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Research review paper

Harnessing self-assembled peptide nanoparticles in epitope vaccine design

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ABSTRACT

Vaccination has been one of the most successful breakthroughs in medical history. In recent years, epitope-based subunit vaccines have been introduced as a safer alternative to traditional vaccines. However, they suffer from limited immunogenicity. Nanotechnology has shown value in solving this issue. Different kinds of nanovaccines have been employed, among which virus-like nanoparticles (VLPs) and self-assembled peptide nanoparticles (SAPNs) seem very promising. Recently, SAPNs have attracted special interest due to their unique properties, including molecular specificity, biodegradability, and biocompatibility. They also resemble pathogens in terms of their size. Their multivalency allows an orderly repetitive display of antigens on their surface, which induces a stronger immune response than single immunogens. In vaccine design, SAPN self-adjuvanticity is regarded an outstanding advantage, since the use of toxic adjuvants is no longer required. SAPNs are usually composed of helical or β-sheet secondary structures and are tailored from natural peptides or *de novo* structures. Flexibility in subunit selection opens the door to a wide variety of molecules with different characteristics. SAPN engineering is an emerging area, and more novel structures are expected to be generated in the future, particularly with the rapid progress in related computational tools. The aim of this review is to provide a state-of-the-art overview of self-assembled peptide nanoparticles and their use in vaccine design in recent studies. Additionally, principles for their design and the application of computational approaches to vaccine design are summarized.

1. Introduction

For hundreds of years, vaccination has been one of the most successful strategies to combat different infectious diseases and, consequently, decrease morbidity and mortality among humans (Skwarczynski and Toth, 2011, 2014). Edward Jenner was the first to vaccinate against smallpox in 1796. Jenner found that an inoculation of the pus from a cowpox lesion on a handmaid's hand to patients infected with smallpox conferred immunity (Stern and Markel, 2005). The aim of every vaccination is to present a particular antigen or set of antigens to the immune system in order to elicit immunity to the pathogen. In addition to the efficient elicitation of immune response, the ideal vaccine should be safe, show long-term stability at ambient temperatures, demonstrate high population coverage, and provide protection after the administration of a single dose. Moreover, the manufacturing, purification, and characterization processes should be effective, require a minimal number of steps, and be affordable to enable broad vaccine use.

The oldest type of vaccines or traditional vaccines consist of either live attenuated and killed microorganisms or inactivated toxins (Skwarczynski and Toth, 2011). The development of these vaccines uses the whole organisms, which is why they are more effective and elicit long-lasting innate and adaptive immune responses (Karch and Burkhard, 2016). Despite these benefits, traditional vaccines have some disadvantages, such as a risk of infection, probability of allergic and autoimmune reactions, and difficulties related to culture, production, and stability. Moreover, they cannot be developed for some diseases, such as cancer and several infectious diseases. Therefore, a new type of vaccines, named subunit vaccines, has been developed that has many advantages compared to the whole organism-based vaccines, including a lack of pathogenic organisms, safety, ease of production, stability, and low allergic and autoimmune responses. Hence, these vaccines are considered efficient (Skwarczynski and Toth, 2011, 2014). Based on the mentioned merits, many researchers, including our team, have worked

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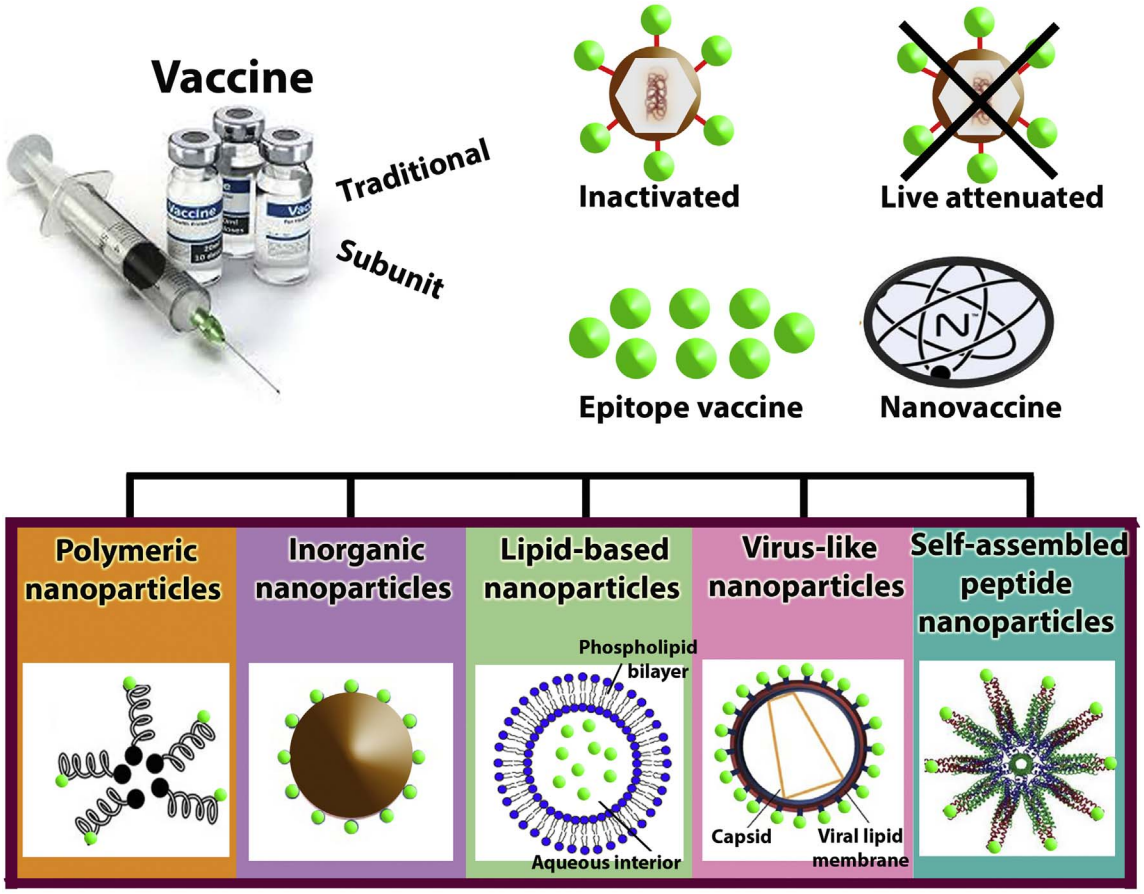

Fig. 1. Several classified nanovaccines according to the types of nanoparticles applied in their structures.

extensively on the development of these types of vaccines (Farhadi et al., 2015; Hajighahramani et al., 2017; Mahmoodi et al., 2016; Nezafat et al., 2017; Nezafat et al., 2014; Nezafat et al., 2016; Shahbazi et al., 2016).

2. Epitope-based subunit vaccines

Subunit vaccines only contain the antigenic fragments of pathogens, which are most frequently protein-based antigens that are capable of stimulating appropriate adaptive immune responses. Some limitations, namely instability, production complexity, low purity, and most importantly, the induction of an autoimmune response, are observed more frequently in protein-based subunit vaccines than in epitope-based subunit vaccines; therefore, epitope-based subunit vaccines are often preferred. They are composed of multiple individual antigenic epitopes from one or several pathogens (Azmi et al., 2014; Nezafat et al., 2017; Skwarczynski and Toth, 2011). These epitopes usually consist of B-cell epitopes, helper T-cell (Th) epitopes, and cytotoxic T-cell (CTL) epitopes. After binding to B-cell receptors (BCRs), B-cell epitopes are activated in two ways: in the presence of Th cells or in a T-cell-independent manner. Generally, in the T-cell-independent pathway, activated B-cells cannot produce long-lasting B-cell responses. During the first step, both types of T-cell epitopes are processed by antigen-presenting cells (APCs), including dendritic cells (DCs), macrophages, and B-cells. Exogenous particles, such as toxins and bacterial pathogens, located on the cell surface are processed and presented to Th cells by *major histocompatibility complex* II (MHC-II). Afterwards, the activated Th cells directly or indirectly stimulate B-cells and CTLs and promote the secretion of cytokines and chemokines; therefore, active Th cells stimulate both adaptive immune and innate immune responses. Endogenous particles, such as viral particles and cancerous cells, which are located in the cytosol, are processed and presented to CTLs by MHC-I. The activated CTLs kill the intracellular pathogens and tumor cells by inducing cell-mediated immunity (Moyle and Toth, 2013; Skwarczynski and Toth, 2014). Thus, when designing most epitope-based subunit vaccines, researchers must identify both T-cell and B-cell epitopes to induce appropriate immune responses; however, low immunogenicity is the major drawback of these types of vaccines. Thus, due to the lack of the whole organism, the ability of these vaccines to stimulate immune responses is much weaker than traditional vaccines. Different approaches have been applied to boost the immunogenicity of subunit vaccines, including the administration of multiple doses of vaccine during the patient's life for long-lasting protection, the use of adjuvants, or the employment of nanotechnological approaches, *i.e.*, designing nanovaccines (Moyle and Toth, 2013). Adjuvants are additional components in vaccines that stimulate APCs and target the innate immune system; in this way, they induce a robust immune response (Foged, 2011). Adjuvants are classified into three groups: 1) delivery systems composed of non-immunostimulatory components, which target and present the vaccine to the immune system, 2) immunostimulators, such as pathogen-associated molecular patterns (PAMPs), which directly stimulate the innate immune system, and 3) a combination of the two mentioned classes, which has the highest efficiency (Foged, 2011; Moyle and Toth, 2013). Many research groups have attempted to develop effective adjuvants, but only few adjuvants are being used in vaccine production due to several disadvantages, including low safety and high toxicity. Adjuvants approved for use in human are aluminum salts (alum), the first approved and a widely-used adjuvant, oil-in-water emulsions (MF59, AS03, and AF03), virosomes, and AS04 (a formulation of monophosphoryl lipid A (MPL) and alum) (Foged, 2011; Karch and Burkhard, 2016).

One promising area that is rapidly gaining attention is the use of