In this issue of Clinical Cancer Research Bommen and colleagues (1) investigate the role of immunoglobulin heavy chain variable 3-23 (IGHV3-23) gene usage in chronic lymphocytic leukemia (CLL). Stereotyped B-cell receptors (BCR) are a common phenomenon in CLL (2). Stereotyped BCRs are strikingly similar BCRs, often arising from the use of common H and L chain V region gene segments that share CDR3 structural features (length, amino acid composition, and unique amino acid residues at recombination junctions). The authors approached the dissection of the 70% of cases that cannot be allocated to a stereotyped subset (Fig. 1). Building on the finding that stereotyped BCRs with highly homologous heavy complementary determining region 3 (HCDR3) regions are absent in CLL cases using the IGHV3-23 gene, the group characterized this subgroup of CLL and reports that IGHV3-23 gene usage may have prognostic value independent of mutational status.

The HCDR3 region represents the crucial part of the BCR involved in antigen interactions. CLL with stereotyped BCR form distinct prognostic subgroups. For instance, a subgroup of cases expressing stereotyped IGHV3-21/IGLV3-21 BCRs is associated with inferior prognosis, despite the fact that most cases carry somatically mutated IGHV3-21 genes (3).

The structure of the BCR is different in CLL clones carrying mutated versus unmutated IGHV genes. The IGHV unmutated cases carry a higher proportion (40%) of stereotyped IGHV-D-J rearrangements with highly homologous HCDR3 regions (2, 4). The likelihood that these patients developed CLL clones with identical antibody V regions just by chance is highly improbable and suggests selection by a common antigen and also supports the hypothesis of antigen-driven processes in the pathophysiology of CLL. It is still unclear whether antigen involvement is restricted to the phase of the malignant transformation, or if the putative antigen(s) may continuously trigger the CLL clone and affect not only a potential progenitor cell but also the bulk of leukemic cells. The latter is underscored by recent work showing intracranial diversification at least for one distinct BCR stereotype (subset 4 according to Stamatopoulos and colleagues; ref. 2) expressing mutated IGHV4-34 rearrangements, although most examined cases revealed no or low levels of intracranial diversification (5).

A central question concerns the nature of potential antigens recognized by CLL cells. In IGHV unmutated CLL the BCR is usually polyreactive to auto-antigens derived from endogenous or exogenous proteins or lipids generated by, for example, oxidative stress (6). Recent data propose cytoskeletal structures like nonmuscle myosin heavy chain IIA (MYHIIA) and vimentin (7), neo-epitopes created by chemical modifications occurring naturally during apoptosis and microbial antigens as potential naturally occurring epitopes. Together with the finding that infections can increase the risk of CLL (8), the data point to the possibility that bacterial infections in synergy with neo-self-antigen as, for example, generated by apoptotic cells or other epitopes, may continuously trigger the BCR. In addition, reactivity of CLL BCR to prostate tissue was shown in one study, indicating that in cases of CLL leukemic prostate infiltration, the tropism to the prostate might be mediated by the CLL BCR (Fig. 1).

Further studies probing phage display libraries for mimetic ligands (mimotopes) of the actual epitopes recognized by CLL immunoglobulins (Ig) revealed that mimotopes for leukemic clones carrying mutated or unmutated CLL Igs differed significantly, with the former binding defined structures and the latter recognizing multiple different epitopes (9). The data suggest that in vivo structurally diverse epitopes could bind surface membrane immunoglobulins (smIgs) of distinct CLL clones, and such interactions could lead to transmission of BCR-mediated signals, which could alter survival and growth. Furthermore, preliminary data indicate that the mimotopes of...
CLL Igs can inhibit the binding of the corresponding clonotypic Igs to their cognate, "native" antigen(s). This approach could serve as a treatment strategy.

Another interesting therapeutic target with respect to "antigenic drive" currently evaluated in clinical trials in CLL is inhibition of spleen tyrosine kinase (SYK) as a key molecule of the BCR signaling cascade.

Recent studies suggest an association of autoimmune hemolytic anemia (AIHA) and Richter’s syndrome to distinct IGHV-structure subgroups. One analysis showed BCR stereotypy as an independent risk factor of CLL transformation to Richter’s syndrome. In this study, CLL cases expressing stereotyped IGHV4-39/IGHV5 BCRs (subset 8 according to Stamatopoulos and colleagues; ref. 2) carried the highest risk of Richter’s syndrome, but the overall cohort was limited in size (10). Recent preliminary data from our group suggest a significant over-representation of highly homologous HCDR3-motifs using unmutated IGHV1-69 genes among patients with CLL and AIHA (11). Interestingly one of those HCDR3-motifs is identical with the BCR shown to recognize MYHIIA as an epitope.

Besides classical antigen-antibody interactions, Bomben and colleagues (1) postulate a different BCR-mediated mechanism in the mutated IGHV3-23 (IGHV3-23) subgroup. In contrast to other IGHV genes that may participate in the formation of stereotyped HCDR3s in CLL, the mutated IGHV3-23 gene rearrangements do not exhibit restricted HCDR3 features. The fact that they are constantly absent from clusters of stereotyped BCRs may lead to the hypothesis that the BCRs using mutated IGHV3-23 might be selected by mechanisms operating...
independently of “classical” antigen recognition in the context of superantigenic interactions, through sequence motifs largely outside the complementary determining regions.

In concordance with the findings of Bomben and colleagues (1), these interactions are known to occur in the large human IGHV3 gene subgroup. In fact, the 13 amino-acid positions that are responsible for recognition and binding of Staphylococcal protein A (SpA), a prototypical superantigen specific for IGHV3 genes, were found to be conserved among the described M IGHV3-23 cases. This goes along with previous suggestions (4) implicating a superantigen-induced mechanism in a prognostic relevant CLL subgroup characterized by the usage of a distinct IGHV gene.

Bomben and colleagues (1) tried to further elucidate the mechanisms of the postulated superantigen-drive in this M IGHV3-23 subgroup by studying gene expression profile and micro-RNA (miR)-regulation in a limited group of samples. Supervised analysis of mRNA expression showed different profiles in M IGHV3-23 cases and mutated cases without IGHV3-23 usage. How the down-regulation of specific genes in cases expressing M IGHV3-23 BCRs should be interpreted in the context of superantigen-driven BCR-mediated mechanisms has to be evaluated. It should be mentioned that previous gene expression profiling analysis showed few but important (ZAP70) differentially expressed genes in IGHV-mutated and IGHV-unmutated CLL.

Based on the data from transfection of the miRs miR-15a and miR-16-1 in leukemic cells (12) and gene set enrichment analysis (GSEA), the differentially expressed genes in the M IGHV3-23 group were suggested to be regulated by miR-15a and miR-16-1. The miR-15a and miR-16-1 expression levels in the M IGHV3-23 subgroup seem to reinforce the relevance of this CLL subgroup. The finding of higher miR-15a and miR-16-1 in the prognostic unfavorable M IGHV3-23 CLL subgroup is intriguing. The authors propose a model in which superantigens interact with the M IGHV3-23 BCR and thereby subsequently increase the initially down-regulated miRs miR-15a and miR-16-1. However, an alternative explanation would be that CLL tumors with IGHV3-23 usage develop because of a different pathomechanism that does not include down-regulation of these two miRNAs, which would result in a different gene expression profile as detected by the authors. Irrespective of potential explanation, confirmatory and further studies are warranted. The study by Bomben and colleagues (1) could substantially increase our knowledge about the prognostic relevant subgroup among IGHV mutated CLL. It also poses the question of where in the pathogenesis antigenic or superantigenic stimulations are at play.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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