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Review article

Poly(lactic acid)-based particulate systems are promising tools for immune modulation

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ABSTRACT

Poly(lactic acid) (PLA) is one of the most successful and versatile polymers explored for controlled delivery of bioactive molecules. Its attractive properties of biodegradability and biocompatibility *in vivo* have contributed in a meaningful way to the approval of different products by the FDA and EMA for a wide range of biomedical and pharmaceutical applications, in the past two decades. This polymer has been widely used for the preparation of particles as delivery systems of several therapeutic molecules, including vaccines. These PLA vaccine carriers have shown to induce a sustained and targeted release of different bacterial, viral and tumor-associated antigens and adjuvants *in vivo*, triggering distinct immune responses. The present review intends to highlight and discuss the major advantages of PLA as a promising polymer for the development of potent vaccine delivery systems against pathogens and cancer. It aims to provide a critical discussion based on preclinical data to better understand the major effect of PLA-based carrier properties on their interaction with immune cells and thus their role in the modulation of host immunity.

Statement of Significance

During the last decades, vaccination has had a great impact on global health with the control of many severe diseases. Polymeric nanosystems have emerged as promising strategies to stabilize vaccine antigens, promoting their controlled release to phagocytic cells, thus avoiding the need for multiple administrations. One of the most promising polymers are the aliphatic polyesters, which include the poly(lactic acid). This is a highly versatile biodegradable and biocompatible polymer. Products containing this polymer have already been approved for all food and some biomedical applications. Despite all favorable characteristics presented above, PLA has been less intensively discussed than other polymers, such as its copolymer PLGA, including regarding its application in vaccination and particularly in tumor immunotherapy. The present review discusses the major advantages of poly(lactic acid) for the development of potent vaccine delivery systems, providing a critical view on the main properties that determine their effect on the modulation of immune cells.

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1. Introduction

Vaccination is a general term describing the direct stimulation of the patient's immune system, towards the induction of an immune response against subsequent infection and diseases [1].

Since Edward Jenner, who developed the first vaccine in 1796 [2], immunization has been an extremely important tool for the effective control of several infectious diseases, as tetanus, yellow fever, pertussis, tuberculosis, *Haemophilus influenzae* type b disease, measles, mumps, rubella, typhoid fever, rabies, cholera, diphtheria, and meningitis. It has allowed the eradication of smallpox and the reduction of 99% of poliomyelitis cases [1,3–5].

Apart from their current application in the prevention of several infections, vaccines hold great promise in controlling other diseases, including cystic fibrosis [6,7], Alzheimer's disease [8,9], acquired immune deficiency syndrome (AIDS) [10,11] and cancer [12,13]. In April 2010, the US Food and Drug Administration (FDA) approved Provenge® (Sipuleucel-T), the first therapeutic cancer vaccine. This is an autologous cellular immunotherapy designed to stimulate an immune response against prostate cancer cells, through the delivery of prostate acid phosphatase (PAP) protein by activated antigen-presenting cells (APCs) [13,14].

Conventional vaccines usually contain molecules that mimic disease-causing pathogens, being often composed by attenuated, inactivated or killed forms of the target microorganism, as toxins or surface proteins [15–17]. However, their use raises several safety issues since pathogenic bioactive material can remain in vaccine formulation, as contaminants [18–20]. Moreover, to maintain the efficacy of these vaccines, strict storage conditions must be followed in order to avoid instability and degradation, or even to circumvent their reversion to the virulent form. In addition, individuals with damaged or weakened immune systems cannot safely receive these vaccines [21,22].

Due to these safety concerns and progression in biotechnology and molecular biology, new vaccines comprising recombinant subunit proteins or peptides, or non-viral vectors to deliver DNA that encodes for a single or multiple antigens have been used as safer alternatives to those highly immunogenic conventional vaccines [23–25]. However, these recombinant vaccines usually require higher amounts of adjuvants, which are entities that stimulate the innate immune system, acting as "danger signals" [24].

Alum and its derivatives were the first vaccine adjuvants approved by the FDA and European Medicines Agency (EMA) for human use. These adjuvants are still present in the composition of the majority of the vaccines currently in clinical use, such as diphtheria, tetanus and pertussis (DTaP) vaccines, the pneumococcal conjugate vaccine and the hepatitis B vaccines [26]. Alum adjuvants are generally well tolerated and are able to increase humoral-mediated immune responses against most of the antigens [27]. Nevertheless, besides significant side effects and safety concerns [28], they induce poor stimulation of cell-mediated immunity and subsequent cytotoxic T-lymphocyte (CTL) responses [27,29–31]. In addition to alum, only two other adjuvants were licensed by the FDA and EMA for human use: AS03 [32], as a component of the pre-pandemic H_5N_1 vaccine Prepandrix®; and AS04 [33], as an adjuvant that combines alum and monophosphoryl lipid A (MPL®), which is used in hepatitis B virus (HBV) (Fendrix®) and human papillomavirus (HPV) (Cervarix®) vaccines [34]. In addition, the oil-in-water emulsion MF59 is another adjuvant already approved for human use in Europe, as a component of the Influenza vaccine FLUAD® [35]. Despite its acceptable safety profile, cases of chills, fever, increased local pain at the site of administration and muscle aches have been occasionally reported [36].

Alternative strategies to overcome the hurdles associated to conventional adjuvant-containing vaccines have involved the formulation of antigens entrapped in particulate adjuvants, such as liposomes, microparticles (MPs) and nanoparticles (NPs) [37]. These particulate vaccines can be formulated using several materials, such as polymers, lipids and inorganic compounds. In particular, biodegradable polymeric NPs have emerged as one of the most promising strategies to trigger and modulate immune responses against vaccine antigens [38–41].

Despite the considerable number of polymers that have been developed and investigated for particle formulation purposes, the thermoplastic aliphatic polyesters have been the most widely used for NP and MP production [39,42]. The aliphatic polyesters constitute a family of various synthetic biodegradable polymers, which include the poly(lactic acid) (PLA) [43–45].

Both PLA and poly(lactic-co-glycolic acid) (PLGA) have been widely explored for drug delivery due to their versatile mechanical properties, ensuring the production of materials with different molecular weights, suitable for a targeted release profile [44,46]. Besides being an undoubtedly promising biomaterial with recognized flexibility of carrier physical properties, PLA has been underexplored in recent reviews that discuss in detail its potential for immune modulation, both in cancer and infectious diseases, especially when compared to its copolymer PLGA.

Accordingly, the present review intends to highlight and discuss the major advantages of PLA as a promising polymer for the development of potent vaccine delivery systems, providing a critical outline of the preclinical data obtained with PLA-based micro- and nanoparticulate systems in this particular field. An overview of several immune mechanisms is provided to support the discussion underlying the main properties of these specific PLA-based carriers, responsible for their adjuvant behavior and overall effect in immune cells.

2. Immune response-mediated mechanisms against extra- and intracellular pathogens

Before describing the strategies underlying the use of delivery systems to modulate immunity it is fundamental to understand the role of each specific set of immune cells and overall nature of the immune response in the destruction of extracellular pathogens or in the eradication of intracellular pathogens or tumor cells.

APCs are a specialized subset of cells that bridges both innate and adaptive immunities. These present distinct mechanisms of action, and the successful interaction between them is fundamental to achieve an effective immune response [47]. Briefly, the innate immunity is a non-specific line of defense against pathogens mediated by physical epithelial barriers, circulating plasma proteins and several types of cells, particularly epithelial cells, phagocytic cells and natural killer (NK) cells [25]. On the other hand, the adaptive immunity is highly specific and thus, only becomes activated when the immune system recognizes characteristic pattern molecules of