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LETTER TO THE EDITOR

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Consider TLR5 for new therapeutic development against COVID-19

Dear Editor,

The recently published paper by Bhattacharya et al[1] in this journal provides information about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine against the treatment of COVID-19 which is very timely.

As of 6 May 2020, 247 503 people died so far due to COVID-19, so an efficient treatment procedure is urgently needed. Therefore, scientists are developing new therapeutics molecules focusing on antiviral drugs and novel vaccines. The toll-like receptor 5 (TLR5) evoke innate immune responses[2] and also act as an immune sensor. The TLR signaling pathway plays a vital role in various host immune defense mechanisms. For immunotherapeutic development, this pathway modulation identified as a drug target for many antibacterial or antiviral drug development.[3] However, TLR5 is expressed in different immune cells such as dendritic cells, monocytes, and so forth. It is also expressed on the respiratory epithelium cells and pneumonocytes in humans.[4] Therefore, TLR5 can stimulate early signaling that provides protective innate immunity against respiratory infection. Respiratory infection is one of the common symptoms associated with COVID-19 and therefore, TLR5 can incite early signaling to generate protective innate immunity against respiratory infections.

Flagellin, a structural protein of bacteria helps in the process of the adhesion and invasion of pathogenic bacteria into host cells and act as a virulence factor; it is reported as a highly conserved protein.[5] Actually, TLR5 can sense, detect, and binds to natural bacterial flagellin as a ligand. Therefore, an early TLR5 activation through flagellin or similar molecule like flagelin may enhance immunogenicity for immunotherapeutic development. This process is found to be effective in several vaccine models.[6] Flagellin enhances immunogenicity against the virus as well. Even the *Salmonella* flagellins are promising candidate adjuvants for influenza virus and in an experiment using mouse model, flagellin therapy was able to decrease influenza-A virus load in the lung.[7]

Several other viral vaccines were developed targeting TLR5. Numerous examples are noted in this direction. West Nile virus vaccine was developed using TLR5.[8] Lentiviral vaccine was developed using cytomegalovirus and TLR5.[9]

The new therapeutic strategy by targeting TLR5 modulation may serve as a better choice for vaccine or adjuvant development of SARS-CoV-2. Using the bioinformatics methods, scientists have shown that an epitope-based peptide vaccine component against SARS-CoV-2 docked successfully with TLR5 strengthening the binding affinity.[1] Another study developed SARS-CoV-2 subunit recombinant vaccines using coronaviruses-S1 subunit that was TLR5 agonists.[10] These studies support our conceptualized idea that TLR5 activation can be an effective therapeutic molecule to eradicate SARS-CoV-2.

We recommend the use of active immunomodulation through TLR5 and activation of the innate immune to fight against SARS-CoV-2 as the main entry point of this virus is angiotensin-converting enzyme 2 receptor respiratory in epithelial cells. Only after entering the epithelial cells the SARS-CoV-2 start to replicate. So, the modulating the immunomodulation of TLR5 can catalyze interferon and inflammatory cytokines, which may aid in minimizing viral replication. Evidently, a subgroup of COVID-19 patients have developed cytokine storm syndrome[11] that might have developed through the initialization of the innate immune cells like neutrophils and increased expression of different cytokines like IL-6. This syndrome is essential to manage COVID-19 patients. The TLR5 immunomodulation through a vaccine or adjuvant therapy may restore damaged immune responses and help patients not to develop cytokine storm syndrome as neutrophil levels are reported to be elevated in COVID-19 patients.[12] The elevated neutrophil level is due to the neutrophil extracellular traps (NETs) and increased reactive oxygen species (ROS). Studies suggest that the deoxyribonuclease I-mediated restoration NETs and ROS along with the TLR5 modulation.[13]

New therapeutic strategy by targeting TLR5 may be the most significant way to treat COVID-19. But, the outstanding questions are: how does TLR5 act to modulate the immune system to control this virus? How the TLR5 induce SARS-CoV-2-related specific antibodies to subside the virus? The answers to these difficult queries will open a new era to understand the complexities surrounding the TLR5 and TLRs signaling systems.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

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