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Error-prone polymerases make efficient immunity

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When B cells encounter a pathogen for the second or third time, an enormous amplification of specificities and increase in antibody affinities is created by selectively mutating the antibody-encoding genes in a process known as somatic hypermutation. The mechanisms of this mutagenesis are unknown. Two papers in June *Nature Immunology* reveal some properties of the DNA polymerases involved in the mutation process.

Rogozin and colleagues from National Institute of Environmental Health Sciences, North Carolina, analysed mutational spectra of 15 immunoglobulin genes and found that consensus motifs RGYW and WA were universal descriptors of somatic hypermutations. Analysis of base-substitution hotspots in DNA polymerase error spectra showed that 33 of 36 hotspots in the human polymerase ? spectrum conformed to the WA consensus. This means that errors introduced by this enzyme during synthesis of the nontranscribed DNA strand in variable regions may contribute to strand-specific somatic hypermutagenesis of immunoglobulin genes at A-T base pairs (Nature Immunol 2001, **6**:530-536).

In the second paper Zheng *et al*. from the National Institute of Aging, examined the frequency and pattern of substitutions in variable immunoglobulin genes (VH6) from the peripheral blood lymphocytes of three patients with xeroderma pigmentosum, whose DNA polymerase ? had genetic defects. They found a decrease in mutations at A and T and a concomitant rise in mutations at G and C. It is probable that polymerase(s) other than polymerase ? may preferentially generate mutations opposite G and C (Nature Immunol 2001 **6**:537-541).

These findings further confuse the present understanding of the mechanism of somatic hypermutation and the challenge is now to define the order in which the error prone polymerases operate, says Ursula Storb, from the University of Chicago, in an accompanying News & Views article.

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