MNT in established, transplantable lymphoma cells significantly extended survival of recipient mice, resulting in a functional cure in 2 cases. Based on the critical role of MNT in both development and maintenance of lymphoma, the investigators propose that inhibition of MNT, perhaps with the help of nifty, targeted degradation approaches that are currently emerging,[6] provides a new strategy to treat and prevent MYC-driven B-lymphoma.

The discovery that MNT synergizes with MYC in B-lymphoma adds to a long list of accomplishments of Cory's group, which has been at the forefront of this field for decades. Beginning with the generation of EμMyc mice in the early 1980s[5] and the detection of BCL2's survival-enhancing activity shortly thereafter,[7] they were first to show that mutations that mitigate MYC's pro-apoptotic function collaborate very efficiently with deregulated MYC expression in neoplastic development. This early insight opened the door to a remarkable sequence of mechanistic and clinical studies carried out by Cory and others that culminated in 2016 in the US Food and Drug Administration approval of the BH3-mimetic BCL2 inhibitor, venetoclax, for treatment of chronic lymphocytic leukemia. The recognition of MNT's oncogenic role in B cells is also significant from a conceptual point of view because it provides an instructive example of a Janus-faced, dually functioning cancer gene that promotes or inhibits neoplastic growth depending on context. Indeed, in mouse models of T-cell lymphoma[8] and human blood cancers such as Sezary syndrome and chronic lymphocytic leukemia,[2] MNT appears to function as a tumor suppressor, just like in the great majority of solid cancers. To illustrate the latter point, MNT is deleted in as many as 10% of cases in The Cancer Genome Atlas dataset (n = 9000), which contains many tumors harboring amplified MYC (21%).[9] MNT's oncogenic function in B-cell lymphoma seems to be the exception to the rule, probably because the combined pro-apoptotic impact of deregulated MYC and loss of MNT overrides the individual tumor-promoting activity of these changes in B cells.

In summary, Nguyen et al demonstrated that MNT promotes MYC-driven B-cell tumors using a mechanism that relies in large measure on downregulation of BIM. The new finding furthers our understanding of MNT's dual function as oncoprotein or tumor suppressor, depending on context, and identifies MNT as a therapeutic target in MYC-dependent B-lineage tumors.

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MYELOID NEOPLASIA

Comment on Pangallo et al, page 1032

Are all splicing mutations the same?

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In this issue of *Blood*, Pangallo et al compare the changes in splicing outcome in patients with rare mutations in splicing factors *U2AF1* and *SRSF2* to the changes due to common hotspot mutations. Many of these rare mutations phenocopy the common ones, suggesting that they have been evolutionarily selected to alter splicing and drive pathogenicity by similar mechanisms.[1]

Mutations in splicing factors are among the most prevalent mutations in myelodysplastic syndromes (MDSs) and acute myeloid leukemia (AML).[2,3] There are as many as 300 proteins and 5 small RNAs associated with the spliceosome,[4] yet only a handful are mutated in myeloid malignancies. In particular, the bulk of splicing factor mutations are found in 3 factors: SF3B1, SRSF2, and U2AF1.[2,3] Additionally, within these factors, mutations are commonly found in hotspots resulting in changes to only 1 or 2 aa.

Initially, it was hypothesized that the splicing factor mutations would converge on common mechanisms to alter splicing and drive disease. Extensive molecular characterizations over the past several years revealed that splicing changes are factor specific.[5] For U2AF1, which has 2 major hotspot alterations, S34F and Q157R, the splicing changes were even mutation specific.[6] These findings suggest that not all mutations lead to the same outcome. Pangallo et al further explored this question by testing whether rare, nonhotspot mutations in SRSF2 and U2AF1 elicited the same or distinct splicing changes. They found that some mirrored hotspot changes, whereas others did not.

To explore the impact of rare mutations on splicing, Pangallo et al performed and

analyzed RNA-sequencing data on cells expressing wild-type, hotspot, or rare mutant versions of SRSF2 and U2AF1. As the rare mutations were sometimes only observed in single MDS/AML patients, in addition to profiling primary patient material, they also generated human K562 cell lines that expressed wild-type, hotspot, or rare mutant versions of the factors.

Comparison of SRSF2 mutants unveiled remarkable overlap with most rare and hotspot mutations clustering together in their splicing pattern. Moreover, rare SRSF2 mutants alter exonic enhancer specificity, as was shown for hotspot mutations both in vivo and using biochemistry,[7,8] suggesting similar splicing mechanisms. In contrast, comparison of U2AF1 containing rare and hotspot mutations showed more divergence. Some rare U2AF1 mutants alter 3′ splice-site sequence preference, as was shown for hotspot mutations,[6] whereas others did not.

In many ways, the results that hotspot and rare mutations are similar are not surprising. The patients who were sequenced were selected by disease state. Thus, this in effect represents a genetic screen performed in humans by nature, with selective pressure for a highly specific phenotype. The results are reminiscent of the outcomes from many decades of yeast genetic screens for phenotypic splicing outcomes performed in the laboratory. It would be expected that mutations in splicing factors found in patients, no matter their location within those factors, would have similar outcomes on splicing, if splicing has anything to do with the disease phenotype. However, this has not been entirely clear. Indeed, the results from Pangallo et al provide a more compelling argument that it does for some splicing factors.

Although the outcomes for all of the SRSF2 mutants cluster together and support the model described herein, the more heterogeneous patterns observed with the U2AF1 mutants indicate a more complex situation. There also are "silent" mutations in both factors that do not significantly change splicing at all. It is unclear whether the clinical features of the patients with "silent" mutations are similar to those that phenocopy. If similar, these "silent" mutations could support the involvement of a nonsplicing function in disease etiology, which has been proposed by other groups.[9,10]

The results also raise the question of why mutations in hotspots are more frequent than those in rare positions. The answer, although not known, must be genomic context, likely the local DNA sequence and chromatin environment, both of which may influence mutation and DNA repair rates.

There are many spliceosome-associated factors whose function in splicing is still murky. As the current results demonstrate that messenger RNA changes from factor-specific mutations are quite canonical, could splicing pattern analysis in MDS/AML be used to identify factors with similar functionality as the major disease-associated splicing factors?

Overall, the work from Pangallo et al suggests that nonhotspot mutations should be considered similarly to common mutations, both in their mechanism and potential treatment.

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Ofori-Acquah et al, page 1044

Heme A1M'ed at the kidney in sickle cell disease

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In this issue of *Blood*, Ofori-Acquah et al investigate hemolysis, hemopexin deficiency, and kidney function in sickle cell disease (SCD) and report that (1) acute elevations in heme lead to kidney damage in hemopexin-deficient states, and (2) a compensatory rise in α-1 microglobulin (A1M) relative to hemopexin concentration is associated with acute kidney injury.[1]

Acute kidney injury causes capillary loss, dysregulated apoptosis, and sustained proinflammatory and profibrotic signaling in animal models and leads to the subsequent development and progression of chronic kidney disease in the general population.[2] Acute kidney injury is observed in 5% to 17% of hospitalizations for vasoocclusive episodes in patients with SCD[3,4] and is associated with a 4.6-fold greater risk for chronic kidney disease progression.[4] The mechanisms for kidney injury are not well understood, and targeted therapies to prevent and ameliorate