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Immunology for covid-19:literature of Review

Areport

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Abstract

With the worldwide spread of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) resulting in declaration of a pandemic by the World Health Organization (WHO) on March 11, 2020, the SARS-CoV-2-induced coronavirus disease-19 (COVID-19) has become one of the main challenges of our times. The high infection rate and the severe disease course led to major safety and social restriction measures worldwide. There is an urgent need of unbiased expert knowledge guiding the development of efficient treatment and prevention strategies. This report summarizes current immunological data on mechanisms associated with the SARS-CoV-2 infection and COVID-19 development and progression to the most severe forms. We characterize the differences between adequate innate and adaptive immune response in mild disease and the deep immune dysfunction in the severe multiorgan disease. The similarities of the human immune response to SARS-CoV-2 and the SARS-CoV and MERS-CoV are underlined. We also summarize known and potential SARS-CoV-2 receptors on epithelial barriers, immune cells, endothelium and clinically involved organs such as lung, gut, kidney, cardiovascular, and neuronal system, The immune response to SARS-CoV-2 reveals a delicate balance between protective effects and harmful pathological reactions and can possibly explain the highly variable disease manifestations in subjects infected with this novel coronavirus. A better understanding of the anti-viral immune response is not only critical for vaccine development but might also provide targets for pharmaceutical and immunological treatment options

Introduction

Infections with the novel coronavirus SARS-CoV-2 resulting in COVID-19 development represent the major medical and scientific challenges of our time. Knowledge on SARS-CoV-2 infection pathways and mechanisms associated with immune defense or immunopathology is growing exponentially, as it is indispensable to design the proper diagnostic and therapeutic strategies. However, there are several knowledge gaps and urgent unmet research needs in our understating of the current pandemics. A group of experts in basic and clinical immunology has joined forces under the umbrella of the European Academy of Allergy and Clinical Immunology (EAACI) to provide a consensus report on the basic molecular and immune mechanisms associated with susceptibility, clinical presentations and severity of COVID-19

IMMUNOLOGY:

DEVELOPMENT AND FAILURE OF AN ADEQUATE IMMUNE RESPONSE

Monocytes/macrophages and DCs play a crucial role in anti-viral responses by linking innate and adaptive immunity. Peripheral activation and accumulation of activated pro-inflammatory monocytes/macrophages within lungs has become one hallmark of symptomatic SARS-CoV-2 infection.(R, Fehr A et,2016) *In contrast, the exact role of interactions between DCs and SARS-CoV-2 has not been determined yet. Previous in vitro experiments showed that different human coronaviruses display either high (229E) or poor (OC43) capacities to infect macrophages***[Yilla M, et,2005]**

*The efficiency of macrophage infection by coronaviruses was negatively correlated with IFN-α production***[Yilla M, et,2005]**

*In COVID-19 patients, ACE2 expression was detected on both lymph node-associated CD68 + macrophages and tissue-resident CD169 + macrophages***[Chen Y, et,2020.2003.2004]**

*It needs to be addressed, however, whether other proven and potential SARS-CoV-2 receptors, such as CD147 or CD209 (DC-SIGN), both being expressed by monocytes/macrophages and DCs can facilitate viral entry to these cells***[Wang K, et:2020.2003.2014]**

*Recently, SARS-CoV-2 particles were found in macrophages, but it remains elusive whether these findings were an effect of active cellular infection or just the consequences of physiological phagocytosis. It is tempting to speculate that SARS-CoV-2, similarly to HIV, can use macrophages as a Trojan horse contributing to viral spread***[Chen Y, et, 2020; preprint: 2020.2003.2027.2004]**

Regardless of the exact mechanism of viral entry, both previously described coronaviruses and the new SARS-CoV-2 can trigger NLRP3 inflammasome activation in monocytes/macrophages, production of high levels of pro-inflammatory mediators such as IL-6, GM- CSF, IL-1β, TNF, CXCL-8, CCL-3,

and enhanced cell death. Subsequently, it may lead to the cytokine storm also known as cytokine release syndrome (CRS) (Figure 4)[Ratajczak M,.2020]

*Some of these cytokines (ie, IL-6) are mainly secreted by macrophages,***[Liao M, 2020; preprint: 2020.2002.2023.2002]**

*and the evidence of macrophage activation syndrome has been reported.77 Thus, beneficial effects of anti-IL-6R treatment on COVID-19 outcomes indicate that therapies targeting macrophage-related activities can become promising means to inhibit the inflammatory storm in the course of coronavirus disease.***[Zhou M,2020]**

*Overloaded, activated and subsequently dying macrophages might contribute to an increase in the levels of plasma ferritin and profound dysregulation of iron metabolism.***[Nairz M,2017]**

*ferritin levels are common clinical findings in patients with severe COVID-19***[Velavan ,2020**

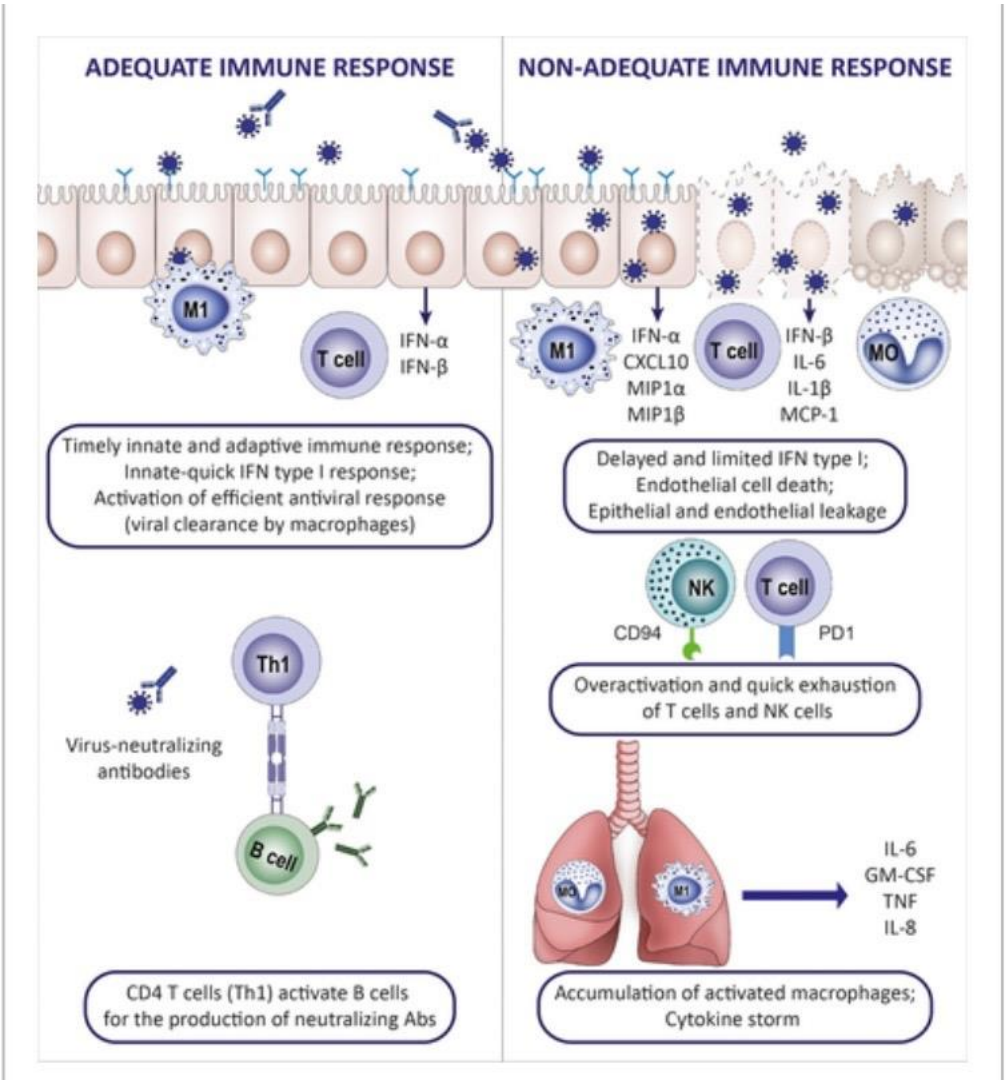

FIGURE 4Immunology of adequate and nonadequate response to SARS-CoV-2 infection. The clinical course of the SARS-CoV-2 infection varies from an asymptomatic to a severe, life-threatening syndrome. The number of asymptomatic carriers is unknown, and virus detection is often accidental. Data on the immune characteristics in this group are lacking. Patients who experience mild symptoms are characterized by a transient, slight decrease in lymphocyte counts and an increase in neutrophil counts in the peripheral blood. Viral clearance in this group is convergent in time with the specific antibody production. Delayed and limited IFN type I response in combination with the overactivation of pro-inflammatory cytokine response has been suggested as a possible mechanistic explanation of hyperinflammatory syndrome in COVID-19 patients presenting with severe clinical manifestations: respiratory insufficiency, kidney failure, thromboembolic, and other complications. Severe COVID-19 is characterized by a systemic cytokine release syndrome (CRS), increased levels of LDH and CRP, hypoalbuminemia, deepening decrease in lymphocyte counts and immune exhaustion of T cells

PCR tests are useful for detecting SARS-CoV-2 RNA in an upper respiratory (preferably a nasopharyngeal) specimens. In addition, a number of diagnostic procedures to assess immunity built against SARS-CoV-2 are still .being developed, validated, and optimized

*Antibody testing is evolving, and the market is flooded with test kits (both ELISA and rapid tests in the form of lateral flow immunoassays). However, only a small number of these kits are certified, and the results need to be interpreted with caution. Preliminary data indicate that COVID-19 presents with a classical antibody response consisting of early induction of IgM, followed by IgA and IgG antibodies (Figure 7)***[Huang AT,et 2020; preprint: 2020.2004.2014]**

*. IgG seems to appear early in the course of clinical presentation probably due to the relatively long incubation period. However, there is not yet enough evidence with regard to the development of long-term protective immunity. Antibody testing is so far more valuable in mapping the situation in individual populations, as planned by the WHO in the Solidarity II project.***[Vogel G, Science. 2020.]** *Test kits for the assessment of SARS-CoV-2-specific T-cell responses for diagnostic use are currently not available*

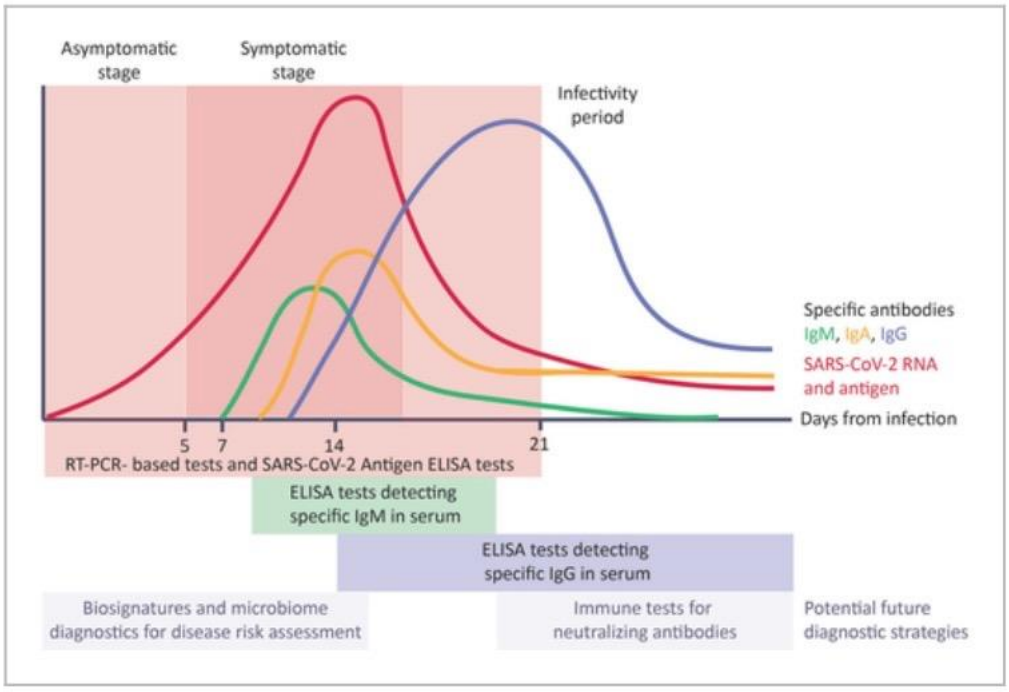

FIGURE 7: Clinical stages of COVID-19 and their virology and immunological assessment. The success of restraining SARS-CoV-2 transmission depends on accurate and timely diagnostics. Asymptomatic patients transmit SARS-CoV-2. RT-PCR-based test detecting the SARS-CoV-2 RNA in posterior conchae nasal swabs are currently the golden standard in the initial phase of the infection. Viral antigens can be detected in patients' blood by means of ELISA tests. ELISA tests allow for detection of virus-specific antibodies in patients' serum. The production of specific IgM starts after about a week from infection and IgM levels decrease with the production of specific IgG (after about 2 wks from infection). Novel diagnostic and risk-stratification strategies could include microbiome profiling and tests detecting neutralizing antibodies

IMMUNOLOGICAL BIOMARKER PROFILING OF COVID- 5 19 FOR PREDICTION OF DISEASE SEVERITY

*The development of serious complications and even fatal outcome in SARS-CoV-2 infection is strongly linked to the patients' immune response resulting in CRS***[ToMehta P,et, 2020***]*

*There is an urgent need for biomarkers that predict patients developing severe complications.***[Sotgiu G, , et,2020]** *date, there is limited information on the biomarkers associated with, or even predicting severe complications in COVID-19. However, there is much similarity on the biomarkers that have been described before for MERS-CoV and SARS-CoV, also β-coronaviruses, but also with sepsis. Many markers have been demonstrated to be increased in SARS-CoV-2-infected individuals. These markers are related to innate as well as adaptive immunity, endothelial cell activation, thrombocyte activation, and leukocyte infiltration***[Huang C,et. 2020]**

*The list of markers related to severe disease, ICU, and even lethality is more limited. In ICU-admitted COVID-19 patients, significant increases of D-dimer, ferritin, LDH, IL-6, high sensitivity cardiac troponin, IL-2, IL-7, G-CSF, MCP-1, MIP-1α, and TNF-α were reported.201 An even more restricted group of markers (IL-10, MCP-3, IL-1ra) were increased in severe and lethal cases. Differences in the biomarkers described are most probably due to the different sampling time during disease and the large heterogeneity between the patients***[Huang C, et, 2020]**

Most likely, single biomarkers will not be predictive. On the other hand, a combination of markers (a biosignature) will help in patient stratification and may even guide patients-tailored therapy

REFERENCE:

41Channappanavar R, Fehr A, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 2016;19(2):181-193.
Wang A, Chiou J, Poirion OB, et al. Nucleus multiomic profiling reveals age-dynamic regulation of host genes associated with SARS-CoV-2 infection. bioRxiv. 2020; preprint:2020.2004.2012.037580.
Liao M, Liu Y, Yuan J, et al. The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing. medRxiv. 2020; preprint: 2020.2002.2023.20026690.
Yilla M, Harcourt BH, Hickman CJ, et al. SARS-coronavirus replication in human peripheral monocytes/macrophages. Virus Res. 2005;107(1):93-101.
Chen Y, Feng Z, Diao B, et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes . medRxiv. 2020; preprint: 2020.2003.2027.20045427.
Wang K, Chen W, Zhou YS, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv. 2020;preprint:2020.2003.2014.988345.
Yang Z-Y, Huang Y, Ganesh L, et al. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN. J Virol. 2004;78(11):5642-5650.

Lozach PY, Burleigh L, Staropoli I, Amara A. The C type lectins DC-SIGN and L-SIGN: receptors for viral glycoproteins. Methods Mol Biol. 2007;379:51-68.
Cai G, Cui X, Zhu X, Zhou J. A hint on the COVID-19 Risk: population disparities in gene expression of three receptors of SARS-CoV. In. www.preprints.org, https://doi.org/10.20944/preprints202002.040
Park MD. Macrophages: a Trojan horse in COVID-19? Nat Rev Immunol. 2020;20(6):351.
Ratajczak MZ, Kucia M. SARS-CoV-2 infection and overactivation of Nlrp3 inflammasome as a trigger of cytokine "storm" and risk factor for damage of hematopoietic stem cells. Leukemia. 2020;1-4.
Chen IY, Moriyama M, Chang MF, Ichinohe T. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. Front Microbiol. 2019;10:50.
Liu LI, Wei Q, Lin Q, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight. 2019;4(4).

McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020;19(6):102537.
Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): A clinical update. Front Med. 2020;14(2):126-135.
Nairz M, Theurl I, Swirski FK, Weiss G. "Pumping iron"-how macrophages handle iron at the systemic, microenvironmental, and cellular levels. Pflugers Arch. 2017;469(3–4):397-418.

, Soares MP, Hamza I. Macrophages and iron metabolism. Immunity. 2016;44(3):492-504.

Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis. 2020;95:304-307. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034
Sotgiu G, Gerli AG, Centanni S, et al. Advanced forecasting of SARS-CoV-2-related deaths in Italy, Germany, Spain, and New York State. Allergy. 2020;75:1813-1815.
Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China Lancet. 2020;395(10223):496.
Yang Y, Shen C, Li J, et al. Exuberant elevation of IP-10, MCP-3, and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcomes. med Rxiv preprint. 2020.
Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. medRxiv. 2020; preprint: 2020.2004.2014.20065771.
Vogel G. These are answers we need. WHO plans global study to discover true extent of coronavirus infections. Science. 2020.

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