



Comment on: “MicroRNA Mimics or Inhibitors as Antiviral Therapeutic Approaches Against COVID-19”

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To the Editor

We read with great interest the article by Hum et al [1] that reviewed the advancement of microRNA (miRNA) therapeutics (including miRNA mimics and inhibitors) used in research and clinical practice for the treatment of viral infections, especially COVID-19. The article presented an optimistic perspective for curing COVID-19. However, based on available research on miRNAs and COVID-19 (including articles, company reports and clinical trials), we cannot be optimistic about the druggability and targetability of miRNA molecules. It is an important fact that since 1993 when miRNAs were discovered and their functions were revealed [2], the US FDA has never approved nor intended to approve any miRNA-based therapeutics (or drugs) for the treatment of any disease.

MiRNAs are endogenous and regulatory RNA molecules. Research on miRNAs has been extremely popular recently and has led to hundreds of thousands of publications but the research has not been directed to treating disease; to date, miRNAs seem to have been quite ineffective. Compared with small interfering RNAs (siRNAs), molecules similar to miRNA discovered a few years after miRNA, miRNAs seem to meet fewer expectations of the scientific community. As early as 2006, the scientists who discovered RNA interference, including interference through siRNA technology, were awarded the Nobel Prize in Physiology or Medicine. As of 2021, three siRNA-based drugs (patisiran [3], givosiran [4] and lumasiran [5]) have been approved by the US FDA, and quite a few other drugs are in Phase 3 clinical trials. However, for miRNAs, the situation is not optimistic. First,

only approximately 10 miRNA-based therapeutics have been entered into clinical trials; second, these tests are in the early stage (Phase 1 or 2) of clinical trials; third, more than a few clinical trials have been discontinued due to serious adverse events and even deaths caused by the unexpected off-target effects of miRNAs in tested individuals [6, 7]. In contrast to siRNAs, miRNAs are partially complementary to target mRNAs in base pairing, which causes miRNAs to regulate tens or even hundreds of genes, and many of these are not related to disease treatment [6, 7]. When using a miRNA drug, that is, inhibiting a miRNA or introducing it in vivo, it is equivalent to altering multiple signaling pathways, thus leading to inevitable toxicities and side effects. Thus, miRNA-based therapeutics are immature and difficult to administer and their use in treating a sudden epidemic disease is not appropriate.

When Hum’s article discussed COVID-19, three points were raised with regard to current studies; however, these give a one-sided perspective. First, some miRNAs are differentially expressed in COVID-19-infected individuals, but the mechanism is not clear. Theoretically, these miRNAs may be potential indicators for detecting COVID-19 (however, currently, nucleic acid testing is being extensively used because of its accuracy and rapidity), but they cannot be used as therapeutic targets of COVID-19 because their specific mode of action is unclear. Currently, the FDA rarely approves drugs with unclear targets or mechanisms. Second, miRNAs can bind and regulate important proteins in humans with SARS-CoV-2 infection, for example, miR-200 and miR-24 are linked to the regulation of ACE2 and Furin. However, these two miRNAs have too many targets. MiR-200 can directly interact and inhibit many genes, including but not limited to ZEB [8], SIP1 [8], C-MYB [9] and ZNF217 [10]. MiR-24 can directly regulate many more genes than PER1 [11], BIM [12] and KLF8 [13]. Most FDA-approved drugs have only one or several similar targets (a tiny minority of drugs have a few targets), and almost no approved drug has many unrelated targets. Third, miRNAs can interact with the genome

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of SARS-CoV-2. On the one hand, miRNAs can regulate the physiological process of the virus by targeting viral genes. However, when controlling viral replication or infection by inducing or interfering with miRNAs, the changes in miRNA expression can trigger many signaling pathways in the host body, which probably causes the unpredicted adverse reactions observed in tested individuals. On the other hand, viruses can be regarded as sponges that absorb functional miRNAs, which drives the host into a pathological state. In this case, treating the host with miRNA induction likely feeds miRNAs to the viral genome. In addition, the genes that these miRNAs can regulate are also altered and lead to changes in subsequent signaling pathways that can trigger serious side effects. Therefore, miRNA-based therapeutics, in the current situation, do not seem beneficial for the treatment of COVID-19.

MiRNAs are products of gene evolution and exist in many species. Undoubtedly, their existence is reasonable because miRNAs have evolved into indispensable components of the balanced network in most creatures. MiRNAs are among the greatest discoveries in the scientific field over the past several decades. MiRNAs exhibit a simple structure and a powerful function, and their discovery has promoted the development of molecular biology and led to the discovery of many physiological and pathological mechanisms. As small and simple gene regulators, miRNA can participate not only in the regulation within the same individuals but also in cross-species signal communication, providing opportunities for microorganisms to invade or infect the host. Continuous research and knowledge focusing on miRNAs can increase our understanding of many diseases, including infectious diseases. In many cases, including COVID-19, miRNAs play important roles in the occurrence and development of disease, and the special functions of miRNA are noticed in diseases and considered targetable molecules. However, miRNA regulation extends in multiple directions within the regulatory network of organisms, thus miRNA-induced or miRNA-inhibited therapies may lead to disordered networks. Therefore, currently, considering the complexity and poor specificity of miRNA-induced regulation, especially in infectious diseases, it is difficult for miRNA-based therapeutics to be considered a safe and effective strategy for treating diseases.

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Declarations

Contributions SZ and FZ conceived of the idea; SZ developed the first draft; all authors approved the final manuscript.

Competing interests The authors declare no competing interests.

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