Nanoparticulate Oral Vaccines – An Update

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ABSTRACT

Being non-invasive in nature, painless and safe, oral delivery of antigens for vaccination is an attractive route of immunization. Oral delivery of vaccines is also a cost-effective strategy. But to escape the acidic environment of the stomach, antigens need to be suitably encapsulated to protect them from rapid degradation. By changing soluble antigens to nanoparticulate forms, it is now realised that better effective oral vaccines may be in the pipeline.

Keywords: Oral Vaccines, Nanoparticles, Particulate Antigens.

I. INTRODUCTION

Oral delivery of antigens for vaccination is an attractive proposition because of being non-invasive in nature, painless and safe for use in infants. Oral delivery of vaccines is also a cost-effective strategy.1-4 To escape the degradative acidic environment of the stomach, antigens need to be suitably encapsulated to protect them from rapid degradation and also, a higher dose may be required for oral vaccination.

We have shown in an earlier work5 that the FDA approved poly-[ε]-caprolactone (PCL) polymer, because of its slow degradation kinetics, gives a prolonged and slow antigen release, making the availability of the antigen for generation of very effective subsequent immune responses, both through the humoral and cell mediated arms. This in itself has an advantage over the conventional alum based vaccine wherein only humoral immune responses are generated with little or no cell mediated immunity.

Particulate antigens and immunological aspects:

The development of an effective adaptive immune response depends on effective presentation of antigenic peptides on MHC class I and MHC class II molecules. The mechanism of antigen internalization significantly influences the efficiency of cross-presentation. Soluble antigens are poorly presented, while particulate antigens, which enter cells via phagocytosis, are presented more efficiently by MHC class I molecules. Hence, more potent CTL responses are generated by particulate antigen delivery systems.

Oral HBsAg Vaccine

Hepatitis B virus infection is a major global health problem with about 30% of the global population infected with HBV and 350 million are HBV carriers. Persistent HBV infection causes chronic hepatitis, liver cirrhosis and hepatocellular carcinoma6. The current hepatitis B vaccination includes three intramuscular injections of HBV surface antigen (HBsAg) with adjuvant (aluminum hydroxide) at 0, 1 and 6 months. In rural India and other developing countries dropout rate is high among individuals who
do not turn up for booster dose. The prolonged period of immunity with less number of booster dose and development of effective systemic as well as mucosal immunity are important grand challenges for HBV vaccination and needs specific innovations. Dialysis patients, HIV-positive individuals, inflammatory bowel disease (IBD) patients, those with celiac disease, the morbidly obese, and the elderly are all at risk of low antibody titer (<10 mIU/mL) after receiving the standard three injected doses. Thus a more efficient vaccine for HBV is very much needed.

Building up on our group’s earlier study we explored the PCL polymer nanocarrier for oral immunization in Swiss albino mice comparing it to the conventional parenteral route of administration. We found a superior antibody response with a higher titer of anti-HBsAg antibody till 2 months following single oral administration compared to other routes of immunization and conventional alum-based HBsAg vaccine. The nanoparticles (NPs) with the antigen were found in the macrophages in small intestinal villi, peripheral lymph nodes and other reticulo-endothelial organs 2 months after oral administration. This study suggests the efficacy of the current nanocarrier system for efficient antigen presentation disseminated in peripheral lymphoid tissues following oral administration with a prolonged antibody response, which can minimize the requirement of booster dose. The oral delivery vehicle with the PCL system may prove to be very effective with requirement for no or reduced booster doses and painless delivery of the vaccine resulting in increased compliance of the population for mass immunization schedule.

Recent trends in development of oral nanoparticulate antigens:

Albrecht RM et al. used correlative instrumental neutron activation analysis and electron microscopy to quantitatively and qualitatively study the gastrointestinal uptake and subsequent tissue/organ distribution of 4, 10, 28, and 58 nm diameter metallic colloidal gold particles following oral administration to mice. In their quantitative studies they found that colloidal gold uptake is dependent on particle size: smaller particles cross the gastrointestinal tract easily. Electron microscopy revealed that particle uptake occurred in the small intestine by persorption through holes created by extruding enterocytes.

D'Souza MJ et al. used particulate delivery to generate immune response against prostate cancer antigens. The aim of this study was to evaluate the efficacy of prostate cancer vaccine derived from a murine prostate cancer cell line, TRAMP C2 in murine model via oral route using aleuria aurantia lectin as a targeting ligand for M-cells in the intestinal Peyer’s patches. The whole cell lysate was obtained from TRAMP C2 murine prostate cancer cell line and was formulated into particles using spray drying process. For in vivo studies, 4-6 week old C57BL/6 male mice were vaccinated orally biweekly for 10 weeks. Serum samples were analyzed at regular intervals to determine serum IgG levels. The mice were then challenged with live TRAMP C2 cells to determine efficacy of the vaccine. The serum IgG levels of vaccinated animals were higher compared to that of controls. Moreover, the tumor growth was retarded significantly in the vaccinated mice compared to that of controls (p < 0.001).

The same group studied a microparticulate vaccine prepared with the use of a spray dryer using whole cell lysate of a murine ovarian cancer cell line, ID8. These particles were designed for oral delivery using enteric polymers such as methacrylic copolymer, Eudragit(®) FS30D and hydroxyl propyl methyl cellulose acetate succinate. These particles were targeted for uptake via microfold cell (M-cell) in Peyer’s patches of small intestine using the earlier M-cell targeting ligand, Aleuria aurantia lectin. The particles obtained were of 1.58±0.62 μm size with a
charge of 12.48±2.32 mV. The vaccine efficacy was evaluated by administering the particles via oral route to C57BL/6 female mice. At the end of vaccination, mice were challenged with live tumor cells. Vaccinated mice showed around six-fold retardation of tumor volume in comparison to non-vaccinated animals for 3 weeks after the tumor challenge (p<0.001). CD8+ T-cell, CD4+ T-cell and B-cell populations in different lymphatic organs were elevated in case of vaccinated mice. They concluded that such a vaccine could potentially be an effective treatment for patients with residual tumor or high tumor-relapse probability.

Cho CS et al.11 have discussed the potential use of thiolated chitosan microspheres as next-generation mucosal vaccine carriers. Chitosan is a natural biodegradable polymer and of great interest in biomedical research due to its excellent properties including bioavailability, nontoxicity, high charge density, and mucoadhesivity. Chitosan microspheres are promising carrier systems for mucosal vaccination, especially via the oral and nasal route to induce enhanced immune responses. Moreover, the thiolated form of chitosan is of considerable interest due to its improved mucoadhesivity, permeability, stability, and controlled/extended release profile.

Bilosomes represent a key advance in oral vaccine delivery because they are more resistant to disruption by gastric acid as well as enzymes. Kesharwani P et al.12 have in their review focused on different aspects of bilosomes including composition, developmental techniques, stability, transitional modifications and scale-up - emphasizing their biomedical potential in oral immunization against various diseases.

Avadi M et al.13 fabricated trimethyl chitosan (TMC) nanoparticles using ionic gelation studied the utility of the particles in the oral delivery of hepatitis B surface antigen (HBsAg) employing solutions that simulated gastric and intestinal conditions. The particle size, morphology, zeta potential, loading capacity, loading efficiency, in vitro release behavior, structure, and morphology of nanoparticles were evaluated, and the activity of the loaded antigen was assessed. Size of the optimized nanoparticles and that of the antigen-loaded nanoparticles were 85 nm and 158 nm, respectively. SEM images revealed a spherical shape as well as a smooth and near-homogenous surface of nanoparticles. Results of the in vitro release studies showed that formulation improved the acid stability of the TMC nanoparticles as well as their capability to preserve the loaded HBsAg from gastric destruction. The results suggest that TMC/HPMCP nanoparticles could be used in the oral delivery of HBsAg vaccine.

Kang SM et al.14 explored the oral route of vaccination with a microparticulate formulation. Microparticles containing inactivated influenza A/PR/34/8 H1N1 virus with Eudragit S and trehalose as a matrix were prepared using the Buchi spray dryer. Particle size distribution of microparticles was measured and the bioactivity of vaccine in a microparticle form was analyzed using a hemagglutination activity test. Furthermore, the efficacy of microparticle vaccines was evaluated in vivo in Balb/c mice. Analysis of serum samples showed that microparticles resulted in enhanced antigen-specific immunoglobulin G (IgG), IgG1, and IgG2a antibodies. Upon challenge with homologous and heterologous influenza viruses, microparticle vaccines showed significantly increased levels of protection.

II. CONCLUSION

Particulate antigens have an advantage over soluble antigens in eliciting strong humoral, cellular and mucosal immune responses. Antigen cross presentation also is enhanced. Antigens suitably entrapped in nanoparticles can thus also be used effectively for oral immunization as they protect the antigens from the acidic environment of the stomach.
while also acting as effective vaccines. The multitude of studies being reported in the area of nanoparticulate oral vaccines promises a new generation of better vaccines effective against infectious agents and neoplastic growths.

III. REFERENCES


