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CURRENT COMMENT

V_H4–21, A HUMAN V_H GENE SEGMENT OVERREPRESENTED IN THE AUTOIMMUNE REPERTOIRE

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In humans, the immunoglobulin heavy chain locus is located in chromosome band 14q32.33 (1,2). Three different elements, V_H, D, and J_H, encoded by gene segments which in germline configuration are separated by thousands of basepairs, are brought together by a recombination machinery in order to generate a functional variable region. The existence of many different V_H, D, and J_H gene segments provides the first substrate for diversifying the repertoire of B cells. Diversity is enhanced by several orders of magnitude by the combinatorial association of these 3 elements and the generation of new amino acids at the V_H–D and D–J_H junctions during the process of rearrangement. Further expansion of the repertoire is accomplished by the mechanism of somatic mutation, which, by acting upon the rearranged gene segments, leads to a practically unlimited spectrum of B cell specificities (for review, see ref. 3).

Current knowledge about the human V_H complex indicates that the repertoire of available functional V_H genes is diverse. Restriction fragment length polymorphism analyses suggest that the total number of germline V_H gene segments is ~100–200, 20–40% of which are probably pseudogenes. Based on nucleotide sequence homology, human V_H gene segments are classified into 6 V_H families which vary considerably in size, from 1 single member to more than 50 (for review, see ref. 4) (Table 1).

The original structural studies of human immunoglobulins were performed at the protein level in patients with monoclonal gammopathies and led to the discovery of the V_H1, V_H2, and V_H3 families (5). Several years later, advances in molecular cloning techniques allowed the definition of 3 new families, V_H4, V_H5, and V_H6 (6–10). The absence of these 3 families from the repertoire of patients with monoclonal gammopathies was attributed to their size (<10 members, as opposed to the V_H1 and V_H3 families, which contain >25 members each). It was not surprising then that the "large" V_H families represent the vast majority of the repertoire.

Bias in V_H gene expression as suggested by analyses of the mouse V_H repertoire in different compartments

B cells are renewed at the pre–B cell stage in the fetal liver and adult bone marrow (11,12). Stem cells carrying the repertoire of germline genes commit to the B cell lineage by rearranging 1 among a pool of potential V_H genes. In mice, it is well established that immature B cells preferentially rearrange 3'-proximal V_H genes, whereas the adult mature repertoire is normalized according to V_H family size (13,14). Since a high percentage of mouse neonatal and adult lipopolysaccharide-stimulated hybridomas react with

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