Lung dendritic cells and IgE: the link between virus and atopy

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'...the virus-FcεRI-atopy axis certainly appears to provide much promise for understanding how and why atopic diseases develop, and more importantly, what could be done to prevent them...'

Atopic diseases, including asthma, have been increasing in the modernized world, reaching epidemic proportions [1,2]. The reasons for this increase are not known. Some have proposed that a decrease in bacterial infections associated with improved public health may be the culprit [3]. The 'hygiene hypothesis', as this theory is called, fails to take into account the fact that some pathogens, particularly viral infections, are associated with increased risks of asthma and atopic disease [3–5]. In particular, severe paramyxoviral infections have been implicated in the development of asthma. The best example of this is respiratory syncytial virus (RSV). RSV is a common pathogen that infects nearly all children by 2 years of age [6]. However, infants who require hospitalization because of a severe RSV infection have been shown to have over a 20-fold greater risk of developing asthma compared with nonhospitalized infants [7]. Furthermore, RSV, parainfluenza, influenza and rhinovirus have been shown to be major causes of asthma exacerbations [8]. In addition to the risk for asthma, many viral infections have been noted to induce production of IgE, although the reason why IgE is produced is unknown [9–16]. The amount of IgE produced has correlated with clinical parameters, including risk of subsequent wheezing in infants and otitis media with effusion in children [9–13,17]. Why a Th1-biased antiviral response would predispose to atopic disease, a Th2-biased response, is not clear, nor is it clear why a Th1 response would lead to production of IgE, the quintessential Th2-biased antibody.

Atopy & paramyxoviral infections: the model

Using a mouse model of viral-induced asthma, we recently explored a potential mechanism that may link the antiviral Th1 response to the subsequent

Th2-atopic response, specifically focusing on the role IgE may play in the development of postviral atopic disease. Because RSV does not cause productive infection in mice, we used an experimental model of asthma that utilizes Sendai virus (SeV). This virus, a natural rodent pathogen, can lead to mouse death, and in the inoculum used in the model usually produces a severe illness with 20% weight loss from which the mice recover [18–19]. SeV, like RSV, is a paramyxovirus and studies have shown similar immune responsiveness and pathology with RSV [18–22]. Mice typically clear SeV approximately days 10–12 postinoculation, but demonstrate lower airway inflammatory changes and airway hyper-reactivity, similar to human asthma, for at least 1 year after infection. Evidence also exists that SeV infection, in addition to the expected Th1 response, induces a Th2 profile as well. In fact, some lymphocytes recruited to the lungs around the time of virus clearance (days 10–12) have been shown to produce the Th2 cytokine IL-13 and express the Th2 transcription factor Gata-3 by day 21 postinoculation [19,23]. SeV infection, like most other viral infections, also leads to the production of IgE, a hallmark Th2-mediated antibody response [4].

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Given that IgE is made during the antiviral response, we undertook studies to determine what would happen during a viral infection in mice genetically deficient in the high affinity receptor for IgE, FcεRI. Somewhat surprisingly, mice deficient in FcεRI failed to develop postviral mucous cell metaplasia [4].

Our investigation identified lung dendritic cells as critical intermediates in the development of postviral atopic disease [24–25]. There are two broad types of dendritic cells: the plasmacytoid dendritic cells (pDCs) and the conventional dendritic cells (cDCs). Upon stimulation, the pDCs secrete large quantities of type I interferon (IFN;

and to a lesser extent IL-12) and are thus important in the antiviral response. cDCs, on the other hand, are the primary antigen-presenting cells as they take up antigens such as viral particles, process them into smaller peptides and present them to T cells in the draining lymph node, resulting in proliferation of virus-specific T and B lymphocytes. Those virus-specific T cells are then recruited to the lung and the formation of virus-specific antibodies from B cells represent the culmination of the antiviral response.

However, it has also been shown that presentation of antigen in the draining lymph node can only occur in the first 24–30 h of viral infection [24,26]. Beyond that window, cDCs no longer migrate back to the lymph node regardless of any stimulation and will remain in the lung for up to 5 days [26]. It does appear that these stationary cDCs are capable of antigen presentation in the periphery, as they express maturation and differentiation markers [24].

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In the setting of a severe viral infection, cDCs in the lung parenchyma (i.e., those that do not migrate to the draining lymph node) express FcεRI in addition to MHC II and co-stimulatory molecules [4]. Interestingly, expression of FcεRI on lung cDCs precedes the development of virus-specific IgE production, although its expression on lung cDCs is type I IFN receptor dependent [4]. The fact that the receptor appears before IgE production is somewhat contrary to the usual understanding that IgE levels drive FcεRI expression, at least on human basophils, mast cells and dendritic cells [27–31]. The critical importance of cDC-expressed FcεRI was demonstrated by the fact that transfer of wild-type cDCs (cells that were capable of expressing FcεRI) into FcεRI-deficient mice before viral infection restored the normal postviral mucous cell metaplasia [4].

To determine a mechanism by which FcεRI on lung cDCs could modulate mucous cell metaplasia, we explored the effect of cross-linking the high affinity receptor with antigen. The reasoning behind this experiment was that FcεRI expressing lung cDCs should have been able to bind viral-specific IgE when it was made. Because both of these events happened before

virus was normally cleared (i.e., before day 10–12), there would still be virus in the lung. Therefore, the virus-specific IgE (bound to cDC FcεRI) should have been able to bind virus, cross-linking the receptor. Interestingly, we found that cross-linking FcεRI on lung cDCs led to the production of CCL28, a β-chemokine [4]. CCL28 is a CD4⁺ and CD8⁺ T-cell chemo-attractant that is able to recruit Th2 cells in an antigen-independent fashion [32]. The importance of CCL28 has been shown in murine models of asthma where blockade of CCL28 prevented airway infiltration by eosinophils, as well as airway hyper-reactivity [33–34]. Furthermore, in humans, CCL28 has been shown to be elevated in the lungs of patients with asthma [35]. The receptors for CCL28, CCR3 and CCR10 are found on a variety of cells critical to asthma pathogenesis (including eosinophils, Th2 cells, Treg cells and natural killer T cells) [33,35–38]. Thus, it seems that CCL28 may regulate the activity of inflammatory cells that are critical to the atopic response. Indeed, in the SeV model, the development of postviral mucous cell metaplasia has been shown to be dependent on Th2 IL-13 production [19]. It seems plausible, therefore, that the lack of mucous cell metaplasia in mice deficient in FcεRI was simply due to a failure of CCL28 mediated recruitment of Th2 cells to the lung post-SeV inoculation. Indeed, supporting this idea, we found the frequency of IL-13 mRNA containing Th2 cells reduced in the lungs of FcεRI-deficient mice [4].

Therefore, we have now demonstrated a potential mechanism linking virus and atopy where severe paramyxoviral infection leads to FcεRI expression on cDCs through the type I IFN receptor. This pathway is outlined in Figure 1, where cross-linking of cDC-expressed FcεRI results in CCL28 secretion, leading to recruitment of CD4⁺ Th2 cells, and ultimately IgE production and IL-13-dependent mucous cell metaplasia – two critical components of the atopic response.

Therapeutic implications

This novel pathway not only increases our understanding of atopic disease, but also creates opportunities for therapeutic intervention. One promising target could be blocking FcεRI expression on cDCs in the lung during a viral response, as this might prevent CCL28 production, recruitment of Th2 cells to the lung and, finally, postviral atopic disease. These cDCs are particularly appealing in that FcεRI is only

Figure 1. Novel paradigm for induction of postviral atopic disease.

(A) Inhalation of a paramyxovirus leads to productive infection of the airway epithelium. Immature DCs in the airway take up viral particles. **(B)** These DCs process the particles and migrate back to the draining lymph nodes, leading to expansion of viral-specific T cells. These T cells may instruct B cells with antibody specificity for viral particles to make antibodies against the virus. Some of these B cells will become plasma cells and make IgE against the virus. **(C)** Those DCs that remained in the lung and did not migrate to the lymph node become mature and express the high affinity receptor for IgE (FcεRI). **(D)** Antiviral IgE will bind DC-expressed FcεRI followed by viral particles binding this IgE. **(E)** The effect of this cross-linking of FcεRI on DCs is the production of CCL28, a chemoattractant that will bring Th2 cells into the lung in an antigen nonspecific fashion. **(F)** These Th2 cells are capable of producing IL-13, which leads to transdifferentiation of airway epithelial cells into mucous-producing cells, thus fully translating the viral infection into a Th2-mediated atopic disease.

DC: Dendritic cell.

expressed after the onset of viral symptoms and therefore the therapeutic intervention could be limited to the small population of cells in the lung, leaving those cDCs migrating back to the draining lymph node unaffected. Of course, we still do not fully understand the mechanisms behind cDC FcεRI expression in the mouse, let alone the human, so this intervention must await greater study.

Currently, a monoclonal antibody against IgE has become available and is now used as a treatment for atopic disease [39–41]. Anti-IgE functions to bind and remove IgE from circulation, preventing the IgE from binding FcεRI on mast cells, basophils and cDCs, preventing the usual clinical effects of allergy. In our novel pathway, anti-IgE could have a potential role as well. Since IgE is produced as the severe viral infection reaches its peak, just prior to improvement in symptoms (based on the mouse model), administration of anti-IgE at (or just before) this time

should block the antiviral IgE from ever binding to cDC FcεRI. This would prevent CCL28 production and the downstream events. However, before this therapy can be recommended, a better understanding of the natural role of IgE in severe viral infections needs to be elucidated. IgE may be important in the downregulation of the antiviral response and blockade of IgE may worsen inflammation or result in persistent infection. Our studies in FcεRI- and IgE-deficient mice have not supported these possibilities, as the mice did not appear to have increased disease (data not shown). Nevertheless, much more research must be undertaken before anti-IgE can be recommended as a therapy to prevent virus-induced atopic disease.

A final target for blockade identified from these studies is CCL28. Again, we do not know the functional significance of CCL28 in an ongoing antiviral response; although our experience with the rodent model does not suggest that

it is necessary for survival from the viral insult. Future studies will help shed light on the normal role of this chemokine in lung physiology.

Conclusion

An explanation for the increasing prevalence of atopic diseases remains elusive. Several different factors have been implicated, including viral infections. While this association between virus and atopy has been established, no mechanistic link had been identified until recently. Our recent data has uncovered a novel pathway linking severe paramyxoviral infection and the development of atopy through FcεRI, cDC and CCL28. The functional consequences of this pathway remain unknown and the pathway has yet to be demonstrated in humans. Nevertheless,

the virus–FcεRI–atopy axis certainly appears to provide much promise for understanding how and why atopic diseases develop, and more importantly, what could be done to prevent them.

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