* and *miR-493* participate in pathways relevant to COVID-19 pathophysiology, influencing inflammatory signaling, immune cell activity, and cellular processes that may shape viral replication and tissue injury. *miR-370* has been linked to the suppression of proinflammatory cytokine production, modulation of lipid- and fibrosis-related pathways, and attenuation of lung inflammatory responses, suggesting a potential protective role during acute infection. *miR-493* has been associated with regulation of apoptosis, immune activation, and stress-response pathways, with alterations in its expression correlating with disease severity in several inflammatory conditions. Because interactions between host miRs and viral or host mRNAs can influence viral entry, replication, and immune dysregulation, understanding the specific mechanisms through which *miR-370* and *miR-493* act is essential for clarifying their relevance in COVID-19. This review synthesizes current evidence on the molecular pathways, validated targets, and potential regulatory roles of *miR-370* and *miR-493* in SARS-CoV-2 infection, highlighting their promise as biomarkers and their possible utility in improving diagnostic and therapeutic strategies for COVID-19.

Keywords: Biomarkers; microRNAs; SARS-CoV-2; Virology

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which arose at the end of 2019.[1] Global surveillance data show that COVID-19 has remained a major worldwide health burden since its emergence, with sustained viral circulation documented across more than 80 countries in recent reporting periods.[2] The

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pathophysiological aspects of COVID-19 mainly comprise the entry of the SARS-CoV-2 virus into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor that is predominantly expressed on cells throughout the lungs, heart, kidneys, and intestines.[3] ACE2 is a transmembrane protein found on the host cell surface that serves as a receptor for the SARS-CoV-2 spike glycoprotein in mediating infection. The spike protein is additionally cleaved and subsequently activated via the cell surface transmembrane protease serine 2 (TMPRSS2) to allow for entry into the cell through membrane fusion. Many microRNAs (miRs) are predicted to interact with components of the SARS-CoV-2 entry machinery, and several have been proposed as potential regulators of ACE2 or TMPRSS2 within the broader host-response pathway.[4]

Additionally, circulating miRs can be released or originated from different biological processes, including (1) passive release from injured or damaged cells due to chronic inflammation or apoptosis, (2) active release through the use of cell-derived membrane vesicles, such as microparticles (exosomes), and (3) active release through the assembly of protein-miR complexes.[5] miRs have been proposed as molecular markers and therapeutic targets for COVID-19 research. As a class of small noncoding RNAs, they modulate gene expression as well as host defenses during SARS-CoV-2 infections[6] and have demonstrated exciting therapeutic potential in several viral diseases, including herpes simplex virus (HSV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and influenza.[7] miRs may inhibit, induce, or enhance gene expression, broadening future therapeutic possibilities and helping to uncover the biopathological mechanisms of diseases.[8] Some miRs play a role in proinflammatory pathway amplification, cytokine storm risk,[9] and regulation of both the innate and adaptive immune responses through several different mechanisms, involving T-cell and B-cell maturation, secretion, and proliferation.[10]

Circulating miR profiles in COVID-19 are shaped not only by viral-induced immune dysregulation but also by host-related factors that independently alter miR expression patterns. Comorbidities such as obesity and type 2 diabetes are characterized by chronic low-grade inflammation, altered lipid metabolism, and endothelial dysfunction, all of which contribute to broad shifts in miR networks, including those involved in antiviral responses and cytokine regulation. These conditions have been shown to modify circulating levels of multiple immune- and metabolism-related miRs, creating baseline heterogeneity that can influence biomarker interpretation in COVID-19.[11,12] Chronic pulmonary diseases similarly alter airway and systemic miR signatures through persistent oxidative stress and inflammatory remodeling, further complicating the attribution of miR changes solely to SARS-CoV-2 infection.[13] In addition to disease-related factors, medications commonly used in patients with COVID-19 also modulate miR expression. Corticosteroids regulate miRs involved in immune suppression and cytokine signaling,[14] while statins influence miRs linked to endothelial stability, lipid metabolism, and inflammatory pathways.[15] Recent clinical studies in COVID-19 cohorts confirm that these comorbidities and medications contribute to interindividual variability in circulating miR profiles, underscoring their relevance as potential confounders when evaluating miR-370 and miR-493 as candidate biomarkers. Integrating these considerations is essential for accurate interpretation of miR-based signatures and for distinguishing disease-specific alterations from background biological variability.[16,17]

Circulating miR measurements are highly sensitive to preanalytical and methodological variables, which must be considered when interpreting disease-associated signatures. Sample type is a major determinant of miR composition: plasma and serum differ in coagulation-related miR release, while exosomal and tissue-derived miRs reflect distinct cellular origins and vesicle-mediated transport pathways. Hemolysis can further alter plasma miR profiles by releasing erythrocyte-enriched miRs, underscoring the need for standardized sample handling.[18] The timing of sample collection relative to symptom onset is also critical in COVID-19, as miR expression fluctuates across phases of viral replication, immune activation, and tissue injury.[19] Analytical factors, including RNA extraction efficiency, choice of endogenous reference miRs (such as miR-16 or U6), and use of exogenous spike-in controls (such as cel-miR-39), substantially influence quantification accuracy and cross-study comparability.[20,21] Recognizing these variables is essential for evaluating miR-370 and miR-493 as potential biomarkers and for distinguishing true disease-related changes from methodological artifacts. Furthermore, multiple miR-profiling studies in COVID-19 have demonstrated extensive dysregulation of circulating and exosomal miRs, linking specific signatures to disease severity,

hyperinflammatory responses, endothelial injury, and thrombo-inflammation in patient serum, plasma, and bronchoalveolar lavage samples.[19,22] Experimental models of viral infection and integrative miR–mRNA analyses further suggest that host miRs can modulate antiviral pathways and the expression of key entry factors and inflammatory mediators.[23,24]

In this regard, one study showed that miR-370 regulates gene expression and mediates biological processes, including cell proliferation, differentiation, and apoptosis. miR-370 has a unique ability to target multiple genes and has been shown to influence gene expression pathways related to cancer, metabolism, and heart disease.[25] In addition, miR-493 regulates gene expression across multiple cellular systems and participates in diverse biological processes, including the differentiation and maturation of specific tissues and organs. Beyond its developmental roles, miR-493 exerts well-documented anti-tumorigenic effects by directly targeting key oncogenes and modulating tumor-suppressive pathways, thereby influencing cell proliferation, apoptosis, and metastatic potential.[26] As a result, the interactions of host miRs and viral miRs contribute to various mechanisms that allow SARS-CoV-2 to escape immune detection while allowing the virus to survive and infect host cells.[27] Studies researching miRs as therapeutics may also serve to identify biomarkers for susceptibility, severity of COVID-19, complications, and their subsequent effects.[28–30] As such, we sought to investigate the role and mechanism of action of miR-370 and miR-493 in COVID-19 studies. Observing the results of recent studies and evaluating the signaling pathways affected through viral infection may hopefully assist in diagnosing and managing COVID-19. miR-370 and miR-493 consistently emerge across independent studies as regulators of inflammation, immune signaling, and tissue-injury pathways that closely overlap with key mechanisms driving COVID-19 severity. Their validated molecular targets and pathway involvement in metabolic, fibrotic, and immune processes make them biologically plausible and previously underexplored candidates for contributing to COVID-19 pathophysiology and serving as potential circulating biomarkers.

Functional Impact of miR-370 in COVID-19

Circulating miR profiling in COVID-19 has consistently shown altered expression patterns, revealing specific miRs and their target genes that correlate with both the presence of the disease and its clinical severity. miR-370, a specific miR, appears to be more involved than other miRs in the control of a wide range of biological processes.[25] miR-370 is relevant for genes involved in the use and response to viral infection processes, including COVID-19.[31,32] In addition, it has been proposed that the coronavirus may alter the expression of some miRs, like miR-370, which may have some significance in disease progression and the immune response against the virus.[33,34] Moreover, miR-370 has been implicated in the modulation of TGF-β–related fibrotic pathways in experimental models, with luciferase reporter and protein-level data supporting its role in fibrosis-associated signaling.[35,36]

Evidence shows that miRs from SARS-CoV-2 bind to the 5′-untranslated region (UTR) of genes. miR-370 can target and down-regulate TGF-βRII and block the phosphorylation of R-Smad proteins. Consequently, it inhibits proliferation, migration, and capillary formation through the miR-370/TGF-βRII/phospho-Smad3 axis.[38]

In another signaling pathway, miR-370 may also play a role in reducing *FBLN5* expression and regulating NF-κB, which is central to mediating the inflammatory response and also has an immune role in several viral infections.[39,40] It has been reported that miR-370 represses the NF-κB pathway through inhibition of LIN28A, and the biological activities of both miR-370 and LIN28A, as a functional target of miR-370, revert through inactivation of the NF-κB pathway.[41] In COVID-19, bioinformatic analyses have proposed potential interactions between miR-370 and components of the ACE2 axis, the primary receptor for SARS-CoV-2,[42] however, direct functional validation (eg, luciferase reporter assays and rescue experiments) remains limited and warrants further investigation.

miR-370 may inhibit SARS-CoV-2 from attaching to and subsequently infecting host cells, thus affecting the severity of symptoms relating to the COVID-19 infection.[33] There is an altered expression of miR-370 in patients, indicating this is a molecular marker that can help understand the various severity levels of the disease.[31] Consequently, it has been proposed that specific signatures of miRs, such as miR-370, allow differentiation in the early diagnosis and severity prediction of COVID-19. This shows there are important miRs involved in the progression of the viral disease (Figure 1).[43]

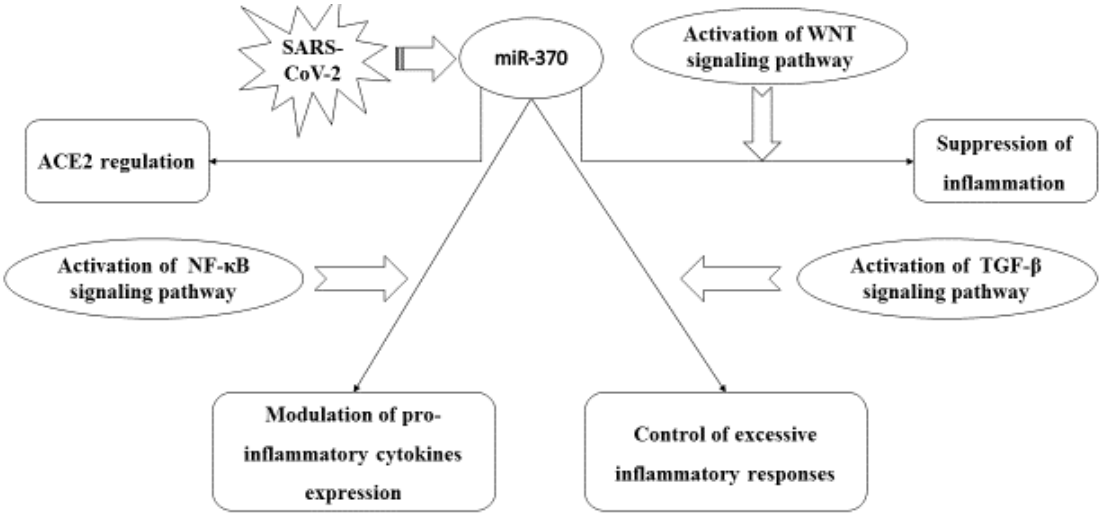

Figure 1. Mechanism of function of miR-370 in COVID-19.

miR-493 and Its Potential Role in Inflammatory Action in COVID-19

miR-493 is another nucleic acid biomarker that has been shown to likely have a role in several biological functions and has a major effect on the regulation of cellular function.[44] miR-493 is complementary to target messenger RNAs (mRNAs) and, thus, allows for the silencing of genes and, consequently, the reduced expression of the target proteins.[45] This may serve as a tumor suppressor when downregulating the expression of oncogenes or upregulating the expression of tumor-suppressor genes through its potential role in physiological states.[46] Likewise, it is engaged in cell growth, differentiation, apoptosis, and the inflammatory response.[47] Because of the many diseases in which it is involved, such as cancer or inflammatory diseases, miR-493 could potentially serve as a marker for diagnosis or as a prognostic marker in the course of a disease.[48–50] miR-493 could also serve a role in modulating the immune response to SARS-CoV-2[51] and the expression of genes that are part of this inflammatory response, potentially impacting how an individual responds to the virus and the intensity of the immune response. If miR-493 controls cytokines, it could alter their production, thus impacting the severity of the immune response. Greater alterations in cytokine production can lead to a cytokine storm, which is a significant response witnessed in some patients with COVID-19.[52,53] Moreover, miR-493 is known to be linked with p53[54,55] and the mitogen-activated protein kinase (MAPK) signaling pathway,[56] which are essential for multiple cellular processes, such as proliferation and survival. miR-493 has the potential to modulate MAPK signaling and regulate the immune response during viral infections.[57] Indeed, MAPK signaling occurs when a cell is facing stress (eg, oxidative stress, ultraviolet [UV] irradiation, cytokines, heat shock, DNA damage, and viral infection).[58] All viruses regulate replication by host kinases. The MAPK pathway regulates host gene expression through the phosphorylation of serine and threonine as a means of converting extracellular signals to intracellular results. MAPK pathways are triggered by the binding of the virus to pattern recognition receptors (PRRs)/Toll-like receptors (TLRs) or by secretory proteins that can elicit activation of extracellular signal-regulated kinase (ERK), such as cytokines. The MAPK pathway has been defined as biphasic because of the position of both the early and late stages of infection as related to virus replication and viral protein expression.[59] In one study, researchers evaluated the prognostic specificity of miR-493 as a potential biomarker for predicting COVID-19 severity. In this study, miR-493 was upregulated in severe COVID-19 compared to healthy controls, thereby supporting its preliminary use as a biomarker.[51] Another study demonstrated that miR-493 expression might also correspondingly affect some level of the inflammatory response. In summary, this information suggests that miR-493 may be a potential candidate biomarker of interest for additional functional mechanisms in viral infections (Figure 2).[60]

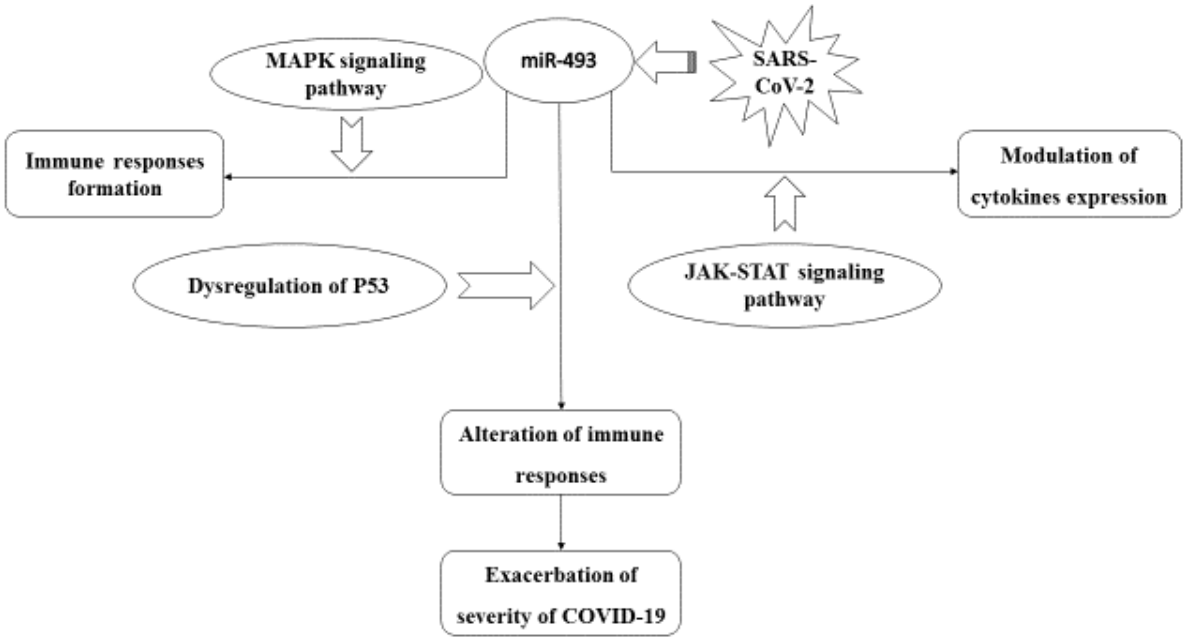

Figure 2. Mechanism of function of miR-493 in COVID-19.

DISCUSSION

We considered the roles of miR-493 and miR-370 in the pathogenesis of COVID-19. We found that miRs with therapeutic potential may also serve as biomarkers to indicate susceptibility, COVID-19 severity, and risk of subsequent complications. We also proposed underlying molecular mechanisms using 2-miR therapy to treat COVID-19. Although miR-370 and miR-493 show consistent associations with inflammatory and antiviral pathways relevant to COVID-19, definitive mechanistic confirmation requires functional studies. Gain-of-function and loss-of-function experiments using miR mimics or antagomirs, luciferase reporter assays to verify direct target binding, and rescue experiments are essential to establish causality. Furthermore, dose–response analyses and evaluation of delivery challenges, particularly exosomal or nanoparticle-based nucleic acid transport, are necessary steps before these miRs can be advanced as validated biomarkers or therapeutic candidates.

Future studies would be well suited to focus on identifying the exact molecular mechanisms of action and testing efficacy in larger and more appropriate clinical studies. The potential influence of miR-370 and miR-493 on COVID-19 pathology should also be examined so that new treatment modalities can be identified.

STATEMENT OF ETHICS

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AI ASSISTANCE DISCLOSURE

There aren't any AI tools were used in preparing this manuscript.

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