REVIEW ARTICLE

Proposal to Explain the Cause of Long COVID Based on the Concept of Host Factor Variants

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Abstract

Long COVID, also known as post-COVID syndrome (PCS), manifests as unexplainable clinical symptoms in some asymptomatic/mildly symptomatic SARS-CoV-2-positive individuals during the acute phase. The symptoms begin even after the nasopharyngeal swab becomes negative for months. This proposal aims to explain the cause of long COVID through the host factors variants concept, which involves cellular variants and major histocompatibility complex (MHC) polymorphism. The roles of antigen-presenting cells (APCs), such as macrophages and dendritic cells, are central to this explanation. Ultimately, this article proposes that blood or white blood cells could be the proper samples for diagnosing long COVID patients.

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Introduction

The incidence of long COVID, also known by many other names such as post-viral sequelae, including post-COVID syndrome (PCS), has been reported to affect 10-20%, or even higher in some reports, of asymptomatic or mildly symptomatic SARS-CoV-2-positive individuals, even when nasopharyngeal swabs have tested negative. Long COVID presents with various symptoms affecting multiple organs. Common symptoms include fatigue, breathlessness, persistent cough, chest pain, trouble speaking, muscle aches, and cognitive dysfunction impacting daily life and household tasks. These chronic symptoms may cause suffering for months or even years, depending on the individual (Chen et al, 2022; Donald et al, 2024).

There is no predictable symptom for diagnosing long COVID, especially in those who were symptomless during the acute

phase. Some individuals may experience continuous symptoms from the acute phase, while others develop symptoms after recovering from the initial illness. Symptoms can relapse intermittently, vary from better to worse, without any clear clinical prognosis indicators (Donald et al, 2024; Pinzon et al, 2022).

SARS-CoV-2 positivity can be found in individuals who have been fully vaccinated, and long COVID can also appear in some vaccinated individuals. Currently, there is no absolute explanation for the cause of long COVID (Mumtaz et al, 2022). Surveys indicate that age, sex, and underlying diseases are associated with its incidence, but the real cause remains unclear and requires further investigation (Chen et al, 2022; Donald et al, 2024; Pinzon et al, 2022).

In fact, besides SARS-CoV-2, post-viral sequelae of other viruses have also been reported. Examples include measles (Buchanan and Bothius, 2012), chikungunya (van Aalst et al, 2017), West Nile virus (Patel et al, 2015), and many others, including hepatitis viral diseases of hepatitis B and C viruses, which can cause chronic infections in approximately 10-15% and 60-70% of cases, respectively (WHO website, 2024). Previously, the host factors variants concept, which includes cellular molecules variants and MHC (major histocompatibility complex) polymorphisms, has been proposed to explain the variable symptoms of SARS-CoV-2-positive people (Pasharawipas, 2024). Herein, the concept will be proposed to extensively explain the cause of long COVID, particularly the roles of cytotoxic T cells (Tc), helper T cells (Th), and antigen-presenting cells (APCs).

This article will propose the association of cellular variants, MHC polymorphism, and the role of APCs in the cause of long COVID, focusing on the roles of Tc and Th cells in relation to viral persistence in APCs. The contents of this article integrate information on various viruses that have been reported to cause post-viral sequelae, including SARS-CoV-2. For the convenience of readers, some details from a previous article by Pasharawipas (2024) will be reiterated.

Cellular variants and viral infection

With the fact that the virus is an obligated intracellular agent that requires a susceptible host cell to replicate, to enter the host cell, it uses the receptor-binding domain (RBD) to interact with the host's cellular molecule(s), which need to have susceptible receptor/co-receptor molecules for viral attachment and entry. There are reports of cellular variants in individuals for susceptibility to viral attachment and entry, which relate to symptomatic severity (Pecoraro et al, 2023; Saengsiwaritt et al, 2022). The insusceptibility between a viral RBD and the host cell variants will not support viral entry and replication in the target host cell. Accordingly, it requires consideration that a viral positive sample does not always represent a viral infection. We should define the terminology to distinguish between "viral infection" and "viral invasion" based on the logic of viral immunology. Viral infection could be used just when the virus can attach to the cellular molecule with its susceptible RBD and enter into the target host cell of the individual. This is opposite to the definition of "viral invasion," which is the incidence that a virus is exposed to a body but does not enter into the target host cell since the viral RBD is not susceptible to host cellular variants. Once a virus invades a body, it does not always result in infection if the cellular variants of the individuals are not susceptible to a viral RBD. This is a logic to explain the cause of variable symptoms in SARS-CoV-2-positive individuals. For most viruses, pathogenesis is related to the host's response to foreign

substances, which is known as an immune-pathogenic syndrome, characterized by the release of pro-inflammatory cytokines (Pirhonen et al, 1999; Hume 2008). If individuals do not have susceptible variants of cellular molecules that enable the virus to attach and enter, they would be asymptomatic or mildly affected. Although the virus does not enter susceptible target cells, it can enter antigen-presenting cells (APCs) such as macrophages and dendritic cells with their broad-acceptable receptors to foreign substances, known as toll-like receptors (TLRs). During this period, viral-exposed individuals might show symptoms due to the release of pro-inflammatory cytokines by APCs. APCs present viral epitopes to induce adaptive immune cells, such as cytotoxic T cells (Tc) and helper T cells (Th), in secondary lymphoid organs (Hume 2008; Kelly and Trowsdale, 2019). During viral presentation by APCs, viral-exposed individuals may show symptoms due to the effects of pro-inflammatory cytokines (Nakamura et al, 2019). This situation differs from viral infection, where the virus enters target cells and replicates extensively. In the cases of individuals genetically susceptible to viral infection, the target cell becomes a source for the virus to multiply, leading to uncontrolled release of inflammatory cytokines and severe symptoms (Kwon et al, 2020). The discussion of long COVID and the critical roles of MHC polymorphisms in individuals will be explored in more detail later.

The relationship between the polymorphism of MHC molecules and individuals' immune responses

MHC (major histocompatibility complex) molecules are a set of molecules located on the cell membrane. There are two classes of MHC molecules: MHC class I and MHC class II. MHC class I molecules are found on the cell membranes of all nucleated cells in the body. In contrast, MHC class II molecules are expressed only on the cell membranes of APCs (antigen-presenting cells) to activate Th cells. Each class of MHC molecules has multiple loci that are recognized as the classical and non-classical loci. In humans, MHC molecules are called HLA (human leukocyte antigen) because they were first studied and discovered in white blood cells. Therefore, HLA is synonymous with human MHC. The classical HLA class I loci include HLA-A, HLA-B, and HLA-C, while the loci for HLA class II are HLA-DP, HLA DQ, and HLA DR.

HLA molecules are inherited co-dominantly from both parents, meaning that each locus in an individual's HLA genome can be either heterozygous or homozygous. Consequently, the number of gene alleles for each class of MHC in any individual is limited to 3–6. For example, an individual who is homozygous at all three loci would have only three gene alleles, while someone who is heterozygous at all loci would have six gene alleles. Because MHC gene alleles are highly polymorphic, the likelihood that two individuals have the same set of gene alleles is less than one in a million and most commonly observed in identical twins.

Studies have shown that individuals who are MHC homozygous are more susceptible to pathogens than those who are heterozygous (Lipsitch and Bergstrom, 2003; Arora et al, 2020). To explain this more extensively, the interaction between MHC molecules and T cell epitopes in forming pMHC complexes to activate T-cell clones is crucial. Normally, MHC molecules do not need to interact with all amino acids of a T cell epitope, which typically consists of approximately 8-20 amino acid residues. MHC molecules require only a few amino acids, about 2-4 residues, of the T cell epitope for interaction to form a pMHC complex (Marzella et al, 2022; Perez et al, 2022). The region of the T cell epitope that interacts

with the MHC groove is called the anchor residue. This allows each MHC allele to bind to many different peptides, provided that the anchor residues are present in those specific T cell epitopes. Thus, any T-cell epitope peptides processed by APCs must contain amino acids that can serve as anchor residues and fit the MHC allele's pocket to form a pMHC complex (Rammensee, 1995; Nielsen et al, 2007). The formation of pMHC is pivotal for inducing the T-cell clones via the T cell receptor (TCR), although many other molecules are involved in the interaction between T cells and APCs (Szeto et al, 2020). Each MHC variant can bind to many different peptides, giving MHC molecules broad interaction with the T cell epitopes presented in APCs. However, each MHC allele has a limitation in binding to certain peptides (Margulies et al, 1993; Sinigaglia and Hammer, 1994; Jensen et al, 2018). It is unlikely that all processed T-cell epitopes can form a pMHC complex with a single MHC allele.

Thus, the MHC alleles of each individual have a limitation in forming pMHC complexes with some peptides if those T cell epitopes do not contain anchor residues compatible with the individual's MHC alleles. This explains why individuals with fewer types of MHC alleles have been reported to be more susceptible to pathogenic infections. It could be due to the limitations in forming pMHC complexes with some foreign substances, including the viral agent, to induce naïve T cell clones of these individuals. In addition to the possibility of viral variants, a lack of compatible MHC alleles in individuals may explain why some people become infected and do not respond efficiently to gain seroprotection even after receiving full doses of viral vaccine (Faneya et al, 2015; Smith et al, 2021).

Therefore, the invasion and infection of any particular foreign substance, including viral antigen, in different individuals results in varying levels of immune responses. To activate Tc cells, individuals require a compatible MHC class I allele to form a pMHC-I complex with a particular viral epitope. Similarly, a compatible MHC class II allele is needed to form a pMHC-II complex for the activation of Th cells.

The role of macrophages and dendritic cells as the antigen-presenting cells

Accordingly, the adaptive immune response requires macrophages and dendritic cells (DCs) to present antigenic epitopes for primary activation. Macrophages and DCs play the role of antigen-presenting cells (APCs) based on their properties to express not only MHC class I but also MHC class II, by forming pMHC-I and pMHC-II for the activation of T cell clones. It is believed that DCs play a more important role in activating T-cell clones (Steinman and Banchereau, 2007), while macrophages are more active in removing apoptotic cells and foreign agents by phagocytosis (Ravichandran, 2010). During the process of acting as APCs, macrophages and DCs produce cytokines as mediators to initiate the procedure of presenting antigenic epitopes.

Playing the role of APCs, macrophages and DCs can capture foreign substances, including viral agents, with toll-like receptors (TLRs). This is an important step. Without engulfing, antigen presentation cannot proceed, and T cell activation is impossible. For most of the infected viruses, there is no evidence showing that the viruses directly cause pathogenesis. As mentioned earlier, as APCs, macrophages and DCs are the main sources of pro-inflammatory cytokines that cause either mild or severe symptoms depending on the viral agents (Wang et al., 2014; Wang et al., 2023). Viral-infected

individuals certainly have viral multiplication from the susceptible target cells, while viral-invaded individuals have limited amounts of viral agents which are engulfed by APCs. There are reports of the findings of viral agents in macrophages and indications that macrophages are target cells of particular viruses. Perhaps, it should be aware that it might be a process of antigen presentation of macrophages. It does not need that a macrophage is a target cell of the particular viruses. It should have more investigation to make this point clear for each of the viral agents that is in a macrophage. This is open for further study.

There are two kinds of macrophages: M1 and M2. M1 mainly produces pro-inflammatory cytokines, while M2 produces anti-inflammatory cytokines. However, both M1 and M2 can alternate their phenotypes with one another (Wang et al, 2014). DCs also have heterogeneous forms and produce various kinds of cytokines, both pro-inflammatory and anti-inflammatory. With more phenotypic forms, so far, DCs have been classified into four distinguished subpopulations: conventional DCs, called cDC1 and cDC2. cDC1 is rare in the body, while cDC2 is more abundant. The other two forms of DCs are pDCs and mo-DCs. We still need to learn a lot more about the phenotypic and detailed information concerning the unique functions and properties of heterogeneous DC phenotypes, although information concerning each phenotype's cytokine production and molecule expression has been described (Balan et al, 2019).

It is interesting to note that macrophages and DCs are generated from the same progenitor and have been reported to be able to alternate their functions with one another. Macrophages have been reported to perform DC functions to a certain degree and *vice versa* (Weisheit et al, 2015). However, there is no conclusive evidence that both cells are the same. This is unlike monocytes and macrophages, which have been classified as the same kind of cell after decades of discovery. There is a question as to why our immunity requires both macrophages and DCs to play more or less the same role of APCs if they are different cell populations. This causes some difficulty in reviewing and integrating the knowledge concerning the mediated role of APCs in linking the innate immunity with the adaptive immunity for the overall picture of this article. Perhaps further studies in this aspect will provide clearer and more conclusive answers in the future.

Herein, however, based on fundamental knowledge, we should conclude that macrophages and DCs are APCs, which are the main sources of pro-inflammatory cytokines during their duties. This should be the cause of pathogenesis for either viral invasion or viral infection. In addition, there is no evidence that macrophages or DCs can clear the viral agent by themselves but require effective Tc. This will be discussed more later on.

Host factors variants concept for explaining the cause of long COVID in asymptomatic SARS-CoV-2 positive individuals

The host factors variants concept has been proposed such that individuals can be classified into eight groups based on the three host factors: (1) viral-susceptible variants of cellular molecules, (2) compatible MHC class I, and (3) compatible MHC class II. This concept helps explain the variable symptoms of individuals after viral invasion. Individuals who do not have susceptible variants of cellular molecules would not be truly infected. Only individuals with susceptible cellular variants experience subsequent severe symptoms. For viral clearance, individuals need to have MHC class I compatibility

to activate Tc cells, which also requires compatible Th cells for further induction into effective Tc and memory Tc cells, including memory B cells. To gain compatible Th cells, MHC class II compatibility of the individuals to the particular viral epitope is crucial.

To explain the cause of long COVID in asymptomatic/mildly symptomatic SARS-CoV-2-positive individuals based on the host factors variants concept, see TABLE 1. These individuals are symptomless or have mild symptoms due to the lack of susceptible cellular variants for the RBD of the virus to attach and enter. Thus, the virus invades the body without replicating in its susceptible target host cell to cause infection. Individuals in group 1 are predicted to be the luckiest, as viral invasion might cause them just minor symptoms or leave them symptomless, with the ability to produce all kinds of adaptive immunity for viral clearance and prevention. They might remain healthy even when exposed to the virus without any vaccination. On the other hand, individuals in groups 2-4 have either or both classes of MHC incompatible with viral epitopes to completely induce effective T cell clones.

Table 1. Classification of individuals who are insusceptible to viral infection and became symptomless/mild symptoms of SARS-CoV-2 invasion while the compatibility of their MHC alleles determines the potential to clear the viral agent from the viral engulfing APCs, which are persistent in becoming the cause of long COVID or post COVID syndrome (PCS)

Individual group	MHC I allele	MHC II allele	Prediction on viral exposure and the possibility to gain post COVID syndrome (PCS)
1	Compatible	Compatible	With the complete production of effective Tc and Th cell clones and all the memory cells of adaptive immune cells, it is unlikely that these individuals will gain PCS.
2	Compatible	Non-Compatible	With specific Tc cells that cannot develop into effective T cells due to the lack of an effective Th cell, only IgM is produced, and no memory B and T cells are formed. PCS is possible in this group.
3	Non-Compatible	Compatible	Although effective Th cells and memory B cells are generated, along with all classes of immunoglobulins, the lack of specific Tc cells still allows for the possibility of causing PCS in this group.
4	Non-Compatible	Non-Compatible	Without the generation of both effective Tc and Th cells, PCS is highly predictable in this group.

Considering the antigen-presenting roles of macrophages and DCs in individuals in groups 2-4, these cells are suspected of storing the viral agent. As mobile cells, they can migrate and disseminate the viral agent to various organs, being sources of pro-inflammatory cytokines that cause the persistent symptoms of long COVID (Marongiu et al, 2021; Kosyreva et al, 2021). As an immune-privileged organ, the central nervous system (CNS) might be accessed by APCs carrying the virus across the CNS blood barrier via a Trojan horse mechanism, causing inflammation and viral CNS infection in long COVID patients (Constant et al, 2022; Stevenson et al, 2014). Additionally, there are reports of persistent viruses in macrophages and DCs in chronic persistent viral infections (Bain et al, 2001; Gowans et al, 2004). Discovering viral particles in APCs based on autopsies of individuals with chronic viral symptoms has been announced (Basolo et al, 2023; Danics et al, 2021). These studies could be keys to integrating knowledge to explain the cause of post-sequelae symptoms of various viral infections, including long COVID. Based on immunological logic, macrophages and DCs have no ability to clear viral agents by themselves. It should be evaluated whether the existing virus in APCs is part of the APCs' duty, more than a viral infection, to present antigenic epitopes to activate adaptive immune cells. T cell epitopes of viral agents require compatible MHC alleles to form appropriate pMHC complexes to induce the T cell receptor (TCR) of

either Tc cells by MHC class I alleles or Th cells by MHC class II alleles. Incompatibility in forming either or both pMHC-I and pMHC II complexes halts the further process to activate the adaptive cellular immunity of T cell clones. This might result in persistent viruses in macrophages and DCs and cause post-sequelae symptoms. Based on this perspective, SARS-CoV-2-engulfing macrophages and DCs might be a cause of long COVID in individuals from groups 2-4 (Table 1). It is speculated that individuals in group 4 might experience more severe and prolonged symptoms than those in groups 2 and 3, as they are unable to develop both effective Tc and Th cells. Conversely, predicting outcomes for individuals in group 2 is challenging; it is uncertain whether activated Tc cells, which do not further develop into effective Tc cells due to a lack of Th cell assistance, can clear the viral-engulfing APCs (Auffermann-Gretzinger et al, 2001; Bedoui et al, 2016; Miyatake et al, 2021). Effective T cell generation requires a tripartite interaction between APCs, Tc cells, and Th cells (Hoyer et al, 2014). This step may be crucial for clearing the viral-engulfing APCs and preventing the persistence of the virus in APCs, which could disseminate to various organs. Further study required.

For individuals in group 3, who lack compatible Tc cells, symptoms might be similar to those in group 4, unless natural killer cells, in combination with IgG antibodies through antibody-dependent cytotoxicity (ADCC), can clear the viral agent (Ma et al, 2021). This presents an intriguing avenue for research, especially for organizations with the potential to conduct clinical studies on HLA alleles in long COVID patients.

In conclusion, this article proposes that long COVID in asymptomatic or mildly symptomatic SARS-CoV-2-positive individuals can be explained by the host factors variants concept. These individuals were invaded by SARS-CoV-2 without significant replication in the target cell. It is predicted that individuals with incompatible MHC alleles of both class I and II (group 4), who cannot generate effective Tc and Th cells, are likely candidates for long COVID. Those with incompatible MHC class I or class II alleles (group 2 and 3) may also be at risk. With the impairment of T cell functions in these individuals, the viral persistent APCs could be the key cause of persistent symptoms in long COVID patients due to the released pro-inflammatory cytokines. Persistent viral APCs may migrate and disseminate to various organs, including the CNS, leading to ongoing symptoms. Additionally, examining the SARS-CoV-2 genome in peripheral blood or white blood cells might provide a diagnostic tool for long COVID and aid in developing treatments to prevent more severe symptoms. This approach warrants further research.

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