

Major Histocompatibility Complex Class-I Genes: Role in Marker Assisted Selection in Caprine and Ovine Species

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Abstract: Major histocompatibility complex (MHC) of vertebrates is a family of multigenes. The cell surface glycoproteins, being the products of MHC, bind and present antigenic peptides to T cells. MHC loci are used as genetic markers to study the disease resistance and in certain cases where variations are observed in response to the infection. This review aims to assess and determine the application of marker assisted selection (MAS) and various roles of genetic information in breeding programmes.

Key words: MHC Genes Polymorphism • Disease Resistance • Quantitative Trait Loci • Marker Assisted Selection • Caprine • Ovine

INTRODUCTION

MHC was discovered by George Snell in 1948 [1]. MHC is a well-organized cluster of genes which are present in all vertebrates except jawless fish. These genes are tightly linked with immunological and non-immunological functions. MHC, known first for its role in histocompatibility, was first discovered during the studies of tissue transplantation in mice. Since then, various other functions and its role in immune regulation have been reported [2]. In all jawed vertebrates, MHC is normally composed of genes of class I, II and III regions which play important roles in adaptive and innate immune responses as well as resistance to a number of infectious and autoimmune diseases [3]. Understanding of the processes that cause disease and disease control could

be improved by detecting those genes which influence disease resistance. MHC genes have been studied for the last thirty years and are considered best candidates for disease resistance [4]. The basic function of MHC is to code for the antigen presenting receptor glycoproteins, which are known as histocompatibility molecules. These molecules trigger the immune response by binding to processed peptide antigens and presenting them to T lymphocytes [5]. Traditional improvement of an animal within population selection was based on phenotypic traits. The use of genetic markers for selection purpose with these phenotypic characters termed as MAS [6]. MHC molecules and genes are beneficial markers in animal breeding as they help in selection for resistance to diseases. The usefulness of genetic markers for both coding and non-coding DNA fragments depends upon

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the heterozygosity coefficient and their polymorphism [7]. Meanwhile, MHC class I genes polymorphism is mostly involved in susceptibility to various parasitic and infectious diseases [8].

Variations in MHC Class I: It has become a paradigm to maintain genetic diversity at the MHC of vertebrates for the manner in which this genetic diversity could be maintained in the natural population [9]. There are various conditions that are associated with MHC and the variation in the MHC is responsible for selection through disease resistance at individual as well as at population level [10]. By developing simple, cost effective and accurate methods of MHC typing for variety of loci, it would be possible to practise marker assisted selection on commercial basis [2]. MHC class I genes have a common feature in many species, that is high level of polymorphism. This shows their role in presenting wide range of pathogen derived peptides to T-cells. The generation of this diversity and its maintenance are controlled by pressure from rapid evolution of pathogens that primarily operate at population level [11].

MHC in Ovine and Caprine Species: Caprine, ovine and bovine MHC's are also referred as caprine leukocyte antigen (CLA), ovine leukocyte antigen (OLA) and bovine leukocyte antigen (BoLA), respectively. In sheep MHC genes are present on chromosome 20 while in cattle and goat on chromosome 23 [5]. MHC markers of goat are also located on the genetic map of sheep and most of the markers of sheep and goat are positioned on bovine maps hence the maps of all these three species could be aligned readily [13]. As compared to other livestock species, OLA is poorly characterized and the information related to its sequence is poor [14, 15]. Meanwhile, the importance of OLA has been increased due to the structural association of MHC molecules in disease resistance and artiodactyls [15].

Overall structure of MHC class I molecules

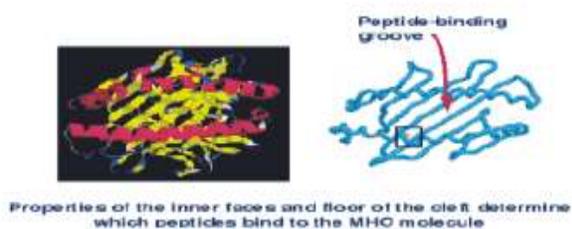


Fig. 1: Structure of MHC class I molecules. Modified from Forsdyke [12]

Polymorphic Nature of MHC Loci: MHC genes are highly polymorphic and clustered within peptide binding groove [16]. This polymorphism is thought to occur due to the long process of evolution and not due to gene mutations, as explained by Andersson [17]. This polymorphism results in differences in recognition of pathogens by the immune system [7]. Polymorphism of MHC class I genes is involved in resistance to various parasitic and infectious diseases [8]. The polymorphic loci of MHC are used as genetic markers in disease resistance studies where variations are observed in response to vaccination or infection [14]. In goat, sheep, dog, pig and cattle, the locus of MHC has been reported as polymorphic [18]. Immunological role performed by MHC depends upon the maintenance of highly polymorphic levels within these genes at the level of population. Large genetic diversity has been predicted by studying MHC in livestock (Sheep and cattle) and other species (Rat, rhesus macaque and horse) [19].

Role of MHC Molecules in Marker Assisted Selection: The gene pool of a population may be affected by different factors and evolutionary processes caused by adaptation to environmental factors. Their influence could be analysed by using markers in high polymorphic regions of genome like MHC [20]. In order to determine the disease associated loci, different strategies and markers could be used such as single nucleotide polymorphisms (SNP's), microsatellites, copy number polymorphism or variants [21]. The critical role of MHC genes and molecules in immune system make these genes a candidate for use in marker assisted selection (MAS) of diseases resistant animals [22].

Marker Assisted Selection: MAS takes in account of the genetic markers and other phenotypic data for selection. MAS was first considered when restriction fragment length polymorphisms (RFLP), the first molecular markers, were explained in various commercially important species. Since then, progress has been made in the development of different types of markers. For the traits having low heritability, MAS is used as a tool to reduce generation interval through early selection, even before maturity and to select those traits which are observed in only one sex [6]. Over the past few decades, advances in molecular genetics have made it possible to identify chromosomal regions and loci that affect important traits in livestock production. MAS can be used either by linking MAS disequilibrium or through gene assisted selection in the

livestock breeding industry [23]. A well planned MAS program considers all traits that are economically important and selection of one trait made at the expense of other traits. Quantitative trait loci (QTL) mapping and genomic research will lead to MAS for precise and efficient selection [24]. MHC genes combined with microsatellite loci behave as highly polymorphic molecular markers and are useful for breeding and conservation programs and potentially linked with resistance against disease [25]. Over direct phenotypic measurement, the strategy of MAS for susceptibility traits of infectious diseases has many advantages. Scalability with flock size and avoidance of drug use are additional advantages of MAS [26].

DISCUSSION

Infectious disease is one of the major issues faced by livestock industry. The genes that control immune responsiveness are present in the region of MHC. MHC genes that are highly polymorphic are key determinants in immune responses [27]. MHC genes are highly polymorphic and expressed as co-dominant markers [5]. There exists orthologous of individual MHC genes among mammalian species and ruminants but the cattle MHC has unique genetic organisation as compared to goat and sheep [28]. In last few decades, extensive genetic maps have been prepared in various animal species used for QTL segregating analysis, MAS and for detecting genes. In order to provide the desired animals needed by the society, molecular markers are expected to serve as underlying tool to breeders and geneticists [29].

Future Prospects: MHC, has been the focus of research because of its diverse functions that extends gradually far beyond transplantation biology. The polymorphism is so high that no two individuals exist with same set of MHC (Class I and II) except identical twins [1]. With advancements in molecular biology and increasing knowledge, efforts need to be made to search and characterize genes which control livestock diseases [30]. Moreover, MHC can help in developing and designing of vaccines based on synthetic peptides composed of one or more T cell epitopes of pathogens [22]. In future, the combination of peptide vaccines using information on binding motifs and MAS against specific diseases will contribute to improve animal health [28]. It is proposed

that the MHC class I genes may be further explored in domestic animals for identification of suitable molecular markers for breeding programs.

REFERENCES

1. Ribic, A., 2012. Immune Privilege Revisited: The Roles of Neuronal MHC Class I Molecules in Brain Development and Plasticity. *Histocompatibility*, Chap, 3: 40-54.
2. Dukkipati, V., H. Blair, D. Garrick and A. Murray, 2006. Ovar-Mhc-ovine major histocompatibility complex: structure and gene polymorphisms. *Genetics and Molecular Research*, 5: 581-608.
3. Liu, H., K. Liu, J. Wang and R. Ma, 2006. A BAC clone-based physical map of ovine major histocompatibility complex. *Genomics*, 88: 88-95.
4. Stear, M.J., A. Belch, K. Donskow-Schmelter, L. Fitton, G. Innocent, C. Ishikane, A. Mateus, L. Murphy, K. Rennie, A. Smith and G. Sayers, 2007. Detection of genes with moderate effects on disease resistance using ovine mhc and resistance to nematodes as an example. *Veterinary Immunology and Immunopathology*, 120: 3-9.
5. Ilhan, F. and F. Özdil, 2011. The structure of MHC (Major Histocompatibility Complex) genes and Molecules in Ruminants. *Analele IBNA*, 27: 83-88.
6. Rothschild, M.F. and A. Ruvinsky, 2007. Marker-Assisted Selection for Aquaculture Species, in *Aquaculture Genome Technologies* (ed Z. Liu), Blackwell Publishing Ltd, Oxford, UK, ch., 12: 201-216.
7. Gruszczyńska, J., K. Charon, W. Swiderek and M. Sawera, 2002. Microsatellite polymorphism in locus OMHC1 (MHC Class I) in Polish Heath Sheep and Polish Lowland Sheep (Zelazna variety). *J. Appl. Genet*, 43: 217-222.
8. Zidi, A., A. Sánchez, G. Obexer-Ruff and M. Amills, 2010. Sequence Analysis of Goat Major Histocompatibility Complex Class I Genes. *J. Dairy Sci.*, 91: 814-7.
9. Paterson, S., K. Wilson and J. Pemberton, 1998. Major histocompatibility complex variation associated with juvenile survival and parasite resistance in a large unmanaged ungulate population (*Ovis aries* L.). *Proc. Natl. Acad. Sci.*, 95: 3714-3719.

10. Trowsdale, J., 2004. The MHC, disease and selection. *Immunology Letters*, 137: 1-8.
11. Ellis, S., 2004. The cattle major histocompatibility complex: is it unique. *Veterinary Immunology and Immunopathology*, 102: 1-8.
12. Forsdyke, D.R., 1995. Entropy Driven Protein Self Aggregation as the Basis for Self/Not Self Discrimination in the Crowded Cytosol. *Journal of Biological Systems*, 3: 273-287.
13. Maddox, J.F. and N. Cockett, 2007. An update on sheep and goat linkage maps and other genomic resources. *Small Ruminant Research*, 70: 4-20.
14. Miltiadou, D., K. Ballingall, S. Ellis, G. Russell and D. McKeever, 2005. Haplotype characterization of transcribed ovine major histocompatibility complex (MHC) class I genes. *Immunogenetics*, 57: 499-509.
15. Gao, J., K. Liu, H. Liu, H. Blair, G. Li, C. Chen, P. Tan and R. Ma, 2010. A complete DNA sequence map of the ovine Major Histocompatibility Complex. *BMC Genomics*, 11: 466.
16. Miyasaka, T., S. Takeshima, Y. Matsumoto, N. Kobayashi, T. Matsushashi, M. Yoshiyuki, Y. Tanabe, K. Ishibashi, H. Sentsui and Y. Aida, 2011. The diversity of bovine MHC class II DRB3 and DQA1 alleles in different herds of Japanese Black and Holstein cattle in Japan. *Gene*, 472: 42-49.
17. Andersson, L., 1996. *The Major Histocompatibility Complex Region of Domestic Animal Species*. Ed. Schook L.B, Lamont S.J. CRC Press, pp: 1-15.
18. Baghizadeh, A., M. Bahaaddini, M. Mohamadabadi and N. Askari, 2009. Allelic Variations in Exon 2 of Caprine MHC Class II DRB3 Gene in Raeini Cashmere Goat. *American-Eurasian J. Agric. and Environ. Sci.*, 6: 454-459.
19. Birch, J., L. Murphy, N. MacHugh and S. Ellis, 2006. Generation and maintenance of diversity in the cattle MHC class I region. *Immunogenetics*, 58: 670-679.
20. Bozkaya, F., A. Kuss and H. Geldermann, 2007. DNA variants of the MHC show location-specific convergence between sheep, goat and cattle. *Small Ruminant Research*, 70: 174-182.
21. Larruskain, A. and B. Jugo, 2013. *Retroviral Infections in Sheep and Goats: Small Ruminant Lentiviruses and Host Interaction*. *Viruses*, 5: 2043-2061.
22. Behl, J.D., N. Verma, N. Tyagi, P. Mishra, R. Behl and B. Joshi, 2012. The Major Histocompatibility Complex in Bovines: A Review. *ISRN Vet Sci.*, pp: 12.
23. Dekkers, J.C.M., 2004. Commercial application of marker- and gene-assisted selection in livestock: Strategies and lessons. *J. Anim. Sci.*, 82: 313-328.
24. Liu, Z.J. and J. Cordes, 2004. DNA marker technologies and their applications in aquaculture genetics. *Aquaculture*, 238: 1-37.
25. Salles, P.D.A., S. Santos, D. Rondina and M. Weller, 2011. Genetic variability of six indigenous goat breeds using major histocompatibility complex-associated microsatellite markers. *J. Vet. Sci.*, 12: 127-132.
26. White, S.N. and D. Knowles, 2013. Expanding Possibilities for Intervention against Small Ruminant Lentiviruses through Genetic Marker-Assisted Selective Breeding. *Viruses*, 5: 1466-1499.
27. Baxter, R.J., 2010. The role of the Major Histocompatibility Complex in immune responsiveness in a Holstein Charolais cattle cross population. The University of Edinburgh, A thesis, pp: 1-239.
28. Amills, M., V. Ramiya, J. Nonmine and H. Lewin, 1998. The major histocompatibility complex of ruminants. *Rev. Sci. Tech. Off. int. Epiz.*, 17: 108-120.
29. Teneva, A., 2009. *Molecular Markers in Animal Genome Analysis*. *Biotechnology in Animal Husbandry*, 25: 1267-1284.
30. Ibeagha-Awemu, E.M., P. Kgwatalala, A. Ibeagha and X. Zhao, 2008. A critical analysis of disease-associated DNA polymorphisms in the genes of cattle, goat, sheep and pig. *Mamm Genome*, 19: 226-245.