The Open Microbiology Journal

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REVIEW ARTICLE

Different Aspects Concerning Viral Infection and the Role of MHC Molecules in Viral Prevention

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Abstract:

Major Histocompatibility Complex (MHC) molecules play a crucial role in inducing an adaptive immune response. T-cell epitopes require compatible MHC molecules to form MHC-peptide Complexes (pMHC) that activate the T-cell Receptors (TCR) of T-lymphocyte clones. MHCs are polymorphic molecules with wide varieties of gene alleles. There are two classes of MHC molecules, class I and II. Both classes have three classical loci HLA-A, -B, and –C are present in class I and HLA-DP, -DQ, and -DR in class II. To induce a compatible T-lymphocyte clone, the T-cell epitope requires the association of the compatible MHC molecule to form pMHC. Each MHC variant possesses a different groove that is capable of binding a different range of antigenic epitopes. Without the compatible MHC molecule, a T cell clone cannot be activated by a particular viral epitope. With the aim of preventing viral transmission, the efficiency of a viral vaccine is related to the existence of specific MHC alleles in the individual. This article proposes the roles of the MHC molecule to prevent viral infection. In addition, the association of the viral receptor molecule with the viral infection will also be discussed.

Keywords: Major histocompatibility complex, pMHC, Viral vaccines, Viral invasion, Viral infection, Viral prevention, Viral clearance.

Article History	Received: December 22, 2020	Revised: February 25, 2021	Accepted: April 22, 2021

1. INTRODUCTION

Viruses are obligate intracellular pathogens and require replication inside the target host cell to cause infection. A virus attaches its particular ligand to the viral receptor on the cell membrane in order to attack a cell [1 - 3]. Some viruses also require a co-receptor molecule for entry. There are reports that variants of viral receptor molecules are susceptible to the corresponding viral infections of the individuals [4 - 7]. Thus, those who are exposed to the viral agents might not always get virally infected if they do not possess the specific variants of the viral receptor molecule(s). This should be an interesting topic for further study.

In humans, the immunogen can induce both innate and adaptive immunity. The immunogen is captured by the primary Antigen-Presenting Cells (APCs), such as macrophages and dendritic cells, to deliver the immunogen from the invading site into the secondary lymphoid organs to initiate the adaptive immune response [8, 9]. APCs randomly cleave antigens into short peptides of 8-20 amino acid residues. For T cell epitopes, the short peptide must be able to combine with the MHC molecule in order to form the MHC-peptide Complex (pMHC) for inducing the compatible T cell clone [9 - 11].

2. THE PRESPECTIVE OF ASYMTOMATIC CASES AFTER VIRAL INVASION

There have been numerous reports of asymptomatic viral infections. Notably, asymptomatic cases have been reported for the Ebola virus, well known as a highly severe infectious agent that causes a high rate of mortality, by Leroy *et al*. [12]. These asymptomatic Ebola cases were identified by the positive detection of IgM and IgG and a high level of inflammatory cytokines. Moreover, Ebola Nucleoprotein (NP) and structural protein 40 (VP40) genes were detected in circulating blood monocytes with lower copy numbers by a reverse transcription-polymerase chain reaction. However, the entire virion was not identified in cell culture. The authors suggested that some individuals were infected with the virus without developing symptoms for unknown reasons. On a different aspect, the results could be explained as followed. The low copy number of the Ebola viral genome in monocytes could be a result of the ordinary process of APCs. The viral agent might just be trapped in the monocyte, which plays the role of an APC. It did not actually enter the target host cell to replicate and could be a reason for the virion disappearance. During the antigen presentation process, APCs usually secrete various cytokines to cause primary symptoms, such as fever and inflammation. This

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could also be applied to the reported higher ratios of asymptomatic cases of other viruses, such as Japanese encephalitis virus [JEV] [13, 14], Dengue hemorrhagic fever [15], Zika [16, 17], Influenza [18], including the most emergent, i.e., SARS-CoV-2 [19, 20]. The presence of the virus within a body, so-called viral invasion, does not mean it is always capable of entering the target cell for replication. The individual must express a specific variant of the viral receptor molecule for viral attachment [4 - 7]. Evidence of asymptomatic cases suggests that viral invasion in the body should be differentiated from the viral infection. The absolute definition of the viral infection should include viral replication in a target host cell and result in the specific pathogenesis of the viral infection.

3. THE ASSOCIATION OF MHC MOLECULES AND INDUCTION OF ADAPTIVE IMMUNE CELLS

There are two classes of MHC molecules, 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 APCs. MHC is the key molecule to present the viral Ag on the cell surface of APC [9, 11]. There are two pathways of antigen processing, so-called 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 [10, 21]. The exogenous pathway creates pMHC-II to induce the compatible Th cell clone [11, 22]. The recognition between pMHC and TCR of a specific T cell clone is called MHC restriction [23, 24]. Meanwhile, the B-cell epitope stimulates B lymphocytes directly through the B-Cell Receptor (BCR) without any association with the MHC molecule [11]. Mainly, BCR recognizes a B cell epitope of an antigen in its native structure. This is different from TCR which recognizes a linear epitope of an antigen that is cleaved by APC before forming pMHC with its compatible MHC allele [25, 26]. The activated B-cell clone can produce only immunoglobulin M (IgM) as the primary humoral immune response. To differentiate into a plasma cell, the B-lymphocyte clone requires promotion by the cognate Th cell [27, 28]. During this period, the B and Th cells play a reciprocal supporting role. B cell plays an APC role to present an epitope to activate the cognate Th for differentiation to be a follicular helper T cell (Tfh), which is an effective Th cell. In return, Tfh sends signals to promote B-lymphocyte differentiation to plasma cells for the synthesis of various immunoglobulin classes and memory B cells [28, 29]. Without the Tfh, the B cell can produce only IgM and no other classes (IgG, IgA, and IgE), including the memory B cell for long-term protection from secondary viral infection. Hence, MHC II is indirectly necessary for the development of B lymphocyte.

4. THE DIVERSITY OF MHC MOLECULES

Each class of MHC genes comprises, at a minimum, three classical loci. The classical class I MHC molecules of humans are HLA-A, -B, and -C,, while the classical class II are HLA-DP, -DQ, and -DR [29, 30]. MHC class I heterodimer is composed of an alpha chain and beta 2 microglobulin. Class I alpha peptide exhibits a high degree of polymorphism. HLA molecules are inherited co-dominantly from the parents. Thus, each locus of the MHC genome in an individual could be either heterozygous or homozygous. Accordingly, the numbers of gene alleles of MHC class I in any individual are limited to 3–6 gene alleles. For example, the individual who has all three loci as homozygous would have only three gene alleles, while those who have all heterozygous loci would have six gene alleles. As the MHC gene alleles are highly polymorphic, the possibility of two individuals having the same set of gene alleles would not be less than one in a million (mostly in identical twins). MHC class II molecules are heterodimers of alpha and beta chains, coded by A and B genes, respectively. HLA-DRB, -DQB, and -DPB genes exhibit a much higher degree of polymorphism than the HLA-DRA, -DQA, and DPA genes. There are two loci of DQA (DQA1 and DQA2) and DPA (DPA1 and DPA2). The combination of the alpha and beta peptides of HLA-II results in the possible variants of HLA- II molecules more than HLA-I molecules. The numbers of alleles and proteins of MHC class I and II, as reported by the WHO Nomenclature Committee for Factors of the HLA System, are shown in Table **1** [30].

Table 1. The number of gene alleles and peptides of each MHC locus of human MHC I and II, as reported by the WHO Nomenclature Committee for Factors of the HLA System [30].

MHC locus	Numbers of gene alleles	Numbers of peptides
MHC class I	-	-
HLA-A	6,291	3,896
HLA-B	7,562	4,803
HLA-C	6,223	3,681
MHC class II beta chain	-	-
HLA-DPB	1,670	1,069
HLA-DQB	1,930	1,273
HLA-DQB	3,536	2,476
MHC class II alpha chain	-	-
HLA-DPA1	216	80
HLA-DPA2	5	2
HLA-DQA1	264	114
HLA-DQA2	38	11
HLA-DRA	29	2

5. THE CRUCIAL ROLE OF MHC IN THE HOST'S IMMUNITY AND VIRAL VACCINE

According to many studies, the efficiencies of specific viral vaccines vary in the global market, and some could be lower than 50% in certain populations [31 - 33]. The recombinant Hepatitis B vaccine, derived from the surface antigen HBsAg, has been claimed to be the most effective viral vaccine in the current market, yet still does not give appreciable efficiency [34, 35]. In a population of Chinese high school students vaccinated with the HBV vaccine as infants and receiving a booster shot, 28.7% (158/551) did not produce anti-HBs antibody (anti- HBV level < 1 mIU/mL). In addition, 63% of them cannot develop seroprotection (anti-HBV level < 10 mIU /mL) [34]. A similar study by Posuwan *et al*. found that 15% of Thai medical students, who had been vaccinated during infancy also showed no response after booster with the

HBV vaccine [35]. This data showed that the HBV vaccines could not provide effective protection for all those who are vaccinated.

As mentioned, the host's immunity requires T-cells, especially Th and Tc cells, for effective immunity to eliminate the viral infection. MHC restriction is the key to activate T-cell clones through TCR. The antigenic epitope requires an MHC molecule to form the pMHC at the MHC groove and induce the compatible T lymphocyte clone. A limited capacity of each type of MHC molecule to bind the viral epitope results in the lacking of the appropriate pMHC to activate the significant T-cell clone. In other words, the affinity differs between each MHC variant, and the distinct antigenic epitopes, subsequently resulting in varying levels of the immune response. Thus, the availability of the MHC allele and the antigen are the key MHC restriction factors for the induction of compatible T-cell clones. A lack of compatible MHC molecules for the viral vaccine epitopes might explain why many individuals do not respond efficiently to gain seroprotection after HBV and other viral vaccinations. 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 variety of MHC alleles in each person.

6. DIFFERENT ASPECTS CONCERNING VIRAL INFECTION AND THE ROLE OF MHC MOLECULES IN VIRAL PREVENTION

This article proposes that the definition of 'viral infection' should be differentiated from 'viral invasion'. The virus is an obligate intracellular pathogen. Only individuals that possess a compatible variant of viral receptor molecules on the target cell membrane are susceptible to the corresponding viral infections. The viral agent in the APCs (such as a macrophage) should be considered as a process of the immune response, not infections, unless the macrophage is an actual target cell of a particular virus. By responding to viral invasion, the macrophage releases pro-inflammatory cytokines during the processing of the viral Ags that subsequently cause some general symptoms, such as fever, fatigue, and inflammation. These symptoms should be called pro-cytokine-inducing symptoms. The positive response of treatment using corticosteroids to block cytokines production of the macrophage supports this opinion [36 - 38]. The general symptoms caused by the cytokines of APCs vary in each individual in which many are shown to be non-symptomatic. The reasons for the varied symptoms in each person require further study.

Only individuals who possess a specific variant of the cellular molecule for the attachment and penetration of the virus have a viral infection. Viral infections show specific symptoms related to the functions of the target host cell. Based on the development of many antiviral drugs by pharmaceutical companies, using the tested antiviral drug on asymptomatic cases could give a false-positive result, when finding out the effectiveness of the drug. It is misleading to evaluate the efficacy of any developing antiviral drug. The introduction of such drugs in the market that are not actually therapeutically effective leads to a problem for public health . Thus, the definition of viral infection should be differentiated from viral invasion.

By using just a part of a viral substance, the so-called subunit viral vaccine has been popular for manufacturing viral vaccines, including SARS-CoV-2. The major part of the viral agent producing the subunit vaccine relates to the viral binding molecule. The main reason is the convenience of manufacturing the vaccine based on molecular biology technology. The subunit viral vaccine has limitations in creating viral epitopes to associate with individuals' MHC variants for the activation of compatible T cell clones. With distinguished variants of MHC molecules, the viral vaccines that provide seroconversion in one population might not do so in other populations. In fact, genomic mutations could occur in all viruses, while RNA viruses have much higher their genomic mutations according to the low efficacy of their RNA polymerase to proofread their genomic replication [39, 40]. Since BCR usually recognizes a conformational B cell epitope in a native structure of an antigen, the genomic mutation of the viral genome could cause the conformational change of a B cell epitope. Thus, the binding affinity of the subunit-vaccine-inducing antibody might be lower or unable to bind the specific B cell epitope of the mutated virus. Perhaps, the mixture of different subunit vaccines of covering all of the viral proteins should be considered. Besides neutralizing antibodies to prevent the viral attachment to the target cell, the antibody against other parts of the viral agent might also have the potential to prevent or cure the viral infection. The antibodies against different parts of viral epitopes can co-operate with the native immune cells, such as Natural Killer (NK) cells, by the Antibody-Dependent Cell Cytotoxicity (ADCC) process [41, 42]. This should be able to increase the efficacy of a viral vaccine for any individual to have protective immunity in the long term based on the existence of the induced memory immune cells. This can increase the potential to produce an effective viral vaccine for all citizens globally. Thus, the crucial role of MHC molecules concerning the immune response of T cell clones is necessary to be included for consideration.

CONCLUSION

In conclusion, we might need to revise the definition of viral infection. The virus is an obligate intracellular pathogen and requires a susceptible host cell for replication. The finding of a viral genome or particle in any part of the body could not always account for the viral infection unless the virus exists in a target host cell. This explains those individuals who are asymptomatic by detection of the viral genome or particle. The individual is just being exposed to the virus, not truly infected. In addition, to produce an efficient viral vaccine for any single individual, it might be necessary to include immunologic host factors since each individual has different MHC alleles for processing a long-life immunologic response.

LIST OF ABBREVIATIONS

Ab	=	Antibody
APC	=	Antigen Presenting Cell
ADCC	=	Antibody-Dependent Cell Cytotoxicity

BCR	=	B Cell Receptor
HLA	=	Human Leucocyte Antigen
HIV	=	Human Immunodeficiency Virus
Ig	=	Immunoglobulin
MHC	=	Major Histocompatibility Complex
Pmhc	=	MHC-Peptide Complex
Tfh	=	Follicular Helper T Cell
Th	=	Helper T Cell
Tc	=	Cytotoxic T Cell
TCR	=	T Cell Receptor

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

The author would like to thank Mr. Rohn Meijer for proofreading this manuscript.

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