B-1a, B-1b and B-2 B cells display unique $V_H DJ_H$ repertoires formed at different stages of ontogeny and under different selection pressures

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Analyses of $V_H D J_H$ rearrangements isolated from murine peritoneal B-1a cells (CD5⁺, IgM^{hi}, B220^{lo}), peritoneal B-1b cells (CD5⁻, IgM^{hi}, B220^{lo}), and conventional splenic B cells provide evidence that a unique repertoire of V_H regions is displayed by each of these B-cell subsets. The B-1a subset is characterized by a low N-region diversity, by a high frequency of sequence homologies in the $V_H - D$ and $D - J_H$ junctions, and by a limited exonuclease nibbling of the terminals of the joining gene segments. Through expansion in ageing mice, B-1a clones with these properties are favoured. B-1b cells are similar to conventional B-2 cells with respect to N-region diversity, but are unique in terms of D gene expression. Thus, while most murine pre-B and B cells preferentially use DSP and DFL gene segments in a given reading frame (RF1), B-1b cells frequently express D genes in another reading frame (RF2). Together, these findings provide structural evidence for a model where B-1a, B-1b and B-2 cells are produced by separate progenitors that are active at different stages of ontogeny.

Key words: B cell development/B-1 cells/immunoglobulin genes

Introduction

It has been suggested that the murine B-cell compartment contains several B-cell subsets that differ from each other in surface marker expression, anatomic location and function. B-1a cells, originally defined by the expression of the pan T-cell marker CD5 (Ly-1) (Manohar et al., 1982; Hayakawa et al., 1983; Kantor, 1991), display a characteristic pattern of cell-surface markers (IgM^{hi}, IgD^{lo}, B220^{lo}, Mac1⁺, IL-5R⁺ and Fc ϵ R⁻) which differs from that displayed by conventional B cells (B-2) (IgM^{lo}, IgD^{hi}, B220^{hi}, Mac1⁻, IL-5R⁻ and Fc ϵ R⁺) (Hayakawa et al., 1983; Kehry and Hudak, 1989; Wetzel, 1989; Waldschmidt et al., 1991). Several functional properties have been defined that distinguish these B-cell subpopulations. Thus, while B-2 cells are continuously generated in the adult bone marrow (BM), B-1a cells appear to be produced preferentially, or uniquely, early in the ontogeny (Hayakawa et al., 1985; Kantor et al., 1992) and are capable of self-replenishment in the adult (Hayakawa et al., 1986b; Lalor et al., 1989). Moreover, B-1a cells have been demonstrated to produce most of the natural serum IgM (Hayakawa et al., 1984; Förster and Rajewsky,

1987) and to contain a high frequency of cells specific for various self-antigens (Hayakawa *et al.*, 1984, 1990; Mercolino *et al.*, 1986). A third B-cell subset, B-1b cells, has been identified in mice. These cells display a pattern of cell-surface markers and functional properties similar to the B-1a population but do not express the CD5 marker (Herzenberg *et al.*, 1986; Kantor, 1991). Although the B-1a and B-1b cells represent only a few percent of the total B cells in the adult spleen and are rare in the lymph nodes, Peyer's Patches and peripheral blood, they are abundant in the spleen of newborn mice and in the peritoneal cavity of adults (Hayakawa *et al.*, 1986a; Marcos *et al.*, 1989).

The origin of B-1a, B-1b and B-2 cells has long been a matter of debate. Each of these subsets has been proposed to represent different lineages of B cells, originating from distinct progenitors active at different points of ontogeny (Herzenberg and Kantor, 1993). In support of this, reconstitution experiments have demonstrated that adult bone marrow essentially fails to give rise to the B-1a population, while the B-1b and B-2 populations are fully or partially restored (Hayakawa *et al.*, 1985; Kantor *et al.*, 1992). Furthermore, grafts of day 13 fetal omentum reconstitutes only the B-1a and B-1b populations (Solvason *et al.*, 1991), and day 8.5–9 paraortic splancnopleura appears to restore only the B-1a population (Godin *et al.*, 1993) while fetal liver day 13–14 gives rise to all three B-cell subsets (Kantor *et al.*, 1992).

The finding that CD5 expression can be induced in splenic B-2 cells after treatment with anti-IgM and IL-6 has been taken as support for an alternative model for the origin of B-1a cells (Cong et al., 1991). Thus, it has been hypothesized that Ig-receptor crosslinking in the absence of T-cell help triggers pre-B cells to become CD5⁺ B-1a cells (Haughton et al., 1993). The probability of receptor crosslinkage by a T-independent antigen (e.g. a selfantigen) would be higher for these cells than for cells produced later in life, since B cells generated early in ontogeny preferentially express multireactive and autoreactive antibodies (Holmberg et al., 1984, 1986; Dighiero et al., 1985; Vakil and Kearney, 1986). As a result, B-1a cells would predominate in early ontogeny. This bias would disappear as a result of increasing diversity in the available repertoire generated in the adult bone marrow.

Repertoire differences may be important in determining the origin of the B-1a, B-1b and B-2 subsets. Previous studies suggest that V gene representation in the B-1 cell repertoire is considerably more restricted than in the conventional B-cell repertoire. For example, 5–15 % of the peritoneal B-1 cells react with bromelainized mouse red blood cells (BrMRBC) (Mercolino *et al.*, 1988). This specificity is almost exclusively associated with the expression of either of two combinations of V genes, $V_H 11/V\kappa9$ or $V_H 12/V\kappa4$ (Reininger *et al.*, 1987, 1988; Pennell et al., 1988; Carmack et al., 1990). Another example of restrictions in the V-region repertoire of B-1 cells derives from the sequence analysis of $V_H DJ_H$ rearrangements isolated from splenic B cells (Gu et al., 1990). B-1a cells present in the spleen at four days after birth were found to display a more limited N-region diversity than B-2 cells. At 1 month of age, B-1a cells have N-additions with an intermediate frequency between the neonatal B-1a cells and conventional B-cells from adult spleen. At several months of age the frequency was found to be increased to the level observed in adult splenic B cells. Corresponding studies for the B-1b population have not been carried out. The insertion of random nucleotides, N-sequences, between the recombining V_{H} , D and J_H segments is rare early in ontogeny because of the low activity of the terminal deoxynucleotide transferase (TdT) at this time (Carlsson and Holmberg, 1990; Feeney, 1990; Gu et al., 1990). It has been argued, therefore, that the presence or absence of N-region diversity could be indicative of the ontogenetic stage at which a cell most likely was made.

In this study, we have addressed the questions of origin, ontogenetic timing and selection of the B-1a, B-1b and B-2 subsets by determining the nucleotide sequence of V_HDJ_H rearrangements of genomic DNA isolated from the different B cell subsets at different time points of ontogeny. The use of genomic DNA instead of cDNA enabled us to compare productive and non-productive rearrangements, allowing the distinction between intrinsic genetic events and cellular selection. We find that peritoneal B-1a cells derived from 8-week- and 5-month-old mice express a high frequency of V_HDJ_H joints with properties characteristic of B cells of fetal and neonatal origin and different from adult B-2 cells. These characteristics appear to be selected for in the B-1a subset, since they are more frequently observed in productive rearrangements as compared with non-productive rearrangements, and in V_HDJ_H rearrangements representing clonally expanded B-1a cells. In contrast, we find no evidence for differences between the peritoneal B-1b subset and the conventional splenic B-2 cells with respect to junctional diversity. B-1b cells share with B-1a cells a preference for using J_H1 gene segments not observed in B-2 cells. Finally, we find that $\sim 30\%$ of the productive $V_{\rm H}J558$ rearrangements in the B-1b subset, but not in the B-1a and B-2 subsets, use D gene segments in a reading frame (RF2) rarely used in other B-cell populations. Together, these data provide evidence supporting the hypothesis that B-1a, B-1b and B-2 cells belong to separate lineages and are generated at different points of ontogeny.

Results

Restricted N-diversity in B-1a but not in B-1b cells

In the B-1a subset, N-region additions have been reported to appear later in ontogeny compared with B-2 cells (Gu *et al.*, 1990). We, therefore, first analysed the presence of N-sequence additions in the peritoneal B-1a and B-1b Bcell subsets and in total splenic B cells (Spl B). V_HDJ_H rearrangements from each of these cell populations were amplified by PCR, cloned and sequenced as described in Materials and methods. Primers specific for either the

 V_H7183 , the V_HJ558 or the V_H11 gene families were used together with a mixture of primers for the four J_H gene segments. The structure of the 3' end of most V_H germline gene segments is not known. Therefore, only N-additions in the junction between D and $J_{\rm H}$ gene segments were considered in this analysis. The nucleotide sequences of the $V_H DJ_H$ junctions isolated are shown in Figure 1 and are summarized in Table I. Productive rearrangements isolated from peritoneal B-1a cells of 8-week-old mice displayed significantly fewer N-sequence additions than the total splenic B cells originating from the same animals. This was observed for $V_H DJ_H$ junctions utilizing either V_H7183 genes (12% in B-1a cells versus 71% in Spl B cells) or V_HJ558 genes (39% in B-1a cells versus 75% in Spl B cells). The observed frequency of N-region diversity in the peritoneal B-1a population was slightly higher than the frequency previously reported for the neonatal splenic B cells (Carlsson *et al.*, 1992a,b). In the case of $V_H DJ_H$ rearrangements utilizing the V_H11 gene segment, a very low frequency of N-additions was observed in the B-1a population, confirming previous results. However, we were not able to isolate any rearrangements utilizing this gene segment from the adult spleen.

Productive rearrangements may be subject to Igmediated selection and, thus, the limited N-region diversity in the B-1a population could reflect that different selection pressures exist for this subset compared with other B-cell subsets. In support of this notion, a significantly lower frequency of N-sequence additions was observed in productive versus non-productive V_H7183 rearrangements from the peritoneal B-1a subset (Table I). In spite of this evidence supporting that selection contributes to the limited N-region diversity in B-1a cells, the frequency of N-sequence additions in the non-productive rearrangements was consistently lower in the rearrangements of the peritoneal B-1a cells compared with Spl B cells. Thus, among non-productive V_H7183 rearrangements isolated, 33% of the B-1a cells and 75% of the splenic B cells contained N-additions. In contrast, V_HJ558 rearrangements lacking N-region additions were not found to be selected for. However, similar to the V_H7183 rearrangements, the frequency of N-region additions was significantly lower in V_HJ558 rearrangements isolated from peritoneal B-1a cells compared with those isolated from Spl B cells.

In contrast to B-1a cells, B-1b cells isolated from the peritoneal cavity of 8-week-old mice displayed Nsequence additions close to the frequencies observed in the splenic B cells at this age (Table I). An exception from this was observed for rearrangements utilizing the V_H11 gene for which the frequency of N-sequence additions is similar to that observed in the B-1a population. We cannot exclude, however, that this result is due to the preferential amplification of DNA from contaminating CD5⁺ cells because of a relative lack of V_H11 expression in this cell population.

J_H and D reading frame usage distinguish B-1a, B-1b and B-2 subsets

The analysis of the junctional sequences from the various cell populations revealed a subset-specific distribution of J_H gene segments. Thus, the J_H1 gene segment was found to be preferentially used by V_HJ558 and V_H11 rearrangements of peritoneal B-1a (Figure 1A) and B-1b

λ B-la 7183 Name & Gene _VH____ Y/N2 P ____ P ___ D ___ P ___ P ___ D BF

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| ja7 1 ja10 1 ja14 1 ja15 1 ja21 1 ja31 1 ja31 1 ja31 1 ja31 1 ja32 1 ja31 1 ja24 1 ja23 3 ja25 1 ja33 1 ja33 1 | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 185.1 165.1 | АG АGA АGA АGA АGA АGA АGA АGA АGA АGA А | AGGGA GAGGA AGGGGGGA GGCC TT AAGG GTTCT TTGG TTCAGAG AGGG | 66 | TGAGCT | TTACTACGGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TTACTACGACAC TTACTACGGTACTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC CCTACGTTACTAC GATGGTTACTAC CCTACGTTACTAC CACTACGTTACTAC CACTACGTTACTAC CACTACGTTACTAC CACTACGTTACTAC CACTACGTTACTAC CACTACGTTACTAC CACTACGTACTAC | GT | G AGGGG C G G G G G | | TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAC 7 TAC TAT GCT / TAC 7 C TAT GCT / C TAC TGG TAC 7 C TAC TGG TAC 7 C TAT GCT / C TAC TGG TAC 7 C TAC TGG TAC 7 C TAC TGG TAC 7 AC TGG TAC 7 | ATG GAC ATG GAC GAC GAC TTT GCT ATG GAC TTC GAT ATG GAC TTC GAT TTC GAT TTC GAT TTC GAT TTC GAT TTC GAT TTC GAT TTC GAC TTC GAC TTC GAT TTC GAC | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 1 | S Q Q 3 1 2 2 5 5 7 1 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 | |
| ja7 1 ja10 1 ja14 1 ja16 1 ja21 1 ja21 1 ja21 1 ja21 1 ja21 1 ja24 1 ja23 3 ja23 3 ja23 3 ja23 3 ja23 3 ja23 1 ja24 1 ja33 1 ja33 1 ja45 1 ja46 1 | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.3 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 185.1 165.1 | хд лда лда лда лда лда лда лда лд | AGGGA GAGGA GGCGGGA GGCC TT AAGG GTTCT TTGG TTGG | 86 | TGAGCT CC | TTACTNGGT CCTRCTA GGG AACTGG TANCTAC AGGTA TCG TTACTACGAC TTACTACGACACT TTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG GATGGTTACTACGGTAGTAG GATGGTTACTACGGTA CTACGGTA TACTACGGTA TTATTACTACGGTAGTAG TTATTACTACGGTAGTAG ACTGGGGA TACTACGGTA | GT | G AGGGG C G G C C C C C C C C C C C C C | | TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAC 7 CTAT GCT / TAC 7 C TAC TGG TAC 7 | ATE GAC GAC GAC ITT GCT ITT GCT GAC GAC ITT GAC ITT GAC ITT GAC ITT GAT ITC GAT I | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 1 2 1 1 | S 2 2 3 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 | |
| ja7 1 ja10 1 ja14 1 ja15 1 ja21 2 ja21 1 ja31 1 ja31 1 ja31 1 ja31 1 ja31 1 ja31 1 ja32 1 ja34 1 ja29 1 ja24 1 ja24 2 ja5 2 ja5 2 ja5 2 ja5 2 ja5 2 ja5 3 ja25 1 ja33 1 ja34 5 ja25 1 ja45 1 ja46 1 ja34 1 ja34 1 ja34 1 ja32 1 ja35 1 ja33 1 ja34 1 ja35 1 ja36 1 ja35 1 ja36 1 ja35 1 ja36 1 ja37 1 ja | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.1 185.1 165.2 165.1 165.1 165.2 2.28 | хд лда лда лда лда лда лда лда лд | AGGGA GAGGA GGCGGGA GGCC TT AAGG GTTCT TTGG TTGG | 86 | | TTACTACGGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TATCATACCAC TTACTACGACACT TTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG ATTACTACGGTAGTAG ACTACGTAGTACTAC GATGGTTACTAC GATGGTTACTAC CTACTACGGTAGTAG ACTACGTAGTACTAC TTATTACTACGGTAGTAG AACTGGGAC TTATTACTACGGTAGTAG ACTACGTACTAC | GT G G | G AGGGG C G G C C C C C C C C C C C C C | λG | TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAC 7 C TAT GCT / TAC 7 C TAT GCT / C TAC TGG TAC 7 C TAC TGG TAC 7 | ATE GAC ATE GAC GAC GAC IFIT GCT ATE GAT ATE GAT ATE GAT ITC GAT I | 4 4 2 3 4 2 1 4 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | S 2 2 3 3 3 2 3 3 4 4 4 4 4 4 4 4 4 4 4 4 | |
| ja7 1 ja10 1 ja14 1 ja15 1 ja21 2 ja21 1 ja31 1 ja31 1 ja31 1 ja31 1 ja31 1 ja31 1 ja32 1 ja29 1 ja29 1 ja24 1 ja25 1 ja35 2 ja5 2 ja5 2 ja5 2 ja5 2 ja5 3 ja25 1 ja33 1 ja34 1 ja34 1 ja34 1 ja33 1 ja31 1 ja31 1 ja34 1 ja33 1 ja33 1 ja2 1 ja3 1 ja33 1 ja33 1 ja33 1 ja33 1 ja3 2 ja3 1 ja3 | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.1 185.1 165.1 | AG AGA AGA AGA AGA AGA AGA AGA AGA AGA | AGGGA GAGGA GGCGGGA GGCC TT AAGG GTTCT TTGG TTGG | 96 | | TTACTNGGT CCTRCTA GGG AACTGG TANCTAC AGGTA TCG TTACTACGAC TTACTACGACACT TTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG GATGGTTACTACGGTAGTAG GATGGTTACTACGGTAGTAG CACTACGGTACTAC CGGG A TACTACGGTA TTATTACTACGGTAGTAG AACTGGGAC | GT G G | G AGGGG C G G C C C C C C C C C C C C C | λG | TAT GCT / CC TGG ? AT TAC TAT GCT / GG TAC ? C TAT GCT / TAC ? AT GCT / C TAT GCT / C TAC TGG TAC ? C TAC S | ATTE GAC ATTE GAC GAC GAC GAC GAC TITT GCT ATTE GAT ATTE GAT TITT GAC TITC GAT TITC GAT TITT GAC | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 1 2 1 1 | S 2 2 3 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 | |
| ja7 1 ja14 1 ja16 1 ja17 2 ja21 1 ja31 1 ja31 1 ja31 1 ja31 1 ja44 1 ja24 1 ja24 1 ja25 1 ja24 1 ja25 1 ja46 1 ja46 1 ja46 1 ja45 1 ja45 1 ja28 1 ja28 1 ja28 1 ja28 1 | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.1 185.1 165.1 | AG AGA AGA AGA AGA AGA AGA AGA AGA AGA | AGGGA GAGGA GGAGATATGG GGCC TT AAGG GTCT TTGG GTCT TTGG AGG A TC | 96 | | TTACTACGGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TRACTAC CC TRACTACGA TTACTACGAGTAGT C TTACTACGGTAGTAG C TTACTACGGTAGTAG CTACGTAGTAG ATTACTACGGTAGTAG CTATAGTAA ACTACGGTAGTAG GATGGTTACTAC GATGGTACTACGGTAGTAG ACTACGGTAGTAG ACTACGGTAGTAG ACTACGGTAGTAG ACTACGGTAGTAG ACTACGGTAGTAGCTAC TACTACGGTAGTAGCTAC TACTACGGTAGTAGCTAC TACTACGGTAGTAGCTAC TACTACGTAGTAGCTAC CACTACGTAGTAGCTAC CACTACGTAGTAGCTAC | GT G G | G AGGGG C G G G C C C G G C C C C C G C | λG | TAT GCT / CC TGG C AT TAC TAT GCT / GC TAC GC / TAC TAT GCT / TAC TAT GCT / C TAC TGG TAC C C TAC TGG TAC C | ATTE GAC ATTE GAC GAC GAC GAC GAC TITT GCT ATTE GAT ATTE GAT TITT GAC TITC GAT TITC GAT TITT GAC | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 1 2 1 1 2 1 2 | S 2 2 3 3 2 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 | |
| ja7 1 ja10 1 ja14 1 ja15 1 ja21 1 ja21 1 ja21 1 ja21 1 ja22 1 ja22 1 ja24 1 ja24 1 ja24 1 ja24 1 ja24 1 ja24 1 ja25 2 ja5 2 ja5 2 ja23 3 ja25 1 ja33 1 ja46 1 ja21 1 ja3 1 ja28 1 ja2 3 ja2 3 ja2 3 ja2 3 ja2 1 ja3 1 ja3 1 ja3 1 ja3 1 ja3 1 ja3 1 | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 185.1 165.1 </td <td>AG AGA AGA AGA AGA AGA AGA AGA AGA AGA</td> <td>AGGGA GGAGATATGG AGGGGA GGCC TT TTGG GTTCT TTGG GTTCT TTGG AGGG A TC TC</td> <td>16</td> <td></td> <td>TTACTACGGT CCTRCTA GGG AACTGG TAACTAC AGGTA TCG TTACTACGAC TTACTACGAC TTACTACGACAC TTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG ATTACTACGGTAGTAG GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC TTATATACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAGCTAC</td> <td>GT G G</td> <td>G AGGGG C G G C C C C C C</td> <td>λG</td> <td>TAT GCT / CC TGG ? AT TAC TAT GCT / GG TAC ? C TAT GCT / TAC ? AT GCT / C TAT GCT / C TAC TGG TAC ? C TAC S</td> <td>ATTE GAC ATTE GAC GAC GAC GAC GAC TITT GCT ATTE GAT ATTE GAT TITT GAC TITC GAT TITC GAT TITT GAC</td> <td>4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 2 1 1 2 2</td> <td>S Q Q S S F S F S F S F S F S F S F S F</td> <td></td> | AG AGA AGA AGA AGA AGA AGA AGA AGA AGA | AGGGA GGAGATATGG AGGGGA GGCC TT TTGG GTTCT TTGG GTTCT TTGG AGGG A TC TC | 16 | | TTACTACGGT CCTRCTA GGG AACTGG TAACTAC AGGTA TCG TTACTACGAC TTACTACGAC TTACTACGACAC TTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG ATTACTACGGTAGTAG GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC GATGGTTACTAC TTATATACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAGCTAC | GT G G | G AGGGG C G G C C C C C C | λG | TAT GCT / CC TGG ? AT TAC TAT GCT / GG TAC ? C TAT GCT / TAC ? AT GCT / C TAT GCT / C TAC TGG TAC ? C TAC S | ATTE GAC ATTE GAC GAC GAC GAC GAC TITT GCT ATTE GAT ATTE GAT TITT GAC TITC GAT TITC GAT TITT GAC | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 2 1 1 2 2 | S Q Q S S F S F S F S F S F S F S F S F | |
| ja7 1 ja10 1 ja14 1 ja15 1 ja21 2 ja21 1 ja31 1 ja31 1 ja31 1 ja31 1 ja31 1 ja31 1 ja32 1 ja29 1 ja29 1 ja24 1 ja25 1 ja35 2 ja5 2 ja5 2 ja5 2 ja5 2 ja5 3 ja25 1 ja33 1 ja34 1 ja34 1 ja34 1 ja33 1 ja31 1 ja31 1 ja34 1 ja33 1 ja33 1 ja2 1 ja3 1 ja33 1 ja33 1 ja33 1 ja33 1 ja3 2 ja3 1 ja3 | 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 185.1 165.1 170.2 2.28 WPARG MVARG | AG AGA AGA < | AGGGA GGAGATATGG AGGGGA GGCC TT TTGG GTTCT TTGG GTTCT TTGG AGGG A TC TC | 66 | | TTACTNCGT CCTACTA GGG AACTGG TANCTAC AGGTA TCG TANCTACCAC TTACTACGAC TTACTACGAC TTACTACGAC TTACTACGGAC TTACTACGGTAGTAG CTACGACGTAGTAG CTACGACGTAGTAG ACTNCGTAGTAG ACTNCGGTAGTAG CTACGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG ACTNCGGTAGTAG TTATTACTACGGTAGTAG TTATTACTACGGTAGTAG TTACT | GT G G | G AGGGG C G G C C C C C C | λG | TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAT GCT / GG TAT GCT / TAC C AT GCT / C TAT GCT / C TAC TGG TAC 7 C TAC 7 C TAC TGG TAC 7 C TAC 7 | ATG GAC ATG GAC ATG GAC ATT GCT ATG GAC ATT GCT ATG GAC ATG GAC ATT GAC | 4 4 2 3 4 2 1 4 1 1 1 1 4 1 1 1 2 1 4 1 2 1 4 1 2 2 4 | S Q Q S 1 2 2 3 1 1 2 3 1 2 3 1 2 3 1 1 2 3 1 1 2 3 1 1 2 3 1 1 2 3 1 1 | |
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| ja10 1 ja14 1 ja16 1 ja17 2 ja21 1 ja31 12 ja21 1 ja31 12 ja21 1 ja31 1 ja44 1 ja45 2 ja5 2 ja6 2 ja5 2 ja6 2 ja5 2 ja5 2 ja5 2 ja5 1 ja33 1 ja33 1 ja30 1 ja20 1 ja20 1 ja20 1 ja20 1 ja20 | 186.2 185.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.1 165.2 WVARG WVARG Scitta 186.2 186.2 165.1 165.1 186.2 186.1 165.1 | AG AGA | AGGGA GGAGATATGG GGCCC TT AAGG GGTCT TTOG GTTCT TTOGGAG AGGG A TC TC GA | 16 | | TTACTNACGT CCTRACTA GGG AACTGG TXACTAC AGGTA TCG TTACTACGAC TTACTACGACACT TTACTACGGTAGTAG CCTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG CATACGTACTAC CATACGTAGTAC CATACGTACTAC CATACGGTAGTAG CATACGTACTACACACACACACACACACACACACACACAC | GT G | G AGGGG C G G C C C C C C | λG | TAT GCT / CC TGG / AT TAC TAT GCT / GG TAC ' CTAT GCT / TAC ' C TAC TGG TAC ' | ATTE GAC ATTE GAC GAC IFTT GCT MATG GAC TATT GCT MATG GAC TATTE GAT ATTE GAT TATE GAC TATE GAC TATE GAC TATE GAC TATE GAC | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 4 2 1 1 1 2 1 1 2 2 4 1 2 1 | S Q Q S 1 2 2 1 2 2 2 3 1 2 2 3 1 2 2 3 1 2 2 3 1 2 2 3 1 2 2 3 1 | 8 4 4 8 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 |
| ja7 1 ja10 1 ja14 1 ja15 1 ja24 1 ja21 1 ja31 1 ja2 1 ja2 1 ja2 1 ja2 4 ja2 4 ja2 4 ja2 4 ja2 4 ja2 4 ja2 4 ja2 4 ja3 1 ja3 1 | 166.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.2 185.1 185.1 185.1 185.1 185.1 185.1 185.1 185.2 185.1 185.2 185.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 </td <td>AG AGA AGA</td> <td>AGGGA GGAGATATGG GGCCC TT AAGG GGTCT TTOG GTTCT TTOGGAG AGGG A TC TC GA</td> <td>16</td> <td>cc</td> <td>TTACTNACGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TATGATTACGAC TTACTACGAC TTACTACGATAG ATTACTACGGTAGTAG CCTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTACTAC ACTNCCGTACTAG CATCACGTACTAC CTACTACGGTACTAC ACTNCCGTACTAC CTACTACGGTACTAC ACTNCCGTACTAC ACTACGGTACTAC TTATTACTACGGTAGTAG TTATTACTACGGTAGTAG TTACTACGGC CTACGG ACTGGGAC</td> <td>GT G</td> <td>G AGGGG C G G C C C C C C</td> <td>λG</td> <td>TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAC 7 C TAT GCT / TAC 7 C TAT GCT / C TAC TGG TAC 7 C TAC 7</td> <td>ATTE GAC ATTE GAC GAC IFTT GCT MATG GAC TATT GCT MATG GAC TATTE GAT ATTE GAT TATE GAC TATE GAC TATE GAC TATE GAC TATE GAC</td> <td>4 4 2 3 4 2 1 4 1 4 2 1 1 1 4 2 1 1 1 2 1 1 2 2 4 1 2 2 4</td> <td>S Q Q S S F S F S F S F S F S F S F S F</td> <td>8</td> | AG AGA | AGGGA GGAGATATGG GGCCC TT AAGG GGTCT TTOG GTTCT TTOGGAG AGGG A TC TC GA | 16 | cc | TTACTNACGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TATGATTACGAC TTACTACGAC TTACTACGATAG ATTACTACGGTAGTAG CCTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTACTAC ACTNCCGTACTAG CATCACGTACTAC CTACTACGGTACTAC ACTNCCGTACTAC CTACTACGGTACTAC ACTNCCGTACTAC ACTACGGTACTAC TTATTACTACGGTAGTAG TTATTACTACGGTAGTAG TTACTACGGC CTACGG ACTGGGAC | GT G | G AGGGG C G G C C C C C C | λG | TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAC 7 C TAT GCT / TAC 7 C TAT GCT / C TAC TGG TAC 7 C TAC 7 | ATTE GAC ATTE GAC GAC IFTT GCT MATG GAC TATT GCT MATG GAC TATTE GAT ATTE GAT TATE GAC TATE GAC TATE GAC TATE GAC TATE GAC | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 4 2 1 1 1 2 1 1 2 2 4 1 2 2 4 | S Q Q S S F S F S F S F S F S F S F S F | 8 |
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| $\begin{bmatrix} a_1 & 1 \\ ja_1 & 0 & 1 \\ ja_1 & 1 & 1 \\ ja_1 & 1 & ja_1 & 1 \\ ja_1 & ja_2 & 1 \\ ja_2 & 1 & ja_2 & 1 \\ ja_1 & 2 & ja_2 & 2 \\ ja_1 & 5 & 1 \\ ja_1 & 2 & ja_2 & 1 \\ ja_2 & 1 & ja_2 & 1 \\ ja_1 & 1 & ja_1 & 1 \\ \end{bmatrix}$ | 166.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 186.2 185.1 196.2 201.4 196.2 21.4 185.1 185.1 185.1 185.1 185.1 185.1 185.1 <td>λG λGA λGA</td> <td>AGGGA GAGGA GGAGATATGG GGCCC TT AAGG GTTCT TTOG AGG TCAGAG AGG TC GA TC TC GA</td> <td>86</td> <td>cc</td> <td>TTACTACGGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TTACTACCAC TTACTACGACACT TTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG TTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ACTACGGTAGTAC CTACTACGGTAGTAG ACTACGGTACTAC GGC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC</td> <td>GT G</td> <td>G AGGGG C G G CAC ATC GGTCTGG CCT</td> <td>AG G</td> <td>TAT GCT / CC TGG / AT TAC TAT GCT / GG TAC / C TAT GCT / TAC GC / AT GCT / C TAT GCT / C TAC TGG TAC // C TAC //</td> <td>AND GAC AND GA</td> <td>4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 1 2 1 1 1 2 2 4 1 2 1 1 3 3</td> <td>S Q Q S S F S F S F ? F F S F S F S F F Q F F S F S F S Q Q F S S Q 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</td> <td>8</td> | λG λGA | AGGGA GAGGA GGAGATATGG GGCCC TT AAGG GTTCT TTOG AGG TCAGAG AGG TC GA TC TC GA | 86 | cc | TTACTACGGT CCTACTA GGG AACTGG TAACTAC AGGTA TCG TTACTACCAC TTACTACGACACT TTACTACGGTAGTAG CTACTACGGTAGTAG CTACTACGGTAGTAG TTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG ACTACGGTAGTAC CTACTACGGTAGTAG ACTACGGTACTAC GGC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC ACTGGGAC | GT G | G AGGGG C G G CAC ATC GGTCTGG CCT | AG G | TAT GCT / CC TGG / AT TAC TAT GCT / GG TAC / C TAT GCT / TAC GC / AT GCT / C TAT GCT / C TAC TGG TAC // C TAC // | AND GAC AND GA | 4 4 2 3 4 2 1 4 1 4 2 1 1 1 1 1 1 1 2 1 1 1 2 2 4 1 2 1 1 3 3 | S Q Q S S F S F S F ? F F S F S F S F F Q F F S F S F S Q Q F S S Q 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | 8 |
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| $\begin{bmatrix} a_1 & 1 \\ ja_1 & 0 & 1 \\ ja_1 & 1 & 1 \\ ja_1 & 1 & ja_1 & 1 \\ ja_1 & ja_2 & 1 \\ ja_2 & 1 & ja_2 & 1 \\ ja_1 & 2 & ja_2 & 2 \\ ja_1 & 5 & 1 \\ ja_1 & 2 & ja_2 & 1 \\ ja_2 & 1 & ja_2 & 1 \\ ja_1 & 1 & ja_1 & 1 \\ \end{bmatrix}$ | 166.2 165.10 | λG λGA | AGGGA GAGGA GGAGATATGG GGCCC TT AAGG GTTCT TTOG AGG TCAGAG AGG TC GA TC TC GA | | CC | TTACTNCGGT CCTRCTA GGG ANCTGG TANCTAC AGGTA TCG TTACTACGACC TTACTACGACACA TTACTACGGTAGTAG CCTACGTAGTAG ATTACTACGGTAGTAG ATTACTACGGTAGTAG GATGGTACTAC GATGGTACTAC GATGGTACTAC CTACGGTAGTAG ACTACGGTAGTAG ACTACGGTAGTAGC TTATTACTACGGTAGTAGCTAC TACTAGGAC ATTACTACGGACACACACACACACACACACACACACACAC | GT G G | G AGGGG C G G CAC ATC G G CAC C C C C C C C C C | AG G | TAT GCT / CC TGG 7 AT TAC TAT GCT / GG TAC 7 C TAT GCT / TAC TG TAC 7 C TAC TGG TAC 7 C TAC | AND GAC AND GA | 4 4 2 3 4 2 1 4 1 1 1 1 1 1 1 1 1 1 2 1 1 1 2 2 4 1 2 1 1 3 3 4 | S Q Q S S F S F S F S F S F S F S F S F | |
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| Function b36 1 | | AGA | | GGA | AGTAACTAC | G | GGAG | | T ATG GAC 4 | S 1 |
| b24 1 | 1 3Ъ | AGA | CGGG | | GGGA | | GGGGGGGGTCT | , | TAT GCT ATG GAC 4 | Q 3 |
| b49 1 b63 1 | | AGA AGA | CAAGGG | | GGGAC CA | | CG | | GG TTT GCT 3 T GAC 2 | Q 1 ? ? |
| b21 1 | | AG | maama | GT | TCTACTATGATTACG | - | | | AC TGG TAC TTC GAT 1 | S 1 |
| b27 1 b52 1 | 15b 15b | AGA AG | TCCTC | TCCC | TTATTACTACGGTAGTAG A TCTACTATGATTACGAC | G | C GGA | | TT GAC 2 AC TAT GCT ATG GAC 4 | F 1 S 1 |
| b71 1 | 1 5b | AG | | т | CAACTGGGAC | | т | | C TAC TGG TAC TTC GAT 1 | Q 2 |
| b9 1 b43 1 | | AGA AGA | CAGG | | gggc C aactggga c | | AGG | | C TTT GAC 2 GG TTT GCT 3 | F 2 Q 2 |
| | 1 13 | AGA | GCG | | TCT | | с | | AC TAT GCT ATG GAC 4 | S 2 |
| b6 1 b17 1 | 1 21b 1 21b | AGA AGA | GATCAGG ATAATA | | ATGATTACG GTAGTAGCTAC | G | GGGG | | AC TGG TAC TTC GAT 1 C TGG TAC TTC GAT 1 | S 1 F 1 |
| b58 1 | | AGA | | | CTGGGA | 9 | GG | | | S 2 |
| b19 3 b64 1 | | AG | G | | TAGTAGCTA | | | | C TAC TGG TAC TTC GAT 1 | F 1 |
| Det | 1 230 | AGA | G | | ATTACTACGGTAG | | | | I GAC 2 | F 1 |
| | nctional | | | | | | | | | |
| b2 1 b4 1 | 1 1 | AG AG <u>A C</u> | | CCCG | TTATTACTACGGTAGTAG GGCT | 0 | λ | | GG TTT GCT 3 AT TAC TAT GCT ATG GAC 4 | F 1 F 1 |
| Ъ8 1 | | AGA | | ccccc | GATTACGAC | G | GGT | | CC TGG TTT GCT 3 | s 1 |
| b10 1 | | AG <u>A C</u> | | | TATAGTAACT | | | | AT TAC TAT GCT ATG GAC 4 | S 1 |
| b13 3 b18 1 | | AGA CA AG | TG | | TGATTACGAC CTATGGTTACGAC | | CCC | | GG TAC TTC GAT 1 AT TAC TAT GCT ATG GAC 4 | S 3 S 3 |
| b23 | | AGA | | | TTACGAC | G | GG | | GAC 2 | S 1 |
| b26 1 b31 1 | | AGA C AGA <u>C</u> | | | TTATTACTACGGTAGTAG TATGATTACGAC | G | | | C TAT GCT ATG GAC 4 C TGG TTT GCT 3 | F 1 S 3 |
| b33 1 | | AGA CA | | AG | TGATGGTTACT | v | с | | C TGG TAC TTC GAT 1 | S 1 |
| b34 1 | | AGA | | | TTACTACGGTAGTAG | _ | | | C TTT GAC 2 | F 1 |
| b39 1 b40 1 | | AGA CA AGA CA | | AGG AGGG | TACTACGGTAGTAGCTAC ACTATAGG | G | X | | GAC 2 GAC 2 | F 3 S 1 |
| b41 1 | | AGA C | | TGGG | ACTATGATTACGAC | | с | | C TAC TGG TAC TTC GAT 1 | S 3 |
| b42 1 b67 1 | | AGA CA AG | т | AGG G | ACTA AACTGGG | | GC | | C TTT GAC 2 C TAT GCT ATG GAC 4 | S,F 3 Q 2 |
| b15 1 | 1 3Ъ | AGA | CATTAGAGNA | • | TACTATA | | cccc | | G TTT GCT 3 | Ŝ 1 |
| b5 1 b51 1 | | AGA AGA | CA C | | TATGGTAACTAC TGATTACGAC | GTA G | • | AGI | I AC TAC TTT GAC 2 GG TAC TTC GAT 1 | 83 81 |
| b65 1 | 1 5b | AGA | CCCTA | | TCTATGATGGTTACTAC | G | AGGG | | T GAC 2 | S 1 |
| b53 1 b55 1 | 17Ъ 17Ъ | AGA AGA | CATGCG CATG | | GATGGTTACT ACTATGGTTACGAC | G | CCT G | | C TTT GAC 2 GG TTT GCT 3 | S 3 S 2 |
| b62 1 | | AG | CAIG | TCCTC | TTATTACTACGG | 6 | CA. | | GG TTT GCT 3 C TAC TGG TAC TTC GAT 1 | 5 2 F 3 |
| b30 1 | | A | ~~~~~~ | CCGGGCCA | GACAGCTCGGGCTA | | G | | GG TTT GCT 3 | F 3 |
| b50 1 b61 1 | | AGA A | CATGTGGGG | | TATAGGT ATGGTAAC | | CGAAG CCT | | AC TTT GAC 2 C TTT GAC 2 | S 3 S 2 |
| b3 5 | | AGA | GGACCCCT | | татдат а стаастас | | AGGGG | | TAC TTT GAC 2 | S 3 |
| b11 2 b29 1 | | AGA AGA | GGT GT | | TATGATTA TATGATT | | GAGG GGGC | | AC TTT GAC 2 TTT GCT 3 | S 3 S 3 |
| b68 1 | | | | G | CTATGATTACGAC | G | A | | GAT 1 | 63 |
| | | | | | | | | | | |
| <u>J558</u> | | | | | | | | | | |
| Namo | Gene | VH | V/N?P | N P | q | n | N | | | |
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| Functio | | | | | | | | | | |
| jb5 2 jb9 1 | 2 186.2 1 186.2 | AGA | AATTGGGGG | с | ATTACTACGGTAGTAGC TTTATTACTACGGTAGTAG | | GGCTTCGTTTG GG | | AC TAT GCT ATG GAC 4 F TAC TTT GAC 2 F | |
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| 7183 | | | | | | | | | | | | | | | | | |
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| \$19 | 1 | 7b | AGA | CA | | | | TCTACTATGGTTACGA | | GAGGG | | | T ATG | | - | s | 3 |
| \$8 | 1 | 11b | AGA | CANACAAC | ic . | | | GATGGTT | | CCA | | TA | GCT ATG | GAC | 4 | s | 1 |
| 83 89 | 1 | 21b 21b | AGA Aga | AGGG | | | | GAC | | CCACTTC | т | | C TTT | | 2 | s | 1 |
| sj s18 | i | 22b | AGA | AGGG | | GAGGG | | ATTACTACGGTAGTAGCTA ATAGTAACTAC | | TGGA | | | GCT ATG | | 4 | F | 1 |
| 824 | i | 23b | AGA | GTGGG | | GAGGG | | TTACTACGGTAGTAG | GT | NG | | C TAC TGG | TAC TTT TAC TTC | | 2 1 | 8 F | 1 1 |
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| s 2 | 1 | 1 | | | | CCTG | | CGA | | G | | | | | 2 | s | 1 |
| s10 | | 1 | | | | GCT | | AACTG | | ÂG | | | | GCT | 3 | ŏ | î |
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| 814 | | 1 | AGA C | | | | | CGGC | | AACCCT | | C TAT | GCT ATG | GAC | 4 | F | 2 |
| s15 s16 | | 1 | AGA C | • | | AGGG | | CTACGGTAGTAGCT | | | | | | | 2 | F | 3 |
| \$21 | 1 | 1 | AGA CA | | | с | | ATGGT TCA | | cccc | GT | AC | TAC TTT | | 2 | S | 3 |
| \$22 | 1 | i | AGA | •• | | AGT | | GTATGGTAACT | | _ | | | TAC TTC | | 1 | F | 3 |
| 86 | 1 | 5b | λG | | | GCGCC | | ACTACGGTAGTAGCTAC | G | т | | C TAC TGG | | | 1 | s | 1 |
| \$11 | i | | AGA | CCCA | | GLULL | | ATTACTACGGTAGT | G | с | | | | GAC | 2 | F | 2 |
| 813 | 1 | 7b | AGA | GG | | | | CCTACTATAGTAACTA | | GTAG | | | | č | 2 | s | 3 |
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| <u> J558</u> | | | | | | | | | | | | | | | | | |
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| 186 | 1 | | AGA | с | | | | ATTACTACGGTAGTAGCT | | | | 20 | m | ~~~ | 2 | P | 1 |
| js7 | ī | 186.2 | | NC | | | | CGGTAGTAGCT | | cc | т | AT TAC TAT | TAC TTT | | 4 | F | 1 |
| js8 | 1 | 186.2 | | TGGG | | | | ATGATTACGAC | | CCCGNN | 1 | AT THE TAT | TTC | | 1 | - | 1 |
| js9 | 1 | 186.2 | | | TGGG | GGATCAA | | ATTACTACGGT TCTATGA | | GG | | | | | 4 F | | 1/2 |
| js20 | 1 | 186.2 | | TGG | | | | GATTAC | | с | | | TT | GCT | 3 | ้ธ | 1 |
| js24 | 1 | 186.2 | | | GAGG | G | | TTACTACGGTAGTAGC | | cc | | с | TAC TTT | GAC | 2 | F | 1 |
| js1 | 1 | C1H4 | AGA | GGGAAGA | | | | ACTATGGTAAC | | A | | | | СТ | 3 | ទ | 1 |
| js13 js18 | 1 | C1H4 C1H4 | AGA AGA | GAAC TCGG | | | | ATAGTAACTAC | | AGAATGG | | | GCT ATG | | 4 | ទ | 1 |
| 1821 | 1 | C1H4 | AGA | λ λ | | | | ACTACGGTAGTAGCTAC GGAC | GT | TCT | GG | | TGG TTT | | 3 | F | 1 |
| js23 | î | C1H4 | AGA | ÂG | | | | TTATTACT | | CINA | | G | TAC TTC AC TTT | | 1 | Q | 1 |
| js17 | ī | 671.5 | | GGGA | | | | TCTAC | | AATCCC | | | AC TIT | | 2 | r S | 1 |
| js19 | 1 | 671.5 | | | | | | | | | | | TAC TTC | | 1 | • | • |
| js12 | 1 | 24.8 | AGA | A A | | | | GACAGCTC | | AGGNCCTC | | TAC TAT | GCT ATG | | 4 | F | 2 |
| js14 | 1 | CH10 | A | | TAT | | | TCTACTATGGTAACTAC | | TCT | | | TAC TTC | | 1 | | 1 |
| js16 | 1 | CH10 | | | | | | GGT | | | | C TGG | TAC TTC | GAT | 1 | F | 2 |
| Non- | func | tional | | | | | | | | | | | | | | | |
| js2 | | 186.2 | AG | | GAGA | | | TACTACGGTAGTAGC | | ccc | | | | | 4 | F | 2 |
| | | | | | | | | | | | | | | | - | • | - |

Fig. 1. CDR3 regions of V_H7183 , V_HJ558 and V_H11 clones derived from PCR libraries of the peritoneal B-1a population (**A**), of the peritoneal B-1b population (**B**) and of conventional splenic B cells (**C**) from 8-week-old mice. Members of the V_H7183 family have been denominated according to Carlsson *et al.* (1992a) and the V_HJ558 family according to Gu *et al.* (1991). When the sequence of the corresponding unrearranged gene is unknown, the nucleotides between codon 94 in the V_H and the D gene segments are assigned V/N?. Nucleotides representing inverted repeats of undigested termini are grouped as P nucleotides according to Lafaille *et al.* (1989). Underlined sequences could be encoded by either the V_H or the D gene segments (end of V_H underlined) or by either the J_H and the D gene segments (end of J_H underlined). D gene segments of the three defined families are denoted F = DFL, S = DSP, and Q = DQ52.

| Origin | VH7183 | | VHJ558 | | VH11 | |
|-----------------|-------------|----------------|-------------|----------------|------------|---------------|
| | Functional | Non-functional | Functional | Non-functional | Functional | Non-functiona |
| B-1a, 8 weeks | 2/17 (12%) | 10/30 (33%) | 11/28 (39%) | 1/7 (14%) | 2/10 (20%) | 1/2 (50%) |
| B1-a, 5 months | 1/2 (50%) | 1/7 (14%) | 2/7 (29%) | 2/3 (67%) | 0/3 (0%) | 1/3 (33%) |
| B-1b, 8 weeks | 10/16 (63%) | 20/30 (67%) | 24/31 (77%) | 9/10 (90%) | 0/6 (0%) | 1/2 (50%) |
| Spleen, 8 weeks | 5.7 (71%) | 9/12 (75%) | 12/16 (75%) | 1/1 (100%) | ND | ND |

^aRepeated sequences were counted only once.

(Figure 1B) origin, but not of Spl B cells (Figure 1C). A similar preference for $J_H l$ has been reported for perinatal $V_H D J_H$ rearrangements and for murine B-CLL cells (Gu *et al.*, 1990). The preference for $J_H l$ was observed in productive and non-productive rearrangements, suggesting that it resulted from a bias in the rearrangement process rather than from cellular selection. No $J_H l$ preference was observed among $V_H 7183$ rearrangements isolated from any of the subsets, implying that the observed bias was V_H gene family specific.

The murine D gene segments are known to use one of the three possible reading frames preferentially (RF1 according to the nomenclature of Ichihara *et al.*, 1989). This preference for RF1 has been reported to be present in all subsets of pre-B and B cells analysed, with the exception of pre-B cells utilizing V_H7183 gene segments

(Huetz et al., 1993), and early B-1a cells (Gu et al., 1990). $D-J_H$ junctions using DSP and DFL (but not DQ52) gene segments in RF2 can potentially lead to the production of a Dµ protein (Reth and Alt, 1984) which, it has been suggested, mediates selection against RF2 and contributes to the preference for RF1. It is therefore remarkable that the B-1b population analysed here was found to display a considerable frequency of RF2 junctions (Figure 1B). Thus, 10 of 30 productive V_HJ558-DFL/DSP rearrangements isolated from the peritoneal B-1b population used RF2. In contrast, RF2 was only rarely found in nonproductive rearrangements of the B-1b subset or in productive or non-productive rearrangements derived from any other B-cell subset, with the possible exception of nonproductive V_H7183-DFL/DSP rearrangements isolated from adult spleen (4/11) (Figure 1C).

B-1a, 5 months 7183 <u>V/N? P N</u> 9 Gene VH Emotional TATGGTTACGAC ATTACTACGGTAGTAGCI a7.36 1 a7.16 1 CCI C TGG TTT GCT 3 S F 1 1 1 CAT CAGT CA a7.1 32 AGA ACTATAGT 5 5 F AC TGG TAC TTC GAT TAC TTT GAC GG TAC TTC GAT GG TTT GCT 2 1 2 GGTAACTAC CGG 3 3 1 3 3 1 a7.14 a7.34 a7.40 a7.35 1 AGA AGA TGG AG AGA AGA AGA 1 1 G 1 7Ъ GGG ATGATGGTTACT 1 3 4 3 0005 AGTGGG GGGTCATCC TC 1 21b 21b TCTACTATG CGGTAGTAGCTA тат GCT ATG GAC TGG TTT GCT a7.5 a7.41 <u>J558</u> Name 1 Gen V/N? P _VH ₽ P ₽ D RF Func 186.2 165.1 CH10 CH10 CH10 CH10 астодд Астасддтадтад Тстастатддтаасти Тдддас адтад Сддтадтадста ai.20 1 AGA AGA CGATGGG CGAA GTGGG TAC TGG TAC TTC GAT Q F S ai.6 2 1 1 1 aj.6 aj.5 aj.8 aj.43 20 A AG GAGO Q/F 3/1 AG VDW32 NVARG2 AGA AG CTACGGTAGTAGCTAC GGTTACGAC T GAC F aj.41 aj.12 1 GAAGGN GOACTEO сτ AGAG Non-functional aj.11 aj.35 aj.25 1 1 1 186.2 VNU3.2 VDW38 ATTACG TGATTACGAC TCTACTATGATTACGAC λGA AGAAGI ATC ATC TTT GAT GAC GCT 8 8 8 GAT TCCT VH11 Name 1 VH ₽ av.5 26 AGA TATCGTAN TAC TGG TAC TTC GAT TAC TGG TAC TTC GAT TAC TGG TAC TTC GAT av.15 TAGTAG ATAGTAA AGA AGA 3 T A T ATA AV. 37 av.12 av.24 av.31 1 2 1 AGA AGA AGA T TT TATA TGG TAC TTC GAT 1 3 3 с S,F 3 AGCCACTTTGCTTG GG CC TGG TTT GCT

Fig. 2. CDR3 regions as in Figure 1, derived from the B-1a population sorted from 5-month-old mice.

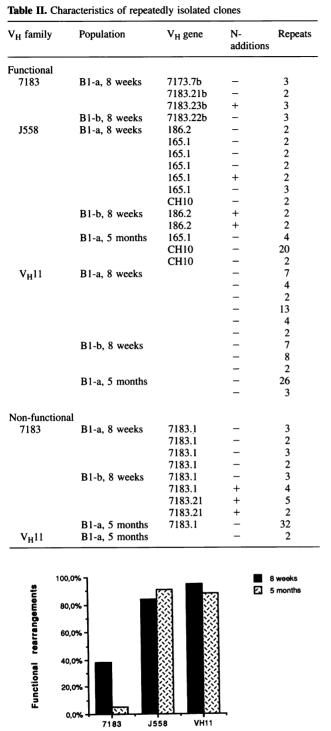
Clonal expansion in the B-1a and B-1b populations To investigate further the proposed changes in V-region repertoires of the B-1a population with age, we analysed $V_H DJ_H$ regions isolated from the peritoneal B-1a cells of 5-month-old mice. The nucleotide sequences of these $V_H DJ_H$ junctions are given in Figure 2. The most apparent difference observed between the B-1a cells isolated from 8-week-old and those isolated from 5-month-old mice was the high number of identical V_HDJ_H rearrangements isolated from the latter (Figure 2 and Table II). Thus, 32 of the 40 $V_{\rm H}7183$ rearrangements and 20 of the 33 $V_{\rm H}J558$ rearrangements isolated from B-1a cells of 5-monthold mice were found to be identical. Repeated $V_H DJ_H$ rearrangements were not isolated from Spl B cells. Repeats did occur, however, in B-1a cells and, to a lesser extent, in B-1b cells of 8-week-old mice (Figure 1). The majority of the repeatedly isolated V_H11 junctions represented previously reported canonical V_H11 sequences predominantly expressed by B-1a cells (Reininger et al., 1987).

All the repeatedly isolated rearrangements utilizing $V_H J558$ or $V_H 11$ gene segments were found to be productive. This agrees with the notion that they were positively selected based upon their expressed V-region specificity. In contrast, the repeatedly isolated $V_H 7183$ rearrangements represented both productive and non-productive junctions. In B-1a cells of 5-month-old mice, one non-productive $V_H 7183$ rearrangement, $V_H 7183$.1 (81x) predominated. It appears plausible that this rearrangement represented the non-productive allele of an expanding B-1a clone expressing a productive $V_H DJ_H$ rearrangement utilizing a V_H gene segment from a different family. This is further supported by the observation that

the frequency of productive V_H7183 rearrangements in the B-1a population decreases significantly between the age of 8 weeks and 5 months (Figure 3). Comparing the ratio of functional and non-functional rearrangements between defined populations in a differentiation pathway can provide information concerning positive versus negative selection. Thus, if a set of V genes is positively selected during differentiation from one stage to another, the frequency of functional rearrangements is expected to increase within this set of V genes. As illustrated in Figure 3, the frequency of productive V_H7183 rearrangements appeared to decrease in B-1a cells isolated at 5 months of age as compared with B-1a cells derived from 8-weekold mice. In contrast, the frequency of productive $V_H J558$ and V_H11 rearrangements was found to remain high (>80%) in 5-month-old mice.

Owing to the repeated isolation of identical sequences from the B-1a population of 5-month-old mice, the number of unique $V_H DJ_H$ rearrangements identified was too low to allow an unambiguous estimation of N-sequence additions. Keeping this reservation in mind, however, no obvious increase in N-diversity was observed compared with the B-1a population isolated at 8 weeks of age (Table I).

In any study based on PCR amplification, one has to be aware of possible artefacts. The repeated isolation of identical $V_H DJ_H$ sequences discussed above could be argued to be the result of such artefacts. However, the following arguments make this highly unlikely. First, in spite of using similar numbers of B cells from each of the populations analysed, the distribution of repeats was distinctly different in the various populations. Repeats were never isolated from total spleen cells. Second, the frequency of repeats isolated was dependent on whether



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Fig. 3. Percent productive rearrangements in the B-1a population. In cases where repeated sequences were found, they were all included in the calculations.

the junctions were productive or non-productive. Third, the number of repeats isolated from the B-1a population increased dramatically in cells isolated from 5 months of age compared with cells isolated from 8-week-old mice.

Characteristics of $V_H D J_H$ rearrangements that are clonally expanded in the B-1a population

To search for common structural features among the $V_H J558$ rearrangements expressed by the expanded clones,

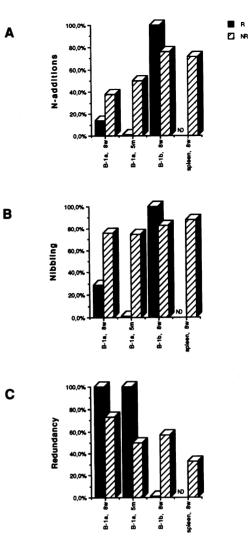


Fig. 4. Comparison of repeated (R) and non-repeated (NR) V_HJ558 utilizing clones with respect to N-sequence additions between the D and J_H gene segments (A), nibbling of the J_H segment (B) and overlapping sequences between the D and the J_H (only sequences lacking P and N nucleotides between the D and J_H segments were considered) (C). Identical sequences were only counted once. Only productive sequences were included in the calculations.

we compared repeated sequences with non-repeated sequences isolated from each of the different B-cell subsets. The repeated sequences were frequently found to display features previously ascribed to V_HDJ_H rearrangements isolated from fetal and neonatal mice. Thus, the repeats contained fewer N-additions (Figure 4A) and a lower frequency of exonuclease nibbling of the 5' terminal of the J_H segment compared with the non-repeated sequences (Figure 4B). The repeated sequences also more frequently contained short stretches of homologous sequences between the D and J_H gene segments (Figure 4C). It has been proposed that these homologous stretches mediate homology joining of the V, D and J gene segments in the absence of N-region diversity (Gu et al., 1990). The frequency of N-additions is less frequent among the repeated sequences, and homology joints would therefore be expected to be more frequent. Even if only $V_H DJ_H$ junctions lacking N-sequence additions are considered, however, homology stretches are more frequent among

repeated sequences. Together, these data further support the notion that the B-1a subset is generated early in ontogeny. In contrast, no evidence for the overrepresentation of these 'perinatal' characteristics among repeated sequences derived from the B-1b subset was obtained. This observation, however, remains uncertain owing to the low number of repeats isolated from this population.

Activation of conventional B cells by antigen results in the expansion of the clones, together with IgH isotype switch and somatic hypermutation. We found no evidence, however, for somatic mutations in any of the populations analysed. This included the highly repeated $V_H DJ_H$ rearrangements isolated from 5-month-old mice (data not shown). The frequency of mismatches compared with the most homologous germline genes were in the range of what could be attributed to errors introduced by the *Taq* DNA polymerase. The observed lack of somatic mutations in the expanded B-1a clones is in agreement with the notion that this B-cell subset is not susceptible to the somatic hypermutation machinery or, alternatively, that they are selected in a manner that does not induce the hypermutation mechanism.

Discussion

B-1a but not B-1b cells share structural features with the perinatal B cells

Our observations confirm and extend previous reports showing that B-1a cells are characterized by a delayed generation of N-region diversity, by a bias towards utilization of J_H1 gene segments, and by a high frequency of homology stretches at the V_H-D and $D-J_H$ junctions. We also find that B-1a cells display a relatively low frequency of exonuclease nibbling of the joining gene segments. Concerning the biased J_H usage this appears to be a result of preferential joining of certain gene segments rather than due to cellular selection since a similar bias is observed in non-productive and productive rearrangements. Moreover, the preference for J_H1 is apparent for V_HJ558 and V_H11 junctions but not for rearrangements utilizing V_H7183 gene segments, suggesting a V_H familyspecific mechanism.

The observation of a low frequency of N-sequence additions in both productive and non-productive rearrangements isolated from the B-1a population implies that these rearrangements were made at a point in ontogeny when TdT activity is low or absent. In contrast, most $V_H DJ_H$ junctions isolated from the B-1b subset contain N-sequence additions. These observations place the generation of B-1a cells at a distinct point of ontogeny preceding the generation of B-1b and B-2 cells. This is in agreement with the observation that B-cell progenitors of fetal day 13 omentum can reconstitute both the B-1a and the B-1b subsets while B cell progenitors of day 8.5 splancnopleura only reconstitute the B-1a subset.

The restricted junctional diversity characterizing the B-1a subset is reminiscent of the fetal and the neonatal B cell repertoire, giving further support to the notion that the B-1a subset is generated early in ontogeny. In contrast, the repeatedly isolated $V_H DJ_H$ junctions of B-1b origin did not display these characteristics. Thus, while the repertoire of B-1b cells and B-2 cells are subject to junctional diversification, B-1a cells to a large extent are

restricted to the usage of gene elements present in the germline, implying that the clonally expanded specificities of the B-1a population have been evolutionarily selected. The functional role of these 'early' specificities remains unknown, but it has been speculated that these 'early' specificities ensure a 'natural' defence against common pathogens in the perinatal immune system (Rajewsky *et al.*, 1987; Kocks and Rajewsky, 1989; Avrameas, 1991) and/or guarantee an idiotypic network control of the emerging immune system (Kearney and Vakil, 1986; Coutinho, 1989; Holmberg *et al.*, 1989).

The perinatal characteristics are selected for in the B-1a population

The perinatal characteristics of the B-1a subset appear to be retained in relatively old mice (5 months), arguing against the idea that the originally generated B-1a repertoire is replaced by clones generated in the adult bone marrow. The perinatal features are most pronounced, however, among the V_HDJ_H junctions repeatedly isolated from the B-1a subset. Analysis of the B-1a cells derived from mice at the age of 8 weeks or 5 months suggest that a few clonotypes in this subset are expanded in the ageing mouse. These findings confirm and extend previous evidence for clonal expansion of B-1a cells expressing various V_H genes (Reininger et al., 1987; Tarlinton et al., 1988; Hayakawa et al., 1990; Pennell et al., 1990). The comparison of repeated and non-repeated V_HJ558expressing clones from the B-1a subset provides evidence for the positive selection of clones lacking N-sequence additions and exonuclease nibbling in this compartment. Clones expressing V_H7183 rearrangements lacking Nsequence additions appear to be favoured in a similar fashion as has been observed for V_H7183 rearrangements of neonatal spleen (Carlsson et al., 1992b). Thus, it would appear that, both in the neonatal B-cell repertoire and in the adult B-1a subset, specificities representing a default pathway of germline encoded specificities are favoured. The suggestion that these specificities are functionally important would appear to be supported by the observation that they are retained and selected for in a subset of the adult system. Moreover, it implies that this functional role in the adult is mediated by a separate cellular subset to which separate rules of cell physiology may apply. An example of this may be the limited diversification of B-1a cells by somatic hypermutations (Tarlinton *et al.*, 1988; Förster et al., 1988) illustrated by the lack of somatic mutations even among the most frequently isolated $V_H DJ_H$ rearrangements of the peritoneal B-1a population.

B-1b cells display structural characteristics distinguishing them from both the B-1a and the B-2 subsets

The B-1b subset has been ascribed functional properties similar to the B-1a population, including a high frequency of self-reactive clones. We find here that these two subsets share some structural properties of $V_H DJ_H$ rearrangements but differ in others. The B-1b population displays Nregion diversity that is more similar to the B-2 population than to the B-1a subset while the bias towards J_H1 usage is similar to that observed in B-1a cells. A feature unique to the B-1b subset is the frequent usage of D segments in RF2. This finding is remarkable as RF2 is selected against

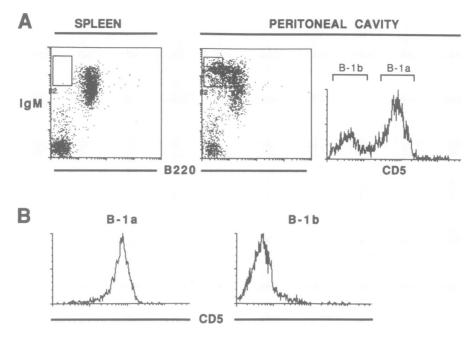


Fig. 5. FACS profiles illustrating the sorting and subsequent analysis of the B-cell populations. (A) Total lymphocytes, forward and side scatter gated, from the peritoneal cavity. The B-1 population (IgM^{hi} , B220^{lo}) was gated and then further divided into B-1a ($CD5^+$) and B-1b ($CD5^-$). The same staining of spleen is included for comparison (left). (B) Analysis of the purity of the sorted populations.

in most pre-B and B cell populations (Kaartinen and Mäkelä, 1985; Ichihara et al., 1989; Gu et al., 1990, 1991). Most D-regions translated in RF2 allow the DJ_Hrearranged locus to be expressed as a Dµ protein (Reth and Alt, 1984), which has been suggested to mediate the elimination of these cells (Gu et al., 1991). The observed presence of RF2 rearrangements in the B-1b population provides evidence that pre-B cells may escape this mechanism. Moreover, the presence of RF2 in B-1b cells appears to be the result of cellular selection since very few RF2 are found among non-productive rearrangements. While the selecting ligand(s) remains unknown, we note that D gene segments read in RF2 encode preferentially hydrophobic amino acid residues. In contrast, RF1 and RF3 very rarely encode such amino acid residues. It remains to be established, however, whether this could constitute a selective advantage of B-1b cells.

As discussed above, the results of the transfer experiments using progenitors from different points of ontogeny have been taken as evidence for different progenitors of B-1 and B-2 cells. This interpretation has, however, been challenged, and an alternative model has suggested that the expressed antibody specificity would direct the B-cell clone into either of the differentiation pathways. In the separate differentiation pathway hypothesis, it has been argued that specificities characteristic of the neonatal repertoire are recruited into the B-1a with a high frequency because of being more prone to crosslinking of their Ig receptors by T-independent antigens. The findings that Nsequences are selected against in V_H7183-utilizing rearrangements in the B-1a population and that the neonatal characteristics are retained among clonally expanded B-1a cells could be interpreted to support this theory. The absence of somatic mutations in these cells is also compatible with the notion of a T-cell independent clonal expansion. However, the observation that the perinatally

overrepresented V_H7183 family, and particularly the $V_H7183.1$ (81x) gene, (Yancopoulos *et al.*, 1984) is negatively selected in the same way in B-1a cells and conventional B cells would appear to argue against this hypothesis. If the recruitment of cells into the B-1a population preferentially occurred among cells expressing 'perinatal' specificities, selection against the very same V_H genes would seem unlikely. Together, therefore, our findings here provide additional evidence for three separate lineages for the B-1a, B-1b and B-2 cells. Each of these subsets displays a characteristic repertoire of V_HDJ_H rearrangements reflecting different constraints in terms of ontogenic timing of the rearrangement process together with cellular selection.

Material and methods

Mice

C57BL/6 mice were bred in the animal facilities at Umeå University and were used for the experiments at the age of 8 weeks or 5 months.

FACS staining and sorting of cells

Peritoneal cells were obtained by flushing the peritoneal cavity with 10 ml RPMI and subsequently washing the cells in BSS. Pools of cells from four to six mice were used for the sorting. 1×10^6 cells were incubated in 25 µl of staining solution [phosphate-buffered saline (PBS), 0.1% sodium azide, 3% fetal calf serum] together with titrated amounts of the following antibodies: anti-mouse B220 (CD45R) labelled with allophycocyanin (APC) (PharMingen), anti-mouse CD5 labelled with fluorescein isothiocyanate (FITC) (Southern Biotechnology Associates, Inc.). Figure 5 illustrates the sorting profile of lymphocytes from 8-week-old C57BL/6 mice of the B-1a (IgM^{hi}, B220^{lo} and CD5⁺) and B-1b (IgM^{hi}, B220^{lo} and CD5⁻) populations. Total spleen was used as a source of conventional B-2 cells. After staining, the cells were washed, resuspended in staining solution and sorted on a Becton Dickinson FACStar plus.

Isolation of genomic DNA

DNA from the sorted cells or splenic DNA was obtained by resuspending and washing the cells in ice-cold PBS followed by lysing the cells in digestion buffer containing 100 mM NaCl, 10 mM Tris-HCl, 25 mM EDTA (pH 8.0), 0.5% SDS and 0.1 mg/ml proteinase K for 12 h at 37°C. After phenol extraction and ethanol precipitation, the DNA was used as template for PCR amplification.

Construction of polymerase chain reaction (PCR) library

For amplification of genomic DNA, DNA from $3-5 \times 10^4$ cells was used as a template. The amplification of V_H gene rearrangements was carried out in 50 µl 35 mM Tris-HCl, pH 8.3, 50 mM KCl, 2.5 mM MgCl₂, 100 ng/ml BSA, 0.5 µM V_H primer, 0.5 µM of a mixture of the four J_H primers and 200 µM of each of dATP, dCTP, dGTP and dTTP. After denaturing, 2.5 U of *Taq* polymerase was added and the DNA was amplified on a thermal cycler (Hybaid Ltd) using 25 cycles of 45 s at 94°C, 1 min at 55°C and 2 min at 72°C per cycle. These cycles were followed by one cycle at 72°C for 10 min. After ethanol precipitation, the PCR product was digested with *Not*I and *XhoI* restriction endonucleases and electrophoresed through a 1.5% agarose gel. A band of the correct size was cut out and the DNA was electroeluted, ligated into the pBluescript (KS-) vector (Stratagene, La Jolla, CA) and transformed into *Escherichia coli* DH5α.

The primers used were:

 $\label{eq:vhi} \begin{array}{l} V_H7183, 5'\text{-}CGCGCGGCGCGCGTGGAGTCTGGGGGGAGGCTTA-3';}\\ V_HJ558, 5'\text{-}CGCGCGGCCGCTGCAGCAGCCTGGGGGCTGAG-3';}\\ V_H11, 5'\text{-}CGCGCGGCGCCGCTGTTGGAGACTGGAGGAGGC-3';}\\ J_H1, 5'\text{-}GCGCTCGAGAAAAAAGCCAGCTTACCTGA-3',}\\ J_H2, 5'\text{-}GCGCTCGAGGGTTTTAAGGACTCACCTGA-3',}\\ J_H3, 5'\text{-}GCGCTCGAGAGAAGAAGTTAGGACTCACCTGC-3',}\\ and\\ J_H4, 5'\text{-}GCGCTCGAGGAGAGGCCATTCTTACCTGA-3'.} \end{array}$

Screening of PCR libraries and DNA sequencing

About 500 ampicillin-resistant colonies from each library were screened by colony hybridization (Maniatis *et al.*, 1982) using the following radioactively labelled probes: pV_H81X (Yancopoulos *et al.*, 1984) was used for screening the V_H7183 library (kindly provided by Dr F.Alt); pVNP.B4 (Yancopoulos and Alt, 1985) was used for screening the V_HJ558 library (kindly provided by Dr F.Alt); and pCP12 (Reininger *et al.*, 1988) was used for screening the V_H11 library (kindly provided by Dr L.Reininger). Plasmid DNA from positive colonies was sequenced by the Sanger dideoxy method (Sanger *et al.*, 1977) using T7 DNA polymerase (Pharmacia, Uppsala, Sweden and US Biochemicals), 7deaza-2'-dGTP (Pharmacia), and the T3 and the T7 sequencing primers.

Sequence comparisons

The sequences were analysed by using the University of Wisconsin program GCG (Genetics Computer Group). The sequences were edited using the program SEQED and compared using the program WORD-SEARCH.

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