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Factors influencing variable symptoms of COVID-19 patients and proposed revision of public policy for COVID-19 pandemic

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Abstract

The uncertainty of the symptoms in those who are SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) positive is an issue that should be discussed in order to reconsider a comprehensive way to deal with this virus outbreak. For the time being, controversy regarding the necessity to vaccinate still exists in the public and might be a significant impact on the global economy and safety of human beings. This article proposes that a variety of cellular molecules (viral receptors/co-receptors) and MHCs (major histocompatibility complex) could be crucial factors explaining the uncertain symptoms in those who infected with viruses. The understanding of these host factors should encourage further research studies and pave the way to develop a new public health policy to deal with COVID-19 and emergent viral epidemic in the future.

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Introduction

There have been reports that many people worldwide have been exposed to certain type of infectious virus without symptom or self-notice. The studies found that various kinds of viral antibodies such as Dengue [1][2], Japanese encephalitis [3], Influenza [4][5], and others [6][7][8][9] including SARS-CoV-2 [9] have been found in major populations who have never been sick with these viruses. For COVID-19, 70-85% of people are asymptomatic or mildly symptomatic, while

10-25% require hospitalization and 1-2% die as a result of the infection [10][11]. For those with severe symptoms, some can survive spontaneously without any specific treatment, while others do not, even though the optimal treatment has been administered. Age and underlying diseases have been suggested to be the main factors causing severe symptoms and mortality [12][13][14]. However, there are reports of survival among ageing patients and those with underlying conditions. Thus, underlying diseases and ageing might not per se be considered the key factor explaining the severity and mortality. In addition, new viral strains due to genomic mutation have also been widely suggested to explain the different symptoms and severity [12][13][15]. However, records show that the new viral strain, SARS-CoV-2 (O-Micron) and many others still cause a similar ratio of asymptomatic cases, severe cases and mortality as the original strain of SARS-CoV-2. Similarly, immune evasion of a virus is another mechanism to explain the cause of pathogenicity and severity, including evading previous immunity and vaccination. Questionably, if the virus evades immunity, why it does not evade everybody? Why do not all vaccinated people become infected? These mysteries require explanation.

Accordingly, this article proposes the concepts concerning variants of cellular molecules and the major histocompatibility complex (MHC) as the critical factors answering these questions. Cellular molecules are associated with viral infection for viral attachment and penetration to the target cell. MHC molecules play a role in inducing the adaptive immune response to increase the efficiency of clearing the virus. Hopefully, this perspective can contribute to the fundamental guidelines for solving and setting better global health systems for the prevention of emergent viruses.

Viral infection

Unlike extracellular organisms, a virus requires a susceptible target cell for replication as it is an obligate intracellular organism. A virus uses its receptor binding domain (RBD) to attach a specific receptor which is a cellular molecule of the target cell. In the meantime, the virus also needs a different cellular molecule as a co-receptor to enter the target cell, some viruses have been found to use more than one cellular molecule as their receptors or co-receptors. For SARS-CoV-2, the original receptor molecule is angiotensin-converting enzyme 2 (ACE2) with transmembrane protease, serine 2 (TMPRSS2), and furin being its co-receptors [15][16][17][18]. The variants of these cellular molecules relate to the susceptibility to the virus. Previous reports show that some variants of individuals' cellular molecules are not susceptible to a virus attaching and entering. Although the individuals are exposed to a virus, the virus is unable to enter the target cells for replication; this includes SARS-CoV2 [16][17][18]. For most viruses, pathogenesis relates to a host's response to foreign substances, known as an immune-pathogenic syndrome. This includes COVID-19, which is due to the release of pro-inflammatory cytokines [19][20][21][22]. If the individuals do not have the susceptible variants of cellular molecules enabling the virus to attach and enter, they would be asymptomatic or mildly affected. Although the virus does not enter the susceptible target cells, it still can enter antigen-presenting cells (APCs) such as macrophages and dendritic cells. During this period, the viral-exposed individuals might show symptoms as the effect of pro-inflammatory cytokines by APCs [19][20][21]. APCs play a role in presenting the viral particle to induce adaptive immune cells such as cytotoxic T cells (Tc) and helper T cells (Th) in secondary lymphoid organs [22][23]. During this period, the viral-exposed individuals might show symptoms as a result of the effect of pro-inflammatory cytokines [6]. This is unlike those who are actually infected

with the virus, where the target cell becomes a comfortable source in which the virus can replicate excessively, causing the uncontrollable release of inflammatory cytokines and severe symptoms in those who are genetically susceptible to viral infection.

Viral immunity

To eradicate and clear the infected viral agents in those who are truly infected with a virus, our body needs to be able to activate the effective Tc. After invasion into a body, the viral agent is captured by APCs which subsequently digest and present the viral epitopes to induce adaptive immune cells [23][24][25]. APCs randomly cleave viral peptides into oligopeptides of 8-20 amino acid residues which are called T cell epitopes. T cell epitopes then combine with the MHC (major histocompatibility complex) molecule to form the MHC-peptide complex (pMHC) which eventually plays a significant role in the activation of a specific T cell clone on its receptor, the so-called T cell receptor (TCR). There are two classes of MHC, class I and II. MHC class I combine with a viral epitope to form pMHC-I, which subsequently activates Tc cell clones [25][26]. MHC class II forms pMHC II to induce Th cell clones, which then play a role in inducing activated Tc to become effective and memory Tc [27]. Eventually, effective Tc can clear the viral-infected cells.

In addition, B lymphocytes also assist with the blocking of viral re-entry to a new target cell by secreting antibodies. The best strategy for the antibody to neutralise the viral agent is to bind the viral RBD. This is the main approach for manufacturing the viral vaccine. The B cell receptor (BCR) recognises B cell epitopes based on the native form of the antigen; thus, it does not require APC and MHC molecules [28]. Initially, activated B cells can synthesise IgM antibodies. To synthesise other classes of immunoglobulins, which are IgG, IgA and IgE, the B lymphocyte clone requires the cognate Th clone to be promoted. During this period, the B and Th cells play reciprocal roles to support each other [29][30]. B cells which also express the MHC II molecule play an antigen-presenting role to the cognate Th cells, which also sends some signals to promote B lymphocytes for differentiation into plasma cells to synthesise various classes of immunoglobulin. Without Th cells, B cells cannot produce other classes of immunoglobulin, except IgM. More importantly, they cannot differentiate into memory B cells. Besides a short half- life, IgM also has a low affinity to bind viral antigens and has a limited ability to combat the virus during extracellular existence. IgG has the highest capacity to bind the virus with strong affinity. The affinity of IgA is second to that of IgG but it plays a great role in mucosal organs, which form the main route of many viral transmissions [31][32], including the SARS-CoV-2 virus. Accordingly, Th cells play a central role in maturing both B and Tc lymphocytes, including memory cells, for long-term protection from secondary viral infection [25][26][29][30].

Immunodominant epitope

The MHC molecules of humans are called human leukocyte antigens (HLA), which are classified into classical and non-classical loci. HLA molecules are inherited co-dominantly from the parents. Thus, each locus of the MHC genome in an individual can be either heterozygous or homozygous. For classical loci, each class of the human MHC has three loci.

Accordingly, the number of gene alleles of MHC class I in any individual are limited to 3-6 alleles [26][27]. For example, an individual who is homozygous for all three loci would have only three gene alleles, while those who have all heterozygous loci would have six gene alleles. As the HLA gene alleles are highly polymorphic, the possibility of two individuals having the same set of gene alleles is at least one in a million (mostly seen in identical twins).

MHC molecules have a pocket which allows some amino acids of the peptide to fit inside. The studies found that each MHC variant has the ability to bind many different peptides [31][32]. This means that MHC molecules have broad specificity to the T cell epitope presented by APCs. However, each MHC molecule can bind to only one peptide at a time since there is only one cleft on each MHC molecule. To form pMHC, the MHC molecule requires only a few amino acids of the T cell epitope, the so-called anchor residue, for interaction [31][33][34]. This allows each MHC allele to bind to many different peptides. Any processed peptides, which are derived from foreign substances by APCs, must contain the amino acids that can fit the MHC allele cleft to form pMHC [35][36]. Subsequently, the pMHC becomes the crucial molecule for inducing a specific TCR of the T cell clone. TCR requires interaction with both the peptide residue and the MHC molecule [35][37]. This conforms to the development of T cell clones in the thymus, which requires positive selection and the ability to work with the self-MHC alleles of the individuals [38][39]. Noticeably, reports have shown that the interaction between each MHC allele and different peptides has a different affinity. Each MHC allele has a limited ability to bind some of the peptides [40][41][42]. It is unlikely that all of the epitopes of foreign peptides are able to form pMHC with a single MHC allelic molecule [43][44]. Accordingly, the MHC allelic molecules of each person have the ability to form pMHC with some of the peptides if they do not contain the anchor residues that are compatible with the individuals' MHC alleles. Individuals who are MHC homozygous are more susceptible to pathogens than those who are heterozygous [45][46][47]. This explains why people with fewer MHC alleles might have some limitations of binding with an immunodominant epitope to form pMHC molecules. A good match of the peptide, the immunodominant epitope and the peptide-binding groove of the MHC molecule are crucial factors for the induction of immunodominant T-cell clones.

Besides the possibility of viral variants, the lack of available MHC alleles and antigens might explain why some individuals become infected and do not respond efficiently to gain seroprotection after viral vaccination [48][49]. Therefore, the invasion of any particular antigen of a virus into different individuals does not guarantee the induction of the same level of immunity because of the limited varieties of MHC alleles in each person.

Perspective to explain various symptoms after viral exposure

Based on the variants of the susceptible viral receptor molecule(s) and the compatible MHC class I and II for immune response against the viral agent, we can classify individuals into 8 groups, as shown in Table 1. After exposure to a virus, there are those who are actually infected and those who are not truly infected (just invaded) by the virus. Groups 1-4 are individuals who do not have the susceptible viral receptor/co-receptor and are not truly infected. They are asymptomatic or have mild symptoms since the virus does not replicate greatly in the target cell. Their immunity depends on the existence of their MHC alleles, as mentioned in Table 1. Groups 5-8 are those who have susceptible viral receptors and could be truly infected. The viral multiplication in the target cell can continuously induce pathogenic cytokines, thus

causing severe symptoms. In more detail, Group 5 contains those individuals who are MHC class I and II compatible to the immunodominant viral epitope. They can activate specific Tc and B cell clones for the development of affective Tc to cure and produce memory B cells for further protection. These people should be able to survive spontaneously if they do not have any related underlying diseases that can cause additional critical symptoms, especially during the first couple of weeks of infection. Individuals in Group 6 might be able to activate the specific Tc clone but cannot develop an effective and memory Tc clone since the particular Th cell is not produced. To clear the viral-infected cell, our body needs effective Tc, not just a primary activated Tc. However, with some kinds of medicine preventing the virus from entering the target cell, such as neutralising antibodies, this might be helpful. Further studies are needed, however. Also, individuals in Group 6 could not be effectively protected by vaccination for the development of memory B cells. It is hard to provide a prognosis for the individuals in this group. It is possible that they can survive but will have chronic symptoms which depend on their living conditions and behaviours. Groups 7 and 8 might be more or less the same, having severe symptoms as the effective Tc clone cannot be developed. Thus, they should not be able to recover spontaneously. However, Group 7 might find it more possible to be cured than Group 8. The memory B cells might be sufficient to cure the viral infection if there is some co-operation of natural killer cells (NKs) and a specific antiviral IgG to eradicate the infected virus. This requires further investigation. At present, there is no antiviral medicine that has actually proven to clear the infected virus, like Tc. Otherwise, it should be able to cure all of the infected patients. In the meantime, if this perspective is correct, individuals from Group 1 might be the source of passive immunisation for patients in Groups 6-8. However, the side effects concerning the incompatible effects of HLA alleles must be taken care of.

Table 1. Classification of individuals based on their susceptibility to viral infection (viral receptor variants) and immune compatibility (MHC class I and II) to fight against the viral agent.

Individual group	Viral receptor variant	MHC I allele	MHC II allele	Prediction on viral exposure
1	Non-susceptible	Compatible	Compatible	No or mild symptoms with the production of an effective Tc cell clone including all of the memory cells of adaptive immune cells
2	Non-susceptible	Compatible	Non-Compatible	No or mild symptoms with the production of a specific Tc cell clone, which can produce only IgM and no memory B or Tc cells
3	Non-susceptible	Non-Compatible	Compatible	No or mild symptoms without the production of an effective Tc cell clone, but which can produce memory B cells
4	Non-susceptible	Non-Compatible	Non-Compatible	No or mild symptoms without the production of effective Tc cell and memory B cell clones
5	Susceptible	Compatible	Compatible	Severe symptoms but can recover completely due to the role of effective Tc. These individuals could be protected if vaccinated
6	Susceptible	Compatible	Non-Compatible	Severe symptoms. Can activate the specific Tc clone but cannot develop an effective and memory Tc. These individuals could not produce memory B cells.
7	Susceptible	Non-Compatible	Compatible	Severe symptoms. Cannot activate the specific Tc clone but can earn protection via viral vaccine. These individuals should be protected if vaccinated
8	Susceptible	Non-Compatible	Non-compatible	Severe symptoms. Cannot produce any effective or memory immune cells. These individuals should be vaccinated frequently. Probably, all will die if they become infected.

Conclusion

With the controversy regarding the necessity to vaccinate, many people have refused to be vaccinated, stating the reason as some SARS-CoV-2-positive individuals surviving without vaccination. Thus, vaccination might not be necessary for them. This perspective explains the uncertain symptoms depending on the different genetics of individuals concerning viral susceptibility and immune response. Based on this aspect, everybody should be vaccinated since we do not know who does (or does not) have susceptibility viral receptor/co-receptors and it is too complicated to identify the cellular variants for every individual. The campaign to ask people to vaccinate regularly should be reconsidered, especially for individuals who showed positivity for SARS-CoV-2 but were asymptomatic or demonstrated mild symptoms. These individuals accounted for 70-85% of the total and classified to be in Groups 1-4 in which they were protected on the basis of their genetic insusceptibility to viral infection. These groups could survive without vaccination. Most of the global population could be safe if effective vaccines have been administered for two or three doses. In fact, vaccination should come with a package to follow-up the seroconversion to detect IgG and IgA. Individuals who produce high levels of IgG and IgA should be assumed to be protected. Hence, these individuals may not need to be vaccinated regularly; they can assume that the memory B cells have been created. Only individuals from Groups 6-8 might need to be vaccinated frequently for the induction of IgM, which has a short half-life. The understanding of this fundamental should provide positive result, more economical approach, setting up the optimal way to handle emergent viruses which is also applicable with other the active viruses, such as Dengue virus, Japanese encephalitis, etc. Studies regarding follow-up the viral mutation might not be needed unless the virus keeps mutating and or uses other molecules to enter the target cells. Then, new devastating epidemics might occur.

Abbreviations

- APC Antigen presenting cell
- BCR B cell receptor
- HLA Human leucocyte antigen
- Ig Immunoglobulin
- MHC Major histocompatibility complex
- pMHC MHC-peptide complex
- RBD Receptor binding domain
- TCR T cell receptor
- Tc Cytotoxic T cell
- Th Helper T cell

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