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Perspective concerning MHC molecules in viral persistence

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Abstract

The persistently viral infected individuals are a major source of viral carriers. The cause of the viral persistency has not been well understood. The key puzzle is that some of the virally infected people can recover without any specific treatment while others persisted with the viral agent. The effective immune cells to eliminate the viral agents are cytotoxic T cell (Tc), natural killer cell (NK), and macrophage. Known as the adaptive immune cell, Tc plays the most crucial role in the immune clearance of the viral agent. To be able to play its active role, Tc requires induction of pMHC which is a complex molecule of MHC (major histocompatibility complex) and a viral epitope. Each specific pMHC activates the compatible Tc clone through its receptor (Tc cell receptor). MHC gene alleles are highly polymorphic. The individual MHC variant possesses a different groove that is capable to bind a different range of antigenic epitopes. Without the compatible MHC molecule, in general, Tc clones cannot be activated by a particular viral epitope. This could be a reason to explain why some of the virally infected individuals cannot clear the viral agent out of their body perfectively and become the source of the viral carriers. This article discusses the association of the MHC molecule and the cause of viral persistency in some individuals.

Keywords: *major histocompatibility complex; MHC molecule; pMHC; viral carrier, viral clearance, viral persistence.*

1. Introduction

Viruses are obligate intracellular parasites that can replicate only inside the target host cell. In general, the specific antiviral drug is not available on the market for the treatment of most of the viral infectious agents. Side effects to the host cells have been reported to be the major problem to develop effective antiviral drugs (Chan, Asriel, Eaton, & Wyatt, 2018; Feng, 2018; Jin et al., 2017). Symptomatic treatment is a major strategy for treating most of the viral infected patients until adaptive immunity is created for the effective elimination of the viral agent. Usually, patients can recover from acute viral infections if their immune responses are produced within a specific period. On average, this requires one to two weeks. However, most viruses cause not only acute but also chronic infection. The definition of chronic viral infection is that the infected virus persists within a host for a longer period, usually longer than six months. The incidence of chronic viral infection is varied by the individual viruses and population.

During chronic infection, individuals might be asymptomatic but can transmit the virus to others (Sharma, Saini, & Chwla, 2005; Furuya-Kanamori et al., 2018). There are two significant types of chronic viral infections: latent and persistent. Firstly, it is a virus factor that causes the latent viral infection. Examples include members of Herpesviridae, such as Herpes simplex virus (HSV) (Bello-Morales & López-Guerrero 2018; Abendroth, Kinchington, & Slobedman, 2010). HSV migrates to preferred cells or organs (such as nerve cells) where the host's immunity cannot

respond, so-called privilege organs. Usually, patients infected with HSV experience latent infection (Kłysik, Pietraszek, Karewicz, & Nowakowska, 2020; Menendez & Carr, 2017). HSV produces latency-associated transcript (LAT) to inhibit cellular apoptosis to avoid the host's immunity. During this time, the virus can keep being dormant in its infected cell without any clinical symptoms to the host (Carpenter et al, 2015; Jaggi et al, 2020). Besides the role of LAT, there were reports that herpes viruses also have a mechanism to interfere with the MHC class I expression of the target host cells (Piguet, 2005). Thus cytotoxic T cell (Tc) cannot recognize and eliminate the viral infected cell (Stone et al, 2011). Accordingly, after acute HSV infection, the virus remains latently infected in all of the infected individuals who have not treated properly during the primary acute infection. Acyclovir has been reported to be an effective antiviral drug to treat acute HSV infection to avoid chronically latent infection (Kłysik et al., 2020).

The other chronic viral infection is viral persistency. The chronically persistent infection could be found in both DNA and RNA viruses. RNA viruses are much higher in their genomic mutation according to the low efficacy of their RNA polymerase to proofread their genomic replication (Duffy, 2018; Malpica et al., 2002). HCV, an RNA virus, is prone to cause a high prevalence of chronic infection. World health organization (WHO) reported that only about 30% (15-45%) of the HCV infected individuals have immune clearance within 6 months without any treatment. The rest of the HCV infected individuals, approximately 70% (55-85%), developed a chronic infection (WHO, 2020). However, many other RNA viruses have been reported to have a much lower prevalence of chronic infection e.g. Ebola (Heeney, 2015), Influenza virus (Morens, Taubenberger, & Fauci, 2009), Sars-Cov-2 (Kang, Wang, Tong, & Liu, 2020), and other RNA viruses (Doi et al, 2016; Hoarau et al, 2010; Lin, Kouyos, Adams, Grenfell, & Griffin, 2012; Meiring, Prozesky, Du Preez, & Verwoerd, 2011). Also, some reports were showing that HCV mutation might not be the only cause for the viral persistency (Fuller et al., 2010; Lapa, Garbuglia, Capobianchi, & Del Porto, 2019). Thus, the genomic mutation of the virus might not be concluded as the only genuine cause of chronically persistent infection.

HBV, a DNA virus, has been reported to cause chronic infection in approximately 10-15% of HBV-infected individuals (WHO, 2020). The chronically infected HBV and HCV individuals are trend to develop liver cirrhosis and hepatocellular carcinoma (Zhao, Liu, Lv, Wang, & Wang, 2017; Urabe et al., 2013). Similar to Herpes viruses, HBV and HCV have also been reported to interfere with the MHC class I expression which was claimed to be the cause of their persistency (Hewitt, 2003). If it is so, all the HBV and HCV infected individuals should become chronically infected. As mentioned, approximately 85-90% of the HBV infected and 15-45% of the HCV infected can spontaneously clear the viral agent. Accordingly, the HBV and HCV persistently infected might not be explainable to cause by just the virus factor as does for Herpes viruses. The cause of viral persistent infection will be the main topic to discuss further in this article.

2. Human immune response to antigen invasion

Based on human immunity, viral particles, as an immunogen, can induce both innate and adaptive immunity. After invasion into a body, the viral agent is captured by the innate immune cells, such as macrophages and dendritic cells, which act as the primary antigen-presenting cells (APCs). The primary immune response occurs in secondary lymphoid organs such as the lymph nodes and spleen (Momburg & Hengel 2002; Hume, 2008). APCs deliver the immunogen from the invading site into the lymphoid organs to initiate the adaptive immune response. APCs randomly cleave antigens into short peptides of 8-20 amino acid residues. The short peptide then combines with the MHC (major histocompatibility complex) molecule to form the MHC-peptide complex (pMHC) which plays a significant role to activate a specific T cell clone (Kelly & Trowsdale, 2019).

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 the APCs. MHC is the key molecule to present the viral Ag on the cell surface of APC (Kelly & Trowsdale, 2019; Momburg & Hengel, 2002; Roche & Furuta, 2015). There are two pathways of antigen processing, so-called endogenous (class I Ag processing) and exogenous (class II Ag processing) pathway. The endogenous pathway creates pMHC-I to activate a specific Tc cell clone (Lu et al., 2012; Momburg &Hengel 2002; Shastri, Schwab, & Serwold, 2002).

The pMHC-I is a complex molecule of a short peptide of approximately 8-12 amino acids and MHC class I. The exogenous pathway creates pMHC-II which comprises a larger epitope size, 12-20 amino acids, and MHC class II. The pMHC-II is a key to induce the compatible Th cell clone (Lázaro, Gamarra, & Del Val, 2015; Momburg &Hengel 2002; Shastri, Schwab, & Serwold, 2002). The recognition between pMHC and TCR of the specific T cell clone is called MHC restriction (Drozina, Kohoutek, Jabrane-Ferrat, & Peterlin, 2005; Shastri, Schwab, & Serwold, 2002).

3. The diversity of MHC molecules

The two classes of MHC molecules each have a different role in the adaptive cellular immune response. Each class of MHC genes comprises, at a minimum, three classical loci. The MHC molecule in humans is designated as human leukocyte antigen (HLA), based on the fact that MHC molecules were first found and studied in the white blood cell. 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 (Rock, Reits, & Neefjes, 2016). MHC class I heterodimer is composed of an alpha peptide and beta-2 microglobulin. Class I alpha peptide exhibits a high degree of polymorphism while beta-2 microglubulin does not. The two chains interact with one another non-covalently. As reported by the WHO Nomenclature Committee for Factors of the HLA System, the numbers of HLA-A, -B, and -C gene alleles (proteins) are 6.291 (3.896), 7.562 (4.803), and 6.223 (3.681) $\times 10^3$, respectively (Robinson et al., 2015). 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. A heterozygous individual has two different gene alleles, while a homozygous has the same gene allele in the locus. 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 also heterodimers alpha and beta chains, coded by A and B genes, respectively. Both alpha and beta chains of MHC class II are highly polymorphism, HLA-DPB, -DQB and -DRB genes exhibit a much higher degree of polymorphism than the HLA-DPA, -DQA, and DRA genes. Thus far, the numbers of HLA-DPB, -DQB, and -DRB gene alleles (proteins) are 1.670 (1.067), 1.930 (1.273), and 3.536 (2.476) $\times 10^3$, respectively while the numbers of alleles (proteins) of DPA, DQA, and DRA are 221 (82), 302 (125), and 29 (2) $\times 10^3$ respectively (Robinson et al., 2015). Nevertheless, the combination of the alpha and beta peptides of HLA-II results in polymorphism more than HLA-L molecules.

4. The association of the MHC molecule and persistent viral infection

As mentioned, the host's immunity requires T cells, especially cytotoxic T cell (Tc) and helper T cell (Th), for the effective immunity to clear the viral agent out of the infected host. MHC restriction is a key to activate T cell clones through TCR of the T cell clone (Sobao et al, 2001; McKiernan et al, 2004). The antigenic epitope of the viral agent requires an MHC molecule to form the pMHC at the MHC groove and induce the compatible T lymphocyte clone. Each of the MHC alleles expresses different forms of grooves (Fan et al., 2018; Provenzano et al., 2006). A limited capacity of the MHC groove to bind the viral short peptides (epitope) results in lacking the appropriate pMHC to activate the significant T cell clone. In other words, the presence of a groove of the MHC variant that can form pMHC with the compatible viral epitopes elicits Tc response (Li & Bouvier, 2004). Thus, the affinity differs between the MHC variant, and the distinct antigenic epitopes subsequently result in varying levels of the immune response (Wooster et al., 2019).

Viral persistent infection can also be found in a low-evolved immune animal. Insects, which lack adaptive immune response, many of which become viral carriers such as dengue hemorrhagic fever (Porter et al., 2005), Japanese encephalitis virus (Thenmozhi, Rajendran, Ayanar, Manavalan, & Tyagi, 2006), West Nile virus (Nielsen, Reisen, Armijos, Maclachlan, & Scott, 2008), and others (Boot et al., 2010; Doi et al., 2016; Gokhale, Vazquez, & Horner, 2014; Kanno, Ishihara, Hatama, & Uchida., 2018; Teunis et al., 2015). The bee, which is an economic insect, can also be persistently infected with its pathologic viruses (Chen et al, 2004; Locke, Semberg, Forsgren, & de Miranda, 2017). Another example of viral

persistent infection in low-evolved immune animals is the penaeid shrimp which is a vital farming commodity in many countries in Asia including Thailand. Over two decades ago, white spot virus and yellow head virus each caused pathogenesis and high mortality in infected shrimps when they emerged (Flegel, 2001; Sritunyalucksana, Srisala, McColl, Nielsen, & Flegel, 2006; Walker & Mohan 2009). Notably, although there is evidence of persistent viral infection in shrimp, mortality declined sharply after several epidemic years once pond management systems such as water quality, feeding system, temperature, and rearing population size were optimized. In poorly managed farms, mortality was reported (Flegel, 2001; Walker & Mohan 2009). This could explain that shrimps perform a kind of unknown mechanism to tolerate infectious viruses. Alternatively, this might also be explained by the incidence of genomic mutation of the viruses which lower their pathogenesis. The previous study, however, reported that the naïve shrimp showed acute infection and high mortality when challenged by a virus that was isolated from occluded, persistent-infected shrimp (Flegel, 2001). Accordingly, the viral genomic mutation should be excluded from the explanation for the cause of the persistent infection in shrimps.

Insects and shrimps possess native immunity but not adaptive immunity. Naturally, innate immunity is not as sufficiently effective in clearing the virus and virus-infected cells as the adaptive Tc. We assume that persistently infected patients cannot clear the viral infected cell because they cannot produce an effective Tc cell for viral clearance. As is the case in infected shrimps, persistently infected patients do not have the adaptive immunity of the cellular-mediated immune response (CMIR). This could be due to the lack of an appropriate MHC-I allelic molecule to interact with the viral epitope, which results in the pMHC not forming to induce an appropriate lymphocyte clone.

Bhaskaran et al., 2019 reported that HLA-B*44 and DRB1*07 had a significant association with persistent HPV-16 infection (odds ratio, *p*-value = 26.3, 0.03 and 4.7, 0.01, respectively). HLA-B*27 and DRB1*12 were significantly associated with both HPV-16^{+} cervical cancer (CaCx) and persistent HPV-16 infection (23.8, 0.03; 52.9, 0.01; 9.8, 0.0009; and 13.8, 0.009; respectively). HLA-B*15 showed a negative association with HPV-16-positive CaCx (0.1, 0.01), whereas DRB1*04 exhibited protection to both HPV-16-positive CaCx and persistent HPV-16 infection (0.3, 0.0001 and 0.1, 0.0002, respectively). Besides, the associations of HLA variants and viral persistent infection of HBV (Ramezani et al., 2009; Pan et al., 2013; Zhu et al., 2016) and HCV (Kondo, Ueno, & Shimosegawa, 2011; McKiernan et al., 2004; Mosaad et al, 2010) have also been reported. These previous studies support the association between the HLA variants and the cause of viral persistent infection in some individuals.

To eliminate the infected cell, the activated Tc must be induced which requires the compatible MHC variants. However, the activated cytotoxic T cell also requires induction of Th for differentiation to an effective Tc for the effective clearance of the infected cell. These survivors can also produce memory cells for long-term prevention and viral clearance. Accordingly, besides the compatible MHC-I alleles, MHC-II also play the important role to clear the viral infected cells (de Almeida et al.,2011; Nishida et al., 2012; Liao et al., 2015). In contrast, individuals who do not have the compatible MHC-I to induce the activated cytotoxic T cell, cannot clear the viral infected cell effectively. These infected patients become severe cases unless the virus compromises to live in the host without any severity, the same as the infected shrimps, that lives in the optimal environment (Fares-Gusmao et al., 2019; Ly et al., 2019; Yin, Ping Huang, & Zhong, 2016). The mechanism to compromise might be a process of adaptation of both virus and a host, in addition to an environment. This subject has been discussed in many different aspects which require further study (Flegel, 2020; Ignuzzi & López, 2019; Pasharawipas, 2011; Zambon, Vakharia, & Wu, 2006).

5. Conclusion

Many previous studies convinced that chronically viral persistent infection is caused by viral factors such as viral mutation and some of the viral mechanisms. This article proposes that the cause of the chronic viral persistent infection might also associate with the existence of the MHC variants of the individual which is a host factor. Viral clearance requires the compatible MHC variants to induce Tc and Th for the effective eradication of the viral infected cell. There is no evidence that native immunity, such as natural killer cells, can fully clear the infectious virus by itself.

The existence of a compatible MHC-I allele to the viral epitope is necessary for inducing the appropriate Tc clone to clear all the virally infected cells. In the main fact, the Tc clone(s) also requires compatible Th to support its efficiency. Thus, besides the MHC-I variants, the existence of the compatible MHC-II allele molecules is also another key to clear the viral infected cell. The MHC molecules, as a key to preventing and restraint a viral epidemic, have been underestimated for their crucial role to eradicate the infected viral agent. Thus, this requires a better understanding of the distribution of MHC alleles in our global community. To prevent the viral pandemic, which becomes the major problem in our global health system including the emergent Sar-Cov-2 virus. Further study to understand the association of the MHC molecule and immune response for every individual should be pursued. The study could be used as a principle for family planning to avoid having younger generations who are prone to be the viral carriers. It, however, might be more practical in animal farms than human beings, for example the pig, which is a reservoir host of the Japanese encephalitis virus (JEV). Pigs with SLA (Swine leukocyte antigen) causing chronic JEV infection should be removed from the system of the animal husbandry industry. In the meantime, pigs with any SLA allelic genes that can clear JEV should be developed for further farming. More important, an effective antiviral drug truly needs to be developed. The drugs might be effective directly to the viruses or promote the role of the NK cell. In addition, passive immunity from people with high levels of antibody titer who have recovered from a viral infection can also be a good choice to eradicate all the viral agents in the persistent viral host. Leaving someone with a chronic persistent infection without a complete cure or believing that it can heal on its own should not be continued, especially with many emergent viruses at present.

6. Abbreviation

Ab: antibody
APC: antigen presenting cell
BCR: B cell receptor
HLA: human leucocyte antigen
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HSV: Herpes simplex virus
HIV: Human immunodeficiency virus
Ig: immunoglobulin
JEV: Japanese encephalitis virus
MHC: major histocompatibility complex
pMHC: MHC-peptide complex
SLA: swine leukocyte antigen
Tfh: follicular helper T cell
Th: helper T cell
Tc: cytotoxic T cell
TCR: T cell receptor

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