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Short Communication

Particulate Vaccines Orchestrating Optimal Delivery and Immune Response

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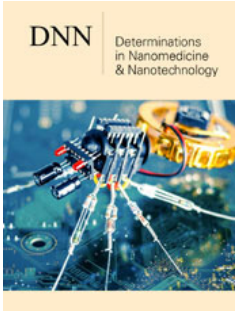

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Abstract

Vaccines play a vital role in neutralizing deadly infectious diseases, and particularly particulate vaccine appears more promising due to its similar morphology with the pathogen. Particulate vaccines are effective in low doses, offset inadequate efficacy of subunit vaccine, and provide danger signals to activate the body's immune system. It further enhances the stability of entrapped antigen and can be well tolerated in both animals and humans. For better understanding of immune response, it is important to know the physical attributes of particulate vaccine such as its size, shape and rigidity. Consequently, tailoring the physicochemical properties of particulates can alter the type and magnitude of immune response. Herein, we briefly review the impact of size, shape and rigidity of particulates in skewing the immune response and its benefits over the soluble form of vaccine.

Introduction

Vaccines played an important role in eliciting an immune response and conferring protection to various infectious diseases [1]. Edward Jenner's approach of using the cowpox material in 1796 intended to generate an immune response against smallpox in humans has now become a widespread practice. Vaccines were traditionally developed as live attenuated vaccines using Louis Pasteur's paradigm of isolate, inactivate, and inject. Despite their enormous success, they have limitations of reactogenicity, safety concerns regarding toxicity, reversion of virulence, and adverse effects such as fewer and anaphylactic reaction [2,3]. These limitations led to the development of subunit vaccines with superior safety profiles and using minimalist composition. It consists of few highly purified antigens to generate a specific immune response and can be prepared inexpensively in large quantities in the laboratory environment. Live attenuated vaccines activate dendritic cells via pattern recognition receptors (PRR's), presenting both antigens and pathogen-associated molecular patterns (PAMPS) However, purified antigens in subunit vaccines were unable to adequately activate sentinel cells and exhibit poor immunogenicity. This has led to the use of adjuvants co-administered with subunit vaccine to boost the incapacitated immune response [1,4].

Particulate vaccine

The delivery of antigen using particulates gained interest in recent years, as it provides numerous benefits over the soluble form of antigen and overcome limitation of subunit vaccines. The particulate vaccine aims to mimic the pathogen structure and facilitate easy recognition by the body's immune system to boost the immune response. Studies have shown that there is up to 30% increase in cellular uptake of the particulate vaccine over soluble form [5]. Particles that undergo cellular internalization via phagocytosis generates small antigenic peptides in phagosomes microenvironment, which are released into the cytosol and shuttled further to cell's surface using major histocompatibility complex (MHC) class I molecules generating cell-mediated immune response. However, particles undergo cellular uptake via endocytosis typically degraded in the endosome vesicles and carried to cell's surface using MHC-II molecules, and thus activates CD4+ T cells.

In conclusion, an antigenic peptide released in the cytosol favoring cellular response and the peptide not exposed to cytosol activates CD4+ T cells [6]. Antigenic peptides derived from extracellular environment loaded mainly onto MHC-II molecules favor humoral response, whereas endogenously synthesized peptides loaded on MHC class I molecules favor cellular response. Particulate vaccines provide the advantage of minimal dose by cross presenting the antigen at 1000-10,000-fold lower antigen concentration compared to its soluble form. Cross-presentation refers to the loading of exogenous antigens on MHC-I molecules and thus activates CD8+ T cells. Cross-presentation is critical for priming CD8+ T cells response to viruses, intracellular pathogens or tumors [7]. Particulate vaccines prepared using encapsulation approach protects the entrapped antigen and release it slowly, and thus eliminate the need for booster doses. This is particularly useful in case of veterinary vaccines, where capturing the wild animals for multiple dosing is challenging [8].

It is important to tailor the vaccine antigen in order to achieve the appropriate response against invading pathogen. Various physical attributes of particulates such as size, shape, and rigidity are critical and can influence the type (humoral vs cellular) and magnitude of an immune response [6]. It was found that nanoparticulate vaccine skewed the immune response towards Th1, due to elevated expression of IFN-Ɣ and IgG2a antibody titers. However, microparticulate vaccine favored Th2 mediated humoral response evidenced from increased induction of MHC-II molecules and elevated expression of IL-4 cytokines. Studies have shown that the uptake of smaller particles (40nm) was higher than that of larger particles (200nm), but the delivery of antigen was 3 times higher for larger particles. Apart from size, the shape of particles can influence the type of immune response. Spherical particles have been found to skew the immune response more towards Th1, evidenced from elevated levels of IFN-Ɣ cytokine expression and IgG2a antibody titers. In contrast, the rod shape particles skewed more towards Th2 mediated immune response, due to their ability to elevate levels of IgG1 antibody titers. Another physical attribute of particles i.e. rigidity can selectively activate the arms of the immune system. While rigid particles consume less energy in cellular uptake and are preferably shuttled to the cell's surface by MHC I molecules compared to soft particles and induce more Th1 mediated cellular immune response than soft particles. Taken together, a cellular immune response is critical in dealing with viruses and cancer cells and can be achieved by tailoring the physicochemical properties of particulate vaccines. Spherical, rigid and nano-sized particulate vaccines are more efficient in producing cellular immune response. Alternatively, the development of humoral immune response preferred in dealing with infectious diseases can be achieved by tailored rod-shaped, micron-sized soft particulate vaccines [2].

About 2.5 million people die globally every year from vaccine-preventable diseases due to lack of medical infrastructure, trained personnel, and cold chain storage facility [5]. According to the Department of Health and Human Services, approximately 76% of vaccines for children (VCF) get exposed to extreme temperature conditions due to improper storage resulting in reduced potency and efficacy [9,10]. There is a need to overhaul the current practices in the supply chain including availability of cold chain storage, packaging that requires minimal space, and development of a vaccine that can withstand extreme temperature conditions. The particulate vaccines are well suited to meet these requirements as they can withstand extreme temperature conditions without losing potency and do not require cold chain storage. Particulate vaccines can be given via oral route and do not require trained personnel and can be inexpensively prepared in large quantities in a laboratory setting [10].

Conclusion

Particulate vaccines offer numerous advantages over soluble vaccines and circumvent limitations of subunit vaccines. These vaccines maintain antigen stability at extreme temperature conditions and are suitable for use as delivery vehicles. It provides a unique platform in generating disease-specific immune response by modulating the physical attributes (size, shape, and rigidity) of particulates at low dose. Future of particulate vaccine appears promising and would meet the unmet needs of existing vaccine delivery system.

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