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Microparticle Vaccines Made from Biodegradable and Biocompatible Poly (Lactide-Co-Glycolide) Polymers

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Abstract

Vaccination is undoubtedly the most effective strategy for disease prevention and eradication. However, significant information obtained recently indicates that future investigations on vaccine development have to include effective adjuvants for enhancing protective immunity against pathogenic infections in animals and humans. Microparticles made from poly (lactide-co-glycolide) (PLG) polymers can be designed as safe and potent adjuvants or delivery systems to encapsulate vaccine antigens for the development of controlled-release Microparticle vaccines. Adjuvant effects of the PLG microencapsulation can protect antigens from unfavorable degradation, allow the sustained and extended release of antigens over a long period, and enhance antigen uptake by antigen-presenting cells (APCs). Although only a countable number of formulations based on PLG-encapsulated technique are available in market, much work still remains to confirm and optimize the stabilization of protein release for presenting to the immune system.

Keywords: Poly (lactide-co-glycolide) (PLG) polymers; Adjuvants; Delivery Systems; Microparticles; Antigen-presenting cells (APCs)

Adjuvant Function and Category

Vaccination is undoubtedly the most effective strategy for disease prevention and eradication. However, significant information obtained recently indicates that future investigations on vaccine development have to include adjuvants for enhancing the protective immune responses against pathogenic infections in animals and humans [1]. Adjuvants are substances used in combination with an antigen to produce a more robust immune response than the antigen alone [2]. This broad definition encompasses a very wide range of materials for adjuvant development. Actually, adjuvants can be broadly separated into two classes, vaccine delivery systems and immune stimulatory agents, based on their main mechanisms of action [2,3]. Vaccine delivery systems are generally particulate, such as emulsions, micro/nano particles, iscoms and liposomes, and their main function is to deliver antigens into antigen-presenting cells. In contrast, immune stimulatory agents are predominantly derived from pathogens and often represent pathogen associated molecular patterns (PAMP), such as LPS, MPL,

CpG-ODN [4], which activate cells of the innate immune system to induce the following acquired immune response.

Most modern vaccines based on subunits of pathogens, such as purified proteins, are likely to be less immunogenic than traditional vaccine antigens and are often unable to initiate a strong immune response [5]. These subunit vaccines therefore require effective adjuvants to aid them to elicit strong immune responses [1]. One of current important issues in vaccinology is the urgent need for the development of new or improved adjuvants to enhance the immunogenicity or effectiveness of vaccines [1,6]. Different adjuvants capable of improving immunity and protection have been described in numerous studies [1,6]. However, the safety concern of an adjuvant is still a crucial issue in adjuvant development [7]. Therefore, vaccine antigens formulated with safe, potent adjuvants that are promised to induce "appropriate" immune responses, particularly cell-mediated immunity, seem more likely to be approved for use.

Poly (lactide-co-glycolide) (PLG) Polymer

Microparticles derived from different biodegradable and biocompatible polymers, including (PLG), alginate, starch and other carbohydrate polymers, can be designed as carriers for proteins or drugs and carry out the main function of vaccine delivery systems [8]. Particularly, PLG polymers approved by the US Food and Drug Administration (FDA) have been extensively used as sutures [9] and drug carriers for many years [10]. Different forms of PLG polymers can be obtained according to the ratio of lactide to glycolide used for the polymerization [11]. In recent ten years, PLG polymers have further become safe and potent adjuvants or delivery systems to encapsulate vaccine antigens for the development of controlled-release Microparticle vaccines [12]. The PLG Microparticles are biodegradable through hydrolysis to break down into the biocompatible metabolites, lactic and glycolic acids, which produce little inflammatory activity and are excreted from the body via natural metabolic pathways [11].

Adjuvant Effects of PLG Microparticles

PLG polymers provide a number of practical advantages in acting as vaccine adjuvants or delivery systems. Adjuvant effects of the PLG microencapsulation can protect antigens from unfavorable degradation [13], allow the sustained and extended release of antigens over a long period [14], and enhance antigen uptake by antigen-presenting cells (APCs), including macrophages and dendritic cells in specific lymphoid regions [15]. These effects strengthen antigen immunogenicity to favorably generate strong specific immunity [12].

Strong cell-mediated immunity elicited by PLG Microparticles appears to be largely a consequence of their uptake into APCs and the delivery of these Microparticle-containing APCs to specific lymphoid compartments following vaccination [8]. Microparticles smaller than 10 μm in diameter are appropriate for direct uptake by APCs [15]. These APCs containing Microparticles then migrate to other lymphoid compartments, such as the spleen and mesenteric lymph nodes, where they effectively present antigenic epitopes to T lymphocytes, especially Th1 and Tc, thereby inducing strong specific cell-mediated immunity [3]. In other words, facilitation of uptake and delivery of PLG Microparticles by APCs can lead to more effective antigen processing and presentation to T lymphocytes capable of inducting cell-mediated immune responses [8,15,16].

Microparticle vaccines made from PLG polymers may fulfill the need for induction of a functional cell-mediated immune response, which is urgently required for eliminating intracellular pathogens located in host cells. Significant earlier studies have further demonstrated that the APCs containing Microparticles can travel to specialized mucosal lymphoid compartments, including mucosal associated lymphoid tissues (MALTs), the inductive sites for stimulating potent immunity following intranasal or oral vaccination [17,18]. Thus, PLG-encapsulated antigens can be designed as effective mucosal vaccines that have potential to stimulate mucosal systems, such as intestinal and vaginal tracksvia intranasal or oral administration [18].

The sustained and extended antigen release appears to substantially enhance and prolong antigen-specific immunity for achieving long-term protection [14]. The release of an antigen from PLG Microparticles is governed by the PLG copolymer degradation rate, which largely depends on the encapsulation conditions including physical properties of PLG polymer such as molecular weight, hydrophilicity and the ratio of lactide to glycolide as well as the Microparticle features such as the size, morphology and encapsulation efficiency [19]. In addition, antigen-loaded PLG Microparticles capable of sustaining release of an antigen also show potential for being designed as a single-dose vaccine without the need for booster doses [20,21]. However, as some sophisticated

events, including enhancement of protein load in PLG Microparticles as well as optimization and stabilization of protein release are involved in the design of a single-dose vaccine [22], the feasibility needs to be assessed in future studies.

Conclusions

Although PLG polymers are potent adjuvants or delivery systems, only a countable number of formulations based on PLG-encapsulated technique are available in market. The future success of PLG Microparticle formulation will mainly depend on commitment of pharmaceutical and biotechnological industries to development of this technology. Additional efforts are needed to confirm and optimize the stabilization of protein release for presenting to the immune system. Future applications of the PLG adjuvant effects are likely to include the development of more site-specific delivery systems for mucosal administration. Mucosal surfaces, such as the gastrointestinal tract, provide the principal sites of entry for many pathogens. Therefore, the development of effective mucosal vaccines formulated with potent adjuvants, such as PLG polymers, that are promised to elicit long-lasting protective immunity at the mucosal sites would be a critical work forward in the enduring control of mucosal infections.

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