Vaccine (2008) **26**, 2043–2055

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vaccine

REVIEW

Archaeosome adjuvants: Immunological capabilities and mechanism(s) of action

Lakshmi Krishnan*, G. Dennis Sprott

National Research Council-Institute for Biological Sciences, Ottawa, ON, Canada K1A 0R6

Received 9 November 2007; received in revised form 11 January 2008; accepted 8 February 2008
Available online 27 February 2008

KEYWORDS
Adjuvants;
Antigen delivery systems;
Liposomes;
CD8 T cell response;
Immune memory;
Antigen presentation;
Vaccination

Summary Archaeosomes (liposomes comprised of glycerolipids of *Archaea*) constitute potent adjuvants for the induction of Th1, Th2 and $CD8^+$ T cell responses to the entrapped soluble antigen. Archaeal lipids are uniquely constituted of ether-linked isoprenoid phytanyl cores conferring stability to the membranes. Additionally, varied head groups displayed on the glycerol–lipid cores facilitate unique immunostimulating interactions with mammalian antigen-presenting cells (APCs). The polar lipid from the archaeon, *Methanobrevibacter smithii* has been well characterized for its adjuvant potential, and is abundant in archaetidyl serine, promoting interaction with a phosphatidylserine receptor on APCs. These archaeosomes mediate MHC class I cross-priming via the phagosome-to-cytosol TAP-dependent classical processing pathway, and also upregulate costimulation by APCs without overt inflammatory cytokine production. Furthermore, they facilitate potent $CD8^+$ T cell memory to co-delivered antigen, comparable in magnitude and quality to live bacterial vaccine vectors. Archaeosome vaccines provide profound protection in murine models of infection and cancer. This technology is being developed for clinical application and offers a novel prospect for rational design and development of safe and potent subunit vaccines capable of eliciting T cell immunity against intracellular infections and cancers.

Contents

* Corresponding author at: National Research Council-Institute for Biological Sciences, 1200 Montreal Road, Building M-54, Ottawa, ON, Canada K1A 0R6. Tel.: +1 613 991 3210; fax: +1 613 941 4475.
E-mail address: Lakshmi.Krishnan@nrc-cnrc.gc.ca (L. Krishnan).

0264-410X/$ – see front matter.
doi:10.1016/j.vaccine.2008.02.026

Introduction

A holy grail of vaccinology is to design and develop potent vaccines capable of evoking a strong cell-mediated immunity, in particular $CD8^+$ T cells. Such a response is imperative for effective vaccines against diseases such as HIV/AIDS, tuberculosis and malaria which are the major infectious disease killers in the world today [1]. Induction of $CD8^+$ T cell immunity is also considered critical for cancer immunotherapy aimed at harnessing one's own immune system to eliminate malignant cells [2]. Thus far, live bacterial and viral non-pathogenic recombinant vaccine vectors have remained the best choice for induction of cell-mediated immunity, particularly $CD8^+$ T cell responses [3–5]. However, such vaccines can be rendered ineffective by pre-existing vector-specific antibodies [6] and/or inflammation due to other infections [7]. Furthermore, such vaccines may induce overt inflammation leading to T cell exhaustion or anergy. Live vectors can also be underattenuated posing a risk of reversion to virulence [8]. Moreover, live vaccines contribute to erosion of previously accumulated memory against disparate antigens [9]. The burgeoning of genomics and proteomics has facilitated the identification of key immunodominant antigens of various pathogens and tumors. Thus, there is an urgent need for new candidate acellular vaccine delivery systems and adjuvants for bolstering subunit antigen-specific cell-mediated immunity and T cell memory.

We have developed a novel vaccine adjuvant strategy constituted by the polar lipids of *Archaea*. The term ''archaeosomes'' ascribed to this delivery system brings together the concept of ''archaea and liposomes''. The distinct features of archaeosomes include: ether polar lipid structures leading to immunopotentiating interactions with the antigen-presenting cells (APCs), ability to direct antigen cargo for MHC class I processing leading to potent induction of $CD8^+$ T cell response, and stability of archaeal lipid cores facilitating profound immune memory. Over several years, we have revealed the varied immunological capabilities of archaeosomes and mapped the mechanisms of action. We herein provide a comprehensive review of archaeosome adjuvants in comparison to conventional ester lipid liposomes and live bacterial vectors. Challenges in commercial development of archaeosomes and perspectives for future improvement are discussed.

Characteristics of T cell immunity

Two signals need to be coordinated for induction of a strong T cell response: signal 1, the interaction of the T cell receptor with the antigen presented in the context of the appropriate MHC molecule, and signal 2, antigen-independent costimulation delivered by the activated APC. The perception of ''danger signal'' by the APC often leads to signal 2 activation, thus linking the innate and adaptive arms of the immune system.

Adjuvants are additives that have been long-used empirically for facilitating APC activation and thus boosting the immune response to co-administered antigen. The new found knowledge that interaction of pathogen-derived molecular patterns (PAMPs) with mammalian APCs via innate immune receptors provides an efficient natural mechanism for host defense against ''danger'' is driving a more rational quest for novel molecular adjuvants [10]. In this context, particulate antigen delivery systems offer many advantages: ability to, target antigen for processing by the APC, provide an antigen-depot that may facilitate long-term memory, and provide immunostimulation often by acting as passive carriers for other PAMPs. Several adjuvants can be included in this category: liposomes, polymeric microspheres, nano-beads, virus-like particles, saponin-immunostimulating complexes (ISCOMS), niosomes, and proteosomes [11–14]. Archaeosomes fall in this category but advantageously are able to self-adjuvant immune responses in the absence of other extraneous PAMP moieties.

Naïve $CD8^+$ T cells are stimulated when peptides from endogenously derived antigens are presented in the context of MHC class I molecules. Although this process can occur virtually in all cells, only peptides derived from intracellular proteins being assembled within the cell are presented efficiently on MHC class I [15]. In contrast, protein antigens from the extracellular fluids that are taken up by APCs through pinocytosis are fragmented within endosomes. The peptides generated are presented in the context of MHC class II molecules to stimulate $CD4^+$ T cells [16]. $CD4^+$ T helper cells differentiate into two phenotypes based on their cytokine secretion patterns: Th1 cells secrete IL-2, IFN-γ, TNFα and elicit inflammatory responses, and aid $CD8^+$ T cell function, whereas Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13 to support B cell proliferation and production of specific antibodies [17].

Following the effector phase of the response >90% of the primed T cells undergo elimination, whereas a small proportion survive to provide long-lived memory [18]. However, memory T cells are of heterogeneous phenotype, and whether their differentiation is linear or parallel is still a subject of controversy [19]. Nevertheless, while activated T cells lower their expression of IL-7Rα, antigen-experienced memory T cells are IL-7Rα^{hi} and $CD44^{hi}$ [20]. Furthermore,