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Review Article

CIENT PERIODIQUE

The Crucial Factors to Producing the Compatible Viral Vaccines for Individuals

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Abstract

Subunit viral vaccine becomes the major choice for manufacturing viral vaccine with a thought of safety reason to prevent side effects in addition to the convenient way of production. However, the success to use subunit viral vaccine to prevent a particular viral infection is very limited. This is different from the time when the Cowpox virus was originally used for vaccination to prevent the smallpox viral epidemic over a century ago. Although the knowledge of immunity has been discovered a lot more than Edward Jenner's period, the effectiveness of most of the viral vaccines could not reach our accomplishment. In view of this, we need to revise our knowledge on the best technology for viral vaccine production. Basically, to induce immunity to prevent a viral infection, our body must produce a specific antibody which needs induction not only by a particular viral antigen but also the molecules called major histocompatibility complex (MHC). Each molecule of MHC alleles plays a key role in the immune response by forming a specific complex with its appropriate epitope to induce a specific T cell clone through its specific receptor. MHC class I is required for inducing cytotoxic T cell while MHC class II is for helper T cell. Helper T cell plays a key role to induce an effective stage of acquired immunity especially a specific antibody which is believed to be a gearwheel to prevent an invasion of the particular viral particle. To produce the viral- specific antibody, class II MHC plays a key role to induce helper T cell and then B cell to

synthesize a specific antibody. Since the MHC gene alleles are highly polymorphic so the possibility that individuals have the same gene alleles would be seldom. Accordingly, a subunit viral vaccine, which contains a limit number of epitopes, would reduce a capacity of an antigen presenting cell, such as a dendritic cell, to process some epitopes to induce the particular helper T cell clones. Subsequently, the corresponding B cell clones cannot synthesize the specific antibody to neutralize the particular infectious viral particle. Accordingly, an alternative notion and principle to develop a viral vaccine for an individual human population will be discussed in this article.

Abbreviation

Ag: antigen
APC: antigen presenting cell
HBV: hepatitis B virus
HLA: human leukocyte antigen
MHC: major histocompatibility complex
TCR: T cell receptor
Tc: cytotoxic T cell
Th: helper T cell

Introduction

Viral epidemics of various viral agents keep being the leading headline in the world. Viral vaccines are believed to be the principal tool for solving the solution. However, there are many controversies for the efficiency of the viral vaccines which have been manufactured from various pharmaceutical companies. Although, there were limited reports for evaluating the various kinds of viral vaccines for both human population and livestock, many researchers have reported the low efficiency of the viral vaccines and none of them can cover up all the population. The recombinant Hepatitis B vaccine which is derived from the protective surface antigen has been considered as the most effective viral vaccine in the market. However, there were approximately 10-15% of the HBV vaccinees who lack seroprotection after the complete doses of the vaccines by various investigations in the different populations [1-4]. There was a report to boost the Chinese high school teens who had been vaccinated with HBV vaccine as infants but became seronegative. The study found that 28.7% (158/551) of these teens did not produce anti-HBs antibody (anti- HBV level <1mlU/mL). In addition, 63% of them cannot develop seroprotection (anti-HBV level <10 mlU/mL) [5]. The similar study by Posuwan *et al* [6] found that 15% of the Thai medical students who had been vaccinated during the infant also showed no response after booster with the HBV vaccine. These studies require further explanation and discussion for the reason. In fact, there is no study to cover up the efficiency of any viral vaccines which can provide seroprotection to all the population. Is it possible that the viral vaccine might be highly efficient only in the tested population but not the others? Accordingly, this article will give an overview and discuss the problem of insufficient efficiency of the viral vaccines in general. In addition, the perspective for the efficient production of the viral vaccine will be proposed.

Association Between Immune Response and MHC Molecules

When a foreign substance entry into a body it would induce an immune response if the substance contains

the molecule with complexity and significantly high molecular weight. The primary antigen presenting cell (APCs) i.e. macrophage and dendritic cell play the major role to activate specific naïve T lymphocytes by processing the foreign substance which is commonly called as an antigen (Ag). The interaction between APCs and T lymphocyte requires a specific recognition [7]. The primary APCs play the role to process the antigen with the requirement of the MHC (major histocompatibility complex) molecules for the activation the compatible lymphocyte clones [8]. MHCs are the sets of molecules located on the cell membrane and classified into 2 classes. Each class comprises a few different loci (locus). The loci of both classes of MHC molecules are categorized as the classical and non-classical loci. Classical MHC loci are the one that manipulates for adaptive immunity while non-classical loci have different functions such as working with NK cells which functions as a natural immunity [9,10]. The MHC molecule of human 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 different animals are nominated differently i.e., pig's MHC is called SLA which stands for swine leukocyte antigen, dog' HLA MHC is DLA as from dog leukocyte antigen. The loci of classical class I MHC of human are HLA-A, B, and C while the non-classical class I are HLA- E, F, and G. The loci of classical class II MHC of human are HLA-DP, DQ, and DR while of the non-classical class II are HLA-DO and DM [10]. This article will mention mainly on the classical MHC molecules which associate to the role of the viral vaccines for immunization of the adaptive immunity.

The Diversity of MHC Molecules

MHC class I expresses in every cell in a body that performs nucleic expression. Therefore, red blood cell does not have MHC molecules [11]. MHC class II molecule can be found only on the immune cells that play the antigen presenting role such as dendritic cell, macrophage and B lymphocyte [12]. Each locus of MHC genes contains definite variant genes, so-called gene allele, and inherits equally from the parent's chromatid from generation to generation. Since the MHC gene alleles are highly polymorphic [11,12] so the possibility that individuals have the same MHC gene alleles cannot be less than one millionth which can mostly be found in those who are an identical twin. Thus, HLAs or any of the MHC molecules are unique to an individual. MHC molecules have high molecular weight and form complex molecule, therefore it qualifies as an antigen. It can induce immune response among the individuals and become the major reason for incompatible organ transplantation [13,14].

The other significant role of the MHC molecule is to induce the naïve T lymphocyte thru its T cell receptor (TCR). In the APCs, MHC molecule forms a complex molecule with a short peptide (T cell epitope), so-called MHC- peptide complex which interacts to the compatible TCR molecule of T lymphocyte clone. This is called MHC restriction. Therefore, the activated T lymphocytes are created for a further immune response [15,16]. Accordingly, the induction of T lymphocyte does not depend on just the availability of T cell epitope but also the allelic MHC variants. Since each class of MHC comprises of three classical loci and each locus cannot have more than two MHC gene alleles. A heterozygous has two different gene alleles while a homozygous has the same gene allele in a locus. Therefore, the numbers of gene alleles of MHC class I, as same as MHC class II, in any individual are 3-6 gene alleles. It has been reported, so far, by the WHO Nomenclature Committee for Factors of the HLA System, the numbers of gene alleles of HLA-A, HLA-B, and HLA-C (MHC class I) are approximately 4.3, 5.2, 3.9 x 103 gene alleles, respectively. In the meantime,

the numbers of gene alleles of HLA-DP, HLA-DQ, and HLA-DR (MHC class II) are 1.1, 1.2 and 2.6 x 10^3 gene alleles, respectively [17]. Therefore, the probability for the individuals to have the compatible MHC gene alleles is very rare.

Antigen Processing and Presentation

As mentioned that antigen requires MHC molecule to form a complex molecule to activate T cell clones, therefore, an antigen requires the process so-called antigen processing. There are two pathways of antigen processing so-called class I and class II antigen processing. Tc cell can be activated by class I MHC restriction [15] while Th requires class II MHC restriction [16]. This process is to combine the short peptides or T cell epitopes to the MHC allele and transport to the cell surface for MHC restriction [15,16]. In addition, the formation of the MHC molecule and the different peptides perform different tertiary structure of the MHC-peptide complex which induces different T cell receptor of the T cell clones [18,19].

Class I antigen processing is an endogenous pathway to present cellular peptide fragments including the infected viral peptide to form a complex molecule with class I MHC molecule and then locates on the cell surface. For the class I antigen processing, the endogenous proteins are degraded by the proteasome to the various short peptide with the size of approximately 8-15 residues [11,15]. These sizes are believed to be the optimal size for fitting within the peptide binding cleft of class I MHC molecule. After degradation, the short peptide then associates to TAP which is a protein that spans the membrane of the rough endoplasmic reticulum to transport the peptide into the lumen of RER (rough endoplasmic reticulum). Then chaperone proteins facilitate the proper folding of class I MHC allele to the compatible short peptides [20-22]. Class I MHC restriction is necessary for the 2 missions of Tc which are the Tc activation by APCs and the attack of the target cell [23,24]. As mentioned that class I antigen processing is an endogenous pathway so it means all the endogenous proteins, both self and non-self peptides, can be processed. However, the class I MHC restriction of self-peptide cannot induce Tc clones since the autologous T cell clones had been deleted by the negative selection procedure in a neonatal stage of T cell development. Thus, only foreign substances, such as a viral peptide, can induce the existed Tc cell clones and produce the adaptive immune response [11,15].

On the other hand, class II antigen processing can process only foreign peptide as called the exogenous pathway. This is because a nascent class II MHC molecule locates in the RER, has been blocked by a peptide so-called Ii (invariant chain) at its peptide-binding cleft to form the class II-Ii complex. The Ii plays the role to prevent the cleft of the class II MHC molecule to be bound by the endogenous peptides. Besides, the Ii also plays a role to facilitate class II MHC molecule to export from the ER in a vesicle. The class II MHC-Ii complex is transported thru the Golgi body into the MHC class II compartment (MIIC). After the degradation of the foreign proteins by acid- dependent proteases in endosomes, Ii is then broken down in stages. However, a small fragment of Ii so-called class II-associated invariant chain peptide (CLIP) still blocks the peptide binding cleft of the class II MHC molecule. To accept a compatible short peptide or T cell epitope, HLA-DM, which has a class II MHC-like structure, play the role to remove the CLIP. Then, a T cell epitope moves on to replace the CLIP to form the stable class II MHC-peptide complex for presentation on the cell surface for the recognition of a compatible Th cell clone [18,25]. It shall be noted that while class I MHC usually binds properly to a short peptide of 8-10 residues, class II MHC prefers considerable larger peptide of approximately 15-20 residues [16].

The Immune Response Against Viral Infection

The viral infection is an obligate intracellular agent because it can proliferate only if it accommodates in a susceptible target cell. However, this does not mean that the viral agent exists only inside the target cell because its progeny must be released from the cell before re-infection to another target cell. Thus, the fight against viral infection by adaptive immunity requires both cellular mediated (CMIR) and humoral mediated (HMIR) immune response of cytotoxic T cell and antibody, respectively. After the invasion of a viral agent, the viral proteins are processed by both antigens presenting cell (APCs) [15] and target cell [26,27]. After being activated by class I MHC restriction of the APC, the activated Tc move to attack the target cell. However, the accomplishment of the Tc function also requires the coordination of Th. The helper T cell plays a key role to promote not only CMIR but also HMIR by inducing a specific B lymphocyte clone to differentiate to antibody-secreting B cells (plasma cells) to produce all classes of specific antibody. In the main fact, Th and B cells have reciprocal interaction with one another [28]. After being induced by a B cell epitope of an antigen, the induced B cell clone also works as a secondary APC for the cognate Th cell clone which also supports B cell for differentiation and creates the memory B cell. The memory B cell clone(s) and the specific antibodies play the gearwheel role to prevent further viral invasion and infection. Although the viral-specific antibody degenerate based on their half-life, the memory B cell can recognize the re-invasion of the same viral agent to promptly produce the specific antibody for the prevention of the viral infection which is the main strategy of the viral vaccine [29].

Crucial Strategies for Viral Vaccine Efficiency

It is obvious that MHC molecules play the important part to modulate the immune response by forming the complex molecule with a degraded short peptide of an antigen to activate Tc and Th thru APCs. Both class I and II MHC molecules are highly polymorphic [17]. Therefore, the individual allelic MHC requires good matching to the degraded short peptides to form the MHC-peptide complex for MHC restriction. More studies are still required to show how an individual allelic MHC interacts to a particular short peptide. Accordingly, some particular Th cell clones cannot be induced if the compatible MHC-peptide complex cannot be formed [19,29,30]. This logic can also be supported by the finding of Benacerraf and McDevitt [31] who reported that different inbred mice respond to produce antibody against a short synthetic peptide differently. C57 mice responded well to the synthetic polypeptide (T, G)-A-L while CBA mice did poorly [10]. A good match of the peptide and the MHC binding groove is important, but certainly not the sole determinant of its presentation. In fact, the formation of a MHC-peptide complex depends on its peptide-loading pathway which is mainly authorized by some of the factors. Besides the protease activity and the availability of chaperones, MHC alleles and the availability of the antigen are the main components for the confluence of the MHC restriction for induction the associated T cell clones. This is to explain why many persons do not respond efficiently to gain the seroprotection after the HBV vaccination as mentioned earlier. It might be assumed that those vaccinees lack the suitable MHC alleles to form the suitable MHC-peptide complex with the HBV-vaccine-derived peptides [32,33].

The crucial immune cell to authorize the achievement of both Tc and B cell is Th cell. Tc cell also requires Th cell for activation. Subsequently, the Tc cell plays an efficient action to eliminate the infected target cell. In addition, Th cell plays a crucial role to activate B cell to differentiate to the antibody-secreting B cells

(plasma cells) and memory B cell. Plasma cells play the actual role to produce all classes of antibodies. Without the cognate Th cell, the B cell can produce only IgM and cannot create a memory cell. The main purpose of giving viral vaccines to the population is to induce memory lymphocytes. The memory lymphocytes can recognize and respond to the epidemic virus much more quickly and effectively before the infected virus can cause pathogenicity. With the reason, an antibody which is produced from B cell is more important to prevent the viral infection than the Tc cell. The compatible antibody can neutralize the viral agent to prevent the viral attachment on the viral receptor of the target cell so the virus cannot enter into the target cell, therefore, no occurrence of viral proliferation. On the other hand, Tc can function only after the target cell has been already infected by the virus since the recognition of the active Tc requires class I MHC restriction of the target cell. With this reason, the induction of memory B cell should be the major target for the production of the viral vaccine. Accordingly, the viral vaccine should contain the suitable and sufficient epitopes to process for the antigen presentation with the compatible class II MHC alleles in the population. This means any particular viral vaccine cannot be considered to be suitable for all over the global. It needs to be suitable for the MHC distribution of the community which also depends on the race and tribe.

It should be a solution to produce the viral vaccine from the wild type viral agent which can cover up all of the epitopes of the virus for induction of our immune response. This might be the explanation for the success of Jenner's cowpox vaccine to prevent the epidemic of smallpox virus over a century ago. The good point to use subunit vaccine is to lower the side effect. However, subunit vaccine might be a reason to give less efficiency to immunize some of the populations. We must reconsider to find a different solution to produce the viral vaccine with the criteria of both efficiency and low side effect. Subunit vaccines which become the technology of choice for production by a recombination molecular technology cover up only a part of the viral proteins. The candidate subunit viral vaccine of a particular virus might give positive seroconversion in the tested laboratory animals which mostly inbred and possess the limited diversity of MHC alleles. The viral vaccines that work in the tested animal or any population do not mean it can provide accomplishment in another population if the MHC alleles are highly different and not compatible with the manufacturing vial vaccine. Therefore, the subunit viral vaccine should be produced specifically for any particular population. However, it might be more convenient to provide the mixture of various subunit vaccines (polytopes) which cover up all the viral epitopes for producing a particular viral vaccine to cover up all the population.

It should be great to make a project to identify the HLA alleles of all vaccinees in a community especially the class II MHC alleles. This would be appropriate for planning the strategy to produce the effective viral vaccine for the particular community. However, HLA identification package is still highly expensive. The cheaper technology for identification HLA gene alleles should be developed to allow all the population to know their HLA typing as same as the red blood cell group. This should be the better way for us to learn and understand the association between the MHCs and the prevention of viral epidemic if it is the genuine reason for the effectiveness of the viral vaccines. The governments of many countries made a false alarm to demand viral vaccines from pharmaceutical companies regardless of any consideration for the appropriate of the vaccine for their population. As we can realize that the expense of viral vaccines is a high-cost budget especially for the under-developed countries, which need to import all kinds of the vaccines. Using the incompatible viral vaccines can be worthless with the astronomical expense. Viral vaccination project can be a dilemma and cause more problems in many aspects, not just public health but also the economy and social problems. People become delusive that they were protected but actually not if they were immunized with the

inappropriate viral vaccine and ignore to follow up seroconversion. It will be helpful if the package of all the viral vaccine includes not only vaccination but also following up the seroconversion. Therefore the pharmaceutical company should have the full responsibility to reimburse all the cost of the vaccines in case that the vaccinees do not produce seroprotection on a certain time.

Conclusion

In conclusion, MHC molecules play an important role to induce adaptive immunity with the combination to the antigen epitope. Each of us has unique variants of MHC molecules which can process only some types of T cell epitope for activation our own immunity to fight and prevent the viral infections. The pharmaceutical company should find a fully efficient way to produce viral vaccines that can provide seroprotection to all vaccinees. The public health ministry and the government must be aware and make the policy to prevent the viral epidemic with a suitable viral vaccine to protect their citizen with the comprehension of these issues.

Competing Interests

This article was written without any conflict of interest.

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