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Cover story

Administration route and carrier dependent effects on vaccine efficacy: Implications for vaccine design

With increasing concerns regarding the use of live attenuated or whole killed pathogens as vaccines, development of subunit-based vaccines has gained momentum over the last decades. Subunit vaccines offer an attractive safety profile and usually contain less impurities or endotoxins, making them more pharmaceutically defined. Unfortunately this tends to render these vaccines less immunogenic than their whole pathogen-based counterparts. The reduced immunogenicity has been overcome by a few popular methods, such as application of adjuvants and inserting antigen into particulate formulations. Inclusion of antigens into nanoparticles simulates the natural way immune cells encounter whole antigens, and naturally it has been shown to increase the uptake of antigen by macrophages, dendritic cells (DC) and B-cells. Adjuvants, such as Toll-like receptor (TLR) ligands, can subsequently activate antigen presenting cells to enhance the proliferation of antigen specific B- and T-cells. It still remains largely unclear how to most effectively combine antigen, carrier system and adjuvant for developing optimum antigen delivery systems. Two studies in this issue emphasize that the size of the carrier system, the formulation of the adjuvant as well as the route of administration influence the immunogenicity of the vaccine. Professor Yvonne Perrie and her team explored the effect of the size of cationic liposomes on the B- and T-cell responses [1]. Using liposomes with different mean diameters they showed liposomes with a mean size of 500 nm are most effectively phagocytosed by macrophages and efficiently prime T-cell responses. Interestingly though, the size of the carrier system does not influence the antibody response.

The immunization route-dependent immunogenicity of cationic liposomes loaded with an antigen (ovalbumin; OVA) and an adjuvant (CpG, a TLG 9 ligand) was explored in another comprehensive study in the issue by Professors Joke Bouwstra and Wim Jiskoot and their group [2]. Mice were immunized intranodally, intradermally, transcutaneously and nasally (as shown on the cover figure of this issue) with OVA and CpG encapsulated into cationic liposomes or a simple physical mixture. They have found that cationic liposomes strongly enhance uptake by DCs of both OVA and CpG as compared with an OVA + CpG solution *in vitro* as well as *in vivo* when administered intranodally. However, after transcutaneous and nasal application the opposite effect was observed. The mice treated with OVA/CpG

liposome showed a lower uptake by DC in the draining lymph node as compared with a solution of OVA and CpG. The authors hypothesize that this effect is due to the barrier function of the skin and nasal epithelium. This is reflected in the resulting antibody response, as the IgG titers after nasal and transcutaneous administration of OVA/CpG liposomes were reduced in comparison with administration of an OVA + CpG solution. Interestingly, encapsulation into liposomes favored a Th1-type response irrespective of the administration route. These studies show that encapsulation of antigen and adjuvant into a cationic liposome can have beneficial effects on both the quantity and the quality of the antibody and T-cell responses, when these formulations are injected *via* conventional routes. When applied mucosally or dermally, however, their bulkiness seems to prevent the antigen from effectively reaching antigen presenting cells.

The highlight featured in the two studies in this issue [1,2] is that there is no one formulation that can be universally applied to various subunit vaccines. The optimum formulation should depend on the type of response required for protective immunity and the intended route of administration. Various formulation aspects, such as particles size, choice of adjuvant, and co-localization of antigen and adjuvant, must be adjusted based on the selected administration route.

References

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