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Application of Controlled Release Mechanisms in Vaccine Delivery

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ABSTRACT

Vaccines, as an essential means of preventive medicine, profoundly impact human health by stimulating an immune response to protect the body from pathogens or treat diseases. However, conventional vaccine delivery methods have limitations such as multiple injections, rapid degradation in vivo, and difficulty in targeted delivery. The development of controlled release mechanisms has overcome these challenges, optimized the immune response and improved the efficacy and safety of vaccines by precisely controlling the time, space and dose of vaccine release in vivo. This review explores the fundamentals, recent applications and future directions of controlled release mechanisms in vaccine delivery, focusing on the design and application of intelligent delivery systems such as biodegradable nanoparticles, self-healing microspheres, scaffolded vaccines and targeted vaccine systems. With the continuous progress of biotechnology and nanotechnology, controlled-release vaccines herald a new direction in vaccine design and delivery and bring efficient vaccine products to global public health.

KEYWORDS

Controlled release; Vaccine delivery; Vaccine design; Intelligent delivery system

1. INTRODUCTION

Vaccines stimulate an immune response to protect the body from invading pathogens or to treat disease and are essential as preventive medicine. Vaccines have greatly improved human health and have played a crucial role in human history [1]. Conventional vaccine delivery has many limitations, such as the need for multiple inoculations, rapid degradation in the body, and difficulties in achieving targeted delivery [2]. To overcome these challenges, controlled release mechanisms have been developed, which optimize the immune response and improve the efficacy and safety of vaccines by precisely controlling the time, space and dose of vaccine release in the body. With the rapid development of biomaterials and nanotechnology, the application of controlled release mechanisms in vaccine delivery is becoming more and more promising. It can help more personalized and precise vaccination strategies reduce the side effects of vaccines and improve patient compliance [3]. This review will discuss the fundamentals, recent applications and future directions of controlled release mechanisms in vaccine delivery to provide new perspectives and strategies for vaccine design and delivery.

2. OVERVIEW OF CONTROLLED RELEASE MECHANISMS

A controlled release mechanism releases cargo according to a predetermined temporal and spatial pattern through a well-designed delivery system to achieve precise intervention in the disease process.

Their core purpose is to optimize vaccine efficacy, prolong the duration of action, reduce injection frequency, and minimize adverse effects [4]. Controlled release mechanisms utilize advanced material science and nanotechnology to design a variety of intelligent vaccine delivery systems, such as using biological barriers or specific tissue properties; through surface modification and binding of targeted ligands, controlled release systems can allow vaccines to be released in specific tissues, enhance immune cell activation and antigen presentation, and achieve drug aggregation and release at specific sites [5]. The characteristics of the delivery system can also be adjusted to precisely control the dosage of the drug to suit the therapeutic needs of different patients.

3. APPLICATION OF CONTROLLED RELEASE MECHANISMS IN VACCINE DELIVERY

3.1. Single-Administration Controlled-Release Vaccine Delivery Systems

Most conventional vaccines require multiple vaccinations (2-3 doses) spaced 4-6 weeks apart to ensure successful induction of individual protective immunity [6]. Repeated hypodermic needles not only bring about accidental needlestick injuries, the transmission of blood-borne infections, and anxiety about needle phobia [7], but also present many logistical challenges, such as difficulty in storage disposal, and administration, especially in developing countries where vaccine non-completion rates are as high as 70% [6]. To increase vaccination coverage, the next generation of vaccines should reduce the reliance on repeated subcutaneous injections [8]. To achieve this goal, in addition to developing single-dose vaccines that provide protective immunity in a single dose, protective immunity can also be generated by prolonging or delaying antigen exposure through slow-release delivery systems to avoid multiple repeated subcutaneous injections [8].

3.1.1. Biodegradable polymer nanoparticles (PNPs)

A common approach used for controlled release is to encapsulate the active ingredient in a bioerodible polymer, which is degraded in the biological environment by chemical bond hydrolysis or physical erosion, a process ranging from two months to two years, and the degradation products can be readily excreted from the body. Biodegradable polymers involved in vaccine manufacturing are categorized into two groups: natural polymers and synthetic polymers. Natural polymers are mainly polysaccharides, and some protein-based materials, such as chitosan (e.g., quaternized chitosan, thiochitosan, carboxymethyl chitosan, and hydroxypropyl chitosan), which have better properties in terms of adhesion, biocompatibility, and solubility [9]. Synthetic polymers primarily used in vaccine delivery systems include polyesters (e.g., polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-glycolic acid) (PLGA), and poly (ε-caprolactone) (PCL)), as well as polyphosphoric anhydride and polyanhydride [3].

Among the natural polymers with well-structured molecular structures, hydroxyl and amine group functionalization of polysaccharides improves their physicochemical properties and controls their biodegradation rate [10]. On the other hand, synthetic biodegradable polymers can arbitrarily tune mechanical properties and degradation kinetics for different applications. For example, the degradation rate of PLGA polymers can be adjusted by changes in the initial molecular weight, the ratio of ethyl cross-ester to propyl cross-ester copolymers and their crystallinity [11].

Although controlled release systems based on biodegradable materials have been commercially successful for a variety of small molecules and peptides, vaccine-containing injectable polymer microspheres are typically prepared by agent-solvent evaporation, spray drying, and coagulation and have not been historically well converted to biomolecules such as protein antigens [12]. In addition, vaccine microspheres prepared by these methods also typically exhibit instability and poor long-term in vitro in vivo release [6].

3.1.2. PLGA active self-healing dispensing

Encapsulating vaccine antigens in PLGA microspheres under mild conditions is essential to avoid damage during preparation and obtain controlled release. A newer approach allows for the separation of particle fabrication from protein loading behavior, thus allowing for the encapsulation of stable proteins. This approach is called active self-healing encapsulation (ASE), where "self-healing" is a unique phenomenon of polymers in which damaged structures such as pores and cracks are healed by the spontaneous rearrangement of polymer chains. For example, PLGA pores spontaneously close on the polymer surface at physiological temperatures, thus closing the pore diffusion pathway [13].

The new self-healing-based approach requires only a simple mixing of porous PLGA and a low concentration (0.64-1 mg/mL) of the target protein solution at near-physiological temperatures (10-38°C) to repair the pores and microencapsulate the protein safely [13]. However, the encapsulation efficiency of this passive self-healing microencapsulation method is low (1.5-13%) [8]. The active self-healing method employs a protein-trapping agent doped into the PLGA pores. When the temperature is increased above the hydration glass transition temperature of the polymer, the trapping agent strongly binds the protein before the dynamic self-healing of the pores on the surface of the PLGA microparticles, efficiently capturing the protein from the aqueous solution within the microparticles [14].

The commonly used protein trapping agents are Alhydrogel, including aluminum hydroxide, aluminum phosphate, and amorphous hydroxy aluminum phosphate sulfate [8]. Biopolymers (e.g., hyaluronic acid, chondroitin sulfate, heparin, chitosan, and dextran sulfate) have also been reported as traps for biomimetic ASEs. These microspheres actively bind, chelate, and stabilize growth factors in vivo, potentially potentiating the biological effects of proteins by acting as cofactors [14].

After these microspheres enter the body, the antigens still encapsulated within the microspheres remain hidden from the immune system until they are released. Using fluorescence detection, it was found that the self-healing particles showed no significant volume degradation in the first two weeks, with only a fluorescence signal from the particles; after three weeks, the polymer particles were visibly degraded in both confocal and SEM images due to the large voids formed by the mass loss of the particles that allowed the antigenic proteins to escape to the outside of the particles and become visible. By the sixth week, the particles were wholly degraded, and all the proteins in them were released and presented to the immune system [8].

This new method not only eliminates vaccine antigen instability joint in agent-solvent evaporation methods but also exhibits high loading (1-1.8 wt%) and encapsulation efficiency (~97%)[13]. This method allows polymer stabilization and long-term release of stable/immunoreactive antigens in vitro, which is ideally suited for protein antigens and has excellent potential for the development of single-administration controlled-release vaccine delivery systems, with further studies such as investigating other protein capture agents and optimizing stability and long-term release kinetics ongoing.

3.1.3. Scaffold vaccines

Scaffold vaccine technology represents a breakthrough in vaccine delivery systems, with scaffolds typically made from biocompatible and biodegradable polymers using gas foaming methods or 3D printing [15, 16], exhibit highly porous structures to control the release of antigens and adjuvants, effectively mimicking the natural process of infection to enhance adaptive immune responses. Compared with conventional push vaccines, scaffold vaccines can more precisely modulate the immune response phenotype, including the activation of antibody subclasses and immune cells, thus potentially reducing the need for repeated injections [17].

Some scientists have compared the immune responses to GnRH-ovalbumin conjugate (OVA-GnRH) after a single injection of three scaffold proteins (porous PLG scaffolds, mesoporous silica rods, and alginate cryopreservative vaccine) and soluble pill vaccine without scaffolds. The results showed that

all scaffolded vaccines produced high levels of anti-GnRH IgG1 antibodies for over one year, whereas soluble pill vaccines without scaffolds were less effective [17].

These findings emphasize the versatility and efficacy of scaffold vaccines in modulating humoral immune responses, their potential to reduce the number of injections, provide long-lasting protection and foreshadow new directions for future vaccine design and delivery.

3.2. Targeted Vaccine Systems

The targeted vaccine system is a precision immunization strategy designed to deliver vaccine components directly to specific immune cells or tissues in the body through specific delivery technologies to elicit an effective immune response. The advantage of this system is the ability to deliver vaccines to their most effective locations in the body, which can enhance the immunogenicity of antigens, increase the level of immune response, and reduce the non-specific distribution of vaccine components in the body, thereby reducing side effects and improving the safety and efficacy of vaccines [5].

3.2.1. Lipid nanoparticles (LNPs)

LNPs provide an effective means of precise delivery and controlled release of RNA vaccine components and play an essential role in enhancing vaccine efficacy and safety. The application of LNPs in mRNA vaccines is particularly prominent; for example, in developing the COVID-19 mRNA vaccine, LNPs played a crucial role in effectively realizing the efficient delivery of the mRNA to the human cells and stimulating the immune response. LNPs play a crucial role in developing the COVID-19 mRNA vaccine [5].

LNP consists of four main lipid components: ionizable lipids, auxiliary lipids, cholesterol, and polyethylene glycolated lipids (PEG-lipids), which can form multilayered vesicle structures to wrap hydrophilic or hydrophobic vaccine components and have better biocompatibility and targeting properties. These lipid components protect the mRNA from nuclease degradation and facilitate the release of the vaccine components in the cytoplasm through the endosomal escape technique, thus facilitating their intracellular delivery and release. The surfaces of the LNPs can be modified to improve their cycling time and targeting, for example, by polyglycolization to improve their stability and prolong their cycling time in vivo [5]. It also can be used to achieve selective delivery to specific cells or tissues by surface coupling of targeted ligands

Although LNPs have demonstrated technical advantages in vaccine delivery, such as improving immunogenicity and stability, achieving targeted delivery and improving cross-presentation of antigens. However, some challenges remain, such as LNP-based mRNA vaccines requiring more cooling and transportation temperatures below freezing. This necessary cold chain makes vaccine distribution costly, up to 80% of the overall vaccination budget [3]. Based on this problem, modern methods of metal-organic frameworks have been proposed that can form protective shells on the surfaces of colloidal liposomes, proteoliposomes, and detergent-solubilized transmembrane proteins to prevent protein denaturation and liposome fusion/degradation [3].

3.2.2. Bacterial ghost-based vaccine delivery system

Bacterial ghost (BG), an empty bacterial envelope of Gram-negative bacteria produced by controlled expression of the cloned gene E, is a potent DNA-based vaccine delivery system against antigen-presenting cells (APCs) and has been used globally as a vaccine delivery system and vaccine adjuvant [18]. Genetic engineering methods are often used to induce the release of bacterial cell contents; in short, after transforming Gram-negative bacteria using heat-inducible plasmids containing lysis genes, the temperature of the medium is raised to about 42°C and the cells are entirely lysed before BGs can be harvested or stored [19]. Unlike the use of inactivated vaccines prepared using methods such as formaldehyde and heat treatment that can disrupt the bacterial surface structure, genetically engineered BGs retain the antigenic properties of natural bacterial membrane components, including

LPS, peptidoglycan, or flagella, and these envelope structures can be effectively recognized and taken up by immune and non-immune cells thereby enabling targeted vaccine delivery and controlled release, inducing very potent and effective humoral and cellular immune responses [20]. BGs also serve as carriers to protect the vaccine from external factors [19].

BGs can effectively target human macrophages, resulting in nearly 100% of cells exhibiting BG signaling. Once in the host, BGs are recognized by pattern recognition receptors (PRRs) on immune cells, inducing the production of pro-inflammatory cytokines and enhancing the expression of co-stimulatory molecules on dendritic cells (DCs), thereby facilitating antigen presentation to T cells [19]. In addition, BGs can enhance the cross-presentation ability of DCs by increasing the expression of MHC-I and MHC-II, stimulating humoral and cell-mediated immune responses [18]. In general, pathogenic bacterial ghost serotypes are well preserved and high concentrations of BGs can provide high immunogenicity [21].

Some Gram-negative bacteria (e.g., Lactobacillus casei, attenuated Salmonella typhimurium, and attenuated Shigella fowleri) are safe as vaccines [18]. The potency, safety, stability, and relatively low cost of bacterial ghosts provide significant technological advantages, and BGs may play an essential role in developing targeted vaccine delivery.

3.3. External Triggers

Controlled release systems will either use an internal stimulus or one of two essential triggers: an external stimulus. Internal triggers utilize internal body conditions surrounding the drug, pH conditions in cellular endosomes, electron affinity of liposomes, and reduction potentials. Examples of external stimuli, on the other hand, include light, ultrasound, temperature elevation, application of electric and magnetic fields, and radiofrequency (RF) to control antigen release from vaccine carriers for precise temporal and spatial delivery of drugs [22]. The design of these systems requires a combination of particle or nanoparticle biocompatibility, drug loading capacity, and responsiveness to external stimuli [22].

The application of ultrasound in delivery includes acoustic flow, hyper chemical and shockwave effects that can facilitate drug release through resonance and cavitation effects; it is entirely noninvasive, controlled and targeted, and can be used to deliver many types of drugs as well as a variety of carriers such as liposomes and nanoemulsions [23]. Light-triggered mechanisms, on the other hand, rely on photothermal effects, photochemistry, and photoisomerization, where heat or chemical reactions break the covalent bonds of the particles, leading to their diffusion or disintegration and release of the drug [24]. Electrically triggered mechanisms are commonly used in implantable drug delivery systems to release drugs via electrochemical dissolution, but there are issues with replenishing the drug payload and power management [25]. In addition, there are radiofrequency and microwave technologies on the other hand, which utilize electromagnetic radiation for heating, X-rays for drug release through interactions with gold nanoparticles and photosensitizers, and external alternating magnetic fields (AMFs) for drug release through inductive heating of magnetic nanoparticles. While these technology institutes have the advantage of depth and time control of tissue penetration, they also face problems, including temperature control, drug loading efficiency, and potential side effects [22].

The intensity and exposure time of external triggers must be carefully controlled to avoid damage to the in vivo environment, and continued research and technological development is expected to overcome these obstacles and advance the clinical application of these innovative systems. In particular, microwave-based systems are seen as up-and-coming technologies for more profound tissue drug delivery and precise release control due to their penetration depth and non-ionizing properties.

4. CHALLENGES AND PROSPECTS

Although controlled release mechanisms show great potential in vaccine development, they still face several technical challenges. Firstly, the biocompatibility issue should not be neglected to ensure that the vaccine carrier materials do not cause excessive immune responses or side effects in vivo. In addition, precisely controlling the release kinetics for optimal immune response is also a problematic issue in current R&D. Finally, scale-up and cost-effectiveness are essential issues facing controlled-release vaccines, which are directly related to the popularity and accessibility of vaccines.

Despite the challenges, the application of controlled release mechanisms in novel vaccine development remains promising. Future vaccines will be more innovative and personalized through advances in nanotechnology and biomaterials science. For example, by combining immunomodulators and adjuvants, controlled-release systems can further enhance the immunogenicity of vaccines and provide longer-lasting immune protection [8]. With the continuous innovation of biotechnology, controlled-release vaccines are expected to play an essential role in cancer treatment, chronic disease management, and the prevention and control of novel infectious diseases [26].

Research on controlled release mechanisms will continue to deepen, especially in the cross-cutting applications in materials science, immunology and disease modeling. With a deeper understanding of disease mechanisms, vaccine design will become more precise, enabling differentiated therapies for specific pathogens or disease states. Meanwhile, with the advancement of clinical trials and the improvement of regulatory policies, more vaccines based on controlled-release technology are expected to be approved and marketed for the benefit of patients.

5. CONCLUSION

The application of controlled release mechanisms in the field of vaccines represents a significant advancement in vaccine delivery technology, which brings new hope for preventing and treating diseases by providing more precise and personalized immunization strategies. Controlled release mechanisms significantly enhance the efficacy and safety of vaccines by optimizing the time, space and dose of vaccine release. Intelligent delivery systems designed using biomaterials and nanotechnology, such as biodegradable polymer nanoparticles, self-healing microspheres, scaffolded vaccines, and targeted vaccine systems, have demonstrated the potential for efficient antigen delivery in specific immune cells or tissues. Second, controlled-release vaccines offer significant advantages in reducing injection frequency, minimizing side effects, and improving patient compliance. Examples include the efficient delivery of mRNA vaccines achieved through lipid nanoparticles and the success of cellular ghosts in the direction of DNA vaccine delivery. In addition, introducing external trigger mechanisms provides more flexible and controllable release strategies for vaccine delivery, such as ultrasound, light, temperature, electric field and other external factors to control the precise release of vaccines. With the continuous advancement of technology and clinical trials, controlled-release vaccines are expected to be widely used in many fields, bringing more innovative and efficient vaccine products to global public health endeavors.

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