Anti-viral Vaccines based on Induced Inhibition of Viral Receptors

Tirasak Pasharawipas*
Microbiology Unit, Department of Medical Science, Faculty of Science, Rangsit University, Paholyothin Rd., Pathumthani, 12000, Thailand

Abstract

Due to the threat of global epidemics from emerging viruses, researchers try to rapidly develop new vaccines based on immunological principles, and often focus on subunit proteins. Although such vaccines can theoretically induce acquired immune responses to prevent viral infection, in reality most fail to give the desired protection in clinical practice. There are also reports that invertebrates can be vaccinated to prevent specific viral infections despite that fact that they are not capable of an acquired immune response. This article proposes that induced inhibition of viral receptors may serve as a cell-membrane based, cellular response mechanism for rapid anti-viral protection in both vertebrates and invertebrates. Since this mechanism does not require memory cells that are normally targeted for development of acquired vertebrate immunity, it offers an alternative approach for the development of vaccines in both invertebrates and vertebrates.

Keywords: Virus; Vaccine; Inducible viral receptor

Introduction

Viral infection

A virus is a protein particle that contains a genome but lacks cellular organelles, and it depends on host cell resources for proliferation. The genome may be either DNA or RNA (a main feature for classification). It is generally accepted that viruses infect target cells by attachment to compatible cellular receptor(s) as a requirement for penetration, followed by proliferation inside cells. Some viruses have been reported to attach to more than one kind of cellular molecule [1]. Besides attachment to the main receptor, some viruses also require a co-receptor(s) [2,3]. It has been reported that individuals not possessing a compatible receptor molecule(s) (either the main or co-receptor molecules) would not be infected upon virus exposure. For example, target cells that lack the CCR5 co-receptor molecule for human immunodeficiency virus (HIV) attachment on the cell membrane cannot be infected by HIV [4]. Also, a specific antibody [5] that binds to this viral attachment molecule or an antagonist for the viral receptor molecule can also prevent viral infection [6-8], and these are major viral blockage strategies used in the development of vaccines to prevent viral infection. However, the strategy is often complicated and not always possible to achieve [9,10]. Long investigation is often needed to understand the nature of molecules that play a role in viral attachment to host cell membranes.

Immunity to viral infection

Higher animals possess both innate and acquired immunity. Innate, non-specific, immunity is believed to be mostly insufficient against viral infection, and subsequent acquired immunity is believed to be necessary to overcome it. Usually, the entire period needed for the acquired immune response to a primary viral infection is at least one week [11,12]. During this delay, the infected host usually shows signs or symptoms of disease resulting from viral pathogenesis. Acquired immunity works synergistically to protect the body from viral infection by a cellular mediated immune response (CMIR) and a humoral mediated immune response (HМИR). In the CMIR, the Tc (cytotoxic T cell), with support from the Th (helper T cell), plays the major role in eliminating viral infected cells, preventing viral maturation and spread to neighboring target cells [11]. The HMIR is induced via specific naïve B cell clones that differentiate into plasma cells, also with Th cell support. They produce antibodies to neutralize viral particles and prevent them from entering target cells. Thus, Tc and antibodies are the key elements in bringing a viral infection to an end. After a primary infection, memory cells of both HMIR and CMIR are generated and they work more efficiently and rapidly in a second infection [12,13] than did naïve B and T cells in the first. Vaccination is basically an attempt to mimic a primary viral infection to induce such memory, without invoking any symptoms of disease.

Since invertebrates are believed to lack acquired immunity, it should not be possible to use vaccination to induce memory for a more rapid and efficient immune response to subsequent viral infection. However, in the past 2 decades cultivated shrimp have become an important economic commodity, and study of their immunity has received more attention due to losses caused, particularly by viral diseases. It was noticed that shrimp disease epidemics caused by yellow head virus (YHV) and white spot syndrome virus (WSSV) showed massive mortality and loss when they first emerged but that losses decreased in succeeding years, despite continued presence of the viruses. There was no clear explanation as to how the viruses could persist in the shrimp without signs of disease unless they were raised in a poor environment or at excessive density [14-16]. It was found that a virus isolated from persistently infected shrimp could cause disease in other shrimp not previously exposed to it, suggesting that the virus had not mutated to low virulence in the persistently infected shrimp [16,17]. Thus, it was plausible to postulate that shrimp (as a representative invertebrate) possessed the ability to defend against viral infections despite their supposed lack of acquired immunity.

Persistent viral infections occur not only in invertebrates, but also vertebrates, for example Hepatitis B virus (HBV) [18,19] and Japanese encephalitis virus (JEV). Both viruses persist in their hosts, human and pig respectively, without any serious signs of disease [20]. This has been explained by the concept of negative selection of lymphocytic
clones during development of immune cells in the neonatal stage. The immune cells accept the viral-infected cells as part of "self" since they existed before the acquired immune system developed [11]. Thus, persistent HBV and JEV infections in these carriers are not examples of acquired immunity but examples of tolerance to the viruses, similar to viral tolerance in persistent shrimp infections. Accordingly, one of the interpretations of this fact is that the individual viral target cells possess a mechanism to limit viral proliferation and that it does not depend on acquired immunity. In addition, there was a report that tolerance to yellow head virus (YHV) in shrimp was correlated with low viral loads [21]. Thus, it is possible that suppression of viral receptor molecules might inhibit viral proliferation and result in viral persistence in shrimp.

**Viral vaccines**

The first well known vaccine that was used to prevent viral epidemics was reported by Edward Jenner for prevention of Smallpox. His vaccine was actually derived from a Cowpox virus, and it was a live vaccine [22]. This led to the notion of producing live attenuated vaccines that have been accepted as highly effective in preventing viral diseases. However, there is some concern regarding the possibility of genetic mutations back to virulence, and this has limited the application of attenuated viruses in public health. In addition, they have sometimes been reported to cause various side effects and they are not advisable for use in immune-compromised persons [22,23]. Inactivated and subunit vaccines are developed with the hope of encountering fewer side effects. However, the inactivated and subunit vaccines are generally reported to be less effective than live attenuated vaccines [11,24]. The difference is usually explained by stating that inactivated viral vaccines probably have lower immunogenicity due to alteration in conformational structure during inactivation [23]. In the case of subunit vaccines, higher efficacy in laboratory studies with animals than in clinical practice might be due to the poor antigenicity of subunit vaccines [23,25,26] or to complications involving the major histocompatibility complex (MHC). It is known that the MHC influences the processing and presentation of T cell epitopes to helper and cytotoxic T cells [11]. Since the human MHC is complex and diverse, MHC molecules for different individuals vary and could affect the process differently [27,28]. Besides the differences between MHC molecules of animals and humans, laboratory animals have limited variation of MHC molecules because most are inbred. Thus, a particular epitope(s) that may perform effectively in inbred animals may not work as effectively in humans who have different and diverse MHC molecules. There will be further discussion on the disappointing outcomes of subunit vaccines in the following section on induced inhibition of viral receptors.

**Questions concerning the roles of memory cells**

To discuss the role of memory cells in preventing viral infections, it is necessary to review some questions concerning the host immune response to viruses. Antibodies synthesized during a primary viral infection do not exist forever but have a limited half-life. Memory B cells (Bmem) are generated after the primary infection and might last for over ten years [11]. However, it is still questionable whether Bmem can respond fast enough to produce antibodies to prevent virus entry into target cells. There is no evidence to show that Bmem can spontaneously secrete all classes of immunoglobulins directly. Usually, activated B cells must differentiate into plasma cells to secrete immunoglobulins. The procedure of Bmem differentiation into a plasma cell occurs within lymphoid organs. Accordingly, time is needed for plasma cells to produce sufficient antibody to be released from the lymphoid organ and neutralize an infectious virus. In addition, B cell differentiation into plasma cells requires the support of Th cells. Do the Th cells need to be generated before antibody production? With all these requirements, could antibodies be available in time to prevent viral entry into target cells? In fact, the time when the virus is being recognized by Bmem cells is also the same time that the virus is attaching to target cells. Accordingly, there is no clear indication that Bmem would respond quickly enough to prevent viral entry into host cells.

Nor would memory Tc (TMEM) be able to greatly influence the early stage of a second viral infection since they cannot recognize the target virus directly either, but only in association with MHC class I molecules on the cell membrane of the target cell [29]. The Tc can function only if the target cell has already been infected. This means that a person who has been exposed to a second viral infection should have infected cells before the Tc response has been induced. Thus, in the following section, the concept of induced inhibition of viral receptors is introduced to describe a possible mechanism for rapid prevention of viral entry into host cells.

**The Concept of Inducible Viral Receptors**

Viral interference is a phenomenon whereby a cell infected with one virus can prevent entry by a second virus. This can involve either homo-viral [30,31] or hetero-viral interference [32,33]. In homoviral interference, a cell can prevent entry of a second, closely related virus. In hetero-viral interference, the cell can prevent entry of closely related plus non-related viruses [34]. Earlier studies hypothesized that the process of viral interference occurred intracellularly more than at the cellular membrane. However, this issue has been controversial and has never reached a final conclusion [35]. One proposed explanation for intracellular interference was based on lack of sufficient cellular resources to support replication of a second virus (i.e., competition for cellular resources) [35]. Another explanation was that defective interfering particles from the primary infection would inhibit replication of the second virus [36]. Although, these first two concepts might be able to partly explain homo-viral interference, they might not easily apply to hetero-viral interference. A third explanation focused on the synthesis of cytokines such as interferon that could prevent infection by the second virus [37,38]. However, the concept of interferon to prevent viral infections has been questioned by many clinical researchers [39,40].

Originally, the concept of inducible inhibition of viral receptors was proposed based on a study of the interaction between bacteriophage VHS1 and its host Vibrio harveyi (VH). As with most such relationships, the VH lysogen (VHL) could not be super-infected with VHS1 [41], possibly by down regulation of genes for the phage receptor. The study revealed that VHL carried VHS1 as an episome and that at cell division, one of the VH daughter cells often did not receive a copy of the phage genome (i.e., it became cured), probably because the speed of viral genome duplication and binary fission were different and independent [42,43]. Despite loss of the phage episome, the cured daughter cells (called pseudolysogens) retained their ability to resist phage entry, indicating inheritance from the mother cell of ability to down regulate the viral receptor protein. A hypothesis concerning inducible viral receptors postulated that cellular receptor molecule(s) is (are) down regulated when it (they) bind to viral ligand(s) preventing viral super-infection [43]. Down regulation of viral receptors after viral binding has been reported in eukaryotic cells [44]. The concept of inducible inhibition of viral receptors proposes that there is a cellular mechanism to prevent secondary viral infections by any virus that binds to the same receptor as the primary virus by down regulation or inactivation of the receptor.
Vaccination by Induced Inhibition of Viral Receptors

Earlier, it was believed that each cell can accept only one kind of viral infection. Later there were reports of dual and multiple viral infections in individual cells [45-47]. There was no obvious explanation why some cells accept only one virus while others accept more, but the inducible viral receptor concept may explain the occurrence of multiple viral infections. For single infections, the viral receptor molecule would be down regulated during the first infection, so a second virus using the same receptor could not enter [43]. However, viruses with different receptors would be able to infect simultaneously. This may provide a way for invertebrates to be vaccinated [48-50].

Induced inhibition of viral receptors may also explain why live attenuated vaccines are more effective than inactivated viruses and subunit vaccines. A live attenuated vaccine would retain the complete composition of the virion and attach to the viral binding molecule(s) on the host cell membrane, just like the wild-type virus. It would also repress (down regulate) the cellular receptor molecules, subsequently preventing viral super-infection. This prevention would be prolonged as long as the condition around the cells was maintained. However, alteration of the conditions resulting from such factors as starvation, immune depression and perhaps aging might result de-repression of the receptors, making the cells once more susceptible to viral attachment and infection. In conclusion, a live attenuated vaccine would better prevent secondary viral infections by better stimulating immunity and by also down regulating all the cellular receptors needed for re-infection.

Alternative Concept of Vaccine Development

According to the concept of inducible inhibition of viral receptors, primary viral infection would prevent secondary viral entry by down regulation of viral receptor molecules in the cell membrane. This would be an immediate event upon secondary virus exposure similar to the phenomenon that occurs after a sperm cell fertilizes an egg and prevents attachment and entry of another sperm cell [51]. This phenomenon could be utilized in the strategy to produce vaccines. The vaccine would need to contain all the viral ligands required for infection by the natural virus in order to induce shut-down of all of the viral binding molecules of the host cell to prevent viral entry (as with a live attenuated vaccine as described above). A subunit vaccine that contained only one ligand or an incomplete set of ligands would not satisfy these requirements, since the missing ligands might still allow some virus to enter. As previously stated, this, in addition to diverse MHCs, could explain why subunit vaccines are not as successful in clinical practice as in laboratory animal trials.

To overcome the disadvantage of possible genomic mutation in live viral vaccines and the subsequent reluctance of the pharmaceutical industry to develop them, the concept of inducible inhibition of viral receptors may be a more attractive and equally effective alternative. The aim would be to identify all the viral receptor molecule(s) on the cellular membrane and to achieve a greater understanding of the interaction of those receptors with individual viruses. This would allow preparation of a cocktail of subunit proteins that would cover the same receptor(s) and prevent secondary viral infections. Live attenuated vaccines seem to be the first choice for vaccines based on the criteria of current immunological theory and their efficacy can also be explained by the concept of induced repression of viral receptors. However, safety concerns cause reluctance in their development and explain the overwhelming preference of the pharmaceutical industry for subunit vaccines. The concept for inducible repression of viral receptors provides an alternate strategy for development of vaccines that can have the advantages of live attenuated vaccines without the associated safety concerns. To achieve this goal, we need for each individual virus a better understanding of the host viral receptor molecules and how they interact with the virus.

Conclusion

The objective of the concept of inducible inhibition of viral receptors is to explain the mechanism of cellular membranes in preventing secondary viral infections. Live attenuated vaccines seem to be the first choice for vaccines based on the criteria of current immunological theory and their efficacy can also be explained by the concept of induced repression of viral receptors. However, safety concerns cause reluctance in their development and explain the overwhelming preference of the pharmaceutical industry for subunit vaccines. The concept for inducible repression of viral receptors provides an alternate strategy for development of vaccines that can have the advantages of live attenuated vaccines without the associated safety concerns. To achieve this goal, we need for each individual virus a better understanding of the host viral receptor molecules and how they interact with the virus.

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