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Recent Trends in Development of Adjuvant of Vaccine

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ABSTRACT

Adjuvants are used as a carrier of antigen in modern vaccine therapy. These are heterogeneous compounds which are administered with antigens to elicit better immune response against co-administered antigens by stimulating the immune responses. Ideally, an adjuvant should not be mutagenic, carcinogenic and teratogenic and it should not produce any autoimmune disease. However, many of the adjuvants used in vaccine preparation have one or another side effect. The present paper describes in brief the history, development and recent trends in the adjuvant of vaccine.

Key words: Vaccine, adjuvant, mucosal vaccine, immune response

INTRODUCTION

Adjuvants are used as a carrier of antigen in modern vaccine therapy. The term adjuvant was derived from Latin that represents adjuvare means aid. Adjuvants are heterogeneous compounds which are administered with antigens to elicit better immune response against co-administered antigens by stimulating the T Helper Cells (TH1) mediated immune response. Ideally an adjuvant should not be mutagenic, carcinogenic and teratogenic and it should not produce any autoimmune disease. However, many of the adjuvants used in vaccine preparation have one or another side effect. As far as the history of adjuvants initially these were supposed to play nonspecific role in immune modulation and their roles were limited to form the depot for the slow release of antigens and up to certain level to target antigen presenting cells.

Initial period of adjuvant therapy reveals the use of aluminium salts and emulsions as commonly used adjuvants. These alum-adsorbed antigens are supposed to induce a strong TH2 response, stimulation of Antigen Presenting Cells (APCs) through the signalling of inflammasome (Li *et al*., 2008). Out of these, alum was most common and safe adjuvant but due to ability to form local granuloma at the site of injection and development of tolerance raised

concern (Rizk *et al.*, 2011). Further addition of oils in the form of Freund's adjuvants to form depot of antigens produced good immunological response with quite common local reactions. Similarly liposomes produced good immune response due to its ability of immuno-modulation but these had low stability. Then the Monophosphoryl lipid A, a purified lipopolysaccharide extracted from Gram negative *Salmonella minnesota*, with the ability to increase the activation of dendritic cells and T-cells along with induction of cytokine production through strong TH1 response showed a glimpse of ideal adjuvant (Hiernaux *et al.*, 1989). It also revealed good immune response in both mucosal and systemic immunity. The trials are still continued with their non-hazardous potential in human. With the similar competence, Liposomes and Immuno-stimulating Complexes (ISCOMs) were also introduced particularly in human vaccines (Sjolander *et al.*, 1998). These were supposed to induce remarkable humoral, mucosal and cellular immune responses. However, due to the development of allergic reactions and inability to universal acceptance these were also not accepted as the ultimate adjuvant. During the same period, synthetic oligo-nucleotides containing immune stimulatory motifs were also reported with the ability to increase the activation of both dendritic and T-cells leading to a shift in cytokine production.

As with the concept of prevention of newly emerging diseases, vaccinology is now a fast-moving branch of science and continuous thoughts are being attempted for the development of such a combination of adjuvant and antigen. It can be applied easily with minimum or no side effect and good immune response and this search has made a collaboration of microbiologists with pharmaceutical personals. The thought behind all these is to have a vaccine which can be safely administered through mucosal routes viz. oral, intranasal or conjunctival routes (Kweon, 2011). As mucosal route has been the method of choice of vaccine delivery nowadays, a concept of particulate delivery systems was suggested to facilitate the antigen uptake by APCs or by increasing the influx of professional APCs into the injection site. This concept of system is based upon the use of polymer nanoparticles. These nanoparticles have been proposed as mucosal adjuvant with all kinds of goodness for vaccines viz., protection from enzymatic degradation, prolong immune response, better presentation of to the mucosal-associated lymphoid tissue with strong bioadhesive performance (Vyas and Gupta, 2007). In general, nanoparticles are of two types, biodegradable and nonbiodegradable. Out of these, two biodegradable nanoparticles are preferred modules of choice for present researchers. Biodegradable particles are further classified in two groups as nanocapsules and nanospheres. In nanocapsules, the drug is confined to a cavity surrounded by a polymer membrane, whereas in nanospheres it is physically and uniformly dispersed in polymeric matrix. The ability of these nanoparticles to bind with and to carry macromolecules like peptides, proteins and nucleic acids for the preparation of vaccines and their biocompatibility with host tissues and cells along with easily manageable size is promoting them to be most effective adjuvant. Encapsulation of bioactive molecules also provides protection against extreme pH conditions, gastric juices, bile and pancreatic secretions and thus maintain the immuno-potentiating ability of encapsulated antigens (Champagne and Fustier, 2007). These particles can be easily synthesized so their size can be adjusted to avoid reticulo-endothelial system to increase the time of exposure of antigens. The important concern is not to have a nanoparticle rather to select a suitable one viz. natural one (chitosan, alginate, carrageenan, albumin, gelatin, collagen etc.) or synthetic one Poly Lactic Acids (PLA), Poly Lactide-co-glycolic Acids (PLGA), Poly Methyl Methacrylate (PMMA), poly ε-caprolactone (PCL), Poly Alkylcyanoacrylates (PACA) and copolymers. The natural one survives for shorter period of time so synthetics are used preferably for quick and sustained drug release. Synthetic one has longer delivery time but had limitations

regarding formulations. Other than these, natural nanoparticles are also derived from the polysaccharide like chitosan and poly D-glucosamine. Chitosan can be easily prepared by the partial N-deacetylation of chitin and is a natural polymer with cationic polymer with high charge density with a nontoxic nature. Its biocompatibility and biodegradability is an another advantage. It has been applied in the preparation of vaccines like diphtheria and tetanus toxoids and with plasmid DNA. Nondegradable nanoparticles might be latex, gold, silica, or polystyrene which can be coadministered with antigen without much adversity. These particles can have positivity and negativity, however, the toxicity and effects of accumulation of these particles in tissues are yet to be answered. Overall in vaccine development, there is a burning need to address the issue of binding of antigens to specific motifs to stimulate immune response and this high binding can be achieved by the high binding affinity of mannose residues to the mannose-binding lectins. Most of the mannose receptors are highly expressed in antigen presenting cells of the immune system, thus the presentation of antigen with nanoparticles or the process of mannosylation can potentiate the ability to induce immune response. With the advancement of molecular cell biology now it is well established that the presence of specific ligands can enhance the targeting to receptors on APCs i.e., Toll Like Receptors (TLRs), to enhance the antigen presentation for immunological response. There are different ligands for different response as TLR3 (for dsRNA from viruses), TLR4 (bacterial lipo-polysacchride), TLR5 (bacterial flagellin), TLR7 (ssRNA from viruses) and TLR9 (bacterial CpG-containing DNA) stimulate TH1 response whereas TLR2 (for bacterial peptide-glycans and lipoproteins) induce TH2 response. Thus, the specific recognition of the antigens directs innate and adaptive immune responses. The role of nanoparticles to elicit humoral, cellular and mucosal immunity is well established (Stano *et al.*, 2012). There is a report regarding the involvement of nanoparticles induced innate immune responses. These induce immune response in a TLR2- and TLR4-dependent manner. More expression of TLRs in the intestinal epithelium is also supportive of oral vaccination. Sometime intracellular receptors are also expressed along side of intestinal epithelium.

CONCLUSION AND FUTURE PERSPECTIVES

Antigens do not always bear immunomodulation role due to smaller size and shorter period of survival, thus an adjuvant needs to be added to compliment the deficit. The adjuvant might be selected on different criterion as formation of depot, slow release of antigen, protection from enzymatic reaction, presentation to APC, triggering of TH1, TH2 cells and binding with specific ligands. Other than this it should not have adverse local and systemic reaction. Present trend in vaccinology is to develop mucosal vaccine for all the vaccination presently available thus in this regard nanoparticles, particularly natural type are the best possible target but adverse effects due to continuous use is yet to be answered.

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