Does NF-κB Signaling Pathway Play a Crucial Role in Pneumonia Induced by SARS-COV-2 Virus Causing COVID-19?

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Dear Editor,

It is well documented that inflammatory cytokines are elevated in most patients with severe coronavirus disease 2019 (COVID-19). Several inflammatory cytokines are significantly elevated in patients with severe COVID-19 than in those with non-severe COVID-19 [1]. The elevated levels of various cytokines and chemokines in patients correlate with the severity of the disease and the risk of adverse outcomes, suggesting a possible role of hyperinflammatory responses in the lung disease during the course of COVID-19. A cytokine storm exacerbates damage to the lungs. An out-of-control inflammatory response may result in pulmonary tissue damage, reduced lung function, decreased lung capacity, and low oxygen saturation. Blockading the activation of cytokines or their receptors is an effective treatment for respiratory inflammation in patients with COVID-19 infection. Because of the crucial role of elevated cytokines and chemokines in lung inflammation, most clinicians have focused on glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) as the first-line known medicines for the attenuation of cytokine release or activation. There is still an ongoing discussion regarding the use of glucocorticoids and NSAIDs for COVID-19 because of their potential negative effects on the immune system that may complicate lung inflammation when accompanied by microbial contamination. However, other central signaling pathways involved in cytokine production and pro-inflammatory processes have been neglected. The nuclear factor-kappa B (NF-κB) transcription factor has emerged as the central regulator of inflammatory processes. It achieves this status through numerous, important, pro-inflammatory factors under its transcriptional control. NF-κB has been implicated as a key player in the pathogenesis of a number of inflammatory diseases, such as rheumatoid arthritis, autoimmunity, and inflammatory bowel disease. Microbial products can activate NF-κB, which results in pro-inflammatory cytokine production. Upstream NF-κB signaling pathway and pro-inflammatory mediators may play critical roles in the pathogenesis of lung injury [2, 3]. In addition, NF-κB is overexpressed in viral infections. Up-regulated NF-κB plays a crucial role in the production of pro-inflammatory cytokine storms and triggers a variety of cellular responses and functions, including dendritic cell maturation, chemotaxis, and cell phagocytosis. NF-κB signaling is also a key regulator of lipopolysaccharide-induced pulmonary inflammation [4]. There is a strong crosstalk between NF-κB and cytokine activation and production, and cytokines and pro-inflammatory mediators activate NF-κB, after which NF-κB activates the cytokine production. This cycle can enter an uncontrolled, positive feedback loop, resulting in the production of a cytokine storm. It is suggested that inhibition of NF-κB up-regulation results in the mitigation of pro-inflammatory cytokine signaling. In addition, several pre-clinical studies have demonstrated the beneficial effects of NF-κB-targeting inhibitors in the prevention and early treatment of lung injury induced by toxic agents in pre-clinical models [4-7]. We suggest that attention be paid to the development of anti-inflammatory drugs targeting NF-κB to prevent or treat pneumonia induced by SARS-CoV-2 virus causing COVID-19. Future studies may recommend the use of safe, approved, NF-κB inhibitors in patients with COVID-19 and associated acute respiratory illnesses as they are likely to have less harmful side effects compared with glucocorticoids and NSAIDs.

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