LYMPHOID NEOPLASIA

Comment on Knittel et al, page 2732

Mouse model of MYD88<sup>L265P</sup>-dependent DLBCL

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In this issue of Blood, Knittel et al report on the expression of MYD88<sup>L265P</sup> in B lymphocytes of mice prone to neoplasms that resemble human diffuse large B-cell lymphoma (DLBCL).<sup>1</sup>

The frequent detection of a highly recurrent, oncogenic, gain-of-function mutation that substitutes a leucine (L) residue at position 265 of the adapter protein myeloid differentiation primary response gene 88 (MYD88) with a proline (P) residue has implicated the mutant MYD88<sup>L265P</sup> allele in the natural history and clinical outcome of an important subset of diffuse DLBCL. However, a genetically engineered mouse model (GEMM) for in-depth mechanistic studies on the role of MYD88<sup>L265P</sup> in the biology and genetics of DLBCL has been lacking. In their article, Knittel and his associates<sup>1</sup> remedy this shortcoming by recapitulating the MYD88<sup>L265P</sup> mutation in B lymphocytes of transgenic mice that go on to develop DLBCL-like neoplasms.

DLBCL, the most common non-Hodgkin lymphoma in the United States, has 2 major subtypes, as defined by distinct gene expression programs that correspond to different putative cells of origin: a germinal center B cell in the case of GCB-DLBCL and a plasmablast (activated B cell) in the case of ABC-DLBCL.<sup>2</sup> Combination chemotherapy results in ~80% 3-year survival for patients with GCB-DLBCL, but achieves only 45% survival for patients with ABC-DLBCL. Thus, ABC-DLBCL patients have an unmet medical need that warrants additional research efforts and new therapeutic options.

A well-established hallmark of ABC-DLBCL is the constitutive activation of the classical NF-κB pathway. In ~40% of patients, this is accomplished by somatic (acquired) mutations in MYD88, an adapter protein of crucial importance for cellular signal transduction pathways that govern pattern recognition, inflammation, innate and adaptive immune responses and, importantly, malignant cell transformation. MYD88 links upstream members of the Toll-like receptor and interleukin-1 receptor superfamily (see figure) with downstream effector hubs that regulate, in addition to NF-κB, Janus kinase signal transducer and activator of transcription (JAK-STAT), mitogen-activated protein kinases (MAPKs), and type-I interferon (IFN) binding to the IFN-α/β receptor signaling in ABC-DLBCL and other cells.

Evidence indicates that the L265P substitution is the most common and most oncogenic representative of a variety of mutations that occur in MYD88 in ABC-DLBCL. Moreover, the L265P exchange is of predictive value for these patients because it is associated with extranodal tumor dissemination and poor clinical outcome.<sup>3</sup> Subsequent to its discovery in ABC-DLBCL,<sup>4</sup> the MYD88<sup>L265P</sup> mutation has also been found in the great majority of patients with Waldenström macroglobulinemia (nearly 100%)<sup>5,6</sup> and a fraction of patients with primary central nervous system lymphoma (~35%), splenic marginal zone lymphoma (~15%), gastric mucosa-associated lymphoid tissue lymphoma (~9%), and chronic lymphocytic leukemia (~3%). These findings demonstrated that MYD88<sup>L265P</sup> is by no means specific for ABC-DLBCL; instead, it is broadly involved in the natural history of a large subset of mature B-lineage neoplasms.

Fully appreciating that lymphoma modeling in transgenic mice enables fundamental and translational studies that are difficult to pursue in humans, Knittel et al<sup>1</sup> used an elegant genetic engineering tool to express the orthologous mouse allele of human MYD88<sup>L265P</sup>, MyD88<sup>L252P</sup>, in laboratory mice. This was accomplished by Cre recombinase-induced activation of an MYD88<sup>L252P</sup> knockin gene inserted into the germline Myd88 locus using homologous recombination (gene targeting) in embryonic stem cells. The investigators took advantage of three different Cre drivers (AID, CD19, and CD22) to express MYD88<sup>L265P</sup> in different B-cell populations. Regardless, transgenic mice from all experimental groups developed lymphoma that shared important features with human ABC-DLBCL. Practical limitations relating to tumor incidence (low) and tumor onset (long) were readily overcome by co-expression of the Myc oncogene. Thus, Knittel et al achieved, for the first time, a GEMM of MYD88<sup>L265P</sup>-driven ABC-DLBCL.

Another advance reported by Knittel et al<sup>1</sup> concerns the collaboration of MYD88<sup>L265P</sup> and deregulated expression of B-cell leukemia
2 (BCL2) in lymphoma development. BCL2 is a survival-enhancing oncoprotein that is frequently overexpressed in ABC-DLBCL by virtue of gene amplification (focal copy number gains) at 18q. The investigators cleverly recapitulated this aspect of the ABC-DLBCL genetic network by combining the MYD88L265P allele with a newly developed inducible BCL2 allele in double-transgenic mice that developed tumors resembling human ABC-DLBCL with full penetrance (100% tumor incidence). Knittel et al propose to use these tumors as a heretofore unavailable model system of actionable BCL2 addiction that lends itself to preclinical co-trials of the BCL2 inhibitors venetoclax (ABT-199) and navitoclax (ABT-263) and the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, which synergizes with BCL2 inhibition in killing ABC-DLBCL cells.

In summary, Knittel et al produced a mouse model of MYD88L265P-driven ABC-DLBCL that should facilitate efforts to design and test new approaches to treat this difficult-to-cure lymphoma. These may include small-molecule IRAK4 and TAK1 inhibitors currently in the preclinical drug pipeline or combination therapies that target BCL2, MAPK, or JAK-STAT in addition to MYD88-NF-kB signaling. Be this as it may, the newly developed MYD88L265P transgene will also be of value for developing GEMMs for human B-cell tumors (eg, Waldenström macroglobulinemia) for which such models are still lacking.

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MYELOID NEOPLASIA

Comment on Wang et al, page 2742

Cytogenetics in CML: more important than you think

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In this issue of Blood, Wang et al describe that 2 groups of additional chromosomal abnormalities (ACAs) beyond the Philadelphia chromosome (Ph) impact prognosis in chronic myelogenous leukemia (CML) patients treated with tyrosine kinase inhibitors (TKIs). At diagnosis, 10% to 12% of patients with chronic phase (CP) CML have chromosomal changes besides the Ph. Among these changes, variant translocations have usually not been considered detrimental to the prognosis of the patients. The other ACAs that have been observed in a minority of patients (5%) have been subdivided into major and minor routes. The major route ACAs, such as trisomy 8, a second Ph, isochromosome 17q or trisomy 19 have been associated with a negative impact on survival. Minor route ACAs have not been investigated to the same extent as major ACAs. Six minor route changes, including five numerical abnormalities (–7, –17, +17, +21, and –Y) and also one structural aberration t(3;21)(q26;q22), were initially described by Mitelman. The classification proposed by Mitelman was based only on the frequency of ACAs. A number of studies have been published on the relationship between ACAs and outcome, and it is clear that the situation remains unclear.

In a large group of patients in the German CML Study IV, 3.6% of patients had a major route ACA at diagnosis. After a median observation period of 5.3 years, for patients with minor and major routes, the 5-year progression-free survival (PFS) was 96% and 50%, and the 5-year overall survival (OS) was 96% and 53%, respectively. In this trial exploring the value of different doses of imatinib and the combination of imatinib with interferon or cytarabine, the times to complete cytogenetic response (CCyR) and to major molecular response (MMR) were longer in patients with major route ACAs. A similar study was conducted by the Italian GIMEMA Working Party on CML. Based on 559 patients enrolled into 3 different trials exploring 2 imatinib dosages (400 mg and 800 mg for different subgroups of patients according to Sokal score), ACAs at diagnosis were associated with worse outcome. In patients with major route ACAs, rates of CCyR and MMR were significantly inferior to those with only Ph translocation, and time to achieve CCyR and MMR were significantly longer. In contrast to the results of the German study, the Italian group did not observe differences between ACA patients and those without, when PFS and OS were considered. However, the current recommendation by the European Leukemia Net is to consider a major route ACA as a warning signal in patients treated frontline with TKI. The detection of ACAs has been considered a feature of the accelerated phase (AP). But the World Health Organization includes ACAs as a feature of the AP only if they are not present at diagnosis (ie, as evidence of clonal evolution).

In the current study, Wang et al revisited the relationship between ACAs detected in
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