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Caprine Arthritis Encephalitis Complex

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Summary

The caprine arthritis encephalitis virus (CAEV) is a lentivirus that persistently infects goats and sheep. The finding that CAEV and Maedi-Visna viruses frequently cross the species barrier between goats and sheep, and vice versa, has changed our view of the epidemiology of these viruses that are now referred to as small ruminant lentiviruses (SRLV).

CAEV is transmitted from infected mothers to their offspring, mainly via ingestion of infected colostrum and milk. This permits the implementation of control measures based on the segregation of newborn kids immediately after birth that successfully cut the seroprevalence in infected flocks, eliminating CAEV induced clinical disease. CAEV induces overt pathology in about one third of the infected animals. The frequency of affected animals varies in different goat families, pointing to an important genetic component in this disease. The principal manifestations are encephalitis and interstitial pneumonia in young animals, whereas arthritis and mastitis predominate in adult goats. The immunopathological mechanisms leading to disease are to date unclear and involve the principal components of the immune system, i.e., the professional antigen presenting cells, which are the principal target of CAEV, and whose activity, e.g., cytokine production, is modulated by the infection, and the B- and T-cell immune responses that are also manipulated by the virus. *In vivo*, infected animals usually have low viral loads, indicating that virus replication is tightly restricted by mechanisms that remain unclear. Finally, the complex biology of SRLV makes them a great challenge for diagnostic laboratories. In this brief review, the literature pertinent to all these aspects is summarized and discussed.

Introduction

This short review is centered on the Caprine arthritis encephalitis virus and its target species i.e., the goat. However, in the light of numerous publications showing that the species barrier between goat and the Maedi-Visna Virus (MVV) or sheep and CAEV are much less tight than was previously thought, the term small ruminant lentiviruses (SRLV) will be used to deal with situations that apply to both viruses and target species.

The purpose of this review is to briefly illustrate the clinical and pathological features of CAEV induced disease, to give an overview of the potential pathogenetic mechanisms leading to clinical manifestations and to present a critical review of the diagnostic tools used to detect infected animals. The molecular aspects pertaining to the virus genetic setup, virus replication and molecular epidemiology of CAEV are beyond the scope of this review and, when appropriate, relevant publications in these fields of study will be suggested to the readers.

The CAEV virus

Taxonomy

The precise taxonomical classification of CAEV, as reported in the universal virus database ICTVdB [1] (<http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdB/>), is the following:

Family: 00.061. *Retroviridae* – Subfamily: 00.061.1. *Orthoretrovirinae* – Genus: 00.061.1.06. *Lentivirus* – Species: 00.061.1.06.007. *Caprine arthritis encephalitis virus* (ICTVdB Virus Code: 00.061.1.06.007. Virus accession number: 61106007.)

Virus Genome And Replication

Analogously to the other lentiviruses, CAEV has a complex genome characterized by the presence of regulatory-accessory genes such as *tat*, *rev*, and *vif*, complementing the essential retroviral genes: *gag*, *pol* and *env* (Fig. 1). As mentioned in the introduction, the molecular mechanisms of virus replication and the activity of the regulatory-accessory genes of CAEV are not dealt with in detail in this short review. Briefly, the Rev protein was shown to mediate the efficient transport of unspliced or uniquely spliced viral RNA to the cytoplasm and therefore, to be indispensable for an efficient virus replication [2]. In analogy to the HIV Tat protein, CAEV-Tat was originally described as transcriptional activator acting on the virus long terminal repeats (LTR). Further studies, however, challenged this interpretation and showed that CAEV-Tat possesses functions such as the capacity of blocking the progress of the cell cycle in G(2), analogous to the HIV *vpr* gene [3-5]. Finally, the *vif* gene was shown to be essential for an efficient virus replication *in vitro* and especially *in vivo* [6,7]. Additional studies have shown that CAEV-Vif interact with cellular proteins [8,9], strongly suggesting that, in analogy to its HIV counterpart, this protein may be involved in protecting the viral genome from the attacks of cellular cytidine deaminases such as those belonging to the mammalian APOBEC3 family [10,11].

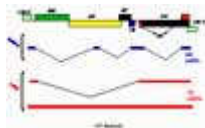


Figure 1. Schematic representation of the CAEV genome. Different multiple spliced mRNA (MS mRNA) are expressed early in the replication cycle of CAEV and their transport to the cytoplasm does not require Rev expression. Singly spliced or unspliced mRNA (US mRNA) are expressed late and depend on Rev to exit the nucleus. See the main text for a brief description of the function of the regulatory-accessory genes. - To view this image in full size go to the IVIS website at www.ivis.org . -

Target Cells *in vivo* and *in vitro*

Monocytes-macrophages and, in analogy to MVV, most likely dendritic cells [12] are the main target cells of CAEV [13]. As shown for MVV infected cells, monocytes carrying the lentiviral provirus in their genome shows little or no viral transcription [14]. These latently infected cells are believed to function as "Trojan horses" [15], capable of spreading the virus to different organs, while eluding the host immune response. The terminal maturation of monocytes into macrophages, which follow the extravasation of these cells in various tissues, activates the expression of the transcription factors necessary for virus replication, setting off the production of infectious virus [16,17].

The cultivation of monocyte *in vitro*, under culture conditions favoring the differentiation of monocytes to macrophages, is routinely used to isolate CAEV, typically by co-culturing infected peripheral blood mononuclear cells (PBMC) with indicator cells such as goat synovial membrane (GSM) cells [16,18,19]. This procedure is relatively inefficient, on the one hand because of the low frequency of virus-infected cells, estimated at about 1 infected cell in 10^6 - 10^7 circulating PBMC [20,21], and on the other hand because numerous SRLV field isolates do not replicate efficiently in fibro-epithelial cells such as GSM cells, routinely used in these co-culture protocols [22], or, while replicating, are not cytopathogenic and therefore difficult to detect without applying cumbersome immunostaining protocols [23,24].

In addition to monocytes-macrophages, several cell types, such as goat endothelial-, mammary epithelial-, granulosa-, oviduct- and microglial cells, are permissive to CAEV infection *in vitro* and *in vivo* [25-34]. The restricted expression of viral antigens and the low number of infected cells, however [35-38], cautions against over-interpreting the biological relevance of these cells in CAEV persistence.

Clinical And Pathological Aspects

In the early 70's CAEV was recognized as a clinical disease of goats. Two forms of the disease were observed, encephalitis of kids, associated with a mild form of interstitial pneumonia, and arthritis in adult goats [39-41]. At that time, the etiology was unknown and the association between the two forms of the disease was not immediately recognized. With the isolation and characterization of the etiological agent [23,42], permitting the first experimental infections, it was formally demonstrated that encephalitis, pneumonia and arthritis are caused by the same virus, i.e., CAEV [43].

Arthritis: Clinical Aspects

Arthritis of the carpal joint is certainly the principal clinical manifestation of CAEV in goats. Only about one third of the infected animals show overt clinical symptoms. This disease affects mainly adult goats and was described as "big knees" disease long before the characterization of the etiological agent (Fig. 2). The distinct frequency of CAEV induced arthritis in certain goat families suggested an hereditary origin of this disease [44] that can now be explained by the way the virus is transmitted from one generation to the next, that is via infected colostrum from mother to kids. Additionally, a genetic predisposition to develop clinically manifest arthritis upon infection has been demonstrated [45-47]. In contrast, no evidence for genetic resistance to infection has been found, although some breed differences in the susceptibility to infection have been suggested [48,49].



Figure 2. Adult Saanen goat with clinical arthritis. The arrow point to the inflamed and turgid carpal joints. - To view this image in full size go to the IVIS website at www.ivis.org . -

Clinically, the disease is mainly characterized by an insidious onset, leading to a permanent, usually symmetrical, inflammatory affection of several joints, with carpalitis and the ensuing swelling of the carpal joints as the most prominent and early manifestation [40, 50]. Sporadically, the affected animals show signs of pain although only in the very late phases of the disease. This certainly contributed to the relatively low awareness of goat owners for this disease [51,52]. Experimental infections with CAEV have revealed a clear association between viral load and the severity of disease in the carpal joints and the mammary gland [19,37,53].

X-ray analysis can detect pathological changes such as soft-tissue mineralization and erosion of articular surfaces. The affected joints contain excessive synovial fluid with abundant mononuclear inflammatory cells present in the aspirate [54].

Arthritis: Pathological and Histopathological Changes

The gross and microscopic lesions in the carpal joints induced by CAEV have been described in detail by several authors [50,55-61]. The affected carpi show periarticular swelling, accumulation of synovial fluid and, in the most severe cases, soft tissue mineralization, appearance of fibrin strings and macroscopic articular surface destruction (Fig. 3). The histopathological examination of the affected synovial membranes shows synovial lining hyperplasia, a prominent hypertrophy of the villi, massive mononuclear cell infiltrations of intima and subintima, and (neo-) angiogenesis.



Figure 3. Gross lesions in an arthritic carpal joint. On the right, the massive hypertrophy of the synovial villi is evident, while on the left, the macroscopic lesions at the surface of the cartilage are visible (arrows). - To view this image in full size go to the IVIS website at www.ivis.org . -

The mononuclear cell infiltrates may be organized in ectopic lymphoid tissue comprising B cell germinal centers and activated T cell mantles. Abundant B- and plasma cells expressing immunoglobulin surround the follicles and are dispersed throughout the inflamed villi [50,56-61].



Figure 4. Ectopic lymphoid tissue with plasma cells infiltration. The left arrow points to a plasma cell stained with an anti-goat IgG serum followed by an alkaline phosphatase labelled secondary antibody and finally revealed with a fast red coloration. The right arrow shows the early organization of the ectopic lymphoid tissue in the synovial membrane of an experimentally infected goat, 33 days post-infection. (Courtesy of H. Pfister). - To view this image in full size go to the IVIS website at

Mastitis

Invasive mastitis is an important clinical manifestation of CAEV and is known as "hard udder" disease in analogy to the "hard bag" disease described in MVV infected sheep [62,63]. The palpable nodules are caused by a severe interstitial mastitis characterized by the infiltration of the mammary gland tissue with numerous mononuclear leukocytes [19,25,26,40,58]. The economic importance of this disease is controversial because the few studies aimed at quantifying the impact of CAEV induced mastitis on milk production have provided contrasting results ranging from no reduction in milk production to up to 15% reduction associated with poor milk quality, for instance reduced butter fat content [51,64,65].

Encephalitis

As mentioned in the introduction, encephalitis was originally observed in the early 70's in the north-west of the United States and was described as leukoencephalomyelitis affecting mainly young animals [39]. Reports from Canada, Germany and Australia followed, indicating that this form of the disease was more widespread than had been suspected [66-68]. Nevertheless, except for some sporadic cases, the incidence of clinically manifested leukoencephalomyelitis in CAEV infected flocks is well below that of CAEV induced arthritis. In analogy to the Visna form of MVV, virulence factors carried by particular strains of CAEV, such as duplication in the long terminal repeats, may determine the neurotropism of these viruses [69-71].

The affected animals are typically between 2 and 6 months old, but also adult animals may develop the neurological form of the disease. At first, the animals have a hesitant shuffling gait when driven, followed by posterior paresis and ataxia, leading to tetraplegia within 1-3 weeks after onset of the symptoms. They are usually afebrile, with cases of mild to moderate fever reported, alert and have a normal appetite [63]. The withdrawal reflexes as well as pain perception are not affected (G. Georgsson, personal communication), while hypertonia and hyperreflexia were also reported [72].

Histologically, inflammatory lesions can be detected in the brain and spinal cord with involvement of the meninges and plexus chorioideus. Lesions are frequently localized in the subpia and subependyma [39,73]. Perivascular, focal accumulation of lymphocytes, macrophages and plasma cells have been described, with additional infiltration of the white matter and proliferation of glial cells. Demyelination is a prominent feature of the histopathological picture, accompanied by malacia and local calcifications in the most severe cases that may also show cavitations extending into the gray matter of the spinal cord [39,66, 67,72-75].

Pneumonia

Lymphocytic interstitial pneumonia was initially described in association with CAEV induced leukoencephalomyelitis in kids and subsequently was also described in adult goats [39,76]. As for the other affected organs, the lung tissue with especially its caudal or cranioventral lobes and the bronchia show infiltration and proliferation of lymphocytes, plasma cells, and macrophages [39,73,76]. Interstitial bronchopneumonia is certainly less prominent in CAEV infected goats than MVV infected sheep [77], however, the lung of infected goats and especially the lung macrophages, obtained by bronchoalveolar lavage, are an important sites of virus replication *in vivo* [19].

Immunopathological Aspects of CAEV Induced Disease

The concept of "slow disease" [78], coined by Sigurdsson in 1954 to describe diseases induced by infectious agents months or even years after the primary infection, is central to understanding CAEV induced pathologies [78]. Sigurdsson used this definition to describe Rida (scrapie in Icelandic) [78], a sheep disease currently known to be induced by prions, and Maedi (Icelandic for shortness of breath) a consequence of MVV infection [79].

As early as in the 1980's, Ashley Haase proposed three crucial questions on the nature of lentivirus induced "slow disease" [21] that remain highly relevant and largely unanswered:

1. How does the virus persist and spread in the face of a vigorous and sustained immune response by the host?
2. What causes the destruction of tissue?
3. Why do the pathological events evolve so slowly?

Restriction of Virus Replication *in vivo*

SRLV cultivated *in vitro* on appropriate virus strains adapted cell substrates, such as goat or sheep synovial membrane cells, chorioid plexus cells or macrophages, usually replicate vigorously, reaching high titers. *In vivo*, however, their replication is greatly restricted. This restriction *in vivo* is certainly an important viral strategy to evade the immune response and to persist in the infected host. The mechanisms of restriction, however, are still unknown. An efficient immune response of the host was suspected at first, but very early it became clear that this was not the answer. Indeed, immunosuppression of MVV infected sheep attenuated the inflammatory response and tissue lesions in the animals but did not increase their virus burden [80,81].

Type I interferon, a pivotal cytokine of innate immunity, and an additional, interferon-like soluble factor released by T cells

upon contacting, in an MHC unrestricted fashion, infected macrophages were proposed as important restriction factors of SRLV replication *in vivo* [82-86]. However, although susceptible to the inhibitory effects of type I interferon, SRLV still replicate to substantial titers in the presence of these antiviral factors [87,88] (and L. Hüsser, G. Bertoni and M. Schweizer, unpublished observations).

Alternatively, virus replication may be restricted *in vivo* because of the selective availability of transcription factors regulating viral replication in particular cells, thus explaining why SRLV replicate in mature, tissue-bound macrophages but are restricted in the circulating monocytes [16,17]. This observation led to the proposal of the elegant Trojan horse hypothesis of virus spread, which postulated that the latently infected monocytes act as a Trojan horse carrying the immunologically invisible viral genome in different target organs where, upon differentiation of these cells into macrophages, the necessary transcription factors become available and virus replication can start [15]. This, however, does not explain why, in persistently infected animals, virus replication is restricted in target cells, such as the synoviocytes and even macrophages, which are capable of sustaining a vigorous virus replication *in vitro* [37,53,89].

Immunopathology and B Cell Immune Response

Experimentally SRLV infected goats and sheep readily seroconvert and several groups have analyzed in detail the antibody response of these animals. The speed of seroconversion in naturally infected animals, however, may span quite a wide range, from a few weeks to several months, therefore making a reliable serodiagnosis of these infections quite difficult [90].

The role of antibody in controlling SRLV infections is rather controversial. Neutralizing antibody is present but not in all infected and seropositive animals and at quite low titers [91]. Neutralization resistant CAEV escape variants have been detected in infected goats, suggesting that this antibody imposes a strong selective pressure on the virus. Yet, neutralization sensitive free virus, along with cell-associated virus, could be isolated from the synovial fluid or blood of infected goats in spite of the presence of this antibody, casting doubt on the relevance of neutralizing antibody in controlling CAEV [92,93]. The recurrent antigenic stimulation caused by the appearance of neutralization resistant variants in the joints was shown to be associated with the severity of clinical symptoms [94].

The antibody response of infected animals is directed to several virus proteins and in particular to the surface expressed envelope glycoproteins (Env), showing broad cross-reactivity between CAEV and MVV antigens [95-97]. The linear B cell epitopes of CAEV Env have been mapped for different strains of the CAEV [98-100]. The strength of this anti-Env antibody response is associated with the severity of arthritis implying that antibody mediated immunological mechanisms contribute to CAEV induced disease [101]. Elevated antibody titers to Env early after infection have been shown to reliably predict the eventual development of arthritis [102]. Goats with progressive arthritis have been found to have high antibody titers to the transmembrane envelope subunit TM and in particular to two immunodominant epitopes of CAEV TM associated with the appearance of disease [98,103]. Finally, IgM and IgG deposits, potentially part of immune complexes formed by viral antigen bound to specific antibody or autoantigens bound to autoantibodies were detected in the joints of sheep with clinical and subclinical synovitis but were never described in CAEV infected goats [104].

Immunopathology and T Cell Immune Response

T cell responses play a crucial role in controlling acute and persistent viral infections and are usually considered to be beneficial for the host [105,106]. Their role in protecting goats and sheep against SRLV is controversial and still unclear. Sheep transiently depleted of CD4 positive T cells, by repeated injections of specific antibody before an experimental infection with MVV, showed drastically reduced numbers of infected macrophages in the afferent lymph draining the site of infection, whereas the numbers of infected dendritic cells remained unaffected [107]. This paradoxical result shows how subtle the balance between the virus and the immune response can be. Recently, immunization experiments with a Gag synthetic peptide inducing a strong CD4 T cell immune response, confirmed that priming a CD4 T cell response transiently enhances virus replication following an experimental infection. The mechanisms responsible for this enhancement are still unclear but GM-CSF, expressed by the responding T cells or activated bystander cells, may play an important role [108].

CD8 positive cytotoxic T cells have been detected in infected goats and sheep and are considered important to successfully control the viral load of persistently infected animals [109-112]. Depletion of these cells in experimentally infected sheep, however, did not have an impact on the viral load, at least in the early phases of the infection, which puts into question the importance of these cells *in vivo* [113].

CAEV infection does not appear to influence the number, phenotype and CD4/CD8 ratio of T cells in chronically infected animals [114], whereas monocytes are significantly reduced [115]. The quality and polarity of the helper T cell response, however, may be affected. Long-term infected arthritic goats had a reduced CD4 T cell proliferative activity upon stimulation with purified Env antigen, compared to clinically healthy animals. In contrast, the affected animals showed higher anti-Env antibody titers as early as three months after experimental infection [102]. A polarized type 2 T cell response to Env antigen, characterized by a dominant IL-4 response and a reduced IFN- γ expression, was described in

CAEV infected goats that were in the process of developing clinical arthritis. Conversely, the infected but asymptomatic control animals showed a stronger IFN- γ response upon Env antigen stimulation, pointing to the beneficial effects of a type 1 immune response in controlling the viral load [116]. This cytokine imbalance appears to be antigen specific and not a generalized phenomenon, as demonstrated by the analysis of the expression of several cytokines in the lymph nodes of goats experimentally infected with a molecular clone of CAEV and showing drastically polarized viral loads [19]. Finally, *in vitro* studies have shown that CAEV directly manipulates cytokine expression in infected macrophages. The manipulation of the spectrum of cytokines produced by professional antigen presenting cells such as macrophages may well be an important factor influencing the quality and quantity of the T cell immune response. The constitutive expression of interleukin 8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1) is increased in infected macrophages, whereas the transforming growth factor β 1 (TGF- β 1) mRNA is down regulated. Furthermore, infected macrophages show an altered response to stimulation with agonists of Toll-like receptors such as lipopolysaccharide (LPS), heat-killed *Listeria monocytogenes*, or *Staphylococcus aureus*. Infected macrophages, compared to their uninfected counterpart, respond to stimulation with the aforementioned ligands with a reduced TNF α , IL-1 β , IL-6, and IL-12 p40 mRNA expression, whereas GM-CSF expression is enhanced or reduced depending on the stimulating agent [117]. These effects are seen only in macrophages expressing the virus at maximal rates. Therefore, the relevance of these observations for the *in vivo* context, characterized by a tight control of virus replication, needs further evaluation.

Diagnosis of SRLV Infections

Besides a diagnosis based on clinical symptoms, serology is certainly the most widespread and convenient method to identify SRLV infections. Additionally, several methods based on the polymerase chain reaction (PCR) have been developed to detect provirus DNA and, by introducing an additional step of reverse transcription (RT-PCR), viral RNA in different diagnostic samples such as PBMC and milk cells. Recently, a comprehensive and critical review on SRLV diagnostic methods has been published, covering serological and PCR based methods [118]. The review reflects the consent reached on this topic by the participants to the first Consensus Conference on SRLV organized by EU COST Action 834 in Lyon, France in 2002 [118]. In this review, only a brief summary of the methods reviewed by De Andrés is presented and special emphasis is put on the diagnostic difficulties caused by the peculiar biology of SRLV and the high variability and plasticity of their genome.

Serological Methods

Agar gel immunodiffusion (AGID), enzyme-linked immunosorbent assay (ELISA), radioimmunoprecipitation (RIPA), and western blotting (WB) are the methods commonly used for the serological diagnosis of SRLV infections. The quality of serological methods is defined by their sensitivity and specificity. Due to the absence of a "gold standard", the calculation of these parameters is particularly difficult for SRLV diagnostics; thus, the reliability of the published figures must be interpreted with caution. AGID is considered highly specific but relatively insensitive and has now been largely supplanted by different ELISA methods, used in monophasic or biphasic setups, based on purified viral antigens, recombinant proteins or recombinant peptides [118]. Additionally, competitive ELISA tests, based on the displacement of monoclonal antibody directed to specific epitopes by the antibody present in a test serum, have been described [118]. Due to their complexity and costs WB and RIPA are used only as confirmatory tests. In addition to the problems intrinsic to the diagnosis of genetically highly variable agents, discussed in the chapter on Caprine Herpesvirus Infection of Goats, the principal problem of SRLV serological diagnosis is certainly the slow kinetic of seroconversion, illustrated by the detection in seropositive flocks of several seronegative animals with positive PCR results [90]. This indicates that serology is certainly a valuable tool to determine the serostatus of a flock but may well fail at the individual level.

PCR Diagnostic Procedure

In the early 90's the first protocols designed to detect SRLV by PCR were published [119-121], raising new hopes concerning a highly sensitive and specific technique that would improve SRLV diagnosis. In spite of the early optimism [122], it became clear that genetic variability, associated with low viral loads, would pose enormous problems for the routine use of this technique [123]. De Andrés et al., appropriately summarized the numerous attempts to use PCR or RT-PCR as a diagnostic tool for SRLV diagnostic: "Overall, the results of these studies show that PCR tests tend to be less sensitive than many ELISA tests, though PCR appears to be able to detect infected animals prior to seroconversion. This suggests that a combination of serology and PCR might be optimal for detecting infected animals". The systematic sequencing of a large number of SRLV isolates confirmed that the design of new PCR primers with broader reactivity is possible but that the development of "pan-SRLV" PCR primers may remain a utopian task [124].

Diagnostic Implications of Genomic and Antigenic Variability

The knowledge accumulated over the last few years on the genetic diversity of SRLV shows an unsuspected variability of their genome [124,125]. This implies that the geographical distribution of different strains may influence the performance of PCR and serological diagnostic tests. Of particular importance in this respect is the finding that CAEV and MVV, once considered species-specific pathogens of goats and sheep, respectively, frequently cross the species barrier, infecting and persisting in apparently inappropriate target individuals and also spreading within the "wrong" target species. First evidence that these viruses were able to cross the species barrier was obtained by experimentally infecting goats with MVV

and sheep with CAEV [126-133]. Subsequently, molecular-epidemiological evidence was obtained indicating that cross-species transmission may occur under field conditions. The phylogenetic analysis of SRLV pol and env sequences obtained from naturally infected sheep in France by PCR and RT-PCR amplification of proviral DNA and viral RNA, respectively, revealed that these animals were infected with viruses more closely related to CAEV than MVV [134-136]. The peculiar SRLV epidemiological situation in France, characterized by the infection of a vast majority of seropositive sheep with viruses phylogenetically related to CAEV (B2 group), was confirmed in a recent, large survey covering different geographic areas and sheep breeds [137]. Additionally, several reports from different countries confirmed these observations indicating that the concept of species barrier in SRLV epidemiology must be revised [124,138-144]. Direct evidence was presented that sheep infected with particular MVV strains (A4) can infect goats [145], while goats infected with a CAEV strain belonging to the B1 phylogenetic group, once considered to be strictly goat specific, infected sheep under natural conditions [146]. Co-infections with different SRLV also occur and recently, a recombinant CAEV-MVV virus was detected in a naturally, dually infected goat [147]. Recombinant viruses, as already demonstrated for HIV [148], may have an important impact on the SRLV epidemiological situation. On the one hand, recombinant viruses may change their antigenic properties and escape detection by routine diagnostic tests. On the other hand, by exchanging or recombining their env genes, known to control the species specificity of SRLV, these viruses may expand the range of species potentially infected by these viruses [22,149,150].

The genetic differences between SRLV strains have obvious consequences on the antigenic characteristics of the viral proteins expressed by these strains. Type specific antigenic determinants are normally localized on Env [99,100], while other gene products such as Gag tend to carry group specific, cross reacting B cell epitopes [95]. The discovery of immunodominant, type specific epitopes in Gag, a key antigen in several serological SRLV tests, raised the possibility that false negative serological results may result from the use of inappropriate SRLV strains for antigen production [139,151]. The variability of the gag gene, especially in the portion encoding for the matrix protein, was confirmed in a detailed analysis of sequences obtained from several field isolates of CAEV [152]. The mapping of the B cell epitopes of the surface subunit (SU) of CAEV Env revealed the presence of an immunodominant epitope (SU5), located in the carboxyterminal region of SU and bridging a constant and a highly variable stretch of the protein [100,153]. Synthetic peptides, based on the deduced amino acid sequences of the SU5 region of several SRLV strains, were applied in an ELISA format and shown to be a very sensitive and reliable tool to detect early seroconversions. Applied in a particular epidemiological situation, such that found in Switzerland, where an efficient SRLV eradication campaign has cut the seroprevalence from 80% in the 1980's to below 1% today, these peptides revealed a problematic picture. A survey of more than 8,000 sera obtained from goats living in certified CAEV negative flocks revealed that more than 10% of the animals were seropositive in an SU5 ELISA (B. Schlup, paper in preparation). The simplest explanation would be that these results represent false positive reactions to the synthetic SU5 peptides. Two lines of evidence tend to exclude this explanation. To begin with, from about 20 animals seropositive in SU5 ELISA but negative in CheKit®, a commercially available whole virus ELISA, and WB, we demonstrated SRLV infections by PCR. Secondly, by plotting the cumulative percentages of sera versus the percentage optical densities (ODP, based on the optical density value of a control serum) obtained in SU5 ELISA, we observed that the SU5 peptides based on CAEV sequences reach the 95% cumulative level at an OD that is significantly lower than that of the SU5 peptides based on MVV sequences (Fig. 5). Due to their similar length and amino acid composition, it is unlikely that the SU5 peptides based on MVV sequences show a higher background compared to the CAEV peptides. Therefore, we interpret the aforementioned results as strong evidence that the Swiss eradication campaign, which successfully eliminated SRLV induced disease in goats, did not succeed in eliminating all SRLV strains circulating in certified CAEV free flocks. The SRLV still circulating appear to be more closely related to MVV than CAEV, which points to the sheep population as a potential source of infection for CAEV free goats. The results of a recent epidemiological study support this conclusion showing that the contact with seropositive sheep is the most significant risk factor for SRLV infection in CAEV free flocks [154]. The positive news for the Swiss CAEV eradication campaign is that, at least up to now, the circulating viruses appear to have a very low virulence. This notwithstanding, the presence of these SRLV imposes the continuation of a tight surveillance plan to monitor the prevalence of these viruses and the possible recurrence of virulent strains.

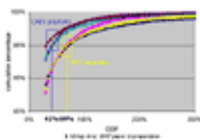


Figure 5. Cumulative percentage curves with CAEV- or MVV- derived SU5 peptides. The curves obtained with different CAEV SU5 peptides cross the 95% cumulative percentage mark at a lower ODP compared to the MVV derived peptides, suggesting that in CAEV free, certified flocks, several animals are seropositive for MVV SU5 peptides. The percentage optical densities (ODP) are calculated based on the optical density value of a control serum reacting in the same OD range with both, MVV- and CAEV- SU5 peptides. - To view this image in full size go to the IVIS website at www.ivis.org . -

Control of SRLV Infections

Shortly after the characterization of CAEV as the etiological agent of caprine arthritis, mastitis and encephalitis, a large serological survey revealed the global spread of this virus and the importance of the animal trade for the spread of this infection [155]. With the aim of limiting the economic losses caused by this virus, different strategies were proposed to

eliminate CAEV from infected flocks. The importance of colostrum and milk intake for the vertical transmission of SRLV was first demonstrated for MVV [156] and subsequently confirmed in CAEV with an elegant experiment involving the exposure of cesarean section-derived kids to different sources of virus [157]. Based on these results an eradication strategy consisting of separating the kids from the seropositive mothers immediately after birth and rearing them with pasteurized colostrum or substitutes, such as cow colostrum, was proposed, tested and shown to be highly effective in blocking the chain of infection between generations [157]. Segregation of kids at birth and rearing with safe milk and colostrum was shown to be superior to other eradication strategies, combining safe feeding with testing and removal of seropositive animals without segregation [158]. Similar results were obtained in sheep, where different eradication methods can substantially cut the numbers of seropositive animals [159-162]. Recent results suggest that in sheep, horizontal infection may play a more important role than was previously thought [163]. Infected colostrum, however, remains a major source of MVV infection for newborn lambs and its intake must be prevented to stop the chain of infection in flocks [164]. As mentioned above, the Swiss CAEV eradication program achieved excellent results segregating kids at birth and rearing them with cow colostrum and milk substitutes, combined with test and culling strategies, applied especially in flocks with very low seroprevalence. Cases of clinical disease have completely disappeared but, as discussed in the chapter on Caprine Chlamydiosis, SRLV were not completely eliminated because of the complex biology of these viruses and the shortcomings of the diagnostic tests available to date.

Vaccination Against SRLV

Over the past 25 years the HIV experience has taught us quite a harsh lesson on the enormous difficulties inherent in the development of an efficient vaccine against lentiviruses [165]. Except for the feline immunodeficiency virus [166], against which a vaccine was developed that was claimed to be efficacious, the development of a safe and efficient vaccine offering broad-spectrum protection has failed to date. SRLV are no exception in this respect. Nevertheless, several vaccination strategies have been tested and quite interesting results obtained. These experimental vaccines will hardly achieve an adequate efficacy to permit their use in the field. The experimental results obtained, however, are valuable data permitting an evaluation of the role of the immune response in controlling or enhancing SRLV replication and spread *in vivo*.

The inconsistent neutralizing antibody response typical of a natural CAEV infection could be overcome by immunizing goats with concentrated, live or inactivated virus emulsified in a strong adjuvant containing inactivated mycobacterium tuberculosis [128]. The potential risks of inducing a robust antibody response, however, were immediately recognized showing that a challenge exposure of vaccinated or persistently infected goats could exacerbate the arthritis symptoms [167-171]. The role of virus specific antibody in driving the manifestation of acute arthritis in these animals remains unclear and, especially for the intra-articular challenges, may just reflect a generalized hyperresponsiveness of CAEV infected goats to antigen-induced arthritis [172]. CAEV antigens do not induce classical enhancing antibody [173-175] and evidence was found that the induction of a CD4 T cell immune response to a conserved region of Gag transiently enhances virus replication *in vivo* [108]. Goats immunized with a recombinant vaccinia virus expressing the CAEV Env and boosted with affinity-purified Env antigen responded with a non-neutralizing immune response. Challenge infection of these goats revealed neither protection nor recrudescence of arthritis [176]. More promising results were obtained using a live vaccine based on a tat deletion mutant of CAEV-CO [177]. This vaccine did not induce sterilizing immunity in all vaccinated animals but significantly lowered the load of the challenge virus that was undetectable in the blood of all animals and detected only by PCR and at the site of injection in 2 out of 4 vaccinated animals. Unfortunately, the tat-deleted vaccine is still virulent inducing mild arthritis in the vaccinated animals, therefore precluding its use in the field [177]. A similar strategy was used to immunize sheep. Vaccination with an attenuated molecular clone of MVV failed to offer protection against a challenge infection with a closely related virulent virus but significantly lowered the viral load in the vaccinated animals [178]. The encouraging results obtained with plasmid-based vaccines against other pathogens encouraged the development of several experimental DNA vaccines against SRLV, expressing different viral antigens, with or without the addition of cytokine genes as potential adjuvants [179-181]. A prime boost protocol using a plasmid expressing the env gene of CAEV followed by booster immunizations with affinity purified Env protein showed no sterilizing immunity but mediated a long lasting control of the challenge virus [182]. Additionally, mucosal DNA immunization of sheep with a plasmid expressing the env gene of Maedi-Visna virus (MVV) protected the animals in the early phases after challenge but did not induce a long lasting immunity capable of controlling viral replication [183]. Finally, the vaccination strategies described above confirmed all the difficulties inherent in developing vaccines against viruses able to persist in the infected hosts. Some of the experimental vaccines described established that the induction of a virus specific but inefficient immune response in the vaccines may have potential harmful consequences, indicating that SRLV are indeed a valid model for the study of vaccine induced disease.

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