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Differences between Children and Adults with COVID-19: It's Right under Our Nose

One of the most interesting and poorly understood aspects of coronavirus disease (COVID-19) is why children have significantly milder disease than adults. This is in contrast to other respiratory viruses such as respiratory syncytial virus (RSV) and influenza, in which children often exhibit much more severe disease than do adults (1). One initial hypothesis was that children have less expression of ACE2 (angiotensin-converting enzyme 2; receptor required for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] viral entry) and TMPRSS2 (transmembrane protease serine 2) (host protease that cleaves spike protein facilitating viral entry) on nasal epithelial cells, limiting tissue infection. However, multiple molecular studies have demonstrated that children and adults have similar epithelial cell expression of *ACE2* and *TMPRSS2* (2, 3), and epidemiologic studies have shown that children harbor live, replicating viruses at similar rates as adults (4–7). Another early hypothesis proposed that children might have a more robust early antibody response to SARS-CoV-2 compared with adults, potentially due to higher exposure to other human coronaviruses (i.e., "cross-reactive" antibodies) (1). This in turn would lead to earlier and more efficient clearance of the virus in children versus adults. Yet serum-neutralizing antibody titers to SARS-CoV-2 and measures of anti–spike protein antibody titers to other human coronaviruses do not appear to be different in children compared with adults (8). One of the current proposed models of how children and adults respond to SARS-CoV-2 infection differently is that children have a more aggressive early innate immune response contributing to viral control, which may ultimately lessen the subsequent adaptive systemic immune response (2, 3, 8).

In this issue of the *Journal*, Koch and colleagues (pp. 206–222) present findings that suggest the type I and II IFN response in the nasal mucosa of children and adults infected with SARS-CoV-2 are similar but that TCR signaling, T-cell activation, and neutrophil chemotaxis may be exaggerated in infected adults versus children (9). The authors performed a cross-sectional analysis of bulk–RNA-sequencing (RNA-seq) signatures from nasal mucosal curettage from children ($n = 36$) and adults ($n = 16$) infected with SARS-CoV-2. The median age of children sampled was 1.9 years, and samples were all collected after hospital admission (most within 5 days of admission). Only two of the adults (median age of 32 yr) required hospital admission. Both groups had a low proportion of subjects supported on supplemental oxygen. For comparison, the authors also analyzed bulk–RNA-seq signatures from children with RSV ($n = 24$) and influenza ($n = 9$). The clinical characteristics of these children were dramatically different from the SARS-CoV-2 cohort (all patients with RSV and influenza were admitted to the ICU and supported on at least high-flow nasal cannula) and were thus used primarily as a positive control for immune-mediated viral responses.

Importantly, the authors first validated prior findings (2, 3) that children and adults do not have differential expression of *ACE2* or *TMPRSS2* in a mixed population of nasal mucosa epithelial and immune cells, irrespective of infection. They next focused on type I and II IFN gene set signatures given the key role IFN signaling plays in the human response to viral infections. They did not observe any differences in type I or II IFN expression signatures between children and adults infected with SARS-CoV-2 (or with clinical outcomes), although IFN signatures were highly correlated with SARS-CoV-2 viral reads in both children and adults. Finally, they applied gene ontology and gene set enrichment analysis to 737 differentially expressed genes between children and adults infected with SARS-CoV-2. A novel aspect of the study involved direct comparisons between adults and children with asymptomatic or mild disease with similarly detectable viral loads. Genes involved in TCR signaling and T-cell activation were enriched in adults compared with children. Similarly, genes involved in neutrophil migration such as *IL-8* were enriched in adults whereas other immune mediators, like IL-18, were enriched in children. This is in contrast to other studies suggesting brisk early innate immune responses in children compared with adults (2, 8) and may partially be explained by a focus in this study on patients with more mild disease.

One of the main strengths of this study is the extensive clinical phenotyping of the enrolled subjects. A major limitation of translational SARS-CoV-2 studies is a lack of clarity on when patients are sampled during their course of illness and a lack of reporting on key clinical factors that likely confound associations between molecular/cellular measurements and outcomes. Most of the children in this study were sampled around 10 days after symptom onset and had low severity of illness. The main limitation of this study is that it is difficult to draw conclusions on the basis of null findings (no differences in *ACE2*, *TMPRSS2*, and IFN response between children and adults). However, other studies analyzing cohorts of similar size have also found no differences in *ACE2* and *TMPRSS2* expression between children and adults, supporting the validity of this finding.

What are the broader implications of the findings reported by Koch and colleagues to COVID-19? First, upper airway expression of the viral entry factors *ACE2* and *TMPRSS2* are likely not different between children and adults, irrespective of infection. Second, the finding that a broad T-cell activation gene set is upregulated in adults compared with children provides an important complement to the recent flow cytometry findings of Pierce and colleagues (8) showing adults have higher CD4 intracellular staining for IFN-γ and other activation markers after stimulation with SARS-CoV-2 spike protein. Finally, more work needs to be done to reconcile our understanding of whether age plays a key role in IFN pathway activation in COVID-19.

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The findings by Koch and colleagues that there were no differences in combined type I and II IFN response genes between children and adults somewhat conflict with prior bulk–RNA-seq findings (2) and single-cell RNA-seq data showing upregulation of IFN-stimulated genes in children compared with adults infected with SARS-CoV-2 (3). It is likely that clinical factors such as differences in the timing of when patients were sampled in their disease course and severity of illness are playing an important role in these conflicting findings.

In summary, the paper by Koch and colleagues confirms the adage from pediatric medical school rotations that "children are not just small adults." There are key distinctions in the immune responses to SARS-CoV-2 between children and adults, and our field should leverage the findings from studies like this to help identify novel therapeutic targets because these distinctions are likely making a big difference to subsequent clinical outcomes. ■

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