Heredity (2007) 99, 241–242

www.nature.com/hdy

## NEWS AND COMMENTARY

**Selection on MHC?**

# A matter of form over function

LA Knapp

*Heredity* (2007) **99,** 241–242; doi:10.1038/sj.hdy.6800986; published online 30 May 2007

The major histocompatibility complex (MHC) contains the most diverse genes known in vertebrates. High levels of polymorphism are often attributed to pathogen-mediated selection for potential immune responses to specific parasites or diseases. Surprisingly, however, little empirical evidence exists to support the hypothesis of pathogen-driven selection. Now, new evidence comes from the study of a small nocturnal lemur living under natural conditions in western Madagascar. In the paper on page 265, by examining neutral microsatellite diversity, MHC-DRB exon 2 polymorphism and parasite burden, Schwensow *et al.* (2007) found that MHC-DRB genotype is important for resistance to nematode helminths. They conclude that MHC polymorphism is maintained through pathogen-driven frequency-dependent selection in wild fat-tailed dwarf lemurs (*Cheirogaleus medius*).

MHC-DRB genes encode proteins that are expressed on the surface of immunocompetent cells, and critical regions of the protein bind foreign antigens and present them to helper T lymphocytes to activate the immune response. X-ray crystallographic studies of the three-dimensional structure of MHC-DRB proteins demonstrate that antigen-binding sites vary in conformation, determining the shape of the foreign antigen they bind to. Therefore, it has been argued that individuals with rare antigen-binding abilities should be more capable of combating diseases, at least in the short term, than individuals with common antigen-binding capabilities. This rare allele advantage would ultimately promote MHC-DRB polymorphism since pathogens require time to adapt to hosts with rare MHC alleles. So, by the time the pathogen has adapted to the host, and the previously rare allele has become common in the population, new mutant alleles would have arisen.

All but a few rare species exhibit extremely high levels of MHC-DRB polymorphism. Humans, for example, possess several hundred MHC-DRB alleles. The mechanisms for maintaining such extraordinary MHC polymorphism in humans and other vertebrates have been hotly debated among immunogeneticists and evolutionary biologists. Within the context of resistance to infectious agents, MHC genetic diversity could be maintained through heterozygote advantage, frequency-dependent selection or even both. Heterozygote advantage results when an individual with many different MHC alleles responds to a wider array of pathogens than an individual with less diversity and, consequently, survives to pass on the genes to the next generation. Frequency-dependent selection is the consequence of the aforementioned rare allele advantage and this explanation appears to be supported by Schwensow *et al.* (2007) work on fat-tailed dwarf lemurs. The authors distinguished 50 different MHC-DRB exon 2 sequences in a population of 149 lemurs and reported that individuals possessed between two and four different sequences. This exceptional degree of diversity is notable. However, it also means that detection of statistically significant associations between parasite burden and specific MHC-DRB sequences would require unfeasibly large sample sizes. To combat the limitation, Schwensow *et al.* (2007) pooled their 50 sequences to form 11 supertypes, based on similarities in the predicted antigen-binding sites of the MHC-DRB sequences. Analyses using the 11 supertypes revealed that one MHC supertype was associated with high intensity and diversity of nematode infections, while another, relatively rare, MHC-supertype was associated with a complete lack of nematode infection. Contrastingly, overall genome heterozygosity, measured using seven polymorphic microsatellite loci, did not differ between infected and uninfected individuals.

Correlations between specific MHC-DRB sequences and resistance, or susceptibility, to specific pathogens have been reported previously for Atlantic salmon, yellow-necked mice, striped mice, hairy-footed gerbils and mouse lemurs (reviewed in Piertney and Oliver, 2006). These studies offer support for the frequency-dependent model of pathogen-driven selection. However, direct empirical demonstration of differential fitness of specific and, most importantly, expressed MHC genotypes in response to pathogens is rare. Only a very small number of studies (Paterson *et al.*, 1998; Lohm *et al.*, 2002; Penn *et al.*, 2002; Wegner *et al.*, 2003) have had the necessary population size and statistical power to detect subtle effects for expressed MHC gene products and therefore the debate over the relative importance of pathogen-driven selection continues.

Identification of supertypes has proven useful for characterizing the antigen-binding specificities of common human MHC, also known as the human leukocyte antigen (HLA) types. The grouping of MHC alleles into supertypes is based on common structural and functional features of expressed MHC genes. In other words, an MHC molecule's form (that is, structure) and function go hand in hand. The connection between an HLA protein's form and function is well understood, since an HLA-DRB molecule's antigen-binding ability is the consequence of its exon 2 nucleotide sequence. Unfortunately, relatively little is known about the transcription and expression of MHC-DRB genes in non-human primates, including lemurs, and Schwensow *et al.*'s (2007) identification of MHC-DRB supertypes in fat-tailed dwarf lemurs seems premature without knowledge about expression of the lemur DNA sequences. Only recently has it become clear that many rhesus macaque MHC-DRB sequences can be detected on the genomic, but not on the cDNA level. de Groot *et al.* (2004) found that approximately 22% of macaque MHC-DRB sequences identified using genomic DNA were actually nonfunctional (that is, pseudogenes). A similar comparison is now in order for fat-tailed dwarf lemurs.

The identification of MHC-DRB genes in wild populations is increasingly popular, especially since functional polymorphism is essentially restricted to exon 2, which is only 270 bp. Given the simplicity of identifying one single highly variable exon using almost any type of biological sample, it is likely that even more research on these genes will be undertaken in future. In 2006, new molecular studies led to the discovery of dozens of previously unreported MHC-DRB sequences in species ranging from bank voles to pandas. Unfortunately, the simplicity of PCR amplifying a single highly informative MHC-DRB exon from DNA can lead to misguided conclusions about protein expression. Schwensow *et al.* (2007) have assumed that sequences without insertions, deletions or stop codons are functional (that

is, form equals function). However, the MHC of most species is characterized by duplication and inactivation of functional genes. Associations between MHC-DRB sequences and pathogen resistance, or susceptibility, require unambiguous identification of functional, transcribed mRNA sequences. In these cases, function will follow form. Until then, conclusions that pathogen-driven selection drives MHC polymorphism based on form, but not function, will be intriguing but premature.

*Dr LA Knapp is at Primate Immunogenetics and Molecular Ecology Research Group, Department of Biological Anthropology, University of Cambridge, Downing Street, Cambridge CB2 3DZ, UK.*

*e-mail: lak26@cam.ac.uk*

de Groot N, Doxiadis GG, de Groot NG, Otting N, Heijmans C, Rouweler AJM *et al.* (2004). Genetic makeup of the DR region in rhesus macaques: gene content, transcripts, and pseudogenes. *J Immunol* **172**: 6152–6157.

Lohm J, Grahn M, Langefors A, Anderson O, Storset A, von Schantz T (2002). Experimental evidence for major histocompatibility complex–allele-specific resistance to a bacterial infection. *Proc R Soc London B* **269**: 2029–2033.

Paterson S, Wilson K, Pemberton JM (1998). Major histocompatibility complex variation associated with juvenile survival and parasite resistance in a large unmanaged ungulate population. *Proc Nat Acad Sci USA* **95**: 3714–3719.

Penn DJ, Damajanovich K, Potts WK (2002). MHC heterozygosity confers a selective advantage against multiple-strain infections. *Proc Nat Acad Sci USA* **99**: 11206–11264.

Piertney SB, Oliver MK (2006). The evolutionary ecology of the major histocompatibility complex. *Heredity* **96**: 7–21.

Schwensow N, Fietz J, Dausmann K, Sommer S (2007). Neutral versus adaptive genetic variation in parasite resistance: importance of MHC-supertypes in a free-ranging population. *Heredity* **99**: 265–277.

Wegner KM, Kalbe M, Kurtz J, Reusch TBH, Milinski M (2003). Parasite selection for immunogenetic optimality. *Science* **301**: 1343.

## Editor's suggested reading

Nespolo RF (2007). A simple adaption to cycling selection: a complex population dynamic explained by a single-locus Mendelian model for litter size. *Heredity* **98**: 63–64; advance online publication, 20 December 2006.

Piertney SB, Oliver MK (2006). The evolutionary ecology of the major histocompatibility complex. *Heredity* **96**: 7–21; advance online publication, 10 August 2005.

Schaschl H, Wandeler P, Suchentrunk F, Obexer-Ruff G, Goodman SJ (2006). Selection and recombination drive the evolution of MHC class II DRB diversity in ungulates. *Heredity* **97**: 427–437; advance online publication, 30 August 2006.

van Oosterhout C, Joyce DA, Cummings SM (2006). Evolution of MHC class IIB in the genome of wild and ornamental guppies, *Poecilia reticulata*. *Heredity* **97**: 111–118; advance online publication, 31 May 2006.