VOLUME - 11, ISSUE - 02, FEBRUARY - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medicine

THE ROLE OF IMMUNITY IN SCRUTINIZING OMICRON VARIANT

Prof Dr M.V. Raghavendra Rao	Department of Medicine, Apollo Institute of Medical Sciences And Research, Jubilee Hills, Hyderabad, Telangana, India. *Corresponding Author
Dilip Mathai	Department of Medicine, Dean, Apollo Institute of Medical Science And Research, Hyderabad, Ts, India
Manick Dass	Department of Microbiology, Apollo Institute of Medical Sciences And Research, Hyderabad, Ts, India
Mahendra Kumar Verma	Department of Biological Sciences, American University School of Medicine, Aruba, Netherlands,

ABSTRACT Immunology is truly a fascinating discipline that meets the challenge and offers opportunity in fighting and checking the spread of diseases. Many viruses infect humans.The corona virus disease 2019 (COVID-19) pandemic has affected hundreds of millions of people over the world, with more than 4.5 million deaths.The introduction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the human population represents a tremendous medical , economic crisis that remains a world health concern.SARS-CoV-2 infection causes excessive production of pro-inflammatory cytokines thereby leading to the development of "Cytokine Storm Syndrome The COVID-19 pandemic triggered an unparalleled pursuit of vaccines to induce specific adaptive immunity, based on virus-neutralizing antibodies and T cell responses.Cytokines are cellular signaling molecules that mediate many biological and immunological actions. Omicron infection can increase immunity against Delta variant, but only if you are vaccinated against coronavirus.

KEYWORDS : Adaptive immune response,"Cytokine Storm Syndrome."Innate immunity,TNF- , IL-6, CCR1, CCR3, cytotoxic T cells,IgG antibodies,Genetic drift,Innate immunity,

INTRODUCTION

After entering into target cells following Spike protein association with its receptor , viral RNA is encapsulated and polyadenylated, and encodes various structural and non-structural polypeptide genes. These polyproteins are cleaved by proteases that exhibit chymotrypsin-like activity

In December 2019, Chinese health authorities identified unusual cases of patients with unknown pneumonia in Wuhan City, Hubei Province

The clinical symptoms of patients included pyrexia, cough, fatigue, acute respiratory distress, reduced or normal white blood cells, lymphopenia, etc

Due to the lack of vaccines and definitive treatment, the number of people dying of lab-confirmed COVID-19 are being increased and most of them are elderly people aged 65 years or more.

Coronaviruses (CoVs) are a member of the Coronaviridae family with positive.sense single- stranded RNA. In recent years, the CoVs have become a global problem to public health.

It seems currently impossible to prove or disprove theories about the origin of this virus

Coronavirus disease 2019 (COVID-19) , caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rather heterogeneous disease

Disease courses range from mainly asymptomatic and mild courses to more severe and critical courses in 10%–20% of symptomatic patients who are at considerable risk of fatality with many different organ systems involved in differing combinations and with variable symptoms

The virus , and the host can contribute to disease heterogeneity suggest that viral genetic diversity, genetic evolution, variable infectivity, observed for COVID-19.

The coronavirus infectious disease 2019 (COVID-19) pandemic has had devastating global impacts on human health and the economy. Caused by a novel virus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 is heterogeneous in clinical presentation and outcome.

While long-term health implications of SARS-CoV-2 infection are unknown, acute symptoms can cause respiratory, intestinal, kidney and neurological complications as well as loss of smell and taste

Chronological record of significant events

Immunity against smallpox.----------Edward Jenner
Coined the term vaccine----------Louis Pasteur
Importance of cells in immunity------.Metchnikoff-
Humoral theory----------Emil Von Behring
Alexin as complement---------- Bordet.
Cellular immunity ----------Robert Koch-
Anaphylaxis----------Richet
Immunological tolerance----------Burnet-
Nature and structure of Antibody---------Edelman and Porter-
MHC genes----------Benacerraf, Snell and Dauset--
Monoclonal antibody----------Milstein
Human Immunoglobulin-G ----------Morell, B Roth-Wicky, F Skvaril -

Transmission

Severe acute respiratory syndrome (SARS) coronaviruses are spread primarily by droplet transmission.Coronaviruses can be transmitted by this airborne route. Transmission by fomites is not very common. It occurs when contaminated surfaces are touched by a person who subsequently touches his eyes, nose or mouth mucosa. High viral RNA load has been recovered from surfaces from the rooms of patients with COVID-19, and viable virus survives on surfaces for at least 1-2 hours. The virus has been detected in blood, body fluids and stools. However, transfusion transmitted COVID-19 has not been

documented so far and is unlikely.

The immune response to viral infections

First phase-1

Innate immune response. General response to any infection . Innate immune response cells secrete interferons1 and other chemicals (cytokines). Interferons interfere with virus replication . Phase 2 is triggered

Second Phase-2

Adaptive immune response. Specific response to the infection

Innate immunity and COVID 19

Innate immunity is the first line of defense against virus invasion. The dendritic cells, macrophages, and neutrophils are the first line of defense and initiate the initial immune reaction upon entry of SARS-CoV-2.Macrophages are the large eaters. The attachment of antigens to macrophage is specific. All the macrophages have specific receptors for C3 component of complement as well as Fc component of antibody. Neutrophils only migrate into tissue if there is inflammation. Macrophages produce secrete IL-6 and IL-I .These cells produce delayed or suppressed type 1 IFN response.Dendritic cells produce proinflammatory cytokines and chemokines like TNF- , IL-6, CCR1, CCR3 and CCR5. These cells show delayed type 1 IFN response.. Natural killer cells are decreased .Exhaustion of NK cells show high expression of NKG2A and low expression of TNF- , IL-2, CD107 , IFN- and decreased cytotoxicity, reduced performance and granzyme secretion The spike glycoproteins (S protein) on the viral envelope binds to its receptor, ACE2, on the surface of human cells to gain entry. This virus entry activates the intracellular pattern recognition receptors (PRRs) that sense the virus associated molecular patterns, such as double-stranded RNA or uncapped mRNA. This triggers the cascade of the cytolytic immune responses, mainly through the type I interferons (IFN) and natural killer cells. Interleukin 6, IL-18 are also released.

Adaptive immunity:

The adaptive response: T cells

Adaptive immunity plays a major role in the clearance of SARS-CoV-2 from the body and consists of cell mediated immunity and humoral immunity.

T cells (cellular response

Types of T cells: CD8+ cytotoxic T cells kill the cells in which the virus is multiplying and help to slow down or stop the infection. CD4+ helper T cells bring in other cells of the immune system and stimulate B-Cells to produce antibodies specific to that virus.

The adaptive response: B cells

B Cells (Antibody response) - produce antibodies that are specific to that virus. - IgM antibodies are produced first and disappear after a few weeks. - IgG antibodies are produced at the same time or 2-3 days later, and titres (levels) usually remain for months or years.

- Memory cells respond rapidly if they come in contact with the same virus again, killing the virus and accelerating an antibody response.

Critical aspects of antibodies (Abs)

Do the Abs neutralize the virus (block it entering cells and multiplying)? Abs develop against different proteins that are part of a virus. Abs against one type of viral protein might neutralize the virus, while others might not. How many antibodies are produced (titre)? Duration: how long do the antibodies persist in the body after infection?

Critical aspects of viral protein.(Antigens)

Antigen stability: Viruses may mutate over time. Viral proteins may change so much that antibodies produced against the virus won't recognize the antigens if they meet again laterThe positive antibody indicates that the person was infected in the past with the virus that causes COVID-19 If IgM and IgG are positive, infection was recent (i.e. within the past few weeks) If only IgG is present, the infection occurred more than a few weeks ago.

Cytokines

Cytokines are Interleukins (ILs),Interferons (INFs), Tumor necrosis factor (TNFs), Colony stimulating factors(CSFs),and chemokines.

These are produced and secreted by a wide variety of cells.Act as intracellular mediators.When released they bind to specific receptors on the surface of other cells.and alter the activity of cells.Cytokines are hormone like substances. About 35 interleukins have been identified.(IL1-IL35) Il4 binds B-Cell.and differentiate B cells into Plasma cells.

TNF

Produced by mast cells ,macrophages and T cells.They are attached to cell membranes.They regulate immune response and inflammation.Responsible for apoptosis. TNF alpha activates neutrophils.

INFs

Interfere viral replication.Two types are present.IFN-Alpha--Viral infection and INF Beta-Increase phagocytosis.INFs helps in antiviral defense.

CSFs

Essential for growth and differentiation of immature leukocytes in bone marrow. Monocyte colony stimulating factor (M-CSF), Granulocyte Macrophage stimulating factor (GM-CSF) Helps in growth of dendritic cells.

G-CSF

Granulocyte colony stimulating factor (G-CSF) Help in development of Neutrophils

Chemokines

Chemocytes act as chemo attractants and signal leukocytes to move.

Complements

Complement refers to a group of large thermo labile enzymatic proteins found in serum and body fluids and it complete antigen-antibody reactions, lysis and phagocytosis. They are Beta globulins. They are neither antigens nor antibodies.

What do we know about the immune response to COVID-19?

Most COVID-19 patients who recovered have antibodies to the SARS-CoV-2 virus detectable in their blood. - Most COVID-19 patients develop antibodies about 1-3 weeks after symptoms start. This is around the time when many patients start to recover. - Patients who have had more severe disease appear to have higher levels of important neutralizing antibodies. - Patients who had mild or asymptomatic COVID-19 have low levels of neutralizing antibodies (or even undetectable levels). - In these persons it is possible the innate immune response and the T cell response cleared the virus - Recent studies have shown that neutralizing antibodies may disappear after 3 months

Cytotoxic T cells, after activation, destroy the virus-infected cells and the antibody-producing B cells target the virus specific antigens. SARS-CoV-2, regulates the MHC class I and II molecules, and inhibits the T-cell mediated immune responses. Patients with COVID-19, higher plasma concentrations of a number of inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF). CD4+ helper T cells, CD8+ cytotoxic T cells, and natural killer cells are very low in patients with severe COVID 19 infections.

The anti-viral immune response is critical to eliminate the virus. The overproduction of cytokines produces a cytokine storm. In fact, in the late stages of COVID-19, cytokine storms are a major cause of disease progression and eventual death. Increased plasma concentrations of both Th1 (eg, IL-1β and IFNγ) and Th2 (eg, IL-10) cytokines are noticed. The stimulation of the humoral and cellular immune response are exerted by virus-specific B and T lymphocytes. IgM and IgG antibodies are detected in about two weeks. The COVID 19 specific IgM antibodies may disappear at the end of the 3rd month. In contrast, the IgG antibody may persist longer, indicating that IgG antibodies are likely to be protective. COVID-19 patients produce SARS-CoV-2-specific neutralizing antibodies. Neutralizing antibodies block the virus from entering the host cells and play a critical role in virus clearance.

"Superhuman immunity" in some COVID 19 individuals Immunity

Shane Crotty, an immunologist, considers "hybrid immunity"; or "superhuman immunity" or "bulletproof as coined by other scientists, to be impressively potent against SARS-CoV-2. Whatever might be the name, this type of immunity brings a ray of hope amidst the COVID-19 crisis.

Recent researches have found an extraordinarily powerful immune response against SARS-CoV-2, in some people, by producing very high levels of antibodies with great flexibility. These antibodies have the capacity to fight off the prevailing as well as future emerging coronavirus variants.

Paul Bieniasz, a virologist at Rockefeller University, says that these people might be quite well protected against all or most of the SARS-CoV-2 variants that may emerge in future.

He further explained these antibodies to have the potential to even neutralize SARS-CoV-1, the first coronavirus, which emerged 20 years ago, which is very different from SARS-CoV-2.

But antibodies of people with the "hybrid immunity" neutralized it, proving the strength of mRNA vaccines in people with prior exposure to SARS-CoV-2.

Another study, published in *The New England Journal of Medicine*, supports this hypothesis. In this study, the researchers' analyzed antibodies of people priorly infected with the original SARS virus -SARS-CoV-1 (back in 2002 or 2003) and who then received an mRNA vaccine this year. Interestingly, these people too demonstrated a high level of antibodies that could neutralize a whole range of variants and SARS-like viruses.

What for people who aren't infected with SARS-CoV-2 ?

John Wherry, an Immunologist at the University of Pennsylvania, stated that they can see some of this antibody evolution happening in people who are just vaccinated, although it is faster in people who have been infected.

Immunity and COVID

India is the world's largest democracy and the covid-19 pandemic has badly affected the country's socio-economic conditions It was reported that among adults with confirmed COVID-19 infection. The available serosurvey data prior to the launch of the vaccination drive, states that children of 10-17 years had seropositivity similar to that in adults but the proportion of <20 yr olds was lower among confirmed COVID-19 cases than expected. This suggests that children are also susceptible as adults to infection, but mostly remain asymptomatic. Further, children who have symptoms have the milder infection as compared to adults.

Amid Omicron spread, virologist says world living under 'two pandemics'

Delta and close relatives, and Omicron and its variants in future," said Dr T Jacob John. The reason for this hypothesis, according to him, is that Omicron is not "fathered, or mothered, by Wuhan-D614G, Alpha, Beta, Gamma, Delta, Kappa or Mu and That much is for sure".

"So in my opinion, this is a variant of unknown proximal parentage but its great-great-grandparent was Wuhan-D614G. We shall see as the pandemic progresses," said John, a former director of the ICMR's Centre of Advanced Research in Virology.

What is antigenic drift?

Small Mutations during replication lead to changes in genes encoding antigens. These are the point mutations. They can help viruses gradually evolve and evade the immune system.

What is Antigenic shift?

Viruses swap whole sections of their genomes, leading to change in antigen genes. Antigenic shift changes large sections of genome. They can produce entirely new virus strains.

Diagnosis

Laboratory Findings Early detection may help to use appropriate antiviral agents. 1. Complete blood count may reveal leukocytosis with mild left shift. 2. Gram stains of the sputum may show few too many polymorph nuclear leukocytes. Radiographic Findings Chest X ray shows perihilar pulmonary edema, or dense opacities. Diagnosis Culture- Influenza virus can be isolated from upper and lower respiratory samples. However, because of the long turnaround time of reports, they are not used routinely.

3. Serology- Complement fixation and hemagglutinin inhibition during the acute phase of the illness and repeat test at 2-3 weeks during the convalescent phase to demonstrate a fourfold rise in antibody titer may be used.
4. Rapid antigen assays- less sensitive in detecting Influenza A infections as compared to RT-PCR assays.
4. Molecular diagnosis- Molecular methods like multiplex PCR / RT PCR are increasingly useful for the detection of omicron variants.

New Biomarkers of Innate and Adaptive Immunity in Infectious Diseases

Recent advances in molecular biology and immunology resulted in a rapid expansion in the field of immune biomarkers. These biomarkers can help make an early diagnosis, evaluate the efficacy of treatment, and improve or predict the disease outcome.

Omicron Treatment:

Delhi, Mumbai, and other big cities in India are experiencing a surge in Covid-19 cases, driven by the Omicron variant. Mumbai recorded a new daily infection peak of 15,166 on Wednesday. While, nearly 90% of new patients had shown no symptoms and only 8% were hospitalised, city officials said in a daily health bulletin. Most of patients are getting treated at home, Dr Shalini Joshi, Senior Consultant of Internal Medicine, Fortis explains Home Isolation Guidelines and treatment guidelines.

Deputy chief public health officer Dr. Howard Njoo and Health Canada's chief medical adviser, Dr. Supriya Sharma, lay out how significantly Pfizer's new antiviral drug, Paxlovid, will affect Canadians in the midst of the Omicron wave.

Corticosteroids and IL6 Receptor Blockers will still be effective for managing patients with severe COVID-19. Other treatments will be assessed to see if they are still as effective

given the changes to parts of the virus in the Omicron variant.

CONCLUSION

The omicron variant is spreading across the globe but so far the strain appears to be less deadly than its predecessors. Tampering down on omicron may increase the risk of antigenic shift to a far deadlier super variant.This will require difficult tradeoffs but it will save lives in long term.We should endmask mandates and social distancing inmost settings not because they don't slow the spread said by Vivek Rama Swamy and Apoorva Ramaswamy. Advances in immunology, immunopathology, and immunopharmacology have already opened a way to a clearer understanding of the nature of viral diseases.Vaccination helps in the Omicron response. Despite the vaccinated individuals starting out with almost identical and low neutralization as the unvaccinated, their neutralization went higher.Neutralizing immunity to Delta was boosted in the vaccinated. Not so in a subset of unvaccinated. In fact, based on neutralization, the vaccinated were better protected against Delta than Omicron. Again, not true for unvaccinated, the study stated."Neutralization of Omicron overall was not very high relative to what comes up with Delta infection

REFERENCES:

1. Zhou, P, Yang, XL, Wang, XG, Hu, B, Zhang, L, Zhang, W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* (2020) 579:270–3.
2. Tortorici, MA, and Veesler, D. Structural insights into coronavirus entry. *Adv Virus Res.* (2019) 105:93–116. doi: 10.1016/bs.aivir.2019.08.002
3. Coronavirinae. (2019). Available online at: https://viralzone.expasy.org/785 (accessed February 5, 2019).
4. Guo Y.-R., Cao Q.-D., Hong Z.-S., Tan Y.-Y., Chen S.-D., Jin H.-J., Tan K.-S., Wang D.-Y., Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. *Mil. Med. Res.* 2020;7(1):1–10.
5. Rabi F.A., Al Zoubi M.S., Kasasbeh G.A., Salameh D.M., Al-Nasser A.D. SARS-CoV-2 and coronavirus disease 2019: what we know so far. *Pathogens.* 2020;9(3):231.
6. Lake M.A. What we know so far: COVID-19 current clinical knowledge and research. *Clin. Med. Lond. (Lond)* 2020;20(2):124.
7. Yang X., Yu Y., Xu J., Shu H., Liu H., Wu Y., Zhang L., Yu Z., Fang M., Yu T. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir. Med.* 2020;8(5):475–481
8. Arezoo Hosseini,a,c Vida Hashemi,b Navid Shomali,a,c Faezeh Asghari,d Tohid Gharibi,a,c Morteza Akbari,a Saber Gholizadeh,e and Abbas Jafarif,* Innate and adaptive immune responses against coronavirusBiomed Pharmacother. 2020 Dec; 132: 110859.
9. Andersen K.G., Rambaut A., Lipkin W.I., Holmes E.C., Garry R.F. The proximal origin of SARS-CoV-2. *Nat. Med.* 2020;26:450–455
10. Kim et al., 2020,D. Kim, J.-Y. Lee, J.-S. Yang, J.W. Kim, V.N. Kim, H. Chang,The Architecture of SARS-CoV-2 Transcriptome,Cell, 181 (2020), pp. 914-921.e10
11. Gupta et al., 2021S. Gupta, W. Wang, S.S. Hayek, L. Chan, K.S. Mathews, M.L. Melamed, S.K. Brenner, A. Leonberg-Yoo, E.J. Schenck, J. Radbel, *et al.*, STOP-COVID InvestigatorsAssociation Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19JAMA Intern. Med., 181 (2021), pp. 41-51
12. Morens and Fauci, 2020,D.M. Morens, A.S. Fauci,Emerging Pandemic Diseases: How We Got to COVID-19,Cell, 182 (2020), pp. 1077-1092
13. Candido et al., 2020D.S. Candido, I.M. Claro, J.G. de Jesus, W.M. Souza, F.R.R. Moreira, S. Dellicour, T.A. Mellan, L. du Plessis, R.H.M. Pereira, F.C.S. Sales, *et al.*, Brazil-UK Centre for Arbovirus Discovery, Diagnosis, Genomics and Epidemiology (CADDE) Genomic Network**Evolution and epidemic spread of SARS- CoV-2 in Brazil,**Science, 369 (2020), pp. 1255-1260
14. **https://www.worldbank.org/en/country/india/coronavirus**
15. **https:// www. mohfw. gov. in/ pdf/ Guideline son Operationalization of CoVID CareServicesforChildrenandAdolescents**
16. **Sergey Morzunov,**Varough Deyde,and Levon Abrahamyan,New Biomarkers of Innate and Adaptive Immunity in Infectious Diseases,Journalof immunology research, Volume – Spl.issue,2017 |Article ID 7047405
17. Haeberle HA, Takizawa R, Casola A, Brasier AR, Dieterich HJ, Van Rooijen N, Gatalica Z, Garofalo RP: Respiratory syncytial virus-induced activation of nuclear factor-kappaB in the lung involves alveolar macrophages and toll-like receptor 4-dependent pathways. J Infect Dis. 2002, 186 (9): 1199-1206. 10. 1086/344644.