Major Histocompatibility Complex Diversity in Dogs & Disease Associations

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Objectives of the Presentation

- Explain the function of the Major Histocompatibility Complex (MHC) in the dog
- Explain why we are interested in the canine MHC
- Describe the canine MHC
- Characterization of the canine MHC
- Extent of variation in the canine MHC
- Disease associations

Overview of the Issue

The Major Histocompatibility Complex (MHC) gene products are critical for the regulation of the immune responses in all higher animals. They are fundamental for explaining variation in susceptibility to infections, immune response to vaccines, the development of auto-immunity and also for transplantation survival.

The canine MHC which is known as DLA (for Dog Leukocyte Antigen) has been extensively studied and shown to be very variable.[1-3] Various DLA alleles and haplotypes have been shown to be associated with several immune mediated diseases[4-9], severity of infection in Leishmaniasis[10] and response to rabies vaccination.[11]

Hypothesis

Many human immune mediated diseases have been shown to have MHC associations. Dogs have similar spontaneously occurring diseases, and if such diseases are also MHC associated, this would provide good evidence that the canine diseases were homologues of the human diseases.

The Canine MHC

The canine MHC comprises three regions of genes which are called class I, class II and class III. The class I region contains several genes, one of which is very polymorphic. This gene is called DLA-88 and there are currently 51 official alleles, although we have identified at least another ten. The class II region has three polymorphic genes, called DLA-DRB1, DLA-DQA1 and DLA-DQB1. The class III region contains genes such as TNFalpha, and has been less well characterised.

DLA class II alleles can be identified using sequence based typing (SBT). Each locus is amplified using locus specific primers. The PCR product is sequenced and the homozygous or heterozygous sequence can be decoded using specialist software programs that compare the sequence to libraries of known alleles. Alleles can be assigned to haplotypes based on previously identified haplotypes. New haplotypes are identified in homozygous animals.

DLA Variation

We have now characterised over 7,000 dogs for their DLA class II alleles and haplotypes for three class II loci. These include dogs from over 150 different breeds with numbers per breed ranging from 1-500. We can see that most breeds have four to five major haplotypes with frequencies greater than 10%. Breeds with large populations, such as Labrador retrievers, tend to have more haplotypes, while breeds which have been through population bottlenecks, such as the Clumber spaniel have fewer haplotypes.

We have typed over 600 dogs from many multi-generation families, and shown that DLA alleles and haplotypes are inherited as expected.

DLA Disease Associations

Clear associations have been shown for several immune mediated diseases. These include diabetes,[5,6] immune mediated haemolytic anaemia,[4] hypothyroid disease,[7,12] anal furunculosis[8] and polyarthritis,[9] It is clear that different breeds can have different DLA associations for the same disease.

Susceptibility to Leishmania infection has been shown to be associated with one DLA-DRB1 allele.[10]

We have also shown that there is variation of response to rabies vaccination that can be attributed to the breed of the dog,[11] which is presumably genetic. Unpublished data indicates that there is an effect of DLA on this vaccine response.

Additional Detail

The Major Histocompatibility Complex (MHC) gene products are critical for the regulation of the immune responses in all higher animals. They provide the basis for self-recognition and are fundamental for explaining variation in susceptibility to infections, immune response to vaccines, the development of auto-immunity and also to allotransplantation and rejection. They are also involved in immune surveillance and tumor immunology. Both MHC class I and II cell surface molecules are responsible for presenting antigens to the T cell receptor. Class I molecules present endogenously derived antigen (e.g. viral) to CD8 positive T cells, while class II molecules present exogenously derived antigens (e.g. bacterial) to CD4 positive T cells.[13]Variability within the amino acid sequence of such MHC molecules influences the repertoire and affinity of peptide antigen binding and this is likely to influence the efficiency of acquired immunity to specific antigens. MHC sequence variability is thus under strong selective evolutionary pressure and consequently, in higher animals, these have become the most polymorphic genes observed at a population level.

When bottlenecks occur in the history of a population, such as those due to catastrophic events, or the establishment of new populations from a relatively small number of founders, major differences in the frequency distribution and extent of alleles can be seen between different populations. This is certainly the case in humans where HLA allele distribution can differ markedly between different populations across the world.[14-17] Similarly differences are seen where closed selective line breeding has occurred, and this is the situation observed in a wide range of domestic dog breeds.[1-3,18,19]

The canine Major Histocompatibility Complex (MHC), which is known as DLA (for Dog Leukocyte Antigen) has been shown to be very variable.[3] As more breeds have been studied, more alleles have been identified.[1,2,19,20] The grey wolf is the ancestor of the domestic dog and we have also investigated the DLA profile of grey wolves from Alaska and Northern Canada.[21]

The dog population is composed of around 400 purebred breeds; each one can be considered to be a genetic isolate with unique characteristics resulting from continuous selection for specific attributes (e.g. short legs, floppy ears or curly coat), from genetic drift or inbreeding. Dogs tend to suffer from the same range of diseases as humans but the genetic complexity of these diseases within a breed is reduced as a consequence of the genetic drift and due to long-range linkage disequilibrium.

It is therefore easier to look for genetic markers for disease in dogs than humans, since fewer cases are needed to give the same power for a study.

Summary

- The canine MHC is very variable with over 200 three locus class II haplotypes identified to date.
- There is little intrabreed variation with most breeds having 4 or 5 frequent haplotypes
- There is great interbreed variation
- Some haplotypes are very common and are found in many breeds
- Other haplotypes are found in few breeds
- Certain haplotypes have been associated with diabetes, hypothyroid disease, immune mediated haemolytic anaemia, and anal furunculosis. There can be different associations in different breeds (similar to different HLA associations in different human ethnic groups)

References/Suggested Reading

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