The complex immunological pathogenesis behind COVID-19

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Since the first appearance of the novel coronavirus disease (COVID-19), in Wuhan, China, in December 2019, it took only a couple of months for the outbreak to be declared as a pandemic by the World Health Organization (WHO)[1,2]. The newly emerged virus belongs to the broad family of viruses known as coronaviruses. The international virus classification commission named the novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based upon its genetic relationship to the original SARS-CoV that caused an outbreak of the disease in 2002-2003.

The clinical symptoms and signs of patients infected with SARS-CoV-2 are not pathognomonic, many times patients develop only part or none of the typical symptoms of COVID-19 infection (Fig.1.). Most patients exhibit mild to moderate symptoms, but approximately in 15% of cases the disease progresses into severe pneumonia and about 5% eventually develop acute respiratory distress syndrome (ARDS), septic shock, and/or multiple organ failure[3]. Severe cases have been mainly reported among elderly and adult patients with comorbidities[4], children and teens usually experience mild symptoms or in many cases go through without any signs or symptoms.

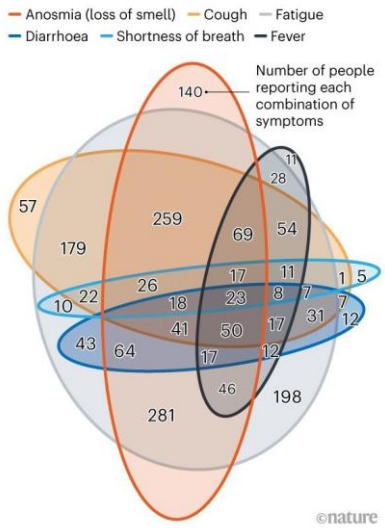

Fig.1. Common symptoms experienced by people who tested positive for COVID-19 (source: https://www.nature.com/articles/d41586-020-00154-w).

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[1] "WHO Director-General's opening remarks at the media ...." https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---20-april-2020.
[2] "[The epidemiological characteristics of an outbreak of 2019 ...." https://www.ncbi.nlm.nih.gov/pubmed/32064853.
[3] "Pathological findings of COVID-19 associated with acute ...." 18 Feb. 2020, https://www.thelancet.com/lanres/article/s2213-2600(20)30076-x.
[4] "COVID-19: immunopathology and its implications for therapy ...." 9 Apr. 2020, https://www.nature.com/articles/s41577-020-0308-3. Accessed 23 Apr. 2020.

The mainstay of clinical treatment consists of symptomatic management and oxygen therapy, with invasive mechanical ventilation for patients with respiratory failure. Currently, no clinically proven specific antiviral agents are available for SARS-CoV-2 infection, but several antiviral drugs (e.g. remdesivir) and repurposed drugs are investigated and being actively tested[5,6] to fight the disease. In addition to vaccine development and approaches that directly target the virus or block the entry of the virus in cells, treatments that address the immunopathology of the infection have become a major focus[7]. Rapid genomic sequencing, open-access data, together with advanced technologies are expected to facilitate our understanding and to give us more knowledge on the pathogen itself, including the host immune response as well as a plan for near future therapeutic options[8].

The occurrence and course of SARS-CoV-2 infection depend on the interaction between the virus and the individual's immune system. Viral factors include virus type, mutation, viral load, viral titer, and viability of the virus in vitro. Immune system related factors include genetics (such as HLA genes), age, gender, nutritional status, neuroendocrine-immune regulation, and physical status. These factors all need to be considered in the treatment strategy.

Currently, the complete immunopathogenesis of the disease is unclear, we don't have a full understanding of all the molecular interactions between SARS-CoV-2 and its host (a.k.a us, people), but we have many pieces of the puzzle and they are crucial in the identification of immunological determinants of a poor prognosis that can help us prevent the worst outcome of COVID-19. With this writing, we aim to summarize some pieces of this puzzle.

Antigen presentation in coronavirus infection

After the virus enters the cells with the help of ACE2 cell surface receptors[9],its antigen (fragmented viral protein particles) will be presented by the major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) and then recognized by virus-specific cytotoxic T lymphocytes (CTLs). HLAs basically will serve as warning flags to alert immune cells and start the process of antibody production to further target and eliminate infected cells. Depending on individual HLAs, our body may be differently equipped to fight off certain viruses, including SARS-CoV-2. Individual genetic variation across MHC genes may help to explain different immune responses to a virus across a population. In particular, understanding how variation in HLA may affect the course of COVID-19 could help identify individuals at higher risk from the disease.

Previous research on related virus strains (SARS-CoV and MERS-Cov) shows that the antigen presentation of SARS-CoV mainly depends on MHC I molecules[10]. Still, MHC II also contributes to its presentation. Numerous HLA polymorphisms correlate to the susceptibility of SARS-CoV,

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[5] "Network Medicine Framework for Identifying Drug ...." 15 Apr. 2020, https://arxiv.org/abs/2004.07229.

[6] "Existing Drugs Could Be Key To Combatting Coronavirus ...." https://www.technologynetworks.com/drug-discovery/news/existing-drugs-could-be-key-to-combatting-coronavirus-outbreak-331473.

[7] "COVID-19: immunopathology and its implications for therapy ...." 9 Apr. 2020, https://www.nature.com/articles/s41577-020-0308-3.

[8] "Immune responses in COVID-19 and potential vaccines ...." https://www.ncbi.nlm.nih.gov/pubmed/32105090.

[9] "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 ...." 16 Apr. 2020, https://www.sciencedirect.com/science/article/pii/S0092867420302294.

[10] "Novel immunodominant peptide presentation strategy ... - NCBI." 15 Sep. 2010, https://www.ncbi.nlm.nih.gov/pubmed/20844028.

such as HLA-B∗46:01[11], HLA-B∗07:03, HLA-DR B1∗12:02[12], and HLA-Cw∗08:01[13], whereas the HLA-DR*03:01, HLA-Cw15:02 and HLA-A∗02:01 alleles are related to the protection from SARS infection[14]. In MERS-CoV infection, MHC II molecules, such as HLA-DRB1∗11:01 and HLA-DQB1∗02, are associated with the susceptibility to MERS-CoV infection[15].

In a recent study, researchers used in silico computer analysis to predict which combination of HLAs might be best at presenting and binding SARS-CoV-2. If certain HLAs can bind well to a large proportion of the virus's proteins, a more protective immune response could be expected, but the stability of the binding will also affect the response. They concluded that individual HLA genotypes may differentially induce the T-cell mediated antiviral response and could potentially alter the course of the disease and its transmission[16].

Activation of the innate and adaptive immune response

SARS-CoV-2 infection can activate innate and adaptive immune responses. The above-described antigen presentation subsequently stimulates the body's humoral immunity (mediated by antibodies and proteins of the complement system) and cellular immunity (activating phagocytes, virus-specific B and T cells, and various cytokines).

Similar to common acute viral infections, the antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG production, which is also the basis for disease diagnosis, aside from RT-PCR testing. The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role[17].

However, two studies, based on the analysis of patients with COVID-19, reported that patients with severe disease frequently had an increased IgG response and a higher titre of total antibodies, which was associated with worse outcome[18,19]. This was suggestive of possible antibody-dependent enhancement (ADE) of SARS-CoV-2 infection. The immunopathological effects of ADE have been observed in various viral infections, characterized as antibody-mediated enhancement of viral entry and induction of a severe inflammatory response[20]. A

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[11] "Association of HLA class I with severe acute respiratory ... - NCBI." 12 Sep. 2003, https://www.ncbi.nlm.nih.gov/pubmed/12969506.
[12] "Novel immunodominant peptide presentation strategy ... - NCBI." 15 Sep. 2010, https://www.ncbi.nlm.nih.gov/pubmed/20844028.
[13] "Epidemiological and Genetic Correlates of Severe Acute ...." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392693/.
[14] "Human-leukocyte antigen class I Cw 1502 and class II DR ...." 29 Sep. 2011, https://www.ncbi.nlm.nih.gov/pubmed/21958371.
[15] "Association of human leukocyte antigen class II alleles ... - NCBI." https://www.ncbi.nlm.nih.gov/pubmed/27512511.
[16] "Human leukocyte antigen susceptibility map for SARS-CoV-2 ...." https://jvi.asm.org/content/early/2020/04/16/JVI.00510-20.
[17] "Profile of Specific Antibodies to the SARS-Associated ...." 31 Jul. 2003, https://www.nejm.org/doi/full/10.1056/NEJM200307313490520.
[18] "Antibody responses to SARS-CoV-2 in patients of novel ...." https://www.ncbi.nlm.nih.gov/pubmed/32221519.
[19] "Immune phenotyping based on neutrophil-to-lymphocyte ratio ...." 16 Mar. 2020, https://www.medrxiv.org/content/10.1101/2020.03.12.20035048v1.
[20] "COVID-19: immunopathology and its implications for therapy ...." 9 Apr. 2020, https://www.nature.com/articles/s41577-020-0308-3.

potential pathogenic effect of antibodies targeted at SARS-CoV-2 would be of major concern for vaccine development and antibody-based therapies[21].

Compared to humoral responses, there is more research on the cellular immunity of coronavirus. The latest report shows that uncontrolled inflammatory innate responses and impaired adaptive immune responses may lead to harmful processes, both locally and systemically. In patients with severe COVID-19 infection, but not in patients with mild disease, the number of CD4+ and CD8+ T cells, B cells, and natural killer cells in the peripheral blood is significantly reduced, a syndrome called lymphopenia[22,23,24].

Cytokine storm in COVID-19

It was observed that most of the damage to the lung in severe cases is due to severe inflammation processes rather than direct damaging effect of the virus itself. In other words, it is the exaggerated immune response, which is responsible for severe pneumonia and, consequently, respiratory failure. Similar to severe cases of SARS, in SARS-CoV-2 patients usually present with fever and cough while the virus is rapidly replicating in their lungs. About a week later, their condition spontaneously improves, as the immune system kicks in. But in some of the cases, a second phase of the disease starts. In these patients, the second stage is much severe, and it is not caused by the virus at all but by patients' "runaway" immune systems. For unclear reasons, especially, but not exclusively, in the case of elderly and/or sick,, the inflammatory response is not turned off, leading immune cells and inflammation-inducing molecules known as cytokines (Fig.2.) including IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, CCL3 and TNF to flood into the lungs. This so-called "cytokine storm" is one of the main mechanisms for ARDS[25].

[21] "Precision COVID-19 Vaccine with Companion Diagnostics ...." https://precisionnanomedicine.com/article/12561-precision-covid-19-vaccine-with-companion-diagnostics.
[22] "Clinical features of patients infected with 2019 novel coronavirus." 24 Jan. 2020, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext.
[23] "Dysregulation of immune response in patients with COVID-19 ...." 12 Mar. 2020, https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa248/5803306.
[24] "Pathological findings of COVID-19 associated with acute ...." 18 Feb. 2020, https://www.thelancet.com/lanres/article/s2213-2600(20)30076-x.
[25] "The Possible Immunological Pathways for the Variable ...." 19 Mar. 2020, http://www.ejgm.co.uk/download/the-possible-immunological-pathways-for-the-variable-immunopathogenesis-of-covid-19-infections-among-7850.pdf.

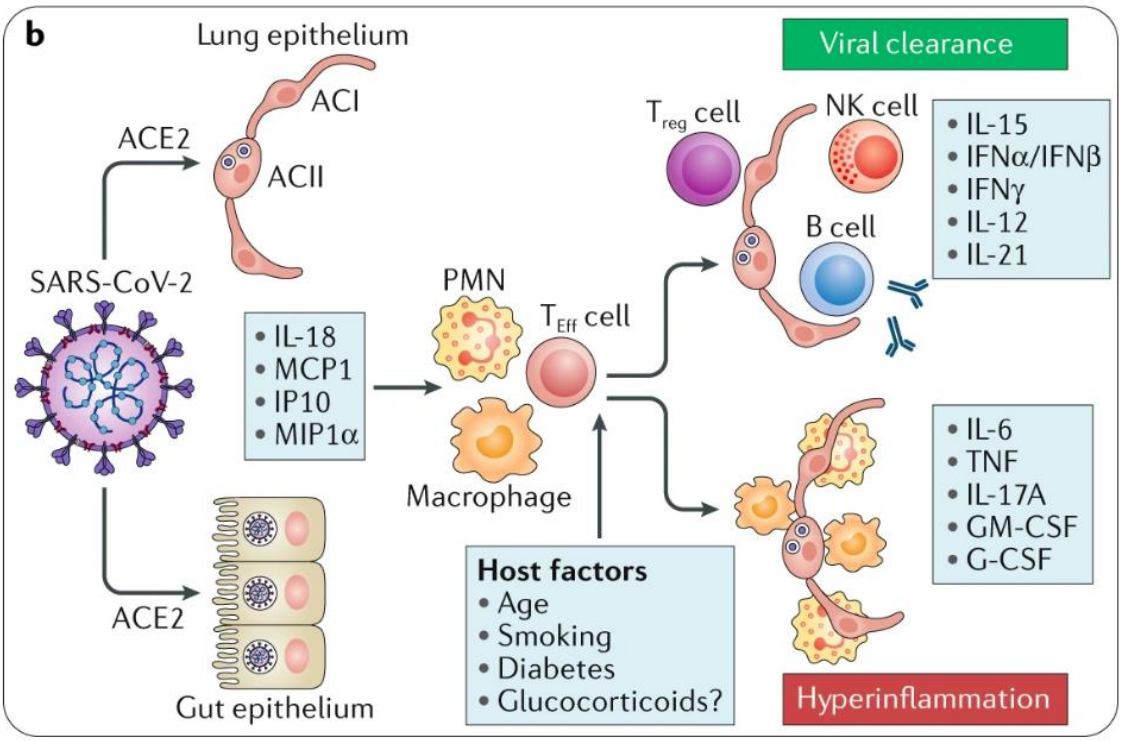

Fig.2. Cytokine pathogenesis of COVID-19 (source: Schett, G., Sticherling, M., & Neurath, M. F. (2020). COVID-19: risk for cytokine targeting in chronic inflammatory diseases. *Nature Reviews Immunology*, 1-2.).

A number of studies have tried strategies to dampen inflammatory responses. Elevated levels of IL-6 and ferritin were found to be a stable indicator of poor outcome in patients with severe COVID-19 with pneumonia and ARDS. One promising clinical trial, using the IL-6 receptor-targeted monoclonal antibody tocilizumab, reported quick control of fever and improvement of respiratory function in patients with severe COVID-19 [20].

While a detailed clinical picture of the COVID-19 pandemic continues to emerge, taking into consideration the complexity of some of the above described immunopathological events, a clearer understanding of these mechanisms and their effects is still vital in the interest of accelerated progress towards improved treatments in COVID-19. Therefore, the aim of this review was to elucidate on the aspects of COVID-19 immunopathogenesis and prompt further thorough investigations.