Perspective Concerning the Relationship between MHC Alleles and Viral Persistence

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Abstract

The viral persistence infection becomes a major problem of public health in terms of the viral epidemic because many of the persistently infected individuals might not show any clinical symptom. The incidences of persistency in different viruses are varied. The highest rate of persistent viral infection is Hepatitis C virus (HCV) which has been reported for 60-80% of the acutely infected patients. This causes the difficulty to the global public health to prevent viral transmission and epidemic. This article proposes a perspective to explain that viral persistence is associated with the appearance of the MHC allele molecules in each person. This relates to the process to induce the appropriate adaptive immunity, especially the effective cytotoxic T cell clone(s), to clear the entire infected virus from the infected host. The comprehension of the viral pathogenesis concerning viral persistence is the fundamental issue to prevent the viral epidemic and further search for an effective strategy to treat the viral persistence infection in the future.

Keywords: *Viral persistency, Viral epidemic, MHC alleles, Adaptive immunity, Cytotoxic T cell, Viral prevention*

1. Introduction

Viruses are the obligated intracellular pathogens and require proliferation inside the target host cell to cause acute viral infection. In general, the viral drug is not the choice for treatment of most of the viral infections because it has the high potential to cause the side-effects to the host cells, thus manufacturing of the viral drugs is not very popular. Accordingly, symptomatic treatment is a major strategy to process to cure the viral-diagnosed patients to control the symptoms until the adaptive immunity is raised up to be able to fight against the invading viral agents. The patients can be recovered if their immunity could be produced in time, which takes approximately a week or two. However, many viruses do not cause only acute but also chronic infection. The definition of chronic viral infection is that the infected virus keeps exist and replicate in a host for a longer time, usually longer than 6 months, although during the time the viruses may cause the symptomless or subclinical symptom to the infected patients. However, the virus agent can transmit to others during this period of time (Last, 2020). There are two major kinds of chronic viral infections, which are latency and persistence. Latent infection is caused by a kind of unique virus that can evade the host's immunity after causing the pathogenesis. The examples of viral latent infections are those members of Herpesviridae such as Herpes simplex and Varicella-Zoster virus (Steiner & Kennedy, 1995; Minarovits, 2006; Thellman, & Triezenberg, 2017). In this case, the viruses locate in the privilege cells/organ such as nerve cells where the host's immunity cannot reach for responsiveness. There is yet knowledge to eliminate the virus from the latently infected individuals. There were reports that using antiviral drugs such as acyclovir, which is the DNA polymerase inhibitor drug, can prevent the latent viral infection in animal models (Dobson, Little & Scott, 1980; Sawtell, Thompson, Stanberry, & Bernstein, 2001). However, this information is still in controversy, especially in a clinical study. The herpesvirus infected patients usually end up with the latent infection (van Lint et al., 2005). Unlike a latent viral infection, on the other hand, the incidence of viral persistent infection of each virus is varied (Peng et al., 1988; Ravi et al., 1993; WHO, 2013; Teunis et al., 2015; Kanno et al., 2018). Among all the viral persistent infections, the Hepatitis C virus causes unusual numbers of viral persistency which could reach 60-80% in some studies (Lavanchy, 2009; Barathan et al., 2018). The incidence of persistent viral infection, as same as any other chronic viral infection, is a major problem of a viral epidemic. Comparing to the latent viral infection, there is not yet an explanation of persistent viral infection. The virus agent keeps proliferating in a healthy immune individual without any major symptom. Thus, this article will present the perspective to explain the cause of the viral persistence which relates to the role of the adaptive immunity, especially the action of the cytotoxic T cell (Tc), also of

the essential role of the major histocompatibility complex (MHC) molecule which is needed for activating the naive lymphocyte clones.

Virus infection requires the viral receptor molecule(s)

As mentioned, a virus is an obligate intracellular pathogenic particle. To maintain its proliferation, the virus does not only need to invade our body but also require entry into its susceptible target host cell. To do so, a particular virus uses its ligand to attach the cellular molecule so-called the viral receptor molecule on the target cell membrane (Campadelli-Fiume et al., 2007; Ploss & Evans, 2012; Sautto et al., 2016; Kumar & Chandran, 2016). The interaction of the viral ligand and the viral receptor molecule leads to the penetration and subsequent proliferation of the virus inside the specific target host cell. Some viruses also require a co-receptor molecule besides the principle viral receptor molecule. For example, HIV requires not only CD4 molecule as its viral receptor but also CXCR4 or CCR5 as its co-receptor molecule (Deng et al., 1996; Coakley, Petropoulos, & Whitcomb, 2005). As known so far, some viruses could enter the target host cell with multiple receptor molecules such as Herpes simplex virus (Spears, 2004; Campadelli-Fiume et al., 2007) while some viruses such as Adenovirus and Coxsackievirus B3 have the common primary receptor which is CAR (Coxsackie and Adenovirus receptor) (Bergelson et al., 1997). The existence of the viral receptor molecule on the cellular membrane could explain the susceptibility of the viral infection of the host. The individuals or animals that do not possess the viral receptor molecules are not susceptible to viral infection. Inside the target host cell, the viral agent can avoid the attack of humoral immunity. The only way for the host to eliminate the intracellular viral agent is the role of the capable cellular immunity.

Viral immunogenicity

Besides infection into the compatible target cell, viral agents also play a role as an immunogen to induce the host's immunity. The part of the antigen that can induce an immune response in the body is called epitope (Groothuis & Needfjes, 2005; Lázaro, Gamarra, & Del Val, 2015). Normally, the immunogen is captured by the innate immune cells such as macrophage and dendritic cells to play a role as the primary antigen-presenting cells (APCs) (Momburg & Hengel, 2002; Hume, 2008; Kelly & Trowsdale, 2019). The primary immune response takes place in secondary lymphoid organs such as lymph nodes and spleen. APCs bring the immunogen from the invading site into the lymphoid organs to process the acquired immune response. APCs randomly cleave antigen to small peptides which are subsequently combined to the molecule so-called major histocompatibility complex (MHC) to form the MHC-peptide complex molecule (Momburg & Hengel, 2002; Lázaro et al., 2015). There are two classes of MHCs which are the class I and II. The MHC class I can be expressed by any nucleated cells while MHC class II molecule can be found only in the APCs. Thus, a mature red blood cell does not express any MHC molecule. The MHC-peptide complex is a result of the antigen processing in APCs to induce the specific T lymphocyte of either cytotoxic T cell (Tc) or helper T cell (Th) clones (Roach & Furuta, 2015; Kelly & Trousdale, 2019). There are also two pathways of the Ag processing, class I and II. The class I antigen processing is to process the short peptides of approximately 8-12 amino acids, as an epitope, to the groove of MHC class I molecule to activate a specific Tc cell clone thru its receptor so-called T cell receptor (TCR) (Zarutskie et al., 1999; Momburg & Hengel, 2002; Shastri, Schwab & Serwold, 2002). Class II antigen processing works with the larger size of an epitope which is around 12-20 amino acids to the MHC class II to form MHC II-peptide complex to induce the susceptible Th cell clone (Drozina, Kohoutek, Jabrane-Ferrat, & Peterlin, 2005; Roach & Furuta, 2015).

Meanwhile, the B cell epitope stimulates B lymphocyte directly through B cell receptor (BCR) regardless of any association to the MHC molecule (Roche & Furuta, 2015). The B cell epitope with approximately 5-20 amino acids of the native structure of the antigen can directly induce B cell clone thru the specific B cell receptor (BCR). Usually, the activated B cell clone can produce only IgM as the primary humoral immune response. To differentiate to plasma cells to produce other classes of immunoglobulin, the B lymphocyte clone requires the cognate Th clone to promote (Murin, Wilson, & Ward, 2019). During this period, the B and Th cells play the reciprocal role to support each other (Asano, Nakayama, Kubo, Yagi, & Tada, 1987). B cell, which also expresses the MHC II molecule plays an antigen presentation role to the

cognate Th which also sends some signals to promote B lymphocyte to differentiate to plasma cells to synthesize various classes of immunoglobulin. This requires various kinds of lymphokines to differentiate to different plasma cells (Berzofsky, 1983; Murin et al., 2019). Without Th cell, the B cell can produce only IgM, not other classes which are IgG, IgA, and IgE. Accordingly, Th cell plays the central role to maturate both B and Tc lymphocyte, including the memory cells for the long-term protection of the secondary viral infection.

The diversity of MHC molecules

As mentioned, there are two classes of MHC molecules, and each class has a different role in a cellular immune response. Each class of MHC genes comprises, at least, three classical loci. The MHC molecule of humans is HLA which stands for human leukocyte antigen (HLA) based on the fact that the MHC molecules were firstly found and studied in the white blood cell. The MHC molecules of other animals are nominated differently, for example, pig's MHC is called SLA, which stands for swine leukocyte antigen, and dog's HLA is DLA as from dog leukocyte antigen. The loci of classical class I MHC of humans are HLA-A, B, and C while classical class II of human's MHC are HLA-DP, DQ, and DR (Agrawal & Kishore, 2000). HLA molecules are highly polymorphic. The molecules inherit co-dominantly from the parents. Thus, each locus of the MHC genome in an individual could be either heterozygous or homozygous. In each locus, a heterozygous has two different gene alleles while a homozygous has the same gene allele. Accordingly, the numbers of gene alleles of MHC class I and II in any individual are limited to 3-6 gene alleles for each class. For example, the individual who has all three loci as homozygous would have only 3 gene alleles while those who have all loci as heterozygous would have 6 gene alleles. Since the MHC gene alleles are highly polymorphic, so the possibility that individuals have the same set of gene alleles would not be more than one in a million which, mostly, can be found in those who are an identical twin. It has been reported, so far, by the WHO Nomenclature Committee for Factors of the HLA System, that the numbers of human MHC class I gene alleles which are HLA-A, HLA-B, and HLA-C are approximately 4.3, 5.2, 3.9 x 103 gene alleles, respectively while the numbers of human MHC class II gene alleles as of HLA-DP, HLA-DQ, and HLA-DR (MHC class II) are 1.1, 1.2 and 2.6 x 103 gene alleles, respectively (Marsh et al., 2018).

Viral persistence

As mentioned, viral persistence is another category of the chronic viral infection which is defined differently from latent infection. During viral persistence, the virus continuously replicates and remains infectious while the latent viral infection remains inactive or dormant in its host cell and does not cause any clinical symptom during the time. With some unknown reason for the viral persistence infection, most of the infected hosts also do not develop any significant clinical symptoms, although the viral replication remains active as same as the host's immunity. It is interesting to look for the reason to explain how viral agents can accommodate the hosts without any critical symptoms. Meanwhile, the host's immunity cannot get rid of the viral agent from the body. As mentioned above, the rates of the persistent viral infections are varied (Peng et al., 1988; Ravi et al., 1993; Lavanchy, 2009; WHO, 2013; Teunis et al., 2015; Kanno et al., 2018; Barathan et al., 2018).

Besides human and other high-evolved immune animals, persistent viral infection can also be found in low-evolved immune animals such as mosquitoes which many become the viral carriers such as Dengue virus, Japanese encephalitis virus, West Nile virus, and others (Lee, Webster, Madzokere, Stephenson, & Herrero, 2019). Penaeid shrimp, which has become the subjects for a research study with a reason for its booming industry as a farming animal in many countries, also performs various kinds of viral persistence infections. The shrimp's viruses such as Infectious hypodermal and hematopoietic necrosis virus (IHHNV), White spot virus (WSV), and Yellowhead virus (YHV) caused the pathogenesis and high mortality to the infected shrimp in the emergent period over two decades ago (Flegel, 2001, Sritunyalucksana, Srisala, McColl, Nielsen, & Flegel, 2006; Moger, Mohan, Venugopal, & Karunasagar, 2011). Interestingly, although there have been the evidence of persistent viral infections, the rate of shrimp mortality has been less and became none after a couple of years of the viral epidemics if the pond-management systems such as the

quality of water, the feeding system and the ratio of rearing shrimp have been paid great attention to maintain its optimal condition. Oppositely, the poor managing farms, with the viral persisted shrimp, kept losing (Flegel, 2001). The study found that challenging of the virus from the occluded persistent infected shrimp to the naïve shrimp population showed acute infected and high mortality (Flegel, 2001; Moger et al., 2011). Accordingly, the viral genomic mutation should be excluded from the explanation. This similar situation also occurred in the insect (Cheng, Liu, Wang, & Xiao, 2016). Insects and shrimps have only native immunity which lacks the effective cytotoxic T cell to clear the infected viral cell. As mentioned, although human has adaptive CMIR, especially the cytotoxic T cell, persistent viral infection still exists in some individuals who have a healthy immune system. This will be a point for further discussion.

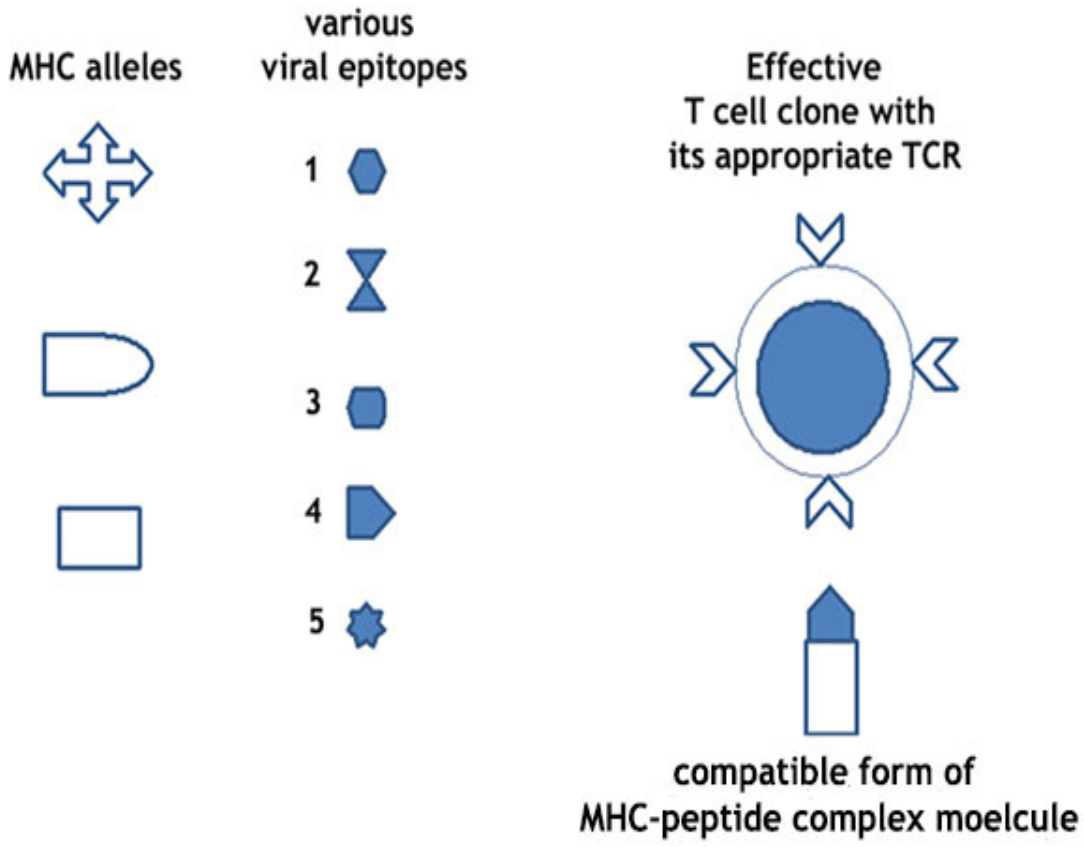

Figure 1 Illustrates the compatible MHC- peptide complex molecule to activate the effective T cell clone through the T cell receptor (TCR). It shows three different forms of MHC alleles which are cross, bullet, and square shape while the viral agent has been processed by APC to various viral epitopes as shown by the numbers of 1-5. Finally, the square shape of the MHC allele forms the compatible complex molecule with the viral epitope number 4 to activate the effective T cell clone to eliminate the infected viral cell. Oppositely, the individuals who lack the appropriate MHC allele cannot form the complex molecule to activate the effective T cell to eliminate the viral infected target cell, thus causes viral persistency.

The association of the MHC molecules and viral clearance

Considering the Ag presentation process, the peptide-MHC complex is the crucial factor to induce the susceptible lymphocyte clones thru the specific receptors of the lymphocytes. After invasion into a body,

as mentioned, viral proteins are processed by APCs based on an immune response pathway (Hume, 2008; Kelly & Trowsdale, 2019). The Ag processing in APC is to induce and activate the susceptible T lymphocyte clones. The immune process to eliminate the viral particles requires adaptive immunity of both cellulars mediated (CMIR) and humoral mediated (HMIR) immune response of cytotoxic T cell and antibody, respectively. After being induced, the activated Tc clone moves to attack the viral infected target cell which also presents the same peptide-MHC class I complex molecule as same as the APC (Cusick & Jindra, 2018; D'Alicandro, Romania, Melaiu, & Fruci, 2018). However, the accomplishment of the Tc clone also requires the coordination of the Th cell (Hoyer et al., 2014). With the support of Th cell, the activated Tc develops to an effective Tc to successfully attack the infected viral cell (Asano et al., 1987; Hoyer et al., 2014). Thus, to generate the specific Tc clone which is the most effective immune cell to attack and eliminate the infected viral cell, the association of the MHC haplotype and the T cell epitope to form the MHC-peptide complex molecule is the crucial process. The disappearance of the appropriate form of the MHC-peptide complex molecule causes the loss of inducement to activate the appropriate Tc cell clone (Hoyer et al., 2014). Thus, the MHC I allele of the individual is a critical molecule for the accomplishment of the viral clearance. Accordingly, figure 1 showed the compatibility of the MHC and the viral epitope to induce the appropriate Tc cell clone.

Perspective to eliminate viral persistence

With all the guidelines, this article presents the cause of the viral persistence infection, which does relate to the MHC class I haplotypes in the individuals. Lack of the appropriate MHC alleles, the viral persistent infected individuals, cannot induce an effective Tc cell clone(s) for the viral clearance as same as shrimp and insect which do not have the adaptive immune response of the CMIR. More specifically, the MHC haplotypes of the persistently infected individuals cannot interact with the crucial viral epitope(s) to form the MHC-peptide complex to induce the appropriate lymphocyte clone(s) for clearance of the viral agent completely. If the compatible complex molecule of MHC-epitope cannot be formed, the appropriate Tc and Th cannot be induced. Thus, there is no effective immune response to eliminate the infected viral cell. This could be the explanation for the persistent viral infection in those virally infected individuals. In comparison with shrimp and insect, native immunity cannot eliminate all the viral agents but act to one another as if a tug-of-war. In this situation, the native immunity does not have the perfect capacity to clear all the viral agents. In contrast, the viral agents cannot extremely proliferate to cause pathogenesis unless the native immunity of the host is less effective with some other reasons such as the inappropriate environment. This could be the reason for the explanation of the subclinical symptom in those viral persistence individuals. Although, based on this concept, it might be too complicated to find a way to clear the viral persistence infection in all the viral carriers of the viral persistence individuals since it depends on the appearance of the MHC allele in the individuals who cannot induce the effective cytotoxic T cell. Besides cytotoxic T cell, natural killer (NK) cell can also play a role to eliminate the infected viral cell but does not require MHC compatibility to recognize the infected viral cell. Unfortunately, the NK cell is less effective than Tc. This might be due to the lack of co-operation from the associated Th. If so, it is possible to enhance the NK cell's activity with some specific cytokines of Th.

2. Conclusion

This article presents the concept to explain the effective strategy to eliminate the viral persistence infection by the role of the CMIR, especially cytotoxic T cell. The effective Tc cannot be activated if the MHC haplotype(s) of the individuals is/are not appropriate to form the MHC-epitope complex molecule(s) to induce the Tc clone. However, this concept requires further studies. It will be a great support if a medical technology to identify HLA typing is developed to make it easier and cheaper for public health services.

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