Research Article

Herpesvirus of Turkeys as a Vaccine Vector in Viral Diseases: Pros and Cons

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Abstract | Viral diseases of poultry have a devastating impact on the livestock industry leading to substantial economic loss in the worldwide economy. Recent advances in biotechnology have permitted the manipulation of viral genomes, thereby gaining a better understanding of the molecular insights of viral diseases. These have spurred the development of safer and efficient vector vaccines, which convey immunogenic genes of interest obtained from vitally important diseases. Herpesvirus of turkeys (HVT) has long been considered a versatile tool owing to its non-pathogenic characteristic, relatively higher transgenic capacity, and enabling the DIVA strategy. Numerous bivalent and multivalent HVT constructs have been generated by various methods and some of these constructs have been made commercially available so far. The efficacy of HVT-vectored vaccines has been assessed either individually or in combination with other vaccine formulations; hence, the optimal competence of these vaccines against viral diseases has been reported. Based on the current knowledge, this article outlines the benefits and drawbacks of HVT-vectored vaccines in combating health-threatening poultry infections and briefly pinpoints the future perspectives for improving the success of poultry vaccines.

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Introduction

The poultry sector has been exponentially growing owing to guard its profitability within the livestock industry throughout the world. Intensive poultry rearing systems enable an average consumer to afford cheap and high-quality protein sources. At this point, rigorous prevention and control strategies against pathogens are crucial to prevent the spread of diseases thereby sustaining long-term mass production. Vaccination is one of the main components of these strategies; therefore, a multitude of killed (KV) and live-attenuated (LAV) vaccines have been developed and introduced to the sector so far (Mottet and Tempio, 2017; Romanutti *et al.*, 2020).

With the advance of molecular biology techniques, vector vaccines have come forward with their superior features in the last decade. In general, a viral vector transduces the gene of interest effectively and stimulate the host immune system against targeted antigens (Ura *et al.*, 2014). Furthermore, recombinant vector vaccines do not revert their virulence; do not require rappels; have limited side effects; and offer differentiating vaccinated animals from naturally infected animals (DIVA) (Hein *et al.*, 2021). In recent years, turkey herpesvirus (HVT) has rapidly emerged as a promising viral vector for poultry. With the aid of genetic engineering technology, several bivalent or multivalent recombinant HVT vaccine (rHVT) formulations have been generated and approved by

authorities in various countries.

The *Mardivirus* genus consists of well-recognized avian herpesvirus species including *Anatid alphaherpesvirus 1, Gallid alphaherpesvirus 2, Gallid alphaherpesvirus 3* and *Meleagrid alphaherpesvirus 1*, the last of which is also known as turkey herpesvirus (HVT). HVT consists of low-virulent, non-oncogenic strains which have been broadly applied to elicit protection against Marek's Disease (MD). However, increased use of HVT in different formulations has given rise to novel variants with enhanced virulence; hence, multivalent vaccines including SB1, 301B/1 or CV1988 strains have been formulated for MD infections (Kim *et al.*, 2020). On the other hand, the concept of recombinant HVT vaccines was initially developed in the early '90s (Marshall *et al.*, 1993), and since then, they have been utilized as a viral carrier against some major poultry diseases in both bivalent and multivalent formulations.

Herpesvirus of Turkeys as a vaccine vector

Multiple approaches have been described to manipulate the herpesviral genome and they have been entitled under (1) bacterial artificial chromosome (BAC), (2) *en passant* mutagenesis, (3) homologous recombination (HR), (4) codon optimization and (5) CRISPR/Cas9 tool (Kamel and El-Sayed, 2019). BAC and HR techniques have achieved widespread application for generating recombinant vaccines, while CRISPR/Cas9 technology has had an increasing trend over the decade. Chronologically, HR based technique was initially described to construct an HVT vector and proved by expressing Newcastle disease (ND) fusion protein (Sondermeijer *et al.*, 1993). Then, the HVT genome turned into a plasmid construct via BAC technology, which also allowed gen manipulations such as insertion or deletion (Baigent *et al.*, 2006). However, these methods were quite laborious and demanding; therefore, targeted DNA nucleases (Bi *et al.*, 2014) had recently become a paradigm-shifting innovation that offered to insert a foreign gene into an exact position rapidly with higher specificity.

The disruption of intergenic regions usually does not alter the virulence of herpesviruses, whereas virulence-associated gene indels do; therefore, the latter is considered to reduce virulence and insert an expression cassette simultaneously. At least eleven non-essential genes have been recognized in the HVT genome so far (Hall *et al.*, 2015) and *US2*, *US7* or *UL40* genes; *US3/US4*, *UL54/UL55*, *UL45/46* or *HVT065/HVT066* intergenic regions have been used for foreign gene insertion. Foremost examples of the recombinant HVT vaccines are Newcastle disease (ND) vaccines. There were two types of conventional vaccines –LAV and KV– available against ND, and both had a plethora of drawbacks. It was quite challenging to provide optimized usage of the LAV vaccine, as it could cause iatrogenic infections, while KV required subcutaneous or intramuscular administration and rappels, also lack of engaging cell-mediated immunity (Dimitrov *et al.*, 2017). Considering these limitations, several HVT vector-based ND vaccines have been generated. Typically, fusion (*F*) gene expression cassettes have been constructed by using Rous sarcoma virus long terminal repeat, chicken β-actin or cytomegalovirus immediate-early promoters and inserted into *US10*, *UL45/UL46* or *US3/US4* positions (Bublot *et al.*, 1999; Dorsey *et al.*, 2002; Morgan *et al.*, 2019). These vaccines are proven to improve clinical signs of disease, elicit immune protection at least 70 weeks, and reduce virus shedding via excretes in chickens and turkeys (El-Khantour *et al.*, 2017; Palya *et al.*, 2014). On the other hand, although HVT-ND vaccines have been used extensively; recent studies have revealed the "immunologic gap" until the fourth week of age in maternal antibody-negative chickens because of delayed immunity (Palya *et al.*, 2014). This entails serious consequences in some geographic areas where the ND is endemic. Therefore, mass vaccination of 1-day-of age chicks with LAV is highly recommended to provide onset immunity in flocks.

HVT backbone has also been considered as an option to induce neutralizing antibodies via foreign gene expression in order to establish protection against infectious laryngotracheitis, which is another significant herpesviral disease of poultry. In this context, the first approach was to target glycoprotein B (gB) which is an essential gene of infectious laryngotracheitis virus (ILTV) functioning as a virus-cell fusion protein (Poulsen and Keeler, 1997). Hence, blockage of gB prevents cell entry of virus thereby blocking the cell binding in the first place. The second was to be expressed multiple proteins of ILTV instead, virulence-associated gI glycoprotein (involves in gE/gI complex) which takes a role in cell-to-cell spread of ILTV (Devlin *et al.*, 2006) along with essential glycoprotein gD, as it induces higher titres of neutralizing antibody and cell-mediated immune responses than gB alone (Ibrahim *et al.*, 2020; Kanabagatte Basavarajappa *et al.*, 2014). All

genes were inserted in intergenic regions of the HVT genome by the conventional HR method (Esaki *et al.*, 2013; Gimeno *et al.*, 2011). The gB expressing HVT was proven to provide adequate protection against virulent ILTV strain after subcutaneous injection to 1-day-old SPF chickens. Furthermore, a single *in ovo* inoculation on the eighteenth day of egg incubation protects 3 to 4 weeks old broiler chickens with 67% and 87% efficacies, respectively (Esaki *et al.*, 2013). Similarly, gI and gD expressing rHVT mitigated the symptoms of ILTV independently of administration routes in 57-day-old chickens and showed more efficacy than fowl poxvirus recombinants (Vagnozzi *et al.*, 2012), although this would be controversial (Johnson *et al.*, 2010). The most significant shortcoming of rHVT-ILTVs is the incompetency of abolishing viral replication in the trachea which may lead to the spread of ILTV through clinically healthy chickens (Barboza-Solis *et al.*, 2021; Johnson *et al.*, 2010; Vagnozzi *et al.*, 2012). To solve this, rHVT-ILTVs has been combined with traditional LAVs of ILTV or fowl poxvirus-vectored vaccines (Guy and Byrd, 2016; Maekawa *et al.*, 2019).

Gumboro disease has been of considerable economic significance due to several reasons. First, it has a remarkable mortality rate arising from virulent infectious bursal disease virus (IBDV) strains in flocks, and the second is to the ability to cause immunosuppression, which results in a susceptibility to secondary infections and possible vaccine failures (Dey *et al.*, 2019; Giambrone *et al.*, 1976; Pejkovski *et al.*, 1979). The first generation of vaccines (LAVs) strictly depended on attenuating viral agents by serially passaging in the embryonated eggs or primary tissue cultures. In general, the level of neutralizing antibody titer correlates highly with the pathogenicity of vaccine strain; however, virulent strains can bring about bursal lesions and immunosuppression in laying hens (Thangavelu *et al.*, 1998). Therefore, most of the commercial LAV vaccines were derived from mild-intermediate strains and applied to hens on the verge of laying period to transfer maternal antibodies to chicks (Müller *et al.*, 2012). Molecular evolution mechanisms have constantly emerged that novel IBDV variants impaired the protection capacity of vaccines so that mild strains had become insufficient in immunizing chickens against these novel field strains (Rautenschlein *et al.*, 2005). Thus, various strategies were pursued to overcome this inefficiency problem. These included combining LAVs with hyperimmune sera, which was defined as an "immune complex vaccine" (Whitfill *et al.*, 1995). The second-generation HVT-vectored vaccines were constructed to respond urgent need for combating very virulent variants. *VP2* gene was sought to make into expression cassette and inserted into intergenic regions or *US7* locus of HVT backbone (Bublot *et al.*, 1999; Darteil *et al.*, 1995). These vaccines were proven to present negligible lesions in bursa after s/c injection in 1-day-old chicks; protect SPF chickens against multiple IBDV strains with a high percentage (>95%) in both s/c and *in ovo* application and induce strong humoral and cell-mediated immune responses. Furthermore, rHVT-IBDV vaccines do not be affected by maternal immunity (Bublot *et al.*, 2007; Gimeno *et al.*, 2016; Tsukamoto *et al.*, 2002). On the other hand, the efficacy of the *US7*-deleted rHVT-IBDV remained weak for MD despite providing full protection against IBDV (Darteil *et al.*, 1995). More recently, the *UL45/UL46* intergenic region was selected to introduce VP2 expression cassette by CRISPR/Cas9 and Cre-Lox tools; however, *in vivo* stability and efficacy of vaccine candidate remained unknown (Tang *et al.*, 2018).

Avian Influenza (AI) virus is a constantly evolving virus owing to its unique eight-segmented RNA genome. Its low-fidelity RNA polymerase activity engenders multiple variations in each gene (antigenic drift), while genetic reassortment mechanism occurring amongst species assists novel recombinant strains (antigenic shift) (Suarez, 2000). For instance, H5 and H7 subtypes of low-pathogenic avian influenza (LPAI) are known to be capable of evolving to highly pathogenetic avian influenza (HPAI), once they disseminate to the avian population (Sutton, 2018). Thus, an abundant number of subtypes and variants have been defined throughout the world. Viral surface glycoproteins neuraminidase (NA) and hemagglutinin (HA) have the ability to induce neutralizing antibody responses against AI virus (Crowe, 2019); however, the humoral immune response of the vaccinated animals triggers the evolutionary pressure on these proteins, thereby continuously assisting the emergence of novel vaccine escaping variants (Chang *et al.*, 2020; Lee *et al.*, 2004; Sitaras *et al.*, 2020). Whole particle KVs have been utilized against several AI subtypes as a part of control measures. These vaccines fail to establish a protective immune response in the presence of maternal antibodies in chicks, or a potential impairment between vaccine and field strains (Fuchs *et al.*, 2009). Nonetheless, KV vaccines afforded to provide

sufficient immunization and reduce transmission between chickens (Swayne *et al.*, 2000). HVT vector rose to prominence as an alternative to KV and fowl poxvirus-vectored vaccines. The most common principle of these rHVT vaccines was to introduce the modified *Hx* gene cassette of HPAI viruses into the *UL45/UL46* intergenic region of HVT using various techniques such as BAC and/or CRISPR/Cas9 tools (Li *et al.*, 2011; Liu *et al.*, 2019). Several experimental evaluations of commercially licensed rHVT-H5 demonstrated that the vaccine significantly reduced the mortality (60-100%) and virus transmission rates depending on the challenged strain, also prevailed over maternal antibodies in chickens (Gardin *et al.*, 2016; Palya *et al.*, 2018; Steensels *et al.*, 2016). On the contrary, other studies pointed out the importance of booster vaccine implementation at 2-3 weeks of age in chickens, since maternal antibodies seemed to rarely interfere in vaccine induction (Kilany *et al.*, 2015; Rauw *et al.*, 2012). rHVT-Hx vaccines enable to set vaccinated animals apart from infected or KV immunized animals in case an *ad hoc* diagnostic method is applied.

The multi-pathogen vaccine concept has led to reap outstanding benefits, which are simply reducing the cost of vaccine production and transportation, also preventing infections by fewer vaccine implementation. In this regard, efforts have been directed towards inserting multiple antigen-expressing gene cassettes into HVT vectors using different techniques. A double recombinant vaccine architecture, rHVT-F-gI+gD, was constructed by placing corresponding gene cassettes into *US2* region by cosmid-based HR method. The *in vivo* challenge studies revealed that the rHVT-F-gI+gD induced excellent protection against NDV (strain GB Texas), ILTV (strain LT 96-3) and MDV (strain GA 5) when it was administered by either *in ovo* or subcutaneous route in 1-day-old chickens. Furthermore, vaccine response did not adversely affect when it was combined with LAVs against IBDV or MDV separately (Gergen *et al.*, 2019). Similarly, rHVT-F-VP2 was assembled using the same method and further tested on chickens. Results showed that this variation was also highly versatile and effective against MDV, IBV and MDV; maintained prolonged immunity and was capable of giving high immune protection (≥ 90%) under field conditions (van Hulten *et al.*, 2021). A recent innovative study has brought three expression cassettes together into one rHVT construct which included *VP2* of IBDV in *UL45/UL46* intergenic region, both *gI* and *gD* genes of ILTV in *HVT065/HVT066* intergenic regions, and *H9* gene of AI in *US2* gene using CRISPR/Cas9 tool (Tang *et al.*, 2020). Taken together, multi-pathogenic rHVT vectors appear to be more advantageous than using a combination of multiple bivalent rHVT vectored vaccines, as the repeated application results in neutralization of virus (Dunn *et al.*, 2019)

Conclusion and Recommendations

Achieving the balance between safety and efficacy is essential to developing an efficient recombinant vaccine. The use of HVT-vectored vaccines in poultry has been in an increasing trend due to their versatility and effectiveness. rHVT vaccines allow *in ovo* or at hatch application options, do not be eliminated by the maternal antibodies of a targeted disease, and most importantly, maintain durable immunity with a single dose. In addition, rHVT enables distinguishing infected from vaccinated animals.

On the other hand, the titer of neutralizing antibody required for the complete protection against targeted disease may delay up to four weeks; therefore, a booster vaccination is needed in most cases. Furthermore, HVT-vectored vaccines must be transported in liquid nitrogen because of the cell-associated nature of HVT. This *natura* also assists to evade maternal antibody thereby increasing the vaccine efficiency.

Overall, rHVT vaccines have delivered a great performance in the induction of systemic immunity. However, local immunity protection is relatively lower which is crucial for combating ILTV or NDV (Romanutti *et al.*, 2020). To address these limitations of rHVT-vectored vaccines, multiple approaches can be implemented to augment vaccine efficacy. For example, deletion of viral immune-mediated genes from the HVT backbone; insertion of immunomodulatory and/or fusion protein gene cassettes to improve cell-mediated immune response; testing various viral or cell promoters for increasing the expression level; combining vector with other immunogens such as new generation vaccine adjuvants should be comprehensively evaluated.

Novelty Statement

HVT vectors are recognized as a reliable tool to develop rational multivalent vaccine design. Thus, many

HVT-vectored vaccine candidates have been commercialized and made available in the field against the major viral diseases of poultry. It is conceivable that the elucidation of virus-host relationships and the perspectives provided by novel vaccine technologies will lead to the development of safer and more effective HVT-vectored vaccines in future.

Conflict of interest

The author has declared no conflict of interest.

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