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Treating fungus-induced allergic asthma: Do VDACs have the answer!

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Alternaria alternata is one of the very common and abundant fungal pathogens to which exposure leads to a severe form of fungal asthma. Life threatening allergic-asthma exacerbations occur during the fungal sporulation season. These exacerbations are caused by a breaking of the normal tolerance against the fungal allergens as a result of their sudden ubiquitous occurrence and abundance. Airway mycosis and subsequent asthma symptoms can be alleviated to some extent by anti-fungal drugs or low dose corticosteroids. Anti-fungals may reduce the fungal content but the reduction in allergic reaction requires corticosteroids to which tolerance often develops. This steroid resistant severe disease is accompanied by an increase in interleukin (IL)-33 and subsequent promotion of the T helper 2 (TH2) allergic airway response (Griesenauer & Paczesny, 2017). There is very little understanding of the mechanisms that drive *Alternaria* allergen-induced IL-33 production and asthma exacerbation.

In this issue of *The Journal of Physiology*, Srisomboon *et al.* (2020) extend their previous work and report the novel finding that allergens from *Alternaria* release IL-33 via the extracellular ATP-dependent pathway involving P2X7 receptors and increased Ca^{2+} uptake across the plasma membrane. More importantly, they demonstrate that ATP was released upon exposure to *Alternaria* allergens (AA) following activation of voltage-dependent anion channel-1 (VDAC-1), which is located in the plasma membrane of airway epithelial cells. This was demonstrated by utilizing inhibitors of VDAC-1, neutralizing antibodies against VDAC-1, and by silencing VDAC-1 expression using RNA interference. Cholesterol depletion by statins such as simvastatin also blocked AA-induced ATP release, intracellular Ca^{2+} increase and plasma membrane expression of VDAC-1. Simvastatin treatment not only prevented AA-induced IL-33 production, but also improved epithelial barrier function after AA exposure. It is proposed that simvastatin acted by reducing cholesterol, which lowered plasma membrane expression of VDAC-1 and VDAC-1/caveolin-1 co-localization.

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Competing interests
The authors have no competing interests.

Stimulus induced release of endogenous ATP into the extracellular milieu has been shown to occur in a variety of cells including airway epithelial cells (Ahmad *et al.* 2006). Extracellular ATP-induced signalling via P2 receptors, activates important cell survival pathways and can be a source of pathogenesis for several chronic lung diseases when perturbed (Ahmad *et al.* 2006). In chronic obstructive pulmonary disease patients, ATP accumulation in the airways correlates with disease severity. Extracellular ATP increases inflammation, and causes bronchoconstriction and coughing. ATP/P2X7 receptors of alveolar macrophages were proposed to participate in the pathogenesis of experimental (ovalbumin induced) asthma (Li *et al.* 2020). Extracellular ATP-induced activation of P2X receptors can act as a danger signal and recruit immune cells during acute lung injury and it has been suggested that P2X7 receptor can be targeted for treating acute respiratory distress syndrome/acute lung injury. Therefore, extracellular ATP has an increasing role in airway disease progression and pathogenesis.

Statins can act on the P2X7 receptor to modulate downstream signalling effects in epithelial cells (Mistafa *et al.* 2008). Because of their anti-inflammatory properties, statins have been investigated in clinical settings for their therapeutic potential for several chronic lung diseases including asthma, although the results are conflicting (Bhattacharjee *et al.* 2015). This could be attributed to the low bioavailability of oral drugs. Formulating statins for inhalational use is another approach that is gaining impetus. The additional cholesterol lowering property for VDAC inhibition, as shown in the study by Srisomboon *et al.* (2020), makes the case for the repurposing of statins much stronger and their use through inhalation is an option worthy of exploration. However, such use of statins may have its limitations and the benefits and risks need to be considered carefully.

Nevertheless, the studies by Srisomboon *et al.* (2020) establish VDAC-1 as a pathway involved in fungal allergen-induced ATP release and IL-33 production and suggest a therapeutic use for cholesterol lowering compounds with respect to reducing fungus-stimulated allergic inflammation. However, additional studies in animal models of allergic airway disease are needed to evaluate the therapeutic potential of these findings.

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