Distinct t(14;19) translocation patterns in atypical chronic lymphocytic leukemia and marginal zone lymphomas

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Received: August 8, 2023.
Accepted: August 14, 2023.
Early view: August 24, 2023.

https://doi.org/10.3324/haematol.2023.283975

Chromosomal translocations, which typically lead to activation of proto-oncogenes, play a major role in the pathogenesis of human B-cell malignancies.[1] In most instances, these translocations involve one of the immunoglobulin (Ig) loci (mostly the Ig heavy [IgH] chain locus) and occur as mistakes of one of the genetic Ig locus remodeling processes V(D)J recombination, class-switch recombination, or somatic hypermutation.[1] Such translocations bring the proto-oncogene under the control of the active enhancers of the respective Ig locus, leading to constitutive and hence deregulated expression of the translocated gene. For several types of B-cell lymphomas, the presence of particular translocation events is almost a disease-defining feature. For example, practically all cases of Burkitt lymphoma carry translocations of the *MYC* proto-oncogene into one of the Ig loci, and mantle cell lymphoma is characterized by the translocation t(11;14) involving the *CCND1* gene and the IgH locus.[1]

BCL3 is a member of the NF-κB family of transcription factors, and its gene was identified in 1987 as the partner of the IgH locus in a translocation t(14;19)(q32;q13) in a case of chronic lymphocytic leukemia (CLL).[2] BCL3 is generally functioning as an activator of the NF-κB pathway, with survival and/or proliferation promoting effects. Only about 1% of cases of CLL carry a t(14;19),[3] so this event is rare and not a CLL-defining event as the other translocation examples mentioned above. The rare occurrence of t(14;19) in CLL raises the question whether they define a particular subset of CLL, or whether CLL with *BCL3* translocations have at least particular features. Moreover, translocations t(14;19)(q32;q13) have also been recurrently detected in other types of lymphomas, in particular marginal zone lymphomas (MZL). This raises the question what the common and distinct features of these lymphomas and of the translocation events are. A first comprehensive analysis of a large series of B-cell lymphomas carrying t(14;19)(q32;q13) was performed by Martin-Subero and colleagues.[4] They showed that lymphomas with this translocation can be broadly separated into two groups. One group is mainly composed of CLL with unmutated Ig variable (IgV) region genes and few additional chromosomal changes, and a second group includes mainly MZL, but also other types of B-cell lymphomas. This second group showed a higher frequency of further chromosomal alterations than the CLL, and mutated IgV genes.[4]

In this issue of Haematologica, Carbó-Meix and colleagues present an in depth integrative multimodal analysis of 13 B-cell lymphomas with a t(14;19), which included IgV gene sequencing, whole genome sequencing, transcriptome analysis, epigenetic DNA methylation analysis and translocation breakpoint sequencing.[5] They confirm that two groups of lymphomas with t(14;19) can be distinguished, one group composed mostly of CLL with unmutated IgV genes and low chromosomal complexity, and a group of mostly nodal and splenic MZL with mutated IgV genes and more chromosomal aberrations. Through the detailed multimodal analysis, numerous further important insights into the pathobiology of t(14;19)-harboring lymphomas were obtained. Regarding CLL with t(14;19), it is shown that they also carry trisomy 12 in nearly all cases, which is generally seen in only 15-20% of CLL. Also several other CLL-typical mutations were detected. However, CLL with t(14;19) often showed an unusual morphology and immunophenotype, and their transcriptomes and DNA methylation patterns distinguished them from typical CLL.[5] Hence, these cases are atypical CLL. The analysis of the translocation breakpoints revealed that all CLL with t(14;19) have a breakpoint upstream of the *BCL3* gene, and that this leads to overexpression of BCL3 in CLL with the translocation in comparison to CLL without that translocation. BCL3 expression in t(14;19)-carrying CLL on the derivative chromosome 14 is likely driven by the IgH 3´ enhancers.[1,5] In contrast, the

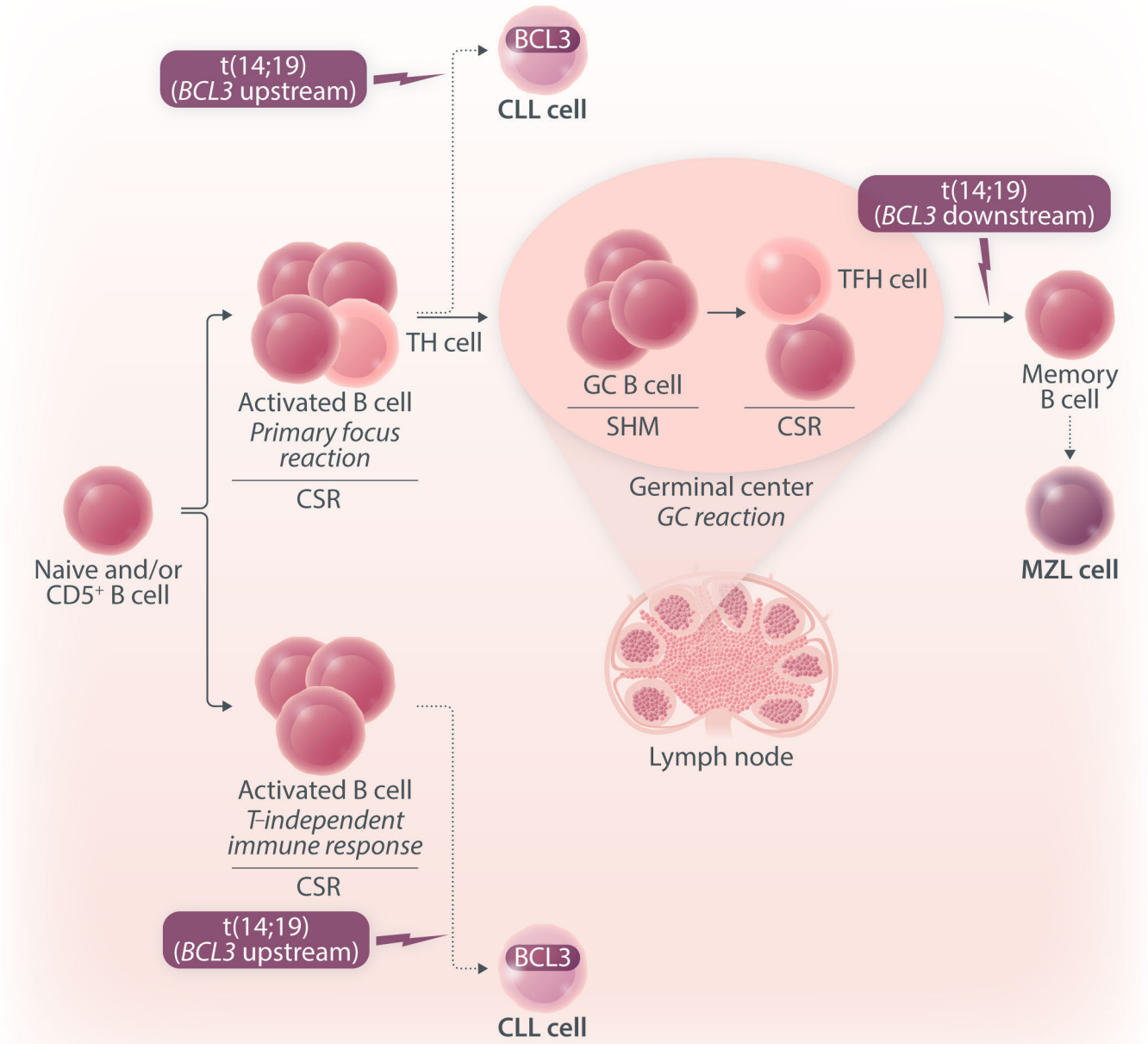

Figure 1. Linking t(14;19) events to B-cell differentiation processes and the development of t(14;19)-carrying B-cell malignancies. The t(14;19) happen as mistakes during class-switch recombination (CSR). CSR mainly takes place during T-cell-dependent immune responses both in the primary focus reaction and the germinal center (GC), but also in T-independent immune responses. Atypical chronic lymphocytic leukemia (CLL) with t(14;19) harbor unmutated IgV genes, indicating that in these cases the translocation either happened in the primary focus reaction or in a T-independent immune response. In these cases, the breakpoint is upstream of *BCL3* and targets this proto-oncogene, as evident by enforced BCL3 expression in the respective CLL cells. CLL is likely derived from CD5$^+$ B cells, which play a major role in T-independent immune responses, but may sometimes also be driven into T-dependent immune responses.[10] Lymphomas with a t(14;19) and a breakpoint downstream of BCL3 are mostly post-GC marginal zone lymphomas (MZL) with mutated IgV genes. In these cases, the translocation presumably happened during the GC reaction. *BCL3* is not the target gene of these events, as the lymphomas lack BCL3 expression. Arrows with dashed lines indicate the final transformation processes from the B cells having acquired a t(14;19) to the fully malignant B-cell clones. SHM: somatic hypermutation; TH: T helper; TFH: T-follicular helper.

second group of mostly MZL showed breakpoints downstream of *BCL3*, and there is strong indication that for those cases, *BCL3* is not the relevant target gene, because these cases did not show BCL3 expression.[5] It remains to be clarified which of the downstream-located gene(s) may be the relevant proto-oncogene(s) of these translocations. As translocation t(14;19) with breakpoints downstream of BCL3 are obviously not targeting *BCL3*, these events should not be considered as *BCL3* translocations. It should be noted that principally *BCL3* could also be a translocation target when positioned on the derivate chromosome 19 in the downstream breakpoint situation. This derivative chromosome carries the IgH Eμ intron enhancer, and there are instances where this enhancer can drive oncogene expression.[6] But apparently, this does not take place in t(14;19) with breakpoints downstream of BCL3.

A further very interesting and novel finding of the work by Carbó-Meix and colleagues was that all breakpoints in the IgH loci were located in one of the IgH switch regions. These are repetitive elements upstream of each IgH constant region gene (except Cδ) in which DNA double strand breaks occur during class-switch recombination. Class-switching

mostly takes place during the germinal center (GC) reaction, and, therefore, it is likely that the precursor cells of the MZL with t(14;19) and mutated IgV genes (as a hallmark of a GC passage), acquired the translocation as a mistake of class switch recombination in the GC (Figure 1).[7] But what about the CLL with t(14;19) and unmutated IgV genes, that presumably did not pass through a GC reaction, but nevertheless have class switching-associated translocations? There are primarily two possible scenarios for this. First, class-switching can also take place in T-cell-independent immune responses, where B cells are activated through strong B-cell receptor signals, often combined with Toll-like receptor signaling.[8] Second, in T-cell-dependent immune responses, a first interaction and cross-wise stimulation of antigen-activated B cells and antigen-specific T-helper cells takes place in the primary focus reaction in the T-cell area or at the border between T-cell area and B-cell follicle (Figure 1). In this initial encounter, class-switching can take place, in the absence of somatic hypermutation in the B cells. There is even recent indication from murine studies that many class-switching events in T-dependent immune responses actually take place before the activated B cells enter the GC microenvironment.[9] Thus, it is principally possible that B cells with unmutated IgV genes acquire class switch-associated translocations t(14;19) in the primary focus reaction and then as premalignant cells further develop into CLL without entering a GC reaction (or enter it briefly, but exit it before initiation of somatic hypermutation) (Figure 1).

A further distinction between the two groups of lymphomas with the distinct types of t(14;19) is the cellular origin of the specific B cells that underwent malignant transformation. MZL likely derive from marginal zone B cells or conventional follicular B cells that were driven into a GC reaction and became post-GC memory B cells before final malignant transformation, whereas CD5$^+$ CLL likely derives from the CD5$^+$ mature B-cell subset in humans (Figure 1).[7,10]

In conclusion, the two types of t(14;19) with breakpoints either upstream or downstream of *BCL3* are associated with distinct B-cell malignancies. Translocations with upstream breakpoints are found in a subset of atypical CLL with unmutated IgV genes and trisomy 12, and lead to upregulated BCL3 expression, whereas t(14;19) with breakpoints downstream of *BCL3* are found mostly in MZL and actually do not target *BCL3*, but presumably one or several downstream located genes. In both instances, the translocation events occur as mistakes of the class switch recombination event, but likely in different types of immune responses. Based on these differences, it is important to distinguish the two types of t(14;19)(q32;q13) in clinical-pathological studies of lymphomas with t(14;19), and it is hence very valuable that Carbó-Meix and colleagues already established and validated a fluorescence *in situ* hybridization assay for this in their study.[5]

Disclosures

No conflicts of interest to disclose.

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