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Review

Major findings and recent advances in virus–like particle (VLP)-based vaccines

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ABSTRACT

Virus-like particles (VLPs) have made giant strides in the field of vaccinology over the last three decades. VLPs constitute versatile tools in vaccine development due to their favourable immunological characteristics such as their size, repetitive surface geometry, ability to induce both innate and adaptive immune responses as well as being safe templates with favourable economics. Several VLP-based vaccines are commercially available including vaccines against Human Papilloma Virus (HPV) such as Cervarix®, Gardasil® & Gardasil9® and Hepatitis B Virus (HBV) including the 3rd generation Sci-B-Vac™. In addition, the first licensed malaria-VLP-based vaccine Mosquirix™ has been recently approved by the European regulators. Several other VLP-based vaccines are currently undergoing preclinical and clinical development. This review summarizes some of the major findings and recent advances in VLP-based vaccine development and technologies and outlines general principles that may be harnessed for induction of targeted immune responses.

1. Introduction

Vaccines remain the most cost effective and successful intervention in controlling and preventing infectious diseases [1]. Until 1980s, traditional vaccine strategies were mainly based on attenuated or inactivated viruses. These strategies have shown good efficacy at inducing potent immune responses in the host characterized by efficient B and T cell responses as well as long lived immunity [2]. However, due to several drawbacks in traditional vaccine strategies such as difficulties in production and safety issues causing contraindications in immune-deficient patients, alternative ways for vaccine development were searched for.

In general, traditional vaccines −based on attenuated or inactivated viruses- have shown superb immunogenicity; mainly due to several key parameters including 1) replication ability of attenuated viruses 2) their repetitive surface geometry 3) particulate nature and 4) ability to stimulate innate and adaptive immune responses. These parameters serve here as paradigms to successful development of vaccines based on virus-like particles (VLPs) [3].

VLPs are multi-protein supra-molecular structures and carry many characteristics of viruses that can be harnessed in vaccine development strategies [1]. VLP-based vaccines therefore exhibit most of the traditional vaccines‘ parameters but exclude their ability to replicate as they lack a viral genome, rendering them a safe template for vaccine development. Most VLPs have a shell constructed of several identical protein copies forming icosahedral or helical (rod-shaped) structures. [4]. VLPs can be produced in more than 170 different expression host systems including bacteria, insect, yeast or mammalian cells, reflecting in part the broad host-spectrum of the viruses which VLPs are derived from [5]. Almost 30% of VLPs are produced in bacterial systems (mainly *E. coli*), where the genes of viral structural proteins are codon-optimized for bacteria and cloned into commercial plasmids under strong promoters. This process ensures high production of the desired recombinant proteins (S. [6,7]. *E. coli* is mostly used for production but

Abbreviations: VLP, virus-like particle; CCMV, cowpea chlorotic mottle virus; HBV, hepatitis B virus; PASP, pathogen associated structural pattern; BCR, B cell receptor; APC, antigen presenting cell; LN, lymph node; SCS, sub capsular sinus; DC, dendritic cell; cDC, conventional dendritic cell; FDC, follicular dendritic cell; IgM, immunoglobulin M; MHC-II, major histocompatibility class-II; MHC-I, major histocompatibility class-I; TLR, toll like receptor; Lys, lysine; a.a., amino acid; NHS, N-hydroxysuccinimide; TAA, tumor associated antigen; Qβ, bacteriophage Qβ; Cys, cysteine; SMPH, succinimidyl 6-(beta-Maleimidopropionam DBCO Dibenzocyclooctyneido) hexanoate; CPMV, cowpea mosaic virus; Tyr, tyrosine; DBCO, dibenzocyclooctyne; HBcAg, : Hepatitis B Core Antigen; MIR, : Major Immunodominant Region; CSP, :Circumsporozoite Protein; Asp, aspartic acid; Glu, glutamic acid; Asn, asparagine; Gln, glutamine; pDC, plasmacytoid dendritic cell; IFN, interferon; HBsAg, hepatitis B surface antigen; CHO, Chinese hamster ovary; CLP, capsid like protein; TMV, tobacco Mosiac Virus; LCMV, lymphocytic choriomeningitis virus; M1, matrix protein; HA, hemagglutinin; NA, neuraminidase

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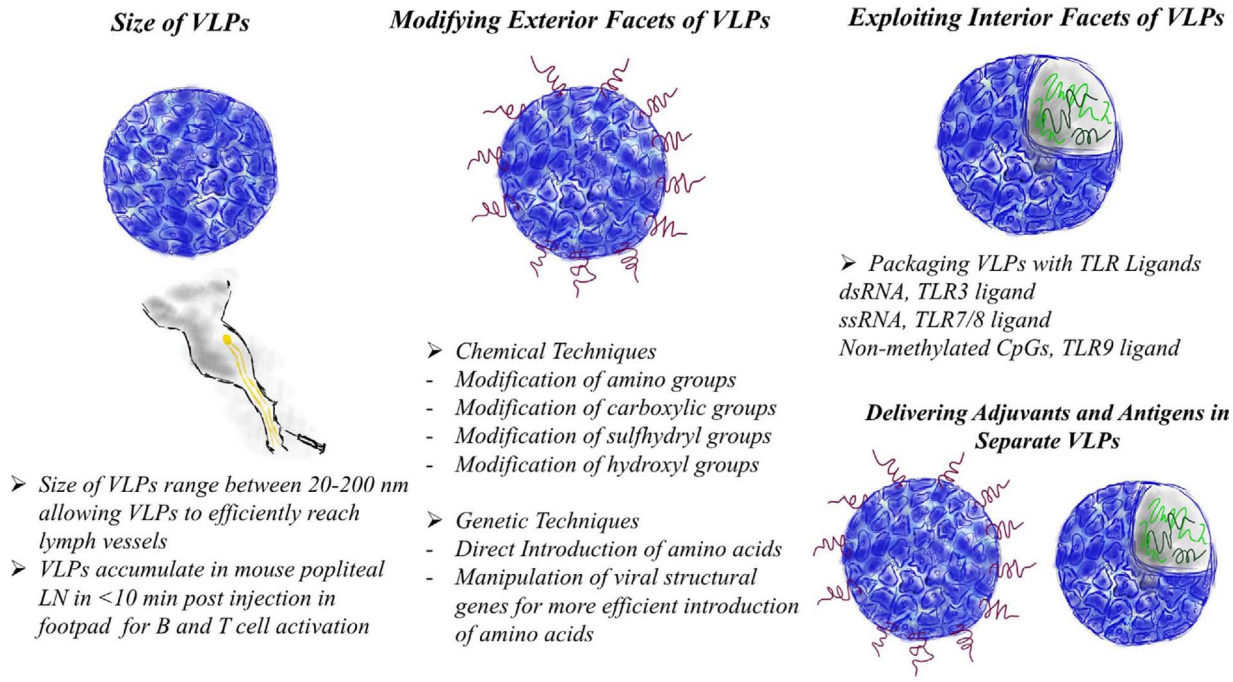

Fig. 1. Major Findings in VLP-based vaccine development and technologies. Importance of VLPs size, modifying exterior facets of VLPs, exploiting interior facets of VLPs and delivering adjuvants and antigens in separate VLPs.

Pseudomonas and *Lactobacillus* have also been used to produce cowpea chlorotic mottle (CCMV-VLPs) and human papilloma virus (HPV L1-VLPs), respectively, for vaccine development [8,9]. The drawbacks of bacterial host systems are that they are unable to introduce post-translational glycosylation modifications in the eukaryotic proteins and the recombinant protein may be contaminated with endotoxins [10]. However, in many circumstances, glycosylation of proteins is not necessary for the induction of protective antibodies and some bacterial strains able to confer glycosylation at specific protein sites have been developed [11]. Experience with VLP-glycosylation appears, however, limited. Endotoxin contamination usually is not a major problem as it may be removed by a simple polishing step [12]. Yeast host expression systems have also been broadly utilized for efficient VLP production such as in the case of the commercially available vaccines against HPV and hepatitis B virus (HBV) [13,14]. Insect and mammalian cell systems have also been used since 1980s for the production of VLPs and more recently, plant cells have been added to the expression tool-box [5]. In general, VLPs can often be rapidly and efficiently produced in vast quantities under optimized cultural conditions. Following successful expression, VLPs will self-assemble into the final shape which usually imitates the symmetry of the original parental virus [15]. Some limitations may apply, as VLP expression in eukaryotic systems may overall be less efficient than if prokaryotic systems are used and long-term stability is often an underestimated parameter for the practical success of a VLP-based vaccine. Virus core proteins sometimes can also be assembled into VLPs; HBV serves as an example of this category where core proteins undergo allosteric alterations during the VLP assembly process ensuring a stable and efficient formation of the viral capsid [5,16].

In general, all VLPs finally form a unique repetitive surface structure making them highly immunogenic vaccine templates. The rigid and repetitive surface structure is a unique and potent geometric pathogen associated structural pattern (PASP) which facilitates cross-linking of B cell receptors (BCRs). Indeed, epitopes displayed in a rigid fashion on a nanoparticle are clearly more immunogenic than the same epitopes displayed repetitively on a flexible polymer [15,17]. Furthermore, many components of the innate humoral immune system are multimeric (pentamer/decamer), which greatly facilitate binding to repetitive structures with high avidity. This causes effective opsonization and uptake of VLPs by antigen presenting cells (APCs) which subsequently augments the adaptive arm of the immune system [18]. The predominant subsets of APCs actively taking up VLPs in the popliteal lymph nodes (LNs) 24 h after injection in the footpad of murine models have been recently classified [19]. These cells include the sub capsular sinus (SCS) macrophages $CD11b^+CDF4/80^+$, different subsets of cDCs including $CD8^-CD11c^+$, $CD8^-CD11b^+$ and $CD8^+CD11c^+$ and finally B cells characterized by ($CD45R^+/B220^+$) [19]. VLPs are also capable of binding natural IgM molecules efficiently and fixing C1q molecule, a process leading to their deposition on follicular DCs (FDCs) [20]. In addition, DCs can capture VLPs in the T cell zone resulting in the activation of the cells in the extrafollicular area [21]. As the innate immune system, including natural IgM and complement, has evolved to recognize particulate and repetitive structures such as VLPs, it may not be necessary to additionally modify VLPs for targeted uptake by DCs to enhance T cell priming and immune responses in general. This may be different, however, if VLPs are used to target drugs to e.g. cancer cells, where a specific label for recognition of cancer cells is desirable [22].

VLP-based vaccines have mainly been designed to target B cells and induce potent antibody responses following activation of T helper cells and presentation on MHC class II molecules by APCs. Yet, antigen-presentation by VLPs is not restricted to MHC class II molecules but is extendable to MHC class I molecules for effective presentation and priming of $CD8^+$ T cells. Their particulate structure and size facilitate their efficient cross-presentation of VLP-derived peptides on MHC class I molecules [23,24]. This phenomenon constitutes an additional advantage of VLP-based vaccines and has been extensively utilized when designing therapeutic VLP-based vaccines for the treatment of cancer and chronic diseases [25–28].