Immune Responses to Coronaviruses with Emphasis in Children

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It is known that there are number of different and harmless seasonal coronaviruses that cause innocent colds in children and adults. In 2004, seasonal human coronavirus (HCoV-NL63) was discovered in the Netherlands [1,2]. Another seasonal human coronavirus (HCoV-HKU1) was discovered in Hong Kong in 2005, but has long been globally circulating, contributing to the same kind of symptoms as NL63, i.e., mild respiratory symptoms in young children, but rarely hospitalizations [3]. However, they are other types of coronaviruses that are probably transmitted from an animal reservoir and animal-to-human infection and they appear to cause severe acute respiratory syndrome (SARS). The first severe coronavirus (sars-CoV-1) causing SARS was discovered in 2003 although symptoms manifested already a year earlier in southern China. In 2012, Middle East respiratory syndrome (MERS) was caused by coronavirus (MERS CoV) which was probably originated from Arab camels.

It has been unclear why the new severe acute respiratory syndrome coronavirus (sars-CoV-2) hits a small minority hard, while vast majority of children appear to be protected and develop mild or no disease [4,5]. The same appears to be true for other coronavirus outbreaks in recent history, such as SARS and MERS where children appear to be less susceptible to illness [4]. Cross immunity due to previous exposure to seasonal coronaviruses may be a plausible explanation for why children appear to be protected and develop mild or no disease [5].

Sars-CoV-1 virus has angiotensin converting enzyme 2 (ACE2) as a receptor [6]. It was recently found that sars-CoV-2 binds to the same uptake receptor that the sars-CoV-1 uses to enter the epithelial cells [7]. The virus uses spike (S) protein in the viral membrane to bind to ACE2.ACE2 is present on the epithelial cells. It is expressed on the i) apical side of pulmonary epithelial cells and enterocytes in the small intestine, ii) on endothelial cells in blood vessels, iii) in the kidneys and heart [6,8]. The distribution of the uptake receptor explains lung and gastrointestinal symptoms and the possibility of renal and cardiac muscle damage late in the last disease phase [9-11].

Cross Immunity and Prolonged Immunity

An immune response to a viral antigen gives rise to memory B cells, antibody secreting plasma cells and memory T cells. Such cells and antibodies can potentially cross-react against other antigens. This is called an immunological cross-reaction and provides cross-immunity to infection. SARS led to immunity for 8-10 years in most people [12], while the disease MERS gave much shorter immunity [13]. It is likely that infection with sars-CoV-2 will result in some immunity; however the duration of the immunity will not be answered until many years.

Patients who survived SARS virus in 2003 produced neutralizing antibodies to the S protein [12]. Such antibodies were present for at least two years after the patients had recovered. This was the first indication that SARS patients could develop long-lasting immunity to SARS virus [12]. In a recent study published in March 2020 it was found that convalescent serum from patients who survived SARS could neutralize binding of the sars-CoV-2 to ACE2, thus blocking the uptake of sars-CoV-2 into the cells [7]. This suggests that there is distinct possibility of cross immunity, wherein immunity and antibody responses to one virus can have a significant effect on another. However, the serum did not block MERS-CoV, one of the deadly coronaviruses. MERS-CoV uses a completely different uptake receptor [14].

Seasonal coronaviruses that cause innocent colds in children lead to the formation of antibodies that last for 1-3 years. One of the four seasonal coronaviruses, human coronavirus NL63 (HCoV-NL63), also uses ACE2 as a receptor [1,2]. This virus causes infection in the flu season. It is estimated that 5% of influenza-like illness is due to NL63 [1,2]. The virus especially affects children and can cause bronchiolitis resulting often in hospitalizations [15-18]. Maternal antibodies seem to protect infants up to the age of three months, and most children seroconvert within the first 20 months of life [18].

Adaptive immunity consists of antibody responses that can neutralize viruses and prevent uptake. A study in 2005 showed that SARS patients developed rising titres of antibody that cross-reacted against seasonal coronaviruses. Antibodies to HCoV-NL63 increased approximately ten times [19]. This may be explained by the fact that the S protein on NL63 binds at the same three sites on ACE2 [20]. Although the S proteins are basically different, antibodies thought to mimic the binding sites on ACE2 and thereby blocking uptake is a plausible explanation [20].

T cells are also crucial for coronavirus immunity [21,22]. T-cell responses are essential to kill virus-infected cells [22] and thus remove the virus source from the body. Successful memory T cells against SARS virus were found 11 years after SARS [23]. Such findings show that people who have undergone SARS infection have prolonged T-cell immunity. It is quite possible that long-lived memory T cells that first responded to childhood coronavirus in childhood and which can now cross-react to similar sars-CoV-2 peptide antigens. However, the role of memory T-cells needs to be elucidated further in future investigations.

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Potential Implications

If it is true that antibodies or T cells against seasonal coronavirus partially protect against sars-CoV-2, then there is probably herd immunity in the population. This in turn can also explain that vast majority of infected patients are not highly infectious. Most people get away with a little cough, headache and abdominal pain. To determine if this is true, one must examine serum for cross immunity from e.g. HCoV-NL63 against sars-CoV-2 and examine the T-cell immunity in the population. Surveys of serum must also be done on a section of the population. It would also provide opportunity to create a new blood product that can be given to seriously ill covid-19 patients, namely convalescent plasma from blood bank donors who have undergone sars-CoV-2 infection [24,25]. Plasma with successful neutralizing antibodies that block binding to ACE2 will then be transferred to covid-19 patients. Such passive immunization will provide neutralizing antibody that can block uptake and further transmit via ACE2. Such antibodies may be newly formed antibodies to sars-CoV-2, further affinity-matured antibodies from memory B cells that previously had antibodies that already bound seasonal coronavirus, or cross-reacting and neutralizing antibodies to seasonal coronaviruses. The goal is to offer such convalescent plasma for the treatment of the sickest.

To conclude that someone has developed immunity, it is wrong to look at antibody responses only, it cannot be ruled out that good T-cell responses may explain lower levels or negative tests for neutralizing antibodies. If children or adolescents have clear reactive T-cells that are clear to attack infected cells, there will be less opportunity for the immune system to develop neutralizing antibodies to S protein. One possible consequence of good T-cell responses is few viruses in the airways [5]. This is one of several reasons for negative PCR testing for sars-CoV-2 [5].

It is the overall immune response from T cells and B cells and provides immunity to the virus and long-term protection. There is a clear possibility of cross-immunity against sars-CoV-2 for T and B cells that have previously protected us from seasonal coronavirus. This is because the coronavirus family shares antigenic properties. Children probably seem to be protected from Covid-19 because: 1) They have a well-functioning or rapidly responding immune system that also does not tend to overreact to the present coronavirus family; 2) The immune system for children and adolescents probably has ample experience with the viral family through exposure to regular seasonal coronavirus. This means that children will have a relevant B-cell immunity that can also be further developed or in advance have T cells that can cross-react once cells become infected with the sars-CoV-2 virus. In contrast, elderly people have age-impaired immune systems, insignificant protective cross-immunity, few T-cells and also insufficient immune response to the infection.

Competing Interests

The author declare that there is no competing interests regarding the publication of this article.

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