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Directional Activation of Intestinal Dendritic Cells by Oral Targeted Multivalent Vaccine

Bikash Sahay, Mahesh Kathania, Jennifer L Owen and Mansour Mohamadzadeh*

Department of Infectious Diseases and Pathology, Division of Hepatology/Gastroenterology & Nutrition, Department of Medicine, and Emerging Pathogens Institute, University of Florida, Gainesville, FL 32601, USA

In the recent past, the search for effective needle-free vaccination has escalated due to recently heightened concerns of pandemic diseases, bioterrorism, and specific disease eradication programs. A 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 harsh gastric juices, *Lactobacillus* species, including *L. acidophilus* or *L. gasseri*, bacteria that can survive and thrive in the gastrointestinal tract, were modified to secrete the antigen of interest in the gut. Second, to assist in the delivery of antigen to the professional antigen presenting cells, a twelve amino-acid long tag 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 lactobacilli 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* species thrive in the low pH of the stomach, using it as a vaccine delivery vehicle protects the vaccine subunit from the harsh acidic environment and protects the vaccine bioavailability. Meanwhile, researchers have also developed both inducible and constitutive expression vectors effective in lactobacilli species to deliver immunogenic antigens [1,4-6]. Although immune tolerance to a commensal inhabitant of the gastrointestinal mucosa was an initial concern with this strategy certain lactobacilli such as *L. gasseri,* are able to overcome tolerance likely via 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 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 inefficient delivery of antigen specifically to DCs because many other cell types also express these receptors and would 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* [1,2,12].

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, immuno compromised 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 wealth of countries such as China and India and poultry consumption increase [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 from all species tested compared to a nonspecific peptide

***Corresponding author:** Mansour Mohamadzadeh, Department of Infectious Diseases and Pathology, Division of Hepatology/Gastroenterology & Nutrition, Department of Medicine, Emerging Pathogens Institute, University of Florida, Gainesville, FL 32601, USA, Tel: (352) 294-4117; E-mail: m.zadeh@ufl.edu

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indicating that this peptide binds to highly conserved regions of its receptor. These results favorably suggest future use of this particular strategy in the development of veterinary multivalent vaccines.

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