Mild SARS-CoV-2 infections in children might be based on evolutionary biology and linked with host reactive oxidative stress and antioxidant capabilities

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to significant morbidity and mortality in elderly individuals. Children typically have mild illness with rare mortalities. Age and co-morbid medical conditions are the most important determinant of the infection outcome. Currently there is no clear explanation for the difference in disease severity and outcome in different age groups. Based on evolutionary biology and translational research this review suggests that the high antioxidant capacity of children leading to a balanced redox state is the key factor for mild SARS-CoV-2 infections in this age group. On the other hand, elderly individuals with low antioxidant capacity and low angiotensin-converting enzyme 2 expression are prone to severe infections by redox-sensitive immune modulation.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has reached 7 million infections worldwide [1]. SARS-CoV-2 has a lower mortality compared with its sister viruses, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, but has higher mortality than four other common coronaviruses (229E, NL63, OC43, HKU1) [2]. An important feature of SARSCoV-2 infections that has puzzled scientists with no clear explanation is the expression of disease severity based on age. Although children and young adults mostly have mild disease, elderly individuals have severe disease with a much higher mortality rate, especially if chronic co-morbid conditions are present such as diabetes mellitus, hypertension and cardiovascular diseases [3].

The reason for milder SARS-CoV-2 infections in children has been addressed in previous publications. Possible explanations discussed in these papers included differences in immunity, inflammatory response, T-lymphocyte profile, level of angiotensin-converting enzyme 2 (ACE2) expression, level of melatonin secretion, less exposure to environmental pollutants and cross immunity from other viruses [4–7]. High frequency of co-morbid medical conditions in elderly individuals can be considered as another explanation but these conditions are unlikely to be a key factor because there is no report of increased SARS-CoV-2 infection severity in children with co-morbid medical conditions. In a news article published on *The Scientist* journal web site on 16 March 2020 coronavirus researcher Dr Baric stated 'I don't think anyone in the field knows why the disease is less robust in extremely young animals or humans' [8]. This review speculates another novel mechanism by which children might escape severe SARS-CoV-2 infections; an explanation that is based on evolutionary biology.

Evolutionary link to disease severity

Bats are the natural reservoir of coronaviruses and chronically shed these viruses without major disease in the host animal. From this perspective, children and bats are similar in the sense that both carry and shed the virus without much ill effect [2]. An interesting feature that both children and bats share is the presence of high metabolic rate, which is required for the cost of the flight in bats and growth and development in children. As growth slows down with age, metabolic rate also decreases and reaches the lowest level in elderly individuals [9,10].

High metabolic rate is associated with high levels of oxidative stress and antioxidant capacity in both bats and children [10,11]. Although metabolic rate decreases to lower levels in elderly individuals, the antioxidant capacity of elderly individuals does not match the level of oxidative stress and this has been seen as an instrumental process in the development of aging and various chronic diseases [12,13]. It is important to note that, given their size, bats have unexpectedly longer life spans (exceeding 20 years) than other mammalians of similar size. Given their high metabolic rate and long life span they are expected to have highly effective antioxidant systems to counteract the effect of their high level of oxidative stress, otherwise they would not live that long [10]. Another commonality between bats and children is the high level of melatonin secretion secondary to the significant amount of time spent in darkness or sleep, respectively. Melatonin is a very potent antioxidant and has significant immunomodulatory effects [7].

Coronaviruses probably co-evolved with bats over long periods [14]. Given the high antioxidant capacity of bat tissues, it is logical to speculate that co-evolution of coronaviruses with bats led to adaptation to an environment that is high in oxidative stress and total antioxidant capacity with a balanced redox state. Under these conditions SARS-CoV-2 is likely to create mild infections whether it is in children or in bats. SARS-CoV-2 infections are likely to become severe in biological environments where low metabolism is coupled with low antioxidant capacity or dysfunctional antioxidant systems, exemplified by elderly individuals or people with high oxidative stress at baseline, such as patients with diabetes mellitus, hypertension or cardiovascular diseases [13]. Even when the basal antioxidant capacity is adequate, faced with additional oxidative stress from a viral infection, elderly individuals or patients with co-morbid conditions might not augment endogenous antioxidant capacity as well as children or young adults, and this might further contribute to disease severity [15,16]. From this perspective, the absence of severe SARS-CoV-2 infections in children can be viewed as an evolutionary artefact of ancestral SARS-CoV-2 adaptation to the physiological conditions of the bat tissues.

Role of oxidative stress and antioxidants in disease severity

The key role of oxidative stress during SARS-CoV infections was shown by Smits et al. [17]. After infecting macaques with the same viral dose of SARS-CoV per body weight, researchers observed more severe lung pathology in aged than in young adult macaques. The levels of viral replication in the lung tissue were similar in both groups but the host response to SARS-CoV was stronger in aged macaques. This finding strongly suggests that severe disease in aged macaques is not caused by increased viral replication or inability to contain the virus but by an abnormal immune response towards the virus. Higher levels of lung inflammation caused by this abnormal pro-inflammatory immune response led to acute respiratory distress syndrome (ARDS) and worse outcome. Differential gene expression profiles identified nuclear factor-κB signalling as a potential source of difference in disease severity. Researchers claimed that the strong pro-inflammatory response in the aged macaques was secondary to a weakened antioxidant defence system disturbing redox balance and leading to activation of redox-sensitive transcription factors such as nuclear factor-κB followed by induction of genes of pro-inflammatories, including interleukin-1B, interleukin-6 and tumour necrosis factor-α. This finding is supported by similar studies in mice and clinical data where severe infections were found to be associated with a significant pro-inflammatory state [18–20].

Various studies have identified antioxidant defences as a key component determining the severity of viral infections. Antioxidant defences are reported to be one of the mechanisms by which mosquito cells survive the dengue 2 viral infection, which typically induce apoptosis in mammalian cells [21]. Viral respiratory infections, including respiratory syncytial virus, human metapneumovirus and influenza virus infections, were shown to inhibit the expression and activity of antioxidant enzymes leading to a decrease in antioxidant capacity during these infections [15,16,22]. The important role of dietary antioxidants during viral infections is clearly documented in a series of experiments by Beck et al. [23]. In one experimental model, coxsackievirus B3 virus, which induced only mild illness in selenium-replete mice, caused lethal myocarditis in selenium-deficient mice. In another model, excess oxidative stress caused by high doses of iron supplementation led to higher mortality from coxsackievirus B3 infection, which was partially offset with vitamin E supplementation. A similar observation was made with influenza virus

infections as well, where selenium-replete mice had mild illness compared with selenium-deficient mice were observed to have severe pneumonitis [23]. The important role of dietary antioxidants during viral infections was also documented in humans. Broome et al. supplemented three groups of healthy people (other than low levels of selenium) with different amount of selenium (0, 50, 100 μg/daily) for 6 weeks [24]. After 6 weeks, each person was given live attenuated polio vaccine. Result showed that selenium supplementation was associated with an increase in plasma selenium level, improvement in antioxidant levels and faster clearance of the poliovirus [24]. Age-related difference in endogenous antioxidant enzyme levels was reported by Abouhashem et al. [25]. Comparison of single lung cell RNA sequencing from healthy young adults and elderly individuals demonstrated significant down-regulation of redox-sensitive enzymes in elderly individuals. The most down-regulated enzyme was superoxide dismutase 3, which is an important antioxidant enzyme and researchers proposed that this might be a reason why SARS-CoV-2 infection is more severe in elderly individuals [25]. Although the exact role of oxidative stress in viral virulence is not clear, it can be secondary to the modulation of the immune system or the increased mutation rate caused by oxidative damage.

Further support for the role of oxidative stress and antioxidant defences comes from research on ACE2. ACE2 plays a major role in determining the level of severity during SARS-CoV-2 infections because not only is it the entry site of SARS-CoV-2 into the cell, but also a significant modulator of oxidative stress and inflammation. ACE2 is expressed in many cell types including alveolar, endothelial and kidney cells. ACE2 is a single polypeptide, single-pass transmembrane protein with carboxypeptidase activity that metabolizes various short-chain peptides, the most important one being angiotensinogen II [26]. There are two main axes of the renin−angiotensin system (RAS). The first involves ACE/angiotensin II/ATR1 and the second involves ACE2/angiotensin 1−7/MasR. These two axes have opposite effects. The ACE axis increases oxidative stress, but the ACE2 axis reduces oxidative stress and has anti-inflammatory properties [27−29].

ACE2 has been reported to have a protective role in acute lung injury (ALI)/ARDS through modulation of the local lung RAS, oxidative stress, redox potential and inflammation [30−32]. In a mouse hyperoxic lung injury model, ACE2 and angiotensin 1−7 have been shown to have significant anti-inflammatory and antioxidant properties, protecting the lungs from injury mainly by inhibiting the nuclear factor-κB pathway [30]. SARS-CoV infection or administration of its spike protein, which binds and reduces ACE2 expression, results in dominance of the RAS ACE axis over the ACE2 axis and this imbalance leads to increased oxidative stress. In a mouse model of ALI/ARDS,

injection of the SARS-CoV spike protein worsens acute lung injury, while blockage of the ACE axis of RAS attenuates the injury, which underscores the important role of local RAS balance in lung disease [31]. Compared with the control group, ACE2 knockout mice were reported to have a worse outcome during influenza virus infection-induced acute lung injury, illustrating the protective role of ACE2 [33]. The protective role of ACE2 in ALI/ARDS has been investigated in humans as well, and soluble recombinant ACE2 has been used in individuals with ARDS in a phase II clinical trial [34]. The association between age and ACE2 expression is not clear. ACE2 expression has been reported to be decreased with age in rat lung [35], increased with age in human olfactory epithelium [36] and unchanged with age in human lung [25]. Studies on human lungs are limited by evaluation of ACE2 expression through RNA without the use immunohistochemical staining as was done by Xudong et al. on rat lung [35]. This difference is important because genetic expression does not necessarily imply cell surface expression. Based on data from rat lungs, the absence of severe SARS-CoV-2 infections in children and young adults can also be a function of high ACE2 expression in these age groups because ACE2 protects against ALI/ARDS by increasing antioxidant capacity, leading to immune modulatory effects.

Apart from its modulatory effects on the immune system, oxidative stress is also known to have significant negative effects on surfactant function in the lungs. In animal models, oxidative stress was shown to cause surfactant dysfunction [37]. During SARS-CoV-2 infections, reduced antioxidant defences in lung tissue might lead to increased surfactant dysfunction and therefore may lead to worse clinical outcome.

Based on the above evidence, it becomes clear that antioxidant capacity and antioxidant response potential of the host are two of the key determinants of SARS-CoV-2 infection outcome. Higher antioxidant capacity of children and young adults combined with their higher ACE2 expression are the likely explanation of the low incidence of severe infections in these age groups. This hypothesis also explains occasional severe infections in the young age groups because irrespective of age, anyone with a reduced antioxidant defence system is expected to have more severe infection. Inadequate dietary intake of antioxidants, high intake of pro-oxidants or heavy alcohol consumption, which all decrease total antioxidant capacity, might be additional hidden risk factors in addition to age and co-morbid conditions [38,39].

Treatment

Strong association between infection severity and host antioxidant capacity makes antioxidant medications the first-line

therapy in the prevention and treatment of SARS-CoV-2 infections, especially in elderly individuals or patients with co-morbidities. Because antioxidant defences exist as a multi-component system, supplementation with one agent is unlikely to produce a consistent beneficial effect. Maras et al. estimated that >90% of Americans do not consume sufficient dietary vitamin E, which is an important part of antioxidant defences [39]. Given the low percentage of the population adhering to healthy diet recommendations and the high prevalence of vitamin insufficiencies it is logical to treat patients with SARS-CoV-2 infections with multiple antioxidant medications including, but not limited to, vitamin E, vitamin C, carotenoids and selenium. Recently, high-dose vitamin C was used in both critically ill and SARS-CoV-2-infected individuals [40]. It is likely that antioxidant treatment has a window period. It is expected to be more effective early on in the disease process before a significant pro-inflammatory response is triggered rather than later and may not make significant difference once severe ARDS develops.

Future research

Future studies should evaluate the role of antioxidant administration in SARS-CoV-2 infections. Further research can be performed on the role of the high metabolic activity as it can be protective against these infections irrespective of antioxidant capacity. Combined administration of levothyroxine, which increases metabolic rate, and antioxidant medications can make the elderly tissues mimic the tissues of a bat or a child and this can be another interesting area of research.

Conclusion

Based on evolutionary biology and available translational and clinical research this review suggests that the difference in disease severity of SARS-CoV-2 infections in different age groups can be secondary to host antioxidant capacity, and antioxidant therapy might be protective against severe SARS-CoV-2 infections.

Funding

Conflicts of interest

The author has no conflict of interest.

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