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

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Dear editor

We have read with great interest the review paper titled "Interplay of TLR4 and SARS-CoV-2: Unveiling the Complex Mechanisms of Inflammation and Severity in COVID-19 Infections", by Asaba et al.[1] In this very informative review, the authors highlighted how the interactions between Toll-like Receptor 4 (TLR4) and the SARS-CoV-2 Spike protein can significantly exacerbate the severity of COVID-19.[1] Accordingly, TLR4 can be considered a molecular target for the development of therapeutic protocols in the context of SARS-CoV-2 infection.

In this letter, we would like to drive attention to the fact that TLR4 gene expression can be under the control of microRNAs, a class of non-coding RNAs extremely important for post-transcriptional regulation of gene expression. For instance, Gao et al found that microRNA-93 affects the TLR4/MyD88/NF-kB signaling pathway.[2] Suppression of TLR4 by miR-145-5p was reported by Wu et al.[3] These reports are important in the context of SARS-2 infection because they suggest that treatment of target cells with ago-miRNA molecules mimicking miR-93-5p and/or miR-145-5p might inhibit TLR4 activity, thereby reducing NF-kB-mediated upregulation of several pro-inflammatory genes.

The "micro-RNA Therapeutics" approach might be considered in future experimental efforts, in order to develop novel treatment strategies that specifically interfere with TLR4 activity, affecting the interplay of TLR4 and SARS-CoV -2. In this context, we strongly agree with Asaba's conclusion that TLR4 inhibition is expected to reduce the overall COVID-19 burden, improving patient outcomes.[1]

With respect to the effects of miR-93-5p on the pro-inflammatory genes, it might directly inhibit production of pro-inflammatory proteins by directly targeting pro-inflammatory mRNAs. This was found in the case of interleukin-8 (IL-8) by Fabbri et al.[4] Accordingly, Gasparello et al demonstrated that the production of IL-8 protein is enhanced in a bronchial epithelial cell line by treatment with the SARS-CoV-2 Spike protein and that IL-8 synthesis and extracellular release can be strongly reduced using an ago-miRNA molecule mimicking miR-93-5p.[5] In addition, miR-93-5p might regulate the expression of pro-inflammatory genes by direct binding TLR4 mRNA, thereby inhibiting NF-kB activity and NF-kB regulated genes. In cells cultured in the absence of external stimulation, an inactive trimer is formed in the cytoplasm between the inhibitory protein IκB and the p50/p65 NF-κB dimer. In this condition, NF-kB is not translocated to the nucleus. By contrast, when external stimuli act on the corresponding receptors (for example, when TLR4 is activated by SARS-CoV-2 through S-protein/TLT4 interactions),[1] phosphorylation of IκB occurs, leading to dissociation of IkB from the trimer, and NF-kB activation. In these conditions, the p50/p65 NF-κB protein translocates to the nucleus and specifically interacts with NF-kB binding sites present in the promoters of NF-κB regulated genes, such as the IL-8 gene (and other genes coding pro-inflammatory proteins, including genes involved in the COVID-19 "Cytokine Storm"), thus causing transcriptional activation. Our hypothesis is that miR-93-5p indirectly inhibits the NF-κB pathway through direct inhibition of TRL4.

In conclusion, further experimental efforts are highly warranted to determine the impact of "microRNA therapeutics" on SARS-CoV-2, especially when the finding that miR-93-5p and miR-145-5p might regulate TLR4 [2,3] is considered together with the excellent review by Asaba et al.[1]

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Disclosure

The authors declare no conflicts of interest in this communication.

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