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Combatting infectious diseases; nanotechnology as a platform for rational vaccine design ☆

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ABSTRACT

Currently, several successful vaccines are available. However, for pathogens with a highly variable genetic composition, and for which serum IgG antibodies are not a useful correlate of protection, effective vaccines are yet to be developed. This is due to a lack of both the understanding of the immunological pathways leading to long-term protection and the ability to translate the available knowledge into a suitable vaccine formulation. Regarding the latter, nanoparticles can be an attractive platform for vaccine development, as they offer multiple options for improving safety and efficacy. For example, side effects might be decreased upon encapsulation of the adjuvant and the concomitant delivery of antigen and adjuvant is a very promising tool for increasing efficacy.
In addition to the many promises, the use of nanoparticles as vaccine carriers should be implemented with caution: the more sophisticated a particle, the more parameters need to be controlled during production and storage.

Contents

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1. Introduction

Prophylactic vaccination arguably is the most successful and cost-effective medical intervention available to mankind. Intensive childhood vaccination programs have drastically reduced morbidity and mortality due to several types of infectious diseases including diphtheria, pertussis, tetanus, polio, measles, mumps, rubella and smallpox, as illustrated by an over 90% decrease in cases and over 99% decrease in deaths in the USA since the introduction of the respective vaccines [1,2]. However, for many other pathogens an effective vaccine is not available yet. The most successful vaccines currently in use were generated empirically, which was effective because the pathogens they protect from were not able to escape immune responses. In contrast, diseases for which efficient vaccines are not currently available, are mostly caused by pathogens mastering either immune escape or immune evasion.

For example, RNA viruses like human immunodeficiency virus (HIV) and influenza virus have the capacity to quickly change their surface antigens due to sequence variability and glycosylation. Thus, in response to for example human neutralizing antibodies, new viruses will emerge that cannot be recognized by these antibodies [3–5]. Alternatively, large DNA viruses such as herpesviruses and poxviruses can evade the host immune responses via immunomodulatory pathways, such as suppression of antigen presentation, suppression of co-stimulation, production of immunosuppressive cytokines or obstruction of pathways of pro-inflammatory cytokines [4]. These evasion strategies are also used by other pathogens such as the bacterium *Mycobacterium tuberculosis* [6] and parasites like for example malaria [7].

Since many pathogens master the art of outwitting host immune responses raised against them, new vaccines will have to be developed that raise strong and broad immune responses that are difficult for the pathogen to counteract. Importantly, the ability to take vaccinology one step further is not only dependent on increasing basic immunological knowledge but also on the development of advanced materials and techniques [8] to implement the knowledge into products that are safe, efficient, stable and cost-effective. For this, nanotechnology is a very useful and promising field. Athough the concept is not new, with liposomes and microparticles for use as vaccine adjuvants already reported in the 1970s [9,10], and immune stimulating complexes (ISCOMs) in the early 1980s [11], currently knowledge is increasing on how nanotechnology can be used to rationally optimize vaccine formulations [12,13].

Here we have attempted to give an overview of the main immunological aspects in the design of prophylactic vaccines and how these immunological challenges can be addressed by implentation of nanotechnology in vaccine design to prevent infectious diseases.

2. Immunological considerations in vaccine design

In essence, what a vaccine is supposed to do, is activating the immune system to raise a protective response against the antigen(s) present in the formulation that will ensure protection upon a subsequent encounter of the host with pathogens bearing (parts of) those antigens, any time after the vaccination. To establish this, the innate immune system needs to be activated and in addition ideally an antigen containing epitopes that can interact with B-cell receptor needs to be included as well as antigens that can be presented on Major Histocompatibility Complex (MHC)II and MHCI molecules, for activating helper (CD4) and killer (CD8) T cells, respectively. Such a diverse immune response will decrease the likelyhood of immune escape and also maximize the number of responsive people [14]. However, it should be taken into account that B-cell epitopes must be formulated in such a way that sufficient eptitopes remain intact up to the point where they interact with B-cells. In contrast, T-cell epitopes are formed in vivo by antigen processing, and thus efficient uptake by antigen presenting cells, preferably dendritic cells (DC), should be optimized [15].

Searching for suitable antigens includes selection for several characteristics, including immunogenicity [16] and conserved presence of this antigen in as many strain variants of the pathogen as possible since these antigens are more likely to be crucial for the fitness of the pathogen and consequently it might be more difficult for the pathogen to evade the immune system as it might not be able to survive when mutations occur in these genes. In addition, for T cell epitopes, the majority of the common human Human Leucocyte antigen (HLA) types should be covered [17].

Importantly, also care should be taken that the selected antigen(s) do not contain an epitope that might reduce the intended immune responses [18,19].

When a useful set of antigens is selected, they should be formulated in such a way that a robust immune response is induced. For this, additional components can be added to the formulation to enhance the immune response to an antigen. These are called adjuvants, derived from the latin 'adiuvare', meaning 'to aid'. However, in the case of nanoparticle-based vaccines, several components can be added that might not traditionally be called 'adjuvants', as they more indirectly optimize the immune response. For example, targeting the particles to certain cell types might not activate those cells more than the antigen alone, but it could be crucial for the induction of the appropriate type of immune response. Since several molecules can be combined in a nanoparticle, it could be stated that the combined characteristics of the components of the particle, except the antigen itself, together represent the overall adjuvant function [20].

Equally important to the adjuvanticity, an adjuvant should also be safe. A component activating the innate immune system should be carefully selected and formulated. Since that is usually the most immunogenic part of a vaccine, it also harbours the most risks on side effects and in case of preventive vaccination, even minor effects might prevent acceptation of the vaccine.

3. Nanoparticle vaccine delivery

Delivery of nanoparticulate vaccines can be addressed to 3 different levels. First, the route of administration; in case of prophylactic vaccines to protect from infectious diseases, delivery to mucosal tissues in the nose or mouth and different areas of the skin are the most practical. Second, by adding ligands that bind to receptors only present on a particular cell type, the vaccine can be specifically delivered to certain cells. Finally, by targeting a specific type of receptor on the cells, it can be influenced to which intracellular compartment the antigen will be directed and thus where and how it will be processed and which type of immune response will be induced. These different levels of delivery are influenced by several vaccine characteristics as described below.

3.1. Administration site

Currently, most vaccines are administered intramuscularly; however, other administration routes are widely explored. For example, for induction of local protection, local vaccination has been proven superior in many cases. In addition, alternative administration routes have some practical advantages, such as allowing easier administration and reduction of needle waste [15]. Alternative administration routes require specific characteristics of the nanoparticle carrier. For example, antigens are not often efficiently crossing the nasal mucosa upon nasal vaccination. This can be improved by the use of nanoparticulate antigen carriers that are composed of, or coated with, mucoadhesive polymers, or by actively targeting cells that can transport the particles across this barrier [21].

In the case of (epi)dermal vaccination, several methods have been developed to enable vaccine formulations to cross the natural barrier of the skin, the stratum corneum, including microneedles, skin disruption methods and jet injectors [22]. And for oral vaccination the vaccine

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