Balancing selection and the maintenance of MHC supertype variation in a selfing vertebrate

S. Consuegra1, A. Ellison1, J. Allainguillaume2, J. Pachebat1, K. M. Peat1 and P. Wright3

1IBERS, Aberystwyth University, Penglais Campus, Aberystwyth SY23 3DA, UK
2Department of Applied Sciences, University of the West of England, Coldharbour Lane, Bristol BS16 1QY, UK
3Department of Integrative Biology, University of Guelph, Guelph, Ontario, Canada N1G 2W1

Despite being probably one of the most studied topics in Evolutionary Biology, the mechanisms of maintenance of major histocompatibility complex (MHC) diversity in vertebrates remain also one of the most debated topics [1].

Ellison et al. [2] studied MHC class I diversity of a selfing Kryptolebias marmoratus population by clustering alleles in supertypes grouped by their physico-chemical similarity, and suggested that the maintenance of highly divergent MHC supertypes despite the loss of diversity after several generations of selfing could be due to overdominance. van Oosterhout [3] presented an intriguing alternative explanation to overdominant selection, according to which diversity could be preserved in the form of divergent supertypes at different loci, provided alleles from different supertypes segregate at different loci. This view would provide a simple explanation for the maintenance of divergent supertypes without the need to invoke overdominance, and would imply that balancing selection acts at the supertype level, instead of acting upon loci variation. However, such an explanation does not necessarily rule out the hypothesis of overdominance. One of the arguments against the overdominant scenario is the potentially high loading cost associated with the maintenance of heterozygosity at the 13 MHC class I loci that had previously been identified by Sato et al. [4] in this species. Although 13 loci had been identified in populations from three different geographical origins, only a maximum of six different loci were present per population [4]. A similar result (maximum five loci per population) was obtained by Fisher [5] in a screening of two different K. marmoratus populations. Ellison et al. [2] did not identify individual loci, but found a maximum of 11 alleles per individual and most importantly, found that MHC variability was closely associated with microsatellite heterozygosity. Thus, individuals with nine, ten and eleven MHC alleles displayed heterozygosities of 0.56, 0.67 and 0.78, respectively for a set of 32 microsatellites. This level of heterozygosity is unusually high for a selfing species, and may suggest that those individuals were the product of recent outcrossing between selfing lines [6]. Thus, given that MHC class I heterozygosity has been reported to be higher than that of microsatellites [4], the results of Ellison et al. [2] also suggest a maximum of 5–6 MHC class I loci per population. Therefore, alleles from different supertypes could potentially correspond to the same locus as it happens, for example, in humans where the three class I HLA loci (A, B and C) are represented by four, five and two supertypes, respectively [7]. Moreover, distinct MHC loci seem to be restricted to different populations and even to different individuals from the same population, that display a variable number of loci, possibly as a consequence of unequal recombination common in the MHC [8]. It, therefore, seems that, as reported in Ellison et al. [2], different selfing lines of K. marmoratus display a variable number of MHC loci, some as low as one or two, that can express alleles belonging to different supertypes and be influenced by overdominant selection.

The role of balancing selection in maintaining heterozygosity at MHC loci was also proposed by Sato et al. [4]. Based on simulations, they explained the
high level of observed heterozygosity (4–44%) by a combination of balancing selection and selfing rates less than 1. Such a scenario would also fit well the population studied in Ellison et al. [2] that displayed an average selfing rate of 0.69 [9], and 30 per cent of individuals with more than one MHC supertype (thus, probably higher loci heterozygosity). Neutral forces, as well as selection, are commonly invoked to explain the patterns of distribution of MHC diversity in natural populations [10]. This seems to be particularly the case in populations that have suffered bottlenecks [11], of which selfing populations can be seen as a particular case, where the intensity of selection is related to the selfing rate [4].

The possibility proposed by van Oosterhout [3] to explain parasite-mediated balancing selection opens an interesting research avenue that clearly deserves further attention, particularly in species such as K. marmoratus that have duplicated MHC genes and are prone to inbreeding. Achieving outcrossing of K. marmoratus has proved difficult under laboratory conditions, but a detailed analysis of MHC composition of successive selfing generations (generated from hermaphrodites with different levels of heterozygosity and different geographical origins) coupled with experimental infections would help to clarify the question proposed by van Oosterhout [3]. In this sense, increasing use of next generation sequencing in MHC studies [12], and the imminent publication of the whole genome of K. marmoratus [13], make this species a particularly good model to study the relationships between inbreeding and immunocompetence.

References