The immune system of children: the key to understanding SARS-CoV-2 susceptibility?

Humanity has repeatedly faced epidemics of known and novel pathogens and the immune system has adapted to survive. Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new zoonotic pathogen, there is no pre-existing immunity and the whole of humanity is susceptible to infection and developing COVID-19 disease.

Adults can be infected with different outcomes, from asymptomatic, mild, moderate to severe disease, and death. Children can also be infected by SARS-CoV-2, but most paediatric cases with laboratory-confirmed SARS-CoV-2 infection are mild; severe COVID-19 disease in children is rare.[1]

Children are more vulnerable to other infections; thus, the important question arises—why are children less susceptible to COVID-19 disease compared with adults? So far, there is no evidence of a lower degree of expression or function of the SARS-CoV-2 receptor (namely ACE2) in children. Thus, studying the innate immune system of children might be the key to understanding protection against or susceptibility to SARS-CoV-2.[2]

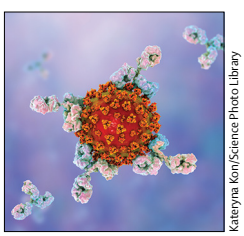
During the first months of life, maternal antibodies[3] protect the child from the microorganisms that the mother has encountered previously. Although water sanitation and hygiene practices have reduced epidemics and vaccines have been developed to prevent potentially lethal diseases,[4] all microorganisms are new for the child. The frequent infections occurring in the first years of life serve to build the pool of memory T and B cells that will prevent reinfection or development of disease by commonly encountered pathogens.[5] Thus, the paediatric immune system is prepared and fit to react to novelty, a function that might be diminished in adults and ineffective in elderly people aged 70 years or older.

Although innate immunity and T cells play a crucial role in the defense against infection, antibodies also play an important role. In the SARS, Ebola, and H1N1 epidemics, convalescent plasma containing antibodies from patients who had recovered from viral infections was used for treatment at the early stage of disease. Human monoclonal antibodies obtained from cloned B cells of a convalescent SARS-Cov-2 might become candidate therapeutics.[6]

In most cases, viral load peaks in the first week of infection and patients generate a primary immune response by days 10–14, followed by virus clearance through the action of high-affinity antibodies and T cells. The response of naive B cells to any novel infection or vaccine occurs through the germinal centre reaction and takes 2 weeks. This is a reasonable time for the response to a vaccine, but it is much too long for the response to infection. In the germinal centre,[7] B cells modify their antibodies through the introduction of somatic mutations in the antigen-binding site of the immunoglobulin variable heavy chain genes. Only modified B cells that express high-affinity antibodies are selected to become memory B cells (MBCs) and plasma cells.

The immune preparedness of children to any novel pathogens, including, SARS-CoV-2 might be based on several factors. First, in the early phases of infection, natural antibodies[8] play a most important role. Natural antibodies, mostly of IgM isotype and generated independently of previous antigen encounters, have a broad reactivity and a variable affinity. They contain the infection during the 2 weeks necessary for production of high-affinity antibodies and MBCs[9] that will clear the virus and prevent reinfection. High-affinity antibodies are expressed by switched MBCs. In humans, natural antibodies are produced by innate or IgM MBCs, a population of MBCs that is generated independently of the germinal centres and is most abundant in children.[10,5] From this population of B cells, sorted from the blood of young adults never exposed to avian influenza virus, we have cloned human antibodies able to neutralise antigenically diverse H1, H2, H5, H6, H8, and H9 influenza subtypes.[11] Thus, innate or IgM MBCs can bind many different unknown microorganisms.

Second, children have the ability to rapidly produce natural antibodies with broad reactivity that have not yet been selected and shaped by the reaction to common environmental pathogens. Following infection, two types of MBC, $CD27^{dull}$ and $CD27^{bright}$ MBCs,[12] cooperate. The two populations are related but have distinct molecular signatures and functions. $CD27^{bright}$ MBCs express highly mutated VH genes shaped



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by antigen. On stimulation, CD27^{bright} MBCs rapidly differentiate into plasmablasts and secrete antigen-specific antibodies, mostly of switched isotype. By contrast, CD27^{dull} MBCs are less mutated, generate few plasmablasts and secrete IgM antibodies. Innate or IgM MBCs are CD27^{dull}. When CD27^{bright} MBCs are used to produce plasmablasts and increase the amounts of antibody, CD27^{dull} MBCs proliferate and rapidly reconstitute MBC numbers.[12] Thus, the interrelationship between CD27^{dull} and CD27^{bright} MBCs might explain the resilience and rapidity of the adult immune response.

Third, when a novel pathogen challenges the immune system, CD27^{dull} MBCs might play a crucial role being capable of a more rapid reaction than naive B cells. They could immediately secrete antibodies and simultaneously enter the germinal centre reaction, where they acquire more somatic mutations and select their BCR on the basis of affinity. In infants and children, most MBCs are CD27^{dull} and thus highly adaptable to new antigens. In contrast, in the elderly, most MBCs are CD27^{bright}. CD27^{bright} MBCs, being highly mutated and specific, recognise their targets but appear incapable of adaptation to new antigens.

We have just started a prospective study aimed at testing our hypotheses discussed above. Our preliminary results in children suggest an early polyclonal B-cell response with production of substantial numbers of plasmablasts, mostly of IgM isotype. This response is not observed in adults with severe disease (who have a depletion of the B-cell compartment). Further studies are ongoing to show the difference in the specificities of the antibodies of children and adults. In addition to antibody production, B cells also have the function to secrete cytokines. IL-10, a potent anti-inflammatory cytokine is produced by neonatal B cells, activated B cells,[13] and IgA plasmablasts. Thus, the child immune response might have the double function of exerting protection and reducing immune-mediated tissue damage, in particular, in the lung.

Evolution has endowed a survival advantage to children to combat known and unknown pathogens. The adult is also well protected by the balance of cells with high and low specificity. With ageing, malnutrition, immunosuppression, and co-morbid states, our immune system loses the ability to adapt to novelty. Although vaccines are the way forward, in emergency situations such as the COVID-19 pandemic, the investigation and use of immune tools that nature has endowed to children might improve management outcomes.

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