Allelic variations of human TCR *V* gene products

D.N. Posnett (*Immunol. Today*, 1990, 11, 368–373) reviewed the allelic polymorphism of major histocompatibility complex (MHC) and T-cell receptor (TCR) molecules. He argued that "The species may avoid extinction by avoiding 'holes' in the species-wide repertoire of MHC molecules" and "... while this system can increase the available TCR *V* gene elements within an individual's TCR repertoire, it is not apparent how the species benefits". Since Darwinian selection processes mainly operate at the level of individual organisms and/or genes, and hardly at the level of a whole species[1–3], I would like to discuss the same findings in terms of the survival of individuals and genes.

A simple benefit of extensive allelic MHC polymorphism is that each individual is expected to inherit different MHC genes from both parents[4,5]. This doubles the repertoire of available MHC molecules per individual, which presumably enables it to present a larger variety of antigenic peptides. A second advantage of MHC polymorphisms is that certain individuals may escape infection from mutating pathogens. A co-evolving pathogen is most likely to adapt to the most common MHC in the population. Thus, any offspring that differs sufficiently from the rest of the population because it inherited a mutated – but functional – MHC gene is expected to have a higher fitness[5–7].

Understanding the polymorphisms of TCR genes is difficult because the potential repertoire of TCRs within an individual may be as large as 10^{11} different molecules[8]. First, as Posnett argued, polymorphic TCR genes enable individuals to increase their TCR repertoire. Within the framework of individual selection this is an evolutionary advantage. Second, it is conceivable that the potential TCR repertoire is largely random and that the repertoire size that has evolved is the one that is required for covering the space of all possible antigens[9]. Whenever there is randomness in the repertoire, many mutations will be neutral and will lead to genetic drift and polymorphisms.

Third, because of genetic erosion, it has been argued[10] that the potential TCR repertoire cannot be larger than the actual repertoire. I would like to discuss this problem in terms of gene selection[1–3]. Any particular TCR is expected to be temporarily expressed in only a few of the individuals of a population. Because in these individuals nonmutated alleles of these TCRs will have a selective advantage over mutated alleles, there is always some selection against deleterious gene mutants. Whether or not this selection pressure suffices remains an open question that depends on the mutation frequency, the population size, the actual repertoire and the potential repertoire.

In conclusion, viewing the evolutionary process at the level of the individual can reveal insights that could not have been attained by searching for a benefit to the species.

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Reply

In his comments, R.J. De Boer makes the point that allelic polymorphism of T-cell receptor (TCR) *V* genes may be due to neutral mutations leading to genetic drift rather than to selective advantages. This is an important distinction because in the former case one might expect to find no significant differences between alleles in terms of immune functions and in terms of relevance to disease susceptibility.

The available data are still incomplete, but two observations favor the presence of selective advantages. First, the described allelic systems (human $V_\beta 1$ and $V_\beta 6.7$, and murine $V_\beta 8.2$ and $V_\beta 17$) are due to replacement mutations resulting in nonconservative amino acid changes. Silent codon mutations (not resulting in an amino acid replacement), which would be expected to occur randomly at a frequency of 0.25 of all observed codon point mutations, have not yet been described in TCR *V* gene exons. Second, the amino acid residues that distinguish TCR *V* gene alleles appear to be situated at critical sites on the TCR molecule that are thought to be involved in Ag/MHC recognition or superantigen binding[1–4].

If further analyses of new allelic TCR genes confirm these first impressions, it will be hard to argue in favor of neutral mutations.

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