Early NK cell activation as a result of MPL and QS-21 combination controls the adjuvant effect induced by the human Adjuvant System AS01


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225 Anti-IL-33 ameliorates asthma onset and progression in response to virus and allergen co-exposure

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Frequent viral lower respiratory infections (vLRI) and allergic sensitisation in early life are independent risk factors for asthma onset, yet together they significantly increase the development of persistent and/or severe asthma. To elucidate the processes that underlie this synergy, we developed an experimental model of asthma by co-exposing mice to an avian specific Pneumovirus and cockroach allergen in both early and later life. Virus/allergen co-exposure synergised in early and later life to induce the hallmark pathological features of asthma. By contrast, the omission of virus or allergen exposure in early life or later life failed to induce disease. Allergen exposure during primary vLRI increased the release of IL-33 and impaired antiviral cytokine production, leading to increased epithelial viral burden, Th2-type inflammation and airway smooth muscle growth. Moreover, this early life response predisposed towards viral challenge-induced airway remodelling in later life. Critically, antibody-mediated neutralisation of IL-33 reversed the dampened antiviral cytokine response mediated by cockroach allergen. Hence anti-IL-33 accelerated viral clearance in early life, and decreased Th2-type inflammation and airway remodelling in early and later life. In summary, we identify IL-33 as a target to attenuate the synergistic interplay between two important environmental insults in the onset and progression of asthma.

277 Pulmonary epithelial-derived TGF-β1 is critical for the inception of innate lymphoid cell mediated allergic airways disease

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Pulmonary epithelial cells play central role in the generation of asthma pathogenesis. The pleiotropic cytokine TGF-β is critical for regulation and development of a range of immune function. However, the contribution of epithelial derived TGF-β in the inception of allergic disease is unknown.

We have utilised a CCSP promoter driven Tet-on system to generate inducible bronchial epithelial cell specific knockouts of TGF-β1. Mice lacking epithelial TGF-β1 displayed no baseline immune defects but on exposure to inhaled allergen exhibited a diminished airway hyperactivity (AHR), BAL inflammation, eosinophilia and pulmonary Th2 cytokines. However, numbers of Th2 cells in the lung and BAL were unaffected. In contrast, frequencies of IL-13+ innate lymphoid cells (ILC2s) were significantly reduced. Similarly, epithelial TGF-β1−/− mice administered with rIL-33 to induce ILC2 driven lung inflammation also showed a reduced AHR, BAL cell recruitment, eosinophilia and levels of Th2 cytokines compared with control mice. ILCs in the BAL appeared to be primed to respond to TGF-β, expressing high levels of TGF-βRII compared with lung, blood and bone marrow ILCs. We have demonstrated for the first time that delivery of rIL-33 into the lung induced a rapid release of TGF-β into the BAL as early as 4 h after a single rIL-33 dose, suggesting an adjuvant function for epithelial-derived TGF-β in the recruitment of ILC2 cells to the lung.

In summary, this novel interaction between ILCs and TGF-β derived from the lung epithelium is a key pathway leading to the generation of early allergic immune responses.

366 A dominant role for the methyl-CpG-binding protein Mbd2 in controlling dendritic cell induction of type-2 inflammation

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Dendritic cells (DCs) direct CD4+ T cell differentiation into distinct T helper subsets that are vital for protection against diverse types of infection. However, the mechanisms employed by DCs to initiate type-2 responses, which are important for immunity to helminth infection as well as being a major contributor to allergic disease, remain poorly understood. We have discovered a crucial role for methyl-CpG-binding domain-2 (Mbd2), a protein that links DNA methylation to repressive chromatin structure, in regulating DC gene expression and ability to promote Th2 immunity in vitro and in vivo against either helminths or allergens. This revealed a novel epigenetic mechanism that is integral to DC promotion of CD4+ T cell responses. Several genes were dramatically dysregulated in Mbd2−/− DCs, identifying potential novel mechanisms that DCs utilise for type-2 priming. The chemokine CCL17, which has previously been associated with recruitment of T cells in type-2 inflammatory settings, was dramatically downregulated in Mbd2−/− DCs. We have found that CCL17−/− DCs display no impairment in type-2 response induction in vitro, but display severely impaired induction of helminth type-2 responses, and house dust mite allergic airway inflammation, following transfer in vivo. This demonstrates that DC secretion of CCL17 is vital for optimal priming of type 2 inflammation in vivo. Ongoing work is investigating the role of Mbd2 and its downstream gene targets in regulating DC type-2 function in fungal settings. These data identify methyl-CpG-binding proteins and the
Can Immunological Advances Enhance Vaccine Design?

Combining immunostimulants in adjuvants can improve the quality of the immune response to vaccines. The Adjuvant System AS01 contains both monophosphoryl-lipid A (MPL) and the saponin QS-21 and is used in the RTS.S malaria candidate vaccine. AS01 induces a transient activation of innate immunity, leading to increased number of activated antigen-presenting dendritic cells, but the impact of combining MPL and QS-21 on innate immune activation has not been investigated. We combined immunological and data analysis tools to identify the mechanism by which AS01 activates innate immunity, leading to improved adjuvant capability. Using a novel statistical framework for mRNA expression analysis, we unravelled the combinatorial effect of AS01 components and identified an emergent early IFNγ signature elicited by AS01. The IFNγ response was mediated by innate cells, including NK cells that secreted IFNγ in the draining lymph nodes (dLN) as early as 2 h after injection of mice with AS01. Depletion strategies showed that NK cells were essential for the development of T cell immunity. Interestingly, a similar activation was observed in the dLN of AS01-injected macaques as well as in the blood of individuals receiving AS01-adjuvanted vaccine.

Our multidisciplinary, cross-species analysis of AS01 mode of action shows that combination of immunostimulants resulted in the induction of novel pathways associated with improved vaccine response. It also highlights a key role for early NK cell activation in AS01 adjuvant effect, providing novel hypotheses on the contribution of this adjuvant in the protection conferred by the AS01-adjuvanted vaccine in humans.

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