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# **How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection?**

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## **Abstract**

Statistical surveys of COVID-19 patients indicate, against all common logic, that people who smoke are less prone to the infection and/or exhibit less severe respiratory symptoms than non-smokers. This suggests that nicotine may have some preventive or modulatory effect on the inflammatory response in the lungs. Because it is known that the response to, and resolution of the SARS-CoV-2 infection depends mainly on the lung macrophages, we discuss the recent scientific findings, which may explain why and how nicotine may modulate lung macrophage response during COVID-19 infection.

**Key words:**  $\alpha 4/\alpha 7$  nicotinic ACh receptors - nAChRs, acute respiratory distress syndrome - ARDS, COVID-19, cytokines, cytokine storm, inflammation, lungs, macrophages, nicotine, SARS-CoV-2

Studies and clinical observations of COVID-19 patients indicate that the main target of SARS-CoV-2, a positive-strand RNA virus causing COVID-19, are the lungs (1). Nevertheless, the anecdotal observations, and, a relatively limited in scope, statistical surveys of COVID-19

positive patients in France and China suggest that the people who smoke are more often asymptomatic or exhibit less severe respiratory symptoms than the non-smokers who often develop an acute respiratory distress syndrome (ARDS) (2). These observations seem to contradict common sense because the impaired function of lungs (for example various degrees of emphysema) in smokers (3) should make them more, not less, vulnerable to the respiratory consequences of the virus attack. To explain these findings, we need to review the reliable, published scientific data on the mechanisms underlying respiratory response to SARS-CoV-2 infection, and possible reasons for the modulatory effects of nicotine on the COVID-19-related inflammation of the lungs.

Studies indicate that the inflammatory response and its resolution in the human lungs depend on the lung macrophages. Lungs contain two main types of macrophages: alveolar macrophages, which are situated in the proximity of the alveolar epithelium, and the interstitial macrophages (which are probably the precursors of alveolar macrophages) located in the parenchyma between the alveolar epithelium and the microvascular wall (4). In the healthy lungs, the alveolar macrophages exhibit the anti-inflammatory phenotype, downregulate the adaptive immune responses, synthesize very low levels of inflammatory cytokines and inhibit inflammation. However, during the infection with pathogenic fungi, bacteria, or viruses, the alveolar macrophages become the first-line responders of the innate immune defense system in the lungs. They switch from the anti- to the pro-inflammatory phenotype, release high levels of inflammatory cytokines, and recruit other types of inflammatory cells to the lungs (4-6). Subsequently, during the post-inflammatory and healing phases, the alveolar macrophages switch back to the anti-inflammatory phenotype that promotes repair of the damaged lungs (4-6). Studies show that the severity of symptoms and high mortality in some of the COVID-19 patients is related to the over-responsiveness of their immune system to the virus, the so-called cytokine storm (7, 9). The pathologic analyses of COVID-19/ARDS patients showed that the alveolar cavities of their lungs are packed with the massive accumulations of macrophages and a low number of B and T cells (9). It has been also shown that these macrophages express the ACE2 (angiotensin-converting enzyme-2) receptors that recognize SARS-CoV, NL63, and SARS-CoV-2 viruses (10, 11). These studies also showed that the viral spike (S) protein that binds to ACE2 receptors and facilitates entry of SARS-CoV-2 to the cells, specifically interacts with the ACE2 receptors in lung macrophages but not with the B and T cells (9). Importantly, the SARS-CoV-2 virus was found inside the alveolar macrophages, macrophages in the pulmonary lymph nodes and spleen, and in the alveolar epithelial cells (9). These findings suggest that in the

ARDS patients, the macrophages, which are directly infected by the SARS-CoV-2 virus, may drive the cytokine storm (9). It has been shown that the positive effects of various anti-inflammatory therapies used in various pathological conditions rely mainly on the inhibition of macrophage infiltration and cytokine production (8). Thus, the administration of any therapeutic that can decrease the cytokine storm should be beneficial for COVID-19/ARDS patients. Besides the ACE2 receptors, the lung macrophages also contain the  $\alpha 4/\alpha 7$  nicotinic ACh receptors (nAChRs) (12). The nicotinic acetylcholine (cholinergic) receptors are stimulated by the neurotransmitter acetylcholine and are present on the cells of the neural system, muscle, and other organs (13). Recent studies showed that in the immune system, the nicotinic ACh receptors present in the immune cells, such as macrophages, regulate the neurotransmitter-mediated signaling in the inflammatory response (12-16). Studies of Lu et al. (13) showed that the activation of ACh receptors in the macrophages inhibits the inflammasome that catalyzes pro-inflammatory cytokines and increases inflammation. Other studies showed that the stimulation of macrophage ACh receptors by acetylcholine (normally released by the efferent vagus nerves) or nicotine (in smokers and nicotine products' users) inhibits pro-inflammatory cytokines production and the inflammatory response. This novel regulatory pathway was named the cholinergic anti-inflammatory pathway (CAP; 14-16). Several studies indicated that in the CAP signaling pathway, the activation of macrophage ACh receptors prevents translocation of the NF- $\kappa$ B factor (that mediates induction of pro-inflammatory cytokines) to the nucleus, and activates tyrosine kinase JAK2/transcription factor STAT3 pathway, eventually, leading to the down-regulation of inflammatory response (14-16), and lessening or eliminating cytokine storm in lungs. This would explain why the nicotine use may lessen or eliminate ARDS in the smoking COVID-19 patients. It also opens the possibility of the use of nicotine or other activators of cholinergic receptors as the therapeutic agents to fight the COVID19 and similar infections.

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