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Understanding the molecular basis of disease is crucial to improving the design and construction of herpesviral vectors for veterinary vaccines

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ABSTRACT

Viral infections are associated with production losses in many animal production industries. Important examples of this are Marek's disease (MD) and bovine respiratory disease (BRD) which are significant issues in the chicken and cattle industries, respectively. Viruses play key roles in MD and BRD development and consequently have also been utilised in vaccination strategies to control these diseases. Despite the widespread availability and use of vaccines to control these diseases both are still major issues for their respective industries. Here the dual role of members of viruses from the family *Herpesviridae* in causation and control of MD and BRD will be discussed. The technologies that may lead to the development of improved vaccines to provide more sustainable control of MD and BRD will also be identified.

1. Introduction

Viral infections are major causes of loss in many animal production systems and as a result significant effort has been made to development effective vaccines. The lengthy task of reviewing the extensive literature associated with the development of vaccines against viral infections has recently been comprehensively dealt with [1,2]. These studies have reviewed the multitude of viral vaccine strategies that have been investigated to improve the health of animals. As a result this review will focus on two diseases of livestock that are strongly associated with viral infections and for which emerging vaccine technologies have been applied to improve vaccine performance to reduce associated production losses. This review will also focus on viral vectors developed from members of the herpesvirus family which are key components of the two selected diseases. Pathways to the development of more effective vaccines based on these vectors will also be discussed. An attempt will also be made to predict those technologies that will provide the impetus for vaccine improvement and more widespread adoption of viral vaccines by livestock industries.

For the purposes of this review, viral vaccines developed *via* approaches that do not involve genetic modifications will be referred to as either live viral vaccines (LV) or modified live viral vaccines (MLV). The LV class includes viruses which have proved useful essentially as isolated without any apparent virulence in the host system of interest. The MLV includes those vaccines that may have been developed using conventional approaches such as extensive passage in the laboratory or the selection of particular genotypes using chemical mutagenesis or drug resistance, such as the selection of herpesviruses strains that are thymidine kinase (TK) negative using the selective phosphorylation of nucleotide analogues. Genetically modified viral vaccines (GMV) include those vaccines where genetic material has been specifically removed to give a particular phenotype or genetic material from another organism has been added to generate an altered phenotype. Further this review will only deal with vaccines which include live viral agents in any of these classes.

2. Common properties

The principal advantage of LV, MLV and GMV is the capacity of the vaccine to mimic the natural infection in the absence or with minimal clinical signs. The end result being the vaccinated animal acquires the type of immunity required for protection from field strains of the virus that cause disease. Therefore these vaccines must strike a balance, if the infection is too severe it may result in disease, if the infection is too mild there might be a reduced immune response that either does not persist or is insufficient to protect from disease in any subsequent exposures to the agent in question. For GMV, which typically involve the deletion of genetic elements, if too many components of the virus are disabled then it may also result in reduced performance as a vaccine. Thus all

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vaccines based on these technologies tread a fine line between protecting from disease known as vaccine efficacy and disease.

In all cases of live viral vaccines pre-existing immunity to the virus has the potential influence the likelihood of addition specific immune responses. This would clearly not be an issue for LV and MLV as the vaccination dose is more likely to act as a boost of the pre-existing immunity thus be of benefit to the vaccinated animal. However for GMV applications if the purpose of the vaccine is to deliver antigens from other pathogens existing immunity to the vector virus could be problematic. It has been reported for some viral vectors that if pre-existing immunity to the vector is too high there is insufficient replication to provide enough of an immune response to the heterologous antigens thus effectively resulting vaccine failure [3,4]. In contrast, it has also been demonstrated that in some cases pre-existing immunity to the vector does not inhibit the generation of immunological responses to the delivered antigen [5]. Due to these conflicting reports it would seem that the potential influence of pre-existing on vaccine performance needs to be empirically determined for the system of interest.

3. Herpesvirus as vectors

The *Herpesviridae* are a family of virus with large double stranded DNA genomes ranging in size from 120 to 240 kbp. Members of the subfamily *Alphaherpesvirinae* have been isolated and characterised from a broad range of species from humans to molluscs [6]. A defining feature of the herpesviruses is the capacity to establish latent infections in the natural host. In response to various stimuli the herpesvirus may reactivate from the latent state and undergo productive infections whereby it can be spread to susceptible hosts. As a consequence of latency, once animals are infected they will carry the virus for life. The alphaherpesvirus infecting livestock species have been extensively studied for the development of animal vaccines, as generally speaking they are readily isolated and propagated in the laboratory. This capacity for ready culture also makes these viruses suitable for use in veterinary pharmaceutical production systems for cost effective production. The alphaherpesviruses are attractive vectors for the LV, MLV and GMV as the genomes encoded numerous genes many of which are not required for viral replication [7]. Further gene studies have identified many genes which are not required for viral replication in the laboratory and the deletion of which can result in the attenuation *in vivo* [7–9]. Alphaherpesviruses have proven to be well suitable for use as LV due to the lack of detectable disease in the host of interest in some cases [10,11]. However in other instances, associated with the intensification of livestock industries and vaccination, virus strains have emerged with the capacity to cause severe diseases [12–15].

With respect to the development of GMV there has been considerable focus on the herpesviruses for the development of vaccine and gene therapy vectors as there are fewer constraints on the size of exogenous genetic material that can be introduced into the viral genomes compared to other viral vector systems. To date there has not been a specific study to address this question for any herpesvirus however it has been estimate that *Human herpesvirus 1* (HHV-1) based vector systems may be able to accommodate up to 50 kbp of foreign DNA [16]. This high loading capacity raises the prospect of developing multivalent vaccines using these vectors.

Members of the alphaherpesvirus subfamily are associated with a number of important diseases of production animals. Marek's disease (MD) and bovine respiratory disease (BRD) are two diseases for which herpesviruses play dual roles as both causative agents and vaccines. Arguably, with the exception of *Porcine herpesvirus 1* (also known as pseudorabies virus) the three most studied herpesviruses used in veterinary vaccine applications are *Gallid herpesvirus 2* (GaHV-2), *Meleagrid herpesvirus 1* (MeHV-1) and *Bovine herpesvirus 1* (BoHV-1). The first two viruses are associated with MD of poultry and later with BRD of intensively finished cattle.

Marek's disease is a potentially fatal T-cell lymphoma of chickens that was first described by Josef Marek in 1907. Outbreaks in unvaccinated domestic and commercial chicken flocks can be devastating with high mortalities. The causative agent for MD is the alphaherpesvirus GaHV-2, classified in the genus *Mardivirus*. The control of MD through vaccination is a veterinary vaccine success story which has been achieved through the use of LV and MLV vaccines for decades [17,18]. However, while these vaccines prevented disease expression, tumour formation, other aspects of the GaHV-2 life-cycle in chickens remained unaffected. The mechanistic route of GaHV-2 infection is well understood it has been demonstrated that following the last phase of GaHV-2 *in vivo* replication at epithelium of the feather follicle, the virus is shed by infected birds in a highly keratinised particulate matter in to the production environment. The particulate matter is small enough to be inhaled by chickens and subsequently engulfed by alveoli macrophages. At this point the GaHV-2 appears to be decapsulated by removal of keratin material and thus able to begin the viral infection cycle intracellularly and subsequently spread to other cells. This intriguing route of infection has made prevention of chickens becoming infected a very difficult prospect. Consequently vaccinated chickens are still susceptible to infection with pathogenic GaHV-2 if it is not completely removed from the production environment which is costly and difficult to achieve. As a result the incoming batch of birds is likely to become infected with GaHV-2 once more completing the virus life-cycle. This continued cycle of vaccination and infection is considered to have driven the evolution of field strains of GaHV-2 with increased virulence that are able to overcome the protection effects of vaccination [15]. Consequently these unique features of the GaHV-2 replication cycle continue to present some difficult challenges in development of sustainable vaccines for continued MD control [19].

The second disease to be considered here, BRD, in contrast to MD, has a complex aetiology. The development of BRD is dependent on a complex interactions with exposure to viral and bacterial pathogens, animal factors, animal management and environmental conditions all contributing to the risk of an animal developing the disease [20]. Studies have implicated multiple viruses such as *Bovine herpesvirus 1*, *Bovine viral diarrhoea virus 1*, *Bovine respiratory syncytial virus* and others in BRD development. While various bacterial agents such as *Mannheimia haemolytica*, *Mycoplasma bovis*, *Pasteurella multocida* and *Histophilus somni* are also commonly isolated from BRD cases. A widely accepted model for BRD development is following arrival at the feedlot, some cattle may be immunologically compromised due to stress causes by multitude of management factors. Subsequent exposure and infection with viruses results in physical damage to mucosal surfaces and/or immunosuppression which predisposes cattle to secondary infections by one or more of the bacterial agents listed above which are able opportunistically colonise the lower respiratory tract resulting a severe or fatal bronchopneumonia [21]. There is also evidence to suggest that *M. haemolytica* and *M. bovis* can act as primary causes of BRD development. Importantly, studies have shown that prior exposure and consequent development of immunological responses to these pathogens can help prevent cattle from developing BRD suggesting that effective vaccination has an important role to play in controlling this disease [22].

4. Vaccination against MD

The natural host for MeHV-1 (or turkey herpesvirus) is the turkey with no associated disease, the virus is also able to replicate efficiently and benignly in chickens. The

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