Biography

Raina MacIntyre (MBBS Hons 1, M App Epid, PhD, FRACP, FAFPHM) is Professor of Global Biosecurity, NHMRC Principal Research Fellow and Head of the Biosecurity Program at the Kirby Institute, UNSW, Australia. She leads a research program in control and prevention of infectious diseases, spanning vaccinology, pandemics and emerging infections, and personal protective equipment. Her area of vaccine expertise is vaccination of older adults and immunosuppressed people, and she has a track record in research on vaccines against measles, influenza, hepatitis A, pneumococcal disease, herpes zoster and smallpox. She has conducted several randomized controlled clinical trials of vaccines and is on the Vaccine Council of 100 for the journal, Vaccine. She has over 400 peer reviewed publications. She has received many awards including the Sir Henry Wellcome Medal and Prize from the Association of Military Surgeons of the US, the Public Health Association of Australia's National Immunisation Award (for her research on adult vaccination), and the Frank Fenner Award for Research in Infectious Diseases.

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Long-term and short-term immunity to SARS-CoV-2: why it matters

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Abstract. The adaptive immune system, regulated by CD4 T cells, is essential for control of many viral infections. Endemic coronavirus infections generally occur as short-term upper respiratory tract infections which in many cases appear to be cleared before adaptive immunity is fully involved, since adaptive immunity takes approximately 1.5–2 weeks to ramp up the response to a primary infection, or approximately 1 week for a recurrent infection. However, the adaptive immune response to SARS-CoV-2 infection will be critical to full recovery with minimal long-lasting effects, and to either prevention of recurrence of infection or at least reduced severity of symptoms. The detailed kinetics of this infection versus the dynamics of the immune response, including in vaccinated individuals, will largely determine these outcomes.

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Introduction

SARS-CoV-2 is the third highly pathogenic coronavirus zoonosis from bats, which have evolved interferon and adaptive immune responses that allow many such viruses to co-exist without disease, but still permitting transmission[1]. In humans, transmission of SARS-CoV-2 to other individuals will typically occur at the peak of viral load in the first 5 days of symptoms[2].

Innate immunity

The earliest mechanism combating an acute, short-lived viral infection of an epithelial barrier, such as with SARS-CoV-2, involves type-1 and type-III interferons (IFN-I and IFN-λ)[3], prior to the adaptive immune response. Therefore, the first phase of the current pandemic is likely due to sufficient evasion of the early IFN response. Amongst patients with severe life-threatening pneumonia, 3% have inborn genetic errors in the IFN-I response pathway[4], and 13% have autoantibodies that prevent IFN-I signalling[5], much higher rates than in the general population. Also, it has been reported that COVID-19 patients with severe disease have lower[6], or delayed IFN production[7,8], consistent with evidence that exogenous IFN can limit coronavirus replication *in vitro*, and that these viruses have non-structural proteins that help evade and antagonise innate immunity[9,10].

Highly specialised circulating plasmacytoid dendritic cells (PDCs) also sense dsRNA and produce large amounts of exogenous

IFN-Is[11]. Importantly, numerically, these PDC's decrease with age[12], which may add to the reasons that older patients do worse after SARS-CoV-2 infection than paediatric and adolescent cases[13], who can be PCR negative in the same household as PCR+ adults[14]. Overall, later adaptive immune responses could become more critical in older patients.

Primary human immune responses to viral infection

Neutralising and opsonising antibodies will likely be extremely important to finally clear all virus in older adults. Neutralising antibody (nAb) responses to viral infections are regarded as the main protective mechanism of effective vaccines[15], and generally require a concomitant CD4 T-cell response to initiate germinal centres where they help B cells increase the avidity of their antibodies by somatic hypermutation and switch immunoglobulin to important sub-classes of IgG[16]. CD4 T cells also help expanded specific B cell clones to generate long-term memory B cells, and are believed to be important also for CD8 T-cell responses[17].

During a primary response, naïve B cells are multipotent with different fate pathways, including: (1) short-term proliferating IgM and IgG antibody-secreting plasmablasts in the circulation and the spleen that are independent of CD4 T-cell help; (2) longer lived plasma cells, generated via germinal centre reactions with CD4 T-cell help, that can mature into bone marrow-resident, non-proliferating cells that produce antibody in large amounts; and (3) memory B cells from germinal centres that can rapidly become antibody-secreting upon re-encounter with antigen in secondary lymphoid tissues (reviewed in Akkaya *et al.*[18]). Important variables include: B cell receptor affinity; antigen structural pattern, especially valency; signalling via TLR's, especially TLR7 and TLR9 for viral antigens; activation of CD4 T cells with expression of CD40, IL-4 and IL-21; and generation of germinal centres[18]. Different B cell fates are mediated by differential expression of transcription factors, Bcl6 in germinal centre B cells, Blimp in plasma cells, and the level of IRF4 expression in response to the affinity and strength of the B cell receptor signalling[18,19]. Empirically, all these different fate decisions can be effective, such as the examples of immunity resulting from: T-cell-independent responses to multivalent pneumococcal vaccine without generating memory B cells[20]; nAb responses, with minimal somatic hypermutation, to highly multivalent virus like particles of the HPV vaccine[21]; and T-cell-associated lifelong nAb responses to measles infection and vaccinia inoculation[15].

Most studies of T cells during human acute viral infections have begun after diagnosis, and exposure date is often unclear, but we closely studied the immune response before and after inoculation of healthy volunteers with vaccinia virus[22]. Typically, the draining axillary lymph node was tender by days 7–8, the inoculation site was edematous at days 9–11, antigen-specific CD4 T cells appeared in the circulation at days 11–14 and serum nAb responses appeared between days 14–21[22], as later confirmed for antigen-specific CD8 T cells[23], and consistent with murine primary responses to influenza infection[24].

Overall, primary adaptive immune responses take longer than the time course of a typical mildly symptomatic SARS-CoV-2 infection, with 65% of such individuals reporting a return to usual health within a median of 7 days from onset of symptoms[25].

Secondary immune responses to viral re-infection

By comparison, annual vaccination to influenza leads to enrichment of circulating antigen-specific CD4 T cells at day 7[26], which is 4–5 days later than the peak and start of the decline of influenza viral titres in human challenge studies[27].

In murine influenza challenge models, large populations of antigen-specific CD8 T cells present in the lungs are associated with shortening the duration of peak viral load in lungs by about 2–3 days, compared to the viral load during the primary response[28].

Antibody responses to SARS-CoV-2 infection

The kinetics of antibody responses to SARS-CoV-2 show that most patients seroconvert with the appearance of specific IgG between day 14 and day 21, peaking around day 30[29], but IgG levels thereafter decrease in serum by about half in the ensuing month[30]. Numerous studies have found nAb in the vast majority of COVID-19 patients, but there is a very wide range of titres, with highest titres associated with severe symptoms[29,31,32].

Acute SARS-CoV-2 infection is associated with a variable increase in plasmablasts in the circulation[33–35], which is resolved during convalescence[35]. These relatively immature B cells spontaneously secrete immunoglobulins independent of CD4 help, but may be short-lived cells, lost soon after viral clearance[18,35]. Overall, the early drop in antibody levels[30] may be mainly due to resolution of the acute plasmablast response.

However, around the time of antibody appearance, COVID-19 patients who go on to develop life-threatening pneumonia begin to exhibit worsening symptoms[2]. This raises the question of whether the immune response could also be unfavourable. It is possible that high levels of opsonising antibodies enhance viral entry into cells with Fc receptors, such as mucosal epithelial cells that transcytose immunoglobulins to and from the lumen at intestinal sites, possibly making the infection worse[36]. Gastrointestinal symptoms are very

common[37], and antibody dependent enhancement could be involved, in addition to direct infection of $ACE2^+$ enterocytes.

Therefore, it is imperative to better understand the role of B cells and antibodies in SARS-CoV-2 infection, as well as vaccination, including: the affinity of naïve B cells for epitopes in spike protein, particularly the receptor binding domain (RBD); does SARS-CoV-2, as an RNA virus, trigger TLR7 and TLR9 signalling in B cells; what are the CD4 epitopes in spike and RBD to help B cells; numbers of naïve CD4 T cells available to respond and form germinal centres; and how much somatic hypermutation is actually required for the most effective nAb. It has been reported that nAb to SARS-CoV-2 may not require a large number of mutations relative to germ-line immunoglobulin gene sequences[38]. While two reports from autopsy studies suggest a lack of germinal centres in fatal COVID-19[39,40], another study did not find abnormal lymph node architecture if tissues with autolysis were stringently excluded[41], so that the role of germinal centres is unresolved.

What do we know from other coronavirus infections?

A study from the Netherlands found that most children were seropositive for antibodies to the nucleocapsid of NL63 by ages 3–6[42]. However, detailed measurements of anti-NL63, or anti-229E or anti-OC43 antibodies, using longitudinal serum samples from adult males over 30 years, shows a pattern of boosted antibodies typically every 1–3 years, presumed to be due to intermittent re-infections, with waning of antibody levels between re-infections[43].

It is also possible that, in these recurrent infections, viral mutation in circulating strains might be as important as waning antibodies, but this is unknown. In the case of HIV-1 infection, chronic viral replication is partly enabled by escape mutants from nAb and chronic germinal centre responses[44]. Therefore, newly arising mutant SARS-CoV-2 strains that can escape nAb[32] will be globally important.

There have been few published studies of memory T cells specific for endemic coronaviruses, and these have shown quite low levels of IFN-γ ELISPOT responses in PBMC, to spike proteins from NL63, 229E or OC43[45], or to nucleocapsid from SARS-CoV-1 in survivors, 17 years after recovery[46]. Notably, these T-cell responses were undetectable in approximately half of the patients studied, which contrasts with the higher prevalence of specific antibodies.

T-cell responses in SARS-CoV-2 infection

Many studies have addressed the early dynamics of the T-cell immune response to SARS-CoV-2 infection[47,48]. During the acute infection, activated, proliferating T cells are readily detected by either flow cytometry[33–35] or single cell RNA sequencing[49], as previously well described for antigen-specific lymphocytes during various other human acute viral infections[22,23,50,51]. Most experimental studies of murine antiviral T cells have concentrated on the acute cytotoxic CD8 T-cell response[28], but eventually it was found that a later germinal centre and nAb response was critical to full viral clearance[52].

Importantly, then, CD4 T-cells responses to SARS-CoV-2 antigens were generally more prevalent in COVID-19 patients than CD8 responses[47,48], although both CD4 and CD8 activated cells are found in some but not all acute patients at day 7[34]. Most studies have used PBMC ELISPOT assays to quantify SARS-CoV-2 specific T cells, but others have used the intracellular cytokine assay or the AIM assay of upregulation of activation markers[47,48], similar to our original OX40 assay[53], to ascribe responses to CD4 or CD8 T-cell subsets. We have confirmed the presence of SARS-CoV-2 specific CD4 T cells in recovered patients in the ADAPT Study at St Vincent's Hospital, Sydney, using the OX40 assay, but like other studies, have found that about half of healthy non-COVD-19 controls had responses to pools of peptides from the full SARS-CoV-2 spike protein sequence, presumably cross-reacting with endemic coronaviruses[54].

SARS-CoV-2 specific memory CD4 and CD8 T cells were still present in recovered patients at 9 months after symptom onset in one study[55], and at 6-8 months in another study, with an apparent half-life of only 3–5 months[56].

We have also concentrated on proliferative CD4 T-cell responses to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein, which we only found in COVID-19 patients and which were highly correlated with the patients' serum anti-spike IgG and IgM antibodies and nAb. Proliferative CD4 T-cell responses will likely allow rapid expansion of RBD-specific CD4 T cells *in vivo*, on re-infection, or vaccination, which will help rapid expansion of RBD-specific memory B cells and boost nAb levels. It has not yet been reported whether the new vaccines induce long-term proliferative memory CD4 T cells.

However, the T-cell response could also possibly be detrimental, since many of the cytokines associated with acute respiratory distress syndrome (ARDS) may involve T cells, particularly those recruiting neutrophils to the lungs, including IL-17 produced by Th17 CD4 T cells[57]. Infected alveolar macrophages may also amplify damaging T-cell pro-inflammatory responses[58], and it has been speculated that development of highly activated cytotoxic T cells may also cause damage by widespread killing of infected epithelial cells in the lung[59].

Recently, two early studies of real-world post-vaccine protection in Israel[60] and in healthcare workers (HCW) in the UK[61] have

reported that vaccine effectiveness was 51% and 72%, respectively. The latter study concluded that HCW will still require PPE and physical distancing, as well as regular testing for asymptomatic infection.

Conclusions

There are many important questions that so far remain unanswered including: (1) whether pre-existing cross-reactive antibodies or T cells influence the outcome of infection; (2) whether, overall, antibodies, T cells and inflammatory cytokines are beneficial or even detrimental; (3) the longevity of natural and vaccinated immune responses; (4) whether individuals with weaker responses are still protected; and (5) whether SARS-CoV-2 mutant strains can evade neutralising antibodies, and could T-cell immunity compensate?

Both short-term innate immunity and the later-to-develop adaptive immunity dictate outcomes to infection, and longer-term adaptive immunity in conjunction with vaccination, will determine whether COVID-19 becomes a relatively benign seasonal illness.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

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