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Review

Micro/nanoparticle adjuvants for antileishmanial vaccines: Present and future trends

Ali Badiee[a,1], Vahid Heravi Shargh[a,1], Ali Khamesipour[b,**,1], Mahmoud Reza Jaafari[a,c,*,1]

[a] Nanotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Center for Research and Training in Skin Diseases and Leprosy, Tehran University of Medical Sciences, Tehran, Iran
[c] Biotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Leishmania infection continues to have a major impact on public health inducing significant morbidity and mortality mostly in the poorest populations. Drug resistance, toxicity and side effects associated with expensive chemotherapeutic treatments and difficult reservoir control emphasize the need for a safe and effective vaccine which is not available yet. Although, Leishmanization (LZ) was shown to be effective against cutaneous leishmaniasis, standardization and safety are the main problems of LZ. First generation killed parasites demonstrated limited efficacy in phase 3 trials and moreover well defined molecules have not reached to phase 3 yet. Limited efficacy in vaccines against leishmaniasis is partly due to lack of an appropriate adjuvant. Hence, the use of particulate delivery systems as carriers for antigen and/or immunostimulatory adjuvants for effective delivery to the antigen-presenting cells (APCs) is a valuable strategy to enhance vaccine efficacies. Particle-based delivery systems such as emulsions, liposomes, virosomes, and polymeric microspheres have the potential for successfully delivering antigens, which can then be further improved *via* incorporation of additional antigenic or immustimulatory adjuvant components in or onto the particle carrier system. In this review, we have attempted to provide a list of particulate vaccine delivery systems involved in the production of candidate leishmaniasis vaccines and introduced some potentially useful vaccine delivery systems for leishmaniasis in future experiments. In conclusion, combination vaccines (adjuvant systems) composed of candidate antigens and more importantly well-developed particulate delivery systems, such as lipid-based particles containing immunostimulatory adjuvants, have a chance to succeed as antileishmanial vaccines.

Contents

1. Leishmaniasis

Leishmaniasis control, especially the zoonotic form of the disease in the regions with limited resources, is not feasible. Moreover, CL treatment is a globally challenging issue. The only available drug against CL is pentavalent antimonial which has limited efficacy

* Corresponding author at: Nanotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, P.O. Box: 91775-1365, Mashhad, Iran. Tel.: +98 511 8823255; fax: +98 511 8823251.
** Co-corresponding author. Tel.: +98 21 88970657; fax: +98 21 88970658.
E-mail addresses: ali.khamesipour@gmail.com (A. Khamesipour), Jafarimr@mums.ac.ir (M.R. Jaafari).
[1] All authors contributed equally to this work.

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accompanied by side effects and even drug resistant species that are reported from different parts of the world [1,2].

Development of an effective vaccine against leishmaniasis is promising, because it has been well known for centuries that long lasting protection is induced upon recovery from CL caused by natural infection or leishmanization (LZ) [3,4]. In addition, protection in an animal model is possible and the mass production of *Leishmania* promastigotes is not difficult. For example, a prophylactic vaccine against canine visceral leishmaniasis (CVL) has been reported in Brazil since 2004 [5]. Decades of effort in *Leishmania* vaccine development resulted in phase 3 efficacy trials of a few first generation *Leishmania* vaccines but currently there is no vaccine available for human leishmaniasis [6]. It seems that the use of an adjuvant and/or delivery system is necessary for almost any modern vaccine particularly vaccines against leishmaniasis. In an animal model, different *Leishmania* antigens, crude or well defined antigens induce strong Th1 immune response and a degree of protection in the presence of a suitable adjuvant but in humans the choice of adjuvant is limited. For example, BCG was used in clinical trials which seems to be the major drawback and one of the reasons of its limited efficacy [3].

2. Vaccine candidates for Leishmaniasis

In general, leishmaniasis vaccine candidates are divided into three types all originating from *Leishmania*; (i) live *Leishmania* including new genetically modified constructs; (ii) first generation vaccines consisting of killed *Leishmania* or parasite fractions with or without adjuvants; and (iii) second generation vaccines which are well defined *Leishmania* molecules including recombinant proteins or DNA [3].

Numerous live *Leishmania* preparations from various laboratories were proposed as candidate vaccines against leishmaniasis but only few of them reached human trials. An inoculation of live *Leishmania major* promastigotes known as leishmanization (LZ) was practiced in several countries including Iran and still is used in a limited scale in Uzbekistan [7]. Although LZ was the most successful control measure against CL, standardization and safety are the main problems of LZ.

Development of *Leishmania* vaccine using whole killed parasites goes back to the 1940s [8] based on the safety profile of long time experience of using whole killed *Leishmania* for immunotherapy and prophylaxis against CL in New World and using LZ and leishmanin in Old World. A few of the first generation *Leishmania* vaccines were prepared and tested in humans in different parts of the world [6,9,10].

Several recombinant proteins or DNA molecules have been proposed as *Leishmania* vaccine candidates but so far only leish-111f made it to early phases of clinical trials [11]. Leish-111f is a recombinant polyprotein of three *Leishmania* antigens consisting of TSA (thiol-specific antioxidant), LmSTI1 (*L. major* stress-inducible 1) and LeIF (*L. braziliensis* elongation and initiation factor) which are fused in tandem and formulated with monophosphoryl lipid A (MPL) in an oil/water stable emulsion using synthetic squalene [11]. In terms of recombinant proteins as vaccine antigens, it seems that the main drawback is a lack of an appropriate adjuvant since almost any *Leishmania* antigen induced protection in animal model when used with IL-12 [12–14]. DNA vaccines effectively engage both MHC classes I and II pathways, thereby allowing the induction of both $CD8^+$ and $CD4^+$ T cells. Other unique features that make DNA vaccination particularly attractive are the long lived production of the antigen and appropriate folding of the polypeptide similar to the situation in natural *Leishmania* infection [15]. Although DNA vaccination against *Leishmania* is considered a promising technology, no development of such *Leishmania* vaccines for use in humans has been reported so far [16].

There are also non-*Leishmania* origin vaccines from sand fly salivary gland antigens. Sand fly saliva contains a vast repertoire of pharmacologically active molecules able to interfere with the host's hemostatic, inflammatory and immune responses. Molecules from the saliva markedly promote *Leishmania* infectivity [17].

3. The role of adjuvants in leishmaniasis

Development of an effective vaccine requires precise information about the adjuvant to be used and the specific formulation which makes it stable, safe and immunogenic [18]. The word adjuvant comes from the Latin word *adjuvare*, which means to help or to enhance. Adjuvants are compounds that serve to enhance the magnitude, breadth, quality and longevity of specific immune responses against co-inoculated antigens, but have minimal toxicity or lasting immune effects on their own. Adjuvants can also be used to enhance the immune response, allowing for antigen-sparing, which is especially valued when more vaccine doses need to be produced than the available amount of vaccine antigen permits [19,20]. The choice of an adjuvant depends on factors such as the nature of antigen (associated/co-administered), the route of administration, the immunization schedule, and the type of required immune response. Moreover, it seems that optimal pharmaceutical parameters should be defined on a case-by-case basis to develop an effective vaccine [21].

Adjuvants used in vaccination against leishmaniasis are divided into two main categories; (i) non-particulate or immunostimulatory adjuvants, as shown in Table 1, including whole micro-organisms or their parts as natural/synthetic bacterial products (monophosphoryl lipid A (MPL), muramyl di- or tripeptides and derivatives (MDP/MTP-PE), Detox®, RC-529, saponins (QuilA, QS21), cytokines (IL-2, IL-12, GM-CSF), CpG oligonucleotides, glucan, imiquimod, and combinations thereof, (ii) particulate adjuvants, as shown in Table 2, including mineral-, lipid-, or polymer-based delivery systems [16,18,22]. An attractive and recent strategy for the rational design of potent adjuvants is the combination of immunostimulatory adjuvants with particulate ones such as AS01®, AS02®, and AS03® (see Table 3) to produce a synergistic or additive effect thereby enhancing the immune response [23].

Most of the adjuvants in the first category which are pathogen-associated molecular patterns (PAMPs), are highly conserved in a broad range of pathogens [24]. The immune system recognizes PAMPs and the endogenous receptors bind microbial ligands including cell wall components, lipoproteins, proteins, lipopolysaccharides, DNA and RNA of bacteria, viruses, protozoa, and fungi to trigger different types of immune responses. These PAMPs