The major histocompatibility complex of ruminants

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Summary

Studies of the major histocompatibility complex (MHC) of cattle over the past twenty years have revealed a reasonably detailed picture of the genetic organisation and function of the genes within this genetic system. Serological and biochemical analysis of lymphocyte cell surface antigens provided the first evidence for highly polymorphic MHC genes in cattle and other ruminant species. The MHC of cattle was thus named the bovine leucocyte antigen (BoLA) system. During the past 10 years, tools of molecular biology have been used to characterise the number of MHC genes, their sequence and fine structure in a number of ruminant species. Although individual MHC genes were found to have clear orthologues among ruminants and other mammalian species, the MHC of cattle, and probably that of sheep and goats, has a unique genetic organisation. Cattle have a class II gene cluster (class Iib region) which is physically distant from all the other MHC genes on the same chromosome. Moreover, genes involved in antigen processing, such as the proteosome subunit locus LMP2, are also found in the class Iib region, demonstrating that these genes need not be in close proximity to other MHC genes to function normally.

The MHC class I and class II gene products of ruminants present processed peptides to T lymphocytes which mediate helper and cytotoxic functions. Identification of peptide binding motifs of cattle MHC class I molecules indicates that ruminant MHC molecules function in a similar manner to those of mice and humans. These functional studies provide a firm molecular basis for a number of well-documented associations with infectious diseases, although a detailed understanding of the immunogenetic mechanisms underlying these associations has yet to be elucidated.

Keywords

Bovine leucocyte antigen - Cattle - Disease resistance - Genetics - Major histocompatibility complex - Ruminants - Sheep.

Introduction

The major histocompatibility complex (MHC) class I genes encode proteins which are chiefly involved in presentation of intracellularly-derived peptides to cytotoxic T cells. The class I molecules comprise an \( \alpha \)-chain that is non-covalently associated with \( \beta_2 \) microglobulin. The \( \alpha_1 \) and \( \alpha_2 \) domains form a cleft that accommodates antigenic peptides which are primarily presented to cytotoxic T cells bearing the CD8\(^+\) (cluster of differentiation antigen) marker (Fig. 1). The class II genes encode proteins that present processed peptides derived from extracellular antigens to helper T cells bearing the CD4\(^+\) differentiation marker. The class II molecules are formed by non-covalent association of \( \alpha \)- and \( \beta \)-chains encoded by distinct genes within the MHC. For the MHC class II molecules, the \( \alpha_1 \) and \( \beta_1 \) domains form the antigen binding site. This review will discuss current knowledge of the structural and functional features of MHC genes in cattle (Bos taurus), sheep (Ovis aries) and goats (Capra hircus). Emerging information on the MHC in wild ruminants, such as red deer (Cervus elaphus) and moose (Alces alces), will also be presented.
Genomic organisation of the MHC region

Linkage and physical map

The MHC region contains a diverse array of genes which are crucial for the initiation of adaptive immune responses. The MHC encompasses a large chromosomal region that maps to chromosome 23 in both cattle and goats (35, 90) and to chromosome 20 in sheep (54). The bovine MHC is designated as BoLA (bovine leucocyte antigen complex), whereas in other ruminants the MHC is named according to the nomenclature proposed by Klein et al. (47). Thus, the MHCs of sheep and goats are referred to as Ovar and Coki, respectively.

The general structure of the MHC is relatively conserved among mammalian species, and is divided into three main regions with different functional roles (Fig. 2). However, as more DNA sequence data accumulate, these boundaries appear artificial because genes with many different functions have been found dispersed among the class I, class II and class III regions. For the purpose of this review, however, these regional designations will be maintained so that comparisons between species can be made more easily.

Physical mapping of bovine chromosome 23 (BTA23) has demonstrated that the class I region encompasses approximately 1,550 kilobases (kb) of DNA, and that there are two tightly linked expressed loci (BoLA-A and BoLA-B) (11). The class III region is constituted by a heterogeneous set of genes related to immunological and other functions, such as the complement factors BF and C4, steroid 21-hydroxylase (CYP21), heat shock protein 70 (HSP70) and tumour necrosis factor α and β (TNFA and TNFB) (49, 66, 76). One of the most notable differences in the genomic organisation of the MHCs of ruminants compared with humans and mice is the splitting of the class II region into two subregions which are separated by at least 15 cM (centiMorgans) (4, 93). The class IIa subregion comprises two clusters of genes, DR and DQ. Physical and genetic mapping have shown that the bovine and ovine DR and DQ genes lie in close proximity (3, 77). The class IIb region includes the DMA, DMB, LMP2, LMP7 and TAP genes (23, 49, 72), which are involved in antigen processing and transport, and other class II-like genes, such as DNA, DOB, DIB, DYA and DYB, whose function is unknown (49). On the basis of linkage analysis, the bovine class II region lies near the centromere of BTA23, whereas the class I region is distal to the class IIa genes (44, 93). A similar organisation is expected for sheep and goats, which are closely related artiodactyls (66, 76). Hybridisation of BTA23 with fluorescence-labelled DYA and class I probes has demonstrated that these two regions physically map at different positions, with DYA centromeric to the class I loci (83). Interestingly, the distance between the class IIa and class IIb subregions varies among individuals, as demonstrated by comparison of the recombination rate using single sperm typing of different bulls (67). Variation in the recombination rate might be due to the existence of a polymorphic recombinational hotspot (4, 44, 67).

Major histocompatibility complex class I genes and molecules

In cattle, the class I region contains about 10 to 20 class I genes (11, 52), whereas the estimated number of class I genes in goats is approximately 10 to 13 (17). At least three class I genes are transcribed in cattle (11, 23, 37, 38) and sheep (41). The class I genes are polymorphic, with 21 distinct BoLA class I sequences (23) and five sheep class I sequences (41) identified to date. The length of the transmembrane domain (37 or 35 residues) is the major criterion for assigning the available BoLA class I sequences to specific loci. Analysis of class I molecules by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF) and peptide mapping also gives strong support for the existence of up to three expressed class I loci in cattle (1, 45). Similarly, the serological available data for sheep suggest that at least three different class I molecules are expressed by lymphocytes (39, 60), while in goats there is evidence for only two distinct class I molecules (46, 66).

The major histocompatibility complex class II region

The class II region in cattle has been characterised using cloned heterologous and homologous class II probes. Restriction fragment length polymorphism (RFLP) analysis
Fig. 2
Genetic linkage map of the major histocompatibility complex region in cattle (10, 53), sheep (20, 82) and goats (50)

has allowed the determination of the number of class II genes, the existence of DQ and DR alleles in strong linkage phase disequilibrium, the probable absence of DP orthologues in mice and humans, and the splitting of the class II region into two distantly linked subregions (23, 49). Complete information on the molecular features of the BoLA class II genes can be found in the last report of the International Society of Animal Genetics BoLA Nomenclature Committee (23, 72) and on the BoLA website (http://www2.ri.bbsrc.ac.uk/bola/bolafram.htm). In sheep, the class II region was elucidated using RFLP analysis (L9, 32, 40, 77). The ovine class II region has at least seven and ten different α-chain and β-chain genes, respectively, and 14 β3 chain related sequences (24). As in other species, RFLP analysis of the goat class II region suggests the existence of multiple polymorphic class II loci (17).

The major histocompatibility complex class IIa subregion

DR genes

The DRA gene encodes the α-chain of the DR molecule. Only one BoLA-DRA allele has been identified on the basis of sequence data (Table I). By contrast, the genes that encode the β-chain of the DR molecule are highly polymorphic. Polymorphism is mainly concentrated in the second exon, which encodes the variable portion of the peptide binding site (Fig. 2). The second exon of one highly polymorphic DRB gene has been characterised in cattle (72), sheep (76), goats (2, 73), red deer (88) and other wild ruminant species (50, 58) (Table II).

The number of DRB genes varies in cattle and sheep. In cattle, there are at least three DRB loci but only one DRB gene (DRB3) is functional. In sheep there may be six different DRB genes, of which at least two are expressed (76). In the red deer and fallow deer (Dama dama), two different DRB genes are transcribed (57, 88). The existence of several β-chain genes increases the possibility of eliciting an effective immune response against pathogen-derived peptides that markedly differ in their structural characteristics.

The analysis of DRB polymorphism has been particularly useful for inferring the evolutionary history of the MHC in ruminant species. The low level of polymorphism in some wild ruminants, such as moose (57, 59), and the considerable differences in allelic frequencies between European and African cattle breeds (58) suggest that selection, genetic drift and population bottlenecks have played an important role in determining the repertoire of ruminant MHC class I and II alleles. In addition, evidence in ruminants suggests that interallelic exchange of short sequence motifs has been of importance in the generation of allelic variability (57, 73, 74).
In the future, considerably more will be learnt about the evolution of ruminants from the sequencing of different MHC genes.

**DQ genes**

In cattle and sheep, some individuals carry a single copy of DQA and DQB genes, whereas others have duplicated haplotypes (Table III) (5, 78, 79, 81, 101). By contrast with the DRA genes, DQA genes are highly polymorphic. This increases significantly the number of different DQ molecules that can be expressed on the cell surface in a given individual, thus expanding antigen presentation capability. In cattle there are two or possibly three DQA genes (8), whereas there are four different DQB genes (81). The DQB1 gene is the most frequent, whereas the DQB2, DQB3 and DQB4 genes can only be found in duplicated haplotypes. DQB1, DQB2 and DQB3 have been shown to be transcriptionally active in animals with duplicated DQ haplotypes (56, 103).

The ovine DQ region encompasses 130 kb, with the DQ1 and DQ2 subregions located 22 kb apart (97). Like cattle, the number of DQA and DQB genes in sheep varies depending on the haplotype (33, 76, 79), and both Ovar-DQA genes are transcribed (78). Phylogenetic analysis of ovine DQB exon 2 sequences shows that they belong to at least two different allelic lineages (95). The DQB genes are also duplicated in the red deer (Cervus elaphus) (89).

**DR and DQ molecules**

In cattle, the surface expression of DR and DQ molecules has been demonstrated using locus-specific monoclonal antibodies and IEF (13, 30, 49). The expression of MHC class II molecules in freshly isolated bovine T cells has also been reported (85). In sheep, four different subsets of class II molecules co-expressed on B lymphocytes have been identified using monoclonal antibodies (68). Three of these subsets showed allelic variation restricted to the β-chain, while in the fourth subset there was also polymorphism in the α-chain (68, 69).

There is evidence suggesting that at least two different sheep DR β-chain molecules are expressed (29). In sheep, CD4⁺ helper, CD8⁺ cytotoxic and γδ T cells express variable levels of DQ and DR molecules (28, 43). In general, the expression of DQ is lower than DR, and there are also expression differences depending on the age of the animal and the immunological compartment being analysed (28, 43). In goats, six different class II DR-like products (BeB1-BeB6) have been identified by IEF (66, 70). These products may correspond to the codominant expression of two loci (66).

<table>
<thead>
<tr>
<th>Species</th>
<th>Name</th>
<th>Molecular features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bos taurus</em></td>
<td>BoLA-DRB1</td>
<td>Encodes a mature protein of 210 amino acids. Monomorphic (91)</td>
<td>(23, 72, 91)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DRB2</td>
<td>Pseudogene (stop codons in the β1 and transmembrane domains). Low polymorphism (2 alleles)</td>
<td>(23, 63, 72)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DRB3</td>
<td>Expressed at low levels. Lacks the glycosylation site at position 19 of the B1 domain. Monomorphic</td>
<td>(23, 64, 72)</td>
</tr>
<tr>
<td><em>Ovis aries</em></td>
<td>Ovar-DRB1</td>
<td>Expressed at high levels. Encodes a mature protein of 236 amino acids. Highly polymorphic (63 alleles)</td>
<td>(16, 23, 72)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DRB2</td>
<td>Pseudogene (lacks the exon 1 and exon 2, and has two premature stop codons and other mutations that render it non-functional)</td>
<td>(7, 76, 79)</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Species</th>
<th>Family</th>
<th>DRB alleles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bos taurus</em></td>
<td>Bovidae</td>
<td>63 (a)</td>
<td>(23, 49, 72)</td>
</tr>
<tr>
<td><em>Ovis aries</em></td>
<td>Bovidae</td>
<td>74 (b)</td>
<td>(76)</td>
</tr>
<tr>
<td><em>Capra hircus</em></td>
<td>Bovidae</td>
<td>28 (c)</td>
<td>(2, 66, 73)</td>
</tr>
<tr>
<td><em>Ovodos moschatus</em></td>
<td>Bovidae</td>
<td>1 (d)</td>
<td>(57)</td>
</tr>
<tr>
<td><em>Bison bison</em></td>
<td>Bovidae</td>
<td>13 (e)</td>
<td>(50, 57, 62)</td>
</tr>
<tr>
<td><em>Gazella dama</em></td>
<td>Bovidae</td>
<td>9 (f)</td>
<td>(50)</td>
</tr>
<tr>
<td><em>Dameloceros darcus</em></td>
<td>Bovidae</td>
<td>1 (g)</td>
<td>(50)</td>
</tr>
<tr>
<td><em>Connochaetes taurinus</em></td>
<td>Bovidae</td>
<td>3 (h)</td>
<td>(50)</td>
</tr>
<tr>
<td><em>Addax nasomaculatus</em></td>
<td>Bovidae</td>
<td>8 (i)</td>
<td>(50)</td>
</tr>
<tr>
<td><em>Oryx dammah</em></td>
<td>Bovidae</td>
<td>9 (j)</td>
<td>(60)</td>
</tr>
<tr>
<td><em>Oryx leucoryx</em></td>
<td>Bovidae</td>
<td>3 (k)</td>
<td>(50)</td>
</tr>
<tr>
<td><em>Giraffe camelopardalis</em></td>
<td>Giraffidae</td>
<td>2 (l)</td>
<td>(50)</td>
</tr>
<tr>
<td><em>Alcel alce</em></td>
<td>Cervidae</td>
<td>11 (m)</td>
<td>(57)</td>
</tr>
<tr>
<td><em>Capreolus capreolus</em></td>
<td>Cervidae</td>
<td>4 (n)</td>
<td>(57)</td>
</tr>
<tr>
<td><em>Rangifer tarandus</em></td>
<td>Cervidae</td>
<td>11 (o)</td>
<td>(57)</td>
</tr>
<tr>
<td><em>Dama dama</em></td>
<td>Cervidae</td>
<td>1 + 1 (p)</td>
<td>(57)</td>
</tr>
<tr>
<td><em>Cervus elaphus</em></td>
<td>Cervidae</td>
<td>43 (q)</td>
<td>(67, 88)</td>
</tr>
</tbody>
</table>

References

111
Table III
Molecular features of the bovine and ovine DQ genes

<table>
<thead>
<tr>
<th>Species</th>
<th>Gene</th>
<th>Molecular features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bos taurus</td>
<td>BoLA-DQA1</td>
<td>Encode a mature protein of 233 amino acids. Highly polymorphic (39 DQA alleles)</td>
<td>(8, 23, 72, 91)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DQA2</td>
<td></td>
<td>(23, 72, 81)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DQA3</td>
<td></td>
<td>(23, 72, 81)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DQB1</td>
<td>Encode a mature protein of 230 amino acids. The DQB genes are highly polymorphic (37 DQB alleles)</td>
<td>(23, 72, 81)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DQB2</td>
<td></td>
<td>(23, 72, 81)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DQB3</td>
<td></td>
<td>(23, 72, 81)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DQB4</td>
<td></td>
<td>(23, 72, 81)</td>
</tr>
<tr>
<td>Ovis aries</td>
<td>Ovar-DQA1</td>
<td>Both DQA1 and DQA2 are transcribed. There are 7 DQA1 alleles and 11 DQA2 alleles</td>
<td>(33, 76, 78)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DQA2</td>
<td></td>
<td>(33, 76, 78)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DQB1</td>
<td>There are at least two DQB genes which are transcribed and highly polymorphic (16 DQB sequences)</td>
<td>(76, 79)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DQB2</td>
<td></td>
<td>(76, 79)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DQB3</td>
<td></td>
<td>(76, 79)</td>
</tr>
</tbody>
</table>

The major histocompatibility complex class IIb subregion

In humans, the DMA and DMB genes encode a molecule that plays a role in the complexing of peptides with class II molecules (84), whereas DNA and DOB encode a protein that might regulate the function of the DM molecule (51). The DMA/DMB and DNA/DOB orthologues have been identified in cattle (65) and sheep (99, 100), respectively (Table IV).

The DY genes and the DIB gene have only been found in ruminants and exhibit a low level of polymorphism. The DYA gene was sequenced in cattle (91) and sheep (98), whereas DYB has only been sequenced from sheep (98). Transcription of the Ovar-DYA gene was detected in transfected mouse L cells (98), but its expression on sheep lymphocytes has not been demonstrated. The BoLA-DYA gene has similarity (69% to 79%) with BoLA-DQA and probably arose by duplication and divergence from a pair of DQ genes (91).

Similar to the DY genes, the DIB gene has a restricted species distribution (86, 87). DIB has been found in several members of the Bovidae (cattle, sheep, gaur [Bos gaurus], American bison [Bison bison] and sand gazelle [Gazella leptoceros]), Cervidae (wapiti [Cervus elaphus], serow [Capricornis sumatraensis] and muntjak [Muntiacus muntjak]) and Giraffidae (87). DIB displays similarity of 67% to 70% with the bovine Y1 and Q1 DQB clones. It has not been possible thus far to detect DIB expression by Northern blot analysis. The cattle class IIb region also contains genes encoding the LMP2 and LMP7 proteasome subunits and the TAP genes, which encode molecules involved in the transport of peptides from the cytosol to the lumen of the endoplasmic reticulum (23, 49).

Peptides bound to bovine major histocompatibility complex molecules

As discussed above, a major function of MHC molecules is to present processed peptide antigens to T cells and thereby initiate an adaptive immune response to specific pathogens.

Table IV
Molecular features of bovine and ovine major histocompatibility complex class IIb genes

<table>
<thead>
<tr>
<th>Species</th>
<th>Name</th>
<th>Molecular features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bos taurus</td>
<td>BoLA-DMA</td>
<td>Encodes a mature protein of 235 amino acids. Transcriptionally active and monomorphic</td>
<td>(23, 65, 72)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DMB</td>
<td>Encodes a mature protein of 245 amino acids. Transcriptionally active and monomorphic</td>
<td>(23, 65, 72)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DYA</td>
<td>Expression not detected. Low polymorphism (3 alleles)</td>
<td>(24, 72, 81)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DYB</td>
<td>Expression not detected. Monomorphic</td>
<td>(23, 72)</td>
</tr>
<tr>
<td></td>
<td>BoLA-DIB</td>
<td>Expression not detected. Monomorphic</td>
<td>(23, 72, 86)</td>
</tr>
<tr>
<td>Ovis aries</td>
<td>Ovar-DMA</td>
<td>Partial sequence (exons 2 and 3)</td>
<td>(76)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DMB</td>
<td>Partial sequence (exons 2 and 3)</td>
<td>(76)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DYA</td>
<td>Transcriptionally active. Monomorphic</td>
<td>(76, 98)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DYB</td>
<td>Not expressed in transfected mouse L cells. Monomorphic</td>
<td>(76, 98)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DNA</td>
<td>Transcribed at low levels. Monomorphic</td>
<td>(76, 100)</td>
</tr>
<tr>
<td></td>
<td>Ovar-DOB</td>
<td>Transcription not detectable. Monomorphic</td>
<td>(76, 99)</td>
</tr>
</tbody>
</table>
The MHC molecules exhibit a high degree of polymorphism that enables presentation of a wide array of peptides which usually differ in their length and sequence. The efficiency of interaction between peptide and MHC molecules may determine the nature and strength of the immune response elicited by T cells and thus may influence disease progression.

Crystallographic analysis of class I molecules has demonstrated that the peptides bound to the antigen binding site are predominantly nonamers, whose amino- and carboxy-terminal residues bind to specific pockets located at the ends of the antigen binding groove (31). Studies have been carried out in cattle to define the structural motifs of peptides that bind to class I molecules (9, 36, 42). Hedge et al. have shown that almost all the peptides bound to class I BoLA-A11 are nonamers, and that position 2 is preferentially occupied by a proline residue (42). Bamford et al. have analysed the repertoire of peptides presented by the BoLA-A20 allele in bovine muscle-derived fibroblast cells infected by the parainfluenza type-3 virus (9). The sequenced peptides are generally nonamers and have a common motif containing lysine and arginine at positions P2 and P9, respectively. Van Lierop et al. studied the presentation of three foot and mouth disease viral peptides by different class I haplotypes and showed that each haplotype has specific selectivity for peptides (94). The magnitude of the response, measured by proliferation and cytokine assays, also depends largely on the haplotype. Taken together, these results suggest that an MHC-based selection of peptides also occurs in cattle.

In contrast to class I molecules, the antigen binding groove of class II molecules is open at both ends and thus is able to accommodate peptides of increased length (10 to 26 residues). In addition, the main binding interactions involve the central part of the peptide. To date, no information is available on the sequences of peptides bound to class II molecules in ruminants.

The major histocompatibility complex genes and their association with disease resistance and productivity

Major histocompatibility complex molecules as receptors for pathogens

Intracellular micro-organisms invade host cells by attaching to proteins that are normally expressed on the cell surface. Involvement of MHC molecules as pathogen receptors has been demonstrated in several cases. Monoclonal antibodies against monomorphic determinants of bovine class I molecules inhibit the binding and entry of Theileria sporozoites into cattle lymphocytes (80). Moreover, in cattle cell lines, class I expression and the rate of sporozoite infection are closely related (80). However, sporozoites only infect lymphocytes while all nucleated cells express class I molecules. Thus, other cell surface components are probably involved in sporozoite attachment. It is also possible that the actual receptor is masked by the binding of antibodies to MHC class-I molecules. In sheep, several polypeptides that interact with the maedi-visna virus have been isolated by virus protein overlay assay, and blocking of this interaction by MHC-class II specific antibodies has been demonstrated (22). Additionally, the pre-incubation of the virus with MHC class II proteins digested with papain inhibits syncytium formation (22). However, both B and T cells express MHC class II molecules in sheep while only macrophages are infected by the virus. Thus, other co-receptors are probably involved in viral entry and infection.

Disease associations

The MHC genes are particularly interesting to animal breeders and veterinary geneticists because they are associated with genetic resistance and susceptibility to a wide array of diseases. The molecular characterisation of MHC polymorphism and the implementation of fast, reliable typing methods (92) constitute a very powerful tool in the design of breeding schemes that may diminish the appearance and severity of diseases in domestic animal species. Understanding of the mechanisms that explain genetic variation in resistance and susceptibility may also be very valuable in the design of efficient peptide vaccines. The description of MHC associations with diseases in ruminants is very broad (49, 66, 76). For this reason, only a few well characterised and representative models will be presented here.

Polymorphism in BoLA-DRB3 is closely related to resistance to bovine leukaemia virus (BLV) infection (102). The bovine leukaemia virus primarily infects B cells. The majority of the infected animals remain asymptomatic. Only one-third of infected animals develop persistent lymphocytosis, a polyclonal expansion of B cells, and about 1% to 5% of infected cattle present tumours (34). Bovine leukaemia virus has a worldwide distribution that results in the loss of millions of dollars each year due to the elimination of animals with the clinical symptoms, condemnation of carcasses with tumours, and the decrease of fat and milk yields (21). Resistance and susceptibility to BLV has been mapped to specific regions of the β-chain of the DR molecule. The two amino-acid-motif glutamic acid-arginine at positions 70 and 71 of the β1 domain have been associated with increased resistance to BLV, whereas the amino acid motif valine-aspartate-threonine-tyrosine at positions 75-78 is associated with susceptibility (102). Individuals carrying the resistance motif show a significant reduction in BLV proviral load (61). There have been suggestions that resistance-associated alleles may promote the early development of a specific subset of T helper cells (Th1) that secrete interferon-γ and interleukin-2 (48), thus contributing to resistance to the early spread of infection in vivo.
Dermatophilosis is another disease that has been mapped to specific amino acid motifs of the BoLA DR molecule. This is an infectious disease which occurs mainly in tropical and subtropical regions, is caused by the actinomycete *Dermatophilus congolensis* and has a strong economic impact by reducing ruminant productivity dramatically. The analysis of MHC class I and DRB3 polymorphism in Brahman cattle of the Martinique Islands has led to the identification of the BoLA-A8 specificity and the DRB3 motif glutamic acid-isoleucine-alanine-tyrosine at positions 66, 67, 74 and 78, together with the lack of serine at position 30, as factors associated with increased resistance to dermatophilosis (55).

Mastitis is the most economically important disease of dairy cattle world-wide. Mastitis is a multifactorial disease that is caused by a great variety of different micro-organisms. Multiple associations between MHC polymorphism and resistance and susceptibility to mastitis have been described (49, 96). A locus associated with somatic cell score in Holstein cattle has recently been mapped to BTA23 (6). Dietz et al. have shown that the DRB3 alleles that are associated with increased resistance to BLV are also linked to a higher resistance against mastitis (25, 26). Despite the fact that there have been a number of studies, often with conflicting results, the frequency with which BoLA alleles have been associated with mastitis resistance suggests that at least one gene within or closely-linked to the MHC influences the outcome of udder infections. If future studies can define more precisely the effect(s) associated with this gene(s), BoLA may be a useful tool for selecting cows with natural resistance to mastitis.

In sheep, the influence of MHC genes on resistance to pathogens has been investigated primarily for parasitic diseases. The increasing resistance of nematodes to anthelmintics has given a strong impetus to this field of research. The studies of Douch and Outteridge defined an association of the class I allele SY1 with a higher resistance to *Trichostrongylus colubriformis* (27). More recent studies have focused on class II MHC genes and resistance to *Ostertagia circumcincta* (15, 75). The Ovar-DRB1 locus accounts for 11% of the variation of faecal egg count, and Ovar-DRB1*0203L512 appears to be associated with resistance. In fact, the substitution of DRB1*0101L526, which is the most frequent allele in the analysed population, results in a 58-fold reduction of faecal egg count in six month-old lambs (75). In *Ostertagia* infection, analysis of the polymorphism of two microsatellites located in the class I and class IIb DY regions revealed that the substitution of the most frequently occurring alleles with resistance-associated alleles yields an 8- and 218-fold reduction in the faecal egg counts, respectively (15).

The caprine arthritis-encephalitis (CAE) virus causes a neural disorder in young kids, usually associated with loss of co-ordination and progressive paralysis, while in adults CAE is associated with arthritis and lameness and, in some cases, with mastitis and pneumonia. The class I allele Be7 was associated with resistance to CAE, whereas the class I specificities Be1 and Be14 have been associated with increased susceptibility (71). Similarly, the class II BeD2 and BeD5 were weakly associated with increased susceptibility to CAE. The genetic resistance to heartwater (cowdriosis) in Creole goats has been associated with the class I CLY and Be1 variants, whereas susceptibility has been associated with Be9, Be22 and Be23 (18).

**Conclusion**

The molecular analysis and fine mapping of disease associations will probably play a central role in animal genetics and veterinary medicine for many years to come. The increasing resistance of pathogenic micro-organisms to antibiotics and other drugs underlines the importance of understanding the molecular genetic bases underlying resistance to infectious diseases. The combination of marker-assisted selection for resistance to specific diseases and peptide vaccines that use information on binding motifs will probably contribute to improved animal health in the future.

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Le complexe majeur d’histocompatibilité des ruminants

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Résumé
Les études menées sur le complexe majeur d’histocompatibilité (CMH) des bovins, au cours des vingt dernières années, ont abouti à une description relativement détaillée de l’organisation génétique et des fonctions des gènes au sein du système génétique. L’analyse sérologique et biochimique des antigènes de surface des lymphocytes a mis en évidence pour la première fois le polymorphisme élevé des gènes du CMH des bovins et d’autres espèces de ruminants. Le CMH des bovins a ainsi été appelé système BoLA (bovine leucocyte antigen system).

Au cours des dix dernières années, les techniques de la biologie moléculaire ont permis de déterminer le nombre de gènes du CMH et de caractériser leur séquence et leur structure fine chez certaines espèces de ruminants. Même s’il s’est avéré que les gènes du CMH ont des orthologues évidents chez les ruminants et dans d’autres espèces de mammifères, le CMH des bovins, et probablement celui des ovins et des caprins, présentent une organisation génétique unique. Les bovins possèdent un groupe de gènes de classe II (région de la classe IIb) physiquement éloigné de tous les autres gènes du CMH sur le même chromosome. De plus, des gènes intervenant dans le traitement des antigènes, comme le locus LMP2 de sous-unité de protéasome, se trouvent également dans la région de la classe IIb, ce qui montre que ces gènes n’ont pas besoin d’être très proches des autres gènes du CMH pour fonctionner normalement.

Les produits des gènes du CMH, des classes I et II des ruminants, présentent aux lymphocytes T des peptides traités, et ces lymphocytes sont les agents de la fonction d’auxiliaire (helper) et de la fonction cytotoxique. L’identification des structures de liaison peptidique des molécules de la classe I du CMH des bovins montre que les molécules du CMH des ruminants fonctionnent de la même manière que celles de la souris et de l’homme. Ces études fonctionnelles permettent une bonne explication moléculaire d’un certain nombre d’associations bien connues avec des maladies infectieuses, même si les mécanismes immunogénétiques qui sous-tendent ces associations restent à éclaircir.

Mots-clés

El complejo mayor de histocompatibilidad de los rumiantes

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Resumen
Los estudios realizados durante los últimos veinte años sobre el complejo mayor de histocompatibilidad (major histocompatibility complex, MHC) del ganado vacuno han ido trazando una imagen razonablemente detallada de la organización genética y las funciones de los genes que configuran dicho sistema genético. El análisis serológico y bioquímico de los antígenos de superficie de los linfocitos brindó las primeras pruebas de la existencia de genes MHC extremadamente polimórficos en los bovinos y otras especies de rumiantes. De ahí que el MHC de los bovinos recibiera el nombre de sistema de antígenos leucocitarios bovinos (bovine leucocyte antigen system, BoLA).
Durante los últimos diez años han venido usándose técnicas de biología molecular para determinar el número de genes del MHC, caracterizar su secuencia y elucidar su estructura fina en diversas especies de rumiantes. Aunque se descubrió que determinados genes MHC poseen claros ortólogos entre los rumiantes y otras especies de mamíferos, el MHC de los bovinos, y posiblemente el de los ovínos y los caprinos, exhibe una organización genética característica. Los bovinos poseen un racimo (cluster) de genes de la clase II (región de la clase Iib) ubicado físicamente a cierta distancia del resto de genes MHC, aunque en el mismo cromosoma que éstos. Por otra parte, algunos genes implicados en el procesamiento de los antígenos, como el locus LMP2 de subunidad de proteosoma, también se encuentran en la región de la clase Iib, lo que viene a demostrar que estos genes pueden funcionar normalmente sin necesidad de una gran proximidad física con otros genes MHC.

Los productos de los genes MHC de las clases I y II de los rumiantes presentan péptidos procesados a los linfocitos T, que median en funciones coadyuvantes (helper) y citotóxicas. La identificación de las estructuras de enlace peptídico de las moléculas de MHC de los bovinos de la clase I revela que las moléculas MHC de los rumiantes funcionan de manera muy similar a las del ratón y el ser humano. Estos estudios funcionales proporcionan una sólida explicación molecular a diversas asociaciones con enfermedades infecciosas de las que existían ya abundantes pruebas. Sin embargo, aún no se comprenden en detalle los mecanismos inmunogenéticos que subyacen a dichas asociaciones.

**Palabras clave**


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**References**


