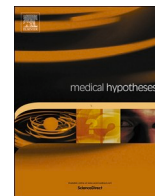




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Letter to Editors

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.

References

- [1] Garcia JS, Sprute R, Stemler J, et al. COVID-19 - Associated Pulmonary Aspergillosis, March-August 2020. Emerg Infect Dis 2021. <https://doi.org/10.3201/eid2704.204895>.
- [2] Hoogveen MJ, Van Gorp ECM, Hoogveen EK. Can Pollen Explain the Seasonality of Flu-like Illnesses in the Netherlands? Sci Total Environ 2021;755(Part 2):143182. <https://doi.org/10.1016/j.scitotenv.2020.143182>.
- [3] Shah RB, Shah RD, Retzinger DG, Retzinger AC, Retzinger DA, Retzinger GS. Confirmation of an Inverse Relationship between Bioaerosol Count and Influenza-like Illnesses, Including COVID-19. On the Contribution of Mold Spores. MedRxiv 2021. <https://doi.org/10.1101/2021.02.07.21251322>.
- [4] Sohn K.M., Lee S.G., Kim H.J., et al. COVID-19 Patients Upregulate Toll-like Receptor 4-mediated Inflammatory Signaling That Mimics Bacterial Sepsis J Korean Med Sci. 2020;35(38):e343. Published 2020 Sep 28. doi:10.3346/jkms.2020.35.e343.
- [5] Aboudounya MM, Heads RJ, Dozio E. COVID-19 and Toll-Like Receptor 4 (TLR4): SARS-CoV-2 May Bind and Activate TLR4 to Increase ACE2 Expression, Facilitating Entry and Causing Hyperinflammation. Med Inflamm 2021;2021:1–18. <https://doi.org/10.1155/2021/8874339>.
- [6] Zulliani-Alvarez L, Marzeda AM, Deligne C, Schwenzer A, McCann FE, Marsden BD, et al. Mapping Tenascin-C Interaction with Toll-like Receptor 4 Reveals a New Subset of Endogenous Inflammatory Triggers. Nature Comm 2017;8(1). <https://doi.org/10.1038/s41467-017-01718-7>.

Andrew C. Retzinger^{a,*}, Gregory S. Retzinger^b

^a Department of Emergency Medicine, West Virginia University, Camden Clark Medical Center, Parkersburg 26101, WV, United States

^b Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago 60611, IL, United States

* Corresponding author.

E-mail address: andrew.retzinger@gmail.com (A.C. Retzinger).

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