Received: 11 April 2020 | Accepted: 13 April 2020
DOI: 10.1002/ppul.24786

COMMENTARY

PEDIATRIC PULMONOLOGY WILEY

Why is Coronavirus Disease 2019 not as severe in children?—A look at type 2 alveolar cells

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Pediatric cases of coronavirus disease 2019 (COVID-19) infection tend to be uncommon based on current available data. In the reported COVID-19 positive cases, symptoms tend to be mild and the overall prognosis good. Almost all reported cases have made a full recovery and there are no reported deaths in children younger than 10 years of age. Interestingly, chest computed tomography findings in children were similar to those in adults with unilateral or bilateral subpleural ground-glass opacities and consolidations with surrounding halo signs.[1] The mild presentation and overall good prognosis of pediatric cases of COVID-19 represent a conundrum without any clear explanation at this time. Theories include children having more active innate immune responses, healthier respiratory tracts, and fewer underlying disorders. There may also be a difference in the distribution, maturation, and functioning of viral receptors that could explain the age-related differences.[2] Children are frequently infected with the slew of viruses responsible for the "common cold" as well as the flu, and they can become severely ill just like adults. Why the difference with COVID-19?

The novel infectious disease that causes COVID-19, severe acute respiratory syndrome coronavirus 2, binds to the angiotensin-converting enzyme 2 (ACE2) receptor facilitating virus entry and replication.[2] Zhao et al[3] demonstrated that 83% of ACE2-expressing cells were alveolar epithelial type II cells (AECII), suggesting that these cells serve as a reservoir for viral invasion. Early pulmonary pathological reports of COVID-19 cases reveal diffuse thickening of alveolar walls consisting of proliferating interstitial fibroblasts and AECII hyperplasia. There is evidence of fibroblast plugs, multinucleated giant cells in the air spaces, indicating varying degrees of proliferative phase of diffuse alveolar damage.[4,5]

AECII cells are regarded as the progenitor population of the alveolus and are responsible for injury repair, regeneration, and homeostatic maintenance. Several years ago Garcia et al showed, in a transgenic mouse model, that increasing levels of targeted AECII depletion correlated with characteristic injury repair outcomes, with histological findings of interstitial hypercellularity, thickened alveolar septae, and fibrotic foci. Depleting AECII by approximately 80% led to a 100% mortality rate, which is essentially what people are seeing with COVID-19: evidence of AECII injury and depletion.[4]

As a pediatric intensivist caring for critically ill children, I am aware of the age-related difference in outcomes between children and adults, especially when it comes to lung injury. I worked with the laboratory that published the findings in Garcia et al and asked the question: "Would "pediatric" or "juvenile" mice respond differently than adult mice to AECII injury and depletion?" The previous study was done in adult mice 8 weeks of age (equivalent to a human age of 30 years). To my knowledge, there had never been any published data comparing targeted AECII injury in different age groups of mice. I took 10-day old mice (approximately equivalent to a human age of 5 to 10 years) and subjected them to targeted AECII depletion. Surprisingly, all of juvenile mice died by day 2 after AECII depletion. The adult mice in the previous study had all survived beyond 12 days post AECII depletion. The juvenile died much more rapidly from lung injury than the adult mice did in the previously published experiment. This was a very unexpected result which showed that pediatric mice responded to AECII depletion and injury much differently than adult mice; suggesting there exists an age-related difference. This must be taken with a grain of salt, as this was a limited experiment. Furthermore, what we are observing in humans with COVID-19 is that the pediatric cases are doing better and surviving compared with the adults and there exist interspecies differences. However, the reports of the differences between pediatric and adult cases of COVID-19 allowed me to think back to my experiment and I believe that one of the answers to treating COVID-19 lies in understanding the biology of the human age-related differences within AECII, the type II alveolar cell, which is also known as the "defender of the alveolus."

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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How to cite this article: Im DD. Why is Coronavirus Disease 2019 not as severe in children?—A look at type 2 alveolar cells. *Pediatric Pulmonology*. 2020;1–2. https://doi.org/10.1002/ppul.24786