Chapter 1

Introductory Chapter: Immunization - Vaccine Adjuvant Delivery System and Strategies

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Additional information is available at the end of the chapter

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1. Introduction

Immunization plays a key role in maintaining human health as it saves millions of lives in the most economical way from lethal pathogens and other fatal diseases each year, thanks to the advanced development of model vaccines, which are biological preparations containing an antigenic agent that resembles a disease-causing microorganism to stimulate the host's immune system, thus providing active acquired immunity to a particular disease and destroying it [1, 2]. Since Jenner's pioneering inoculations in the late eighteenth century, vaccines have been successfully developed to combat various diseases and each year saved numerous lives from, mostly, lethal infections and now also certain cancers [3, 4]. Especially, taking advantage of the tools discovered in microbiology and immunology, vaccines have recently obtained great achievements as demonstrated by their successful performances in conquering some formidable pathogens, such as smallpox and rabies, which are used to claim many lives. However, the list of pathogens for which there exist no vaccines is still long, and, in particular, many pathogens, such as human immunodeficiency virus (HIV), herpes simplex virus (HSV), and Ebola virus (EBV), are still posing a big threat to human life, therefore needing urgently the effective products to cope with their infections [5].

Vaccines can stimulate the host immune system to develop an armament of immunity capable of clearing the abnormalities after administration, because they are developed with the antigenic components that are featured by pathogens or neoplasms and usually include three types: the live attenuated microbes, killed microbes, and just purified antigens (Ags) of microbes or neoplasms [6]. The former two consisting of live attenuated or killed microbes are the conventional vaccines with high immunogenicity but, unfortunately, are also linked to a relatively poor safety profile as they possess the potential to revert the virulence and induce the drifted immune responses leading to incontrollable immunity as well as unacceptable inflammations. In contrast, the third one with purified Ags, called a subunit vaccine, has

defined components to induce immune responses aiming just at the matched targets causing few safety concerns and thus can be employed to fight the infectious pathogens as well as malignant neoplasms that are carrying the identical Ags [7]. Presently, subunit vaccines are attracting more and more research interests owing to also their diverse applications, adaptive functions, and numerous advantages over the whole microbe-based conventional ones, and these aspects may well be comprehensively summarized as follows [8]:

1. Their defined noninfectious components effectively confine capricious reversion to virulence while reducing significantly the risk of allergic or autoimmune response [9].
2. Their production may avoid the use of dangerous microorganisms but may be carried out with solid-phase peptide synthesis in a reproducible, scalable, and economical manner, providing an alternative tool to obtain products to conquer certain pathogens that are problematic to culture (e.g., sporozoites for malaria vaccines) for attenuation of virulence [10].
3. Ags in subunit vaccines are generally water-soluble allowing them to form a solution together with cryoprotectants such as disaccharide, followed by freeze-drying into the stable anhydrous fitting storage and transportation in a controlled temperature chain (CTC) or completely at room temperature [11].
4. Also, subunit vaccines can be tailored with certain pathogen-/damage-associated molecular patterns (PAMP/DAMP) to be recognized by APCs for efficient activation, even including several peptide epitopes targeting different stages in the life cycle of a pathogen [8, 12, 13]; obviously, this is particularly useful for developing anticancer vaccines, wherein whole protein can hardly be used due to its similarity to the endogenous human proteins and carcinogenic properties [14].

However, unfortunately, subunit vaccines often have a rather weak immunogenicity, due to lack of the immunostimulatory components broadly shared by pathogens while being distinguishable from host molecules, which are collectively referred to as pathogen-associated molecular patterns (PAMPs) [15] able to bind to and trigger mammalian pattern recognition receptors (PRRs), such as the TLRs (toll-like receptors), NOD-like receptors (the nucleotide-binding oligomerization domain-like receptors), RIG-I-like receptors (retinoic acid-inducible gene-I-like receptor), and C-type lectin receptors, thus playing an adjuvant role to activate the innate immunity, followed by sponsoring a series of adaptive reactions involved in establishing the Ag-specific immunity [16].

Thus, while subunit vaccines are regarded as a safer product than the whole microbe-based conventional ones, they are also poorly immunogenic and often require an adjuvant or a vaccine adjuvant-delivery system (VADS) able to target the professional Ag-presenting cells (APCs), such as dendritic cells (DCs) and macrophages (MPs), to make full use of Ags and boost their immunostimulatory activity [17–21]. A vaccine adjuvant is defined as a non-specific immunopotentiating substance but capable of enhancing the body's immune response to the Ag or changing the type of immune responses, when administered either alone in advance or simultaneously together with the vaccine Ag. Although its immune-boosting mechanisms remain elusive, an adjuvant is argued to fulfill the functions involving, roughly, two aspects: (1) generating damages on host cells/tissues, thus sending dangerous signals out to activate

the immune system and (2) binding to PRRs and exciting the innate immune cells, such as DCs, MPs, histiocytes, and mast cells, which subsequently initiate the innate immune responses to sponsor the subsequent adaptive immune responses [22, 23]. Accordingly, vaccine adjuvants may well be classified into two types: type I, the natural or synthetic substances with intrinsic adjuvanticity, squalene/squalane, saponin, chitosan, hyaluronic acid (HA), and various pattern recognition receptor agonists (PRRas) and type II, the micron-/nanometer-sized particles, such as alum (insoluble aluminum salt) and vaccine adjuvant-delivery systems (VADSs) that are carriers engineered with at least two fundamental functions, i.e., adjuvanticity and Ag delivery. VADSs are usually constructed with a variety of biocompatible nanoparticles (NPs) made of various organic or inorganic materials, such as liposomes, ISCOMs (immune-stimulating complexes), polymeric NPs, VLPs (virus-like particles), emulsions, and the inorganic NPs, which are often incorporated with type I substances to further enhance their immunopotentiating functions [6, 24].

2. Immune responses for establishing the Ag-specific immunity

Always confronting and fighting with dangerous pathogens, mammals have gradually evolved to form a complexed defensive immune system, which can be classified into subsystems of the innate immune system versus the adaptive immune system [25]. The innate immune system consists of surface barriers, complement system, and various leukocytes including the phagocytes (macrophages, neutrophils, and dendritic cells), innate lymphoid cells, mast cells, eosinophils, basophils, and natural killer cells, which fulfill the role of non-specific immune defenses responding to pathogens in a generic way conferring short-lasting immunity against a pathogen [26]. For this, mammalian leukocytes are evolutionarily equipped with receptors able to recognize certain pathogen components bearing specific structural characteristics, such as free bacterial and viral DNA, lipoproteins, lipopolysaccharides, and flagellins, which are pathogen-/danger-associated molecular patterns (PAMPs/DAMPs) [27]. These functional receptors are expressed by host immune cells, such as TLR1 to TLR13, NOD-like receptors, RIG-I-like receptors, and C-type lectin of mannose receptors, which are collectively called pattern recognition receptors (PRRs), with each capable of selectively binding to specific PAMPs/DAMPs of pathogens, leading to the activation of the innate immune cells, which subsequently sponsor the immuno-responses of the whole immune system, thus providing the bases for defending against pathogens [28].

However, establishing the Ag-specific immunity for defending against pathogens involves several complex immune pathways going with the orchestration of numerous immunocytes, cytokines, and chemokines and starts, usually, upon the activation of APCs for innate immune reactions triggered by their internalized antigenic substances (Ags) that they distinguished as dangerous signals through, in most cases, the process of PRR-PAMP/DAMP recognition [23]. Briefly, positioned at the frontier of pathogen/vaccine recognition, APCs first take up, in a size-dependent manner (e.g., NPs with a size of <150 nm are taken up by APCs by clathrin-mediated endocytosis, while microparticles by phagocytosis); the Ags appeared in peripheral tissues or in the draining lymph nodes (dLNs), wherein APCs will mature and process the

internalized Ags into pieces with epitopes, which are finally bound to MHC-II (major histocompatibility complex II) and/or MHC-I and displayed on cell surfaces for presentation to T cells [29]. MHC-I molecules are assembled in the endoplasmic reticulum (ER) with stabilization by chaperone proteins (including calreticulin, Erp57, protein disulfide isomerase (PDI), and tapasin) and are loaded, under tapasin mediation, with exogenous (viral or self-originated) Ags, which are translocated from the cytoplasm into the ER by TAP (transporter associated with antigen presentation) for presentation via T-cell receptors (TCRs) to $CD8^+$ T cells for their activation [30]. MHC-II molecules are assembled in the ER, stabilized by an invariant chain (Ii) and transported through the Golgi to fuse with a late endosome forming the MHC-II endosome compartment (MIIC) with an acidic interior containing proteases cathepsin S and cathepsin L, which when activated will digest Ii, leaving in the peptide-binding groove of the MHC-II a residual class II-associated Ii peptide (CLiP), which later is exchanged for an antigenic peptide (usually exogenous Ags) derived from a protein degraded in the endosomal pathway for presentation via T-cell receptors (TCRs) to $CD4^+$ T cells for their activation [30].

During Ag presentation, a substantial number of various signaling cytokines such as interleukins and interferons, as well as chemokines, are secreted by matured APCs and other immunocytes to promote the MHC-II-Ag epitope-triggered $CD4^+$ T-cell differentiation into either T-helper type-1 (Th1) cells that will secrete IFN-γ, IL-12, and IL-2 or Th2 cells that will secrete IL-4. Then, Th1 cells will further secrete IL-12 and IFN-γ facilitating the MHC-I-Ag epitope-triggered $CD8^+$ T cells to proliferate and differentiate into the Ag-specific cytotoxic T lymphocytes (CTLs), thus establishing the cellular immunity while forming memory T cells [31, 32]. Meanwhile, the Th2 cells mature to favor Ag presentation to B cells via B cell receptors (BCRs) and to secrete IL-4, IL-6, and IL-10, which are also beneficial for promoting the Ag-activated B cells to proliferate and differentiate into plasma cells to produce the anti-Ag antibodies, establishing finally the humoral immunity while forming memory B cells [33]. With memory T and B cells, upon encountering pathogens, both humoral and cellular immunity can be rapidly established; while humoral immunity neutralizes the extracellular pathogens during or before the infection and thus is fitting for the prophylaxis of pathogen invasion, cellular immunity is mainly responsible for destroying already infected or abnormal human cells and therefore may be employed for the clearance of the cell-hidden pathogens or malignant tumors, through specialized TCR recognition of the precisely matched Ags nestled in the groove of MHC-I on cells [12].

3. Immunization: vaccine adjuvant-delivery system and strategies

In designing the NP-based VADSs, what should be emphasized is that the differently sourced Ags are processed and trigger immune signal transduction in different ways [34]. Usually, the internalized exogenous Ags delivered by NPs are processed intracellularly by APCs into small antigens just inside the endolysosomal vesicles and then loaded favorably on MHC-II molecules, leading to activation of CD4+ T cells to differentiate into Th2 cells, which will further stimulate production of antibodies by B cells [8]. In contrast, the endogenous Ags, such as viral Ags, cancer components, and intracellular-degraded proteins, are usually presented in the cytosol and often

loaded on MHC-I molecules, allowing for further activation of $CD8^+$ T cells to differentiate into CTLs and to engender cellular immunity [35]. However, it is generally believed that, though not well understood, provided the exogenous Ags are transported via membrane fusion or other ways engendering Ag lysosome escape into the cytosol, they can also be processed via MHC-I presentation in just the same manner as that for endogenous Ags, and this process is known as Ag cross presentation [36]. This provides the basis for designing the NP-based VADS which are exogenous particles favoring of inducing humoral immunity but may be adorned with materials that can facilitate APC internalization in the membrane fusion manner or promote endolysosome escape and cross presentation of Ags to induce cellular immunity, thus expanding VADS into various applications, including mainly prophylaxis of infections, treatment of autoimmunity diseases, and immunotherapy of cancer [12]. In particular, as a multifunctional VADS, NPs modified with different materials with intrinsic and specific adjuvanticity, such as TLRas (e.g., MPL and CpG ODN), squalene, and saponin (e.g., water-soluble QS-21), though showing individually distinctive features, share some key characteristics in immune-boosting functions [37]. Summarily, these multifunctional Nps as a VADS trigger immunoresponses with features including, mainly, early activation, though at different levels, of innate immunity, which will subsequently translate into strong antibody and cellular responses to the delivered antigens [5]; a wide breadth of adaptive immunity is able to confer protections against heterovariants of pathogens; for example, vaccines delivered by liposomes containing MPL can defend against influenza viruses or human papillomavirus (HPV) strains that are not contained in the vaccines [38]; significant enhancement of the immunoresponses and the efficacy of vaccines in the elderly who show a waning immune responsiveness to infection and vaccination, as shown for vaccines formulated with MPL-liposomes against herpes zoster virus [39]. These results, together with the feasibility of large-scale manufacture and the track records of acceptable safety profiles of many liposome-based medications, pave the way for developing novel multifunctional liposomes to be used as a VADS for producing the vaccine products fitting humans of different age against infections with a high toll of morbidity and mortality.

Conflict of interest

All the authors declared no conflict of interest.

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