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Immunogenetic landscape of Waldenström Macroglobulinemia: correlation with clinico-biological features, prognosis and comparison with physiological memory-B cells and plasma cells

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Background

The cell origin of Waldenstrom macroglobulinemia (WM) tumour cells remains uncertain but may correspond to memory B-cells (MBC) or plasma cells (PC). Molecular features of the B cell receptor of lymphoid malignancies have been widely used to address this question. Only few studies have investigated the immunoglobulin heavy chain variable region (IGHV) repertoire in WM. We aimed to characterize the IGHV repertoire of a large cohort of WM patients, to compare it with those of normal bone marrow (BM) B-cell subpopulations, and to evaluate potential associations of IGHV specificities with main clinical and biological characteristics.

Methods

DNA was extracted from a retrospective cohort of 186 WM samples, either from BM (n=163) or blood (n=23). DNA was also extracted from FACS-sorted MBC and PC fractions of BM samples from 4 healthy donors. Sequencing of the IGHV region was performed using a next-generation sequencing (NGS) methodology developed by our team[1]. Conventional cytogenetics and molecular analyses using a NGS targeted panel (21 genes) were also carried out.

Results

From the initial 186 cases, 175 (94.1%) displayed at least one productive IGHV rearrangement and were retained for further analysis. Median age at diagnosis was 65 years and median follow-up was 56.1 months. *MYD88* and *CXCR4* were mutated in 94 % and 29 % of cases respectively.

The IGHV repertoire was clearly biased with genes from the IGHV3 subgroup used in 80.0% of cases. Six genes (IGHV3-7, IGHV3-15, IGHV3-23, IGHV3-30, IGHV3-72, IGHV3-74) contributed to almost two-third (62.3%) of the entire cohort repertoire, with IGHV3-23 being the most frequent (26.9%) (**Figure 1**). Complementarity-determining regions 3 (CDR3) were short with a median length of 13 aminoacids. Most cases exhibited somatic hypermutation (SHM) with a median rate of 7.3%. IGHV3-23 genes had a significant higher SHM rate (8.5%). Furthermore, 26 cases (14.9%) had subclones differing by their SHM rate, indicating *in vivo* intraclonal diversification. Seventeen samples (9.7%) showed two productive IGHV clonal rearrangements, with only 7 having two distinct clones by flow cytometry.

MBC and PC sorted from healthy donors also used predominantly genes from the IGHV3 subgroup but the IGHV3-23 gene appeared to be less frequent (14.3% and 14.4%, respectively) than in WM cases with longer CDR3 (median 15 aminoacids) and less SHM (4.9% and 6.9%, respectively).

We did not observe any significant association between IGHV subgroups and main clinical and molecular features. However, the presence of two clonotypes impacted outcomes, with a 5-year PFS and OS of 30% and 82% for this population compared to 51% and 98% for the rest of the cohort (P=0.06 and 0.001, respectively) (**Figure 2**). In multivariate analyses, only age and the presence of

two clonotypes remained significant for poorer OS. Finally, we did not confirm the pejorative impact of IGHV4 subgroup usage[2].

Conclusion

WM cells display a biased IGHV repertoire with features suggesting a role for antigen stimulation in their development. There was no clear correlation between IGHV gene usage and other biological or clinical parameters, excepted for biclonality which negatively impacted outcome.

1- Langlois de Septenville A, Boudjoghra M, Bravetti C, Armand M, Salson M, Giraud M, Davi F. Immunoglobulin Gene Mutational Status Assessment by NextGeneration Sequencing in Chronic Lymphocytic Leukemia. Methods Mol Biol. 2022;2453:153-167

2- Wang J, Yan Y, Xiong W, Song G, Wang Y, Yu Z, et al. The Landscape of Immunoglobulin Heavy Chain Gene Repertoire in Lymphoplasmacytic Lymphoma / Waldenström Macroglobulinemia. Blood. 5 nov 2021;138(Supplement 1):1346.

Figure 1 : IGHV repertoire biases in WM Frequency of IGHV gene usage in a cohort of 175 WM cases. IGHV genes above 5% are colored in blue

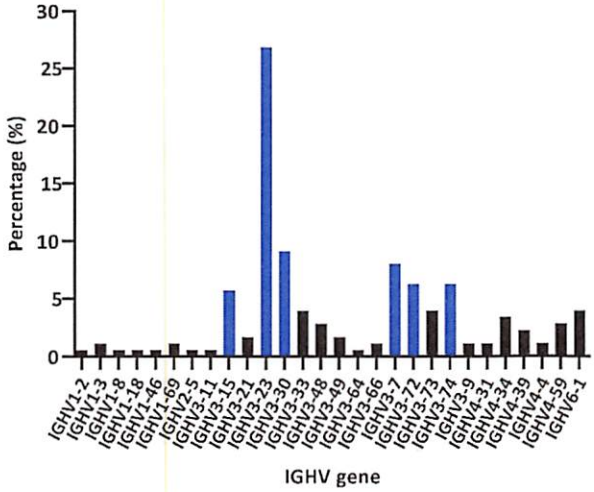

Figure 2 : Kaplan-Meier curves for progression-free survival (PFS, left panel) and overall survival (OS, right panel) according to IGHV subgroup genes and the presence of one or two productive rearrangements. PFS (A, C, E) and OS (B, D, F) according to the presence (red) or absence (blue) of the following characteristics: IGHV3 (V3) subgroup genes (A, B), IGHV4 (V4) subgroup genes (C, D), number of productive rearrangements (E, F). Dashed lines represent 95% confidence interval. P values are indicated in each survival plot.