Chapter 8

Electrotransfer of DNA vaccine

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DNA vaccines

DNA vaccine is an attractive strategy to induce immune memory. Bacterial plasmids are constructed and optimized to express in vivo a protein that will induce an immune response. Preclinical studies have shown that plasmid DNA encoding antigens provides protection in small animals and to a lesser extend in large animals for a wide range of diseases e.g. prophylactic viral and bacterial infections as well as therapeutic cancer vaccines. Several DNA vaccines have been licensed for veterinary use or are under clinical trials for human use.

DNA vaccine comprises several key elements. A promoter is inserted upstream the sequence of the antigen of interest to drive expression in mammalian cells and a polyadenylation signal is located downstream. The production of plasmid DNA requires the presence of a replication origin and of a specific marker able to select plasmid-containing bacteria after transformation and during the amplification process. The use of antibiotic resistance genes as selection markers for plasmid production raises safety concerns which are often pointed out by the regulatory authorities and a new generation of plasmid backbones devoid of antibiotic resistance marker has emerged.

DNA vaccines are attractive due to their stability, low cost, easy production and ability to induce a broad immune response. Allowing the in vivo expression of the antigen by the transfected cells, DNA vaccines ensure a closer resemblance to the antigen than recombinant proteins, with

are able to stimulate all three arms of adaptive immunity: antibodies, helper T cells (Th) and cytotoxic T lymphocytes (CTL) and they contribute to the stimulation of innate immunity. The safety profile of DNA vaccines is generally considered as good and neither observable integration of the DNA in the host genome nor autoimmunity has been reported in human clinical trials.

A number of studies demonstrated the robustness of DNA plasmid encoding pathogen and tumor antigens to elicit immune response. DNA vaccines induce a predominantly Th1 response, CTL response and antibodies but both the delivery route and the administration method have been shown to influence the type and the magnitude of the immune response. To elicit CTL responses, the antigen needs to be present in the cytoplasm of antigen presenting cells (APC). The protein is either directly produced by transfected APC or reaches them through endocytosis by APC of the protein produced by other transfected cells (cross presentation). Peptides derived from the protein degradation bind to the major histocompatibility complex (MHC) class I or class II. Peptide association to MHC class I stimulates CTL while binding to MHC class II stimulate Th cells. Although DNA vaccines were initially developed to introduce antigen to MHC class-I processing pathway to induce CTL, they have also been shown to generate protective antibody responses: a transmembrane or secreted protein can activate B cells for antibody production.

In the past years, many efforts have been made to improve their immunogenicity and clinical potential relying on the use of electroporation, codon optimisation of the plasmid constructs or co-administration of adjuvants.

Electroporation-mediated delivery of DNA vaccines

Even if naked plasmid DNA vaccines injected in muscle can induce an immune response, a relatively low magnitude of response is usually induced in large target species.

Electroporation addresses two limitations of the poor immunogenicity of DNA vaccines. (i) By inducing a transient membrane permeabilization and by promoting electrophoresis of the negatively charged DNA, it facilitates DNA uptake in the host cells. Thereby the antigen expression is strongly enhanced, usually by two orders of magnitude, in the muscle or the skin. (ii) By creating a low level of inflammation at the site of

injection/electroporation, it enhances the recruitment of APC to the injection site.

Consequently, electroporation-mediated delivery of DNA vaccines enhances up to100-fold the immune responses elicited compared to simple injection. It is a useful strategy to increase both humoral and cellular responses in small and large animals including primates. A survey of the preclinical studies indicates that electroporation-mediated DNA vaccination induces long-lasting and robust cellular responses characterised by the induction of CTL, interferon γ and interleukin-2 by CD4+ and CD8+ T cells. Antibodies are usually detected. Combination with adjuvant (e.g. TLR-9 stimulation by CpG or interleukin-12) enhances the potency of DNA vaccination.

Two major organs have been investigated for DNA immunisation by electroporation. The skin is an immunocompetent organ with many resident APC e.g. Langerhans cells cover approximately 20% of the skin surface. It is easily accessible. Protein expression is limited to a few weeks. In contrast, the muscle induces a long term and stronger expression of the protein but contains few APC. Most of the preclinical studies indicate that a stronger humoral response is observed after intramuscular electrotransfer of the DNA than after intradermal electrotransfer.

Several electroporation-mediated DNA vaccinations are currently under clinical trials as therapeutic vaccines against cancers (e.g. melanoma or prostate cancer) and chronic infectious diseases (e.g. HIV, HCV). The uncompleted data suggest that electroporation-mediated vaccination is well tolerated and improves DNA vaccine potency. Devices are also been optimized to enhance immune response and/or improve patient comfort.

Recommended papers

DNA vaccines

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