Session III: Genetic Basis and Pathogenesis

of WM and IgM Related Disorders

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Presenter: R. Garcia-Sanz

Immunoglobulin Gene Rearrangements in Waldenström's macroglobulinemia. Ramón García-Sanz, Patricia Martín-Jiménez, Enrique M. Ocio, María E. Sarasquete, Marcos Gonzalez, Jesus F. San Miguel. Hematology Department. University Hospital of Salamanca, SPAIN.

We have updated the characterization of complete VDJH and incomplete DJH rearrangements in 106 IgM monoclonal gammopathies: 56 symptomatic WM, 36 asymptomatic WM and 14 IgM Monoclonal Gammopathies of Uncertain Significance (IgM-MGUS). Monoclonal VDJH rearrangements could be amplified in 86% of patients. VH was biased in WM, since the most frequently used family and single segments were VH3 and VH3-23 (75% and 22%, respectively), which markedly differs from the repertoire in normal B-cells and MM. VH3-23 segment was never selected in Ig-MGUS (0% vs. 27%, $p<0.05$). VH4-34, frequently selected normal circulating B cells, B-CLL cells, and others such as B-ALL and diffuse large B-cell lymphoma, was never selected in our WM cases and only in one IgM-MGUS. In the same line, the VH1-69, VH3-07 and VH3-21, usually overrepresented in B-CLL, were selected by 0%, 0% and 3% of our IgM monoclonal gammopathies. In addition, the highly frequent selection of the VH3-23 seems to be highly frequent in WM. This repertoire is clearly different to CLL but quite similar to MM. Accordingly, these findings reinforced similarities between WM and MM in opposition to studies that have emphasized that WM and B-CLL are closely related disease. Monoclonal incomplete DJH rearrangements were detected in 43% of our IgM monoclonal disorders. Only one case of IgM-MGUS displayed an incomplete DJH rearrangement, in opposition to the symptomatic or asymptomatic WM cases (7% vs. 51%, $p<0.01$). Somatic hypermutation with >2% deviation from the germline was seen in 91% of all cases, without significant differences between different symptomatic, asymptomatic and MGUS cases. However, using the number of mutations as continuous variable, symptomatic cases demonstrated a higher grade of somatic hypermutation (SHM), since the median percentage of changes was 6.54%, 7.14% and 9.11%, although differences did not achieve statistical significance (K-W, $p=0,277$). VH segment usage seemed to be responsible of such difference, since VH3-23 segments, never used in MGUS, displayed a higher grade of SHM than the rest of segments. These findings did not relate with any specific clinical characteristics, although time to therapeutic requirement was shorter in unmutated patients, with no statistically significant differences. In addition, none of the patients with unmutated VH segments has died until now.