FROM GENES TO IMMUNITY: DNA VACCINES FOR INFECTIOUS DISEASE CONTROL

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ABSTRACT

Recent advancements in vaccine technology have introduced DNA vaccines as a promising tool in veterinary medicine. These vaccines deliver genetic material from a pathogen to safely trigger immune responses without the risk of causing disease. In animals, DNA vaccines use plasmids carrying genes for protective antigens, and often incorporate self-adjuvanting nanomaterials to enhance effectiveness. They primarily stimulate immunity through the MHC class I pathway, leading to strong cellular responses. Compared to conventional veterinary vaccines, DNA vaccines offer benefits such as improved safety, stability, ease of production, and the ability to rapidly design vaccines for emerging animal diseases. They also hold great potential in preventing zoonotic infections and certain cancers in animals. Though some challenges remain, continued research is helping to refine these vaccines for broader application in veterinary practice.

KEYWORDS: DNA vaccines, Immune response, Plasmid vectors, Nanomaterials, Zoonotic diseases

INTRODUCTION

Traditional vaccines, including live attenuated, inactivated, and subunit/recombinant types—have played a pivotal role in disease control but are often limited by complex production processes, reduced efficacy, and the risk of adverse immune reactions. While subunit and recombinant vaccines are safer, their low immunogenicity remains a concern. Over time, vaccine development has progressed through three distinct generations, each addressing some of these limitations. However, traditional approaches still face challenges, particularly in combating certain infectious diseases. Gene-based vaccination, a hallmark innovation of 21st-century immunology, introduces specific segments of pathogen DNA or mRNA to elicit immune responses without the risk of causing disease. DNA vaccines typically use bacterial plasmids encoding microbial antigens. Although their transfection efficiency may be low, intramuscular administration can sustain antigen expression for several months. However, the use of naked DNA can result in variable gene expression.

In the early 1990s, the introduction of DNA vaccines reached a significant milestone with the approval of India's ZyCoV-D in 2021 for COVID-19. These vaccines work by delivering plasmid DNA encoding protective antigens, leading to targeted immune responses. Initially based solely on plasmid DNA, recent advancements have incorporated self-adjuvant nanomaterials to improve immunogenicity. Unlike conventional

vaccines, DNA vaccines rely primarily on MHC class I-mediated antigen presentation, effectively activating CD8+ T cells and generating strong cellular immunity. Overall, DNA vaccines represent a transformative step in vaccinology, offering enhanced safety, stability, and adaptability positioning them as a promising platform for combating a wide range of infectious diseases and beyond.

ADVANTAGES OF DNA VACCINES

Gene therapy, particularly via DNA vaccines, is emerging as a transformative approach in modern medicine due to its stability, scalability, high yield, cost-effectiveness, and ease of production. When combined with effective delivery systems, DNA vaccines can elicit strong and targeted immune responses. Optimal delivery depends on factors such as cost-efficiency, cell specificity, and safety. DNA vaccines are especially promising for cancer prevention and treatment, offering design flexibility and simplified manufacturing. Compared to conventional vaccines, they provide enhanced immunogenicity and long-term protection. Incorporating chimeric cytokine genes alongside antigen-encoding plasmids further amplifies the immune response. Notably, DNA vaccines stimulate both humoral and cellular immunity, essential for targeting complex diseases like cancer and viral infections. By mimicking natural infections, they effectively induce T cell-mediated responses. The expressed antigen is also presented by APCs to activate $CD4^+$ helper T cells, which in turn stimulate B cells to proliferate, undergo class switching, and differentiate into plasma cells that produce specific antibodies. Although there may be a delayed onset of immunity, the protection is durable and not compromised by maternal antibodies, making them suitable even for young animals.

DISADVANTAGES OF DNA VACCINES

While DNA vaccines offer significant promise, concerns remain regarding the potential integration of plasmid DNA into the host genome, which could lead to mutations. However, current evidence indicates that such integration occurs at a much lower frequency than naturally occurring mutations. Key challenges include improving delivery efficiency and addressing issues such as antibiotic resistance markers and antigen tolerance. Adjuvants and nanocarrier-based delivery systems are crucial for enhancing immune responses. Recent advances in nanocarrier modifications have shown potential in overcoming rapid DNA degradation and improving cellular uptake. Both viral and non-viral vectors are used for DNA delivery, each presenting distinct advantages and limitations. Although DNA vaccines elicit strong cellular immunity, their humoral response is generally weaker than that induced by recombinant protein vaccines, often necessitating booster doses. In comparison, mRNA vaccines offer improved antigen presentation and carry a reduced risk of genomic integration, making them an attractive alternative. Overall, while DNA vaccines represent a versatile and scalable platform, ongoing research is essential to optimize their delivery, safety, and immunogenicity for broader veterinary clinical and field application.

DNA VIRUSES AS VECTORS

Delivery of naked DNA often leads to inconsistent gene expression, prompting the development of viral vector-based systems that leverage the natural infectivity and replication mechanisms of viruses to enhance gene delivery and expression. A variety of nucleic acid delivery approaches—including viral, mechanical, electrical, and chemical methods—have been employed to overcome the low immunogenicity typically associated with DNA vaccines. Efficient delivery systems are essential for directing DNA to antigen-presenting cells (APCs), thereby eliciting strong and specific immune responses. Nanocarriers, in particular, improve DNA stability and enable targeted delivery to specific tissues, increasing vaccine efficacy. Despite the inherent challenges of

crossing cellular membranes and barriers, recent advances in delivery technologies offer significant potential for enhancing the effectiveness and consistency of DNA vaccines.

STRUCTURAL AND FUNCTIONAL INSIGHTS INTO DNA VIRUSES USED AS VECTORS

Since the 1980s, viral vectors have played a central role in gene therapy, providing efficient platforms for foreign gene delivery and expression. Common viral vectors include retrovirus (RV), lentivirus (LV), adenovirus (Ad), adeno-associated virus (AAV), and herpes simplex virus (HSV). These vectors exhibit high transfection efficiency, effectively bypassing endosomal barriers and facilitating nuclear gene delivery through nuclear localization signals.

Adenovirus (Ad), a non-enveloped double-stranded DNA virus, is widely used in vaccine development. Its variants—replication-defective, conditionally replicating, and helper-dependent—can accommodate inserts up to 37 kb. The ChAdOx1 vector, derived from a chimpanzee adenovirus, has demonstrated robust immune responses against COVID-19, Zika virus, and cancer. Recombinant AAV (rAAV), a non-enveloped single-stranded DNA virus, uses receptor-mediated endocytosis for cell entry and can carry genes up to 14 kb. It has been extensively engineered for safe and efficient gene delivery. Retroviruses (RV) and lentiviruses (LV) are RNA viruses capable of delivering transgenes of approximately 9 kb. Unlike RVs, LVs can transduce both dividing and non-dividing cells, increasing their utility in treating diseases like HIV, sickle cell anemia, and certain cancers.

Beyond viral systems, non-viral delivery platforms, especially nanoparticle (NP)-based methods, have gained traction due to their versatility and reduced immunogenicity. NPs encapsulate DNA via electrostatic or covalent interactions, enhancing stability, cellular uptake, and targeted delivery—particularly useful in cancer DNA vaccines. They can be engineered to respond to the tumor microenvironment, optimizing controlled release and immune stimulation.

Nano-vaccines, incorporating nanomaterials, offer superior delivery of plasmids or antigens to immune sites such as lymph nodes, thereby eliciting stronger and more durable immunity. Among these, liposomes—lipid bilayer vesicles—efficiently carry both hydrophilic and hydrophobic molecules. Cationic liposomes form stable complexes with DNA, although their short half-life and cytotoxicity are mitigated through PEGylation.

Polyethyleneimine (PEI), a cationic polymer, promotes DNA delivery via its proton sponge effect but poses cytotoxicity risks, often addressed through composite formulations. Chitosan, a biocompatible biopolymer, offers sustained release and low toxicity, with transfection efficiency improved through chemical modification. PLGA, a biodegradable copolymer, provides controlled DNA release but struggles with low encapsulation and delayed expression.

Emerging systems include exosomes, which are natural nanocarriers with minimal immunogenicity and long circulation times, and virus-like particles (VLPs) that mimic viral structure for enhanced stability and cellular uptake. Microalgae such as *Chlamydomonas reinhardtii* are being explored for DNA vaccine production due to their safety, scalability, and capacity for post-translational modifications. Physical delivery methods like electroporation significantly increase transgene expression by temporarily permeabilizing cell membranes. Gene guns, which propel DNA-coated particles into cells, also offer alternative strategies for DNA vaccine delivery, especially in research and immunization settings.

CONCLUSION

DNA vaccines represent a transformative advancement in immunization, offering improved safety, scalability, and immune response compared to conventional vaccine platforms. Although challenges such

as limited immunogenicity and concerns over genomic integration remain, ongoing innovations in design and delivery continue to address these limitations. The approval of the Indian ZyCoV-D vaccine underscores their clinical potential, particularly in addressing emerging infectious threats like SARS-CoV-2. Incorporating nanomaterials and advanced delivery systems—such as liposomes, polyethyleneimine (PEI), chitosan, and exosomes—has significantly enhanced the stability, targeting, and overall efficacy of DNA vaccines. Beyond infectious diseases, their adaptability and strong cellular immune activation make them especially promising for cancer therapy and gene-based interventions. While some hurdles persist, continued research and technological progress are likely to expand the scope and impact of DNA vaccines, paving the way for their broader adoption in both human and veterinary medicine.

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