Codon usage bias directs somatic hypermutation to the complementarity-determining regions and away from the framework regions of antibody genes

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During the 2-3 weeks of a germinal center reaction, the affinity of antigen-specific B cell receptors may increase by 1-3 orders of magnitude. Responsible for this dramatic improvement in affinity is the micro-evolutionary dynamics that takes place in the germinal centers. Here the B cell receptors are diversified via somatic hypermutation, and the cells carrying mutant receptors undergo selection based on their ability to bind the antigen.

Analyses of the distribution of mutations along the variable region of non-selected antibody genes demonstrated that the frequency of mutations is elevated in complementarity-determining regions (CDR), compared to the framework regions (FR). CDR are therefore not only more diverse than FR, but also more diversifiable during somatic hypermutation. Here I will show that this effect is due to the concentration of nucleotide motifs (AGC and WAN, with W = A or T, and N = A or C or G or T) which are especially prone to somatic hypermutation in CDR. Also, the specific codon usage of FR makes these regions less mutable than alternative encodings with an unbiased codon usage. Compositional biases related to the mammalian somatic hypermutation mechanism are present in species that diverged soon after the emergence of the vertebrate immune system. This argues that at least some components of somatic hypermutation are phylogentically old, and are shared between vertebrate species.