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COVID-19 mRNA vaccine responses in patients with primary B-cell deficiencies

Vaccination for SARS-CoV-2 remains an important tool for protecting high-risk individuals from infection and disease. However, the safety and immunogenicity of the 2 COVID-19 mRNA vaccines in patients with primary immunodeficiencies (PID) remain unclear.

The study by Pham et al (p 907) evaluated the safety and immunogenicity of 2 doses of the BNT162b2 (Pfizer-BioNTech) and mRNA1273 (Moderna) vaccines in 33 PID patients with B-cell defects. The T-cell response to SARS-CoV-2 spike protein was evaluated by an interferon-gamma release assay (IGRA). IgG responses to the spike protein were assessed by an ELISA and, if positive, by measuring the levels of antibody blocking spike protein receptor binding domain (RBD) binding to ACE2, a surrogate test for viral neutralization.

Key findings included the following:

- Most patients (77.4%) mounted a SARS-CoV-2-specific T-cell response, including 80.0% and 66.7% of patients, respectively, with common variable immunodeficiency or other antibody deficiencies (see Figure).

- Though SARS-CoV-2 spike protein RBD IgG antibodies were produced in half of the patients with B-cell defects, only 2 of the 16 subjects with positive spike protein IgG (6.1% of the overall study group) had neutralizing activity ≥50%.

- SARS-CoV-2 mRNA vaccinations were well tolerated. Thus, 2 doses of either of the SARS-CoV-2 mRNA vaccines robustly stimulated T-cell immunity in most PID patients whereas, in those with B-cell defects, spike protein-specific IgG was not reliably induced and, when present, conferred minimal neutralizing activity. These findings predict that a 2-dose mRNA vaccine regimen will likely provide minimal protection from SARS-CoV-2 infection for most PID patients with B-cell defects, with such protection even more limited in cases of infection with variants, such as delta or omicron. Additional doses of mRNA vaccines and primary prophylaxis with appropriate mAb therapy should be considered to prevent COVID-19 infection in this high-risk population. [https://doi.org/10.1016/j.jaci.2021.11.022]
New biology underlying atopic dermatitis risk

Genetic factors modulate the risk of atopic dermatitis, a common chronic inflammatory skin disease. In their study, Sliz et al (p 1105) completed a genome-wide meta-analysis of atopic dermatitis using biobank resources from FinnGen, Estonian Biobank, and UK Biobank. The study included data from up to 796,661 participants, of whom 22,474 were suffering from atopic dermatitis. The authors identified 30 genetic loci, 5 of which were not associated with atopic dermatitis in prior genome-wide studies (see Figure). The key findings included the following:

- The loci harboring missense variants in desmocollin 1 (DSC1) and serpin family B member 7 (SERPINB7): the substitutions p.Pro575Arg in DSC1 and p.Cys379Tyr in SERPINB7, were predicted to be deleterious or disease-causing according to various in silico estimates.

- Conditional analyses on atopic dermatitis associations for these missense variants abolished the significant associations, further supporting the perception that they may drive the atopic dermatitis risk associations in the 2 loci.

- One of the novel loci was near IL22 and IFNG encoding genes. In this locus, computational evidence suggested a possible regulatory mechanism for the detected association, involving altered binding of a transcription factor EGR2 (early growth response 2) that has been previously implicated in atopic dermatitis susceptibility in the Chinese Han population.

- A suggestive association ($P = 2.77 \times 10^{-7}$) near genes IL-22 receptor subunit alpha-2 (IL22RA2) and IFN-γ receptor 1 (IFNGR1) was identified, providing additional evidence that IL-22 and/or IFN-γ may play a role in modulating the risk of atopic dermatitis.

The study provided new information on the genetic pathways underlying atopic dermatitis, which may help in developing future treatment strategies. https://doi.org/10.1016/j.jaci.2021.07.043
Multisystem inflammatory syndrome in children (MIS-C) is a postinfectious syndrome seen 4-6 weeks after COVID-19 exposure or infection in children, with some reports in younger adults described. It is a clinically very impressive presentation, often associated with shock and cardiac mechanical dysfunction, as well as a massive inflammatory response. Autopsy findings of the myocardium show T cell and scattered macrophage infiltrate. MIS-C incidence is approximately equivalent to Kawasaki disease—uncommon but not extremely rare. Diagnosis can be difficult. Underlying mechanisms, especially in terms of how the infectious event may lead to the final immune-mediated assault on the patient, remain elusive. Using spectral flow cytometry that allows for very large flow cytometry panels (in excess of 40 markers), Huang et al (p 912) immunophenotyped antigen presenting cells, T lymphocytes, and NK cells in MIS-C patients, and evaluated cytokine expression. These patients were all treatment naive, which is a rarity in a study of patients with MIS-C due to their precipitous clinical course. Comparisons were made to other febrile control patients. The authors made several key findings:

- Conventional type 1 dendritic cells (cDC1s) were activated, with upregulation of CD86 and CD275, as well as upregulation of unique markers, including CX3CR1, a receptor for fractalkine. cDC1s participate in antigen cross presentation as one of their major functions. Macrophage CD169 also was highly upregulated. Other antigen presenting cell subtypes were downregulated.
- NK cells demonstrated an activated but exhausted phenotype. CD38 on specific sub-populations of NK cells was downregulated frequently. These NK cell findings may be less specific for MIS-C, but are perhaps sensitive discriminators of disease.
- Several cytokines were upregulated. Most notably and most novel: IL-27 was markedly upregulated in MIS-C patients at their first presentation in the emergency room.

Taken together, these findings in tandem with other reported findings suggest that vascular endothelial injury, which is widely accepted as being a key feature of MIS-C, may induce cDC1s to interact with T cells (shown in previous studies to also express CX3CR1 in MIS-C) at the endothelial interface or in lymph nodes. Antigen cross presentation may be a factor in the development of subsequent autoimmunity. NK cell findings imply a dysregulated hyperinflammatory state similar but not identical to that seen in macrophage activation syndrome. Upregulated IL-27, if validated prospectively, could be a robust marker of identifying patients with MIS-C in the emergency department from other febrile patients, and potentially could also be a target for therapy. https://doi.org/10.1016/j.jaci.2021.10.015
IFN-β may be an ultimate ILC2 killer

The chronic inflammation of airways observed in allergic asthma is characterized by increased expression of type 2 cytokines, such as IL-5 and IL-13. Group 2 innate lymphoid cells (ILC2s), which reside in mucosal organs, produce large quantities of type 2 cytokines, and promote the development of Th2-type CD4+ T cells. Increased numbers of activated ILC2s are associated with allergic airway diseases, and the polymorphisms of ILC2-related genes are identified in genome-wide association studies, suggesting that ILC2s can be a potential therapeutic target for these diseases. However, our knowledge has been limited regarding the molecular mechanisms that regulate ILC2s and effective strategies to suppress them.

In this issue, using mouse models of ILC2-mediated acute airway inflammation, Tei et al (p 1044) investigated various Toll-like receptor (TLR) agonists, and reported the following key observations (see Figure):

- Among the TLR agonists, polyinosinic-polycytidylic acid [poly (I:C)] most effectively inhibited ILC2-mediated inflammation. Poly (I:C) provoked strong interferon responses in the lungs, especially for IFN-β, which suppressed type 2 cytokine production by ILC2s. IFN-β was $100 \times$ more potent than a sister cytokine IFN-α.
- IFN-β effectively inhibited the actions of cytokines that activate signal transducer and activator of transcription 5 (STAT5), such as IL-2, IL-7, and TSLP, and promote the expression of a transcription factor GATA binding protein 3 (GATA3) (which is indispensable for differentiation and survival of ILC2s), causing them to die by apoptosis.

Thus, the authors identified that IFN-β inhibits survival and effector functions of ILC2s by disrupting the protective actions of STAT5-activating cytokines. Administration of IFN-β may provide a new strategy to treat diseases involving ILC2s, such as allergic asthma.

https://doi.org/10.1016/j.jaci.2021.07.041
Sensitization to Der p 37 is associated with asthma

More than 100 million patients suffer from allergic symptoms such as rhinitis, asthma, and atopic dermatitis due to house dust mite allergy. Molecular diagnosis with recombinant allergens allows determining the patient’s IgE sensitization profile and the association between molecular IgE sensitizations and allergic symptoms. In this issue, Huang et al (p 1031) identified a new *Dermatophagoides pteronyssinus* allergen, designated Der p 37, which was expressed in *Escherichia coli* as recombinant allergen. Key findings were:

- **Der p 37** was a new *Dermatophagoides pteronyssinus* allergen with homology to chitin binding proteins, that is located in the peritrophic membrane of fecal pellets.
- Der p 37 showed IgE reactivity with approximately 25% of house dust mite-allergic patients.
- IgE reactivity to Der p 37 was associated with an increased risk of house dust mite-associated asthma.

These findings show that Der p 37 might be of great importance because it may serve as a marker for strong house dust mite sensitization and asthma.

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