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ETIO-PATHOGENESIS OF SMALL RUMINANT LENTIVIRUS INFECTIONS: A CRITICAL REVIEW

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Abstract

RLVs are retroviruses belonging to the genus Lentivirus (subfamily Orthoretrovirinae). The earliest report of a disease whose pathological pattern suggest the SRLV infection was in Nederland, in 1862. Since then, several reports of clinical cases and scientific research, proved the wide dissemination of SRLV infections (Maedi-Visna in sheep and Caprine Arthritis-Encephalitis in goats) throughout all countries with large number of sheep and goats. In 1998, it was published a phylogenetic analysis of SRLV and it was proved the cross-species transmission of CAEV and MVV strains; moreover, in 2010, phylogenetic reconstructions supported the existence of SRLV cross-species transmission between domestic and wild small ruminants. SRLVs is a genetic continuum of lentiviral species (MVV, CAEV) in sheep and goats with evidence based of cross species transmission. The high genetic variability of SRLV, generate the classification of the viral genotypes into five groups and several subtypes, based on the phylogenetic analysis of two long genomic segments: the gag-pol segment (1.8 kb) and the pol segment (1.2 kb). Pathogenesis of lentiviral infections is the result of several particular factors, as the virus strain, the genetics of the host and the microenvironment. All this are influencing the tropism of lentivirus to a particular host animal or cell, tissue or organ. Till present, despite the huge and increasing speed in bio technics, the pathogenesis of SRLV infections, either in goat or in sheep, is not completely understood and the interaction of the host with those viruses is not fully known.

Key words*: SRLV infections, Maedi-Visna, Caprine Arthritis-Encephalitis, MVV, CAEV.*

HISTORY

The ovine progressive pneumonia was first reported in Nederland, in 1862, when D.C. Loman described in a Texel rams imported from Spain a sickness with laboured breathing he called *zwoegerziekte zwoegerziekte* (Loman, 1862).

At the beginning of the XXth century, W. Robertson (1904) described in South Africa, a chronic catarrhal pneumonia called *Jagziekte*, further followed by D.T. Mitchell in 1915 and E.V. Cowdry in 1925 with detailed epidemiological, etiological, clinical and lesional studies (Robertson, 1904; Mitchell, 1915; Cowdry, 1925).

The first data on the ovine progressive interstitial pneumonia or Montana disease in USA were published in 1923 by H. Marsh, but his official reports were recorded as early as 1915 (Marsh, 1923). Two years later E.V. Cowdry published his studies concerning the origin of the epithelial proliferations in Jagziekte of South Africa (Cowdry, 1925).

Comparing the description of the Montana disease with the Jagziekte description they concluded that they were probably identical (Cowdry and Marsh, 1927).

Later G. De Kock (1929) take into consideration the neoplastic nature of the lesions of *Jagziekte* in sheep (De Kock, 1929).

Despite of informations accumulated in first three decades of XXth century, in 1930's Iceland registered a devastating disease of sheeps, with 20% to 30% loses in animals older than 2 years of age; the disease characterised by a chronic progressive pulmonary pathology, named Maedi, presented high similarity with the diseases was described by E.V. Cowdry and E.V. Marsh (Marsh, 1923; Cowdry, 1925; Cowdry and Marsh, 1927; Sigurdsson, 1952).

Introduction of Maedi in Iceland was suspected to occur following the import of Karakul rams from Germany in 1933: the first clinical signs appeared six years later, when the disease has been already spread in several Iceland sheep herds (Georgsson, 1990).

A similar disease, called la bouhite, was reported in France in 1942 (Lucan, 1942).

In Iceland too, a new demyelinating

transmissible disease appeared in sheep, this neurological disease was called Visna (Sigurdsson et al., 1957).

In the next period, Icelandic researchers conducted several studies concerning the aetiology of the Maedi and Visna. Sigurdsson et al. (1960) manage to isolate the etiologic agent of Visna disease and Sigurdardottir and Thormar (1964) isolated the etiologic agent of Maedi disease. After that, serological investigations proved the identity of both isolates, concluding that Maedi and Visna diseases have the same aetiological agent (Sigurdardottir and Thormar, 1964).

The pulmonary lesions Jagzieke and Maedi were described in Indian goats in 1964; between 1969 and 1981, sporadic cases of Visna or Visna-like syndromes were described in goats from Germany, Sweden and Australia (Rajya and Singh, 1964; Stavrou et al., 1969; Weinhold and Triemer, 1978; O'Sullivan, 1978; Sundquist, 1981).

In 1974, in United States, in young goats were reported nervous and respiratory lesions as those of the Maedi-Visna in sheep. The history of the clinical signs in the herd, revealed the occurrence of the disease in 1966 and the association of neuronal and respiratory signs with several cases of progressive arthritis in adult goats (Cork et al., 1974). However, the chronic arthritis in goats caused by a retrovirus was described six years later. The virus isolated from goats proved to be serologically different from ovine Maedi-Visna Virus (MVV) and was designated as Caprine Arthritis-Encephalitis Virus (CAEV) (Crawford, et al., 1980).

The phylogenetic analysis of small ruminant lentiviruses (SRLV) published in 1998 by R.G. Zanoni proved the cross-species transmission of CAEV and MVV strains. Also, he identified at least six different clades with no clear separation of SRLV strains derived from goats or sheep (Zanoni, 1998). In 2004, C. Shah et al. published a new phylogenetic analysis and proposed the reclassification of caprine and ovine lentiviruses as a consequence of regularly sheep-to-goat transmission of CAEV and MVV isolates (Shah et al., 2004). Six year later, phylogenetic reconstructions performed by C. Leroux et al. supported the existence of SRLV cross-species transmission in domestic and wild small ruminants and the classification of SRLVs was improved with new sequence groups and subtypes (Leroux et al., 2010). Actually, mutations and recombination are continuous processes which extend genetic diversity of SRLVs and conduct to emergence of new variants which can escape detection with current diagnostic tools (Minardi da Cruz et al., 2013). For this reason, we can consider that, depending of the epidemiological status and density of domestic and wild small ruminants, the number of the SRLV's subtypes could be much higher and the identification and characterization is a matter of time.

ETIOLOGY AND TAXONOMY

SRLVs are retroviruses belonging to the genus *Lentivirus* (Table 1). *Lentivirus* is a distinctive genus of *Retroviridae* family (subfamily *Orthoretrovirinae*) that include viruses able to produce chronic and persistent infections in humans, monkeys, felids, equines, cattle and small ruminants (Gifford, 2012).

Table 1. Genus and type species of *Retroviridae* family (Leroux et al., 2010)

Genus	Virus species	Animal host
Alpharetrovirus	*Avian Leukosis Virus* *Rous Sarcoma Virus*	chicken
Betaretrovirus	*Jaagsiekte Sheep RetroVirus* *Enzootic Nasal Tumor Virus*	small ruminants
	Mouse Mammary Tumor Virus	mouse
	Mason-Pfizer Monkey Virus	monkey
Gammaretrovirus	*Feline Leukemia Virus*	felids
	Murine Leukaemia Virus	mouse
Deltaretrovirus	*Human T-Lymphotropic Virus type 1 and 2*	human
	Bovine Leukaemia Virus	domestic cattle
Epsilonretrovirus	*Walleye Dermal Sarcoma Virus*	fish
Spumaretrovirus	*Equine Foamy Virus*	equids
	Simian Foamy Virus	monkey
Lentivirus	*Human Immunodeficiency Virus type 1 and 2*	human/primates
	Simian Immunodeficiency Virus	monkey
	Feline Immunodeficiency Virus	felids
	Equine Infectious Anemia Virus	equids
	Bovine Immunodeficiency Virus	cattle
	Small Ruminant LentiViruses • ***Maedi-Visna Virus*** • ***Caprine Arthritis Encephalitis Virus***	**small ruminants**

SRLVs is a genetic *continuum* of lentiviral species (MVV, CAEV) in sheep and goats with cumulative evidence of cross species transmission (Leroux et al. 2010). The high genetic variability of SRLV, generate the classification of the viral genotypes into groups and subtypes based on phylogenetic analysis of two long genomic segments: gag-pol segment

(1.8 kb) and pol segment (1.2 kb) (Shah et al., 2004; Ramirez et al., 2013).

SRLVs has been divided into five geno-groups. To date, three of these geno-groups (A, B and E) were divided into subtypes (Table 2).

Table 2. Groups and subtypes of small ruminant lentiviruses
(Shah et al., 2004; Minardi da Cruz et al., 2013; Kuhar et al., 2013)

Groups	Subtypes	Prototype isolates
A	A1–A13	*South African Ovine Maedi-Visna virus* *MVV K-1514 (Iceland)* *MVV EV1 (Scotland)* *Classical MVV strains* *Worldwide isolates*
B	B1–B3	*CAEV Cork (USA)* *Classical CAEV strains* *Worldwide isolates*
C		*Goat and sheep isolates from Norway*
D		*Goat isolates from Switzerland and Spain*
E	E1, E2	*Goat isolates from Italy*

The geno-groups worldwide distributed, A and B, proved to have several distinct isolates, classified in 13 subtypes and three subtypes, respectively (Kuhar et al., 2013). The genotype A include the classical MVV strains, the genotype B include the classical CAEV strains, the isolates from goats and sheep are in genotype C and in the genotypes D and E are the isolates from goats (Minardi da Cruz et al., 2013).

Figure 1. Small ruminant lentiviruses (SRLV) structural genes (*gag*, *pol* and *env*), regulatory genes (*vif, tat* and *rev*) and non-coding long terminal repeat regions (LTRs). *gag*: encodes the capsid proteins; *pol*: encodes the viral enzymes protease, reverse transcriptase and integrase; *env*: encodes the envelope glycoproteins; *vif*: involved in virus replication and pathogenicity; *tat*: is a *vpr-like* gene, promiscuous activator of viral and cellular promoters; *rev*: essential gene for post-transcriptional transport of viral mRNAs from nuclei to cytoplasm; U3, R, and U5 regions of LTRs: deliver the signals of viral transcription and integration into the host genome (Narayan et al., 1983; Ryan et al., 2000; Lesnik et al., 2002; Valas et al., 2008; Gifford, 2012; Stonos et al. 2014).

Lentiviruses are enveloped, slightly pleomorphic, spherical viruses. The mature particles have approximately 100 nm in diameter. The envelope have tiny spikes (about 8 nm) dispersed evenly over the surface. The core structure is cylindrical and composed of the *gag* proteins: p24, p17, p9, and p7 (Figure 1) (Clements and Zink, 1996).

The SRLV genome is comprised of two identical, positive, single sense, stranded RNA subunits (8.4–9.2 kb) (Ramirez et al., 2013). A RNA subunit contains three structural genes (gag, pol and env), three regulatory genes (tat, vif and rev) and long terminal repetitive regions, non-coding (LTRs) (Gifford, 2012; Stonos et al. 2014).

PATHOGENESIS

Pathogenesis of lentiviral infections is the result of several particular factors, such as: the virus strain, the animal host and the microenvironment; all this influence the tropism of lentivirus to a particular host animal and cell, tissue or organ. (Table 2). (Narayan, 1990; Ryan et al., 2000; Ramirez et al., 2013).

Table 3. Factors involved in pathogenesis of *Lentiviruses*
(Narayan, 1990; Ryan et al., 2000; Larruskain and Jugo, 2013)

Biological properties of *Lentiviruses*
(1) integration of the proviral DNA into host cell DNA; (2) replication in cells of the monocyte/macrophage lineage; (3) increased ability of the viral genome to make mutations; (4) spreading mainly by exchange of blood, inflammatory exudates and certain body secretions; (5) slow replication of the virus.
Characteristics of the lentiviral infections
(1) long period of incubation (months to years); (2) insidious onset of clinical disease; (3) several months of clinical evolution; (4) slow progressive inflammatory diseases.
Characteristics of the SRLVs
(1) not cause immunodeficiency; (2) proviral DNA escapes detection by the immune system by persisting in monocytes; (3) subverting antimicrobial defences' role of macrophages and dendritic cells; (4) lifelong infections.

The genetic variability of SRLV strains is due to the high rate of mutation and to high frequency of the recombination events associated with the virus replication in the host (Minardi da Cruz et al., 2013).

This variability leads to variation of the virulence, to the differences of host/organ tropism, and to the antigen diversity, the last one affecting the detection of infected subjects (Larruskain and Jugo, 2013).

In lentiviral infections, the factors that influence the frequency of mutation and of the recombination into a host are co-infection with different strains (including cross-species infections) (Pisoni et al., 2007) and the host's selection pressure (host restriction factors and immune response) (Butler et al., 2007).

Genetic differences between SRLVs strains have urged their systematization in groups and subtypes, with CAEV-Co and MVV-K1514 as prototypic virus strains in goats (Caprine Arthritis-Encephalitis) and sheep (Maedi-Visna) for these infections (Sonigo et al., 1985; Saltarelli et al., 1990; Shah et al., 2004; Minardi da Cruz et al., 2013; Kuhar et al., 2013).

Unfortunately, it is not enough information concerning the sequence of the virus variants circulating among different hosts worldwide (Shah et al., 2004), so the meta-analysis of virus factors in correlation with the host's genetics and environment is not yet possible. However, pathogenesis of lentivirus infections has proved to share similar mechanisms that are controlled by highly conserved fragments of their genome (Haase, 1986).

The first evidence of SRLVs variability was proved by the identification of antigenic variation in infected small ruminants (Leroux, et al., 2010), but the knowledge about the innate and the acquired immune responses to SRLV are not fully understood. However, a number of host related factors proved to interfere in the pathogenesis of SRLVs infections: (1) population stratification; (2) sample size (affects power to detect association); (3) the phenotype; (4) the age (older animals have a longer time of exposure); (5) the gene effect (genes involved have small/moderate effects); (6) the presence of other diseases (facilitate lentiviral pathogenesis) (Larruskain and Jugo, 2013).

The cellular receptors for classical MVV and CAEV strains have not been conclusively identified (Larruskain and Jugo, 2013), but seem to be different (Blacklaws, 2012).

Crespo et al. (2012) supposed that mannose receptor may be involved in the lentivirus pathogenesis of small ruminants.

The genetics of the host proved to have small or moderate effects in pathogenesis of Caprine Arthritis-Encephalitis and Maedi-Visna.

A few studies were carried out on the role of the host's genetics in the lentivirus pathogenesis of small ruminants: those have been focused on the MHC genes Class I and II, on the cytokine's genes and the cytokine receptor's genes, on the Toll-like receptor (TLRs) genes and on the transmembrane protein gene 154 (TMEM154) (Larruskain and Jugo, 2013). G. Ruff et al. (1993) studied the implications of the allele CLA Be7 of MHC Class I gene in Saanen goats with caprine arthritis (CAE), while Larruskain et al. (2012) studied the allele OMHC1*205 of the same gene in ewes with Maedi-Visna and viral pulmonary adenocarcinoma disease.

The alleles of MHC class II associated with the Maedi-Visna pathogenesis in sheep are DRB1*0403, DRB1*07012, DRB1*0325 and DRB2*275 (Larruskain and Jugo, 2013).

The genes for cytokine and for cytokine receptor, studied for their implication in Maedi visna virus infections in sheep were: *Interleukin-1beta* (*IL1β*), *Interleukin-2/Interleukin-2 receptor* (*IL2/IL2R*), *Interleukin-4* (IL4), *Interleukin-6* (IL6), *Interleukin-8* (IL8), *Interleukin-10* (IL10), *Interferon-gamma* (*IFNγ*), *Tumor Necrosis factor-alpha* (*TNFα*), *Tumor growth factor beta-1* (*TGF-β1*), *Granulocyte macrophage stimulating factor* (*GM-CSF*), *Chemokine (C-C motif) Receptor 5* (*CCR5*) (Woodall et al., 1997; Legastelois et al., 1997; Zhang et al., 2002; Larruskain et al., 2013).

Also, studies upon the goat genetics, have been conducted for evaluation of cytokine and cytokine receptor genes involvement in the pathogenesis of the caprine arthritis-encephalitis, and the following genes has been supposed to have small or moderate effects: *Interleukin-2/Interleukin-2 receptor* (*IL2/IL2R*), *Interleukin-4* (IL4), *Interleukin-8* (IL8), *Interferon-gamma* (*IFNγ*), *Tumor growth factor beta-1* (*TGF-β1*), *Monocyte chemoattractant protein 1* (*MCP-1*), *Granulocyte macrophage stimulating factor* (*GM-CSF*) (Lechner et al., 1997a, 1997b; Cheevers et al., 1997).

TLR7 and TLR8 (transmembrane signaling molecules that trigger the immune response mechanisms) genes and their single nucleotide polymorphisms have been incriminated in individual susceptibility of Tsigai breed to Maedi Visna virus infection (Mikula et al., 2010).

The TMEM154 allele and the haplotype variants have been associated with SRLV infection and has been proposed as a genetic marker in the ewes' selection (Heaton et al., 2012).

Concerning restriction factors developed by host to control retroviral infections, several intracellular defence strategies have been

identified and described. One of this is the ovine tripartite motif protein 5 alpha (TRIM5α) that can restrict Maedi-Visna virus DNA synthesis (Jáuregui et al., 2012).
Current evidence of the host genetics involvement in the pathogenesis of small ruminant lentivirus and in the clinical expression of the associated disease motivates the research to uncover new host control pathways leading to develop antiviral therapies (Larruskain and Jugo, 2013).

CONCLUSIONS

In light of the gained data, it is ascertained that the pathogenesis of SRLV infections in the goat and in the sheep are not completely understood and the interaction of host with those viruses is not fully known

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