Epithelial immunomodulation by aerosolized Toll-like receptor agonists prevents allergic inflammation in airway mucosa in mice

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Epithelial Immunomodulation by Aerosolized Toll-like Receptor Agonists Attenuates Allergic Responsiveness in Mice

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Background
Allergic asthma is a chronic inflammatory respiratory disease associated with eosinophilic infiltration, increased mucus production, airway hyperresponsiveness (AHR), and airway remodeling. Epidemiologic data has revealed that the prevalence of allergic sensitization and associated diseases has increased in the twentieth century. This has been hypothesized to be partly due to reduced contact with microbial organisms (the hygiene hypothesis) in industrialized society. Airway epithelial cells, once considered a static physical barrier between the body and the external world, are now widely recognized as immunologically active cells that can initiate, maintain, and restrain inflammatory responses, such as those that mediate allergic disease. Airway epithelial cells can sense allergens via myriad expression of Toll-like receptors (TLRs) and other pattern-recognition receptors (PRRs).

Methods
We sought to determine whether the innate immune response stimulated by a combination of Pam2CSK4 (“Pam2”, TLR2/6 ligand) and a class C oligodeoxynucleotide ODN362 (“ODN”, TLR9 ligand) when delivered together by aerosol (“Pam2ODN”), can modulate the allergic immune response to allergens.

Results
Treatment with Pam2ODN 7 days before sensitization to House Dust Mite (HDM) extract resulted in a strong reduction in eosinophilic and lymphocytic inflammation. This Pam2ODN immunomodulatory effect was also seen using Ovalbumin (OVA) and A. oryzae (Ao) mouse models.

Conclusion
The immunomodulatory effect was observed as much as 30 days before sensitization to HDM, but ineffective just 2 days after sensitization, suggesting that Pam2ODN immunomodulation lowers the allergic responsiveness of airway epithelial cells. Furthermore, Pam2 and ODN cooperated synergistically suggesting that this treatment is superior to any single agonist in the setting of allergen immunotherapy.