Splenic marginal zone lymphoma (SMZL) is frequently associated with HCV infection and autoimmune disorders. Previous studies demonstrated a biased usage of immunoglobulin heavy variable genes (IGHV) and, in some cases, stereotyped B-cell receptors (BCRs). This characterization, however, is mainly based on the heavy chain alone, even if strong evidences are emerging on the role of light chain (Bikas et al. Leukemia 2012).

The aim of this study was to analyze IG light variable genes (IGLV) of SMZL BCRs, VL-VH pairing and structural information and to investigate the sequence-structure-antigen (AG) relationship. To this end, we analyzed the VL-VH paired sequences of BCR from 52 SMZL pts (38 BM and 14 PB) diagnosed according to Matutes criteria (Leukemia, 2008). Sequences were analyzed using the IMGT/DBs and the IMGT/V-QUEST tool. The PIGS web server was used to build 3-D models of all antibodies (Abs). The Ab structures were compared using LGA and clustered together according to a score accounting for structure and sequence similarity. Using the DIGIT DB and tools, all the clusters were analyzed and compared to other IGs.

Based on the IGHV nucleotide sequence identity to the germline, 7 sequences (13%) were considered 'truly unmutated' (100% sequence identity), 20 (39%) were 'minimally or borderline mutated' (97.0-99.9%) whereas 25 (48%) were 'significantly mutated' (<97%). IGHV families were used as follows: IGHV3 (58%), IGHV1 (27%) and IGHV4 (15%).

The majority of pts carried kappa light chain (69%). The most frequently used IGLV families were IGLV3 (38%) and IGLV1 (28%), the most frequent IGLV family was IGLV1 (56%).

In conclusion, the multi-layered characterization of the sequence and structure properties of paired VL-VH in SMZL identified a non-random pairing between heavy and light chains. Structural cluster analysis identified Abs with similar physicochemical properties, similar mutation rate and similar HCV status in a fraction of our dataset. Comparing Abs of our cases to a large dataset of human annotated Abs derived from the DIGIT DB, a subset resulted similar to CLL or autoimmune clones, whereas other Abs appeared more similar to polyreactive Abs and to Abs possibly targeted by superantigens. These findings could explain the large diversity observed in the IGs expressed in SMZL and provide new insights in SMZL pathogenesis.

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