ASSOCIATE PROFESSOR ASHRAFUL HAQUE (Orcid ID : 0000-0003-2260-0026)

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COVID-19: Searching for clues among other respiratory viruses

Catriona Nguyen-Robertson[1*], Justine Mintern[2], Ashraful Haque[1] and Anne Camille La Flamme[3]

[1]Department of Microbiology and Immunology, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia

[2]Department of Biochemistry and Molecular Biology, The University of Melbourne, Melbourne, Australia

[3]School of Biological Sciences, Victoria University of Wellington, Wellington, New Zealand

*Corresponding author email: c.nguyen-robertson@student.unimelb.edu.au

The respiratory tract requires robust immune defences due to its constant exposure to antigens – air pollutants, allergens, and microbes. SARS-CoV-2, the respiratory virus that causes COVID-19, poses a challenge to our immune system in the infected lungs as well as globally in the prevention of its spread. Following the declaration of pandemic status by the World Health Organisation, researchers worldwide have been called arms to develop diagnostic tools, treatments, and prophylactic vaccines to combat the COVID-19 outbreak.

There has been an increasingly rapid stream of information made immediately accessible online at an unprecedented rate, and this information provides a description of the pandemic in real-time. Many key questions about COVID-19, however, remain unanswered because this virus is a new human pathogen and because there is a significant time lag from an individual becoming infected, to then becoming symptomatic, to seeking care and finally being confirmed and reported. In mid-January, there were still only 41 laboratory-confirmed cases, and now there are over 723,000 confirmed cases.[1]

New diagnoses will always precede recovery (or death) by days to weeks, meaning that what we see in real-time is merely the tip of the iceberg. Regional differences in case reporting and number of people tested, and the skewing of those cases being reported towards those with greater severity have made it difficult to predict the outbreak dynamics and determine effective prevention measures (e.g. mortality rate, transmissibility, and so on). To fill the knowledge gap as we increase our knowledge of SARS-CoV-2, outbreak measures have also largely been based on knowledge of similar respiratory viruses.

In this Trending Virtual Issue of *Immunology and Cell Biology*, we present a series of reviews and original articles that highlight key defence mechanisms employed against various respiratory viruses, with an emphasis on influenza. We hope this collection may provide clues for improving immunity to SARS-CoV-2, and preventing severe and life-threatening complications due to COVID19. Innate immune cells, such as airway macrophages and dendritic cells (DCs), form part of the first line of defence in the respiratory tract. Previous infections or vaccinations support the development of specific adaptive immunity including mucosal antibodies and tissue-resident memory T (T_{RM}) cells, which join the innate immune system in the frontline defences. This issue pulls together aspects of innate and adaptive defences as depicted in Figure 1 to better understand our immune defences against respiratory viruses.

Sensing by the innate immune system via pathogen recognition receptors is critical to establish protective immunity against respiratory viruses. Mifsud *et al.* (① in Figure 1) demonstrated that the toll-like receptor 2 (TLR-2) agonist, S-(2,3-bis(palmitoyloxy)propyl) cysteine (Pam_2Cys), can provide antigen-independent protection against influenza A virus challenge by inducing an influx of innate immune cells into the lungs and increasing the production of pro-inflammatory cytokines upon viral challenge.[2] Not only does this TLR-2-mediated response protect against primary influenza infection, it additionally reduces the severity of secondary *Streptococcus pneumonia* infections, thus providing both immediate and long-term protection (② in Figure 1).[3] Mifsud and colleagues hence propose a Pam_2Cys-based vaccine for use in the midst of an influenza outbreak, which may prove useful as an adjuvant for a SARS-CoV-2 vaccine.

Lung-resident macrophages play an integral role in maintaining homeostasis in the lungs and responding to viral pathogens, as outlined in a review by Puttur *et al.* (③ in Figure 1).[4] Upon challenge, lung-resident macrophages are highly phagocytic and are primary inductors of innate immune defences through pro-inflammatory cytokine signalling and stimulation of protective antibody responses.

Natural killer (NK) cells also are important in anti-viral immunity, predominantly by rapidly killing virus-infected cells, as well as priming other immune cells through the production of cytokines. NK cells induce apoptosis in virus-infected host cells by producing cytotoxic granzyme B in a mechanism regulated by endogenous cytosolic granzyme B inhibitor, serpinB9.[5] Mangan *et al.* (④ in Figure 4) describe the importance of serpinB9 in enhancing cytotoxic killing by NK cells early in viral infections, and later, $CD8^+$ T cells.[6]

Bridging the innate and adaptive immune systems, there is increasing evidence that innate-like mucosal-associated invariant T (MAIT) cells play a role anti-viral immunity (⑤ in Figure 1).[7] MAIT cells typically recognise microbial ligands using their TCRs, but can also be activated in a TCR-independent manner. The production of type 1 IFN, IL-12 and IL-18 by monocytes activates MAIT cells (and NK cells) to produce IFN-γ and granzyme B.[7, 8] Through the induction of the inflammasome, TLR-8 and, to a lesser extent, TLR-3 signalling induces the production of IL-18, which in turn, activates MAIT cells early on in infection.[8]

Integral to viral clearance and the formation of immunological memory is the adaptive immune response. $CD8^+$ cytotoxic T cells recognise viral peptides that are presented by MHC-I molecules of infected cells. Szomolay *et al.* (⑥ in Figure 1) developed a combinatory peptide library and method for scanning viral peptides recognised by individual MHC-I-restricted T cell clones[9], a useful tool to delineate the requirements for effective $CD8^+$ T cell-mediated immunity against particular viruses.

Following clearance of acute respiratory viral infection, $CD8^+$ memory T cells populate the lung mucosal tissue to contribute to immune defence against secondary encounters with the same virus. During infection, DC-priming controls the generation of lung-resident memory T cells,[10] and inflammatory monocytes contribute to their longevity and persistence (⑦ in Figure 1).[11] Interestingly, innate factors required for the generation of primary anti-viral responses by $CD8^+$ T cells are not always required for effective recall responses to secondary challenge with an antigen or virus (⑧ in Figure 1).[12]

Antibodies also mediate processes that aid in viral clearance, such as neutralisation, antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). In addition to neutralising extracellular viruses to inhibit their entry into host cells, the antibody Fc region acts as a binding site for Fc receptors (FcR) and complement factors. ADCC and ADCP initiated when immune cells, including NK cells, macrophages, monocytes, and neutrophils, are activated via their FcR receptors binding IgG bound to viral antigens on the surface on infected host cells. Complement factor C1q also interacts with IgG or IgM, bound to viral particles or infected cells, to form the membrane attack complex to a similar end. The uptake of opsonised virions also aids viral clearance by enhancing phagocytosis. A review by Vanderven and Kent (⑨ in Figure 1) discusses the

protective and therapeutic potential of Fc-mediated antibody functions in anti-viral immunity.[13] Additionally, Almudevar (⑩ in Figure 1) proposes a model for the regulation of follicular dendritic cells, which are responsible for the long-term persistence of antibodies, with particular emphasis on antibody longevity following vaccination.[14]

When considering inducing protective immunity to respiratory viruses with a vaccine, both the virology and host-pathogen responses must be considered. For example, Lawler *et al.* (⑪ in Figure 1) observed that viral latency genes were not required in a vaccine for protective immunity against murid herpesvirus-4, and therefore can be deleted to generate safe and effective vaccines.[15]

The airways employ multiple anti-viral mechanisms that span both the innate and adaptive immune systems. The innate immune response acts rapidly in a pro-inflammatory fashion to limit viral load and impacts subsequent adaptive responses. A thorough understanding of the virus-host interactions during respiratory infections will be pivotal to ultimately meet the challenges we face with SARS-CoV-2 and similar viral infections. We hope this collection may provide clues for improving immunity to SARS-CoV-2, and preventing severe and life-threatening complications due to COVID19.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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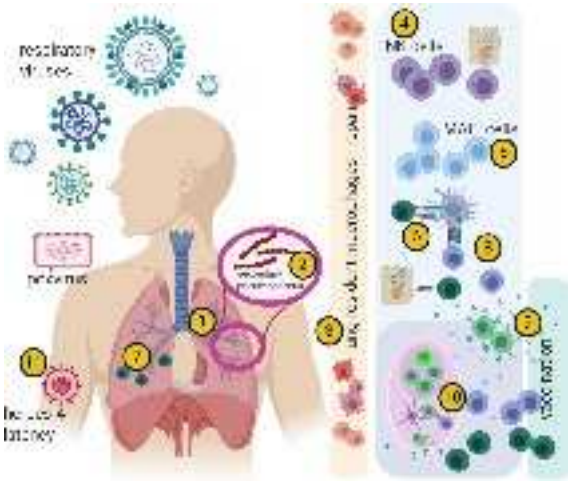
FIGURE LEGENDS

Figure 1. Innate and adaptive immune processes during respiratory viral infections. The circled numbers in the figure link to the selected Virtual Issue articles as noted in the text.



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