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Journal of Controlled Releasejournal homepage: www.elsevier.com/locate/jconrel**Cover Story****Enhanced mucosal vaccination by biodegradable nanoparticles**

Mucosal administration of vaccines offers many advantages over injection, including easier administration, reduced adverse effects, and induction of both systemic and mucosal response at the sites of antigen entry. The most attractive route for mucosal immunization is the oral route for obvious reasons. Oral immunization with non living antigens, however, has not been very successful because of degradation in the harsh gastrointestinal environment and poor absorption. Various studies have shown increased antibody responses when antigens are orally administered in the nanoparticle formulations. Oral vaccination by nanoparticles has a long history. Oral vaccine delivery is different from oral delivery of protein drugs. Delivery of peptide and protein drugs requires delivery of an accurate amount of each drug. For example, oral delivery of insulin will be very difficult, if not impossible, due to the stringent requirements of accurate dosing and accurate timing. Oral vaccination, on the other hand, is relatively easier, because of less stringent requirement of dosing and timing. Nevertheless, development of oral vaccine delivery systems has been slower than expected.

Nanoparticles for oral vaccine delivery have been commonly prepared using biodegradable poly(lactic-co-glycolic acid) (PLGA) or bioadhesive polymers such as chitosan (CS) and its soluble derivative, N-trimethyl chitosan (TMC). Although most of the polymers used in microencapsulation of vaccines allow protection of the antigen from degradation, their effects on interaction with intestinal surface and on antigen uptake have not been examined in detail. Furthermore, the mechanisms of innate defense and adaptive immune protection at the mucosal surface induced by these nanoparticles are not clearly understood. The study by Professors Préat and Jiskoot in this issue addresses the question on the fate of an encapsulated antigen after oral delivery [1]. It was designed to understand the mechanisms by which oral administration of antigen-loaded nanoparticles induces an immune response and to analyze the effect of the nanoparticle composition on these mechanisms. Nanoparticles made from CS and TMC loaded with a model antigen ovalbumin (OVA) were prepared by ionic gelation with tripolyphosphate. Intraduodenal vaccination with

OVA-loaded nanoparticles led to significantly higher antibody responses than immunization with OVA alone. TMC nanoparticles induced anti-OVA antibodies after only a priming dose. Professors Préat and Jiskoot and their group found that transport of OVA-loaded TMC nanoparticles by Caco-2 cells or follicle associated epithelium model was higher than OVA-loaded CS or PLGA nanoparticles. They also found that the TMC nanoparticles, but not CS or PLGA nanoparticles, had intrinsic adjuvant effect on dendritic cells. Thus, it appears that nanoparticles with certain composition can increase the M-cell dependent uptake and enhance association of the antigen with dendritic cells. These findings provide new insights into mucosal vaccination using nanoparticles.

The study by Professors Préat and Jiskoot emphasizes the importance of a mechanistic approach for optimization of mucosal, in particular oral, immunization. The study also shows that it is important to understand the interactions of nanoparticles with the gastrointestinal tract, (e.g., bioadhesion and uptake by specific cells) as well as with dendritic cells. Nanoparticles made of specific polymers, e.g., TMC nanoparticles, provide a new strategy for effective oral delivery of various vaccines.

Reference

- [1] B. Slüter, L. Plapied, V. Fievez, M. Alonso Sande, A. des Rieux, Y.J. Schneider, E. Van Riet, W. Jiskoot, V. Préat, Mechanistic study of the adjuvant effect of biodegradable nanoparticles in mucosal vaccination, *J. Control. Release* 138 (2009) 113–121.

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