inhibited by DMF was the NF-kB-regulated proto-oncogene Bcl3. Bcl3 is highly expressed in CTCL cells, where it has a prosurvival and immunosuppressive function. Therefore, the findings of Nicolay et al indicate that the DMF-mediated Bcl3 suppression potentiates the DMF-mediated NF-kB inhibition, thus enhancing the DMF-induced cell death in CTCL cells.

To study the impact of DMF in vivo, the authors then developed 2 CTCL xenograft mouse models with different cutaneous localizations of the T-cell infiltrate, and showed that both oral and parenteral DMF treatment reduces the tumor growth. The oral effectiveness of DMF underlines the clinical relevance of this study as DMF has been used only as an oral, but not as a parenteral, medication. In addition, DMF prevented the CTCL tumor spreading to distant organs, and enhanced cell death in primary tumors as well as in distant metastases, leaving the surrounding tissues widely unaffected. None of the mice experienced severe side effects by the DMF treatment; this underscores the excellent tolerability of the drug due to the high specificity of the DMF-induced cell death on malignant T cells.

Can DMF become the new therapeutic option in CTCL? DMF restores apoptosis in CTCL cells by inhibiting the constitutive activity of NF-kB, while having a minimum effect on healthy T cells. In the xenograft mouse models, the DMF-induced apoptosis of CTCL cells does not only inhibit tumor growth, but also prevents tumor spreading from skin to distant organs. This is highly important, as containment of CTCL cells in the skin is associated with a more favorable prognosis. The oral effectiveness of DMF may be quickly translated into oral CTCL treatment. These features of DMF render it a promising drug with few side effects; DMF may be better tolerated than most established CTCL treatment regimens. Altogether, the findings by Nicolay et al strongly suggest a prompt evaluation of DMF treatment in CTCL patients in a clinical trial.

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Comment on Hunter et al, page 827

WM, MYD88, and CXCR4: following the thread

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In this issue of Blood, Hunter et al describe how different genotypes cause different phenotypes and clinical features in Waldenström macroglobulinemia (WM). For a long time, WM has been diagnosed without the benefit of using specific genetic abnormalities to make the diagnosis. As is the case with other B-cell lymphoproliferative disorders (LPDs) with many abnormalities within a disease category, the association was not strong enough to support a specific diagnosis. Thus, although WM is typically associated with del(6q21) or del(13q14), their frequencies are well below 100%, at 40% and 10%, respectively (lack of sensitivity), and the abnormalities are also present in other B-cell LPDs (lack of specificity). This landscape was revolutionized <5 years ago, when the Dana-Farber Cancer Institute group published their results on whole-genome sequencing in 30 cases of WM. In that study, the myeloid differentiation primary response 88 (MYD88) L265P mutation was seen in 90% of cases, a finding that they and other groups were soon able to reproduce in larger series of patients. This result and the very low frequencies reported for the commonest B-cell LPDs have converted the MYD88 L265P mutation into a very useful tool for the diagnosis of WM.

The second most frequently mutated gene in WM is CXCR4, which occurs at a frequency of ~30% of cases, two-thirds of which are C1013G, and is almost exclusively present in MYD88-mutated WM. Mutations of this gene, which are known to play a key role in cell adhesion to bone marrow (BM) stroma, are thought to cause WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) disease. In WM, somatic mutations of CXCR4 are associated with activating and pro-survival signaling of tumor cells, as well as the possible acquisition of resistance to several drugs, including Bruton tyrosine kinase (BTK) inhibitors.

These observations, together with several clinical findings, portray a WM landscape in which various genomic subgroups exist:
MYD88\textsuperscript{WT}, MYD88\textsubscript{L265P}/CXCR4\textsuperscript{WHIM} and MYD88\textsubscript{L265P}/CXCR4\textsuperscript{WT} (see figure).\textsuperscript{1,4} The most important factor supporting this initial genomic subclassification of WM is the differential response to BTK.\textsuperscript{7} However, the biologic reasons for the genetic translation into different clinical and treatment response subgroups are still unclear because the intermediate steps between the genomic abnormalities and the final phenotypes have yet to be identified.

In this issue, Hunter et al report their results of next-generation transcriptional profiling (“RNAseq”) in 57 patients with WM, and compare their results to those from B cells from normal controls. Accordingly, global transcription profiles and those associated with mutated MYD88, CXCR4, ARID1A abnormal cytogenetic, including 6q-, and familial WM are described and compared with those from normal B cells and the genomic WM counterpart. Some results are related to the B-cell origin of WM cells, such as the upregulation of VDJ recombination-related genes and the lack of expression of the class-switch recombination gene AICDA, which may explain why WM cells cannot undergo immunoglobulin class switching. The lack of similarity between WM and normal memory B cells raises the possibility of a different cell of origin of the WM cell than previously thought.\textsuperscript{8} However, it could also reflect the heterogeneity that is increasingly being discovered in the memory B-cell compartment.\textsuperscript{9} Furthermore, the expression of genes related to B-cell differentiation suggests that MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT} can be derived from a cell in early stages of B-cell differentiation, which implies that MYD88 unmutated cases should be considered as having a disorder that is distinct from conventional WM. Interestingly, CXCR4 was overexpressed in all cases, irrespective of the CXCR4 mutation, which may explain why no substantive differences have been observed between the outcomes of mutated and WT CXCR4 cases.

The study also discovered separate transcriptional profiles for MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT}, MYD88\textsubscript{L265P}/CXCR4\textsuperscript{WHIM}, and MYD88\textsubscript{L265P}/CXCR4\textsuperscript{WT} cases, which highlights the pivotal role for MYD88 and CXCR4 signaling in WM. First, MYD88\textsuperscript{WT} patients had much more heterogeneous RNA expression and differential RNA expression in >1000 genes than in MYD88\textsubscript{L265P} cases. These differences included the downregulation of the NF-\kappaB pathway, which could account for changes in treatment sensitivity.\textsuperscript{5} Once again, this distinction is evidence that the MYD88\textsuperscript{WT} WM could be considered as a distinct entity. Second, CXCR4\textsuperscript{WHIM} mutations were responsible not only for the normalization of TLR4 signaling, driven by the presence of the MYD88\textsubscript{L265P} mutation, but also for the alternative activation of the TLR7 pathway. Likewise, CXCR4\textsuperscript{WHIM} cases were associated with the normalization of many tumor suppressors that are overexpressed in response to the MYD88\textsubscript{L265P} mutation. Together, these differences help explain the diversity of WM described in previous studies. However, the article goes even further than this in revealing the existence of additional transcriptome variations associated with other genetic abnormalities, such as ARID1A mutations, 6q deletions, and familial genetic predisposition. This discovery reinforces the idea that WM is a heterogeneous disorder, just as (it is becoming increasingly clear) all neoplastic disorders.

In summary, WM can be divided into 3 genetic subgroups (MYD88\textsuperscript{WT}, MYD88\textsubscript{L265P}/CXCR4\textsuperscript{WHIM}, and MYD88\textsubscript{L265P}/CXCR4\textsuperscript{WT}) in which the genetic lesions initiate a cascade of downstream consequences that explain the final 3 clinical phenotypes, and probably justify different therapeutic approaches. The latter will require well-designed clinical trials accompanied by basic and translational research projects (likely requiring international cooperation to ensure sufficient patients and resources) to provide a definitive answer. The path toward personalized therapy is coming to WM.

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Comment on Grisouard et al, page 839

Somatic JAK2 mutations and their tumor phenotypes

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In this issue of Blood, Grisouard et al use transgenic mice to describe the phenotype associated with the human polycythemia vera (PV)-associated JAK2 exon 12 mutation (JAK2-N542-E543del) and demonstrate Stat1-independent erythroid-only proliferation.1

Activating JAK2 mutations can arise from chromosomal translocations or point mutations/deletions/insertions. The former result in JAK2 fusion proteins that always involve the JAK2 kinase domain (JH1), in association with an oligomerization domain from one of several partner proteins, which promotes constitutive JAK2 phosphorylation and signal activation. Tumor phenotypes associated with JAK2 fusion proteins include both myeloid and lymphoid neoplasms with a certain degree of phenotypic specificity (see figure):2 ETV6-JAK2 [t(9;12)(p24;p13)] has been associated with T or B acute lymphoblastic leukemia (T-ALL or B-ALL; and STRN3-JAK2 [t(9;14)(p24;q12)] with B-ALL; and SEGC11A-JAK2 [t(4;9)(q21p24)] with HL. B-ALL has also been associated with JAK2 point mutations/deletions/insertions, involving the JH2 pseudokinase domain; these include a JAK2 exon 14 mutation (L611S) reported in a single case of B-ALL1 and recurrent JAK2 exon 16 mutations seen in 18% of patients with DS-associated B-ALL.4 The latter always affect the arginine 683 residue (eg, R683G, R683S, and K539L, and R541-E543delinsK).9 These mutations also involve the JH2 pseudokinase domain adjacent to its border with the JH3 domain, spanning residues 536 to 547. Compared with PV patients with JAK2V617F, those with JAK2 exon 12 mutations were younger and displayed higher hemoglobin levels, primarily erythroid proliferation, absence of bone marrow tri-lineage hyperplasia, and lower incidence of leukocytosis or thrombocytosis; however, survival and rate of disease complications were reported to be similarly affected by the 2 mutation variants.9

The abovementioned specificity of JAK2 exon 12 mutations to PV and, in particular, to the erythrocytosis phenotype, has been recapitulated in animal models. In their original description,3 Scott et al used JAK2K539L retroirval mouse models and induced marked erythrocytosis, which was more pronounced than was seen in JAK2V617F mice; in contrast, although leukocytosis accompanied the erythrocytosis phenotype in both instances, its degree was significantly higher in JAK2V617F mice. The approach taken by Grisouard et al used JAK2-N542-E543del transgenic mice and generated an even more erythroid-specific phenotype, without leukocytosis, thrombocytosis, or myelofibrosis. Multiple factors might have contributed to the overlapping but apparently distinct phenotypes observed between the JAK2K539L and JAK2-N542-E543del mice, including the different strategies of genetic engineering applied in constructing the animal

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