Journal of Inflammation Research Dovepress

Open Access Full Text Article RESPONSE TO LETTER

Interplay of TLR4 and SARS-CoV-2: Possible Involvement of microRNAs [Response to Letter]

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Dear editor

We have carefully reviewed Gambari and Finotti's letter concerning our recent review, "Interplay of Toll-like Receptor 4 (TLR4) and SARS-CoV-2: Unveiling the Complex Mechanisms of Inflammation and Severity in COVID-19 Infections". Their thoughtful comments provide a valuable perspective that deepens the scientific discourse on therapeutic strategies, particularly by exploring microRNAs (miRNAs) as regulatory agents within the TLR4/MyD88/NF-κB signaling pathway.

Their suggestion to employ specific miRNAs - such as miR-93 and miR-145-5p - as modulators of TLR4 signaling aligns closely with our goal of attenuating the heightened immune response associated with severe COVID-19 cases. As Gambari and Finotti aptly highlight, miRNAs could serve as precise regulators of TLR4-driven cytokine production, thus dampening the intensity of the inflammatory cascade that can lead to adverse clinical outcomes. Specifically, applying miRNA mimics, such as miR-93-5p, which targets pro-inflammatory pathways, offers a promising approach to modulate the TLR4/NF-κB axis, potentially reducing cytokine storm severity.

Their approach to miRNA-based therapeutics introduces a sophisticated therapeutic paradigm. This strategy, which extends beyond the direct inhibition of TLR4, may allow modulation of downstream inflammatory mediators and enable a finely tuned immune response. Such a multi-tiered strategy could address the immune dysregulation observed in severe COVID-19 cases, minimizing hyper-inflammation while preserving essential antiviral functions.

Further, Gambari and Finotti also present evidence indicating that miRNAs can inhibit NF-κB-mediated expression of key pro-inflammatory cytokines, such as IL-8. IL-8 is crucial in recruiting and activating neutrophils, which can amplify inflammation and lead to tissue damage. Elevated IL-8 levels and increased neutrophil counts correlate with severe COVID-19 and poorer clinical outcomes. Targeting this pathway with miRNAs like miR-93 and miR-145-5p may offer a precise approach to modulating inflammation by reducing excessive cytokine production, thus curbing harmful inflammation while preserving essential antiviral responses. This approach suggests that miRNA-targeted therapies could extend beyond TLR4 modulation to affect a wider range of inflammatory pathways. By acting as a secondary regulatory layer, miRNAs could help maintain immune balance, offering a multi-level intervention that enhances therapeutic outcomes. These findings underscore the potential of combining TLR4-targeted treatments with miRNA modulation to manage COVID-19's intricate inflammatory processes effectively.

Taken together, Gambari and Finotti's insights reinforce the significant potential of miRNA-based strategies to precisely regulate the complex inflammatory pathways implicated in COVID-19. Their contributions underscore a promising scientific foundation for leveraging miRNA modulation to achieve targeted immune response control, opening new avenues for robust and effective therapeutic interventions in COVID-19 and beyond.

Disclosure

The authors have no conflicts of interest regarding this communication.

Received: 30 October 2024
Accepted: 30 October 2024
Published: 7 November 2024

https://doi.org/10.2147/JIR.S503739