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# Transposons in the MHC: the Yin and Yang of the vertebrate immune system

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Recent research on transposable elements (TEs) in the major histocompatibility complex (MHC) proposed that TEs may play an adaptive evolutionary role in the vertebrate immune system (Doxiadis *et al*., 2008). Here, I argue that although transposons will undoubtedly affect the evolution of the MHC, their increased density in this region may be an evolutionary inevitability, given the genomic architecture of these genes. The MHC is an evolutionary innovation of the jawed vertebrates in their race against organismal parasites; however, functional epistasis and high gene diversity of this multigene family may have rendered the MHC prone to the onslaught of genomic parasites.

Transposons are genomic parasites that exploit their host's resources for their own reproduction and they seem to have the upper hand in the coevolutionary arms race by their potential to out-replicate the host genomes in which they reside (Jordan *et al*., 2003). Indeed, TEs constitute a large proportion of the vertebrate genome, and on average more than 40% of the mammalian genome consists of these parasitic elements (Margulies *et al*., 2005). TEs are often deleterious to their host and can disrupt coding regions of the genome, induce recombination between copies of the repeats and affect the splicing of the targeted genes (van de Lagemaat *et al*., 2006). However, just as any other mutation, TEs do provide genetic variation that is the substrate for natural selection. This variation might be crucial to some gene regions, particularly to the MHC, as according to the Red Queen's hypothesis, the immune system of the vertebrate host is involved in a coevolutionary arms race with fast-evolving organismal parasites.

Although severely detrimental and lethal TEs are likely to be purged from the gene pool by natural selection, some TEs have been 'domesticated' by their hosts (Miller *et al*., 1999). These TEs may have gained a regulatory role (van de Lagemaat *et al*., 2003), or have become part of a gene (Feschotte and Pritham, 2007). Currently, the paradigm is that TEs are not merely 'selfish elements', but that they can play a constructive role in adaptive evolution. The potential functional role of TEs or TE-derived sequences can be inferred from their nucleotide sequence conservation (Lowe *et al*., 2007), the donation of TE sequences in promoter regions (Jordan *et al*., 2003) and the lower than expected rate of TE interruption by other newer transposons (Abrusán *et al*., 2008).

Furthermore, TEs have a non-random distribution throughout the genome, and they show an increased density in the MHC in a wide range of vertebrates. Recently, Doxiadis *et al*. (2008) showed that the polarity of TEs—whether they are oriented in sense or antisense—affects the stability of the MHC gene region. Sense-oriented TEs are able to promote gene duplications and deletions by gene-conversion-like events, and thus form novel region configurations. In contrast, antisense-oriented retroelements seem to promote evolutionary stability, possibly by reducing the recombination rate with other MHC haplotypes (Doxiadis *et al*., 2008).

The equilibrium frequency of TEs will, however, not only be determined by natural selection, but also by other evolutionary forces; for example, the transposition activity of the transposon (that is, the 'mutation rate'), random genetic drift and the recombination rate. The interaction between these evolutionary forces, as well as the epidemiology of transposons within host genomes, will govern the population genetics and dynamics of TEs. Given that the effective population size of most vertebrates is relatively small, genetic drift may play an equal, if not more important, role than natural selection in the population genetics of vertebrate TEs. In addition, differences in the recombination rate may also explain the variation in density of TEs across the vertebrate genome.

Recently, van Oosterhout (2009) proposed a new theory of MHC evolution, coined Associative Balancing Complex (ABC) evolution, which may explain why the density of TEs is relatively high in this genomic region. Although traditional theories of balancing selection were developed for single genes, ABC evolution takes into account the effect of epistasis and high MHC gene diversity. Functional epistasis between the immune genes reduces the effective rate of recombination in some areas of the MHC (Stenzel *et al*., 2004; Gregersen *et al*., 2006). These so-called haploblocks are characterized by strong linkage disequilibrium, and the low recombination rate reduces the efficacy of purifying selection (Haddrill *et al*., 2007). TEs and other deleterious mutations can become fixed in all copies of a particular haploblock in a process analogous to Muller's (1932) Ratchet. They can accumulate as a 'sheltered load' (Stone, 2004) when they are recessive so that their effects are not expressed in heterozygote condition. The high gene diversity (heterozygosity) and linkage disequilibrium in the MHC region thus facilitate the accumulation of recessive deleterious mutations and TEs. This may explain why there are over 100 heritable diseases associated with the human MHC (the human leukocyte antigen) (de Bakker *et al*., 2006), and why these genetic polymorphisms are not removed by natural selection (van Oosterhout, 2009). In the MHC, purifying selection is considerably less efficient than in many places elsewhere in the genome, which means that in their wake, transposons have made the human MHC into a hotbed of heritable diseases and disorders.

In summary, some TEs in the MHC may confer selective advantages, for example, by suppressing recombination, promoting gene duplications and deletions (Doxiadis *et al*., 2008), and by reinforcing epistasis and balancing selection on the immune genes (van Oosterhout, 2009). Similar to point mutations, TEs provide important genetic variation for selection, but according to the 'nearly neutral theory', the majority of the polymorphisms that are present in the population will have a nearly neutral or slightly detrimental effect on fitness (Hughes, 2007). Transposons simply seem to have targeted the MHC because the genomic features that have made this immune gene family such an efficient defence against

organismal parasites, also rendered it vulnerable to these genomic parasites.

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