Secondary genomic alterations in non-Hodgkin's lymphomas: tumor-specific profiles with impact on clinical behavior

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Lymphoid neoplasms are a very heterogeneous group of tumors with different biological characteristics and clinical evolutions. Current knowledge about these neoplasms has increased dramatically thanks to multidisciplinary research integrating data from morphological and phenotypic studies to molecular and genetic approaches. The heterogeneity in these neoplasms is due in part to the diversity of the cell populations of the immune system that give rise to these tumors and the complexity of the mechanisms involved in their pathogenesis. One of the most powerful methods for revealing the great complexity of these tumors is the analysis of their genetic alterations, which has allowed the definition of specific entities and provides the basis for the identification of target genes involved in the initiation and progression of the tumors. In the current issue three articles investigate the profile of genetic alterations in small B-cell lymphomas,[1] mantle cell lymphomas (MCL)[2] and diffuse large B-cell lymphomas (DLBCL)[3] providing new insights on the relevance of these changes in the clinical and biological behavior of these neoplasms.

Genetic alterations in lymphomagenesis

Certain genetic alterations are considered the primary aberration essential for the initiation of the tumors. This primary event is followed by increased genomic instability that generates secondary chromosomal abnormalities which are selected for their role in facilitating the survival and progression of the tumor cells. The most well-known primary genetic mechanisms are specific chromosomal translocations that are associated with particular types of non-Hodgkin's lymphomas (NHL). Usually, these translocations result in the activation of an oncogene involved in proliferation, cell differentiation, cell survival or cell signaling pathways. The better prognosis of the tumors in which these translocations are the sole aberration and their occasional detection in healthy people support the hypothesis that additional secondary alterations are needed for the progression of the lymphoma. The spectrum of these secondary genetic alterations is complex and includes a wide variety of overrepresentations, losses and rearrangements of different chromosomal regions that may harbor important target genes for the biological behavior of the tumor. Interestingly, the large amount of data generated in the last years on the genomic aberrations of these neoplasms suggests that, as for the primary events, the profile of secondary alterations may be relatively specific to each type of lymphoma.

Primary genetic alterations: chromosomal translocations

The most common recurrent primary alterations in B-cell neoplasms are non-random reciprocal translocations involving the immunoglobulin (*IG*) loci. B cells are particularly susceptible to DNA damage because of the remodeling events that take place in their *IG* genes during the VDJ recombination in the bone marrow and the somatic hypermutation and class switch recombination processes in the follicular germinal centers. Three of these paradigmatic translocations are the t(8;14)(q24;q32), t(11;14)(q13;q32), and t(14;18)(q32;q21) that deregulate the expression of *MYC*, *CCND1*, and *BCL2* and are found in virtually all cases of Burkitt's lymphoma (BL), MCL, and follicular lymphoma (FL), respectively. These target genes may also be translocated to the *IG* light chains kappa (2p12) and lambda (22q11.1) loci instead of the heavy chain (14q32). Mucosa-associated lymphoid tissue (MALT) lymphomas are genetically characterized by the presence of the t(11;18)(q21;q21) in 20-40% of the tumors, depending on the site of origin, and the less common t(1;14)(p22;q32), t(3;14)(p13;q32), and t(14;18)(q32;q21). Notably, three of these translocations target two genes (*MALT1* at 18q21 and *BCL10* at 1p22) involved in the same pathway of NF-κB activation triggered by B-cell receptor signaling. Unlike the previous lymphomas, DLBCL comprise a heterogeneous group of neoplasms associated with different *IG* translocations involving *BCL6* (3q27), *MYC* (8q24), and *BCL2* (18q21), which may occur individually or associated in the so-called *double hit* lymphomas. These translocations may occur as sole genetic alterations or in the context of more complex karyotypes.

Secondary genetic alterations: chromosomal imbalances

Besides the above mentioned primary chromosomal translocations, the study of the genetic alterations in most lymphoid neoplasms at diagnosis reveals characteristic patterns of genetic instability in terms of copy number gains/amplifications, losses and different rearrangements. In most types of lymphomas an increased number of secondary alterations has been associated with the patients' prognosis and, therefore, these secondary events seem to influence the evolution of the tumor. Secondary genetic alterations were initially identified by conventional cytogenetics. However, during the past decade many studies have used comparative genomic hybridization (CGH) which only requires genomic DNA from the tumor samples and enables an easy and reliable characterization of

chromosomal imbalances allowing the delineation of minimal altered regions. Bacterial artificial chromosome (BAC) and oligonucleotide arrays, introduced more recently, provide a higher resolution of these alterations.

The results obtained with conventional CGH in different studies can be easily compared because the technique is more standardized than the array platforms in which the targets and level of resolution are highly variable among studies. A review of the literature and our own data reveals distinctive patterns of secondary chromosomal alterations in different types of lymphomas (Table 1). Secondary alterations can be classified into three types: i) those that are highly characteristic of single entities; ii) alterations shared by only two types of lymphoma; and iii) common alterations in most of the tumors with different incidences and usually associated with disease progression.

Most of the lymphomas studied show alterations in ~70-90% of the cases (Figure 1). Chronic lymphocytic leukemia (CLL) is the neoplasm with the lowest number of altered cases (63%) and the lowest mean number of imbalances per case (2.5). At the other end of the spectrum, MCL show the highest number of altered cases (93%) and one of the highest numbers of alterations per case (mean: 5). Moreover, the aggressive blastoid variants of MCL carry highly altered genomes (mean alterations per case: > 10). Notably, MCL show imbalances with a frequency above 15% in 12 of the 16 (75%) regions analyzed (Table 1).

According to the frequency and distribution of these secondary alterations, B-NHL can be divided into two groups (Figure 1). One branch comprises all types of DLBCL and FL that cluster together with the germinal center B-cell (GCB) subtype of DLBCL. Activated B-cell (ABC) DLBCL shows the highest number of alterations per case. The other main branch of the cluster contains the rest of B-NHL with MCL and CLL being more closely related. These two types of lymphoma have high frequencies of 13q and 11q21-q23 losses. Despite their different biological behaviors, MCL and CLL do

Table 1. Secondary alterations in B-cell non-Hodgkin's lymphoma: frequency of gains and losses detected by comparative genomic hybridization.

	GAINS (%)							
	1q+	*2p+*	*3q+**	*7p+**	*8q+**	*9p+*	*12q+**	*18q+**
CLL	0	0	0	0	0	0	65	0
MCL	0	0	70	27	32	0	30	26
FL	10	10	10	21	0	0	18	29
SMZL	11	0	31	0	0	0	18	11
ABC DLBCL	12	15	33	10	10	0	0	34
GCB DLBCL	10	17	0	15	11	0	33	10
PMBCL	0	47	16	0	11	56	0	16
BL	43	0	0	0	0	0	26	0
MM	45	0	40	0	0	0	0	0
	LOSSES (%)							
	1p-	*6q-**	*7q-*	*8p-**	*9p-**	*11q-*	*13q-**	*17p-**
CLL	0	0	0	0	0	24	65	32
MCL	33	37	0	33	30	36	63	30
FL	25	21	0	0	0	0	0	15
SMZL	0	10	16	0	0	0	0	10
ABC DLBCL	0	40	0	10	0	0	0	18
GCB DLBCL	0	22	0	0	0	0	0	0
PMBL	0	0	0	16	0	0	0	0
BL	0	0	0	0	0	0	17	0
MM	0	13	0	10	0	0	39	0

*For simplification only chromosomal arms are indicated. Minimal altered regions and alterations with a frequency <10% are omitted. *Common secondary alterations. An extensive literature review of CGH alterations for each disease was performed and is available in the Online Supplementary Appendix.*

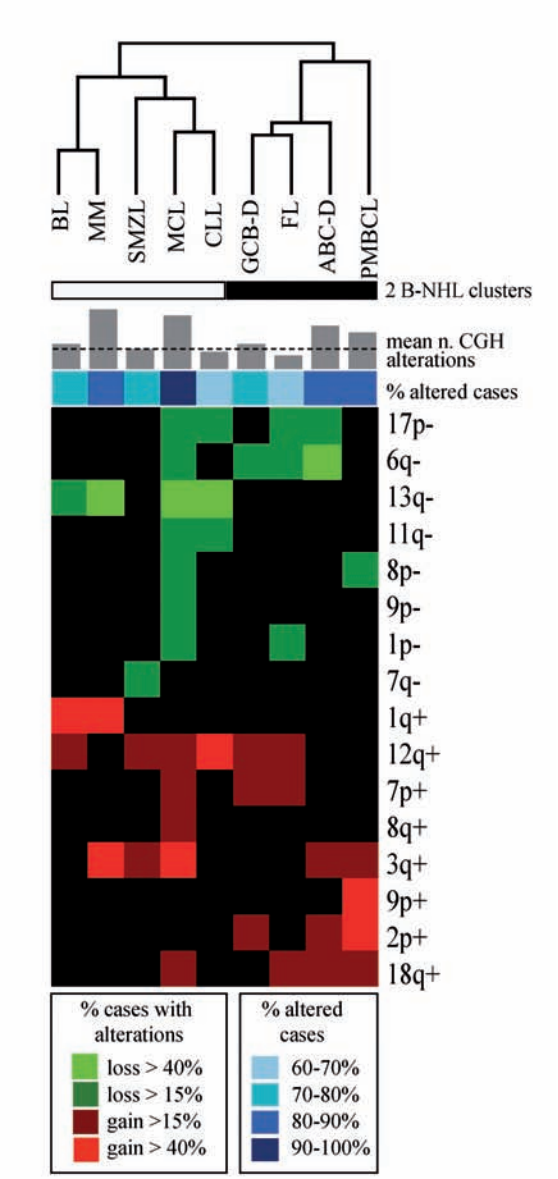

Figure 1. Hierarchical unsupervised clustering analysis of secondary genomic alterations in B-cell non-Hodgkin's lymphoma detected by comparative genomic hybridization. The analysis was performed with 16 frequent lost and overrepresented chromosomal regions. Losses and gains detected in >15% of the cases are represented in green and red, respectively, and in bright green and bright red when the alteration was detected in >40% of the cases. Increased percentages of altered cases, detected by CGH, are indicated by increasing intensities of blue color. The mean number of CGH alterations per case was plotted and a mean of three alterations/case is represented by a discontinuous horizontal line. The two different clusters of B-NHL are underlined with white and black bars. ABC-D and GCB-D indicate activated B-cell and germinal center B-cell DLBCL, respectively.

have several similarities in their chromosomal profiles. However, the distribution of the genetic alterations in CLL seems to be related to the mutational status of the *IGH* gene whereas this association has not been clearly observed in MCL. Thus, 13q14 loss, particularly as a sole abnormality, is more frequently found in CLL with mutated *VH* genes and is related to a better outcome, whereas 11q and 17p losses are found in *VH* unmutated cases and are associated with a poor prognosis.[4] In MCL 17p deletions are associated with a poor prognosis whereas, in contrast to CLL, 11q losses do not predict outcome and neither of the two alterations seems to be related to the mutational status of the *VH* genes.[5]

Secondary chromosomal alterations associated with specific lymphomas

Two common alterations closely related to specific lymphomas are 7q losses and 9p gains observed in splenic marginal zone lymphoma (SMZL) and primary mediastinal B-cell lymphomas (PMBCL), respectively. Loss of 7q is detected in 16% of SMZL by CGH but this incidence increases to >40% of cases when the minimal common deleted region at 7q23-q32 detected by molecular techniques is considered. Recent proposed targets include *miR-29b-1* and *miR-29a*, whose regulated gene seems to be *TCL1A*, frequently overexpressed in SMZL.[6] Gains of 9p are found almost exclusively in PMBCL with an incidence of 56%, as detected by conventional CGH, and up to 70% by array-CGH. The minimal region does not always include *JAK2*, the initially proposed candidate gene.[7] PMBCL are also characterized by frequent gains/amplifications of 2p14-p16 including *RELA* and *BCL11A* genes in 47% of cases. Small subsets of DLBCL and FL also show this alteration although at lower frequencies (10-17%). Finally, a highly specific alteration in FL is 10q23-q24 loss. Although the frequency of this alteration as detected by conventional CGH, is less than 10% and ~13% by array-CGH,[1] no other lymphoma type seems to carry this alteration.

Secondary alterations characteristic of two types of lymphoma

The best example of a common secondary alteration frequently detected almost exclusively in two types of lymphoid neoplasm with an identical overlapping region is 11q21-q23 loss in CLL and MCL. It is not, however, clear that the target gene of this region is the same in both entities. *ATM* is included in this region and seems the target in MCL. 11q losses are detected in 36% of MCL and virtually all cases carry an inactivating mutation in the remaining allele of the *ATM* gene.[8,9] In contrast, 11q21-q23 losses are observed in 24% of CLL but only ~36% of these cases carry *ATM* mutations. Only *ATM* biallelic defects in CLL are related to defective responses to cytotoxic chemotherapy and poor overall survival.[10]

Some alterations targeting the same chromosomal arm but with only partial or non-overlapping regions are also seen in some lymphomas. For example, chromosome 1q gains are detected in nearly half of all cases of multiple myeloma (MM) and BL. However, the whole chromosome arm tends to be gained in MM whereas in BL the minimal gained region is restricted to 1q23. The putative target genes are still unknown. Similarly, 1p losses are relatively frequent events in MCL (1p21-p31) and FL (1p35-p36), but there is no common region of overlap, suggesting that distinct pathogenetic mechanisms and genes are involved.

Common secondary alterations

Several chromosomal imbalances are commonly found in different NHL and some of them are considered 'high risk alterations' because they are associated with clinical progression of the disease. These regions may contain genes that confer growth advantages or the possibility of escaping apoptosis or cell cycle arrest triggered by the accumulation of increasing genomic instability. In some of these regions several tumor suppressor genes have been identified, such as the *TP53* gene in 17p13, *CDKN2A* and *CDKN2B* in 9p21, and *RB* in 13q14.

Interestingly, the high frequency of 13q losses in CLL and MCL (65% and 63%, respectively) can usually be delimited to the 13q14 cytoband. The potential target gene remains elusive, although a recent study using microarray profiling coupled with copy number analysis in a large cohort of CLL patients identified a complex and heterogeneous pattern of 13q14 homozygous and heterozygous deletions that include together or alternatively *miR15a*, *miR16* and *RB* in association with deregulation of genes not included in the deleted areas such as *LATS2* and *PHLPP*.[11] Chromosome 13q losses may have additional complexity since they are not restricted to the centromeric region (13q14) in MCL in which a high frequency of 13q33-qter losses is also observed.

Losses of 6q are also complex. They are found in most types of B-NHL and at least four minimal regions have been delimited. Interestingly, a minimal deleted region at 6q21 includes the *PRDM1/BLIMP1* gene, which is an important regulator of B-cell differentiation into plasma cells. Biallelic inactivation of this gene by deletions and mutations has been reported in 24% of ABC-DLBCL. In addition, in a subset of cases without 6q deletion the gene is inactivated by epigenetic mechanisms.[12]

Chromosome 8p losses are recurrently detected in MCL, but also less frequently in other types of lymphomas. The target gene in this region is still unknown. Similarly, common secondary gains of 3q, 7p, 8q, 12q, and 18q are found in more than 30% of MCL, but are also detected in other NHL. The minimal regions vary in different lymphomas. Some putative target genes have been suggested (*MYC*, *CDK4*, *MDM2*, *BCL2*) following studies using BAC-array and expression arrays.

Clinical significance of chromosomal alterations

An increased number of chromosomal alterations is usually associated with poor prognosis in most of the lymphomas examined. In addition, some common secondary alterations such as abnormalities in chromosomes 1, 6, 9, and 17, are also associated with a poor clinical outcome, suggesting that they include genes

that are crucial for tumor progression. The most frequent abnormality associated with poor overall survival, progressive disease, high risk of relapse, or drug resistance in most B-NHL is 17p loss, usually coupled with a mutation of *TP53*. In SMZL the only known adverse prognostic factor is the loss or mutation of this gene.[13] However, the relationship between 17p deletions, *TP53* mutations and poor prognosis has not been consistently found in other lymphomas. These conflicting results may be due in part to the existence of other target genes in the lost 17p region. Alternatively, it may be that not all *TP53* mutations are associated with the same prognostic value. Thus, in DLBCL *TP53* mutations in the DNA-binding coding regions are more highly associated with poor prognosis than mutations in other segments of the gene.[14] Besides 17p and *TP53*, other secondary alterations are associated with prognosis in different types of NHL but the target genes of these regions are not well known. Loss of 11q is an adverse prognostic indicator in CLL whereas 13q14 losses are associated with better outcome.[4] In MM, 1p, 1q, and chromosome 13 abnormalities are strongly associated with poor outcome.[15] In FL the loss of 6q25-q27 is the strongest predictor of short survival, even in multivariate analysis including all clinical risk factors.[16] In MCL gains of 3q and losses of 8p, 9p, usually targeting biallelic *CDKN2A* deletion, 9q and 13q14 were associated with a poor clinical outcome in at least two different studies each.[2,17-20] Interestingly, 3q gains and 9q losses have prognostic value independently of proliferation, which is considered the strongest prognostic parameter in these lymphomas.[20] Finally, 18q21 gains/amplification, including *BCL2* and *MALT1*, are associated with shorter survival and high risk of relapse in DLBCL.[3,21]

New insights into secondary chromosomal alterations in B-NHL

The present issue of the journal offers three interesting papers on secondary chromosomal alterations in large series of B-NHL investigated by fluorescence *in situ* hybridization (FISH) and/or array-CGH. Ferreira *et al.*[1] describe various lymphoma-specific and common alterations in different low grade B-cell lymphomas detected by array-CGH. Their results are concordant with previous findings from metaphase CGH studies but they expand the information by including tumors for which there is very limited information such as nodal marginal zone lymphomas and lymphoplasmacytic lymphomas. The increased resolution of the array-CGH also allowed a more precise delimitation of the boundaries of the minimal altered regions. Their results confirmed MCL as the most altered type of small B-cell lymphoma, whereas CLL, SMZL and nodal marginal zone lymphoma were the least altered tumors. The increased resolution of the array-CGH enabled the detection of ten independent lost regions in 6q. Finally, from examining the genes included in the common altered regions they concluded that these common chromosomal alterations target genes and pathways that are relevant for B-cell lymphomagenesis (NF-κB pathway, Polycomb group family, DNA repair checkpoint pathways, and miRNA).

The article by Sander *et al.*[2] describes the incidence of 16 alterations detected by FISH in a large series of MCL. Their findings correlate well with results from previous CGH and array-CGH studies but they also detected alterations that were present only in subclones of the tumor. Furthermore, they studied the impact of cytogenetic abnormalities on survival and found that loss of 13q14 was associated with a poor prognosis, whereas a trend was observed for the loss of 9p21. The association between 13q14 loss and short survival in MCL contrasts with the situation in CLL in which 13q14 losses are overrepresented in cases with a better prognosis,[4] suggesting that although 13q14 losses are frequent in both CLL and MCL, the target genes and pathogenetic mechanisms in the two lymphomas are different.

Finally, the study by Dierlamm *et al.*[3] delimited the minimal region of 18q gain/amplification in DLBCL including both *MALT1* and *BCL2* genes, although *MALT1* but not *BCL2* overrepresentation was detected in one case. 18q gain/amplification was associated with the ABC subtype of DLBCL and an unfavorable prognosis. These findings and our previous results in an independent large series of DLBCL[22] suggest that the 18q21 alteration may play an important role in the progression of DLBCL. Although the findings in the present study would favor *MALT1* over *BCL2* as the potential target gene, the common overrepresentation of both genes and their involvement in cell survival pathways suggest that both may contribute to the more aggressive behavior of the tumors. A recent study by Ngo *et al.*, using loss-of-function RNA interference screening, showed that *CARD11*, an upstream element of *MALT1* in the NF-κB activation pathway after B-cell receptor signaling, is essential for the survival of ABC but not GCB DLBCL cells.[23] Further evidence for *CARD11* being an oncogenic mechanism in DLBCL is the recent finding of activating mutations in its coiled-coil domain in a subset of ABC-DLBCL cases (~10%). These mutations result in constitutive NF-κB activation in the absence of antigen-receptor signals.[24] These results and the common *MALT1* amplification and overexpression present in ABC-DLBCL strongly support the pivotal role of the activation of the *CARD11/MALT1/NF-κB* pathway in DLBCL, particularly in the ABC subtype.

Concluding remarks

The review of the literature that we have presented and the three articles published in the current issue of the journal highlight the importance of secondary chromosomal alterations in NHL. These genomic abnormalities do not occur randomly and their profiles seem relatively tumor-specific. The close relationship of some of these alterations and the outcome of the patients suggest that they target genes important for the progression of the tumors. Some of these genetic alterations with prognostic significance are tumor-specific but others are detected across all types of lymphomas suggesting that they probably involve common pathogenetic pathways. A better understanding of these

alterations and the potential genes targeted by them may improve our diagnostic ability and provide new pathogenetic information for the design of innovative therapeutic strategies.

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