Immunoglobulin heavy chain gene rearrangement involving V-V region recombination

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In the course of analysis of IgH gene rearrangement in primary human leukaemias by using PCR gene amplification (1), we encountered a highly unusual variable-diversity-joining (V-D-J) structure in a case of acute lymphoblastic leukaemia (patient 26-3) in which the V domain appeared to be composed of a hybrid between two distinct V region genes. Nucleotide sequence analysis of PCR-amplified DNA (fig. 1) revealed a 3' VH5 family member, V251 (2), separated from a DXP4-J4 rearrangement (3, 4) by a 110bp stretch of sequence displaying >80% homology to the 3' end of VH3 family members (shown aligned in fig. 1). The VH251 reading frame is interrupted by a stop codon at position 259 (fig. 1). Deletion of 3 codons from the 3' VH251 coding sequence compared to the known germline VH251 sequence (2) implies that the V-V recombination must have occurred somatically. The presence of an apparently normal VH3-DXP4 junction (with accompanying putative 'N' region addition) suggest that an initial V-D rearrangement event involved a proximal germline VH3 gene (eg. see ref. 5) followed by recombination with a more distal (upstream) VH251 gene. Although cryptic heptamer recognition sequences have not been described in germline VH3 genes around codon 59 (position 218 in fig. 1), loss of the heptamer-nonamer recognition sequences from the VH251 gene together with the presence of a short non-homologous region reminiscent of 'N' region addition at the point of VH251-VH3 fusion (fig. 1) suggests that V-V region recombination may have been mediated by recombinase (6), perhaps by a mechanism similar to that involved in V region replacement (5, 7, 8).

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REFERENCES

- Deane, M. and Norton, J.D. (1990) *B. J. Haem.* in press.
- Humphries, C.G. *et al.* (1988) *Nature* **331**, 446-449.
- Ichihara, Y. *et al.* (1988) *EMBO J.* **7**, 4141-4150.
- Ravetch, J.V. *et al.* (1981) *Cell* **27**, 583-591.
- Reth, M. *et al.* (1986) *Nature* **322**, 840-842.
- Lewis, S. and Gellert, M. (1989) *Cell* **59**, 585-588.
- Kleinfield, R. *et al.* (1986) *Nature* **322**, 843-845.
- Yancopoulos, G.D. *et al.* (1986) *EMBO J.* **5**, 3259-3266.
- Berman, J.E. *et al.* (1988) *EMBO J.* **7**, 727-738.
- Matthyssens, G. and Rabbitts, T.H. (1980) *Proc. Natl. Acad. Sci. USA* **77**, 6561-6565.

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1  TACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCACATGCCCGGAAAGGCTGGAGTGGATGG
68  GGATCATCTATCTCTGGTGAATCTGATACACAGATACAGGCCGTCTTCCAAGGCCAGGTACCATCTC
135  AGCCGACAAGTCCATCAGCACCCGCTACCTGCAGTGAGCAGCCTGAAGGCTCGGACACCGCCATG
VH251  TATTACTTTAGGGTACACGCCGCTGTGTGAAGGAGGAGTACCATCTCAAGAGATGATTCAAA
9-1    GAC.ACA.ACT...T.AC.C...
12-2   CACCACA.A.T...G...
VH26   AGCACATACT...GA.AC..C...G...C.G...CA...G
269    AGCATCGCCTATCTGCAATGAACAGCCTGAAACCGAGGACACAGCCGTATTACTGTACTACGA
      .A..CGCTG...
      .A.TCACTG...
      .A..CGCTG...
336    AGAGCGCGAGCTTACGATTTTGGAGTGGTTATATATAGGGCGTAACCTTTGACTA
      DXP4      N'      J4

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Figure 1. Sequence of 26-3 V-D-J gene rearrangement. Position 1 corresponds to codon 27 in VH251 (2). Germline VH3 sequences are shown aligned from codon 59 in 9-1, 12-2 (9) and VH26 (10). An in-frame termination codon in 26-3 at position 259 is underlined.