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Immunity to Bovine Herpesvirus 1: I. Viral lifecycle and innate immunity

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Keywords

bovine herpesvirus 1 (BHV-1), bovine respiratory disease complex (BRDC), latency, innate immunity, pathogen recognition receptor (PRR), immune evasion

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Immunity to Bovine Herpesvirus 1: I. Viral lifecycle and innate immunity

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Abstract

Bovine herpesvirus 1 (BHV-1) causes a variety of diseases and is globally distributed. It infects via mucosal epithelium, leading to rapid lytic replication and latent infection, primarily in sensory ganglia. Large amounts of virus can be excreted by the host on primary infection or upon recrudescence of latent infection, resulting in disease spread. The bovine immune response to BHV-1 is rapid, robust, balanced, and long-lasting. The innate immune system is the first to respond to the infection, with type I interferons (IFNs), inflammatory cytokines, killing of infected host cells, and priming of a balanced adaptive immune response. The virus possesses a variety of immune evasion strategies, including inhibition of type I IFN production, chemokine and complement binding, infection of macrophages and neutrophils, and latency. BHV-1 immune suppression contributes to the severity of its disease manifestations and to the bovine respiratory disease complex, the leading cause of cattle death loss in the USA.

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1. Introduction

Bovine herpesvirus 1 (BHV-1) causes a variety of diseases (Gibbs and Rweyemamu, 1977) and infection is worldwide (Beer, 2012). The diseases it causes are costly both in direct disease effects and in lost trade. Immunosuppression by BHV-1 potentiates secondary infections, and it is a major component of the bovine respiratory disease complex (BRDC), which has a large economic impact on the cattle industry in the USA (Jones and Chowdhury, 2007; Anon, 2011).

BHV-1 has been found to infect a number of artiodactyl species, and is closely related to viruses infecting other domestic and wild ungulates (Thiry *et al.*, 2006). It is considered the prototype herpesvirus species of ruminants (Robinson *et al.*, 2008). BHV-1 is also similar to the (human) type species of its genus (*Varicellovirus*), subfamily (*Alphaherpesvirinae*, α HV), and family

(*Herpesviridae*, HV) and demonstrates similar life-cycle events. The human HV viruses, and the α HV viruses of veterinary importance such as BHV-1, have been extensively studied.

Although similar in many respects to the human immune response to human herpesvirus 1 (HHV-1), the differences in the bovine immune system, physiology, lifestyle and BHV-1 proteins mean the bovine immune response to BHV-1 is unique. The impact of the diseases caused by BHV1, and the promise of their mitigation by immunologic means, make understanding BHV1 infection and the bovine immune response to it important and relevant.

2. BHV-1 life-cycle

2.1. Classification

BHV-1 is a member of the HV family, whose type species is HHV-1, also known as herpes simplex virus 1 (HSV-1).

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Membership in the family is based on virion architecture: a core containing a linear double-stranded (ds) DNA genome, an ~100 nm icosahedral capsid of 162 capsomers, an amorphous tegument, and an envelope containing viral glycoprotein (GP) spikes (Pellett and Roizman, 2007). HV specify a large number of enzymes for DNA synthesis, processing of proteins, and other functions. The genome synthesis and capsid assembly occurs in the host cell nucleus. Production of infectious progeny results in the destruction of the host cell. All HV are able to remain latent in their hosts (Pellett and Roizman, 2007).

BHV-1 is a member of the α HV sub-family, whose type species is HHV-1. Members of this subfamily are classified based on variable host range, short reproductive cycle, lytic infection of cells, and ability to establish latency primarily in sensory ganglia (Pellett and Roizman, 2007). The α HV include numerous viruses of veterinary importance, including the varicelloviruses noted below and gallid herpesvirus 1 (infectious laryngotracheitis virus) and gallid herpesvirus 2 (Marek's disease virus). Such viruses may be studied as α HV models and for disease control purposes (Mettenleiter, 1996; Pomeranz *et al.*, 2005).

BHV-1 is a member of the genus *Varicellovirus*, whose type species is human herpesvirus 3 (HHV-3), also known as varicella-zoster virus (VZV). Membership in the genus is based on wide tissue tropism and genome arrangement (Cohen *et al.*, 2007). The varicelloviruses include suid herpesvirus 1 (SHV-1, pseudorabies virus, or PRV), equid herpesvirus 1 (EHV-1, equine abortion virus), equid herpesvirus 4 (EHV-4, equine rhinopneumonitis virus), and felid herpesvirus 1 (FHV-1, feline viral rhinotracheitis, or FVR) (Davison, 2010).

Isolation of BHV-1 was first reported in the USA in 1956 (Madin *et al.*, 1956). Subtypes 1.1, 1.2a, and 1.2b, formerly including 1.3a and 1.3b that are now a separate species (BHV-5), were identified by genetic and antigenic analysis (Engels *et al.*, 1981; Misra *et al.*, 1983; Brake and Studdert, 1985; Metzler *et al.*, 1985; Wyler *et al.*, 1989) and were associated with geographic range and prevalence of clinical manifestations (Edwards *et al.*, 1990; van Oirschot *et al.*, 1995; D'Arce *et al.*, 2002).

2.2. Virion structure

2.2.1. Genome

There are six sequence arrangements of the dsDNA genomes of HV, based on the presence and location of repeats of terminal sequences. BHV-1 takes the D form, in which the terminal sequence is repeated in an inverted orientation internally. The genome segment between the repeats (unique short, or U_S) exists in two orientations relative to the unique long (U_L) segment (Pellett and Roizman, 2007).

The genome of BHV-1 was first mapped by Mayfield *et al.* (1983), and later sequenced by an international consortium (Schwyzer and Ackermann, 1996). The genome maps of BHV-1.1 and -1.2 (Mayfield *et al.*, 1983) and BHV-5 (Engels *et al.*, 1986) were determined and percent identity of BHV-1.1 to BHV-1.2 (95%) and BHV-1.1 to BHV5 (~85%) calculated.

Seventy-three open reading frames (ORFs) were identified in the 135,301 base pair (bp) genome (Glazov *et al.*, 2010). Genes of HV overlap, and are not spliced (Pellett and Roizman, 2007). Of the 73 genes, 33 were found to be essential to *in vitro* replication, 36 were not essential, with the status of 2 dual-copy genes inconclusive (Robinson *et al.*, 2008). Most, but not all, of the genes of BHV-1 conform to HHV-1 homologs in location, sequence (Whitbeck *et al.*, 1994) and replication requirements (Robinson *et al.*, 2008). Of the 71 BHV-1 proteins, 67 are conserved in each of HHV3 and HHV-1 (Davison, 2010). Eight of 73 genes (spread among regulatory, capsid, tegument, and membrane proteins) differed from HHV-1 in their requirement for *in vitro* replication (Robinson *et al.*, 2008). Four ORFs are unique to BHV-1: Circ; UL0.5; UL3.5; and US1.5 (Schwyzer and Ackermann, 1996). Some genes are conserved across all HVs, including those that encode DNA polymerase, major capsid protein UL19 [virus protein (VP) 5], tegument protein UL7, and some envelope GPs such as gB. Others are conserved at the subfamily level; for α HVs, examples include latency-associated genes and gL (Pellett and Roizman, 2007; Davison, 2010). Genes and products of various HVs were named for positions of their restriction endonuclease fragments on gels, gene position on mapped genomes, sequence of expression or identification, and HHV-1 homolog. This can be particularly confusing when the genome position in a virus is not the same as the 'genome position name' of the HHV-1 homolog.

Host RNA polymerase II is responsible for viral DNA transcription (Roizman *et al.*, 2007). Viral gene transcription is temporally regulated, in immediate early (IE, or α), early (E, or β), early/late (leaky late, γ 1), and true late (γ 2) phases (Seal *et al.*, 1992; Roizman *et al.*, 2007).

IE genes are defined as those transcribed in the absence of *de novo* viral protein synthesis. In HHV-1, IE transcription is induced by the tegument protein α -trans-inducing factor (TIF) (VP 16), occurs in the first 2–4 h after infection, and includes transcripts for six proteins (Roizman *et al.*, 2005). Several of these encode regulatory proteins that stimulate expression of E and late (L) genes (Smiley, 2004), and one [infected cell protein (ICP) 0] is involved in blocking host cell silencing by the nuclear domain ten protein of promyelocytic leukemia (PML) nuclear bodies (Tavalai and Stamminger, 2009).

In BHV-1, α -TIF also stimulates IE gene transcription by a different mechanism (Misra *et al.*, 1995). BHV-1 IE transcription units 1 and 2 (IEtu1 and 2) encode homologs of HHV-1 ICP0 and ICP4, plus Circ and ICP22,

respectively (Jones and Chowdhury, 2007). bICP0 is a transactivator for all viral promoters and the bICP0 transcript is constitutively expressed during productive infection (Jones and Chowdhury, 2007). bICP0 apparently does not bind to specific DNA sequences, suggesting that it activates by interacting with cellular transcriptional machinery (Jones and Chowdhury, 2007). bICP0, 4, and 22 activate E genes.

E (or β) gene transcription occurs 4–8 h after HHV-1 infection. β gene proteins include enzymes and DNA-binding proteins involved in DNA replication. $\gamma 1$ genes are only moderately stimulated by DNA replication, and they can be difficult to differentiate from β and from $\gamma 2$ genes. gB and gD genes are $\gamma 1$ in HHV-1 (Roizman *et al.*, 2007), but in BHV-1 the proteins are produced as early as 2–4 h after infection (before DNA replication) (Baranowski *et al.*, 1996). $\gamma 2$ genes are defined as having almost no production without DNA replication, and are largely involved in virion assembly. gC is a $\gamma 2$ protein. Most capsid, tegument, and envelope GPs are encoded by γ genes.

In addition to the ORFs identified in the BHV-1 genome, ten micro RNA (miRNA) genes have been identified, encoding 12 mature miRNAs with 14 miRNA-encoding loci. Two are located close to the origin of replication.

2.2.2. Core

For HHV-1, there is no specific protein coating the DNA in the core. There are polyamines, which are suggested to neutralize the DNA for better packing within the capsid (Roizman *et al.*, 2005).

2.2.3. Capsid

The capsid of HHV-1 is made up of 162 capsomers with $T=16$ icosahedral symmetry. The capsid is composed of an outer layer and an intermediate shell, with potential channels between the core and outside of capsid. The outer shell is composed of four proteins. VP5 is the major capsid protein, with five copies in each penton capsomere and six in each hexon capsomere (Roizman *et al.*, 2007). VP5 is conserved across α HV (Davison, 2010) and BHV-1 VP5 is an essential gene (Robinson *et al.*, 2008).

2.2.4. Tegument

The space between the envelope and the surface of the capsid is mostly unstructured in HHV-1, but contains a variety of viral proteins (Roizman *et al.*, 2007) differentially located in an inner and outer layer. They play a wide variety of roles, from capsid transport during entry and egress to regulation of transcription, translation, and apoptosis (Kelly *et al.*, 2009). In BHV-1, the tegument protein VP8 (UL47) is the most abundant protein in the virion (Carpenter and Misra, 1991) and appears to act as an RNA-transporting protein (Verhagen *et al.*, 2006). VP22 of BHV-1 is similar to that of HHV-1, but has some

differences in cellular localization (Harms *et al.*, 2000; Zheng *et al.*, 2005). VP22 activities include microtubule reorganization and intracellular trafficking. UL41 encodes the viral host shutdown (VHS) protein of BHV-1 – it is conserved in α HVs (Muylkens *et al.*, 2007). In other α HVs studied, VHS is an mRNA-specific RNase that triggers rapid shutoff of host cell protein synthesis (Smiley, 2004). It degrades both viral and host mRNA, but the viral mRNA continues to accumulate (Roizman and Taddeo, 2007).

The tegument also contains cellular and viral transcripts (Roizman *et al.*, 2007), as well as non-coding RNA (Amen and Griffiths, 2011). The RNA may be structural, or may code for an immunoregulatory protein as is known for HHV8. miRNAs are also known to be packaged in the virion (Amen and Griffiths, 2011).

2.2.5. Envelope

The α HV envelope consists of a lipid bilayer acquired from host cellular membrane, with virus-encoded proteins imbedded in it (Roizman *et al.*, 2007). Twelve envelope proteins have been described for BHV-1, ten of which are glycosylated, whereas two are not (gN or UL49.5 and US9) (Jones and Chowdhury, 2007). The ten GPs are named gB, gC, gD, gE, gG, gH, gI, gK, gL, and gM (Turin *et al.*, 1999). gB, gC, and gD are considered ‘major’ or more abundant GPs, and others (e.g. gE and gH) as ‘minor’ GPs (Baranowski *et al.*, 1996). Most GPs are homologous in function and structure to those specified by HHV1 but there are clear differences in sequences and roles (Turin *et al.*, 1999).

There are striking differences between the varicelloviruses HHV-3 and BHV-1; gE is essential in HHV3, but not in BHV-1, and gD is essential in BHV-1, but not present in VZV (Robinson *et al.*, 2008; Davison, 2010). The gN of HHV-1 and SHV1 is glycosylated, whereas UL49.5 is a ‘false GP’ in BHV-1 (Muylkens *et al.*, 2007). GP complexes of BHV-1 were variously named by their positions in polyacrylamide gels, by their molecular weights, by apparent homology with the GPs of other HV including HHV-1, and finally in accordance with the homologous HHV-1 GPs. The three major BHV-1 GPs can serve as examples: gB (named GVP 6/11a/16, 130 K/74 K/55 K, gI, and gB); gC (named GVP 3/9, 180 K/91 K, gIII, and gC); and gD (named GVP 11b, 150 K/77 K, gIV, and gD).

Five envelope GPs are involved in HHV-1 attachment and entry, as well as fusion of infected cells: gB, gC, gD, gH, and gL (Spear *et al.*, 2000; Rey, 2006). It is believed similar mechanisms apply to all α HV except those lacking gD, e.g. HHV3. The homodimer gC first binds non-specifically, possibly electrostatically (Cohen *et al.*, 2007) to the host cell membrane glycosaminoglycans. Binding by other GPs (e.g. gB non-specifically to those same receptors, or gD specifically to its receptors) can contribute to binding, and gC is not required for attachment. This is followed by the homodimer gD binding to one of the three cellular receptors that vary

by cell type and species, although they are usually homologous (Connolly *et al.*, 2001). The three types of receptors are: herpesvirus entry mediator (HVEM) A; members of the nectin family; and 3-O-sulfated heparin sulfate. The use of receptors is specific for each of the closely related α HV studied (HHV-1, HHV-2, SHV-1, and BHV-1) (Campadelli-Fiume *et al.*, 2000; Spear, 2004). The use of multiple receptors by any one α HV may be due to the receptors' presence and absence on various cell types (e.g. epithelium versus T cells) and their presence on various cell surfaces (e.g. apical for primary infection, tight junctions for cell-to-cell spread) (Spear, 2004).

In describing fusion of the viral envelope with the cell membrane, the differences in gB and gD among the α HV make comparisons difficult. It seems all HVs require gB and gH/gL for entry and cell-cell fusion, and some (including HHV-1 and BHV-1) also require gD (Spear *et al.*, 2006; Atanasiu *et al.*, 2010). gD of HHV-1 has a receptor binding face and a fusion activation face. The nectin-1 and HVEM binding sites are distinct, and the amino- and carboxyl-terminal peptides of gD play a role in covering or revealing binding sites (Di Giovine *et al.*, 2011). gD assumes a different conformation in the absence of receptor, bound to HVEM, and bound to nectin-1 (Spear *et al.*, 2006). It is believed that gD-receptor binding results in a displacement of the gD C-terminal region, triggering virus envelope – cell membrane fusion by gB or gH/L (Krummenacher *et al.*, 2005).

'Lead roles' in fusion have been assigned to each of gB and gH. gB is a homotrimer with fusion domains similar to the vesicular stomatitis virus fusion GP (Heldwein *et al.*, 2006). Homologs within the HV are highly conserved. A furin protease site is present on almost all gB homologs (including BHV-1 gB), but not on HHV-1. Since gH/gL did not resemble any documented viral fusion protein at a structural level, Atanasiu *et al.*, (2010) proposed that receptor-activated gD alters gH/gL, which in turn up-regulates the fusogenic potential of gB. Conversely, Roizman *et al.*, (2007) proposed fusion is due to a fusion peptide (Tu and Kim, 2008) and heptad repeats of gH, possibly activated by gB and conformationally altered gD. In this model, gL may block exposure of the repeats if not activated.

2.3. Virus entry into the host

The 'portals of entry' for BHV-1 are the mucous membranes of the upper respiratory tract, the genital tract, or the conjunctiva (Muylkens *et al.*, 2007). Direct nose-to-nose contact or aerosol over short distances can result in infection (Mars *et al.*, 1999, 2000). Genital infection can result from mating, or via infected semen (Muylkens *et al.*, 2007). It has been proposed that the first cells infected with HHV3 are the epithelium and T cells (Abendroth *et al.*, 2010; Arvin *et al.*, 2010).

Although BHV-1 subtypes were associated with different routes of infection, this may have been due to geographical isolation and common transmission. Each subtype will infect by the less-common route (Muylkens *et al.*, 2007), and no difference in tropism was found using ovine respiratory and genital mucosal explants (Steukers *et al.*, 2011). However, it should be noted that an anti-gC monoclonal antibody (MAB) was described that failed to react with all BHV1 genital isolates tested (Rijsewijk *et al.*, 1999), and gC differences in HHV-1 and -2 do influence cell tropism properties (Muylkens *et al.*, 2007).

2.4. Dissemination in the host

Intracellular BHV-1 virions were detected at 10 h post-infection, with transmission to adjacent cells occurring at that time (Babiuk *et al.*, 1975). gE (Rebordosa *et al.*, 1996), gI, and gG are important to cell-to-cell spread of HHV-1. gD, gB, and gH/L are required for cell-to-cell spread by BHV-1, with contributions from gE and gG (Trapp *et al.*, 2003; Muylkens *et al.*, 2007). It has been noted that microvesicles secreted by HHV-1-infected cells (light [L]-bodies) contain tegument proteins that can prepare cells for infection (Meckes and Raab-Traub, 2011).

Extracellular BHV-1 virions were detected at 12–13 h post-infection (Babiuk *et al.*, 1975), which would allow infection of adjacent and non-adjacent cells. The virus may spread by viremia, leading to, e.g. abortion or systemic disease. Viremia may be cell-free (Kaashoek *et al.*, 1996) but is more likely via infected lymphocytes (LC) (Nandi *et al.*, 2009).

2.5. Latency

Neurons of the peripheral nervous system are infected by cell-to-cell spread (Jones and Chowdhury, 2007). In a BHV-1 respiratory infection, this involves the trigeminal ganglia (TG), usually only first-order neurons. BHV-1 does not invade the central nervous system via the olfactory pathway as BHV5 does, due to differences in gE (Al-Mubarak *et al.*, 2004; Chowdhury *et al.*, 2006). High levels of virus gene expression and infectious virus are detected in the TG 1–6 days after infection (Jones and Chowdhury, 2007). Then lytic gene expression and infectious virus levels drop, but viral genomes can be detected, and latency-related (LR) and ORF-E transcripts are produced at high levels. LR transcripts are detected early after neuron infection (Devireddy and Jones, 1999) and may have a role in determining the outcome of neuronal infection (Jones and Chowdhury, 2007).

BHV-1 LR gene products inhibit cell proliferation, bICP0 RNA expression, and apoptosis (Lovato *et al.*, 2003; Jones *et al.*, 2006). BHV-1 LR protein appears to prevent cell cycle progression in neurons, with enhanced

survival of infected neurons (Schang *et al.*, 1996). The LR gene is antisense to bICP0, which is a transactivator for all viral promoters. Expression of the BHV-1 LR gene alone promotes survival in cell cultures stimulated to enter programmed cell death (Ciacci-Zanella *et al.*, 1999). The LR gene contains two ORFs, and the LR RNA is alternatively spliced in TG at day 7 (the transition to latency). The alternate transcript codes for a fusion of one ORF and part of the other, and the resulting protein binds two host cell proteins that can induce apoptosis, including BH3-interacting domain death agonist (Bid). It also binds an 'enhancer-binding protein' (C/EBP- α), which stimulates lytic gene transcription in other HVs. ORF-E is a small ORF within the LR promoter (and antisense to LR), which may maintain neuron function after infection (Jones and Chowdhury, 2007).

In HHV-1, miRNAs are expressed during latency that target ICP0 and ICP4, lytic genes (Boss and Renne, 2010). One of the 12 mature miRNAs encoded in BHV-1 is antisense to the LR gene (Glazov *et al.*, 2010).

BHV-1 latency may also be established in cells of lymphoid origin. BHV-1 DNA has been detected in lymphoid tissues when infectious virus was undetectable (Jones and Chowdhury, 2007). However, LR-RNA is not extensively expressed in those tissues (Winkler *et al.*, 2000).

Upon reactivation, bICP0 expression is stimulated, likely due to host entities (E2F family members) acting on early promoters (Workman and Jones, 2010). LR and ORF-E expression drop, and expression of other (lytic) genes is readily detected (Jones and Chowdhury, 2007). Dexamethasone treatment can trigger reactivation. It stimulates expression of cellular transcription factor C/EBP- α (described above), which interacts with the early promoter of bICP0 (Workman and Jones, 2010). Upon reactivation, α HV can spread from the infected neuron to adjacent cells at the axon synapse and along the axon's length (Tomishima and Enquist, 2002).

2.6. Transmission from the host

Virus is excreted from the host for 7–10 days after infection (Jones and Chowdhury, 2007), with some reports of 10–17 days with 10^{10} TCID₅₀ (Straub, 1990). Nose-to-nose contact, aerosol, breeding contact with infected prepuce or vaginal epithelium, artificial insemination with infected semen, and even mechanical transmission by ticks has been reported (Straub, 1990).

2.7. Consequences of infection

Diseases caused by BHV-1 include infectious bovine rhinotracheitis (IBR) (McKercher *et al.*, 1955), conjunctivitis (McKercher *et al.*, 1959), infectious pustular vulvovaginitis (Kendrick *et al.*, 1958), infectious pustular

balanoposthitis (Huck *et al.*, 1971), and abortion (Ormsbee, 1963) in adult cattle, as well as encephalitis (French, 1962a, 1962b), enteritis (Gratzek *et al.*, 1966), and generalized disease (Van Kruiningen and Bartholomew, 1964) in calves.

BHV-1 is also a significant initiator of and contributor to 'shipping fever' pneumonia (Yates, 1982; Hodgins *et al.*, 2002; Ellis, 2009), a fibrinous pneumonia caused by bacterial infection that is usually with *Mannheimia haemolytica* and less commonly *Pasteurella multocida* or others, subsequent to viral infection combined with other factors. BHV-1 infection does this by increasing susceptibility to secondary bacterial infection of the lower respiratory tract through injury to and induction of other changes in the tract and its cells, as well as through the local and more generalized immunosuppression described in later sections and elsewhere (Yates, 1982; McChesney and Oldstone, 1987; Tikoo *et al.*, 1995; Babiuk *et al.*, 1996; Hodgins *et al.*, 2002; Ellis, 2009; Levings and Roth, 2013).

The BRDC that includes BHV-1 respiratory disease and shipping fever is the leading cause of cattle death loss in the USA (Anon, 2011a), and has been estimated to cost the US cattle industry US\$3 billion annually (Jones and Chowdhury, 2007). The cost of BHV-1 and associated disease has resulted in extensive vaccination in North America, and to eradication campaigns in some European countries, including an expensive national program in Switzerland using a (serology) test-and-remove strategy (van Drunen Littel-van den Hurk, 2006).

3. The bovine innate immune response to BHV-1

3.1. The mammalian and bovine responses to alphaherpesvirus infections

The most studied mammalian immune systems are those of mice and humans. Aspects have been studied in other species due to zoonotic diseases, the species' economic importance, as disease models, or to discern origins or commonalities. Some features appear to be fundamental and are conserved among vertebrates, jawed vertebrates, or mammals (Hirano *et al.*, 2011), allowing useful generalizations or extrapolations. However, there are also differences in strategies, component members, sequences and so possibly modes of action [e.g. of interleukins (IL)] between mammalian orders, families, genera, and species.

It has been noted that 'Cattle specific evolutionary breakpoint regions have a higher density of species-specific variations in genes having to do with lactation and immune responsiveness' (Bovine Genome Sequencing and Analysis Consortium *et al.*, 2009). Investigations of bovine-specific immune phenomena have been hampered by a lack of reagents (Rouse and Babiuk, 1978; Boysen *et al.*, 2006), which is being addressed by

the US Veterinary Immune Reagent Network and the European 'Immunological Toolbox' (Entrican *et al.*, 2009). The interactions of stress, nutrition, and fertility with the innate and adaptive immune systems are important for cattle (Lippolis, 2008). The innate immune system (particularly phagocytic cell function), is susceptible to stress and nutrition impacts in cattle (Roth and Perino, 1998), and stress including social factors may impact their adaptive immune system (Salak-Johnson and McGlone, 2007).

Most of what is known about immunity to α HV was first elucidated in the HHV-1-mouse system, and then confirmed or expanded in HHV-1/2-human and other systems, e.g. SHV1-mouse or -swine. Studies of beta- and gamma-HV (β HV and γ HV) have also been instructive, but revealed differences in viral strategies, e.g. γ HV employ more molecular mimicry than do α HV (Pellett and Roizman, 2007).

In most cases, cattle are able to overcome a primary BHV-1 infection, so the primary immune response provides valuable information for primary, secondary, and passive immunity. The subject has been well reviewed at intervals (Rouse and Babiuk, 1978; Wyler *et al.*, 1989; Tikoo *et al.*, 1995; Babiuk *et al.*, 1996; Engels and Ackermann, 1996; Muylkens *et al.*, 2007). Briefly, the first insult results in interaction with non-specific soluble factors (constitutive and induced), which recruit innate immune cells to the site and activate them. These immune cells secrete more cytokines, kill virus-infected cells, and bridge to the adaptive response, including by presenting antigen (Ag) to LCs. Helper T cells then activate macrophages (M ϕ) and natural killer (NK) cells, and promote the proliferation of specific cytotoxic T lymphocytes (CTLs). Later, peaking after the infection is largely resolved, virus-neutralizing (VN) and other antibodies (Abs) are detectable. They likely help with clearing extracellular virus and with cellular cytotoxicity, and then can protect the host from reinfection.

The bovine innate immune response to BHV-1 is the focus of the remainder of this review. The bovine adaptive immune response to the virus and vaccination to prevent the diseases BHV-1 causes are the subjects of another review (Levings and Roth, 2013).

3.2. Non-immune barriers

The organism can protect itself from infection through avoidance of infected cohorts or materials (Medzhitov *et al.*, 2012). Mucous secretion and ciliary action of epithelia, coughing, and sneezing, antimicrobial substances in the air surface liquid, enzymes in tears and saliva, and tight junctions between epithelial cells protect the host from infection (Roth and Perino, 1998; Ackermann *et al.*, 2010; Keele and Estes, 2011). The host must also have the correct receptors to be infected by a virus; e.g. humans beings are not infected by many

non-human animal or plant viruses (Mayer, 2011). Once infected or colonized, the host may tolerate the foreign organism (Medzhitov *et al.*, 2012). Non-specific components of inflammation such as fever and the low pH of infiltrates may hamper viral infection (Mayer, 2011). Intracellular repression, e.g. cellular silencing of transcription (Roizman *et al.*, 2005) and stress-induced shutdown of translation (Buchkovich *et al.*, 2008), are additional, non-immune responses to infection.

3.3. Innate immune system components and activities

The first response to viral infection involves the innate immune system, which is able to recognize and resist or kill foreign organisms. Should the infection continue, the innate response will have primed the more powerful adaptive response (Iwasaki and Medzhitov, 2010; Shetnten and Medzhitov, 2011), which in turn uses many of the tools in the innate system. Innate and adaptive immune cells have a complex interaction in α HV infections (Schuster *et al.*, 2011).

3.3.1. Infected cells

Infection of non-immune (e.g. mucosal epithelial) cells triggers molecular signals for the infected and neighboring cells, including antimicrobial peptides (Klotman and Chang, 2006; Ackermann *et al.*, 2010) and interferons (IFNs). Many of the same triggers and signals are used in innate immune cells. Pathogens express signature molecules, known as pathogen-associated molecular patterns (PAMPs), essential to their survival and pathogenicity (Kawai and Akira, 2006; Meylan and Tschopp, 2006; Kumar *et al.*, 2011). These are recognized by conserved, germline-encoded host sensors known as pathogen recognition receptors (PRRs). Several families of PRRs are known to play a role in host defense, including toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and cytosolic DNA receptors (Ackermann *et al.*, 2010; Kumar *et al.*, 2011). Danger-associated molecular patterns (DAMPs) are generated by injured or dying cells or are present in the extracellular matrix, and can modulate the activation of PRRs (Tolle and Standiford, 2013).

The distribution of TLRs that recognize the PAMPs of herpesviruses varies by cell type and by species (Carty and Bowie, 2010; Paludan *et al.*, 2011). Ten bovine TLRs have been identified with specific but overlapping PAMP specificities (Ackermann *et al.*, 2010). Bovine TLR sequences reveal 66–86% nucleotide or amino acid (aa) sequence identity with their human/murine homologs (Werling *et al.*, 2006). Natural TLR variants enhance the risk of severe infections in cattle (Seabury *et al.*, 2010). Four TLRs (2/6 heterodimer, 3, and 9) have been shown to play a role in HSV resistance in mice. They act through

MyD88 (Chew *et al.*, 2009). TLR2 in association with TLR1 (Paludan *et al.*, 2011) or TLR6 (Chew *et al.*, 2009) recognizes GPs upon attachment. Once the capsid is internalized, viral dsDNA is recognized by TLR9 in the endosome. When the viral DNA is transcribed, higher order (ds, stem-loop) RNA molecules are recognized by TLR3 (Paludan *et al.*, 2011). When activated, the TLRs induce different signaling cascades depending on the adaptor protein, ultimately leading to the activation of the transcription factors NF- κ B, AP-1, and IFN-regulatory factor (IRF)-3 (Martinon *et al.*, 2009). HHV-1 infection results in MyD88-dependent and TRIF-dependent signaling (Vandevenne *et al.*, 2010). TLR activation results in the production of antimicrobial peptides, inflammatory cytokines and chemokines, tumor necrosis factor (TNF)- α , and costimulatory and adhesion molecules, as well as in the up-regulation of major histocompatibility complexes (MHCs) (Martinon *et al.*, 2009).

The RLR family includes two RNA helicases, RIG-I and melanoma differentiation associated gene-5 (MDA5), which were identified as cytoplasmic, viral RNA sensors (Martinon *et al.*, 2009). The higher-order RNA molecules produced after HV transcription are also recognized by RIG-I (products of RNA polymerase III) or MDA5 (replication intermediates) in the cytoplasm (Paludan *et al.*, 2011). Upon viral stimulation of the two RLRs, NF- κ B and IRF3/7 are activated and, in turn, induce the transcription of type I IFN (Ackermann *et al.*, 2010).

NLRs are categorized in subfamilies and variably distributed on innate immune cells and epithelia. HHV-1 is believed to trigger NALP3 (Chew *et al.*, 2009). NLRs stimulate cell activation, signaling through caspases (Martinon *et al.*, 2009). In the M ϕ inflammasome, caspase-1 activation results in cleavage of pro-IL 1 β to active IL-1 β and active IL-18 (Ackermann *et al.*, 2010).

HHV-1 viral dsDNA is recognized in the cytoplasm by DNA-dependent activator of IFN-regulatory factors (DAI) (Paludan *et al.*, 2011). This results in induction of type I IFN and other genes involved in innate immunity (Takaoka *et al.*, 2007).

3.3.2. Type I IFNs

The IFN family of cytokines is grouped into types I, II, and III. There are five human type I IFNs: IFN- α (13 subtypes), - β ; - ϵ ; - κ ; and - ω . There is one type II IFN (IFN- γ), and three type III (lambda) IFNs (IFN- λ 1–3 or IL-28A/B and IL-29). Type I and III IFNs are expressed in many cell types but type II is expressed in NK and T cells (Paladino and Mossman, 2009).

Bovine IFN- α class 1 (10–12 members) and class 2 (15–20 members) each show greater sequence homology with their human homologs than with the other bovine class (Ohmann *et al.*, 1987). Five bovine IFN- β genes were identified, unlike the one in humans. The bovine IFN- γ is encoded by one gene with introns, similar to other species (Ohmann *et al.*, 1987). A bovine type III IFN

(bovine IFN- λ 3) was identified and characterized, including characterization of its anti-viral activity (Segundo *et al.*, 2011). The receptor for IFN- λ (IL-28R α) is expressed by a limited range of cells, but includes epithelium, so mucosal epithelium can respond to IFN- λ (Perez-Martin *et al.*, 2012).

IFN- α or - β binds Jak/Stat receptors on adjacent cells, resulting in expression of a variety of anti-viral factors, with activities from virus-binding to replication inhibition (Ackermann *et al.*, 2010). Type I IFNs induce resistance to viral infection, increase MHC I expression and Ag presentation, activate dendritic cells (DC) and M ϕ s, and activate NK cells to kill virus-infected cells (Murphy *et al.*, 2008). IFN- β signals result in production of IFN- α subspecies and other IFN-stimulated genes (ISG) including IRF-7. IRF-7 activation results in up-regulation of IFN type I and in a full range of ISG. IFN- λ stimulation has much the same effect, but in a more limited set of cells (Perez-Martin *et al.*, 2012).

In BHV-1 infection, type I IFN is present within 5 h post-infection (Babiuk *et al.*, 1996). It is induced in the infected cell and in cells recruited to the site, and reaches peak levels in nasal secretions and blood by 36–72 h post-infection. Type I IFN levels remain elevated until virus replication ceases (Babiuk *et al.*, 1996). IFN- α regulates polymorphonuclear neutrophil (PMN), NK, and M ϕ effector activities and influences T-cell trafficking (Tikoo *et al.*, 1995). Locally induced IFN after aerosol BHV-1 infection was reported as providing partial protection from a second infection with BHV-1 or other viruses (Cummins and Rosenquist, 1980, 1982; MacLachlan and Rosenquist, 1982; Ohmann *et al.*, 1987). Intranasal (IN) and intramuscular (IM) treatment with recombinant bovine IFN- α 1 reduced clinical signs but not virus shedding of BHV-1 (Babiuk *et al.*, 1987). Correlation of IFN genotype and clinical outcome of BHV-1 infections has been demonstrated (Ryan and Womack, 1997).

Six proteins encoded by HHV-1 inhibit IFN expression or action: ICP0; ICP27; ICP34.5; US11; vhx; and US3 (Paladino and Mossman, 2009). HHV-1 ICP0 blocks IRF-3 and prevents IFN- β transcription. BHV-1 ICP0 inhibits IFN-dependent transcription (Henderson *et al.*, 2005) by reducing IRF-3 protein levels, likely through degradation (Saira *et al.*, 2007). This leads to reduced IFN- β promoter activity. In addition, bICP0 inhibits the ability of IRF-7 to activate IFN- β promoter activity, but does not reduce IRF-7 protein levels (Jones and Chowdhury, 2007; Jones, 2009).

3.3.3. IL and TNF- α

Bovine IL and TNF- α homologous to human and murine members have been described, with varying degrees of sequence similarity. These include: IL-1 α and -1 β (Maliszewski *et al.*, 1988); IL-2 (Cerretti *et al.*, 1986), IL-6 (Droogmans *et al.*, 1992), IL-7 (Cludts *et al.*, 1992), IL-10 (Hash *et al.*, 1994), IL-12 (Zarlenga *et al.*, 1995), IL-18

(Shoda *et al.*, 1999), and TNF- α (Cludts *et al.*, 1993). Their functions appear to be similar to the human/murine homologs, as measured by response to similar stimuli (White *et al.*, 2002). The major pro-inflammatory cytokines that are responsible for early responses are IL-1 α , IL-1 β , IL-6, and TNF- α . The balance of these with anti-inflammatory cytokines (for example IL-4, IL-10) determines the status of the inflammation.

In BHV-1 infection, pro-inflammatory cytokines, produced by infected cells and M ϕ s, cause an influx of PMNs and induce ICAM-1 on epithelial cells, to which leukocytes adhere. With increased vascular permeability, immune cells migrate to the site of infection. IL-1 and IL-6 stimulate GM-CSF production, contribute to M ϕ differentiation, and prime M ϕ s to release other molecules such as TNF- α (Babiuk *et al.*, 1996). IL-2 supports the growth and differentiation of Ag-activated T cells. IL-1 β and IL-2 have each been shown to enhance anti-BHV-1 responses when administered to infected calves (Turin *et al.*, 1999).

3.3.4. Chemokines

Chemokines are a family of low molecular weight chemoattractant cytokines. Chemokine expression may result in monocyte or LC homing to the site of infection, where the cells can differentiate or be activated. Bovine chemokines and chemokine receptors (homologs to human members) have been identified and similarities but also differences noted (Son and Roby, 2006; Widdison *et al.*, 2010; Widdison and Coffey, 2011). BHV-1 gC is a chemokine-binding protein, blocking activity (Bryant *et al.*, 2003) and preventing LC homing (Jones and Chowdhury, 2007).

3.3.5. Complement

The complement (C) system is well conserved across vertebrates (Zhu *et al.*, 2005), although the bovine C5a receptor has differences from human or murine homologs (Nemali *et al.*, 2008). The C cascade can be activated by three pathways: alternate (spontaneous), lectin, and classical (Ab). The latter is discussed elsewhere (Levings and Roth, 2013). C can neutralize virus particles either by direct lysis or by preventing viral penetration of host cells. HHV-1-infected cells are killed by direct C lysis (Ohmann and Babiuk, 1988). BHV-1 infected cells were killed by C-dependent neutrophil-mediated cytotoxicity (CDNC) (Ohmann and Babiuk, 1988).

Cells infected with BHV-1 (and HHV-1) express gC on the cell surface, which can function as a receptor for the cleavage product C3b (Ohmann and Babiuk, 1988; Favoreel *et al.*, 2003). It has been proposed that CDNC is due to cross-linking of C3b between the viral gC on the virus-infected cell and the receptor on the PMN (Babiuk *et al.*, 1996). The C3b receptor has also been proposed to prevent C action on the virus or the infected cell (Muylkens *et al.*, 2007). In addition, it has been suggested SHV1 incorporates host C regulators in its viral envelope

to regulate the spontaneous activation of the alternate pathway (Favoreel *et al.*, 2003).

3.3.6. Macrophages, neutrophils, and plasmacytoid dendritic cells (pDC)

Innate immune system cells include phagocytic and other cells that express PRRs that can recognize PAMPs. They do not have memory, but can be primed in some cases. Included in this category are the M ϕ , PMN, and DC.

M ϕ s have TLRs, scavenger receptors, and other PRRs on their surfaces, and engulf extracellular pathogens. They are important in BHV-1 infection, as shown by transfer experiments (Rouse and Babiuk, 1977). Early in the infection (after 3–4 days) they are a primary contributor of IFN- α production, believed to be important in limiting viral spread (Tikoo *et al.*, 1995). Later they are stimulated by IFN- γ from T cells to kill virus-infected cells in a non-MHC restricted way (Campos *et al.*, 1989, Babiuk *et al.*, 1996). The activity is detectable as early as 2 days after infection in lung parenchymal cells and 5–7 days after infection in peripheral blood (Tikoo *et al.*, 1995). BHV-1 infects M ϕ s, interfering with functions (Roth and Perino, 1998) such as TNF and other cytokine production, and with participation in antibody-dependent cell-mediated cytotoxicity (ADCC) (Tikoo *et al.*, 1995). BHV-1 infection of peripheral blood mononuclear cells (PBMCs) leads to their apoptosis (Muylkens *et al.*, 2007). Epitopes on gC are similar to that of a M ϕ receptor, suggesting immune evasion through molecular mimicry (Fitzpatrick *et al.*, 1990).

Neutrophils have PRR and receptors for C, and are the principal cells engulfing pathogens (Murphy *et al.*, 2008). Bovine PMNs are the principal source of α -defensins, and also produce (with epithelial cells) β -defensins and cathelicidins (Ackermann *et al.*, 2010). It was observed that PMNs prevented BHV-1 plaque growth without Ab, in a way that did not require contact (Rouse and Babiuk, 1977). PMNs were the most effective cells in ADCC assays, destroying infected cells more quickly and completely, with less antiserum (Grewal *et al.*, 1977). BHV-1 interferes with lung PMN activities (Roth and Perino, 1998; Muylkens *et al.*, 2007), and PMN from BHV-1-infected animals had reduced anti-bacterial functions such as reduced chemotactic and phagocytic capacity (Tikoo *et al.*, 1995). Epitopes on gC also cross-react with epitopes on PMNs, again suggesting immune evasion through molecular mimicry (Fitzpatrick *et al.*, 1990).

pDC express TLR7 and TLR9 in endosomes, with which they sense viral nucleic acids (Gilliet *et al.*, 2008). They internalize Ag, including by means of Fc γ II α (Lanzavecchia and Sallusto, 2007), and rapidly produce large amounts of type I IFNs when stimulated (Barchet *et al.*, 2005). pDC produce 1000 times the type I IFN of other cells, can produce TNF- α and (in mice) IL-12 when stimulated, and can present Ag. So they are key bridges from the innate immune response to the adaptive one (Reizis *et al.*, 2011). pDC have been identified in

cattle – they generated high levels of type I IFN in response to the TLR9 agonist CpG (Reid *et al.*, 2011). pDC have been described as the ‘professional producers’ of type I IFN in response to all human and mouse HVs tested (Baranek *et al.*, 2009). Although no reports of bovine pDC response to BHV-1 have been published, bovine pDC interacting with immune-complexed virus were the major source of type I IFN production during acute FMDV infection in cattle (Reid *et al.*, 2011).

3.3.7. NK cells

NK cells are derived from a common lymphoid progenitor with T cells and B cells, but have been categorized as an innate immunity cell. They mediate cytotoxicity as CTLs do (by degranulation), but the killing is not MHC-restricted. Cytotoxic granules are released onto the surface of the bound target cell, and the granule contents (perforin and granzymes) penetrate the cell membrane and induce programmed cell death. NK cells have multiple receptor types: killer lectin-like receptors (KLRs); killer cell immunoglobulin (Ig) -like receptors (KIRs); and natural cytotoxicity receptors (NCRs) (Murphy *et al.*, 2008). NK cells can undergo a clonal-like expansion following virus infection in human beings and mice, and previously primed NK cells can mediate secondary memory responses in mice in spite of lacking recombination activating gene (RAG)-recombinase-dependent clonal Ag receptors (Paust and von Andrian, 2011; Sun *et al.*, 2011).

Bovine NK cells have been identified as constitutively expressing homologs of the human NK receptors NKp46, CD244, and CD94, and the granule proteins granulysin and perforin (Endsley *et al.*, 2006). Multiple receptors have been identified on NKp46 (CD335) expressing, CD3⁻ LCs, including multiple KIRs and a single Ly49 (Boysen and Storset, 2009). NK cells produce IFN- γ (Boysen and Storset, 2009). Two sub-populations (CD2⁺ and CD2⁻) were distinguished, both cytotoxic, both producing IFN- γ and transcripts for KIR, CD16, CD94, and KLRJ (Boysen *et al.*, 2006).

NK-like cells (CD2⁺, CD4⁻, and CD8⁻) were stimulated by cytokines to kill BHV-1-infected cells without MHC restriction (Babiuk *et al.*, 1996). NK killing was dependent on Ag expression, with gB and gD being primary targets and gC of lower importance (Babiuk *et al.*, 1996). NK cells scan host cells for both stimulatory and inhibitory signals. The reduction in MHC production that many cause α HV should increase NK targeting. Some HV target both signals for reduction using miRNAs, but this activity is not among those listed for α HV when summarized by Griffin *et al.* (2010). Some α HV-infected cells do internalize gB, which should reduce NK targeting (Deruelle and Favoreel, 2011). Blocking of host cell apoptosis by BHV-1 and other α HVs is described elsewhere (i.e. CTL section Levings and Roth, 2013).

3.3.8. Interferon gamma

IFN- γ is produced predominantly by NK and natural killer T (NK T) cells as part of the innate immune response, and by CD4⁺T-helper 1 (Th1) and CD8⁺ CTL effector T cells as part of the adaptive immune response (Schoenborn and Wilson, 2007). IL-12 produced by Ag-presenting cells (APC) stimulates NK and T cells to produce IFN- γ (Jaime-Ramirez *et al.*, 2011). The bovine IFN- γ is encoded similarly to other species (Ohmann *et al.*, 1987).

Type II IFN is involved in the immune response to HHV-1 (Paladino and Mossman, 2009). It is ‘a predominant response after BHV-1 infection’ (Campos *et al.*, 1989) and is necessary for the activation of non-MHC restricted cytotoxic activities mediated by M ϕ s. HHV-1 US3 modifies the IFN- γ receptor post-transcriptionally, resulting in inhibition of ISG induction (Paladino and Mossman, 2009).

3.4. Innate-like intermediates

Four innate-adaptive evolutionary intermediates have been described for human beings and mice: $\gamma\delta$ T cells, B-1 cells, NK T cells, and natural Abs (Murphy *et al.*, 2008).

Human and murine T cells expressing $\alpha\beta$ and $\gamma\delta$ TCRs are said to perform non-overlapping roles in the immune response. $\alpha\beta$ T cells are located primarily in secondary lymphoid organs, recognize peptides in association with MHC I and II, and respond by facilitating the production of Ab or by lysing infected target cells. $\gamma\delta$ T cells represent a small percent of cells in the thymus and secondary lymph tissue, are abundant at epithelial surfaces and use fewer gene segments (to encode the TCR) to recognize a wider variety of Ags, including non-classical MHCs, heat shock proteins, and lipids (Lee *et al.*, 2010). Some $\gamma\delta$ T cells appear to recognize Ag without presentation (Murphy *et al.*, 2008). Bovine $\gamma\delta$ T cells have different characteristics (Levings and Roth, 2013).

B-1 cells are a separate lineage of B cells (distinct from conventional, or B-2 cells) that produce large quantities of multi-reactive IgM, IgG3 and IgA (natural Ab) (Tarakhovskiy, 1997; Hardy, 1992). Such CD5⁺ cells are found in various proportions and locations by species, and CD5 expression in cattle may represent activation (Haas and Estes, 2001). Naessens (1997) suggested all bovine B cells are of the B-1 lineage because they lack IgD.

NK T cells express TCRs using one invariant α chain, paired with one of a few β chains, and they produce cytokines rapidly (Murphy *et al.*, 2008). It has been posited that cattle don’t have NK T cells based on their lack of a functional CD1d gene and a failure to react to a potent NK T stimulus (Van Rhijn *et al.*, 2006).

4. Summary/conclusions

BHV-1 is an α HV infecting a variety of artiodactyl species. Its 135,301 bp genome includes 73 genes, whose transcription is temporally regulated. The 12 envelope proteins include five GP involved in viral attachment and entry. Infection results in both rapid lytic replication and latent infection, primarily in sensory ganglia.

The infected cell recognizes the pathogen's components and replicative intermediates by means of a variety of PRRs, and responds using internal signals and signaling of other cells via IL to express anti-viral factors. Pro-inflammatory cytokines produced by infected cells and M ϕ result in recruitment and activation of innate immune cells. These cells, including M ϕ s, PMNs, pDCs, and NK cells, use similar PRRs and signals, phagocytose the pathogen or kill infected cells, and if insufficient to clear the infection, prime and bridge to the adaptive immune response.

The virus possesses a variety of immune evasion strategies, including: inhibition of type I IFN production by multiple mechanisms; binding of chemokines and C cleavage products; infection of M ϕ s and PMNs resulting in reduced function; immune evasion via molecular mimicry; and latent infection with decrease of structural gene expression. In summary, there is a delicate balance between viral infection, host response, and viral evasive measures in BHV-1 infection and immunity in cattle.

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