2 (BCL2) in lymphoma development. BCL2 is a survival-enhancing oncprotein 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.8

In summary, Knittel et al1 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 currently in the preclinical drug pipeline small-molecule IRAK4 and TAK1 inhibitors.

In summary, Knittel et al1 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 currently in the preclinical drug pipeline small-molecule IRAK4 and TAK1 inhibitors.

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Ph^+ cells of patients with CML and their outcome in the TKI era. The issue with the previous studies was that the heterogeneous group of minor route ACAs was not fully investigated. For example, the 3q26 rearrangement, a minor route ACA, is actually associated with TKI resistance and poor prognosis. More complex trisomy 8, a major route ACA, is considered a good prognostic ACA when occurring alone, whereas it is detrimental when associated with other chromosomal changes at initial diagnosis. Thus, the main objective, which is quite new, was to propose a revised classification of ACAs. In this paper, a large group of 608 CML cases treated with TKI had bone marrow (BM) biopsy with conventional G banding cytogenetic analysis at baseline and at 3–12 month intervals thereafter. Overall, patients with emergence of 2 or more ACAs simultaneously had a worse survival. When single, the 6 more frequently detected ACAs were trisomy 8, –Y, extra Ph, i(17)(q10), –7/del(7q), and 3q26.2 rearrangements. Two groups of patients were identified: the first group included trisomy 8, –Y, and an extra Ph with a relatively good response and better survival; the second group included i(17)(q10), –7/del(7q), and 3q26.2 rearrangements with a relatively poor response and worse survival. Of note, patients with –Y showed no significant survival difference from patients who had no ACAs. The timing of ACA emergence was also evaluated. In group 1, trends to higher CCyR and MMR rates were observed in patients with ACAs at diagnosis compared with patients with ACAs arising during the CML course. In addition, trisomy 8 and an extra Ph (that are both major route) had no significant impact on survival when they developed during the CP (no other concurrent AP features). In this study, two minor route changes, not well characterized in prior studies, 3q26 rearrangement and –7/del(7q) are clearly identified as ACAs associated with a poorer prognosis. The prognostic significance of 3q26 abnormality has been already detailed. Ph^+ ACAs were not considered in this paper. Unlike Ph^+ ACAs, Ph^- ACAs do not affect outcomes except in rare cases of myelodysplastic syndrome-associated abnormalities, which are typically accompanied by cytopenia.

Thus, physicians caring for CML patients should understand that, although molecular testing is important, there is still a place for careful cytogenetic analysis (ie, the type, frequency, timing of emergence of ACAs, and the phase of the disease) of their CML patients. In cases with insufficient molecular response, ABL1 mutations should be considered and performed in parallel with BM cytogenetic analysis. A relationship between ACAs and the initial clinical scoring system (Sokal, Euro, Eutos, and ELTS) would be of interest. It would be extremely helpful if all CML working groups could collaborate in order to increase the value of subsequent studies, allowing a deeper analysis of all ACAs individually and also exploring their potential relationship. No doubt, a study based on thousands of CML cases treated with TKIs would be of immense value.

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Fibrin fixes fibrosis

Ton Lisman  UNIVERSITY OF GRONINGEN

In this issue of Blood, Joshi et al demonstrate that the interaction between fibrin and αMβ2 on leukocytes reduces the development of liver fibrosis in a mouse model of cholestatic injury.1

Importantly, administration of leukadherin-1, a small molecule that enhances the fibrin–αMβ2 interaction, reduces already established fibrosis, suggesting that this interaction is a promising therapeutic target.

Cholestatic liver diseases are a significant clinical challenge. They may adversely affect the quality of life due to pruritis and fatigue, for which limited treatment options are available. In addition, patients may develop cirrhosis with symptoms of portal hypertension, hepatic encephalopathy, and eventually liver failure. Despite advances in medical management, liver transplant is the only therapeutic option for patients with end-stage disease. Therapeutic interventions that would slow down disease progression would, therefore, be of interest.

There are, unfortunately, significant knowledge gaps that need to be filled before a fibrin-directed therapeutic intervention is ready for clinical trial. First, the fibrin–αMβ2 interaction reduces fibrosis in a model of cholestatic liver disease, but does not appear to affect fibrosis development in a model of noncholestatic disease. This selectivity may be explained by the observation that the fibrin–αMβ2 interaction reduces bile duct hyperplasia, a phenomenon exclusively observed in cholestatic liver disease. The
Cytogenetics in CML: more important than you think
Francois Guilhot