

Directional Activation of Intestinal Dendritic Cells by an Oral Targeted Multivalent Vaccine

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Abstract

Parenteral injection is the most common route of administration for vaccines and therapeutics. Despite their frequent use, needle-based immunizations have several limitations; (i) needle phobias that are common in both adults and children, (ii) the requirement of trained medical personnel to administer vaccines, creating a limitation for mass vaccination, and (iii) accidental needle sticks, a serious concern in both developed and developing countries. Possible alternatives to injections have recently emerged and include (i) dermal and (ii) oral administration of vaccines. Here, we describe a methodology developed in our laboratory using intestinal bacteria that are considered safe for human consumption. Additionally, we have designed a dendritic cell (DC)-targeting sequence that delivers antigens directly to DCs. In this report, we discuss how DC-targeting peptide binding is not limited to human and murine antigen presenting cells; rather, it consistently binds with DCs of different species. Our data suggest that a DC-targeted oral vaccine platform could be used to develop vaccines for a variety of host animals.

Keywords: Dendritic cells; Multivalent vaccine

Introduction

Recently, the search for effective needle-free vaccination has escalated due to heightened concerns of pandemic diseases, bioterrorism, and specific disease eradication programs. Needle-free vaccination could assist with mass vaccination due to its easy and fast delivery, and by providing improved safety, decreased cost, and reduced vaccination-associated pain, thus, improving compliance. There are two major hurdles in the development of a successful oral vaccine: (i) protection of the antigen of interest from low gastric pH and digestive enzymes, (ii) and delivery of the antigen to dendritic cells (DCs) that are professional antigen presenting cells. To overcome these challenges, two approaches were taken. First, in order to protect the antigen from a harsh gastric environment, *Lactobacillus* species, including *L. acidophilus* and *L. gasseri*, bacteria that can survive and thrive in the gastrointestinal tract, were modified to secrete the antigen of interest in the gut. Secondly, to assist in the delivery of antigen to professional antigen presenting cells, a twelve amino acid long "targeting" peptide was added to the immunogenic vaccine subunit [1,2].

Lactobacillus Species as an Antigen Delivery Vehicle

Mucosal surfaces are the major route of entry for most of the pathogens that cause disease. Thus, vaccines capable of inducing a mucosal immune response can strengthen the defenses at the mucosal layer and protect against infection. Different species of *Lactobacillus* have been used as dietary components of human food for centuries and are considered safe for human consumption. Certain species of *Lactobacillus* are also a part of the normal gut microbiota [3]. Since *Lactobacillus* thrive in the low pH of the stomach, using this bacterium as a vaccine delivery vehicle protects the vaccine subunit from the harsh acidic environment and maintains vaccine bioavailability. Meanwhile, researchers have also developed both inducible and constitutive expression vectors effective in *Lactobacillus* to deliver immunogenic antigens [1,4-6]. Although immunotolerance to a commensal inhabitant of the gastrointestinal mucosa was an initial concern with this strategy, certain *Lactobacillus* such as *L. gasseri*, are able to overcome tolerance, likely via their strong innate adjuvant properties [7,8]. Using

L. gasseri, our laboratory has been able to deliver the protective antigen (PA) of *Bacillus anthracis* to vaccinated mice to resist this potential agent of bioterrorism [2]. Additionally, another group has used *L. gasseri* for the successful delivery of *Salmonella* antigens [9].

Targeting Dendritic Cells to Enhance the Immune Reaction

Dendritic cells (DCs) are the most effective antigen presenting cells in humans and domestic animals, with the unique ability to present antigen and activate naïve T lymphocytes, thus, playing a critical role in the induction of specific primary immune responses. Expression of a variety of surface receptors, such as C-type lectins (e.g., mannose R, DC-SIGN, DEC-205), Toll-like receptors (TLRs), receptors for the Fc portion of antibodies (FcRs) and complement receptors (CR3, CR4), allow these cells to efficiently bind antigens [10]. Captured antigens are subsequently processed and efficiently presented to rare antigen specific T lymphocytes due to the constitutive expression of class II MHC molecules and co-stimulatory/regulatory molecules, including CD40, CD86, and B7-H1 on mature DCs. Therefore, antigen delivered specifically to DCs, as opposed to B lymphocytes or macrophages that require activation to express co-stimulatory molecules, reduces the dose requirement of antigen for immune stimulation and has emerged as a potential vaccination tool to induce protective immune responses [10]. Utilization of traditional receptors (e.g., class II MHC molecules, CD11c, TLRs) for antigen targeting does not result in efficient delivery of antigen specifically to DCs because many other cell types also express

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these receptors and compete with DCs for vaccine binding. With the goal to discover a specific DC-targeting peptide moiety, a phage display library was sequentially absorbed with monocytes, T cells, B cells, and Langerhans cells and then screened for the ability to bind human myeloid-derived DCs [11]. The obtained sequence was then tested for its in vitro binding capacity and its application in antigen delivery in a murine model of oral vaccination by fusing this DC-targeting peptide to PA of *Bacillus anthracis* [1,12].

Because of their ease of administration, oral vaccine strategies are currently under development or in use for *Bordetella bronchiseptica*, the primary causative pathogen of the contagious respiratory disease complex, infectious tracheobronchitis or “kennel cough”, which is commonly seen in dogs housed together in pet stores, kennels, and animal shelters. This disease can also affect cats and occasionally, immunocompromised humans [13]. Oral therapeutic strategies are also used in rabies control programs that target ownerless pet populations in enzootic areas by vaccinating via palatable bait [14]; for oral vaccination of foals against pneumonia caused by *Rhodococcus equi* [15]; to protect newly born calves from scours, diarrhea caused by *E. coli*; and via administration in the drinking water of poultry to prevent or mitigate Newcastle disease, fowl cholera, and avian encephalomyelitis. In fact, poultry are likely the most heavily vaccinated domestic species, with the intensity of production expected to dramatically increase in the next few decades as the economies of countries like China and India improve and poultry consumption increases [16]. To expand upon the applicability of this targeting peptide as an antigen delivery agent in domestic animals, we tested its ability to bind DCs from multiple species of veterinary importance. We found significantly higher binding of DC-peptide to the DCs isolated from peripheral blood from all species tested, including canine, feline, equine, bovine, porcine, and avian species when compared to a non-specific peptide, indicating that this peptide binds to highly conserved regions of its receptor, the identity of which is currently under investigation in our laboratory. These results favorably suggest future use of this particular strategy in the development of veterinary multivalent vaccines.

Conclusions

Current vaccination methods employ needle-based administration, which has certain limitations that include the requirement of trained personnel, the risk of accidental needle sticks, and other constraints. To overcome these shortcomings, we have developed a combinatorial approach that delivers the DC-targeted antigenic protein to intestinal dendritic cells. This approach not only provides a platform for the development of an oral vaccine for human patients, but also allows for the possibility of the generation of oral vaccines against pathogens of veterinary importance.

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