Bovine Herpesvirus 1

Part 1 (of 2): Virology and Disease

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Introduction

Bovine Herpesvirus 1 (BHV-1) is one of the main contributors of the Bovine Respiratory Disease (BRD) complex and is responsible for severe economic losses in the beef industry throughout the world. It is a virus that elicits a strong immunogenic response in the host animal, that can be effectively stimulated with vaccination. Understanding this virus and its effect on host animals will aid in making sound management decisions.

Viral Classification

The International Committee on Taxonomy of Viruses (ICTV) is a body governed by the International Union of Microbiological Societies (IUMS) that is responsible for developing and maintaining an internationally agreed upon classification system for all viruses. The ICTV regularly release an updated virus taxonomy database, of which the 2019 release indicated 6590 classified virus species (available from: https://talk.ictvonline.org/taxonomy/). Table 1 gives the complete taxonomic classification of BHV-1.

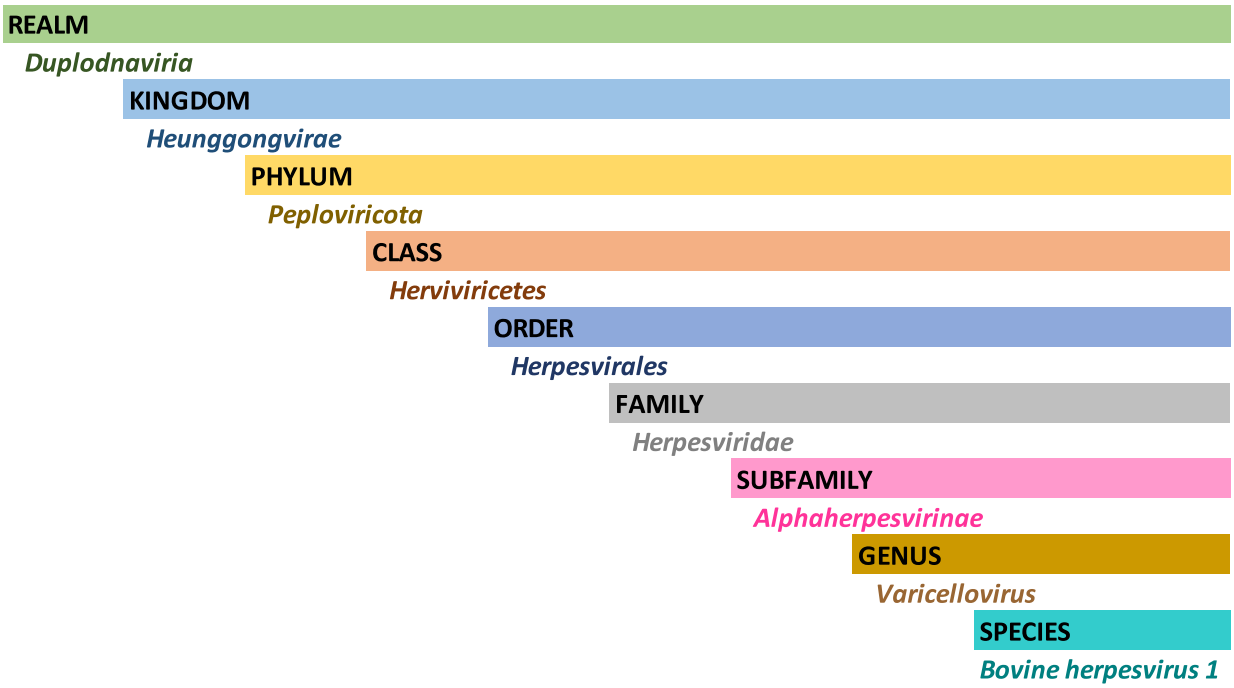

Table 1: Taxonomic Classification of *Bovine Herpesvirus 1*.

Alphaherpesviruses are grouped together due to genomic similarities and they consequently also share many characteristics, such as productively infecting fibroblasts and epithelial cells - often causing blister-like lesions in the latter. The genus of Varicelloviruses commonly establish latency in cells of the sensory nervous system and species of this genus can be found in a wide range of mammalian hosts. It is

important to note that even though found in a wide range of hosts, each of these individual viruses are fairly host specific and do not commonly cross species barriers.
One well-known human example would be *Human Herpesvirus 3* (Varicella-Zoster Virus) responsible for causing chickenpox (varicella) in children and shingles in adults.

BHV-1 Life Cycle

Transmission

Transmission of BHV-1 occurs mainly via contact with virus-containing mucosal droplets from infected animals. This excretion of mucosal droplets is referred to as *shedding* and result from active infection from a field strain or potentially as a result of vaccination with a live vaccine strain.

Direct contact (animal - animal, or animal - fomite) is accepted as the most common mode of transmission, although airborne transmission can also occur. Airborne transmission across distances of up to 3.85 meters have been recorded, permitting ideal environmental conditions, with specific reference to temperature and relative humidity.

In addition to mucosal droplets as vehicle for transmission, semen from infected bulls can be contaminated with BHV-1.

Peak shedding of virus occurs 4 – 6 days after an acute infection and the total days of active shedding ranges from 10 to 17 days in the case of respiratory infections. Shedding from bulls with a primary preputial infection can continue for several weeks. Latently infected animals are considered lifelong potential shedders.

Attachment and Penetration into the Host Cell

Figure 1 depicts the structure of a typical herpesvirus such as BHV-1. The double stranded viral DNA is enclosed in an icosahedral protein coat (called a plasmid), which in turn is surrounded by a lipid membrane (called an envelope) that is dispersed with various glycoproteins.

These glycoproteins play an integral role in the attachment of the virus to the host cell membrane (through binding to specific receptor molecules), penetration and entrance into the cell cytoplasm. They are also involved in the rest of the viral life cycle and are recognised as major antigens by the host immune system.

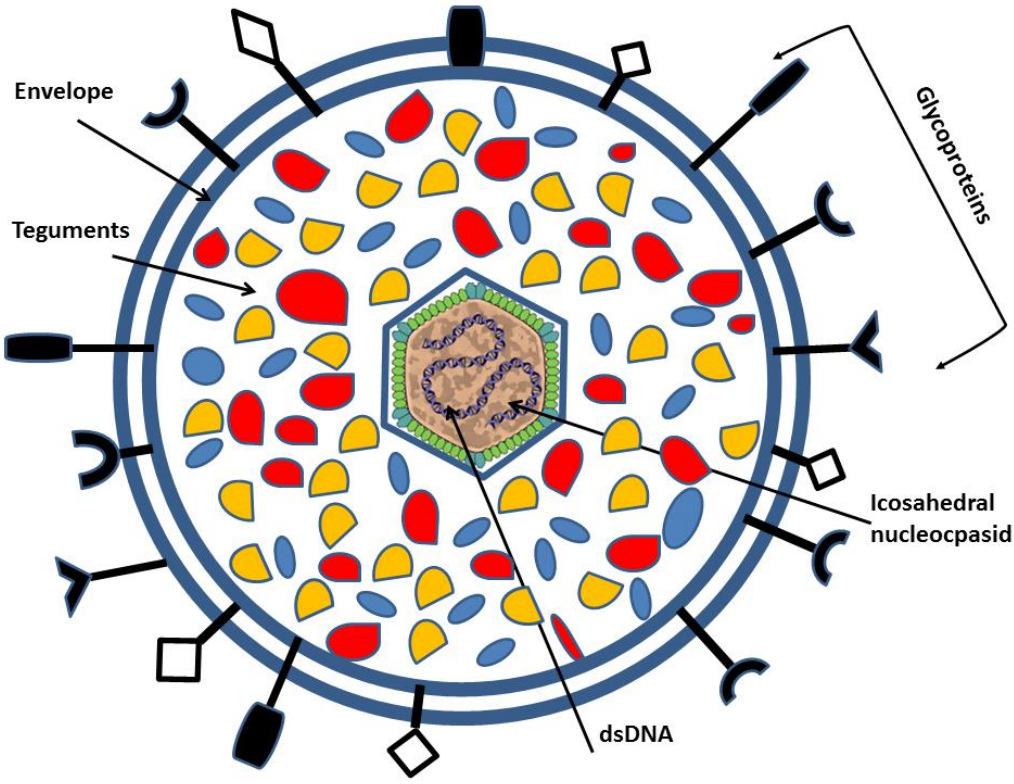

Figure 1: Schematic Representation of a Herpesvirus
Available online from: https://glycopedia.eu/e-chapters/herpesvirus-induced-glycans/Herpesviruses

Virus Replication and Export

In the intracellular stage of the viral life cycle, BHV-1 is transported into the nucleus of the cell. Inside the nucleus, the viral DNA highjacks the cellular (transcription and translation) mechanisms to synthesize viral protein. New virus becomes enveloped when it buds through the nuclear membrane and travels to the cytoplasmic membrane from where it is released from the cell.

In a *lytic infection* the host cell undergoes apoptosis (programmed cell death), thereby releasing numerous new viral particles into the intercellular space where they can infect new cells and repeat the process. Viral replication starts within 2 hours from infection and completion of the first lifecycle, whereby replicated virus is released, occurs within 8 hours. In the case of a *latent infection* the viral DNA remains intracellular for extended periods of time without inducing apoptosis.

Latency

A latent infection can develop from infection with a field strain or an attenuated vaccine strain. The infection dose does not affect the development of latency and (regardless of infection dose) BHV-1 is believed in most cases to enter a state of latency. Neither vaccination nor colostral antibodies can prevent initial replication and the development of latency.

Latent BHV-1 DNA reside mostly in neural cells of the trigeminal ganglion in the case of respiratory infection and in the sacral ganglion in the case of reproductive infection. Latency *may* also occur in non-neural sites such as peripheral blood and lymph nodes.

Reactivation from latency that result in excretion of infectious virus can be induced by various stressors, such as transport, concurrent infections (with for example Parainfluenza-3) or exogenous corticosteroid administration.

Disease Syndromes

As described above, BHV-1 has a *lytic cycle* that triggers apoptosis and the clinical signs that are commonly observed are the result of destruction of virus infected cells.

Infectious Bovine Rhinotracheitis (IBR)

The disease that results from a respiratory infection with BHV-1 is commonly referred to as IBR. As a disease/condition IBR is extremely contagious and can even reach 100% morbidity in a group, with disease status ranging from subclinical or mild to severe. Often though it is seen in conjunction with other pathogens that cause pneumonia. The immunosuppressive effect of IBR along with epithelial destruction (that incapacitate the mucociliary escalatory system in the upper respiratory tract) predispose an affected animal to secondary bacterial infection that leads to bacterial pneumonia and high mortality rates. Due to this, BHV-1 is often termed "the most important viral pathogen in the BRD complex".

Clinical signs that may be observed is pyrexia, increased respiratory rate (or even dyspnoea with laboured breathing), coughing, teeth grinding, decreased feed intake, anorexia, nasal discharge (clear to mucopurulent), excessive salivation, lacrimation, conjunctivitis ("winter pink-eye"), nasal hyperaemia ("red nose"), pustules and ulceration.

Macroscopic diagnosis of the above conditions will be rhinotracheitis, pharyngitis and laryngotracheitis and when complicated with secondary bacterial infection the diagnoses may progress to bronchopneumonia and pleuritis. Pregnant BHV-1 seronegative cows that contract IBR can develop a viremia that can cause foetal infection, which in turn will lead to foetal death and abortion.

Infectious Pustular Vulvovaginitis (IPV)

The genital form is mostly caused by a different subtype as the respiratory form, but vesicular lesions remain the main clinical symptom due to the lysis of mucosal cells. IPV develops 1 – 3 days after mating, with the first clinical signs being frequent urination and an elevated tail (as a result of pain, affected cows are reluctant to have contact between the tail and the vulva). Pyrexia, depression, decreased feed intake and anorexia are typical symptoms, along with pustules and ulcers in the superficial genitalia. Most of these lesions heal 10 – 14 days after their onset, but there are some cases that may produce a purulent vaginal discharge for several weeks. Similar to IBR there is always a possibility of secondary bacterial infection, that may progress to metritis.

Infectious Pustular Balanoposthitis (IPB)

This is basically the male form of IPV, with similar lesions in the mucosa of the penis and prepuce. The recovery period is also 10 - 14 days for visible lesions, but it is important to note that it might take several weeks for full recovery and ability to return to mating. Again, secondary bacterial infection can complicate the healing process and is quite common.

If a bull contracts IPB during the mating season, it is important to withdraw the bull from the cow herd. If the bull is allowed to continue mating, not only does it potentially spread the disease, but it might

result in scar tissue formation that can have various negative sequalae such as adhesions, annular constriction and penile distortion.

Encephalitis

The neurologic form of the disease is caused by BHV-5, that used to be classified as subtype BHV-1.3 and is usually seen in calves. The virus is presumed to infect the animal via the respiratory route, from where it travels through the trigeminal ganglion to the central nervous system. General neurological symptoms such as ataxia, tremors, recumbency with paddling and opisthotonos are observed. Prognosis are poor and coma and death can be expected 4 days after the onset of clinical symptoms. Animals that do recover are often blind.

Other

Generalised neonatal disease has been described where various mucosal organs are affected, resulting in respiratory disease, conjunctivitis and diarrhoea. This form is usually fatal to the neonate and it has been observed that it often coincides with abortion storms in a naïve herd.

Summary

BHV-1 is a double stranded DNA virus capable of infecting various cells, with proliferative reproduction taking place in epithelial cells of mucosal surfaces. The virus can enter either a *lytic pathway*, where cell lysis leads to the vesicular lesions commonly observed, or a *latent pathway* in which the host immune system is evaded which leads to infected animals becoming life-long carriers.

Infection with BHV-1 can lead to various diseases, depending on the route of infection (e.g. respiratory or reproductive), although most of these syndromes share certain clinical signs due to similar cellular destruction caused by the virus. Immunosuppression leading to secondary bacterial infection is a frequent complication.

Part two of this series will take a deeper delve into the host immune response to BHV-1, vaccinology and control measures to mediate the disease.

The author can be contacted for a full list of references.

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