EDITORIAL
COPD

The contribution of *Aspergillus fumigatus* to COPD exacerbations: a "sensitive" topic

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Fungal sensitisation appears to play an important role in COPD disease progression https://bit.ly/30NcEcL

Cite this article as: Connell D, Shah A. The contribution of *Aspergillus fumigatus* to COPD exacerbations: a "sensitive" topic. *Eur Respir J* 2020; 56: 2002223 [https://doi.org/10.1183/13993003.02223-2020].

Aspergillus fumigatus is a ubiquitous mould that can cause a spectrum of clinical disease ranging from invasive aspergillosis to allergic sensitisation depending on the host immune response [1]. The role of fungi and, in particular, *A. fumigatus* in driving COPD progression has been debated for many years. Susceptibility to invasive aspergillosis in COPD patients has been long reported and is now established as a significant risk factor [2]. The importance of fungi in COPD pathophysiology has curiously been raised for many years in the development of equine COPD which has been shown to be related to hypersensitivity to fungi (including *A. fumigatus*) in poor quality hay and straw bedding [3].

Bafadhel *et al.* [4] showed previously that ~50% of stable COPD subjects at baseline had culturable filamentous fungi of which 75% were *A. fumigatus* and was significantly associated with increased inhaled corticosteroids. 13% of those with *A. fumigatus* positive cultures had sensitisation which was associated with worse lung function. In addition, the FUNGI-COPD study group showed a prevalence of 16.6% *A. fumigatus* during acute exacerbations of COPD, with multivariate regression analysis showing previous exacerbations in the past year and concomitant *Pseudomonas aeruginosa* as risk factors for presence of *A. fumigatus* [5]. The prevalence of *Aspergillus* sp. sensitivity in COPD has been further confirmed in studies revealing a prevalence between 8.5% and 18% [6, 7]. Sensitisation to *A. fumigatus* was associated with presence of bronchiectasis, possibly suggesting a role in COPD-related bronchiectasis. The pathogenic and clinical significance of these findings overall has been unclear, however.

More recently, significant focus has been placed on deciphering specific endotypes in COPD, with confirmation of an "eosinophilic inflammation" predominant subgroup with improved response to corticosteroids and, also, significant interest in possible application of novel biologics targeting type-2 mediated immunity [8, 9]. How this relates to fungal sensitisation is again unclear.

In this issue of the *European Respiratory Journal*, Tiew *et al.* [10] report their findings from a prospective multicentre study, systematically analysing cross-sectional fungal sensitisation in a large COPD cohort alongside non-disease controls and its association with metagenomic analysis of outdoor and indoor air

Received: 8 June 2020 | Accepted after revision: 11 June 2020

fungal sampling and patient-related outcomes. Confirming previous findings, they show that patients with COPD have a high frequency of sensitisation across a broad range of allergens, including fungi, and this is associated with an increased frequency of exacerbations independent of severity or stage of COPD. When performing unsupervised cluster analysis, an identified subgroup of fungal predominant highly sensitised COPD patients showed greater symptoms, exacerbation frequency and lower lung function.

The authors further highlight sensitisation to specific commonly encountered outdoor fungi as determined by metagenomic sequencing of air samples with subjects sensitised, again showing increased exacerbation frequency. Lastly, sequencing of indoor air sampling in a smaller cohort of subjects showed correlation between indoor air allergen abundance (of which the majority were fungal), and symptoms and worse lung function.

This study importantly confirms previous findings showing increased prevalence of fungal sensitisation in a large multicentre cohort of COPD patients compared to non-disease controls and the association of this endotype with increased severity of disease, as determined by exacerbation frequency and lung function. This paves the way for further future translational studies considering type 2-mediated immunity specific biologic therapy. Previous phase 3 studies, in particular concerning interleukin-5 targeted therapy have been inconclusive, but broadly highlight the importance of endotyping (*e.g.* eosinophilic predominant inflammation) to better identify a target population [11]. This study highlights the potential for fungal sensitisation as another endotype that is associated with increased severity of disease, with possible future therapeutic options.

Although susceptibility to *A. fumigatus* infection in COPD has been shown in animal *in vivo* and human *in vitro* studies, analysis of the association of cross-sectional fungal sensitisation to patient-related outcome in this study is limited in causal inference [12, 13]. There is increasing evidence of the importance of neutrophils and neutrophil extracellular trap (NET)-related inflammation in COPD, with increased neutrophil elastase associated with increased severity of disease [14]. Release of host double-stranded DNA (dsDNA) through NETosis has been shown to drive type-2 mediated immunopathology in mouse models, highlighting the possibility that fungal sensitisation may simply reflect a by-product of increased neutrophilic inflammation, which is driving exacerbation frequency secondary to a variety of infective stimuli [15]. Equally, this may result in a synergistic effect resulting in further neutrophilic influx, creating a circular driver of disease progression as postulated in figure 1. Inter-kingdom species interaction given the established association of *A. fumigatus* with *Pseudomonas aeruginosa* colonisation, alongside the effects of corticosteroids, which inhibit type-2 mediated immunity and neutrophilic inflammation, yet increase fungal burden and susceptibility to bacterial infection, adds to the complex pathological mechanism [5, 16, 17]. Further longitudinal studies are clearly needed to decipher the evolution of type 2 mediated

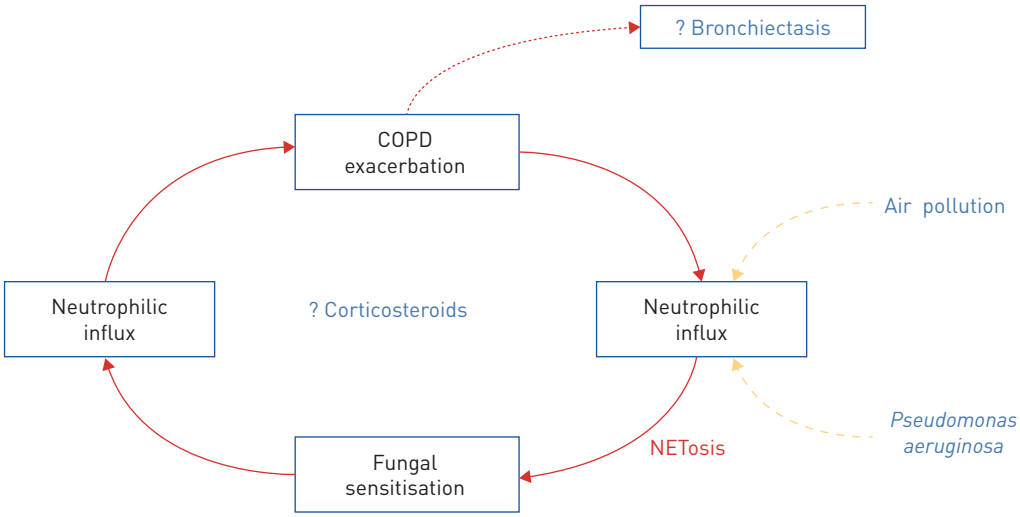

FIGURE 1 Figure showing postulated circular mechanism driving fungal sensitisation in COPD. COPD exacerbation results in neutrophilic influx and NETosis, resulting in dsDNA release and type-2 mediated fungal sensitisation in a subgroup of individuals. This then further triggers further neutrophilic influx and COPD exacerbations continuing the ongoing inflammatory cascade and COPD progression. The effects of air pollution and *Pseudomonas aeruginosa* added to neutrophilic inflammation are suggested, with the unknown complex effects of corticosteroids highlighted. Whether this ongoing inflammatory progression results in the development of bronchiectasis is again unclear and is presented as a possible outcome. NET: neutrophil extracellular trap.

immunity, fungal sensitisation, neutrophilic inflammation and effects on disease severity in COPD and development of bronchiectasis.

Tiew *et al.* [10] also correlate fungal sensitisation with presence of outdoor and indoor fungi identified through metagenomic sequencing. We are constantly exposed to a wide range of environmental (both outdoor and indoor) mould and the consequences and implications of this in the context of chronic lung disease have been unclear. In southeast Asia, use of local hand-rolled cigarettes or "bidi" has been additionally shown to increase rates of fungal sensitisation in COPD [18]. This study highlights the association of fungal sensitisation to outdoor and indoor mould and increased severity of disease. The association of indoor abundance of allergens in a smaller subject number with increased exacerbation frequency could represent a potential translational therapeutic avenue; however, the effects of outdoor mould exposure are clearly more difficult to tackle. There is additional considerable and understandable worry regarding the effects of air pollution on lung health, in particular in the southeast Asian subcontinent where this study was performed. The effects of air pollution on type-2 mediated immunity and allergy have been well reported [19]. Although Tiew *et al.* [10] do not report rates of air pollution in this study: a better understanding of the link between air pollution and fungal sensitisation potentially driving chronic lung disease severity could strengthen a one health approach to improving air quality and lung health. The current significant shifts in air pollution related to coronavirus disease 2019 may uniquely present an opportunity to understand effects of air pollution on environmental fungal exposure.

We are steadily understanding more about the diverse implications and aetiology of fungal sensitisation and infection in chronic lung disease, and this study adds another piece of evidence in the increasing call for multicentre longitudinal prospective studies that would improve our understanding of the host-pathogen relationship and, importantly, identify clear endotypes to pave the way for targeted therapeutic trials.

Conflict of interest: D. Connell has nothing to disclose. A. Shah reports grants and speaking fees from Gilead Sciences, grants from Vertex Pharmaceuticals and speaking fees from AstraZeneca.

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