Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to Editors

TLR4 involvement in COVID-19 predicts a seasonal risk of *Aspergillus* superinfection: A call for vigilance

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Introduction

Aspergillus superinfection often accompanies severe COVID-19, even in immunocompetent individuals [1]. An inverse relationship between the incidence of COVID-19 and seasonal pollens [2] and mold spores [3] has recently been demonstrated. The relationship appears to be due to competition between airborne bioaerosols and SARS-CoV-2 virions, for a shared receptor on pulmonary epithelial cells [3]. As the shared receptor, Toll-like receptor 4 (TLR4) has been implicated because: 1) it accounts for the inflammatory signaling characteristic of severe COVID-19 [4,5], 2) it is intimately involved in the inflammation elicited both by sharply seasonal respiratory viruses and by multiple species of fungi, 3) COVID-19 prognosis correlates with radiographic involvement of alveoli, the epithelial cells of which are rich in TLR4, 4) age-dependent hyper-responsiveness of TLR4, especially in the context of interactions with TLR5, can account for the age-dependent severity of COVID-19, and 5) fibrinogen D-dimers, composites of TLR4 ligands [6], are markedly elevated in persons with severe COVID-19. That TLR4 be involved in the processing of bioaerosols like respiratory viruses and mold spores is also expected on phylogenetic grounds: the receptor is retained by fish that breathe air, but lost by those that do not, and the eponymous Toll receptor controls the antifungal response of *Drosophila*. Engagement of TLR4 by bioaerosols is imagined to occur akin to the engagement of hook-and-loop adhesives. Instead of loops, however, spinous processes of the bioaerosols engage TLR4 'hooks,' effecting an innate immune response. If TLR4 is inundated with SARS-CoV-2 virions, the immune response against airborne spores of *Aspergillus* is abated, rendering the spores free to grow and propagate on pulmonary epithelium. Early in the spring, when the dynamic equilibrium between airborne species of virions and spores is in transition, spores will accumulate within airways, unattended by TLR4. This will be especially true in environments in which contaminated organic materials and decaying vegetation are prevalent, including farms, wood and food industries, waste handling plants and slaughterhouses. Given this new appreciation of the interplay between respiratory viruses and mold spores, it behooves those tending patients with severe COVID-19 to be especially vigilant for *Aspergillus* co-infection during the spring, when mold spore counts are on the rise.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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