From genetics to the clinic of chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is characterized by the clonal proliferation and accumulation of mature and typically CD5-positive B-cells within the blood, bone marrow, lymph nodes, and spleen. CLL is a heterogeneous disease with a variable clinical course. Genomic markers are among the strongest prognostic factors in CLL.

Chromosomal aberrations, *IGHV* and *TP53* mutation status are well-established and essential to discriminate between a more indolent course of disease and a high-risk CLL, which requires an alternative treatment regimen. Approximately 80% of CLL patients carry chromosomal alterations. The initiating chromosomal aberrations comprise del(13q) in about 55% of cases, and trisomy 12 in 10–20% of cases. Del(11q) is seen in about 10% of cases and del(17p) in about 5–8% of cases, but these aberrations are usually acquired at late stages of the disease. Del(13q) causes the loss of miRNAs (miR-15a and miR-16-1), which initiates leukemogenesis. Del(11q) causes the loss of the *ATM* gene, which encodes a DNA damage response kinase *ATM*. Del(17p) typically deletes the tumour suppressor gene *TP53*. More than 80% of cases with a del(17p) also carry mutations in the remaining *TP53* allele, resulting in a functional disruption of the TP53 pathway. *TP53* mutations and del(17p) are therefore collectively categorized as genetic *TP53* aberrations.

IGHV mutation status is a strong prognostic factor: Early-stage CLL cases with unmutated *IGHV* show shorter time to first treatment and decreased overall survival (OS) in multivariate analysis. Intriguingly, stimulation also occurs in specific *IGHV* subsets via recognition of epitopes on the BCR molecule itself by the heavy chain complementarity-determining region HCDR3. In addition to the number of mutations, the usage of a specific VH gene is also prognostic for outcome. V3–21 usage was shown to be a prognostic factor independently of mutation status.

Additional recurrent somatic gene mutations have been identified in *NOTCH1*, *ATM*, *BIRC3*, *MYD88*, and *SF3B1*. *SF3B1, ATM, and BIRC3* may describe CLL with adverse outcome, whereas *NOTCH1* is predictive for resistance against CD20 antibodies. Integration of novel drivers into a small set of key pathways forms the basis for future pathogenetic and therapeutic implications.

The survival of CLL cells also depends on a permissive microenvironment of cellular components. Macrophages, T cells, or stromal follicular dendritic cells stimulate crucial survival and pro-proliferative signalling pathways in leukaemic cells by secreting chemokines, cytokines, and angiogenic factors or by expressing distinct surface receptors or adhesion molecules.