GENETICS

Splicing the pieces of the chronic lymphocytic leukemia puzzle

B-cell chronic lymphocytic leukemia (CLL) is the most common type of leukemia and it is characterized by the accumulation of impaired mature B lymphocytes in the blood and bone marrow. Although it progresses slowly in many cases and these patients may have normal active lives for decades, substantial morbidity and mortality is still observed in approximately 50% of patients. As prognosis depends on the subtype of CLL, it is very important to characterize genetically each case and great efforts have been invested recently in elucidating the molecular mechanisms that drive this disease. Now, Catherine Wu and her collaborators have found five new genes adding more pieces to the genetic puzzle of CLL.

To identify sets of genes that are crucial in the development of CLL, the researchers used parallel sequencing and compared the DNA from both the malignant lymphocytes (CD19$^+$CD5$^+$) and matched normal tissue from 91 samples from patients with CLL. They identified nine genes with significant mutation frequencies, four of which (*TP53*, *ATM*, *MYD88*, and *NOTCH1*) had been described previously in CLL and five of which (*SF3B1*, *FBXW7*, *ZMYM3*, *DDX3X*, and *MAPK1)* had no established roles in this type of leukemia. Of these newly identified mutated genes, *SF3B1* —encoding for the subunit 1 of the splicing factor 3b, a core member of the U2 small nuclear ribonucleoprotein (U2 snRNP) complex—was mutated in 15% of patients. Because most human genes undergo RNA processing and splicing after transcription, the investigators examined whether mutations in *SF3B1* led to alterations in the splicing of transcripts derived from genes involved in cancer-related processes. "We found that leukemia cells from patients harboring mutations in *SF3B1* had increased intron retention compared to those without *SF3B1* mutations" says Wu. Moreover, Wu and colleagues described how some patients had several interacting mutations that resulted in either activation or inactivation of key pathways generally affected in CLL such as DNA damage and cell-cycle control (in which *TP53* and *ATM* have major roles), Notch signaling (*FBXW7* and *NOTCH1*), inflammatory pathways (*MYD88*, *DDX3X*, and *MAPK1*), and RNA splicing (*SF3B1* and *DDX3X*).

These newly identified patterns of genetic lesions provide insights into the molecular basis of CLL, and establish mutations in genes involved in the RNA splicing machinery as potential therapeutic targets for the treatment of CLL.

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Original article Wang, L. *et al*. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N. Engl. J. Med.* **365**, 2497–2506 (2011)