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RESEARCH LETTER

Detrimental impact of allergic airway disease on live attenuated influenza vaccine

Sreeja Roy | Clare M. Williams | Yoichi Furuya

Department of Immunology and Microbial Disease, Albany Medical College, Albany, New York

Correspondence
Yoichi Furuya, Department of Immunology and Microbial Disease, Albany Medical College, 7 Albany, NY, USA.
Email: furuyay@amc.edu

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To the editor,

Historically, live attenuated, as opposed to inactivated, vaccines have been highly successful against many infectious diseases (see Ref. 1). However, curiously, seasonal live attenuated influenza vaccines (LAIV) or "Flumist" have not demonstrated superior efficacy when compared to inactivated influenza vaccines (IIV), especially in the past several influenza seasons.[2,3] This is in striking contrast to animal models in which Flumist consistently exhibits a clear advantage over IIV in inducing not only robust humoral immunity but also cytotoxic T cell immunity,[4-7] which is believed to be important in cross-protection against mismatched influenza viruses.[8-11] The reason for this discrepancy between human and animal data is not fully understood, but host factors have been suggested to contribute to highly variable LAIV efficacy.[12] Given that chronic conditions, such as asthma, are highly prevalent among adults, that is, 1 in 13 (7.7%) adults in the United States according to centers for disease control and prevention (CDC),[13] we propose that they can negatively impact vaccine efficacy.

To test our hypothesis, we utilized mouse models of allergic airway disease (AAD) to assess LAIV efficacy in asthmatic mice (Figure 1A). LAIV-elicited systemic IgG responses were significantly diminished in AAD mice (Figure 1B,C). Antibody class switching is a complex process that involves a number of different stimuli.[14] In particular, cytokines are known stimuli that direct antibody isotype switching. For example, the type 1 cytokine IFN-γ drives class switching to IgG2a and the type 2 cytokine IL-4 promotes switching to IgG1.[15] Since mouse models of asthma are known to trigger type 2-biased immune responses,[16,17] it is plausible that the type 2 cytokine environment in AAD mice is suppressing type 1 immunity-based LAIV. Indeed, analysis of IgG subclasses shows that type 1 immunity-associated IgG2a was downregulated in AAD mice following intranasal (i.n.) LAIV vaccination (Figure 1B,C). Consistent with the systemic antibody profile, mucosal IgG and IgG2a antibodies were also suppressed in AAD mice (Figure 1D). In addition, mucosal IgA titer was reduced in mice with AAD (Figure 1D). We next investigated the protective efficacy of LAIV in AAD vs non-AAD mice. While LAIV-immunized AAD mice were protected against homologous challenge (data not shown), the cross-protective efficacy against heterologous infection was severely compromised (Figure 1E). This observation is consistent with our previous report that live influenza virus infection establishes inferior mucosal antibody immunity in AAD mice.[18] Taken together, our results show that AAD is a host-associated factor that can negatively impact LAIV efficacy. Our finding may help explain why LAIV efficacy is highly variable in humans. The implication of our finding is that vaccine research should consider the impact of host factors such as chronic diseases for evaluation of experimental vaccines because the magnitude of interference may differ depending on the vaccine type.

It is important to note that LAIV is not recommended for individuals with asthma due to increased incidence of wheezing post LAIV administration.[19,20] Further, people with severe asthma are often excluded from clinical trials that evaluate LAIV efficacy. Therefore, the use of LAIV among asthmatics has been relatively limited and whether asthma exacerbation has a negative effect on the efficacy of LAIV in humans remains unknown. In addition to asthma, other conditions that induce lung inflammation may also impact the

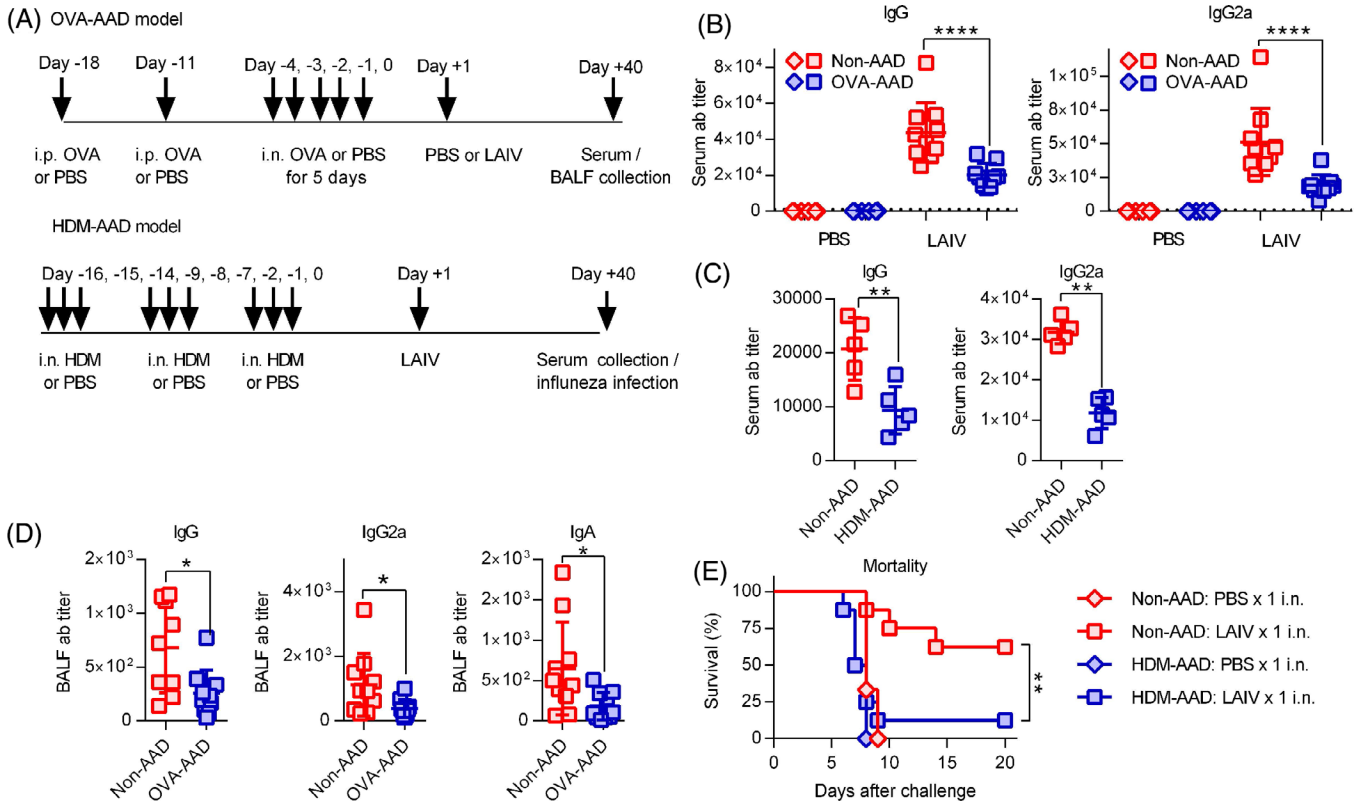

FIGURE 1 Allergic airway disease negatively impacts LAIV. A, A schematic diagram of the ovalbumin (OVA)- and house dust mite (HDM)-induced AAD and LAIV vaccination protocol. For OVA-induced AAD, BALB/c mice were i.p. immunized twice with 10 μg of OVA in 4 mg of alum. The sensitized mice were challenged i.n. with 100 μg of OVA in PBS once daily for 5 days. For HDM-induced AAD, BALB/c mice were treated i.n. with 50 μg of HDM in PBS three times per week for 3 weeks. At day 1 post allergic challenge, mice were vaccinated i.n. with 4×10^6 FFU of FluMist Quadrivalent 2015-2016 formulation (MedImmune). B-D, Serum and BALF samples collected 40 days after vaccination were tested for anti-influenza antibody levels by ELISA (6-10 mice per group). The results shown are representative of two similar experiments. $^*P < .05$; $^{**}P < .01$; $^{****}P < .0001$ as assessed by student's *t*-test or ANOVA. E, Forty days after vaccination, the AAD mice or non-AAD mice were infected i.n. with a lethal dose (2×10^4 PFU) of H1N1 PR8 strain. Survival was monitored for 20 days (3-8 mice/group). The data shown is representative of two independent experiments. Survival was analyzed using the Kaplan-Meier log-rank test. $^{**}P < .01$

efficacy of LAIV, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[21,22] SARS-CoV-2 is particularly concerning given the high prevalence of asymptomatic infections, and therefore vaccine recipients may unknowingly receive LAIV vaccination while infected with SARS-CoV-2.

Further research efforts are clearly warranted to elucidate the precise mechanism by which allergic lung inflammation interferes with the B cell immunogenicity of LAIV. Knowing the detrimental immune pathway that exists in AAD mice may help design a better vaccination approach to circumvent the negative interference imposed by host factors.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Yoichi Furuya, Sreeja Roy
Data Curation: Yoichi Furuya, Clare M. Williams
Formal Analysis: Yoichi Furuya
Funding Acquisition: Yoichi Furuya
Writing—Original Draft Preparation: Yoichi Furuya, Sreeja Roy, Clare M. Williams
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Yoichi Furuya had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The data that support the findings of the study are available from the corresponding author upon request.

ORCID

Yoichi Furuya https://orcid.org/0000-0001-6856-2737

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