International Journal of Biological Macromolecules xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Chitosan-based particulate systems for the delivery of mucosal vaccines against infectious diseases

Bijay Singh[a], Sushila Maharjan[a], Ki-Hyun Cho[b], LianHua Cui[c], In-Kyu Park[d], Yun-Jaie Choi[b], Chong-Su Cho[b,*]

[a] Research Institute for Bioscience and Biotechnology, Kathmandu 44600, Nepal
[b] Department of Agricultural Biotechnology and Research Institute for Agriculture and Life Sciences, Seoul National University, Seoul 08826, Korea
[c] Department of Animal Science, College of Agriculture Science, Yanbian U niversity, Yanji, JiLin, 133002, China
[d] Department of Biomedical Sciences, BK21 PLUS Center for Creative Biomedical Scientists at Chonnam National University, Research Institute of Medical Sciences, Chonnam National University Medical School, Gwangju 61469, Korea

ARTICLE INFO

Article history:
Received 30 July 2017
Received in revised form
23 September 2017
Accepted 11 October 2017
Available online xxx

Keywords:
Chitosan
Mucosal vaccine
Antigen delivery

ABSTRACT

Given that most pathogens enter the body at mucosal surfaces for infection and mucosal immune responses act as the first line of defense against the invading pathogens, mucosal vaccination is the most effective method to prevent infectious diseases. However, the development of mucosal vaccines requires an efficient antigen delivery system which should protect the antigens from physical elimination and enzymatic degradation, target mucosal inductive sites, and appropriately stimulate the mucosal and systemic immunity. Accordingly, polymeric particles have garnered much attention because the physicochemical properties of polymers can be adjusted to resolve the issues associated with mucosal vaccine delivery. Particularly, chitosan-based polymeric carriers are the most promising vehicles for mucosal vaccine delivery because chitosan is biodegradable, biocompatible and mucoadhesive in nature. Similarly, chitosan can be modified with chemical and biological molecules to develop delivery carriers for controlled or targeted therapy. Moreover, they can be converted to various formulations, such as solid, liquid and gel, with a wide range of particle sizes. In this review, we highlight and discuss advances in the development of chitosan-based particulate systems, specifically for the delivery of mucosal vaccines against infections.

Contents

* Corresponding author.
E-mail address: chocs@snu.ac.kr (C.-S. Cho).

https://doi.org/10.1016/j.ijbiomac.2017.10.101
0141-8130/

1. Introduction

Mucosal surfaces (nasal, respiratory, oropharyngeal, gastrointestinal and urinogenital) are the most common routes of entry of many pathogens (viruses and bacteria) for infection. It is now increasingly evident that local mucosal immune responses play a pivotal role in protecting against these invaders. Vaccination is the simple way of boosting the immunity to fight off the infections. Unlike parenteral vaccination, mucosal vaccination not only provides humoral and cell-mediated immune protection at mucosal sites but also confers systemic immunity [1]. Besides, mucosal vaccines have garnered much attention due to their ease of administration, high patient compliance and feasibility of mass vaccination.

Although several mucosal routes (nasal, pulmonary, oral, vaginal and rectal) are available for vaccine administration, the nasal and oral routes are more effective to induce immunity at distant mucosal sites in addition to the local site of vaccine delivery [2,3]. However, both routes of vaccine delivery have their own pros and cons. While oral route has the largest mucosal surface area and specialized epithelial cells termed microfold cells (M cells) for the higher possibility of antigen uptake, the route is compromised by harsh gastric pH and enzymes for antigen degradation thereby necessitating protective formulations to overcome the barriers of the oral delivery route. On contrary to oral route, antigens delivered through nasal route do not confront with pH and enzyme barriers requiring only a low dose of antigen for delivery. However, vaccine delivery through nasal route is compromised by rapid mucociliary clearance, inefficient antigen uptake, and poor patient acceptability.

A number of formulations have been developed to improve the efficacy of mucosal delivery. These formulations, usually prepared from polymers, are in use as delivery systems because they protect the antigens from degradation, increase the residence time of antigens at mucosal surfaces, release the antigens at specific sites and target M cells to enter into immune compartments. Although a vast array of polymers, both natural and synthetic, have been recognized for their potential to deliver mucosal vaccines efficiently, chitosan holds a special position due to its unique properties. Chitosan is a natural polysaccharide and hence it is biodegradable and biocompatible. It is cationic, non-toxic and mucoadhesive in nature. Chitosan can be modified with chemical and/or biological molecules and they can be converted to various formulations, such as solid, liquid and gel, with a wide range of particle sizes.

2. Mucosal immunity

Mucosal surfaces represent a major portal of entry for many pathogens and the immunological activity occurred at these surfaces by mucosal immune system plays a key role, as the first line of defense, to protect these surfaces from the external invaders. The mucosal immune system consists of an integrated network of tissues, lymphoid and constitutive cells, and effector molecules (antibodies, cytokines, and chemokines) [4]. These factors respond to pathogens (or mucosal vaccines) through a complex orchestration of cellular processes stimulating innate and adaptive immune responses to confer protection (Fig. 1).

Mucosal immune responses are initiated in organized mucosa-associated lymphoid tissues (MALT), namely gut-associated lymphoid tissue (GALT) or Peyer's patches in the small intestine and bronchus-associated lymphoid tissues (BALT) in respiratory tracts. The MALT is a highly compartmentalized immunological system that functions independently from the systemic immune system, and it consists of large populations of antigen presenting cells (dendritic cells, T lymphocytes) and plasma cells (B lymphocytes). In the presence of signals, antigen-specific antibodies produced by the plasma cells are secreted to mucosal surfaces as secretory IgA (sIgA) which can bind, neutralize and eliminate the pathogens from the body. As sIgA is the very first line of defense against the invading pathogens, induction of potent IgA responses is a pre-requisite for successful mucosal vaccination.

Above all, the critical barrier to successful antigen delivery is to pass pathogens or antigens from mucosal tissues to immune compartments through M cells. The M cells are specialized epithelial cells, specifically located on the follicle-associated epithelium (FAE) in mucosal tissues, that capture and transport foreign particles across the epithelial barrier to underlying lymphoid cells [5]. The transcytosed particles are then passed either to B cells to activate the secretion of sIgA (mucosal response) or to dendritic cells which present antigens to T cells to initiate the production of IgG (humoral response). Hence, considering the key role of M cells in antigen delivery across the epithelial barrier, M cells are the most amenable targets for antigen delivery in the mucosal route to induce mucosal immunity.

3. Mucosal vaccine delivery by particulate systems

The use of polymers as carrier systems has flourished in mucosal vaccine delivery as they offer an advantage of delivering antigens to a specific target site. The other benefit of polymeric carrier systems is the way they control the release of antigens, slow or burst, from their grip in the mucosal sites. In the case of oral delivery, the antigens should be protected from harsh gastric pH, bile juices and digestive enzymes in the gastrointestinal (GI) tract. To overcome these barriers in GI tract, the encapsulation of antigens in polymeric particulates such as microparticles and nanoparticles has emerged as a promising approach for mucosal delivery [6,7]. The choice of polymeric particulate systems for antigen delivery arises from their ease of modifications to tune up physicochemical properties such as surface charge, hydrodynamic size, and solubility of the particles. Besides, polymeric particles have the capability to enhance the immune responses to mucosally delivered antigens. In many cases, particulate antigens have greater access to immune compartments in MALT through M cells compared to soluble antigens [6]. Additionally, particulate antigens also find their way through paracellular route to enter to underlying lymphoid cells from FAE in mucosal tissues [8].

Naturally, innate immune system interacts with invading pathogens through a ligand-receptor interaction between pathogen associated molecular patterns (PAMPs) of pathogens [9] and pattern recognition receptors (PRRs) of the cells of immune system [10]. Various cells, including neutrophils, macrophages and dendritic cells express PRRs on their cell surfaces which recognize a pathogen as an extracellular particulate antigen. Upon detection of PAMPs on pathogens, PRRs trigger inflammatory responses that not only destroy the invading pathogens but also activate the adaptive immune system. In the same way, polymeric particles with antigens mimic natural pathogens and efficiently present to

Please cite this article in press as: B. Singh, et al., Int. J. Biol. Macromol. (2017), https://doi.org/10.1016/j.ijbiomac.2017.10.101