Mutations in RNA Splicing Machinery in Human Cancers

Benjamin Ebert, M.D., Ph.D., and Olivier A. Bernard, Ph.D.

Massively parallel sequencing of cancer genomes is revealing a panoramic view of the genetic drivers of human neoplasms. In this issue of the Journal, Wang et al. describe an analysis of the coding sequences of samples from 91 patients with chronic lymphocytic leukemia. The disease is characterized by the accumulation of mature B lymphocytes, and its genetic basis is being rapidly elucidated.

Wang et al. leveraged the large number of samples studied to identify sets of genes that are critical to the development of chronic lymphocytic leukemia. By sequencing both the malignant lymphocytes (CD19+CD5+) and matched nonmalignant control DNA from each patient, the authors pinpointed mutations that occurred somatically. By identifying genes and pathways with recurrent mutations, they highlighted the developmental drivers of chronic lymphocytic leukemia. Finally, the authors elegantly integrated the mutation data with known biologic information to define five key pathways of chronic lymphocytic leukemia that are affected by mutation: DNA damage and cell-cycle control, Notch signaling, inflammatory pathways, Wnt signaling, and RNA splicing.

The identification of mutations in genes involved in RNA splicing was highly unexpected, but it converges remarkably with recently published studies making use of genome sequencing in myelodysplastic syndromes. SF3B1, which encodes a core member of the U2 small nuclear ribonucleoprotein (U2 snRNP) complex, was mutated in 15% of the 91 patients in the current study, primarily as a recurrent, heterozygous missense mutation, K700E. A separate study published recently in the Journal reported SF3B1 mutations in 20% of patients with myelodysplastic syndromes and 65% of patients with refractory anemia and ring sideroblasts. Moreover, mutations have been reported in multiple components of the spliceosome in 45 to 85% of patients with myelodysplastic syndrome. SF3B1 mutations also occur in 1 to 5% of samples from a wide range of tumor types, which indicates that mutations in RNA splicing factors are a widespread cause of oncogenic transformation.

The vast majority of human genes undergo RNA splicing after transcription, which means that mutations in the RNA splicing machinery could potentially alter the maturation of messenger RNA for most genes and the subsequent production of protein (Fig. 1). In addition, RNA splicing is linked to the epigenetic regulation of gene expression. In particular, SF3B1 has been reported to interact with the polycomb repressive complex, an important regulator of hematopoiesis. Genes encoding members of these complexes are mutated in hematologic cancers.

The finding of SF3B1 mutations in both chronic lymphocytic leukemia and myelodysplastic syndromes resonates with the recent finding of TET2 mutations in both lymphoid and myeloid cancers. These developments raise the provocative possibility that SF3B1 mutations might in some cases occur initially in hematopoietic stem cells, with additional mutations then being acquired in either the lymphoid or the myeloid lineages and causing chronic lymphocytic leukemia or myelodysplastic syndromes, respectively. Consistent with this hypothesis, stem cells from patients with chronic lymphocytic leukemia have recently been reported to be abnormally lymphoid-primed, a finding that suggests that chronic...
lymphocytic leukemia could also derive from a stem-cell defect.\(^8\)

The genetic characterization of chronic lymphocytic leukemia has the potential to refine the molecular classification and estimation of prognosis for this disease. Patterns of genetic lesions, such as the association of SF3B1 mutations with deletion in chromosome 11q and with ATM mutations, provide clues about the molecular circuitry of chronic lymphocytic leukemia cells. The identification of mutations in genes encoding the RNA splicing machinery raises the intriguing possibility that the spliceosome could be a therapeutic target for the treatment of chronic lymphocytic leukemia and myelodysplastic syndromes.\(^9,10\)

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Division of Hematology, Brigham and Women’s Hospital, Boston (B.E.); and INSERM, Unité 985, Institut Gustave Roussy, Villejuif, France (O.A.B.).

This article (10.1056/NEJMe1111584) was published on December 12, 2011, at NEJM.org.


Copyright © 2011 Massachusetts Medical Society.