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RESEARCH ARTICLE

Perspectives Concerning Various Symptoms of SARS-CoV-2 Detected Individuals

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Abstract:

After exposure to SARS-CoV-2, varying symptoms of COVID-19 ranging from asymptomatic symptoms to morbidity and mortality have been exhibited in each individual. SARS-CoV-2 requires various cellular molecules for penetration into a target host cell. Angiotensin-converting enzyme2 (ACE2) acts as the viral receptor molecule. After attachment, SARS-CoV-2 also requires the transmembrane protease serine-2 (TMPRSS-2) and furin molecules, which serve as co-receptors for penetration into the target cell and for subsequent replication. In the meantime, a major histocompatibility complex (MHC) is required for the induction of adaptive immune cells, especially cytotoxic T cells and helper T cells, to clear the virally infected cells. This perspective review article proposes different aspects to explain the varying symptoms of the individuals who have been exposed to SARS-CoV-2, which relates to the polymorphisms of these involved molecules.

Keywords: SARS-CoV-2, Viral receptor molecules, Polymorphism, Major histocompatibility complex, Viral infection, Viral clearance.

Article History	Received: August 24, 2021	Revised: September 13, 2021	Accepted: October 1, 2021

1. INTRODUCTION

Various symptoms have been reported among those who tested positive for SARS-CoV-2. Approximately, 25-35% are asymptomatic, while 15-20% developed severity and about 2-5% have critical symptoms [1, 2]. There were reports of asymptomatic viral infections with many other viruses such as Japanese encephalitis virus [3, 4], dengue virus [4 - 6], Zika virus [4, 7, 8], influenza virus [9, 10], and others [11 - 15]. These studies were mostly evidenced by the findings of antibodies against the individual viral antigens in the sera of those who have never shown any specific pathogenesis caused by the viruses [3 - 15]. So far, there is no clear explanation for the varying symptoms in each individual. Although underlying diseases were assumed to be the cause of the severity, this has not been clarified. The severity and underlying diseases are not consistently correlated with the virally exposed persons since some individuals with underlying diseases might not have the severity. On the other hand, some individuals who have no underlying diseases might have severe symptoms. Thus, the cause of asymptomatic individuals requires further study and explanation. A clear explanation could be important for the public health care system. The development of new antiviral drugs should be studied with the appropriate viral exposed individuals. Studying the tested antiviral drug with the asymptomatic cases could give a false-positive result for interpretation of the effectiveness of the drug. To put non-actual-therapeutic effect drugs on the market would pose a problem for public health [16].

In general, monitoring the patients' symptoms is a major strategy for treating the viral infected patients until adaptive immunity is generated for the self-effective elimination of the viral pathogen. Adaptive cellular mediated immunity is a major key that plays a role in eliminating the infected virus using the cytotoxic T cell [17, 18]. The cause of uncertain symptoms in the virally exposed individuals has not been clearly elucidated. It has been suggested that viral mutation could be a reason for the uncertain symptoms of viral infections [19, 20]. In the case of the SARS-CoV-2 variants, each variant showed unpredictable symptoms in a population, but still, the ratios of asymptomatic, mild, and severe symptoms are more or less the same as the original strain [21 - 23]. This article presents the perspectives to explain the causes of different symptoms of the SARS-CoV-2 detected individuals.

1.1. SARS-CoV-2 Infection Requires the Susceptible Cellular Receptor Molecules

Similar to all other viruses, SARS-CoV-2 is an obligated intracellular agent that requires replication inside the target host cell. In order to attack a compatible host cell, such viruses use their particular ligands to interact with the viral receptor molecule on the cell membrane. SARS-CoV-2 uses its

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receptor-binding domain (RBD), spike, to bind the cellular molecule of a target host cell, a viral receptor molecule, known as angiotensin-converting enzyme-2 (ACE-2) [24]. Following the interaction, transmembrane protease serine 2 (TMPRSS2) [24 - 27] and furin [26 - 28] molecules have been reported to act as co-receptor molecules to enhance the entry of the virus into the target cell, such as alveolar epithelial cell.

There are reports of polymorphisms of ACE2, TMPRSS-2, and furin molecules. The association of these variant cellular molecules and the susceptibility and severity of SARS-CoV-2 infection has been suggested in many studies [24 - 28]. Most of the studies reported that TMPRSS-2 variants are highly responsible for the susceptibility of the SARS-CoV-2 infection [24 - 27]. Some reported that TMPRSS-2 and furin molecules have a cooperative action to promote the SARS-CoV-2 entry into the target host cell [26, 27]. To gain entry into the target host cell, the susceptibility of these cellular molecules is associated with the SARS-CoV-2 ligand for attachment and penetration.

1.2. The Controversy Concerning the Definition of Viral Infection with Viral Invasion

As an intracellular agent of the virus, including SARS-CoV-2, it is different from the extracellular organisms, such as most bacteria, which can multiply without necessarily being inside the target host cell to cause infection. Hence, it should be stressed that the viral agent must replicate inside a susceptible target cell to cause infection. As proposed in a previous report [16], there is a need to distinguish between the term "viral infection" from "viral invasion." Viral invasion is based on the fact that the virus could adhere to any part of the body but cannot enter and replicate properly in the target host cell. This is because the viral invaded host does not have the variants of ACE-2, TMPRSS-2, and furin cellular molecules for the viral attachment and penetration. However, although the invading virus cannot replicate in the individuals, it still has the potential to activate their own immunity by the initiative role of antigen-presenting cells (APCs) [29, 30].

During the invasion of a virus that qualifies as an immunogen, both innate and adaptive immunity can be induced. The viral substance is captured by the primary APCs, such as macrophages and dendritic cells, to deliver the viral substances from the invading site into the secondary lymphoid organs to initiate the adaptive immune response. There are reports suggesting that macrophages are the target cells of many different viruses such as the dengue virus [31], Ebola virus [32], hepatitis C virus [33], influenza virus [34], measles [35], and other coronaviruses [36]. According to previous reports, it has been interpreted and considered that all of these viruses can infect macrophages. Questionably, can macrophages be the target cells for many different viruses? Alternatively, can this just be a part of the process to present the viral antigen to induce the adaptive immunity of macrophages which can phagocytose the invading agents and have the role of the APCs? If macrophages are a target cell of these viruses, they should be destroyed and defect to the induction of adaptive immunity, which plays a key role in eliminating the viral pathogens. All of those asymptomatic virally invaded individuals should be defective to produce any antibodies against the viruses.

As the primary APCs, macrophages and dendritic cells play the role of presenting the antigenic epitopes to activate the compatible T cell clones, which are helper T cell (Th) and cytotoxic T cell (Tc). Th cell plays a role in activating the susceptible B cell clones for differentiation to be an antibody-secreting B cell (plasma cell) and memory B cell. During the APC's processing of the antigen, various cytokines are also released for the communication of the immune cells, which subsequently might cause some kinds of general and mild symptoms such as fever, headache, sore throat, *etc*., which might be unnoticed and ignored by the virally invaded individuals. This explains the individuals who have antibodies against the particular viral agents without any registered history of the viral infection, which has been falsely called asymptomatic viral infection [3 - 15].

1.3. The Crucial Role of MHC Molecules Concerning Immune Response

The APCs randomly cleave antigens into short peptides of 8-20 amino acid residues. For the T cell epitope, the short cleaved peptide must be able to attach to the MHC allelic variant in order to form the MHC-peptide complex (pMHC) to induce the compatible T cell clone [37, 38]. With their high polymorphism, MHC molecules are required to play a crucial role in activating adaptive immune cells and are classified as class I and II. The MHC class I molecules can be expressed by any nucleated cells, while MHC class II molecules can be found only in the APCs. MHC plays a key molecule in presenting the viral Ag on the cell surface of APC [39 - 41]. There are two pathways of antigen processing, which are endogenous (class I Ag processing) and exogenous (class II Ag processing) pathways. The endogenous pathway creates a pMHC-I complex to activate a specific Tc cell clone [37, 38]. The exogenous pathway creates pMHC-II to induce the compatible Th cell clone [39]. The recognition between pMHC and T cell receptor (TCR) of the specific T cell clone is called MHC restriction [38 - 40].

Individuals with suitable MHC variants of both class I and II experience self-recovery by the effective role of the compatible Tc cell clones. They can also produce memory cells for long-term viral clearance. Th promotes Tc differentiation to enable it to be the effective Tc and memory Tc. Accordingly, besides the compatible MHC-I alleles, MHC-II also plays a crucial role in clearing the virally infected cells. There were reports showing the association of the MHC variants and viral persistent infection, *e.g*., human papillomavirus (HPV) [41, 42], HBV [43, 44], HCV [45, 46], and others [47 - 53]. These studies showed the cause of the defect in eliminating the virally infected cells in some individuals which are associated with their MHC variants. In order to have complete viral clearance, the cooperation of the susceptible Tc and Th clones is needed. This requires induction by the appropriate MHC alleles of the individuals. Individuals who have some kinds of MHC variants would have no or less efficient Tc cell clones for the viral clearance. The adaptive Tc clones of these individuals are unlikely to clear the virally infected cell.

A further study is required to understand the interaction of T cell epitopes of the Tc and Th cell clones based on the MHC alleles of each individual, which are presented by the APCs. This should help us improve the strategy used in search of truly effective drugs to cure the viral infected patients in the correct direction.

1.4. Pathogenesis based on SARS-CoV-2 Invasion and Infection

There is no clear evidence of how SARS-CoV-2 causes COVID-19. However, many studies reported that the symptoms of COVID-19 relate to immune-pathogenic agents referred to as cytokine storms [54 - 56]. A cytokine storm is a severe immune reaction with an enormous amount of pro-inflammatory cytokines and chemokines. Cytokine storm has also been recognized as pathogenesis of many other infectious viruses such as influenza virus [57, 58], respiratory syncytial virus [59, 60], Ebola virus [61, 62], dengue [63, 64], and other coronaviruses [36, 65].

There are two different kinds of cytokines that can be classified as a positive (pro-inflammatory) and a negative (anti-inflammatory) regulator of inflammation. The cooperation of the various pro-inflammatory cytokines is the major key for the destruction of involved tissues and organs. The incidence can lead to acute respiratory distresses (ARDS) and multiple organ failure [66, 67]. The pro-inflammatory cytokines include tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), IL-6, and interferon-gamma (IFN-γ). On the contrary, transforming growth factor-beta (TGF-β), IL-4, IL-10, and IL-17 are the major cytokines that have an anti-inflammatory action [66 - 69]. Cytokine storm is defined by a situation whereby the excessive amounts and activity of pro-inflammatory cytokines are over the activity of the anti-inflammatory cytokines [67, 69].

The balance of the positive and negative regulation of cytokines maintains the normal function of innate immunity. Th1 is considered a pathogenic Th cell that releases pro-cytokines, while Th2 produces anti-inflammatory cytokines such as IL-4, IL-10, and IL-17. The imbalance activity of Th1 and Th2 is seen as a possible reason for the extensive severity, which causes morbidity and mortality in the SARS-CoV-2 infected patients [69, 70]. The individuals who have the susceptible receptor/co-receptors for the entry of the SARS-CoV-2 into their target cells would have a higher load of the SARS-CoV-2 agents. There were reports that the viral load is associated with the severity of the SARS-CoV-2 infection, which relates to the pathogenesis of the cytokine storms [71, 72].

This explains the cause of the severe symptoms of the SARS-CoV-2 infected patients, which are different from the individuals who are just being invaded by the virus. The viral invaded individuals would be asymptomatic or mildly symptomatic. The amount of the viral agents that are processed in APCs would be limited. They do not have excessively replicated viral agents to activate the pathogenic Th1 cells. The severe cases are those individuals who have the susceptible cellular molecules of ACE-2 and co-receptors for the SARS-CoV-2 replication. Thus, these individuals are those who are truly infected by the virus. In addition, these SARS-CoV-2 severely infected patients who do not have the susceptible Tc cell clones to clear the SARS-CoV-2 infected cell could have a worse prognosis. Without the effective Tc cell clones, the patients cannot depend on the Tc cells to clear the ongoing replicating virus. Thus, the situation of lacking the effective Tc cells clone induces Th1 cells to compensate by over-expression of excessive amounts of pro-inflammatory cytokines, which subsequently cause cellular destruction to the tissues and organs.

1.5. Perspectives Concerning Various Symptoms of SARS-CoV-2 Detected Individuals

The cause of uncertain symptoms after exposure to the viral agent should be determined based on two main factors; virus and host. The virus needs to have a ligand for interaction with the susceptible variant of the viral receptor molecule on the host cell. The virus that can infect one individual might not be able to infect the other which do not have the susceptible variants for the viral penetration. Logically, the viral mutation could keep mutating in any part of its genome. Its new variant might maintain infectivity to the same person and might develop to infect another person who once has not been susceptible to the original strain. Thus, the dynamics of viral infection could change from time to time. The strategy to prevent the epidemic should relate to our comprehension of the virus and host interaction and requires further study. This explains why some people who are evaluated with viral reinfection may actually be experiencing reinvasion. This also explains the individuals and animals who were detected to have the viral genome by the RT-PCR and do not have any symptoms or just have mild symptoms. The chain reaction (RT-PCR) cyclic threshold (Ct) values might be helpful in the evaluation to differentiate between viral infection and viral invasion.

Accordingly, after exposure to SARS-CoV-2, individuals could be classified into 4 groups, which are: (1) those who are not infected, without susceptible receptor/co-receptor, but can produce complete immunity because of their compatible MHC variants, (2) those who are not infected and cannot produce complete immunity against the viral agent because of a lack of compatible MHC variants, (3) those who are infected and produce the complete immunity against SARS-CoV-2 agent, and (4) those who are infected but cannot produce the particular immunity to fight the viral agent. Group 1 and 2 are asymptomatic or mild symptoms. Group 3 is a severe group, which is the same as group 4. However, in group 3, it is possible to recover with one's own immunity, and there is a higher potential to survive, while group 4 is the most severe group and needs appropriate medicine because these individuals cannot produce the appropriate immunity to clear the virally infected cell. If it is so, the challenging point is to search for a way to identify the differentiation among virally exposed individuals of each group which should be an advantage for the health care system. In order to evaluate the effectiveness of any medicine, it should be done with only those in group 4 as the main target. Using the drug to treat all of those who are detected with the SARS-CoV-2 could give a false-positive result.

CONCLUSION

This article proposes two issues concerning the SARS-CoV-2 epidemic. Firstly, it suggests differentiating the terminology of viral invasion from viral infection. This is based on the fact that the virus is an intracellular pathogen that causes infection. The viral agent found outside the susceptible target host cell just invades a body and does not cause infection. Besides the detection of the SARS-CoV-2 genome, viral load should also be used for evaluation to follow up the differentiation of viral infection and viral invasion. In addition, pro-inflammatory cytokines and anti-inflammatory cytokines should be used as additional indicators to differentiate between asymptomatic (invasion) and symptomatic infection (true infection) in those who were detected with the SARS-CoV-2 amplified genome. The most appropriate cytokines for evaluation of SARS-CoV-2 infection require further study, although IL-6 and IL-10 might be the best candidates, as reported in some studies. Secondly, this article proposes that the individuals' immune-genetic MHC alleles could be the key to explaining the cytokine storm in the severe SARS-CoV-2 infected patients. These patients cannot activate the effective susceptible Tc clone to clear the SARS-CoV-2 infected cell. Subsequently, this causes over-expression of Th1 to produce exaggerated pro-inflammatory cytokines, as explained. Hopefully, these opinions will be accepted for determination and further studies to help us understand the SARS-CoV-2 pandemic for setting up the appropriate strategy of prevention and treatment.

LIST OF ABBREVIATIONS

ACE2	=	Angiotensin-Converting Enzyme2
TMPRSS-2	=	Transmembrane Protease Serine2
MHC	=	Major Histocompatibility Complex
RBD	=	Receptor-Binding Domain
Ct	=	Cyclic Threshold
Tc	=	Cytotoxic T Cell
Th	=	Helper T Cell
MHC	=	MHC-peptide Complex
TCR	=	T Cell Receptor
IL	=	Interleukin

AUTHOR'S CONTRIBUTION

This entire article is written by Tirasak Pasharawipas.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

FUNDING

None.

ACKNOWLEDGEMENTS

The author would like to thank Mr. Rohn Meijer for proofreading this manuscript. The article is dedicated to Dr. Jack Roy McClelland (December 16th, 1918-May 3rd, 2021) for his dedication to education and generosity towards humanity.

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