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Exploiting receptor biology for oral vaccination with biodegradable particulates

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Abstract

The effective delivery of antigens via the oral route is an extremely desirable goal. Mucosal delivery of antigens stimulates mucosal and systemic immunity without affecting maternal antibodies and reduces the need for sterile needles or trained personnel. To date, there are very few commercially available oral vaccines and despite numerous reports in the scientific literature to show the success of biodegradable antigen carriers, none of these have achieved commercial status. Nevertheless, many studies have shown the great potential of biodegradable antigen carriers for oral vaccination in preclinical studies, but a more rational approach may be to specifically target antigen-loaded biodegradable microspheres to cells in the mucosal immune system which transport and process antigens for T cell recognition. Modern cell and molecular biology techniques have unearthed a wealth of information regarding important receptors involved in the capture of luminal antigens by microfold or membranous (M) cells and receptors on dendritic cells (DCs) which may allow future targeting of antigens to specific DC phenotypes, thus directing the immune response appropriately.

In this review, we consider the use of currently available biodegradable antigen carriers and speculate on how these may be improved to more efficiently target mucosal effector sites.

Keywords: M cell; Oral vaccination; Dendritic cell; Biodegradable carriers; Mucosal immunity; Targeted delivery

Contents

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1. Introduction

The advent of mass vaccination programmes proved to be one of the greatest medical achievements of the 20th century. Most currently available vaccines require intravenous (i.v.) or subcutaneous (s.c.) delivery of antigens. However, over the past 15 years, numerous studies have assessed the potential of orally delivered antigens on the induction of mucosal and systemic immune responses. Mucosal delivery is the only vaccination route to induce effective B cell class switching and the development of secretory IgA-producing plasma cells. This is evident when comparing oral or s.c. administered poliomyelitis vaccines [1]. However, although the oral polio vaccine has advantages, such as a lack of a need for sterile needles, a reduced need for trained personnel and the possible induction of herd immunity in unvaccinated individuals, it also has disadvantages, such as the possible reversion to virulence and the possible induction of disease in immune-compromised populations reviewed [2]. Subunit vaccines which can be efficiently delivered to mucosal tissues, therefore, have great potential. However, subunit vaccines are less efficacious than live attenuated vaccines and they require adjuvants.

The gastrointestinal (GI) tract is a very hostile environment, with regions of low and high pH, high degradative (enzymic) activity and lipid solubilising ability (biliary phospholipids and bile salts). There is a tendency also for soluble antigens to induce tolerance rather than immunity. For these reasons, many laboratories have investigated the use of biodegradable antigen carriers which protects antigens in transit through the GI tract whilst delivering antigens in a particulate, rather than a soluble, form. Unfortunately, the vast majority of these studies have employed a "dope and hope" strategy whereby antigens encapsulated in biodegradable carriers are administered to laboratory animals by oral gavage, in the hope that a proportion of these will be transported through the intestinal epithelium and to immune effector sites. Few of these studies have reported that this method effectively protects animals against subsequent pathogen challenge and none of these studies have transferred to human volunteers.

In this review, we discuss the potential of biodegradable delivery systems for oral vaccination and speculate on how future studies may be improved by direct targeting of encapsulated antigen to cells involved in intestinal antigen sampling (M cells) and antigen-presenting cells (APCs), which are required for the development of mucosal immunity, in particular dendritic cells (DCs) residing in the subepithelial dome (SED) of Peyer's patch (PP) tissue.

2. Mucosal antigen sampling and effector sites

Intestinal epithelium provides a barrier function which prevents easy access of pathogens to underlying tissue [3,4]. Absorptive enterocytes do not readily transport biodegradable microspheres but can take up and present soluble antigens, in conjunction