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Immune response to maedi-visna virus

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TABLE OF CONTENTS

1. ABSTRACT

The ovine maedi-visna virus (MVV) was the first lentivirus to be isolated and characterized 1957 in Iceland. MVV leads to a life-long, persistent infection with slow development of lesions in the lung and the central nervous system (CNS). The main target cells of MVV are of the monocyte/macrophage lineage and it does not infect T-lymphocytes or cause immune suppression like human immune deficiency virus (HIV). In spite of a fairly good immune response, including both neutralizing antibodies and cytotoxic T lymphocytes, the virus persists in the host and establishes a life-long infection. There are strong indications that the pathological lesions are immune-mediated and vaccination attempts have not only failed to induce sterile immunity but have occasionally caused increased viremia and more severe disease.

2. INTRODUCTION

Maedi and visna are two disease manifestations in sheep caused by a lentivirus that was brought to Iceland with the importation of apparently healthy sheep of the Karakul breed in 1933. Maedi, an Icelandic word meaning dyspnea, is used for a slow progressive interstitial pneumonia, visna meaning wasting, is used for a slow progressive inflammatory disease of the central nervous system, resulting in paresis or paralysis. Due to the long preclinical period and the insidious onset of maedi and visna, the diseases had spread unnoticed to many flocks when first recognized 6-7 years after the importation (1). The Icelandic breed of sheep originally brought to the country by the viking settlers were extremely susceptible. The diseases were described by Sigurðsson and co-workers (2-5) and the virus was then isolated, first from a visna

brain and then from maedi lungs (6, 7). The viruses were shown to be serologically related, and early transmission experiments indicated that visna and maedi were but different organ manifestations of infection with the same virus (8, 9), giving rise to the present name maedi-visna virus (MVV). On the basis of these diseases, together with pulmonary adenomatosis and scrapie, Björn Sigurdsson (10) formulated the classification of slow infections distinguishing them from acute and chronic infections. Maedi-visna virus is the prototype of the lentiviruses, a subgroup of non-oncogenic retroviruses that derive their name from Sigurdsson´s concept of slow infections (10-12).

MVV was the first lentivirus to be isolated, but lentiviruses have now been isolated from several mammalian species, including humans. The lentivirus of goats, caprine arthritis encephalitis virus (CAEV) is the closest relative of MVV and together they are called small ruminant lentiviruses (SRLV). There is evidence of cross species transmission of MVV and CAEV between sheep and goats (13-15). Lentiviruses of sheep are recognized worldwide and are known by different names such as maedi-visna virus (MVV), ovine progressive pneumonia virus (OPPV) and ovine lentivirus (OvLV).

The MVV exhibits typical retrovirus morphology (16) and the same basic biological features as other animal lentiviruses and the human immunodeficiency virus (HIV) (17). The MVV genome contains the three structural genes common to all retroviruses *gag, pol* and *env*, which encode the internal proteins (Gag), catalytic proteins (protease, reverse transcriptase, integrase and dUTPase) and envelope proteins respectively, as well as three small ORFs, which encode the regulatory and accessory proteins vif, tat, and rev (18-22). The Tat of both MVV and CAEV have been shown to be Vpr-like rather than a transactivation protein (23, 24).

The cellular receptor(s) for MVV has not been determined. The primary target cells of MVV *in vivo* are cells of the monocyte lineage, but viral replication occurs when monocytes differentiate to macrophages (25-28). Replication has also been demonstrated in dendritic cells (27, 29). Unlike the primate lentiviruses lymphocytes are not target cells in MVV infections.

MVV has a very long incubation period and during the initial outbreak in Iceland there was no evidence of clinical disease until 6 years after the importation of the Karakul sheep (30). This feature has been substantiated in several experimental infections. Transmission of MVV is mainly from ewe to lamb by colostrum and milk (31-33) and also through inhalation of respiratory secretions (30, 34). After infection and onset of disease symptoms there is generally a progressive clinical course. Various organ systems are affected and histopathologically the lesions are characterised by chronic inflammation. The most common symptom of maedi is dyspnoea becoming particularly obvious if the affected animal is exercised (2), whereas in animals with visna, gait is affected with paresis of the hindquarters progressing to paraplegia (5). Besides the lungs and the central nervous system (CNS) the mammary glands are also a MVV target organ, resulting in mastitis (35, 36) and in some cases also the joints, leading to arthritis (37, 38).

3. IMMUNE RESPONSE

3.1. Humoral immunity

MVV specific antibodies are induced in natural and experimental infection. These antibodies have been detected by various methods such as virus neutralization (6), complement fixation (39) immunofluorescence (40, 41) agar gel immunodiffusion (AGID) (42-44), passive hemagglutinaton (45), ensyme-linked immunosorbent assay (ELISA) (46), Western blot (47) and radioimmunoprecipitation (RIPA) (48, 49). The first test used was a complement fixation test (39) and virus neutralization test (50). ELISA is now considered to be the most sensitive and the serological test most often used in diagnosis of MVV (51). In experimentally infected sheep the complement- fixing antibodies were shown to arise 3-4 weeks after experimental infection (50) which is similar to what is seen in ELISA (52, 53). MVV persistently infected sheep have been shown by precipitation to make antibodies against most of the viral proteins (54). In immunoblotting antibodies have been detected against the precursor and mature gag antigens (p55, p35, p25, p17 and p14), against the env antigens (gp135 and gp 44) (47, 53, 55-57) and also against Rev in RIPA (49). The antibodies that are first detected in Western blot, in both naturally and experimentally infected sheep, are against the p25, and gp135 precedes the gp44 response (47, 53, 55, 56).

Several studies have mapped immunoreactive regions in Gag and Env of MVV and CAEV (58-67). The most immunodominant epitopes of the *env* gene of CAEV were found to map in the C-terminus of gp135 and in the N-terminus of gp44, where a highly conserved structure that corresponds to the immunodominant epitope of HIV and other lentiviruses is located (58, 59, 64, 67). We got similar results in a study with MVV, where we expressed nine overlapping peptides covering the *env* gene, five in gp135, three in gp44 and one covering the signal peptide. The peptides were expressed in *E.coli* as glutathione transferase fusion peptides. Serum antibodies from experimentally infected sheep, either with a visna strain or a maedi strain, were tested for binding to the peptides in immunoblot. Sera from all the eleven sheep tested bound to the C-terminal peptide of the gp44 and to the peptide containing the immunodominant epitope of the gp135 (unpublished results). In the same study we expressed seven overlapping peptides covering the entire *gag* gene, three for p25 (capsid), two for p16 (matrix) and two for p14 (nucleocapsid). Of these, the C-terminal peptide of p16 seemed to contain the most conserved epitopes, binding to all sheep sera tested. However, p25 is considered to be the first antigen recognized by the infected host (47, 56, 63) but it may not bind to all antisera due to genetic heterogeneity (68).

Neutralizing antibodies are important components of an effective immune response to many

pathogens. In experimental MVV infection, type-specific neutralizing antibodies are detected 1 ½ - 4 months post infection, and other more broadly neutralizing antibodies appear up to 4 years later in most sheep (8, 50, 69). One type-specific neutralization epitope has been mapped in the fourth variable domain of the MVV gp135 (70). The persistence of the virus in the face of a strong immune response has long been a puzzle. It has been proposed that one way for the virus to escape the immune response is by continuous change of epitopes through mutation (71). Antigenic variants and neutralization escape mutants have been documented for MVV like other lentiviruses (71-74). However, two studies found no evidence for the involvement of the antigenic variants in progression of the disease (73, 74). The role of neutralizing antibodies in delaying disease progression in lentiviral infection is not fully established. It has been disputed whether antigenic variants of lentiviruses arise as a result of immune selection. Although antigenic variants of lentiviruses can be selected in the presence of antibodies *in vitro* (75, 76), the functional role of antibodies under *in vivo* conditions is uncertain. Neutralization antibodies are absent or of a very low titer in infections with the American MVV strain (OvLV) and CAEV (77-80). However, we have obtained evidence for selection of antigenic variants by antibodies in experimental MVV infection with the Icelandic visna strain K1514 which induces a very good neutralizing antibody response in sheep (81). Twenty sheep were inoculated with visna strain K1514 and of 61 virus isolates that were tested for neutralization, ten turned out to be antigenic variants. All the escape mutants were isolated at time points when only the type-specific antibodies were acting, before the emergence of the broadly reactive antibodies. The association between the appearance of the antigenic variants and the presence of type-specific neutralizing antibodies but absence of the broadly reacting antibodies was shown to be statistically significant. Furthermore, the antigenic variants had mutations in the neutralization epitope region that were 96% non-synonymous compared to 53% of non-synonymous mutations in other parts of the env gene. Together, these results strongly indicate that the humoral immune response is effective at limiting the spread of virus in an MVV infection. Neutralizing antibodies have been found in the cerebrospinal fluid (CSF) of experimentally infected sheep where they are locally produced. The appearance of neutralizing antibodies in the CSF seems to coincide with the disappearance of free infectious virus from the CSF about 3-4 months after experimental infection (50).

MVV specific IgM serum antibodies have not been carefully looked at in MVV infection (82). Increase in the IgM levels in CSF during visna has been reported (83) and furthermore IgM granular deposits have also been observed in synovial membranes and upper layer of cartilage in MVV infected sheep (84). It is not known if this IgM was MVV specific. With ion-exchange chromatography it was demonstrated that both complement-fixing and neutralizing antibodies belong to the IgG1 subclass (82). Furthermore no IgG2 serum antibodies were found in immunoblot. The response to MVV seems therefore to be restricted to IgG1 (85). In contrast sheep infected with the parapox virus Orf or immunized with MVV Gag p25 in adjuvant raise IgG2 antibody titers (85). The pathological consequences of this lack of IgG2 in MVV infection is not clear. In ruminants there are only two major subclasses of IgG, and IgG1 is the predominant one (86, 87). In the sheep there is no evidence that production of interferon-γ (IFN-γ) correlates with production of IgG2 as it does in mice (88). However, in preclinical and clincal cases of CAEV phases of progressive arthritis have been associated with dominant IgG1 responses to the surface envelope of CAEV, whereas long term progressors have a relatively biased IgG2 surface envelope response (89-91). This is in line with observations in HIV infection where CD4 Th1 responses combined with IgG2 antibodies and IFN-γ producing CD4 cells are predictors of long-term progressors (92).

3.2. Cellular immunity

The most apparent differences between infection with SRLV and infection with the primate lentiviruses is that the SRLVs do not infect T lymphocytes nor do they cause T-cell depletion, and the overall CD4/CD8 ratio in blood is not significantly changed in animals that develop clinical disease (93-95). In viral infections, CD4 helper cells are pivotal both for production of antibodies and in maintenance of CD8 cytotoxic T cells (CTLs) and therefore play a critical role in immune defences against viruses. They can also have a direct role in protection as is suggested in HIV infection by strong correlation between proliferative CD4 T-cell response and persistently infected long-term non-progressors (96, 97) and also by presence of T helper cells in HIV exposed but uninfected individuals (for review see 98). Cell mediated immunity in MVV infection has been demonstrated by antigen specific cell proliferation against whole virus (93, 99-101). The proliferative assay was shown to measure mostly CD4 response although CD8 cells also responded in some individuals (102). In studies performed on initial MVV-host interaction within lymph nodes proliferative response was detected one week after infection (103). Recombinant gag antigens p25, p16 and p14, were shown to elicit a MHC class II restricted T-cell proliferative reponse (53, 104). The same antigens were used to raise T cell lines from persistently infected sheep that proliferated in response to viral antigens expressed by autologous macrophages (53). We have shown that sheep immunized either with the Gag precursor or the whole Env protein, expressed in insect cells, responded to whole virus in proliferation assay (105). In CAEV infected or vaccinated goats, virus specific CD4 T-lymphocytes have been shown to proliferate in response to CAEV antigens (89, 106).

In HIV-1 infection it has been well documented that cytotoxic T lymphocytes (CTLs) play a significant role in protection from virus replication and disease progression but also that their impact is ultimately limited by the emergence of viral escape mutants (for review see 107). CTLs have also been demonstrated in HIV exposed but non-infected individuals, suggesting a possible role of CD8 CTLs in prevention of establishment of HIV infection (for review see 98). Virus specific CD8 cytotoxic T-cells have been demonstrated after *in vitro* stimulation of

lymphocytes from MVV infected sheep and in one case also without *in vitro* culture, pointing to a high frequency in that animal (108). The CTLs could be stimulated by autologous MVV infected monocyte-derived and alveolar macrophages and they could also lyse those same cells (109). CAEV specific CD8 CTLs have also been demonstrated (110).

3.3. Immune response- protective or deleterious?

As in other lentiviral diseases, both excessive and deficient immune responses seem to play a role in pathogenesis. Neutralizing antibodies have been shown to have some protective effect in intracerebral MVV inoculation experiments. CNS lesions were less severe and clinical disease more rarely observed in sheep with earlier rise and higher titers of neutralizing antibodies. Sheep with the lowest initial titers and/or the slowest rise in titers had the most severe lesions (111, 112). There are no reports on enhancing antibodies in neither MVV nor CAEV infection, but these have been observed in other lentiviral infections such as HIV (for review see 113) and in vaccination trials against feline immunodeficiency virus (FIV) (114). There is some evidence for the role of T cells in limiting acute MVV infection although it seems incapable of clearing it. Evaluation of the primary MVV immune response was done by lymphatic cannulation. Sheep were inoculated subcutaneously and the events in the lymph nodes draining the inoculation site and in the efferent and afferent lymph were monitored. Within a few weeks post infection there was vigorous immune reaction in the lymph node, activation of CD4 and CD8 T cells as well as plasma cells. After the development of the specific immune response, the number of virus infected cells decreased and was maintained at low levels without disappearing altogether (103). An impaired T-cell proliferative activity has been shown to correlate with the subsequent development of arthritis and a higher viral load in CAEV infected goats (89).

Although the cellular immunity is able to control primary MVV infection, the long term protective effects are not obvious and depletion of CD8+ cells does not affect primary MVV infection in sheep (115), whereas CD4+ cells are necessary for an establishment of the infection of macrophages (116). On the other hand several reports support a major role of the immune response in the pathogenesis of MVV. Early lesions in experimental MVV infection of sheep were almost abolished by immunosuppressive treatment with antithymocyte serum and cyclophosphamide (117). However, treatment of MVV infected lambs with cyclosporin A (CSA) that selectively suppresses activation of T-cells, gave ambiguous results. Virus isolation was more frequent in CSA treated lambs than in the controls, but there was no difference in the development of brain lesions. It can not be excluded that the CSA was administered in too low doses as it was given orally (118). Hyperimmunization with ovine and caprine lentiviruses has also been reported to increase the severity of the disease (119, 120). It is likely that the damaging immune response is directed against virus-induced antigens rather than host antigens (121-123).

Visna is the central nervous system manifestation of the virus characterized by a brisk inflammatory reaction frequently accompanied by a breakdown of myelin (124, 125). Immune activation in the brain of visna infected animals is well established. It appears that lesions may in large part be due to amplification of the immune response to viral antigens with a great influx of macrophages and lymphocytes and secretion of cytokines resulting in non-specific tissue damage (126). There is MVV induced expression of class I and II major histocompatibility complex (MHC) antigens in the brain of MVV infected sheep (80, 127). The induction of MHC antigens on microglia was mainly found on or adjacent to inflammatory infiltrates of the white matter and correlated with severity of lesions (127). The induction of MHC molecules is probably due to cytokines secreted by inflammatory cells and activated microglia. Productive MVV infection of sheep microglia *in vitro* resulted in increased levels of mRNA of the proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (128) and TNF-α expression was detected in perivascular macrophages in the brain of a sheep infected with neuroadapted virus (80).

Maedi is the manifestation of the virus in the lungs as a progressive lymphocytic interstitial pneumonia (129). The role of the cellular immune response in the pathogenesis of the lung infection has also been suggested. In the bronchoalveolar lavage fluid (BALF) of MVV infected sheep there is upregulation of activation markers such as major MHC class II and leukocyte function antigen-1 (LFA-1) and LFA-3 together with a significant loss of CD5 (130-132). Increased levels of cytokine mRNA such as IL-6 and 10, granulocyte macrophage colony stimulating factor (GM-CSF), tumor growth factor β1 (TGF−β1) and IL-2 receptor (IL-2r) are also seen (133, 134). In the lung tissue of sheep with lesions IFN−γ, IL-1β, 4 and 10 and IL-2r were shown to be upregulated but not tumor necrosis factor α (TNF-α) or TGF-β (133). GM-CSF was hyperelevated in the lungs and its expression in alveolar macrophages correlated with the presence of lung lesions (134). CD8 T lymphocytes were shown to be increased in BALF and in regional lymp nodes and could be correlated with the severity of the lung pathology (130, 135). In chronic progressive synovitis, one of the manifestation of MVV, MHC class II antigens are elevated in the joints of clinically infected sheep as well as CD8 cells in the synovium (38, 136). The CD4/CD8 ratio in blood is not significantly changed in MVV infected animals (80, 93), but it can be decreased in the target organs of the virus like BALF, synovial fluid and cerebrospinal fluid because of the higher levels of CD8 cells as compared to CD4 cells (93, 130, 135, 136). In experimentally induced visna both macrophages and CD4 and CD8 positive T lymphocytes infiltrate the brain (80, 93). The overall CD4/CD8 ratio in CNS is within the normal range of blood but the distribution of these lymphocytes varied within the CNS lesions. CD4 positive lymphocytes were more numerous in perivascular sleeves whereas CD8 positive lymphocytes predominated in the diffusely infiltrated neuroparenchyma, possibly as an indication of migration to their targets. Accordingly the CD4/CD8 ratio was reversed in the CSF where the total number of CD8 positive lymphocytes correlated with the severity of lesions (93). It is not known if these CD8 cells are cytotoxic. Virus

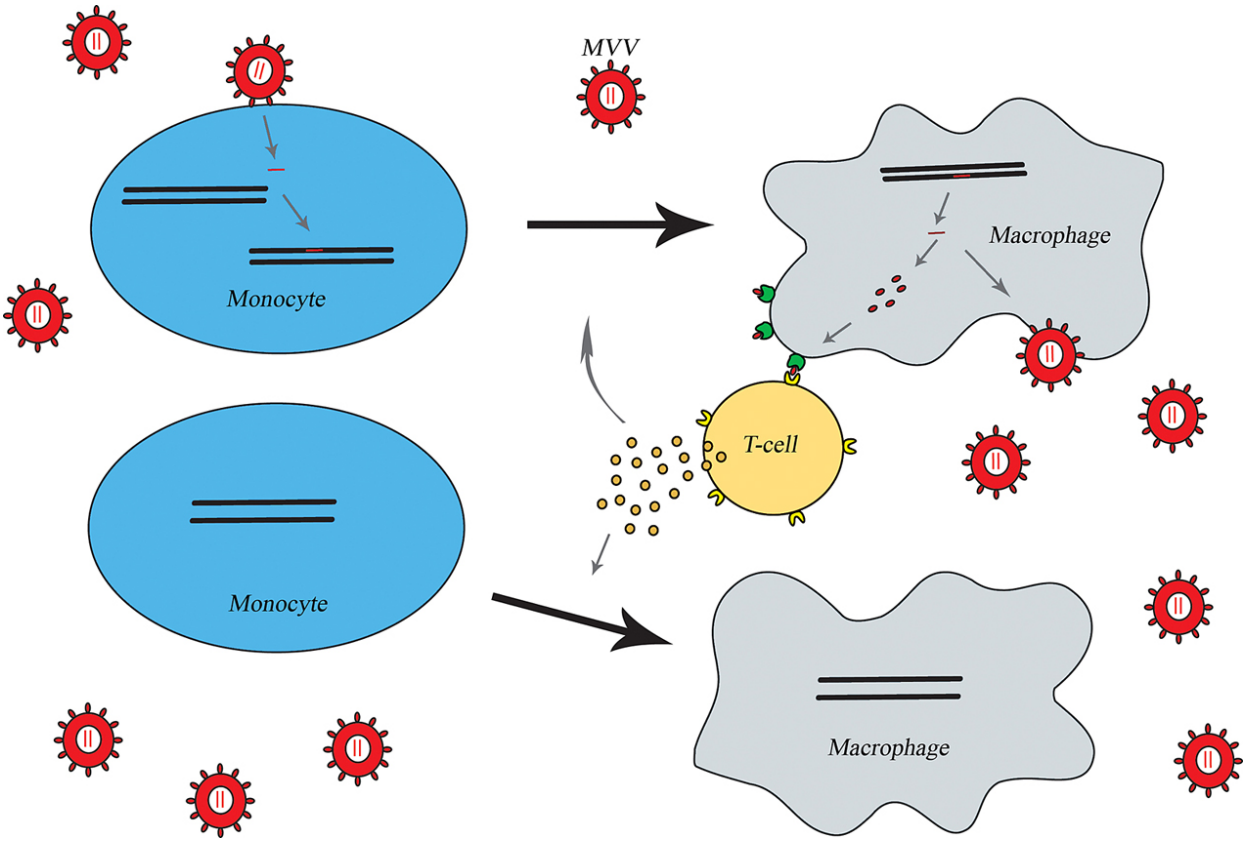

Figure 1. Immune activation in maedi-visna mediated lesions. Differentiated macrophages enable continuous presentation of viral antigens to T-lymphocytes. In return the activated T-lymphocytes produce more cytokines that induce differentiation of monocytes to macrophages.

specific CD8 cytotoxic T cells have been isolated from the cerebrospinal fluid (CSF) of patients with AIDS dementia complex (137) and also from CSF and brains of SIV infected rhesus macaques (138). The role played by CTLs in the central nervous system in lentiviral infections is not clear. They may serve to inhibit viral replication but could also contribute to lesion development through cytokine production or cytotoxicity.

There is clearly an ongoing immune activation in MVV mediated lesions and production of cytokines that induce differentiation of monocytes to macrophages. Differentiated macrophages enable continuous presentation of viral antigens to T-lymphocytes. In return the activated T cells produce more cytokines creating a vicious circle (Figure 1).

4. VACCINATION ATTEMPTS

More that 20 years have passed since human lentivirus, HIV, was discovered and despite great efforts there is no safe effective vaccine in sight (for review see 139-143). Vaccination attempts against the MVV, that are listed in Table 1, have likewise all been unsuccessful in producing sterile immunity and besides, MVV and CAEV immunizations have been shown to increase lesion severity (119, 120).

Whole virus, killed either by heat or chemicals and injected with or without Freund´s incomplete adjuvant and aluminum hydroxide, induced precipitating antibodies, but gave no protection after a challenge intravenously (144). Similar results were obtained with UV inactivated virus and Freund´s complete adjuvant. The animals developed antibodies detectable by complement-fixation, ELISA and gel diffusion but no neutralizing antibodies. There was no protection upon challenge given intravenously. Negative results were also obtained by immunizing with the envelope glycoprotein gp 135 (145).

Sheep vaccinated subcutaneously, repeatedly, with inactivated virus in immuno-stimulating complexes (ISCOMs), also developed antibodies measured in ELISA but no neutralizing antibodies. These antibodies gave no protection upon challenge intravenously, thus the sheep showed the same frequency of virus isolations from blood and organs as unvaccinated control animals (unpublished).

We tried to use an attenuated, non-pathogenic, molecular clone of MVV for vaccination. Sheep were inoculated twice intratracheally with a high dose of the attenuated MVV clone LV1-1KS1 and all of them became infected. They were challenged ten months later with a highly pathogenic MVV clone by the same route. The vaccinated sheep were not protected. However, virus was

Table 1. Maedi-visna vaccination attempts

Antigen	Adjuvant	Site of injection	Challenge	Results	Reference
MVV Env-DNA/plasmid	none	mucosal/vulva	10^3 $TCID_{50}$, intratracheal	Early protective effect	147
Attenuated virus	none	mucosal/trachea	10^3 $TCID_{50}$, intratracheal	Partial protection	146
Recombinant Gag/Env	FCA[1] and FICA[2]	subcutaneously	10^4 $TCID_{50}$, intravenous	No protection	105
Inactivated virus	ISCOM[3]	subcutant	10^3 $TCID_{50}$, intravenous	No protection	Unpublished
Inactivated virus	FCA[1]	intramuscular	10^5 $TCID_{50}$, intranasal	No protection	145
Inactivated virus	FICA[2]/alum[4]/none	intramuscular	10^5 $TCID_{50}$, intravenous	No protection	144

[1] Freund´s complete adjuvant, [2] Freund´s incomplete adjuvant, [3] Immune stimulating complexes, [4] Aluminium hydroxide

isolated more frequently, both from the blood and the lungs, of the unvaccinated controls than of the vaccinated animals, indicating a partial protection (146).

The Gag and the Env proteins produced in the Baculovirus system were used for immunization. The sheep developed high antibody titers in ELISA and a proliferative response to whole virus (105). They were challenged intravenously and virus was isolated from blood a few weeks after challenge.

Mucosal injection with gene gun was used to immunize sheep with plasmid expressing the *env* gene of MVV and boosted with plasmids, expressing *env* and IFN-γ. The sheep were challenged intra-tracheally. Within a month post-challenge, the viral load in the vaccinated group was lower and 2 months later, neutralizing antibodies were detected in all the control animals but in none of the vaccinated animals, suggesting a significant early protective effect. The vaccine protective effect disappeared after two years post-challenge (147).

Several vaccination attempts have been done against CAEV in the goat, with inactivated virus that resulted in more severe arthritis (120), with attenuated tat-deleted CAEV (148) and with surface envelope prime-boost vaccination resulting in partial protection (149, 150).

5. PERSPECTIVE

Maedi visna virus infects monocytes/ macrophages and dendritic cells. It does not infect lymphocytes nor cause immune suppression. In spite of a fairly strong humoral and cellular immune response this does not clear the infection from the host, which persists throughout the life-span of the animal but does not always lead to clinical disease. Immunization or vaccination against MVV can be a double-edged sword due to the apparent dual function of the immune response. The cellular arm seems to play a prominent part in lesion severity, whereas an early rise in neutralizing antibodies might have the opposite effect. It is therefore of great importance to dissect out the antigens and the types of immune response that are beneficial rather than deleterious to the animal.

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