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The Role of DNA Vaccine as a Control Measure for Viral Diseases

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Abstract: DNA vaccines represent a new leading edge in vaccine technology. Eventually, the factors that will make a DNA vaccine attractive for a certain disease will include its reduced cost, its ease of transport and administration, its ability to act in the face of maternal antibodies, the ability to differentiate diseased animals from vaccinated animals and the vaccine itself is unable to cause an outbreak. In this paper an overview of the design and formulation of DNA vaccines with molecular adjuvants is given. However, several important questions must be addressed for animals use, including whether or not the vaccine is effective and safe. Another important question to be considered is how to apply this developing technology in a wide range. This review will scrutinize some important veterinary diseases and their DNA vaccine technology relevant to these diseases as well as their advantage and disadvantages and the urge to develop new techniques for delivery and more efficient adjuvants.

Key words: DNA vaccines · Viral diseases · Infectious diseases · Veterinary use · Adjuvant

INTRODUCTION

Animals are of global importance in society either in the developed and the developing world. Shipping of animals and climatic change plays an important role in transmission of disease which poses a greater threat than ever before. The demand for animal vaccines has increased widely with the urge of efficient and economically viable manner. DNA vaccines are emerging as a new method of vaccination for animals. DNA vaccination is a genetically engineered DNA preparation, injected to protect animal, human, bird or fish against disease through producing antigen and resulting in a protective immune response. There are different kinds of vaccines. First generation vaccines which are either live attenuated or killed (inactivated) vaccine. Live attenuated vaccine induces cellular immunity by activating both T- helper cells and T- killer cells. The main disadvantage of attenuated vaccines is the possibility that the attenuated virus may retain its pathogenicity and revert to a dangerous form. While killed vaccine induces mainly humeral immunity which may be not suitable to give efficient immunity for some viruses. Another type of vaccine is the second generation vaccine, which are called subunit vaccines. Subunit vaccines consist of defined protein antigen or recombinant vaccine that is able to stimulate T- helper but not killer cells [1]. While the third generation vaccines are DNA vaccine which are certain sequence of the viral gene inserted in a specific vector. The host cells synthesize the pathogen proteins using the DNA vaccine introduced into it and subsequently process these proteins because they are considered as foreign proteins and present it on their surface. Different range of immune response is triggered and the immune response is alerted [2].

DNA Vaccine Design and Formulation: DNA vaccines are designed to encode the most immunogenic regions of an antigen as an attempt to focus the immune response on a synthetic sequence that is more representative of pathogen diversity. Thus, the host immune response is better skilled and responds more effectively to divergent pathogens [3]. Moreover, formulation of DNA vaccines in liposomes or micro-particles has been reported to increase the uptake of plasmid DNA by cells, thereby increasing the immunogenicity of several different vaccines [4]. For example, a DNA vaccine against influenza formulated in the lipid compound Vaxfectin (Vical) found to induce protective antibody titers and T-cell responses [5].

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A further method to improve DNA vaccine immunogenicity is the insertion of additional plasmids, or additional inserts in the same plasmid, encoding molecular adjuvants. Several studies have shown that co-delivery of plasmids encoding cytokines, chemokines or co-stimulatory molecules can enhance immune responses. Unlike traditional adjuvants, which stimulate nonspecific inflammation, molecular adjuvants can alter the adaptive immune response [6].

Current Use, Advantages and Disadvantages: Few DNA vaccines have been approved for human use worldwide, while veterinary vaccines has established as new and important method for vaccination. DNA immunization gives many advantages over the traditional forms of vaccination because they induce the expression of antigens that resemble native viral epitopes, while live attenuated and killed vaccines are often altered in their protein structure and antigenicity. Plasmid vectors can be constructed and produced quickly. DNA vaccines encoding several antigens or proteins can be delivered to the host in a single dose, via direct injection, or injection with electroporation or gene gun to induce immune responses. Rapid and large-scale production are available at costs considerably lower than traditional vaccines and they are also very temperature stable making storage and transport much easier. Another important advantage of genetic vaccines is their therapeutic potential for ongoing chronic viral infections. DNA vaccination may provide an important tool for stimulating an immune response in HBV, HCV and HIV patients [7].

Administration and Mechanisms: Over the past decade of clinical research and trials, several possible routs of plasmid delivery have been found. Successful immunization has been demonstrated after delivery of plasmids through intramuscular, intradermal and intravenous injection. The skin and mucous membranes are considered the best site for immunization due to the high concentrations of dendritic cells (DC), macrophages and lymphocytes. DNA-coated gold particles with a gene gun also have been used by intradermal injection. The plasmid DNA can be diluted in distilled water, saline or sucrose. There has also been positive demonstration of pro-injection or co-delivery with various drugs [8].

When a plasmid vector expressing the protein of interest (e.g. viral protein) is injected into the skin or muscle of the host, the protein is processed endogenously and intracellularly into small antigenic peptides by the host proteases. The peptides then enter the lumen of the endoplasmic reticulum (E.R.) by membrane-associated transporters. In the E.R., peptides bind to major histocompatibility complex (MHC) class I molecules. These peptides are presented on the cell surface in the context of the MHC class I. Subsequent CD8+ cytotoxic T cells (CTL) are stimulated and they evoke cell-mediated immunity. CTLs inhibit viruses through both cytolysis of infected cells and non-cytolysis mechanisms such as cytokine production. The viral protein can also be presented by the MHC class II pathway by antigen presenting cells (APCs) which elicit helper T cells (CD4+) responses. These CD4+ cells are able to recognize the peptides formed from exogenous proteins that were endocytosed or phagocytosed by APC, then degraded to peptide fragments and loaded onto MHC class II molecules. Finally, B cells are stimulated and antibody production is stimulated. This is the same manner in which traditional vaccines work [9].

DNA in Veterinary Use: DNA vaccines should be studied for various diseases in animal species, as they are cheap than current commercial vaccines and likely sufficient to offer protection as well. DNA vaccines are used in farm animals for protection against Bovine respiratory disease complex [10], Bovine respiratory synctitial virus [11], Bovine viral diarrhea [12, 13], West Nile virus [14] and Foot-and-mouth disease [15]. While in pigs they are used for protection against Porcine reproductive and respiratory syndrome virus [16] and swine influenza [17]. In poultry the main targeted virus avian is influenza [18]. In addition, they are used in fish mostly against infectious hematopoietic necrosis [19]. They are used in bigger scale in companion animals against Feline immunodeficiency virus [20], Feline leukemia virus [17], Rabies [21] and Canine oral melanoma [17]. Moreover, DNA vaccines are not only targeting pathogenic agents, but also being used as cancer vaccines for companion animals. These vaccines include plasmids encoding tumor antigens that induce the formation of antibodies that are expected to target tumor cells in the vaccinated animals, leading to the regression of tumors [22].

Advantages and Disadvantages: The DNA is conceptually considered safer and more stable than conventional vaccine because they are non-live and non-replicating, which leaves little risk for reversion to a disease causing state or secondary infection. DNA vaccines have the ability to induce both cellular and humoral protection since antigens can be delivered and processed intra-

cellularly. DNA vaccines are also prevailing in that they have extended boosting capability, since the vaccine can be administered repeatedly without inducing neutralizing antibodies to the plasmid. The original concerns associated with the DNA vaccines were the potential for genomic integration and development of anti-DNA immune responses. Comprehensive research has found little evidence of integration and the risk for integration appears to be significantly lower than that associated with naturally occurring mutations. Initiation of anti-DNA immune responses after DNA vaccination has been monitored in multiple studies and clinical trials, but confirmation of increased production of such responses or changes in other clinical markers of autoimmunity have not been reported. Generally, several studies have reported that DNA vaccines are well tolerated and have a desirable safety record [22].

CONCLUSONS

A great progress has been made for immunization protocol under assessment in clinical trials of DNA vaccines. The goal of DNA vaccination will be the progress of effective immunization strategies against viral diseases. Advancements in antigen design, better formulations, insertion of molecular adjuvants and physical methods of delivery have greatly enhanced the immunogenicity of DNA vaccines. On the other hand, the advantages of DNA vaccines such as reduced cost, its ease of transport and administration, its ability to act in the face of maternal antibodies, the ability to differentiate diseased animals from vaccinated animals and the reduced probability of the vaccine to cause an outbreak render them very attractive to be used.

The improvement of DNA vaccine immune potency must be achieved, through promising technologies as improved formulations or simple electroporation, or alternate vaccination strategies should be considered, such as prime–boost approaches, cytokine gene adjuvants or other adjuvant formulations.

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