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Genetic evolution in chronic lymphocytic leukaemia

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A B S T R A C T

Next-generation sequencing provides a comprehensive understanding of the genomic, epigenomic and transcriptomic underpinnings of chronic lymphocytic leukaemia. Recent studies have uncovered new drivers, including mutations in non-coding regions, and signalling pathways whose role in cancer was previously unknown or poorly understood. Moreover, massive scale epigenomics and transcriptomics have supplied the foundations for the cellular origin of the disease. Some drivers could be targeted pharmacologically, and the ability to detect mutations present in minority subclones might even allow treatment before clonal selection occurs, thus preventing disease refractoriness. As our understanding broadens and ongoing technological innovation propels new achievements, we will certainly learn how to apply it in our daily practice.

Introduction

Chronic lymphocytic leukaemia (CLL) is a lymphoid neoplasm characterized by the monoclonal accumulation of mature CD5-positive B cells. While some patients remain asymptomatic and have a

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normal life expectancy, others develop a progressive disease that could eventually become refractory to therapy. CLL is often preceded by a pre-leukaemic phase called monoclonal B-cell lymphocytosis (MBL), which is defined as the presence of small B-cell clones of CLL phenotype in the blood and no evidence of a lymphoproliferative disorder (i.e. absence of lymphadenopathy, organomegaly, cytopenia or B symptoms) [1]. Two molecular subtypes have been described according to the mutational status of the variable region of the immunoglobulin heavy chain (*IGHV*) gene. Around half of CLL cases undergo somatic *IGHV* hypermutation as they pass through the germinal centre, and these patients with mutated *IGHV* (mCLL) display an indolent CLL. In contrast, patients with unmutated *IGHV* (uCLL) generally have an aggressive form of the disease [2,3]. Chromosomal aberrations are frequent in patients with CLL and also provide valuable prognostic information: del13q14 is associated with a favourable outcome, while del11q22-q23 and del17p13 confer an adverse prognosis [4].

The advent of next generation sequencing (NGS) techniques together with potent bioinformatic pipelines has fuelled cost- and time-effective studies of cancer genomes [5–7]. In the particular case of CLL, NGS studies have identified recurrently mutated genes such as *NOTCH1*, *SF3B1*, *BIRC3* and *MYD88* [8–11], and have also delineated the transcriptome and epigenome of the disease [12,13]. In this review, we will highlight the most relevant achievements in this area and discuss how they could translate into clinical practice.

Genomic aberrations

Structural abnormalities

The importance of cytogenetic aberrations in the outcome of patients with CLL is well established (reviewed in Ref. [14]). Initial efforts were made using chromosome banding analysis (CBA) after Giemsa staining, a technique that was able to identify abnormalities in only 50% of patients, probably due to the low mitotic rate of CLL cells [15]. These results were consistently improved with the advent of fluorescent in-situ hybridisation (FISH) so that, with a relatively low number of probes, genomic aberrations could be found in 80% of patients [4]. In view of these results, FISH became the gold-standard method for cytogenetic assessment and has remained so to date even though it only evaluates specific genomic regions and not the entire genome. In parallel, the results of CBA could be improved when tumour cells were incubated with novel mitogens (e.g. DSP30 and IL2), which are capable of detect aberrations in 80% of patients [16], including 20–35% of those who have “normal” FISH results [17]. Moreover, single-nucleotide polymorphism (SNP)-arrays also interrogate the entire genome and could be a suitable alternative to FISH for detecting deletions or amplifications [18–20].

Irrespective of the technique used, the most common structural aberration in CLL patients is del13q14, which is present in 50–60% of cases. This deletion, affecting the microRNAs *miR15-a* and *miR16-1*, reduces the expression of these genes, which are implicated in the regulation of apoptosis and the cell cycle [21]. In addition, translocations involving 13q14 with a variety of chromosomal partners are also relatively frequent and generally disrupt the *miR15-a*/*miR16-1* locus as well [11,22]. Trisomy 12 is generally considered the second most frequent aberration in patients with CLL, occurring in 15–20% of patients, although the gene involved remains unknown. It often appears as a unique cytogenetic alteration but it can also be associated with others [23]. Importantly, both del13q14 and trisomy 12 are nowadays associated with a favourable/intermediate prognosis and considered early CLL-founding events, since they are usually present in most tumour cells [4,24]. In contrast, other common chromosomal defects such as del11q22-q23 (disrupting *ATM* and/or *BIRC3*) and del17p13 (disrupting *TP53*) are initially subclonal events that expand over time as a function of their proliferative advantage or environmental pressures (e.g. therapy), and confer an adverse prognosis [24]. Although the genes located in these regions (*ATM*, *TP53* and *BIRC3*) are frequently inactivated by deletions, in about a third of cases they are inactivated by either point mutations but also by mutations or copy number neutral loss of heterozygosity [25–27]. Novel candidate CLL driver genes recently identified in regions of copy number alterations (CNA) as