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DNA Vaccine: An insight

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Abstract

Referred to as third generation vaccines by researchers, DNA vaccines are the most promising vaccines in combating the pathogenesis of many infectious pathogens. DNA vaccines involve the insertion of gene encoded plasmid DNA which is purified directly into the host in order to induce an immune response. In addition to traditional intradermal, oral mechanisms of administration, novel gene gun techniques are utilized. Being able to induce both the humoral and cellular arms of the adaptive immune response, DNA vaccines harbor many advantages in comparison with the traditional vaccines. Although currently available for the veterinary use to some extent, there is growing health and safety concerns over the implementation of DNA vaccines in human vaccine requirements. This review explores the composition, mechanisms and pros and cons of DNA vaccines. The future is enlightening for the success in clinical trials of DNA vaccines with hopes to implementing better standards of vaccination.

Keywords: DNA vaccines, infectious diseases, immune response

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Introduction

Infectious diseases account for a large portion of the mortality and morbidity in humans all around the globe with more numbers in poor and developing countries. With new and emerging infectious agents being added to the list, it is imperative to research diverse options of treatment and prevention. From the development of a vaccine against smallpox, vaccine development has proven to be a successful option in overcoming infectious diseases. Vaccines have been developed to counteract the pathogenesis of pathogenic infectious agents such as viruses, bacteria, and protozoans. Nevertheless, it is a

challenge to develop effective vaccines against many pathogens with the constantly changing genetic makeup of viruses (Zheng et al., 2018).

Vaccination stimulates the immune system to mount an immune response in advance to meet with the actual pathogen. This is done by using an infectious agent or its components which are altered so that there is no disease development, but elicits an immune response (Zheng et al., 2018). Therefore when the actual pathogen is met at any point, the body can successfully counteract the pathogen before it causes any harm to body tissues.

The vaccine development usually recognizes and classifies vaccines as first-generation and second-generation vaccines. The first-generation vaccines include; live attenuated, killed or inactivated, subunit, and toxoid vaccines. These first-generation vaccines elicit the immune response in two methods. This happens either by specific antigens against which the immune system reacts directly or by introducing live attenuated infectious agents which elicit synthesizing the antigens that subsequently prime the immune system. The live attenuated vaccines are made by removing the virulating capacity of the pathogenic organism by weakening it so that it is not capable of causing disease. Inactivated or killed vaccines are made by inactivating microorganisms with chemicals or gamma rays. These act primarily through the induction of cellular and humoral mechanisms of adaptive immunity and generally do not provide lifelong immunity (Dai et al., 2019). Subunit vaccines are prepared by using either synthetic or recombinant antigenic peptide proteins from viruses. As the subunit vaccine does not have any live component of the viral particle, it is much safer with lesser side effects than other vaccines. Toxoids are a type of vaccine that includes bacterial toxins which can give rise to an immune response. As there are safety concerns with these non-live or attenuated methods, new vaccine methods are pursued (Kallerup et al., 2015; Tahamtan et al., 2017).

Second-generation vaccines are also termed recombinant vaccines. They are made by genetic engineering involving two types. The first type involves modifying genetic engineering methods to non-agonize an infectious agent by either eliminating or causing mutations in genes responsible for microbes (Vetter et al., 2006). The second, gene vaccines, are the most recent vaccine type that is being researched with great potential. These involve DNA vaccines with directly injected plasmids that have the ability to express the desired gene within the body's cells. In this method, the recombinant protein is produced in the body and placed in the immune system. This method gives rise to many advantages such as the stimulation of both B- and T-cell responses, improved vaccine stability, the absence of any infectious agent, and the relative ease of large-scale manufacture (Yadav et al., 2020).

Mechanism of DNA vaccines

a) Composition

Plasmid DNA, when injected into the skin or muscle, induces immune responses to encoded antigens. To start with generating a DNA vaccine, the interesting antigen-encoding gene is inserted into a bacterial plasmid. This is carried out under the control of an appropriate eukaryotic promoter. In most instances, it is the CMV promoter from cytomegalovirus. There is a difference in codon usage preference between bacteria and eukaryotic cells. This leads to the antigen gene being often modified by point mutation to improve the efficiency of gene expression. This DNA from bacteria which is purified and detoxified is then administered to the host animal. Among the plasmids that have been taken up by appropriate cells and made their way into nuclei, the host cell will use its own gene transcription and protein expression machines to produce the interesting antigen. This expressed antigen when recognized as a foreign and result in mounting an immune response against it (Lowrie et al., 2000; Williams, 2013).

b) Administration

The DNA vaccine was originally administered by intramuscular injection or via a gene gun to the skin. Other methods of delivery include intranasal, electroporation, and topical applications.

The conventional needle injection is inoculated intramuscular, intradermal, or intratumor by using solutions such as saline as the carrier. Needle injections are widely used in bringing about Th1 responses. Although this is an inexpensive, well-established practice with no need for special devices and training, the transfection efficiency and immunogenicity are low. Further, since a large amount of plasmid DNA is needed, this leads to an increase in total cost (Alpar et al., 2002; Wang et al., 2008).

The gene gun is often used to increase Th2 responses. Plasmid DNA is coated on a gold surface. Then it is introduced into the cells by using compressed helium gas as an accelerator affecting the progenitor and Langerhans cells. This involves direct transfection or cross-presentation of gold nanoparticles that are coated with DNA. This gene gun technique requires lesser DNA, coated particles are stable, and the cold chain is not needed. In the gene gun method gold cytokines and the B cells which are charged up by the coated beads enter directly the cytoplasm and hence shed proteins to produce antibodies (Weiss et al., 2002; Wang et al., 2008).

Nasal vaccination or vaccination to other mucosal tissues is also possible. In nasal method involves transferring plasmid DNA to the nasal and lung nasal surfaces. Vaccination using plasmids containing HIV genes which are administered via the nose and the intravaginal route results in induction of a high level of Th2 response to HIV viral antigens.

The electroporation method gives a very strong Th1 cell-type response. This form of administration results in an induction of immunity of about ten-fold or greater to the response induced by other plasmid DNA vaccination techniques. However, this method involves high voltage, which in turn has delayed its use in medicine needing modified more effective methods (Wang et al., 2008).

DNA vaccination by topical application on the skin is another useful method of immunization. This is a simple method that is painless and cost-effective. However, the level of immune response is relatively low (Choi et al., 2006).

c) Immune responses

The immune response of DNA vaccines relies on the host cells to take up the DNA and produce the immunogenic protein in vivo. This directs the antigen through endogenous Major Histocompatibility Complex (MHC) class I presentation pathways, helping to activate better Cytotoxic T Lymphocyte (CTL) responses. The DNA appears either to integrate into the chromosomal DNA or to be maintained for long periods in an episomal form and is often taken up by dendritic cells or muscle cells in the injection area. Since muscle cells express low levels of class I MHC molecules and do not express costimulatory molecules, delivery to local dendritic cells may be crucial to the development of antigenic responses to DNA vaccines (Kowalczyk and Etrl, 1999).

Humoral response

The Immunization with plasmid DNA is identified to induce antibody responses in a variety of proteins in animal species. *In vivo* animal models have proven the protective properties of the humoral response generated by DNA vaccination. However, it is recognized that the antibody response in humans from the DNA vaccine is not that encouraging. In mice, although the antibody response from the DNA vaccine is weak at the beginning, it then peaks and reaches a plateau between 1-3 months after a single DNA immunization. Also, antibody production increases in a dose-responsive manner with either a single injection or multiple injections of DNA. The resulting antibody response can be long-lived. Upon comparison of antibody responses from DNA, protein, and live virus vaccines were compared, the response from the DNA vaccine is generally weaker than the other vaccines. Also, the antibody response from the DNA vaccine is not encouraging. DNA vaccination induces the production of many subtypes of antibodies, including IgG, IgM, and IgA. Moreover, in most cases, antibodies generated by DNA vaccines are skewed toward IgG2a due to the fact that the CpG motifs on plasmid DNA stimulate the production of the Th1 cytokine. DNA vaccination may be effective at inducing a long-term antibody response in some animal species (Gurunathan et al., 2000; Cui, 2005).

Cellular immune response

The DNA vaccine can induce cellular immune responses, including a CTL response. Both the CD4 T-cell response and the CD8 T-cell response from DNA vaccination are discussed here. The T helper cells can be categorized into Th1 and Th2 type cells. Th1 cells produce IFN-b exclusively, whereas Th2 cells produce IL-4, IL-5, and IL-13 exclusively. The CpG motif in bacterial DNA induces the production of a variety of proinflammatory cytokines, including IL-12, TNF-a, and INF-g, showing that the DNA vaccine

generally skews the response toward Th1. The CTL response can also be induced by a live vaccine. However, it is difficult to induce it with a protein-based vaccine. It is understood that the CTL response induced by a DNA vaccine is comparable to that from a live viral vaccine. Also, the DNA vaccine can induce a CTL response against both dominant and subdominant epitopes. This is useful in the development of a DNA vaccine for tumor immunotherapy. With time, tumor cells are often tolerant to the CTL response against the dominant epitopes of tumor-specific or tumor-associated antigens. Hence, inducing a successful CTL response to the subdominant epitopes on these antigens is needed for tumor killing. Regarding the memory cellular immune response, it has been shown that the frequency of antigen-specific CD4 T cells measured by proliferation remained elevated for 40 weeks post-vaccination (Gurunathan et al., 2000, San Zhao et al., 2000).

Pros and Cons of DNA vaccines

Advantages

DNA vaccines have many advantages with significant potential over the existing vaccine approaches. There is no denaturation or modification as the encoded protein is expressed in the host in its natural form. The immune response is directed to the antigen in the same way that would be expressed by the pathogen. Thereby, both humoral and cell-mediated immunity would be induced. This is safer than the non-DNA vaccines which would require live attenuated preparation, which incurs additional risk. The DNA vaccines act to prolong the expression of the antigen, which results in enhancing the immunological memory induction (Abdulhaqq et al., 2008).

The gene gun delivery method which involves coating gold microscopic beads with the plasmid DNA allows for rapid delivery of the vaccine to large populations without the need for huge numbers of needles and syringes, improving both safety and cost.

DNA vaccines are highly specific and the expressed immunizing antigen is subjected to the same glycosylation and post-translational modifications as natural viral infection. Moreover, multiple variants of an antigen can be inserted into a single array of plasmid vaccines. So, the same plasmid vector can be custom-tailored to insert DNA encoding a variety of proteins. This makes the way to making a variety of DNA vaccines for different pathogens at the same time.

Logistic advantages of DNA vaccines include the relative ease and low cost of production and transportation. This makes DNA vaccines suitable for production in the developing world as well. No refrigeration of the plasmid DNA is required, therefore reducing the burden of long-term storage (Khan, 2013).

Disadvantages

Most of the disadvantages of DNA vaccines are based on health and safety issues. The safety issues involve the concern of the activation of oncogenes. This is thought to happen because of the genomic incorporation of immunizing DNA and eliciting anti-DNA antibodies, but this has been rarely detected in experimental studies. A reduced level of immunogenicity is another disadvantage of plasmid vaccines. In order to overcome this, sufficient adjuvants must be used. It is suggested to combine with cytokines such as IL-4 or GM-CSF which stimulate the immune responses or C3d oligomers as an adjuvant for B-lymphocyte cells. Even booster immunization with the relating antigen as a protein is also helpful in resolving such drawbacks (Siegrist and Lambert, 1999; Khan, 2013)

Clinical Trials and the future

Current DNA vaccine trials are focused on several infectious diseases and cancer therapy. Cancer therapy including Melanoma, Breast cancer, Colorectal cancer, Prostate cancer, Ovarian cancer, Cervical cancer, Renal cancer, and B-Cell lymphoma, Lung cancer, Hepatocellular cancer, Sarcoma (Robinson and Pertmer, 2000, Yang et al., 2014).

DNA vaccines for infectious diseases mainly target HIV prevention and treatment. Apart from that, Hepatitis B, Hepatitis C, Human Papilloma Virus(HPV), Influenza (seasonal, pandemic), Malaria, Measles, Ebola virus, Severe Acute Respiratory syndrome, Marburg hemorrhagic fever, West Nile virus, Herpes simplex virus are also potential DNA vaccines candidates (Yang et al., 2014, Lee et al., 2018).

Currently, there are no DNA vaccines licensed for human use and are still ongoing clinical trials. However several vaccines have been licensed for veterinary use. (Gary and Weiner, 2020) Since the widespread development of DNA vaccines for use in humans is still in its early stages, the risks associated with the use of this strategy are still largely unknown. In summary, depending on the route, antigen, species, and so on, a DNA vaccine may induce a very comprehensive and potent immune response.

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