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Virus-Like Particles: A future candidate vaccine in livestock and poultry

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Introduction

Virus like particle (VLP) which mimic conformation of native virus with multi structural protein component but lack viral genome yielding safer vaccine even without adjuvant. VLPs are not having drawbacks of live attenuated vaccines like reversion, re-assortment and recombination as it is not having genome. Due to its expression of characteristic surface of viruses (capsid protein), it can elicit strong humoral immune response by cross linking B-cell receptor results in production of antibodies against capsid proteins. It is also strong enough to produce Tcell –independent IgM antibodies (Brun et al., 2011) and cytotoxic T lymphocyte responses (Gamvrellis et al., 2004).

Production of VLPs

Most of the VLPs are produced for variety of viruses using the baculovirus expression system because of its high expression level and the ability to form VLPs with multiprotein . Apart from baculovirus, other expression systems like Yeast (for HBV), mammalian cells, E.coli and vaccinia virus also used for development of VLPs. Production of VLPs for multiple interacting capsid proteins is challengeable than VLPs formed by one type of major protein. Co-expression and self assembly of several capsid proteins enable the production of VLPs without viral genome and similar to authentic viral particles. Large amount of recombinant proteins at high density cell culture conditions in baculovirus expression system gives the advantage of large scale VLP based vaccine production.

Advantages of VLPs from whole virus and recombinant subunit vaccines,

a. No need to propagate pathogenic organisms
b. Repetitive and ordered surface structures
c. Multivalent as well as particulate in nature
d. As they are non-infectious and non-replicating , they are safer than other vaccines
e. Stable in extreme environmental conditions
f. Can be used as carrier to express foreign antigen
g. Can be used for DIVA strategy as they are not expressing nonstructural protein.

How VLPs works

a. High order and multivalent structure expression simulate the PAMPs (unique to microbial antigen) trigger innate immune system through TLRs and PRRs (Plummer and Manchester, 2011).

b. Induce strong humoral response by cross-linking BCR by its repetitive surface structure and also elicit IgM in T-cell independent way (Bachmann and Zinkernagel, 1997).
c. PAMPs property and particulate nature of VLPs enhance the uptake, processing and presentation by APCs especially dentritic cells through MHC-II and MHC-I (cross-presentation) pathway.

VLP based vaccines in human and veterinary field

Vaccines for Hepatitis B (Recombivax® and Engerix®) And Human Papillomavirus (Gardasil® and Cervarix®) are available commercially. For other diseases like hepatitis C virus, Ebola, Marburg, Hantavirus, Lassa virus, SARS and Chikungunya viruses, VLP based vaccines are in progress. In case of animal disease, though several vaccines are in the study, the only licensed and commercially available vaccine is for porcine circovirus type 2 (Porcilis PCV®) and for classical swine fever (Bayonac® CSF) also it is in current use (Meeusen et al., 2007). There are several VLP based vaccines (Table 1) which are in developmental stage as well as in animal studies for number of livestock and poultry diseases.

Table 1. Few important VLP based vaccines in veterinary field (Crisci et al., 2012)

Pathogen	Components	Expression system	References
IBDV	VP2, VPX, PP	Baculovirus	Martinez-Torrecuadrada et al., 2003
FCV	VP1	Baculovirus	Di Martino et al., 2007
PCV2 (Licensed)	ORF2 protein	Baculovirus	Fort et al., 2009
Influenza virus	HA, NA, M1 and M2	Plants Baculovirus	Lopez-Macias et al., 2011
Papillomavirus	L1 and L2	Baculovirus	Hainisch et al., 2012
NDV	NP, M, F and HN	Avian and mammalian cells	McGinnes et al. (2010) and Morrison. (2010)
FMDV	P1, 2A and 3C	Baculovirus	Cao et al., 2009
BTV	VPs	Baculovirus	Roy et al., 1992
Rotavirus	VPs	Baculovirus	Bertolotti-Ciarlet et al., 2003

VLPs as antigen delivery system

Apart from induction of immune response against homologous viruses, VLPs can also be used for the delivery of heterologous antigens by developing chimeric VLPs. Foreign antigens can be incorporated to the VLPs by genetic fusion or conjugation and such VLPs present antigens from different pathogens in a repetitive configuration by working as vaccine vectors (potent immunogen) and also work as adjuvants. For example, VLPs derived from hepatitis B virus containing a neutralizing epitope of FMDV (VP1 protein) induced strong immune response by eliciting virus neutralizing antibodies than corresponding FMDV-peptide in guinea pigs (Clarke et al., 1987). Similarly VLPs derived from poliyoma virus by incorporating tumor antigens (Pircher et al., 1990), parvovirus derived VLPs with LCMV nucleoprotein and NDV derived VLPs with Nipah virus, respiratory syncytial virus and Influenza virus (Morrison et al., 2010) developed as vaccine vectors.

Challenges

Though the VLP vaccines have been used since 1980s, only very minimum number of vaccines commercialized currently. The main challenge is to produce VLP based vaccines in large scale that too with complex structure and for enveloped viruses. Complexity of baculovirus expression system based VLPs are higher when compared to yeast and bacteria and also baculovirus is very safe to vertebrates. But the disadvantage of baculovirus expression system is coproduction of infective baculovirus particles which are difficult to separate and they interfere with VLP based vaccine immunogenicity (Hervas-Stubbs et al., 2007). So it should undergo several steps of downstream separation process leads to higher the cost of production. Limitation in VLP based vaccine vector (chimeric VLPs) is to determine the compatibility of peptide with assembly of VLP and its immunogenicity once inserted. Under the host immune pressure, pathogens undergo mutation (antigenic variation) which render the VLP vaccine ineffective and will be effective for highly conserved B or T cell epitopes only.

Conclusion

Because of inherent properties like particulate structure, multimeric antigen expression and non-infectious nature, VLPs can be a potent vaccine candidate for the induction of innate, humoral and cellular immune response in livestock and poultry. Due to the fulfillment of DIVA requirements, VLP based vaccines attract the researcher to exploit its advantages to develop potent marker vaccine in the veterinary field. Encouraging results in this area highlight the VLP-based technology for the development of economically feasible new generation vaccine and vaccine vectors not only in human but also in livestock field in the near future.

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