

Evidence mounts that viruses drive atopic development

Jerome A. Sigua, MD,^a and Mitchell H. Grayson, MD^{a,b} Milwaukee, Wis

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Viral respiratory tract infections, especially early in life, have been associated with a markedly increased risk of both allergic disease and asthma.¹ Although much effort has been focused on understanding this risk, the mechanisms linking a viral respiratory tract infection with atopic development still have not been fully elucidated. Hypothesizing that defects in the antiviral immune response might underlie the development of postviral atopic disease, Kaiko et al² explored the effect of Toll-like receptor (TLR) 7 deficiency on disease development.

In the human subject much of the viral risk of atopic disease has been associated with early-life severe respiratory syncytial virus (RSV) infection. RSV is a single-stranded RNA paramyxovirus that is a human, but not rodent, pathogen. The fact that RSV is not a natural rodent pathogen raises concerns over its use in some models, primarily because RSV infection in mice does not lead to clinically severe disease. Two other single-stranded RNA paramyxoviruses that are natural rodent pathogens and do induce severe clinical disease are Sendai virus (SeV) and pneumonia virus of mice (PVM). Genetically, PVM is more closely related to RSV than SeV, and it is this virus model that Kaiko et al² studied in neonatal (1-week-old) mice.

Although others have documented translation of viral infection into atopic disease with the PVM model, the current study specifically examined how a genetic loss of TLR7 affected disease development.³ TLR7 recognizes single-stranded RNA, and therefore mice deficient in TLR7 would be predicted to have a defect in single-stranded RNA viral clearance.

Indeed, in this report the authors found that loss of TLR7 was associated with an increased viral load that translated into a more pronounced asthma-like response, as characterized by a T_H2 cytokine milieu, airway hyperreactivity, and tissue eosinophilia. Whether this increase in atopic disease was a direct effect of the increased viral load/infection severity was not tested. With SeV, a direct correlation was seen between severity of the illness and the development of an asthma/atopic response, and therefore it is quite likely that a similar effect occurs with PVM.⁴

SeV was also shown to drive the development of atopic disease through production of antiviral IgE (ie, IgE directed against

SeV).⁴ It is intriguing to consider that a similar event might be occurring in the PVM model. The authors did measure total IgE levels, and these were found to increase with repeated infections (and was further enhanced in the TLR7-deficient mice); however, unlike the SeV model, a single viral inoculation did not appear to induce much of an increase. This might represent a difference in the antiviral immune responses between neonatal and young adult mice (because the subsequent inoculations were in older mice and the SeV data were from young adult mice) or might simply reflect a kinetic difference between SeV and PVM.

Using SeV, we have demonstrated that exposure to an innocuous antigen during the peak of the antiviral immune response was sufficient to drive IgE production against the antigen along with symptomatic allergic disease.⁵ Other groups using RSV and influenza (an orthomyxovirus) have subsequently documented this same mechanism in the development of allergic disease.^{6,7} The authors of the current article examined the effect of cockroach allergen exposure during viral respiratory tract infection to determine whether PVM infection could also drive allergic disease against a nonviral antigen. Although exposure to a protein antigen during infection with SeV, influenza, or RSV all drove allergic sensitization in wild-type mice, PVM was only able to drive IgE production against a nonviral antigen in the setting of TLR7 deficiency. Again, it is unclear whether this was simply related to the viral load and severity of infection or whether it really was a TLR7-dependent process.

One interesting component of the current study is that the authors have claimed that the development of postviral atopic disease is strain independent with PVM. This is in contrast to SeV (C57BL/6 mice) or RSV (BALB/c mice), in which there are strong strain dependences. Unfortunately, the data presented in the current report do not allow a direct comparison between the C57BL/6 and BALB/c models but does raise a question about the similarity of the responses. Perhaps this will be more adequately addressed in a subsequent study.

Another area that could have been explored more in the current report was examination of the cellular mechanisms in play. Although an increase in IL-13-producing innate lymphoid cell numbers with PVM infection was shown, it is not clear that they were responsible for the majority of IL-13 production. Although, the IL-13-producing innate lymphoid cell numbers were further augmented in the TLR7-deficient animals, it is unclear whether this was also a result of increased viral replication and disease severity. The authors do show that depletion of CD4-expressing cells decreases after viral atopic disease, but whether this occurs through memory cell depletion, as claimed, is not well defined. In fact, in the SeV model there is a clear requirement for CD4 T cells in the development of the early phase of atopic disease, and therefore a similar issue could occur with PVM. In the SeV model a well-documented cellular mechanism was shown to link the initial viral infection to subsequent acute and chronic atopic disease.^{4,8-11} It would be interesting to determine whether similar mechanistic pathways also were operative in PVM infection. Unfortunately, these pathways were not examined in the current report, but

From ^athe Section of Allergy and Immunology, Department of Pediatrics, and ^bthe Department of Microbiology and Molecular Genetics, Medical College of Wisconsin. Disclosure of potential conflict of interest: M. H. Grayson has received grants from the National Institutes of Health/National Heart, Lung, and Blood Institute and Merck and is the Deputy Editor of the *Annals of Allergy, Asthma, and Immunology*. J. Sigua declares that he has no relevant conflicts of interest.

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Corresponding author: Mitchell H. Grayson, MD, Medical College of Wisconsin, MACC Fund Research Center, Rm 5064, 8701 Watertown Plank Rd, Milwaukee, WI 53226. E-mail: wheeze@allergist.com.

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hopefully, they will be explored in future studies so that the broad applicability of these mechanistic pathways can be illuminated.

In summary, this is an interesting study that adds to our understanding of the potential mechanistic roles played by antiviral immune responses against single-stranded RNA viruses in the development of allergic disease and asthma. It is intriguing to think that TLR7 is an important risk factor for translating a viral infection into atopic disease and that genetic defects in TLR7 could predispose to atopy. However, it is more likely that TLR7 defects are associated with an impaired antiviral immune response, leading to increased viral load and more severe infection. It is this increased severity (not the TLR7 defect) that subsequently drives the heightened risk of postviral atopic disease, likely through pathways similar to those outlined in other models of virus-induced atopy. In this vein the exploration of these pathways in the PVM model (with or without TLR7 deficiency) would be a welcome addition to our knowledge base because this would allow a more direct comparison between the different viral insults. All in all, this report significantly adds to the mounting evidence for a mechanistic pathway (or pathways) linking severe viral respiratory tract infection with the development of both asthma and allergic diseases.

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