Role of Adjuvants in Immunogenicity

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Vaccination is the best way to prevent and reduce the damage caused by infectious diseases in animals and humans. Several vaccines are used for prophylactic purposes before the pathogen infects, while therapeutic vaccines strengthen the immune system after infection with the pathogen. Adjuvants are molecules, compounds, or macromolecules that enhance non-specific immunity and, in collaboration with antigen(s), can improve the body's immune responses and change the type of immune response. The potential and toxicity of adjuvants must be balanced to provide the safest stimulation with the fewest side effects.

Keywords: veterinary vaccines ; adjuvant ; Immunogenicity

1. Introduction

In its original sense, the purpose of vaccination is to mimic the natural immunity of non-pathogenic components and establish a robust immune response and long-term protection against infection. However, the use of pathogenic components or organisms close to them is still in question [1][2].

Vaccine production has historically been recognized as one of the most successful public health experiences. Vaccine advances owe much to the "isolate, inactivate, and inject Louis Pasteur" model [3][4]. Edward Jenner first noticed about a hundred years earlier that cowpox infection made people immune to smallpox infection. In the late 1800s, Louis Pasteur made the first classical vaccines, creating what we now call vaccination [5]. For the first time, in 1881, Louis Pasteur used the word vaccine for immunogens that were used for diseases other than smallpox. Pasteur's research showed that it was possible to weaken or inactivate microbes. Studies on fowl cholera and anthrax led to the concepts of chemical inactivation as a means of reducing the pathogenicity of microorganisms. In the rabies studies, they investigated an alternative strategy to reduce or eliminate the pathogenicity of serial passage in animals (lapinization or passage of rabbits) or other animal-derived tissues. These studies resulted in the successful control of anthrax and especially rabies [6]. Research by Salmon and Smith (1886) clearly showed that some microbes could be completely inactivated (killed), which led to successful immunization against typhoid fever, tuberculosis, rinderpest, and foot and mouth disease (FMD) [7]. Gaston Ramon at the Pasteur Institute developed the principles of weakening and inactivating microbial toxins. To create anatoxin, a tetanus toxin was inactivated by heat and formalin in 1924 which showed a better effect with aluminum hydroxide adjuvant. In the early 20th century, these advances in process and formulation produced horse sera with anti-diphtheria and Tetanus toxin neutralizing antibodies were developed and refined for preventive use [6].

In the mid-1950s, veterinarians routinely used brain tissue-derived rabies vaccines in dogs. The main biological products used at that time included rabies vaccine, canine distemper virus/hepatitis vaccine and antisera, hog cholera vaccines and antisera, leptospirosis bacteriens, and clostridial toxins. With the development and increase of production capacity over time, the vaccination of companion animals was expanded and rabies vaccines for cats, feline herpes virus, parvovirus in cats and dogs and calcivirus in cats were produced. The term vaccine is now used to describe many therapeutic or prophylactic formulations and products that stimulate active immunity in the vaccinated animal [6].

According to studies, vaccination is the best way to prevent and reduce the damage caused by infectious diseases in animals and humans [8]. Vaccines are recognized as one of the most essential and practical public health indicators. In the last century, they have saved countless lives, so they are considered for treating and preventing diseases. In addition, the World Health Organization recommends vaccination to prevent diseases [9].

Several vaccines are used for prophylactic purposes before the disease to protect the body against possible exposure to the pathogen, while therapeutic vaccines strengthen the immune system after infection with the pathogen. Antigens from vaccines used for prevention are usually taken by antigen-presenting cells (APCs), such as dendritic cells (DCs), and then prepared and processed. These cells migrate to the lymph nodes after puberty and then present antigens to B cells, CD4 and CD8, to detect possible infectious bodies. Therapeutic vaccines have been developed and designed to enhance

tumor antigen delivery and cellular immune responses against tumors. In this regard, adjuvants are injected at the initial site of the tumor to promote the accumulation of DCs. As DCs mature and differentiate, tumor antigens are delivered to CD4 and CD8 cells. In the next step, the number of CD8T and natural killer cells (NK cells) increases to identify cells at the primary, metastatic, and distant cancer stages in the body [10][11].

Vaccines are classified into two types: live attenuated and inactivated. Inactivated vaccines contain pathogens that chemical treatments have killed. They are safer and more stable than live attenuated vaccines (LAVs) and cannot reactivate, even in immunosuppressed patients. However, they are less effective in inducing immunity than LAVs and usually require multiple doses to induce a humoral response, which is often not permanent. Current examples of vaccines in this category include those for polio (i.e., inactivated polio vaccine-IPV), hepatitis A, rabies, and influenza [5].

Immune systems can detect the causative agents of living diseases, constantly trigger a specific immune response, and help the immune system acquire immune memory because they behave similarly to natural infectious carriers. The most serious concern with using this type of vaccine is the possibility of reverting to a pathogenic state. The delay in immunogenicity or induction of abortion in the host receiving the vaccine is among the problems of using this type of vaccine. On the other hand, inactivated vaccines are safe, do not have pathogenic problems, and are easier to produce. Nevertheless, in most cases, several stages of immunization are required for long-term safety, and we need a large amount of antigen. It may also fail to provide local safety and to adequately activate all safety agents, although a meaningful way to improve their performance is to use adjuvants [12][13]. Adjuvants correct the poor immunogenicity of inactivated and subunit-based vaccines. These compounds significantly increase the vaccine's immunogenicity by acting as an immunomodulatory and delivery system [5].

Vaccines can be administered by injectable, oral, or inhaled methods. Due to its non-invasive nature, oral administration has no pain or discomfort. However, oral vaccines should be resistant to the pH conditions of the gastrointestinal tract, and, of course, their bioavailability is not reduced. Nowadays, most vaccines are injected because they are more effective and practical [14][15][16].

Today, some of the most widely used veterinary-licensed vaccines to control livestock infectious diseases use Edward Jenner's experimental technology. Jenner used the live attenuated virus to create immunity against smallpox, which he called the vaccine. After Jenner, Louis Pasteur invented another way to make a vaccine by using live microorganisms. In general, vaccines in veterinary medicine increase production and protect people who work in veterinary medicine [17].

When vaccines are used optimally, they can prevent the manifestations of diseases, reduce the transmission of diseases, reduce the need for medication, and improve the health and well-being of animals. They can prevent the transmission of diseases that are common between humans and livestock to ensure human health indirectly [18]. There are challenges in creating an optimal vaccination program, one of which is dealing with the great diversity of animals because there is no optimal unified program for vaccination. Moreover, the use of vaccines in animal health is not limited to the protection of animals, and it is mentioned in public health programs as one of the main elements of public health. With the availability of conditions, management modeling strategies and possible plans will be related to such things, such as (I) (DIVA) protective vaccines against common human diseases, (II) an effective predictive model, and (III) enforceable policy measures to prevent and control dangerous human and animal diseases in local, state, and national areas [19][20].

Producing vaccines in veterinary medicine has advantages and disadvantages compared to the production of human vaccines, such as smaller market sizes and lower selling prices. At the same time, there is greater complexity and range among hosts and pathogens. Therefore, less investment is made in the research and development of animal vaccines. For example, the market value of the most successful animal health vaccine ever produced against foot-and-mouth disease (FMD) is 10–20% of the market value of the papillomavirus cervical cancer vaccine in humans. However, there is less pre-clinical monitoring of the production of veterinary vaccines. Veterinary scientists can do research sooner than human vaccine providers. Therefore, the return on investment in this field and the time to launch their sales are shorter [2].

The next step in vaccine development is the use of engineered nanoparticles (NPs) that serve as vaccine delivery platforms that can protect the antigens of the vaccine and, at the same time, are innovative adjuvants that can fine-tune immunity. In addition to their function, NPs show an intrinsic adjuvant activity that, after being internalized by APCs, allows NPs to form a complex that induces and absorbs immune cells [5][21].

2. Role of Adjuvants in Immunogenicity

2.1. Adjuvant Mechanism in Immunogenicity

According to the studies, the mechanism of action of an adjuvant has been identified only to the extent that it generally stabilizes and increases the supply of antigens or acts as a modulator of the immune system. An adjuvant may have more than one mechanism of action. For example, adjuvants that help maintain the structure of the antigen at the same time can also increase the vaccine's quality and shelf life. Antigens that affect antigen delivery can affect countless points in this complex process. Antigens are often carried to lymph nodes during an immune response by dendritic cells. The antigen-APCs include dendritic cells, macrophages, and B lymphocytes, which process antigens and deliver epitopes to T cells in the form of MHCs. APCs provide signals to initiate an immune response, such as auxiliary stimulation by B7 family molecules. Any adjuvant that increases antigen uptake by these cells increases the expression of Major histocompatibility complex (MHC) molecules and improves the immune response by increasing cell migration to the lymph nodes. Some adjuvants reduce the liver's effect on the gene by trapping and providing a continuous supply of antigens to antigen-supplying cells locally at the injection site. New microparticle adjuvants can create long-term (1–6 month) depots and gradually release a certain number of other adjuvants that may be effective by saturating Kupffer cells in the liver and reducing hepatic antigen uptake. The reactions are activated by the interaction of helper T cells and CTL with antigens present in MHCI or MHCII molecules. Although antigens are presented differently, antigens on MHCII molecules are generally absorbed outside the APC cells by phagocytosis. However, antigens in MHCI molecules are from the cytoplasm of all cells supplying this molecule. Most adjuvants can effectively stimulate helper T cells and humoral immunity [22].

The results of one study showed that APC activation occurs when pattern recognition receptors on the surface of antigen-supplying cells attach to protected areas in bacterial lipopolysaccharides, carbohydrates, or other parts. If this hypothesis is correct, adjuvants can mimic the original signals. In fact, many adjuvants are bacterial derivatives or similar compounds of proteins, carbohydrates, or bacterial DNA. However, this model is not accepted for oil emulsion additives, saponins, or alum. According to the second model, APCs act by detecting internal signals released by damaged cells, stressed cells, and dying cells. According to research, necrotic fibroblasts or blood vessels can act as highly effective adjuvants and affect the function of neutrophils after vaccination with some adjuvants. Adjuvants, such as liposomes, deliver antigens to pathways that lead to their expression in MHCI molecules and produce the CTL response. Cross-presentation of antigens from two different pathways may sometimes be important in the production of Cytotoxic T lymphocytes (CTLs). Another mechanism of activity of adjuvants is the effect on the immune system, which is the mechanism of modulating the immune system and stimulating the cytokine network of the immune system. Increasing and decreasing the concentration of cytokines affect the type of immune response. Cytokines, such as interferon-gamma (IFN-γ), IL-2, and IL-12, are associated with type I helper T cell (THI) responses and cellular immunity, and cytokines IL-4, IL-5, IL-6, IL13, and IL-10 may be associated with TH2 responses and humoral immunity [22].

There is a hypothesis related to the activity of the NLRP3 (NALP3) inflammatory receptor. An intracellular pattern recognition (PRR) receptor of the NLR family is activated during the innate immune response to recognize bacterial (such as lipopolysaccharide) compounds, zymogenesis, and toxins, to announce stress and cell damage to other members of the immune system. After oligomerization of NLRP3 protein units, the activity of the inflammatory complex begins, and then the enzyme caspase1 is activated to stimulate the proteolytic breakdown of precursor molecules. This complex eventually triggers the production of immune responses by inflammatory cytokines of the IL-1 family, including IL-1β and IL-18 [23][24].

2.2. Immunogenicity Mechanism of Multiple Adjuvants

Aluminum adjuvants elicit strong innate immune responses that include the invasion of macrophages, neutrophils, mast cells, natural killer cells, CD11b+ monocytes, and dendritic (DC) cells [25][26]. Upon entry of CD11b+ monocytes, they are differentiated into inflammatory dendritic cells at the injection site [27]. These cells are essential for the activity of alum as an adjuvant. In addition to their role in creating an innate immune response, granulocytes trigger an acquired Th2 response and the production of IgM antibodies. After stimulation with alum adjuvant, primary macrophages produce E2 (PGF2α) and IL-1β (IL-6). PGF2α can stimulate the Th2 response, and thus the T cell response is effective in injecting induced alum. On the other hand, PGF2α has a direct effect on B cells and increases IgE production [28][29][30].

These particulate adjuvants increase mass formation to facilitate phagocytosis. Carbohydrate polymers such as mannan can bind antigens to antigen-supplying cells by binding to carbohydrate receptors. Carrier proteins such as bovine serum albumin (BSA) (KLH) and diphtheria or tetanus toxoid provide haptens or carbohydrate antigens through T cell uptake. Some adjuvants also appear to stimulate the cytotoxic T lymphocyte (CTL) response by placing antigens in specific parts of antigen-supplying cells [22].

MF59 water-based oil adjuvant activates more immune cells than alum, resulting in a higher injection of vaccine antigen at the injection site. Moreover, MF59 increases the number of APCs in draining lymph nodes (DLN) compared to alum or adjuvant-free vaccines [25].

Some studies link the apoptosis-associated Speck-like effects of MF59-dependent proteins to ASC (CARD), common moderators of inflammasome complexes, while others mention an MF59 adjuvant effect independent of NLRP3 and Caspase1 inflammasomes [31]. Therefore, it is possible that ASC has a function independent of the inflammasome or has a role in the inflammasome other than NLRP3 [32].

Saponins may stimulate cellular immunity to antigens by altering the levels of these two classes of cytokines, although they naturally only stimulate the production of antibodies. Several immune-stimulating adjuvants increase the expression of MHC molecules on APC cells, either directly or by producing cytokines. According to some hypotheses, the APC must first activate and initiate an immune response [22].

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