Taking it up a notch in MCL

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In this issue of Blood, Kridel et al describe recurrent NOTCH1 mutations in mantle cell lymphoma (MCL) by next-generation sequencing of patient samples and cell lines. They further demonstrate a negative prognostic impact of NOTCH1 mutation in their cohort of patients and sensitivity of MCL cells to NOTCH1 inhibition in vitro, suggesting a novel role for NOTCH1 in this disease.1

Mantle cell lymphoma accounts for 6% of non-Hodgkin lymphomas and remains a challenging clinical problem, with median survival of patients being approximately 4 to 5 years.2 Cyclin D1 overexpression is found in the majority of MCL, but additional genetic lesions are needed for lymphomagenesis and continue to be characterized.

Kridel et al apply a powerful shotgun sequencing approach to discover novel pathogenic lesions in MCL. Along with mutations in genes anticipated to be involved in MCL pathogenesis such as TP53, ATM, and Cyclin D1, they found an unexpected result: recurrent NOTCH1 mutations were seen in 12% of patients (14/121) and 20% of cell lines (2/10) studied.

The NOTCH1 gene encodes a transmembrane protein that functions as a ligand-activated transcription factor.3 The NOTCH1 protein is cleaved by γ-secretase inhibitors, allowing its active intracellular form to migrate to the nucleus and bind to cofactors, leading to transcription of downstream targets. Activating mutations in NOTCH1 have been best described in T-cell ALL4 and more recently in B-cell chronic lymphocytic leukemia.5 The majority of mutations found by Kridel and colleagues were in the PEST domain (see figure), which presumably lead to abnormally overactive NOTCH1 signaling because of impaired degradation of its active intracellular component.3

Furthermore, Kridel et al report an intriguing association between NOTCH1 mutation and shorter overall survival in MCL, suggesting a prognostic role for NOTCH1 in MCL. They go on to show that a subset of MCL cell lines may be sensitive to NOTCH1 inhibition, both by γ-secretase inhibition and transfection of a dominant negative NOTCH1 cofactor. Both these findings warrant further independent confirmation because of the heterogeneity of treatments in their patient cohort and the limited number of MCL cell lines in which NOTCH1 expression was linked to both mutation and sensitivity to its inhibition.
NOTCH1 is hypomethylated and over-expressed in primary MCL, but its role has not been explored in this disease. The findings of Kridel and colleagues demonstrate the power of next-generation sequencing to expand our understanding of tumor pathogenesis, and pave the way for future studies examining the prognostic and therapeutic implications for NOTCH1 signaling in MCL. Recent studies suggest that NOTCH1 mutations can have context-specific oncogenic or tumor-suppressor roles in human cancers, so the precise contribution of NOTCH1 mutations to the pathogenesis of MCL and other B-cell malignancies remains an interesting and open area for future investigation.

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Comment on Rücker et al, page 2114

Unveiling the complexity of CK+ AML

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In acute myeloid leukemia (AML), cytogenetic abnormalities are present in more than half of patients and these chromosomal alterations are critical factors that determine response to chemotherapy and survival.1,2 Historically, metaphase analysis has stratified AML patients into 1 of 3 cytogenetic categories (ie, favorable, intermediate, and adverse),3 although recently a new category (monosomal karyotype [MK]), associated with dismal prognosis, has been described.3,4 Unfortunately, the molecular mechanisms predisposing the genetic instability observed in patients with complex and monosomal karyotype have remained elusive.

TP53, the most commonly mutated tumor-suppressor gene in human cancers, is the master regulator of cell cycle, playing a major role in determining the fate of cells that contain damaged DNA. Upon DNA damage, the tumor protein p53 can delay cell-cycle progression, allowing cells to either repair their damaged DNA or initiate programmed cell death. In the absence of the normal activated p53 protein, either because of loss of tumor-suppressor function mutations and/or deletion of genetic material, cells containing damaged DNA can survive and proliferate, which contributes to malignant transformation. Although most TP53 missense mutations cause loss of p53-dependant tumor-suppression function, hotspot mutations located at 4 codons (175, 248, 249, and 273) may also acquire gain-of-function properties to promote tumorigenesis. In fact, these gain-of-function TP53 mutations have been associated with genetic instability, leading to recurrent interchromosomal translocation, and defective G2/M checkpoint inactivation of the Mre11/ATM-dependent DNA damage responses.5,6

In an attempt to better understand the molecular mechanisms associated with complex chromosomal rearrangements, Rücker et al, on behalf of the German–Austrian AML Study Group (AMLSG), determined the molecular and genomic profile of TP53 in a large group of AML patients with complex karyotype and the clinical and prognostic features associated with these alterations.7 Their findings suggest that abnormalities in TP53 are commonly found in AML with complex and monosomal karyotype and negatively impact the outcome of these patients, independent of other variables. Using a combined approach to detect both DNA copy number abnormalities as well as the mutational status of TP53, the authors established that nearly 70% of AML patients with a complex karyotype have a biallelic inactivation of TP53.8 AML patients with mono- or biallelic TP53 alterations were older, which is consistent with the higher frequency of complex and monosomal karyotypes in older patients.4 In addition, these patients presented with unique features, such as high degree of genetic complexity and correlation with specific genetic alterations, such as 5/5q- and concomitant −5/5q− and −7/7q−. Interestingly, although a positive correlation between cytogenetically defined MK+ AML and TP53 alteration was noted (> 85% of cases), a correlation could not be established when MK was determined using more sensitive methods (DNA copy loss array data). Clinically, abnormalities in TP53 were independently associated with chemoresistance, measured by lower complete remission rates and higher rates of refractory disease, and dismal median and 3-year overall survival rates that did not seem to be improved by allogeneic hematopoietic stem cell transplantation (alloHSCT); albeit the sample size was small.

The results presented by Rücker et al are extremely significant as they begin to unveil the molecular mechanisms of leukemogenesis in AML patients with complex karyotype. However, several questions remain in light of this report. First, what are the molecular leukemogenic mechanisms in the nearly 30% of AML patients with complex karyotype and lack of TP53 alterations? A recent report suggests that amplifications of the 1q chromosome region, which contains the potent p53 inhibitor MDM4, were identified in nearly 20% of patients with leukemic transformation after chronic-phase myeloproliferative neoplasms.8 As expected, these amplifications were always mutually exclusive from TP53 mutations. Thus, could other downstream (ATM) or upstream (MDM2) regulators of the p53-signaling pathway also be involved? These questions have not been fully explored to date. Next, could differences in the baseline clinical characteristics, chemosensitivity, and prognosis be uncovered in patients with hotspot mutations (codons 175, 248, 249, and 273) who also have gain-of-function properties? Finally, and likely most importantly, how can the dismal

References

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