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Review Article

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Covid-19 and Nanovaccines

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Abstract

Infectious and epidemic diseases are one of the most important factors threatening social life. Vaccines have started to be developed to prevent the spread of these diseases among people. In particular, the use of biological substances such as serum or blood transfusion from individuals exposed to the disease has come to the fore in the fight against epidemics. Today, vaccines are recognised as one of the most effective tools in controlling epidemics. Modern vaccines are developed as a result of scientific research and development processes and are widely used worldwide. According to the characteristics of vaccines, live virus, inactivated virus, viral carrier-containing, nucleic acid-based, virus-like particle (VLP), and protein subunit vaccines are developed with many different techniques. In order to enhance the effectiveness of these techniques and generate a stronger immune response, nanotechnology has emerged as a significant tool. Nanoparticles (NPs) are defined as structures with dimensions of 100 nm or less, which form the basis of nanoscale materials and thus nanotechnology. There are many types of NPs. NPs can work both as a drug delivery system to improve antigen processing and as an immunostimulatory adjuvant to induce and enhance protective immunity. NPs provide advantages such as the ability to transport, protect, stabilise and deliver vaccine antigens to the target tissue. In addition, NPs can increase vaccine efficacy by strengthening the immune system response. Nano vaccines have the potential to induce rapid and long-lasting cellular and humoral immunity. Nano vaccines provide more flexibility in reducing the number of doses required. This feature makes them ideal in situations where a large number of organisms will be vaccinated with multiple doses. These advantages have proven especially relevant in the context of the COVID-19 pandemic. Vaccine studies for COVID-19 use a variety of techniques, including inactivated virus, attenuated live virus and recombinant protein-based vaccines, as well as new types of vaccines, including RNA, DNA and viral vector-based vaccines. Recently, vaccine strategies for SARS-CoV-2 have been reviewed with a focus on nanotechnology. Many NP-based vaccine studies are being conducted to combat COVID-19, the biggest global health crisis of recent times. NP-based vaccines will play a critical role in limiting the spread of COVID-19 and will enable the prevention of future outbreaks.

Keywords: Covid-19, Vaccine, Nanoparticles

Introduction

Throughout human history, infectious and epidemic diseases have been the most significant threats to societal life. These diseases are classified as endemic, epidemic, or pandemic according to their spread within the community. An endemic is defined as the constant presence of a disease within a specific geographic area. An epidemic is the rapid and unexpected spread of a disease within a population, while a pandemic refers to an epidemic that has spread across

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multiple countries or continents, affecting a large number of people globally. While many disasters are limited to their geographical regions, infectious diseases can impact all of humanity (1-3). To eradicate these health crises, various treatments are being developed. Additionally, efforts are being made to develop vaccines to prevent the spread of diseases among people.

From the past to present, the process of treating epidemics with vaccines has evolved using various methods. In particular, methods such as the use of biological materials like serum or blood transfusion from individuals exposed to the disease have been prominent in combating epidemic diseases (4-6). The vaccine developed by Edward Jenner in 1796 against smallpox marks a significant milestone in the modern history of vaccines. Jenner observed that people infected with the cowpox virus gained immunity against smallpox (7). In subsequent periods, scientists like Louis Pasteur and Robert Koch discovered that microbes cause diseases, and these discoveries played a crucial role in the development of vaccines. Pasteur developed the rabies vaccine in 1885, marking a turning point in the use of vaccines to combat epidemic diseases.

Today, vaccines are considered one of the most effective tools in controlling epidemic diseases. Modern vaccines are developed through scientific research and are widely used globally. Thus, they constitute a vital strategy to prevent or control the spread of epidemics. The term ‘’vaccine’’ is derived from the ‘’vaccinia virus’’ which was used to protect against smallpox. A vaccine is defined as a biological material that, when administered to a living organism, induces an immune response against infectious diseases, allowing the body to develop immunity by producing antibodies against foreign substances. Vaccination is considered one of the most effective intervention methods to preventing and controlling diseases by protecting against infectious agents (8, 9).

Vaccines can be categorized based on their properties into many types, including live virus, inactivated virus, viral vector-based, nucleic acid-based, virus-like particle (VLP) containing, and protein subunit vaccines and numerous different techniques used to develop them. One of the methods used involves utilizing the original virus. Vaccines for diseases such as mumps, measles, and rubella use a weakened form of the virus, allowing the body to combat this virus and gain immunity. For influenza viruses, key features of the virus are extracted and the virus is gradually inactivated. Another intriguing method involves VLP-containing vaccines. These are formed by genetically engineering and assembling viral proteins, resulting in VLPs. For example, the Human Papillomavirus (HPV) vaccine is produced using this technology (10). Success in vaccine studies has led to significant reductions in infectious diseases (11, 12). Alongside immunological studies on vaccines, there is an increasing need for new technological advancements to ensure the safety and rapid development of vaccines against newly emerging infectious diseases such as COVID-19 (13). With the advancement of biotechnology, NPs have recently been applied in significant applications and represent a promising field of study. They are used particularly in drug delivery systems, imaging technologies, and biosensors (14).

Nanoparticles (NPs)

NPs are defined as structures with dimensions of 100 nm or less, forming the basis of nanomaterials and, consequently, nanotechnology. Nanotechnology refers to the production and control of matter on a very small scale. This framework is critical for understanding the potential

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effects of nanotechnology products on health (15, 16).

NPs are designed to perform their functions with minimal side effects and high efficiency. Their unique physical and chemical properties of NPs are of great importance in approaches to the treatment of many diseases. Understanding how engineered NPs interact with the immune system is essential because these interactions govern their biodistribution and therapeutic effectiveness efficacy. Many nanotechnology-based designs exploit these interactions to further enhance targeted delivery, as immune cells can overcome physical barriers that restrict the passive accumulation of NPs at disease sites (17, 18). There are many types of NPs, including liposomes, dendrimers, emulsions, polymeric NPs, quantum dots and carbon NPs. Liposomes, one of the most widely used NP types, are employed to improve drug efficacy and safety (19). Emulsions contain oil in mixtures stabilized with surfactants to maintain shape and size. The lipophilic material can be dissolved in an organic solvent which is then emulsified in the aqueous phase. Emulsions, such as liposomes, are also used to increase the effectiveness and safety of various compounds (20). Chitosan NPs are used as drug delivery systems. Polymer-drug conjugation enhances tumor targeting and killing efficiencies by increasing permeability and retention capacity, facilitating lysosomal drug delivery at the cellular level after endocytic uptake (21). Ceramic NPs are emerging as porous inorganic systems for drug delivery, particularly biocompatible materials like silica, titania, and alumina, which are being investigated for cancer treatment (22). Gold NPs possess highly suitable chemical and optical properties for therapeutic applications and biomedical imaging. Metallic particles such as iron oxide NPs, range from 15 to 60 nm, and are classified superparamagnetic agents. These particles can be coated with phospholipids, dextran, or other compounds to increase stability and are used as active or passive targeting agents (23). Additionally, carbon NPs, nanotubes, and fullerenes are also used for these purposes. Fullerenes are carbon allotropes composed of 60 carbon atoms arranged polygonal structure. These NPs are characterized by numerous binding sites that can be functionalized for tissue binding. Carbon nanotubes are among the most commonly used NP types due to their high electrical conductivity and properties. Quantum dots are NPs made from semiconductor materials with fluorescent properties. These characteristics make quantum dots important for biological applications (24).

The size, charge, morphology, composition, hydrophobicity, and mode of action of NPs influence their toxic effects and immune responses. The shape of NPs determines their localization within host cells and plays a key role in the rate at which antigen release into the host cells (25). It has been observed that spherical gold NPs are internalized more effectively and induce a stronger immune response compared to rod-shaped NPs. The hydrophobicity of NPs plays a crucial role in the recognition of hydrophobic parts, interaction with immune cells, and soluble proteins. Surface modification of NPs alters ligand specificity and interaction with antigen-presenting cells (APCs), potentially enhancing the immunogenicity of the molecule (26, 27). NPs are more widely used than other types of nanomaterials in vaccine development. There are significant differences in the pharmacokinetic properties, transport, release rate, and biocompatibility of NPs based on their types. These differences have important effects on antigen recognition (28).

Nanoparticle Vaccines

Vaccination plays a crucial role in reducing the spread of many infectious diseases. While next-generation vaccine studies continue, safe and efficient vaccine production is essential. NP vaccines are a type of vaccine that applies non-replicative structures, ranging in size from 1 to 1000 nm, produced through recombinant expression or chemical synthesis (29).

Nanotechnology has significantly advanced vaccine development, particularly with the incorporation of the nanocarrier-based delivery systems in recent years, leading to the emergence of "nanovaccinology." Understanding immune responses modulable by NPs is crucial for achieving desired effects and plays a significant role in NP-based vaccine formulations. NPs can function as both a delivery system and an immune-stimulating adjuvant to enhance and induce protective immunity (30). NPs play a critical role in vaccine development by carrying, protecting, stabilizing antigens, and targeting specific tissues. Moreover, NPs can enhance vaccine efficacy by strengthening immune system responses (31).

There are two main advantages to using NPs in vaccines. Firstly, NPs serve as adjuvants (32). NP-based applications act effectively as adjuvants, enhancing vaccine stability, providing protection against early degradation, and assisting in the presentation of antigens to antigen-presenting cells (APCs). In essence, conjugated or adsorbed antigens can enhance their antigenicity and can function as antigens themselves, mimicking the properties of pathogens like viruses. Secondly, NPs can trigger both adaptive immune responses and innate immune responses. Due to their high specific surface areas and functionalities, NPs are used as antigen carriers to improve antigen processing and presentation. These properties of NPs enable effective targeting of cells and controlled release of antigens (29).

NPs are employed to prepare vaccines in a controlled manner and to develop therapeutic strategies for various acute and chronic inflammatory diseases (33). Several NP-based therapeutic strategies have been developed to regulate T cell activity against bacterial, viral, or fungal infections in some research studies (34).

Nano vaccines have the potential to induce rapid and long-lasting cellular and humoral immunity. They can be administered through various methods, predominantly intravenous, oral, intranasal, and transdermal routes. Nano vaccines are designed to mimic the size and shape of viruses to facilitate recognition by immune cells (35). They consist of nanoscale particles that attach to components to stimulate the immune system. Nano-based formulations are being developed for the treatment and detection of various zoonotic diseases such as Salmonella, rabies, and influenza (36).

Liposomes, immunostimulatory complexes (ISCOMs), VLPs, emulsions, dendrimers, inorganic and polymeric NPs are utilized in vaccine research. Inorganic NPs are employed both as adjuvants and delivery tools to enhance immune responses to antigens. Major types include gold, silica, carbon, aluminum-based, calcium phosphate, and magnetic NPs (34, 37). Silica-based NPs, in particular, contain abundant silanol groups on their surfaces which can introduce specific functional groups for targeting vaccine molecules to cells. Alum salts are widely used as adjuvants in vaccines to enhance antigen-specific immune responses against diseases like diphtheria, tetanus, and influenza (38). Calcium phosphate is utilized as a mucosal adjuvant. Polymeric NPs are highly sought after in vaccine applications due to their biocompatibility, stability, biodegradability, and ease of surface modification (39). Liposomes are NPs consisting of lipid bilayer membranes surrounding a hydrophilic core. Known for their immunogenicity, low toxicity, and manufacturability, making them valuable in NP vaccine research (40).

Emulsions are utilized as vaccine delivery systems. Nano-scale emulsions consist of two immiscible liquid phases, comprising an emulsifier and an excipient. These nano-sized vaccines can be divided into water-in-oil or oil-in-water emulsions, either carrying antigens or mixed with antigens for vaccine administration. NPs are used as adjuvants in vaccine development, and MF59, which is used in influenza vaccines, acts as a safe and potent vaccine adjuvant. ISCOMs are cage-like particles approximately 40 nm in size. ISCOM-based vaccines are employed to capture hydrophobic antigens, enhancing both antibody and cellular immune responses (38, 41)

Dendrimers are frequently employed in vaccine applications. It has been observed that dendrimer-encapsulated antigens generate strong antibody and T cell responses against H1N1 influenza, Ebola virus, and Toxoplasma gondii (42). VLPs utilize protein structures to create particles devoid of infectivity and genetic material. VLPs are non-replicating structures designed for a rapid response against outbreaks. These particles enhance the immunogenicity of weak antigens. VLP vaccines represent a commercialized class of NPs (38).

Nano vaccines offer advantages, such as reducing the required number of doses and providing greater flexibility. This feature makes them ideal for situations where multiple doses need to be administered to a large number of individuals (43). Recent advancements in nanotechnology have demonstrated the versatility of vaccine designs and the numerous advantages of NP-based formulations. Studies have shown that NPs can continuously release antigens and effectively stimulate the immune system by carrying multiple antigens (44). NPs can encapsulate various vaccine components, such as proteins, mRNA, DNA, and molecular adjuvants. NP-based influenza vaccines under development have been shown to induce strong and broad protective immune responses, yielding significant results (45). Another study examined the effects of cationic NPs on enhancing the efficacy of cancer vaccines. It was demonstrated that the administration route of NP vaccines influences the magnitude and quality of cellular immune responses. This study highlights the promising potential of cationic NP cancer vaccines for specific immunotherapy against cancer (46).

Covid-19 and Nanovaccines

Coronavirus is an enveloped virus classified as RNA viruses. COVID-19 emerged in China in 2019. The primary target of the coronavirus in the human body is the lungs. The SARS-CoV-2 virus contains spike proteins irregularly arranged on its capsid. These spike proteins recognize and bind to the host cell receptor ACE2 (angiotensin-converting enzyme-2) found in lung cells (47). Once viral particles enter the lung cells, they replicate very rapidly. This rapid replication causes damage to the alveoli in the lungs. The high affinity of the SARS-CoV-2 S protein for the human ACE2 receptor indicates its high transmissibility (48). When the lung epithelium is damaged by the coronavirus, proinflammatory cytokines are released as an immunological response. This leads to acute respiratory syndrome and multiple organ damage (49).

In the development of vaccines for COVID-19, various techniques are used, including

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inactivated virus, live attenuated virus, and recombinant protein-based vaccines, as well as new types of vaccines such as RNA, DNA, and viral vector-based vaccines (50). Some of the vaccines developed for COVID-19, which has affected the whole world, have been developed using NP vaccine technology. Nanotechnology plays a significant role in the presence of pandemics that pose a major threat to the world, such as SARS-CoV-2. Since SARS-CoV-2 spreads via droplets containing small viral particles during talking, breathing, coughing, and sneezing, nanotechnology and nanomedicine is used for virus detection and neutralization. Therefore, NPs are customized to neutralize these viruses (51). There are many advanced nanotechnology-based COVID-19 vaccines, which are classified into three categories according to their functional components: nucleic acid-based, virus particle-based, and viral protein-based (52).

Upon binding to ACE2, SARS-CoV-2 enters the host cell, where viral protein are expressed, inducing cell-mediated immunity. This is the fundamental principle behind the development of all nucleic acid-based vaccines (53).

Organic NPs suitable for vaccination against SARS-CoV-2 must have specific features, such as targeted drug delivery, controlled drug release, biocompatibility, and non-toxicity. Extracellular vesicles, polymeric and lipid-based NPs, liposomes, dendrimers, and micelles are among the most well-known organic NPs (54). The human cell membrane is composed of phospholipids. Therefore, lipid NPs are known to be highly biologically compatible with the plasma membrane and human cells (55).

Accurate and early diagnosis plays a critical role in limiting the spread of COVID-19, enabling the prevention of future pandemics. Nanotechnology is based on molecular techniques and that target specific pathogens. In the field of NP applications for detecting SARS-CoV-2, RNA can be extracted using high-affinity silica-coated iron oxide NPs. Recently, diagnostic strategies for SARS-CoV-2 focusing on nanotechnology have been reviewed (56). Molecular-based nanotechnological techniques for evaluating the RNA viruses exhibit superior sensitivity compared to antibody-based methods and serology. In addition, a lateral flow antigen test based on colloidal gold NPs has been developed. Colloidal gold NPs offer some advantages over PCR methods in detecting antibodies against the virus instead of the RNA virus itself (57).

NPs interact with proteins in SARS-CoV-2, giving them a different biological identity and enabling early diagnosis. A carrier molecule is necessary to facilitate the entry of mRNA into cells, commonly using lipid NPs (58). These vaccines, developed through mRNA technology, transfer the mRNA molecule containing the genetic information of SARS-CoV-2 into lipid NPs. These vaccines have demonstrated that synthetic polymer NPs containing tumor proteins recognizable by the body's immune system are included. Therefore, it is believed that they will evolve into applications that can be used in the treatment of many diseases in the future (59).

In a study, a nanoparticulate vaccine was produced using ferritin NPs to visualize the S protein or its subunits of SARS-CoV-2. This vaccine was observed to provide strong neutralizing antibodies and cellular immune responses in animal models. Therefore, it is considered a promising vaccination approach against SARS-CoV-2 and other coronaviruses (60).

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In another study conducted against the global COVID-19 pandemic, NP vaccines capable of binding covalently to the receptor-binding domain (RBD) and HR subunits of SARS-CoV-2 were developed. Ferritin-based NPs were found to induce more neutralizing antibodies than protein subunit monomers. The NP vaccine was observed to protect mice exposed to the virus from SARS-CoV-2 infection (61).

Advances in nanostructured materials for fighting the virus in the treatment and vaccine development of SARS-CoV-2 continue to progress daily, aiming to eliminate the virus with the help of nanomedicine in the ongoing COVID-19 pandemic (62). Technology has been developed to rapidly detect SARS-CoV-2 using gold NPs (63). Additionally, technologies that can neutralize SARS-CoV-2 in the external environment using nanomaterials such as silver NPs have been developed (64).

The observation that NPs and viruses operate at the same scale has made the nanotechnology approach powerful in vaccine development. NPs replicate the functional and structural features of viruses, making nanomedicine a significant pathway in innovative vaccine development technology (65).

Conclusion

COVID-19 emerged in China in 2019. Various techniques are used in vaccine studies for COVID-19, including inactivated virus, attenuated live virus, and recombinant protein-based vaccines, as well as new types of vaccines, RNA, DNA and viral vector-based vaccines. With the advancement biotechnology, nonoparticle systems have been developed and are now being used in vaccine studies. NPs offer advantages such as ability to carry, protect, stabilize and deliver antigens to the target tissue. Additionally, NPs can increase vaccine effectiveness by enhancing the immune system response. Today, NPs are used in the development of many vaccines. Numerous NP-based vaccine studies are being conducted against COVID-19, which one of the biggest global health crisis recently. NP-based vaccines will play a critical role in limiting the spread of COVID-19, allowing for the prevention of future epidemics.

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