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Capripoxviruses as Vaccine Vectors: A Review

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The era of vaccination dates back to over 200 years when Edward Jenner established human vaccination against smallpox. With the final declaration of eradication of smallpox by World Health Organization (WHO) in 1980, started a new generation of recombinant DNA technology. The advent of this technology *facilitated* researchers to develop vectored vaccines expressing heterologous antigens from different pathogens. Among them, poxvirus based vectors are most widely used vaccine vectors due to unique properties of this ds DNA virus, in terms of large genome size and insertion and deletion of comparatively wider stretch of specific genes, without compromising the ability of vectored virus to replicate *in vitro*/*in vivo*. This led to the generation of broad spectrum vectored vaccine backbone capable of inserting multiple epitopes of variety of pathogens, thus producing immunity against multiple diseases with a single injection. These recombinant vectored vaccines have an obvious potential in prophylaxis against devastating diseases in developing countries where cost, labor, lack of awareness about vaccination are main hindrances in successful control/eradication of diseases. In this review we have focused on various capripoxvirus based vectored vaccines with special reference to animal diseases, their future potential in developing countries like India, to be capable of protecting from multiple diseases.

Keywords: Vaccination, *in vitro, Vaccine Vector.*

The remarkable contribution made by Edward Jenner in 1798 in the field of immunology and vaccinology, with large-scale use of vaccinia virus, eventually led to the worldwide eradication of smallpox, the most dreaded viral disease in the human history[1]. The emergence of the field of recombinant DNA technology in early 1970's led to the use of various viral vectors to clone and express genes of foreign origin. During 1980's, despite the eradication of smallpox from the human population, the interest in the vaccinia virus expressing genes of various micro-organisms grew up rapidly among molecular biologists[2]. One of the breakthroughs was the use of vaccinia virus as a vector to express rabies virus glycoprotein, which ultimately led to the successful eradication of rabies in Belgium, along with the Grand Duchy of Luxembourg in 2001[2]. In Maryland, the seroprevalence of rabies reduced to 92% among terrestrial animals within a period from 1997 to 2007, after oral vaccination of raccoons with recombinant vectored vaccines containing baits[3].

A variety of vaccines including inactivated, attenuated and subunit vaccines comprising of immunogenic proteins of various micro-organisms have been developed to combat infectious diseases. However, various disadvantages of these vaccines have been recorded. The killed vaccines elicit inadequate immune response, have temporary immunity and higher cost of production, higher dose requirement of antigen, and hypersensitivity reactions due to the use of adjuvant, are the inherent drawbacks in

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using them. Live attenuated vaccines are prepared by sufficiently attenuating infectious organisms by passaging them in either the heterologous host system or in the cell culture. These live attenuated vaccines provide long lasting immunity, adequate protection against disease but have disadvantages in terms of reversion to the virulence, maintenance of the cold chain in tropical countries and at times, with the consequences of abortion in pregnant animals.

Poxviruses like vaccinia virus, owing to their large genome size, can accommodate a large part of deletion in their genome without compromising their ability to replicate in the cells and can, therefore, insert a number of genes of foreign origin (~25 kb), leading to the production of multivalent vaccines[4,5]. Successful large-scale use of vaccinia virus as a vaccine vector has led to a tremendous development in the field of vaccinology. Since then a variety of attenuated poxvirus strains has been explored as vaccine vectors, e.g. fowlpox virus, canary poxvirus, capripoxvirus, targeting many important pathogens.

However, large-scale use of the vaccinia virus as an expression system has raised various safety issues over its broad host range, ability to infect and cause disease among laboratory personals handling it. There are reports of transmission of vaccinia virus from vaccinated persons to susceptible animal species, and as a cause of severe illness in human immunodeficiency virus-infected (HIV) patients[6]. This raises serious safety issues of its use as a vaccine and the possible risk assessment involved for the species infected accidently [2]. This has led to the production of genetically attenuated strains of vaccinia virus as an alternative vaccine vector[7,8] by deleting genes involved in nucleic acid metabolism, host interactions, and assembly of virions[9]. Example of one of such vectors developed is Modified Vaccinia virus Ankara (MVA), with mutations in genome and is considered as a safer alternative for humans[10,11]. Apart from that some animal poxviruses with naturally restricted host ranges have been evaluated as vaccine vectors[12–16] e.g. avipoxviruses and capripoxviruses.

Remarkable features of these recombinant vectored vaccines include increased thermostability of freeze-dried preparation[17], ability to induce both cellular and humoral immune response[18], the low cost of production, ease of administration and being able to differentiate between infected and vaccinated ones[2]. Moreover, the recombinant vaccines expressing foreign genes, overcome the constraints of using multiple injections, are economical, reduce extra health care visits, less labor intensive, lessen the stress to animals, and make vaccination schedule more flexible by the addition of new immunogens[19]. Their use is advantageous in the areas where diseases caused by vaccine virus used as a vector and the antigens it is expressing are enzootic.

Member viruses of the genus *Capripoxvirus* (CPV) i.e. sheep poxvirus (SPPV), goatpox virus (GTPV), and lumpy skin disease virus (LSDV) of the family *Poxviridae* have proved to be effective recombinant vectors to induce protective immunity against several other viruses[20–23]. These three species of CPV share 96 to 97% nucleotide identity[24] and are restricted to ruminants only, with no documented human infections[25]. Furthermore, attenuated CPV vaccines are still used widely in Africa and the Middle East to control ruminant poxvirus diseases[26]. The use of a CPV based vector to deliver expressed antigen to ruminants also induces immunity to the CPV vector, thus increasing the efficacy of the vaccine[27] to protect against multiple diseases. This review updates the vital information about capripoxvirus vectored vaccines available to control various diseases of livestock.

Rinderpest virus

During the 1980s, vaccinia virus was explored as a vaccine vector for expressing rinderpest H-protein gene. On inoculation, rabbits produced neutralizing antibodies and resisted challenge with virulent rinderpest virus[28.] Using the same technique for capripoxvirus, KS-1 strain for expressing F gene of rinderpest virus after being inserted into the thymidine kinase gene region, was able to protect against both LSDV and rinderpest[14]. Later on H protein gene of rinderpest virus was expressed in KS-1 strain with the production of higher levels of rinderpest virus neutralizing antibodies than did a similar dose of recombinant capripoxvirus expressing F protein gene[29.] Later on trials in African Zebu breed of cattle with a mixture of recombinant capripoxviruses expressing either F or H gene, protected cattle for

6 or 12 months from rinderpest virus challenge[30] and revealed 50% protection up to 2 years and 30% after 3 years post-challenge with a lethal dose of virulent RPV. All the 4 animals and 2 of 5 vaccinated cattle survived the infection with virulent LSDV after two years and three years, respectively. Also, long term potency of the recombinant capripoxvirus-rinderpest recombinant vaccine in lyophilized form stored at 4°C for up to 1 year was also revealed[21].

Peste des petits ruminants (PPR)

Romero et al. developed capripoxvirus recombinant vaccines (rCPV) expressing either H or F gene of rinderpest virus. Both the constructs provided protection to goats against a lethal challenge of PPR virus. The rCPV-H produced high titer neutralizing antibodies compared to rCPV-F, which failed to stimulate the detectable level of neutralizing antibodies, but still provided protection against lethal PPR virus challenge, indicating the role of cell-mediated immunity in protection against PPR virus challenge[31]. Further, Chen et al. used goat poxvirus as a vector for expressing H (rCPV –PPRVH) and F gene (rCPV – PPRVF) of PPR virus and in accordance to the previous reports rCPV –PPRVH was found to be a more potent inducer of virus neutralizing antibodies compared to rCPV –PPRVF. Furthermore, use of two doses of the vectored vaccine was able to protect sheep and goats for about one year as well was able to overcome the pre-existing immunity against CPV vaccine in the field conditions[32]. Moreover, the vaccine was thermally stable and protected against both virulent GTPV and PPR virus challenge.

In another study, Berhe et al. developed a recombinant capripoxvirus (rCPV) vaccine by inserting F gene of PPRV into the genome of the attenuated capripoxvirus strain KS-1. The dose as low as 0.1 PFU of this recombinant vaccine was able to protect goats against challenge with a virulent PPRV strain[20]. Caufour et al. investigated the impact of pre-existing immunity to both capripoxviruses and PPR viruses against rCPV. To mimic the pre-existing immunity in animals, animals were first immunized with an attenuated capripoxvirus vaccine strain (KS-1) or the attenuated PPRV vaccine strain (Nigeria 75/1), and subsequently, inoculated with a mixture of capripoxvirus recombinants expressing either the hemagglutinin (H) or the fusion (F) protein gene of PPRV. Finally on challenging the animals with a virulent CPV and virulent PPRV strain, those vaccinated against CPV with prior exposure to PPRV were completely protected as compared to those vaccinated against PPR with prior exposure to CPV. The later animals showed mild clinical signs of PPR disease with no post-challenge neutralizing antibody response against PPRV[33].

Blue tongue

A recombinant capripoxvirus vaccine construct expressing a major core structural protein VP7 of Bluetongue virus serotype 1 (BTV-1) was developed. Sheep vaccinated with this recombinant vaccine construct produced neutralizing antibodies response to VP7 and on challenge with a heterotypic strain of BTV-3, six of eight animals survived the infection, demonstrating the first report on cross-serotype protection among BTV serotypes[23]. In 2007, a separate group of workers individually cloned and expressed BTV proteins into the thymidine kinase gene of the Kenya Sheep (KS-1) vaccine strain of capripoxvirus. But in contrast to the previous work done by Wade-Evans et al., only partial protection was observed in sheep against a virulent strain of BTV-2, which can be attributed to the inadequate level of protein expression, or immune response and inability to form virus-like particles[22].

Rabies

An attenuated vaccine strain of LSDV (Neethling) was used as a vector for expressing the rabies virus glycoprotein. This rLSDV–RG recombinant virus construct was able to induce high levels of anti rabies neutralizing antibodies as well as rabies-specific T cell proliferative response in immunized cattle. After booster vaccinations, the level of neutralizing antibodies persisted for several months as demonstrated by ELISA and neutralization assays[12]. In another study, LSDV being confined only to ruminants was evaluated as a replication-deficient vaccine vector for use in non-ruminant hosts e.g. rabbits and mice. Both the cells of ruminant and non-ruminant origin supported the expression of rLSDV-encoded rabies glycoprotein gene while complete maturation of rabies virus was observed only in permissive cells of bovine origin. The rLSDV-RG was able to produce neutralizing antibodies response in rabbits and cell-mediated immune response specific to

rabies virus in BALB/c mice[34]. This rLSDV-RG vaccine was able to confer lifelong immunity against LSD after a single shot.

HIV

Shen et al. investigated LSDV (Neethling), a replication-deficient vector for use in the humans to express HIV gag, reverse transcriptase (RT), tat and nef as a polyprotein (grttn). The recombinant (rLSDV-grttn) was tested for safety and efficacy studies in immune-compromised mice. It was found that DNA vaccine prime, and rLSDV-grttn boost, produced 3 fold more IFN- gamma as compared to the DNA vaccine prime, and rMVA-grttn boost, by the HIV-specific cells. Furthermore, DNA vaccine prime and rLSDV-grttn boost led to the production of IL-2 by HIV-specific $CD4^+$ cells[35]. In one study, rLSDV as a booster to rMVA prime, expressing HIV-1 genes gag, reverse transcriptase, tat, and nef, with one additional Env gene expressed in rMVA was evaluated in rhesus macaques. Results demonstrated that these two heterologous poxvirus vectors can elicit a broad $CD4^+$ and $CD8^+$ T-cell responses to the HIV antigens[36].

Rift Valley fever (RVFV)

A number of live attenuated and inactivated RVFV vaccines are available which induce neutralizing antibody response in humans. Since the attenuated vaccines produce teratogenic effects on lambs after vaccinating pregnant ewe[15,41] and the inactivated vaccine are expensive, require high dose[38], makes their use unfeasible. Therefore, the efforts are being directed towards the production of RVFV vaccines by reverse genetics[39] and other new-generation RVFV vaccines.

Wallace et al. compared the efficacy of glycoprotein (GP) and nucleocapsid (NC) genes of RVFV, expressed in different expression systems and evaluated their ability to protect mice from virulent virus challenge. Onderstepoort vaccine strain of LSDV as a vector expressing the glycoproteins (G1 and G2) and the crude bacterial extract containing truncated G2 glycoprotein developed neutralizing antibodies and fully protected the mice on challenging with virulent RVFV. Although DNA vaccine constructs expressing G1 and G2, DNA vaccine followed by a booster of rLSDV-RVFV as well as purified NC protein failed to seroconvert mice and provided protection level of 20%, 40%, and 60%, respectively. On the further evaluation of its protection efficacy in sheep, rLSDV-RVFV seroconverted for both RVFV and LSDV[15]. Soi et al. developed recombinant vaccine construct by inserting the Gn and Gc glycoprotein genes of RVFV into the TK gene locus of KS1 strain of capripoxvirus. The recombinant construct (rKS1/RVFV) was able to induce protection in terms of production of neutralizing antibodies in both mice and sheep on challenging with virulent RVFV[40]. Ayari-Fakhfakh et al. tested the efficacy of two vaccines, an attenuated RVFV, and a recombinant KS-1-vectored RVFV construct to evaluate the potential of an inbred MBT/Pas mouse as a model for RVFV vaccine. Both neutralizing antibody response as well as cell-mediated immunity involving CD8 cytotoxic cells, was observed [41].

DISCUSSION

The development of recombinant capripoxvirus vectored vaccines described in the present review rely mainly on the cloning and recombination strategies adopted for developing vaccinia virus-based recombinant vaccines. In the recent past, vectored vaccines have revolutionized the field of new generation vaccines and has made a tremendous contribution to combat against major pathogens of veterinary importance e.g. vaccinia virus recombinant expressing haemagglutinin (H), neuraminidase (N1), nucleoprotein (NP), matrix proteins (M1 and M2), and IL-15 of H5N1 influenza virus[42]. This multivalent recombinant viral construct was able to provide complete protection in mice against challenge infection as well as provided evidence of co- expression of multiple viral components in a single poxvirus vector backbone.

Development of these multivalent recombinant vaccines expressing conserved epitopes of pathogens and improving their presentation into the immune system to produce appropriate immune response would reduce multiple injections required while providing a cost-effective product[41]. Due to large genome size of poxviruses ~200-300kb, many poxvirus genes are dispensable for growth of the virus *in vitro* or in *vivo* and their deletion frequently leads to virus attenuation for the natural host e.g. development of a recombinant vaccinia construct, by inserting the rabies virus glycoprotein gene into the

thymidine kinase gene locus of the Copenhagen strain of vaccinia virus[43]. The resulting vaccine construct was successfully used as a live oral vaccine used in baits for foxes in Europe and United States.

Due to safety concerns related to the use of vaccinia virus as vaccine vector, a no. of other non-replicating attenuated virus strains derived from various species were assessed for using as vectors for expressing foreign genes e.g. fowlpox, canarypox, pigeonpox, penguinpox, quailpox[44], swinepox, sheeppox, goatpox, leporipoxviruses, and parapoxviruses exist[20,45].

Capripoxviruses mentioned in this review have been shown to be effective vaccine vectors for use against several pathogens of human and animal origin with dual or multivalent vaccine potential.

However, for livestock farmers in developing countries like India, the cost is the major factor impeding the success of recombinant capripoxvirus based vaccines to combat numerous diseases affecting livestock. Therefore, development of a single recombinant vaccine expressing multiple vaccine antigens of different pathogens affecting livestock of that particular area will be highly economical. Moreover, the multivalent recombinant vaccine would enable differentiation between infected and vaccinated animals (DIVA).

The ability of these recombinant vaccines to induce both cellular and humoral immune responses for long periods, and increased thermostability, makes these vectors ideal for developing recombinant veterinary vaccines for developing countries[46]. Most of the work in the field of capripoxviruses has been directed towards expressing the single immunogenic protein to a level capable of inducing immune response sufficient to provide protection. However, expressing multiple immunogens to an adequate level, capable of providing protection by inserting genes in locus other than TK gene has to be explored e.g. ribonucleotide reductase gene and intergenic region[12].

In order to improve the efficacy of recombinant vaccines, some of the immunomodulatory genes identified in the poxvirus genome have to be deleted viz. IL-10 homolog, GM-CSF inhibitory protein, EGF homolog, interferon resistance gene (IFR), and dUTP ase homolog[47].

Various variables such as titer of the vaccine, route of administration, and the possible use of adjuvants, are some of the major considerations to be kept in mind for achieving full protection against virulent field strains in small ruminants.

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