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Education

Immunosenescence and severity of COVID-19

EDUCATION

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ABSTRACT

Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes coronavirus disease 2019 (COVID-19). It is associated with significant morbidity and mortality, and socio-economic disruption globally. Increasing age and ageing-associated comorbidities such as obesity, type 2 diabetes, and chronic cardiac, respiratory, kidney and liver diseases are associated with greater risk of adverse outcomes including severe illness, hospitalisation, intensive care admission, and death. Older individuals are disproportionately affected regardless of pre-existing comorbidities. Ageing-related changes to the immune system result in a less effective response to novel pathogens. Atrophy of the thymus and a consequentially reduced T cell receptor (TCR) repertoire may be responsible for the increasing severity of infection with advancing age, as T cells play a crucial role in viral clearance both generally and in COVID-19. Vaccination programmes are currently gaining momentum and could potentially provide a route out of the pandemic.

Relevance

Viral pandemics are not uncommon; H1N1 influenza, Ebola, Zika, SARS, Middle East respiratory syndrome (MERS), and now COVID-19 have been a significant cause of public disturbance, morbidity, and mortality over the past two decades. We are likely to continue to encounter novel viral pathogens increasingly commonly in the coming years. Medical students should therefore develop an understanding of the immune response to viruses and take this opportunity to familiarise themselves with the features of the COVID-19 pandemic. An appreciation of immunosenescence is also key as our communities continue to age.

Take Home Messages

- Symptoms of COVID-19 are heterogenous; individuals can be asymptomatic, have mild flu-like symptoms or severe respiratory disease and systemic complications.
- A potent T cell and B cell response is present with SARS-COV-2 infection, with antibodies targeting the viral spike protein.
- Immunosenescence is associated with a poorer response to novel and evolving pathogens.
- Vaccines show high efficacy against COVID-19 and mass vaccination programmes could be the route out of the pandemic.

The coronavirus disease 2019 (COVID-19) pandemic has caused significant morbidity and mortality and socio-economic disruption globally. Increasing age and age-related comorbidities such as obesity, type 2 diabetes, chronic cardiac, respiratory, kidney and liver diseases are associated with greater risk of adverse outcomes. (1–3) This includes a heightened risk of severe illness, hospitalisation, escalation to intensive care, and death. Care homes with elderly residents have thus seen disproportionately higher mortality rates. (4) Whilst the combination of ageing and chronic inflammation – "inflammaging" – associated with ageing-related disease states may have a part to play in the severity of COVID-19, (5) the potential role of ageing-related decline in the effectiveness of the immune system deserves further scrutiny to understand the underlying mechanisms and optimise preventative measures for older persons.

COVID-19 predominantly presents with fever and cough; other symptoms described include anosmia, sore throat, myalgia, and gastrointestinal disturbances. (6-8) It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded ribonucleic acid (RNA) enveloped virus which primarily targets the cells of the respiratory tract.

SARS-CoV-2 belongs to the betacoranavirus genera within the coronaviridae family of viruses, alongside SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV). The emergence of these three novel coronaviruses have produced great public concern over the past two decades. However, among the coronaviridae family are globally endemic non-SARS-like CoVs' which produce mild upper respiratory tract infections indistinguishable to that produced by influenza. (9)

SARS-CoV-2 infection begins by infiltration of the virus into the host cell. Similar to SARS-CoV-1, the SARS-CoV-2 virus utilises the angiotensin-converting enzyme 2 (ACE2) receptor on host cells for entry. A serine protease, transmembrane protease serine 2 (TMPRSS2), facilitates this entry through a viral structural spike (S) protein. The viral RNA is released into the host cell; it is replicated by RNA-dependent RNA polymerase and undergoes translation to form viral proteins. These come together in the endoplasmic reticulum-Golgi intermediate compartment and become contained within vesicles. These newly formed virions trigger the same infective process in new cells. (9)

SARS-CoV-2 targets the cells of the respiratory tract, which results in the damage caused to be predominantly in the respiratory tract. Whilst many individuals remain asymptomatic, COVID-19 can rapidly progress into a systemic disease associated with a severe inflammatory syndrome, profound lymphopenia, and coagulopathy. (9,10) With SARS-CoV-2 infection, there is increased infiltration by monocytes, macrophages, and neutrophils which release proinflammatory cytokines and chemokines, termed 'cytokine storm'. These are likely responsible for diffuse alveolar damage (oedema and fibrosis), alveolar collapse, and damage to other organs including the spleen, liver, and bone marrow. (9) Cytokine storms, a common immunopathological event in SARS-CoV-2 infection, results in uncontrolled systemic inflammation and can produce acute respiratory distress syndrome (ARDS). (10) For patients with severe COVID-19 infection, common laboratory findings include lymphopenia, thrombocytopenia, and deranged renal indices. (6,8,11) Bilateral ground-glass opacities and patchy shadowing are also characteristic radiological changes on chest CT. (6,8)

THE IMMUNE RESPONSE TO VIRAL INFECTION

The immune system is complex and pervasive, with an overall function to prevent or limit infection. (12) It comprises of numerous cell types that either circulate throughout the body or reside in a particular tissue. Each cell type plays a unique role, with different ways of recognizing problems, communicating with other cells, and performing their functions.

OVERVIEW OF THE INNATE AND ADAPTIVE IMMUNE RESPONSE

The first line of defence against pathogens is the innate, or non-specific, immune response. Its main purpose is to immediately prevent or limit the spread and movement of pathogens throughout the body. It detects viral infections by using pattern recognition receptors (PRRs) which react to pathogen-associated molecular patterns (PAMPs) (Figure 1). The PRRs include toll-like receptors which recognise the lipids, lipoproteins, proteins, and nucleic acids of pathogens, and retinoic acid-inducible gene-I-like receptors which recognise the nucleic acids of RNA viruses. When a virus invades a host cell, PRRs initially recognise the viral nucleic acid and promote the synthesis of type I interferons. Interferons are major antiviral molecules which act to limit viral infection by promoting macrophage phagocytosis of antigens and directing natural killer (NK) cells to destroy infected cells. Cells of the innate immune system (primarily dendritic cells) present pathogenic antigens for recognition by T lymphocytes, in order to initiate the adaptive immune response. (13)

The second line of defence against pathogens is the adaptive (acquired) immune response and is only found in vertebrates. It is specific to the pathogen. Once a viral pathogen is detected, the adaptive immune system is mobilised. Adaptive immunity plays the most important role in completion of viral clearance. The cluster of differentiation 8 ($CD8^+$) and $CD4^+$ T cell effector subtypes produced by the thymus are vital components of the adaptive immune response against viral infections. The $CD8^+$ cytotoxic cells exert their effects by utilising pro-inflammatory mediators and other mechanisms of direct pathogenic destruction, whilst $CD4^+$ helper cells primarily support proliferation of B cells to produce virus-specific antibodies.

EXPOSURE TO NOVEL PATHOGENS, ADAPTIVE IMMUNITY, AND AGEING

Immunosenescence, a term that collectively describes the processes that occur in ageing-related immunodeficiency, is associated with impaired responsiveness to new/evolving pathogens. Involution and reduced function of the thymus is a recognised component of immunosenescence. The thymus, as the central haematopoietic site for production and maturation of T lymphocytes and development of T cell receptor (TCR) repertoire, (14) is a major component of the adaptive immune system (Figure 2). It is essential for establishing a functional TCR repertoire in early life; congenital absence of the thymus (DiGeorge syndrome), for instance, results in profound immunodeficiency. The rate of thymic T cell production is greatest in early life and begins to decline from infancy until death. Thymic atrophy causes progressive loss of functional thymopoiesis and naive T cell output.

Naive T cells appear crucial in the adaptive immune response against novel pathogens. The ability of the immune system to respond to new antigens is highly dependent on the TCR diversity of the naive T cell compartment. New T cell responses only occur if naive T cells that recognise the new antigen are present in the periphery. A study of ageing-related changes in TCR repertoire compared blood samples obtained from healthy individuals between the ages of 6 to 90 years and observed that TCR diversity significantly decreased with age. (15) Of the changes that occur in the ageing immune system, thymic involution is by far the most dramatic and universal. Ageing-related decline in naive T cell numbers and TCR diversity may therefore impair the immune response to a new viral infection such as SARS-CoV-2. It is also recognised that thymic involution is accelerated by obesity and diabetes, (16,17) two major risk factors for greater severity and mortality of COVID-19. (2)

IMMUNE RESPONSE IN COVID-19

Upon infection, SARS-CoV-2-specific T cells are recruited from the randomly formed naive T cell pool. T cell activation is a feature of acute COVID-19 infection; SARS-CoV-2-specific T cell pools (CD8+ and CD4+) have been identified in 70–100% of patients in the recovery phase of the illness. (18) CD4+ T cells activate a potent B cell response which initiates the production of neutralising antibodies. The main target of these antibodies is the SARS-CoV-2 spike protein and its receptor-binding domain (19) – an important target in global vaccine efforts. Functional exhaustion of CD4+, CD8+ and NK cells have been observed in affected patients; counts correlate inversely with disease severity and recover during convalescence. (20) It is unclear if the magnitude of T cell exhaustion is greater in older patients or if this is associated with increased risk of adverse outcomes.

SARS-CoV-2 specific antibodies can be detected in most infected individuals 10–15 days after the onset of symptoms. (21) Antibody titres peak on average 23 days following the onset of symptoms and decrease thereafter – to undetectable levels in some patients. The antibody threshold required for protection against reinfection is not yet understood. A study from Sweden, a country unique amongst its neighbours in Western Europe in its policy of relaxed public health measures during the pandemic, (22) systematically mapped the functional and phenotypic characteristics of SARS-CoV-2-specific T cell responses in four cohorts: unexposed individuals, patients with acute COVID-19, convalescent individuals, and exposed family members. (23) The study, which included 206 participants, found that T cell activation was a key part of acute COVID-19 infection. Acute phase SARS-CoV-2-specific T cells displayed a highly activated cytotoxic phenotype that correlated with disease severity, whereas convalescent phase SARS-CoV-2-specific T cells were polyfunctional and displayed a stem-like memory phenotype. Furthermore, in the absence of detectable circulating SARS-CoV-2 antibodies, exposed family members and convalescent individuals with a history of asymptomatic and mild COVID-19 exhibited robust memory T cell responses months after infection. That SARS-CoV-2 elicits broad and highly functional memory T cell responses is consistent with immunity observed with other viral infections and vaccination programmes. Following infection by the closely-related SARS-CoV-1, virus-specific memory T cells were shown to persist for many years and may therefore provide some protection from reinfection or severe disease. However, the small sample size and lack of information of age distribution in this study limits its generalisability to older persons.

SARS-CoV-2 reactive CD4+ cells have also been identified in 40–60% of uninfected individuals, suggesting cross-reactivity from previous exposure to other "common cold" coronaviruses. (18) This may partially explain the varying degrees of severity seen within similar age-groups with exposure-naive individuals potentially being at risk of worse outcomes. Yet, the marked heterogeneity in clinical severity of COVID-19 may also be the result of other differences in the adaptive immune system, namely the robustness of the T cell response. Studies comparing the presence of SARS-CoV-2-specific T cells in different age groups during or following infection would be of value, as they would determine the contribution of a weakened T cell response to the age-related disease severity seen in COVID-19. Such studies would also predict the potential shortcomings of vaccination programmes for older individuals. If they were to show that the T cell response to COVID-19 is less robust with advancing age due to thymic involution, achieving long-term immunity via vaccination may be more challenging in older people.

COVID-19 VACCINES

The United Kingdom, the first to commence a mass vaccination programme, has prioritised people aged 65 years and over, people who are at high risk from coronavirus (clinically extremely vulnerable), people who are at moderate risk from coronavirus (clinically vulnerable), people who live or work in care homes, and health and social care workers. (24) The BNT162b2 mRNA vaccine, developed jointly by Pfizer/BioNTech is recommended to be administered in two doses at least 21 days apart. Published trial data has shown the vaccine was highly effective at 95% in preventing Covid-19 beyond 7 days after the second dose. (25) The adenovirus vector-based AZD1222 vaccine, co-developed by the University of Oxford/AstraZeneca, is also recommended in a two-dose regimen, given at least 4 weeks apart. Published trial data have reported vaccine efficacy after two doses of 62% in participants who received two standard doses and 90% in participants who received a low

dose followed by a standard dose with overall vaccine efficacy across both groups of 70%. (26)

It is of interest that the Pfizer/BioNTech vaccine is an mRNA-based vaccine. There are 2 types of RNA currently being researched for use in vaccination: self-amplifying viral RNA and non-replicating mRNA. mRNA vaccines only encode the antigen needed and contain untranslated regions whereas self-amplifying RNAs encode the viral machinery needed for replication and eventual protein expression. mRNA vaccines utilise an encoded antigen from the infectious agent which is then subsequently expressed by cells in the body. (27) This is in contrast to conventional vaccines which utilise the actual antigen from the virus to initiate an immune response. There are significant advantages to mRNA vaccines: they can be produced incredibly rapidly as attenuated viral particles are not needed and can be produced at scale due to the synthetic nature of production.

The Pfizer/BioNTech vaccine utilises a lipid nanoparticle platform which enables effective delivery into cells and dampens innate immune sensing to increase mRNA translation. (28) The mRNA encodes the receptor binding domain of SARS-CoV-2 which is a key site for neutralising antibodies. Another mRNA vaccine, the mRNA-1273 vaccine produced by Moderna, also utilises the lipid nanoparticle platform described above. It has been shown to have 94.1% efficacy at preventing COVID-19 after two doses given 28 days apart. (29) The Moderna vaccine has been approved in the UK, but it is not yet in use at the time of writing.

The Oxford/Astra-Zeneca vaccine (approved and in use at the time of writing), in contrast, uses a simian adenovirus vector ChAdOx1 which holds the actual spike glycoprotein from SARS-CoV-2. (26) Several other vaccines are already in limited use or approaching clinical use in many countries, such as Sputnik V (human adenovirus vector-based vaccine) from Russia, Covishield (a franchise version of the Oxford/Astra-Zeneca vaccine) and Covaxin (inactivated virus vaccine) from India, and CoronaVac and Sinopharm (both inactivated virus) vaccines from China.

Vaccination is seen as the most anticipated exit strategy out of the current pandemic. In the UK, the Vaccine Taskforce has been set up to ensure that the population has adequate access to these vaccines. (30) Their approach has been to diversify the UK population's access to a wide range of vaccines in different formats especially those that elicit immune responses in individuals who have higher mortality risk such as those older than 65. The Vaccine Taskforce is working in tandem with the Joint Committee on Vaccination and Immunisation to facilitate the decision-making on which groups of the population gets vaccinated first. (31) The current list puts those in care homes, health, and social care workers and those above 80 years of age at the top. The list then trickles in decreasing age down to those 50 years old and above with the rest of the population coming last. Vaccination has taken the media spotlight in recent weeks as the ultimate solution to the pandemic. Once mass vaccination programs are underway and further data is collected, only then can definitive conclusions be drawn on these vaccines.

In recent weeks, new variants of the SARS-CoV-2 virus have been detected in circulation in the UK. One "UK variant" is said to contain the N501Y mutation of the spike protein which has been thought to increase binding affinity to the ACE2 receptor. (32) The P681H mutation is also present in this variant which creates a furin cleavage site on the spike protein which has been shown to promote entry into respiratory epithelial cells and transmission in animal models. However, vaccine manufacturers have already begun work on testing vaccine efficacy against new and emerging variants across the world. As mutations accumulate over time, it is likely that vaccines will need to be reconfigured to counter them in the near future, much like with the influenza vaccine. (33)

THE FUTURE OF COVID-19 IMMUNITY

Despite many months since the onset of the pandemic, the future of the COVID-19 immune landscape remains uncertain. Epidemiological modelling by Saad-Roy et al. has predicted multiple scenarios for the course of the COVID-19 pandemic over the next 5 years based on the interaction of various factors including the nature of the adaptive immune response, non-pharmaceutical interventions, and vaccination. (34) Global efforts to develop treatments for COVID-19 have focused on drug repurposing, immunotherapies including convalescent plasma and monoclonal antibodies, and vaccines. (35)

Whilst there is currently great interest in neutralising antibody cocktails to reduce viral load and minimise risk of progression to severe disease with COVID-19, (36) halting or reversing thymic involution could prove to be the holy grail of immune protection. Thymus regeneration and reversal of immunosenescent trends have been shown to be possible in healthy men aged 51–65, the age range that just precedes the collapse of the TCR repertoire, with recombinant human growth hormone therapy. (37) Based on evidence from animal models that growth hormone has thymotrophic and immune reconstituting effects, this trial demonstrated reversal in some ageing-related immunological changes including increases in naïve T cells. Moreover, thymosin alpha-1 (Tα1) – a peptide hormone produced by thymic epithelial cells that supports T cell production, differentiation, and maturation – may reduce COVID-19 mortality by promoting thymic output. (38) Tα1 levels decline with age. In the study by Liu et al. of 76 patients with severe or critical COVID-19 infection, fewer patients in the Tα1-treated group required mechanical ventilation (2/36 compared with 11/40 in the control group) and fewer Tα1-treated patients died (4/36 compared to 12/40). Therefore, whilst still experimental, thymic regeneration may also prove life-saving and further research in this field is advocated.

CONCLUSION

Ageing-related thymic involution and its impact on immunosenescence plausibly contributes to worse outcomes seen in the elderly with COVID-19. Understanding the impact of immunosenescence on the magnitude and duration of SARS-CoV-2 vaccine-induced immunity is crucial to establishing dosing schedules in the elderly. It should be ensured that older individuals are proportionally represented in vaccine studies as it is well-recognised that vaccine efficacy declines with age as a consequence of immunosenescence. This will further inform which patient groups should be specifically targeted in mass-scale immunisation. A successful vaccination strategy can significantly alter the dynamic of the pandemic. Effective public health measures however must remain in place until this process is at a more advanced stage and whilst we better understand the impact of emerging variants on vaccine-induced immunity especially in older individuals.

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