Emerging Design and Prospect of Vaccine Delivery System and Potential Vector for Treating Covid-19

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Abstract

The new coronavirus COVID-19 is erupting worldwide, and tens of thousands of lives have been taken by the new coronavirus. The development of vaccines against this virus is imminent. An efficient and safe vaccine delivery system can effectively deliver antigenic substances to the lesion and cause a positive immune response.

Reasonable use of delivery vectors can also improve prevention efficiency and simplify immunization procedures. The vaccine delivery systems currently applied in research and development can generally be divided into biological vectors (such as viruses or bacteria) and chemical vectors (such as microneedles or liposomes). This review summarizes the current development and application prospects of vaccine vector and provides new ideas for the development and design of new coronavirus vaccines.

Keywords: Vaccine; Delivery System; COVID-19

Introduction

Vaccines are the most ideal tools to resist microbial infections, with the lowest cost and minimal damage to the body. The infectious diseases that humans have eliminated so far have been achieved through vaccines. The immune effect of a vaccine depends on the choice of antigen and adjuvant, vaccination route, delivery system and many other aspects. Among them, the vaccine delivery system can carry antigenic substances to the body and boost immune respond. In addition to improving the immune effect of the vaccine by changing the method of antigen presentation and recruiting antigen cells, the delivery system for vaccine design will also improve the storage and slow release of antigen components by protecting the antigen and affecting the location of the antigen. It has great significance to stimulate the immune system for a longer period, reduce the number of immunizations, simplify the vaccination procedure and improve the effectiveness of vaccination. Vaccine delivery systems can be divided into two types: biological vectors and chemical vectors [1]. An important consideration in the use of delivery systems is to effectively use the loading capacity and corresponding characteristics of vectors to improve or enhance the effectiveness of traditional vaccine formulations.

This review will summarize the current research progress of vaccine vectors and the fields of application. At the same time, we will also introduce the latest developments of the new coronavirus vaccine which are currently under development and clinical trials and hope to provide new ideas for the study of new vaccine vectors against coronavirus.

Biological vector vaccine

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Virus vector

Viruses are the smallest and simplest parasitic forms of life that have survived a long natural evolution process without cell structures. They can usually enter specific types of cells with high efficiency, express their own proteins and produce new virus particles, so viruses can be transformed into vectors for transferring and expressing foreign genes. Infection of host cells with unmodified viruses can carry their own genome into the cell and use the host cells to complete their own reproduction, which can eventually cause human disease. Therefore, the viral vector used in vaccine design is to remove the cause of its genome, retaining its function of carrying the gene into the host cell and assembling the ideal foreign gene into a viral vector. Viral vectors used in vaccine design require low toxicity, high efficiency, large capacity and can control gene transduction and expression. Viral vectors currently used for vaccine research mainly include lentiviral vector, poxvirus vectors and adenovirus vectors.

Lentiviral vector

Lentiviral vector refers to a viral vector derived from human immunodeficiency virus-1 (HIV-1), which can effectively integrate foreign genes or foreign shRNA into the host chromosome, to achieve the purpose of persistent expression of the target sequence [24]. In terms of infectivity, it can effectively infect various types of cells such as neuronal cells, liver cells, cardiomyocytes, tumor cells, endothelial cells, stem cells, etc. to achieve a good gene therapy effect. Therefore, in in vitro and in vivo experiments, lentivirus has become one of the common vector forms for expressing foreign genes or foreign shRNAs and is gaining more and more extensive application. At present, two of the vaccines against the COVID-19 that have entered clinical phase 1 are based on lentiviral vectors (LV-SMENP-DC vaccine and Pathogen-specific aAPC) [25,26].

Poxvirus vector

Poxvirus plays a very important role in virology, immunology and vaccinology. In 1798, British doctor Edward Jenner prepared a live vaccine from cowpox virus for the prevention of smallpox (variola) and achieved success, laying the foundation for immunology. In 1980, the World Health Organization announced that humans had eliminated smallpox and recommended that no more smallpox vaccination. In this year, humans successfully used recombinant DNA technology to develop the vaccinia virus (VV) into a viral vector that efficiently expresses foreign genes. This vector can be used in the development of vaccines for the prevention of diseases unrelated to the pox virus and provide important technical methods. Poxvirus is the largest of all viruses. The viral genome is linear double-stranded DNA, about 130 to 375 kb and contains about 185 open reading frames (ORFs). Due to the strong immunogenicity of poxviruses, they will mask the immune response of the antigens they carry as a vaccine vector. A series of modified attenuated poxviruses have been used as vaccine vectors. The most widely used one is the improvement of orthopoxvirus Ankara vaccinia virus (modified vaccinia virus Ankara, MVA) [2] and New York attenuated vaccinia virus (NYVAC), fowlpox virus (avipox virus) fowlpox virus (FPV) and canary Pox virus (canarypox, ALVAC).

Poxvirus as a viral expression vector has the advantages of large capacity for inserting foreign genes, easy construction of multivalent vaccines, and easy establishment of large-scale production processes that meet GMP requirements. The most important thing is that poxvirus can effectively stimulate the body’s humoral immune response and cells. For the immune response, at least more than one hundred foreign genes have been well expressed in poxvirus vectors [3]. Due to looser regulatory requirements and a more effective evaluation system, at least 9 recombinant poxvirus vector vaccines used in animal husbandry have been commercialized, including 6 ALVAC vector vaccines, 2 FPV vector vaccines and 1 VV vector vaccine. These vaccines mainly deliver virus pathogen-associated antigens that cause infectious diseases in livestock: rabies virus, Newcastle disease virus, avian or equine influenza virus, West Nile virus, canine distemper virus and feline leukaemia virus [4]. Recombinant fowl pox virus (rFPV) is the first commercially available live vector vaccine type, which expresses the main immunogen of avian pathogens and has significant vaccine cost-effectiveness in preventing avian infectious diseases. These live vector vaccines effectively deliver the hemagglutinin or surface glycoprotein of the target virus, stimulate the animals’ adaptive immune responses, and provide effective protection.

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**Adenovirus vector**

Adenovirus (Adenovirus, Ad) is a vector commonly used in the development of gene therapy drugs. Adenovirus particles have a diameter of 70 nm to 90 nm and no envelope. Although gene therapy drugs and vaccines have diametrically opposed requirements for vector immunogenicity, Ad has many advantages as a vaccine vector compared to other viral vectors: (1) It has high immunogenicity and can induce both innate immunity and adaptive immune responses of mammals; (2) its large genome makes it easy to perform DNA recombination; (3) adenovirus DNA does not integrate into the host chromosome and will not cause insertion mutations; (4) The pathogenicity and recombination of adenovirus are low and the structure of adenovirus is stable. At present, Ad as a vector is widely used in vaccine research for important infectious diseases and malignant tumors. However, due to the widespread of Ad in nature, the body's pre-immune response to the vector is a major problem that hinders the clinical application of adenovirus vector vaccines. Currently, it is gratifying that the COVID-19 (Adenovirus type 5 vector that expresses S protein) vaccine constructed with adenovirus Type-5 vectors has also entered the clinical phase I. It is believed that soon, the new coronavirus vaccine based on adenovirus will be put into use [27].

In addition to HIV and EBOV, adenovirus vector vaccines that are undergoing preclinical research and entering clinical trials are also influenza virus, dengue virus and hepatitis C virus. Besides, adenovirus vector vaccines have also been developed to treat infections caused by *Mycobacterium tuberculosis* and malaria resulted from *Plasmodium falciparum*. Because of its excellent immunogenicity and safety, AdHu-5 is the most widely used serotype in the early stage of adenovirus vector vaccine research, but due to the widespread neutralizing antibodies in the population, the clinical application of AdHu-5 vector vaccine has been greatly restricted. Current research is turning to the rarer human adenovirus serotypes, such as AdHu-26, AdHu-35, or non-human primate adenoviruses like chimpanzee adenovirus.

**Bacterial vector**

*Listeria* vector vaccine

*Listeria monocytogenes* is a Gram-positive bacterium that causes invasive listeriosis in humans and animals, especially when the immune function is impaired or low. Currently, some attenuated *Listeria* has been used to deliver a variety of viruses and tumor-associated antigens, including human papillomavirus (HPV) 16E7, HER-2/neu, high molecular weight melanoma-associated antigen, prostate specificity Antigen (prostate-specific antigen, PSA), etc. Preclinical studies in mouse tumor models have shown that these vector vaccines have significant immunogenicity and can cause regression of related tumors that are positive for the target antigen. Recombinant Lm-HPV16E7 (ADXS11-001) conducted a clinical phase I trial in cervical cancer patients. The test data showed that this vector vaccine has a good safe condition and effectiveness, confirming its potential development value [7]. Secreted attenuated *Listeria* vector vaccine expressing human CD24 can effectively enhance Th1 and Th2 type immune responses, reduce disease symptoms, and prolong the survival time of tumor-bearing mice [8].

*Salmonella* vector vaccine

*Salmonella* is a Gram-negative bacterium. Currently, two serotypes of *Salmonella* are used as vaccine vectors: *Salmonella typhimurium* and *Salmonella typhimurium*. During natural infection process, *Salmonella* enters the host through the oral route, invades specialized antigen-transporting membrane cells (M cells) in the follicle-related epithelium, parasites in the Peyer’s node of the small intestine, accumulated in the intestinal-associated lymphoid tissue, migrates to the mesenteric lymph nodes, and ultimately spreads to liver and spleen. *Salmonella* expresses a variety of PAMPs (such as flagellin and lipopolysaccharide), triggering a wide range of innate and adaptive immune responses and can also stimulate mucosal immunity. It can be administered orally and avoid injection routes, so it is more attractive as a vaccine vector. Sources of antigens carried in reported studies include infectious bacteria, viruses, and tumor-associated antigens [9,10].

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Although both are intracellular infections, the immune responses triggered by the different subcellular localization of *Listeria* and *Salmonella* after expressing antigens are also different. After entering the antigen-presenting cells by phagocytosis, *Listeria* can escape from the bacteriophage and directly enter the cytoplasm of the infected cells. The antigen carried by the vector will be displayed as an endogenous antigen by the MHC class I molecules on the cell surface, resulting in strong cellular immune response. However, *Salmonella* lacks a phagosome escape mechanism. The vector-carrying antigen as an exogenous antigen combined with MHC class II molecules displays and mainly triggers Th2 type immune responses. The resulting differences also determine their different applications as vaccine vectors [11].

**Lactobacillus vector vaccine**

Nowadays, the live vectors used in recombinant bacterial vaccines are mostly attenuated pathogenic bacteria, and there are certain hidden dangers in the use of safety issues. Therefore, people have focused on some safe and harmless bacteria, hoping to use it as a vector to develop safer vaccines. Lactic acid bacteria (LAB) has long been used in various fields of the food industry, such as the production and preservation of fermented products, and is a generally recognized as safe (GRAS) microorganism. At present, in addition to genetically engineered bacteria used for food fermentation, the function of lactic acid bacteria as a vector for presenting therapeutic proteins or antigens has become a research hotspot.

*Lactococcus* and *Lactobacillus* are model strains of lactic acid bacteria used in vaccine delivery vehicle research, especially as an ideal vector for mucosal immune vaccines. It has unique advantages: Firstly, it is commonly used vaccine biological vectors, such as *Salmonella* and Poxviruses, etc., even attenuated pathogens still have certain risks and lactic acid bacteria are a food-grade microorganism, especially for certain populations such as the elderly, infants and young children have better safety; Secondly, lactic acid bacteria are Gram-positive bacteria and do not produce pro-inflammatory substances such as lipopolysaccharides, so their antigenicity is very weak. As a vector, they do not cause a strong immune response; also, lactic acid bacteria themselves secrete less protein, which reduces the interference of the external secretion source protein, and does not produce extracellular proteases, thereby ensuring that the secreted protein is not degraded and the integrity of its structure and function; in addition, the lactic acid bacteria have metabolic activity in all intestinal segments, directly contacting the intestinal mucosa, and promoting the presentation of foreign proteins to the mucosa. *Lactococcus* vector vaccine expressing HPV-16 (human papillomavirus type 16) E7 antigen shows important application potential in preventing viral diseases [12], expressing β-lactoglobulin (BLG) [13] in the prevention and treatment of chronic digestive diseases and *Lactobacillus* vector vaccine expresses antioxidant protein [14] in the treatment of gastrointestinal inflammatory diseases, which is shown the good efficacy in many relevant animal model tests. The first lactic acid bacteria vector vaccine to enter the human trial stage is a recombinant IL-10 *Lactococcus* vector vaccine for the treatment of Crohn’s disease [15], but in clinical stage IIA, the vaccine is not as good as the placebo group in mucosal healing, which shows statistically significant differences. Although lactic acid bacteria are ideal vectors for carrying foreign antigens, the relevant antigens can be presented to the host immune cells at the mucosal level by intranasal or oral administration. However, the lactic acid bacteria vector vaccine faces many technical problems that need to be solved from experimental research to clinical application.

**Chemical vector**

**Liposome**

Liposomes are closed, centripetal vesicles composed of phospholipids and other polar amphoteric molecules with double-layered lipid membranes. They have the role of immune adjuvants and vectors for protein or polypeptide antigens bound or coupled to them. Liposomes are naturally targeted and can target antigens to the reticuloendothelial system, thereby being preferentially absorbed by antigen-presenting cells; moreover, they also have a slow-release effect on the wrapped antigen, reducing the dose of antigen and the number of inoculations. In fact, high concentrations of antigens in the liposome can independently activate certain T cells. Considering
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In this review, we overview the current status and prospects of vaccine vector research and highlight the latest progress of vaccines against COVID-19 which are currently in clinical trials. From a global perspective, the difficulty of research and development of new drugs continues to increase, and the speed and effectiveness of development have slowed down significantly. As a result, drug release system research and development have become one of the fastest-growing fields in the pharmaceutical industry. At the forefront, the application of the vaccine delivery system can improve or change the immune response of traditional vaccines, optimize the effect of vaccination, and simplify the vaccination procedures. In common vaccine delivery systems, viral vectors, bacterial vectors, and chemical vectors represented by liposomes and microneedles each have advantages, disadvantages, and different applications in practical applications. The rational use of vaccine delivery vectors can be to a large extent. To achieve vaccine improvement goals. With the development of modern biotechnology and materials science, a variety of technical methods are used to develop new vaccine delivery vehicles. The technological progress of vaccine delivery vehicles will also inject new vitality into innovations in the field of vaccines.


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