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A Mini-Review: Nanoparticles as Vaccine Delivery System

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Vaccination has proven to be one of the most important medical breakthroughs in history. Three important features must be present in every vaccine that is effective over time: Safety, stability, and the ability to elicit a sustained and sufficient immune response with a modest number of doses are all important requirements. To develop protective immunity against diseases, vaccinations using attenuated or dead entire animals (first generation), subunit vaccines (second generation), and RNA or DNA vaccines (third generation) have all been employed . Traditional vaccines, on the other hand, have issues such as returning to their virulent condition or only giving protection for a short period of time. As a result of these limitations, scientists have resorted to recombinant proteins, such as subunit vaccines, which target a specific portion of the pathogen. Subunit vaccines are preferred over live or inactivated whole organism vaccines because they are more pure and identified with respect to cell receptoes, have a better safety profile, and are easier to scale up. Despite their advantages, subunit vaccinations have certain disadvantages. For example, most antigens are only mildly immunogenic on their own, necessitating the inclusion of an adjuvant in the formulation.

Keywords: Nanoparticals; vaccination; drug delivery.

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1. INTRODUCTION

1.1 Nanoparticales in Vaccination

To achieve the proper balance between the advantages of enhanced immunogenicity and the risks of negative effects, the right adjuvant must be chosen. In addition to improving immunogenicity, adjuvants can reduce the amount or number of doses required for protective immunity [1]. As a component in vaccine formulations, nanoparticles have attracted a lot of interest in the lab [2]. Most viruses have a dimension in the nano-size range [3] which allows the immune system to digest them effectively, resulting in a strong immunological response. As a result, nanomaterials are currently being used to induce desirable immune responses for both preventive and therapeutic purposes. They're used as immunostimulants to stimulate immune responses and/or as delivery methods to speed up antigen processing or prevent premature degradation of antigen [4]. Nanotechnology enables nanoparticle characteristics such as size, shape, and surface charge to be customized to match specific application demands, resulting in a broad spectrum of nanoparticles. Many biological and synthetic nanoparticles have been approved for human use [5], and many more are now undergoing clinical or pre-clinical testing [6]. The use of nanoparticles in vaccine formulations has traditionally been predicated on the idea that antigen and nanoparticle components must be linked for the purpose generate an adjuvant effect [7]. Attachment of nanoparticles to antigens is generally accomplished by conjugation, adsorption, or encapsulation. The study did reveal, however, that an adjuvant effect may be achieved by simply combining nanoparticles with a sub-unit protein antigen [8].

Due to the functioning processes of nanotechnology-based vaccine formulations, nano-carriers can be employed in vaccination applications. Phagocytic cells like macrophages and dendritic cells (DC) readily ingest particles smaller than 10 mm . By enhancing antigen cellular absorption, this feature has been exploited to enhance antigen recognition and presentation effectiveness [9]. Solid nanocarriers can preserve protein-based antigen vaccines while also allowing them to reach gut-associated lymphoid tissue and mucosa-associated lymphoid tissue, allowing both oral and mucosal vaccine administration [10]. Antigen dispersion could be aided by surface-modified nanocarriers. The mannose, scavenger, and toll-like receptors (TLR) are all expressed by immune cells [11]. Nanocarriers coated with immune cell-targeting compounds such as polysaccharides, antibodies, and peptides might be utilized in vaccines to target overexpressed receptors, resulting in targeted and selective immune responses [12].

The immune system's response to silver nanoparticles (AgNPs) has been studied [13]. The key findings showed that enhanced humoral immune responses led to the development of neutralizing antibodies in two protein models. Surprisingly, when administered rabbit subcutaneously, In one protein model , AgNPs had the same effect as a commercially available adjuvant (such as Alum). In addition, no toxicity was discovered in the AgNPs adjuvant concentration range utilized, which is a positive development in the adjuvant industry [14]. Exotoxin A from *Pseudomonas aeruginosa* was used in an Iraqi study to administer a vaccination to rabbits. The isolated toxin's molecular weight was estimated to be 71 KD [15].

The antigenic characteristics of the toxoid alone, AgNPs (silver nanoparticles bio-synthesised by *Pseudomonas aeruginosa*) alone, and mix antigen were investigated, followed by an investigation into the immunological role of AgNPs as a delivery method. It was carried out by four groups of New Zealand rabbits, After the vaccination period, the first group was inoculated with toxoid alone, the second group with AgNPs alone, the third group with mix antigen, and the fourth group was deemed a control group and immunized with normal saline, Some immunological parameters were examined, and the results were as follows: Due to AgNps' immunoadjuvant activities, the immune response of silver nanoparticles with toxoid antigen was greater than that of toxoid alone and AgNps alone [16].

Tirrell and colleagues describe the creation of self-adjuvant group A streptococcal vaccines using peptide amphiphile micelles [17]. When a group of dialkyl hydrophobic moiety and a streptococcus B lymphocyte antigen were covalently bound and exposed to water, the researchers discovered that, the alkyl tails hydrophobic contacts caused the antigen and a group of dialkyl hydrophobic moiety to self-assemble into micelles. Following vaccination with these micelles, mice produced a strong IgG1 antibody response that was comparable to responses seen after a soluble peptide was

combined with two conventional adjuvants. Stayton and coworkers show that pH-responsive anionic endosomolytic polymer (for the cytoplasmic delivery) nanoparticles improve MHC-I antigen presentation [18] .Antigen-loaded nanoparticles made from hyperbranched and cross-linked polymer structures outperformed soluble antigen or antigen-loaded nanoparticles made from linear polymers in vitro. The biocompatibility and safety of carbohydrate-functionalized polyanhydride nanoparticles were investigated by Narasimhan and his colleagues [19]. Capsular polysaccharides (CPS) at high doses causes CD95 to become overexpressed, lowering antigen-presenting cell populations' immunogenicity and survival. CPS-loaded albumin-based nanoparticles prepared as a vaccine against *Neisseria meningitides* were shown to induce expression of co-stimulatory molecules and act as antigen depots, and high doses of CPS result in decreased immunogenicity and viability. Development of a poly (lactic-co-glycolic acid) particle vaccination to protect against allergies induced by home dust mites [20]. Nanoparticles have a lot of potential for improving vaccine delivery, and it's becoming clear that nanoparticles will be necessary for each sickness for improve the disease's therapeutic response. Prior to testing and usage, the safety, route of administration, and formulation properties of each vaccine formulation must be carefully examined [21,22]. Nano-immun stimulators such as inorganic NPs (iron and silica) have been used in the past for this purpose. Liposomes (cholesterol and lipids), polymeric NPs (chitosan, PLGA, PVPONAlk, -PGA), and virus-like particles are all examples of polymeric nanoparticles [23].

1.1.1 Types of nanoparticles used in vaccines

1. Inorganic NPs: gold, carbon, and silica are examples of inorganic NPs.
2. Polymeric NPs: PLGA (polylactic-co-glycolic acid) or PLGA (polylactic-co-glycolic acid) (lactic acid; PLA).
3. Liposomes: Liposome production is a spontaneous process in which lipid hydration allows the development of a lipid bilayer surrounding an aqueous core. Liposomes come in a variety of shapes and sizes, incorporating biodegradable phospholipid-based unilamellar and multilamellar vesicles (e.g., phosphatidylserine, phosphatidylcholin and cholesterol). Because of their structural flexibility and adaptability, liposomes may contain both hydrophilic and hydrophobic compounds. Hydrophilic molecules are enclosed inside the phospholipid bilayer, whereas hydrophobic molecules are absorbed into the watery core.
4. Virus-Like Particles: A viral membrane creates a monomeric complex with a high density of epitopes in these particles. By fusing proteins to particles or expressing several antigens endogenously, more proteins can be produced in VLPs.
5. Dendrimers: Polypropyleneimine (PPI) and polyamido amine (PAMAM) are example of three-dimensional dendrimers consist of, mono-dispersed, hyperbranched nanostructures formed of a combination of amines and amides [23].

1.2 Nanoparticles and Immune System

Foreign antigens may be protected by the immune system, which is split into two forms of immunity: innate immunity and adaptive immunity Innate immunity is the nonspecific and first line of the body's defense system, which relies on pattern recognition receptors (PRPs) to recognize broad and conserved molecular patterns found on pathogens (pathogen-associated molecular patterns, (PAMPs). [24].

As both a result, early identification and subsequent pro-inflammatory responses are dependent on the innate immune system. Antigen specificity refers to the adaptive immune system's ability to respond solely to the organism that initiated the reaction. The immune system has two types of immunity: innate and adaptive. [25]. The two main mechanisms involved in cellular interactions with nanoparticles are cellular uptake (which involves adhesion to the cell surface and internalization) and cellular immune responses (which leads to nanoparticle penetration) [26].

The incorporation of antigenic components into nanoparticles has aroused interest, with the goal of delivering antigen to antigen presentation cells (APCs) more effectively, then boosting their maturation and antigen pass to trigger a powerful immune response [27,28]. DCs (Dendritic cells) and macrophages are commonly targeted in vaccine development as specialized APCs capable of swallowing and digesting antigen. A detailed knowledge of the absorption mechanisms of DC and macrophages, as well as their interactions with nanoparticles, is required for the creation of successful nanoparticle vaccines [29,30]. The size, charge, and form of

nanoparticles all have a role in antigen absorption, according to research.

The efficiency of antigen absorption into dendritic cells is greatly boosted when nanoparticles are used to transport antigens; in certain cases, uptake can be increased by 30 times [31,32]. Similarly, studies have compared the absorption of micro- and nanoparticles showed that APCs absorbed NPs far more readily. Chithrani and his colleagues investigated the influence of NP size on cell absorption by treating HeLa cells with various gold nanoparticle sizes (14-100 nm) and measuring their gold content using inductively coupled plasma spectroscopy. The ideal size for absorption was found to be 50 nm, and uptake peaked within the first two hours of exposure before plateauing between four and seven hours [33].

Because T helper cells are activated, AgNPs can interact with the immune system, and the immune system may identify AgNPs (Th). This strategy incorporates adaptive actions on the surface of antigen presentation cells (APC) (Fig. 1). T-cells detect a foreign antigen complex containing MHC on its surface via their TCR (TCRAPC macrophages, dendritic cells, and B cells are the three types of APC macrophages present in the immune system). APC aids the innate response by transferring cytokines, which cause Th cells to develop into Th1 and Th2 subsets. Other immune system cells, such as cytotoxic T cells (Tc) and macrophages (MØ), are stimulated by these T cells [34, 23].

The first is cytotoxicity, which includes lysing cells that express certain antigens. The second kind (delayed hypersensitivity) is characterized by the production of cytokines, which trigger an inflammatory response [35]. When antigen is identified, T-lymphocytes are transformed into

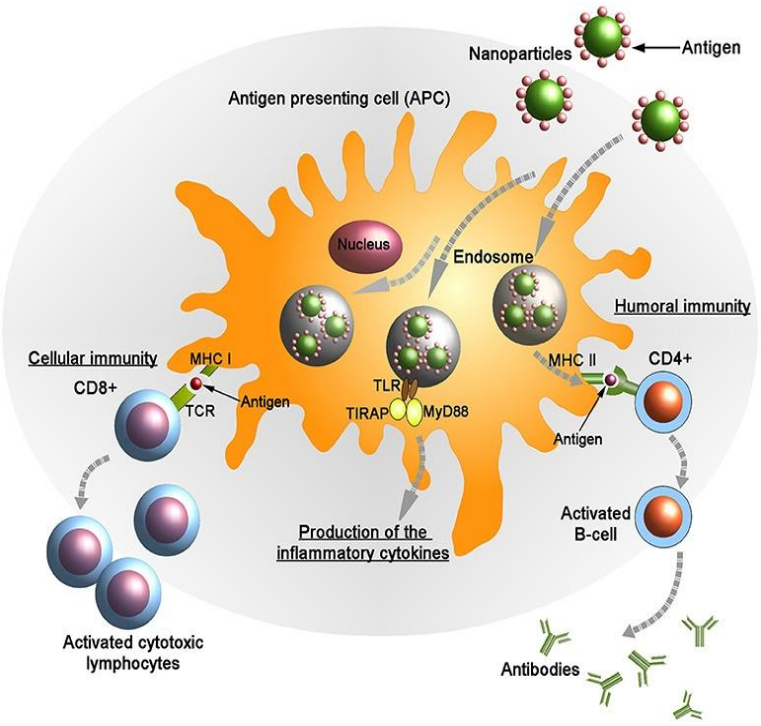

Fig. 1. Antigenic chemicals are delivered to antigen-presenting cells using ground nanoparticles (APCs). Endogenous antigens are delivered to CD8+ T lymphocytes on the surface of APCs via a complex containing class I major histocompatibility complex (MHC I). After connecting with MHC I and the T-cell receptor (TCR) in the presence of co-stimulatory chemicals and cytokines, activated CD8+ cells induce cytotoxicity, which kills infected cells. Class II MHC molecules on the APC surface also transport antigens to helper (CD4+) T cells. B-cells, which produce antimicrobial antibodies, are subsequently activated by CD4+ cells. When adapter proteins MyD88 (myeloid differentiation marker 88) and TIRAP (TIR domain containing adaptor protein) colocalize with TLR (toll-like receptor), TLR activates the NF-B pathway and promotes the production of pro-inflammatory cytokines. [23]

large activated cells, activated express IL-2 receptors. T-lymphocytes are then differentiated into cytokine-producing, functionally active small lymphocytes. Some cytokines help B-cells produce antibodies, kill tumor and other target cells, reject grafts, stimulate hematopoiesis in the bone marrow, and induce delayed hypersensitivity allergic reactions, among other things. Fibroblast immunity is the name for this type of immune response [36].

1.3 Nanoparticles and Cytokine

Cytokines are important signaling molecules that diverse cells generate in response to environmental stimuli. Some cytokines have the capacity to stimulate immune cells, resulting in protection against a wide range of diseases. Cytokines, on the other hand, are prone to early degradation, which limits their ability to contribute to the development of host immunity. Furthermore, the unregulated production of cytokines as immune responders can occasionally have negative consequences [37]. Several research have sought to manufacture tailored nano carriers to provide effective and regulated delivery of cytokines to specific locations for overcome these constraints. This approach decreased toxicity, increased circulation time, and enhanced antigen-specific T-cell responses when compared to free cytokines [38,39]. Nanocarriers carrying the growth factors granulocyte macrophage colony stimulating factor (GM-CSF) and interferon alpha (IFN-α) have showed promise in cancer treatment [40]. In addition, nanocarrier conjugated cytokines have shown promise in treating infectious illnesses. IL-12-embedded microspheres, for example, produced significant anti-tuberculosis immunity [41]. This effect was attributed to the development of high antibody titers as a result of the microsphere vaccinated mice's prolonged and regulated release of IL-12 [42].

Other study (42)demonstrate the potential of pH-responsive biodegradable carbonate apatite (CA) nanoparticles as CpG ODN delivery vehicles that can enhance the production of type-I IFNs (such as IFN-α) relative to that induced by CpG ODNs and can augment the adjuvant effects of CpG ODNs in vivo. In contrast to CpG ODNs, CA nanoparticles containing CpG ODNs (designated CA-CpG) induced significant IFN-α production by mouse dendritic cells and human peripheral blood mononuclear cells in vitro; and production of interleukin-12, and IFN-γ was higher in CA-CpG-treated groups than in CpG ODNs groups. CA nanoparticles carrying CpG ODNs (named CA-CpG) triggered substantial IFN-α production in mouse dendritic cells and human peripheral blood mononuclear cells *in vitro*, and CA-CpG-treated groups produced more interleukin-12 and IFN-α than CpG ODNs-treated groups.

2. CONCLUSION

There have been many of different NP as delivery systems reported, each with its own set of benefits over traditional vaccine administration approaches. Rather of using complete (live or dead) germs to stimulate an immune response, this new generation of vaccines employs microbe components to imitate how antigens are given during natural infection. Your immune response to these antigens is usually insufficient on its own, needing the use of an adjuvant to boost it. It has previously been proven using alum-based adjuvants, but it typically fails to produce a cellular immune response and can trigger a host reaction. NPs are a novel form of antigen delivery technology that not only stimulates a variety of immune system components but also has a high level of biocompatibility. The size of NPs is one way that they can induce varied immune responses. To get to the cells that will be treated, non-traditional pathways are employed. Whether antigens are decorated on the surface of the NP for presentation to antigen-presenting cells or encapsulated for delayed release and longer exposure to the immune system, the method they are delivered has a big influence on the immune response. Immunological chemicals can be added to NPs to boost immune responses, and molecules can be added to increase in vivo stability (polyethylene glycol). Several of the NP delivery techniques mentioned in this article have the ability to activate cellular and cellular inflammatory cells. An effective and preventive vaccination, on the other hand, is likely to cause both responses and should be tailored to the pathogen in issue. While these delivery molecules may appear to be a promising candidate for future vaccination techniques, there are several potential drawbacks to be aware of, particularly those linked to cytotoxicity. Because NPs are so new to medicine, they don't have a lengthy track record of human safety. To adequately address these problems, more research into NP's toxicity is necessary if it is to be acknowledged as a new and more extensively licensed way of delivering new and more broadly licensed vaccines for human use.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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