be an early somatic event in radiation-driven breast transformation. *c-MYC* and *PVT1* are almost always amplified together in human tumors, and the *PVT1* long noncoding RNA was recently identified as a key regular of MYC-driven oncogenic transcriptional activity by augmenting protein stability[8] (see figure). There is also evidence that the *PVT1* promoter directly regulates *MYC* transcription, independent of long noncoding RNA expression.[9] Knockout of *PVT1* reduces MYC protein levels and attenuates tumorigenic potential of cells.[8] Other data also suggest a role for dysregulated MYC in radiation-induced breast transformation. Specifically, Best et al[5] identified a SNP in the *PRDM1* gene associated with radiogenic cancer risk (predominantly breast cancer) in pediatric Hodgkin lymphoma survivors. PRDM1 is a negative regulator of *c-MYC* transcription, but PRDM1 upregulation in response to ionizing radiation is attenuated in cells carrying the risk variant, leading to elevated *c-MYC* expression and acquisition of a pro-proliferative phenotype.[5] Collectively, these studies provide compelling evidence that dysregulated MYC is a common feature of radiogenic breast cancer during the early stages of transformation. As such, it is plausible that the *PVT1* SNP identified by Opstal-van Winden et al also operates via MYC to affect risk of radiogenic breast cancer, although additional work is required to determine functionality of the rs10505506 variant.

Pending independent validation, the data presented by Opstal-van Winden and others[5] could aid the development of personalized risk-adapted strategies for the clinical management of Hodgkin lymphoma patients, including alternative treatments and posttherapy surveillance for therapy-induced breast cancer. Such approaches could prove important in pediatric and young adult Hodgkin lymphoma patients where the risk of radiogenic breast cancer is particularly high and associated with premature death.

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REFERENCES

1. Opstal-van Winden AWJ, de Haan HG, Hauptmann M, et al. Genetic susceptibility to radiation-induced breast cancer after Hodgkin lymphoma. *Blood*. 2019;133(10):1130-1139.
2. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst*. 2005;97(19):1428-1437.
3. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol*. 2007;25(12):1489-1497.
4. Fung C, Bhatia S, Allan JM, Oeffinger KC, Ng A, Travis LB. Second cancers. In: Devita VT, Hellman S, Rosenberg SA, eds. Cancer: Principle and Practice in Oncology. 11th ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2018.
5. Best T, Li D, Skol AD, et al. Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. *Nat Med*. 2011;17(8):941-943.
6. Wade MA, Sunter NJ, Fordham SE, et al. c-MYC is a radiosensitive locus in human breast cells. *Oncogene*. 2015;34(38):4985-4994.
7. Wade MA, May FE, Onel K, Allan JM. Does radiation-induced c-MYC amplification initiate breast oncogenesis? *Mol Cell Oncol*. 2015;3(1):e1010950.
8. Tseng YY, Moriarity BS, Gong W, et al. PVT1 dependence in cancer with MYC copy-number increase. *Nature*. 2014;512(7512):82-86.
9. Cho SW, Xu J, Sun R, et al. Promoter of lncRNA gene PVT1 is a tumor-suppressor DNA boundary element. *Cell*. 2018;173(6):1398-1412.e22.

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MYELOID NEOPLASIA

Comment on Christen et al, page 1140

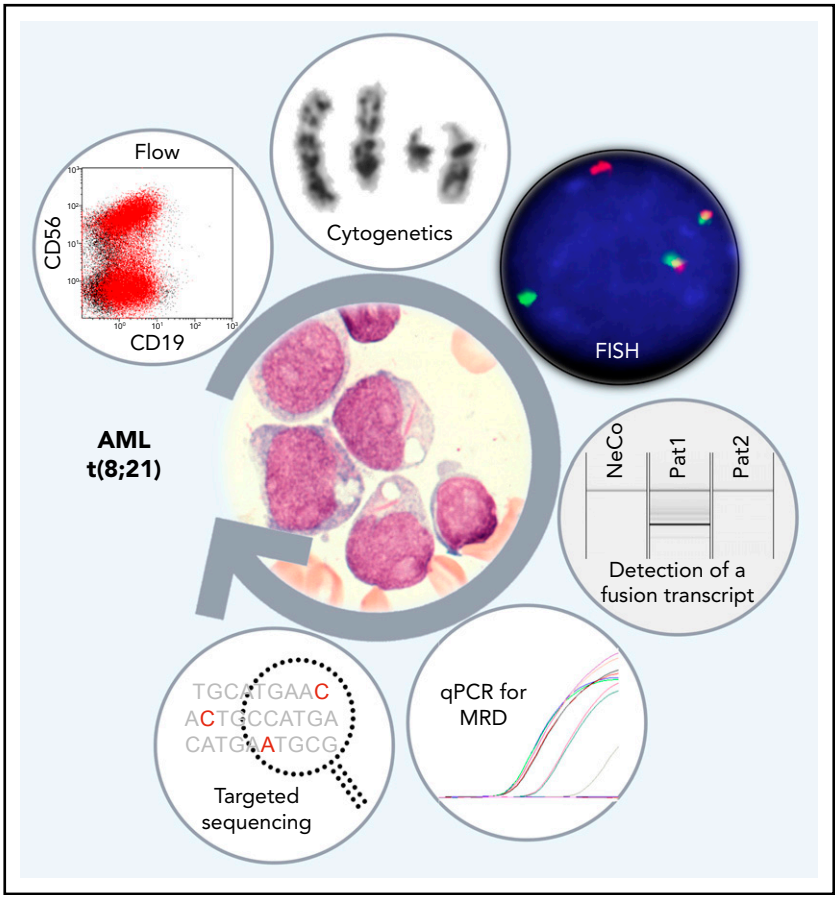
More than a fusion gene: the *RUNX1-RUNX1T1* AML

Torsten Haferlach and Manja Meggendorfer | MLL Munich Leukemia Laboratory

In this issue of *Blood*, Christen et al investigated the largest cohort to date of 331 patients with acute myeloid leukemia (AML) and t(8;21).[1]

These patients have AML with specific morphologic features such as dysplasia in granulopoiesis (90% of patients) and eosinophilia and are mostly classified as AML with maturation (90%; formally called French-American-British [FAB] M2) or AML without maturation (10%; formally called FAB M1).[2] This subtype of AML is also diagnosed by immunophenotyping that shows the coexpression of CD19 or PAX5 and CD56. The cytogenetics show a typical pattern of loss of the sex chromosome and del9q. These characteristics resulted in *RUNX1-RUNX1T1*–mutated AML being designated as a separate World Health Organization (WHO) entity within the category of AML with recurrent genetic abnormalities. The diagnosis is made irrespective of bone marrow blast cell counts.[3] *RUNX1-RUNX1T1*–mutated AML also demonstrates secondary cooperating mutations in *KIT*, *KRAS* or *NRAS*, and *ASXL1* as well as in *ASXL2*.[4,5] *RUNX1-RUNX1T1* was one of the first fusion genes to be used for minimal residual disease (MRD) monitoring.[6] Based on these diagnostic definitions, the best clinical practice to follow after standard chemotherapy needed to be determined, including the meaningfulness of allogeneic transplantation in first complete molecular remission (CMR).[7,8]

Today, large sequencing studies including exome sequencing or whole-genome sequencing (WES) are possible. In their article, Christen et al provide a comprehensive characterization of this specific WHO entity in 331 patients based on a screening that included 66 recurrently mutated genes. They found that 95% of patients had at least 1 additional mutation, with a mean of 2.2 driver mutations per patient. Recurrently mutated genes affecting the RAS/RTE signaling pathway were present in nearly two-thirds of patients and other epigenetic regulators in nearly half the patients. Several previously unexpected genes were found to be mutated. Data using deep sequencing (45 000×) in 62 samples from patients in complete remission demonstrated persistent mutations in 12 samples, including 5 patients who were quantitative polymerase chain reaction–negative for *RUNX1-RUNX1T1* at the time of the analysis. In multivariate analysis, *JAK2*, *FLT3*-ITD^{high}, and *KIT*^{high} were identified as significant negative prognostic factors. Furthermore, it was demonstrated that one-third of patients



The figure illustrates the diagnostic methods in AML with t(8;21) in clockwise direction. Diagnostic workup includes morphology (center panel) and flow cytometry, as well as cytogenetics and fluorescence in situ hybridization (FISH). Polymerase chain reaction–based assays allow specific detection of fusion transcripts. MRD monitoring with highly sensitive assays (eg, quantitative polymerase chain reaction [qPCR]) are standard. With the increasing knowledge of additional gene mutations and the genetically unstable behavior of this disease during follow-up and relapse, a comprehensive molecular screening (targeted sequencing) will become important.

studied by WES both at diagnosis and at relapse were genetically unstable and did not fully reproduce the genetic landscape of the diagnostic sample at relapse.

Therefore, this comprehensive study clearly demonstrates that patients with AML and t(8;21) at diagnosis should, according to WHO gold standards, be studied by morphology, immunophenotyping, and cytogenetics. In addition, a molecular genetic screening at diagnosis not only for *RUNX1-RUNX1T1* but also for a gene panel seems to be warranted. Furthermore, findings at relapse may have implications for prognosis and especially any targeted treatment. This may be of particular importance for patients in CMR for *RUNX1-RUNX1T1* but with secondary mutations still detectable in low levels (see figure).

Because the capacity for panel sequencing and WES will increase rapidly worldwide over the next few years,[9] AML with *RUNX1-RUNX1T1* should be comprehensively investigated at diagnosis, during follow-up for MRD monitoring, and at relapse to individualize treatments, including targeted approaches toward driver genes. Genetics at relapse can hold additional important information. This study definitively sets the stage.

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REFERENCES

1. Christen F, Hoyer K, Yoshida K, et al. Genomic landscape and clonal evolution of acute myeloid leukemia with t(8;21): an international study on 331 patients. *Blood*. 2019;133(10):1140-1151.

2. Haferlach T, Bennett JM, Löffler H, et al; AML Cooperative Group and ECOG. Acute myeloid leukemia with translocation (8;21). Cytomorphology, dysplasia and prognostic factors in 41 cases. *Leuk Lymphoma*. 1996;23(3-4):227-234.

3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.

4. Krauth MT, Eder C, Alpermann T, et al. High number of additional genetic lesions in acute myeloid leukemia with t(8;21)/RUNX1-RUNX1T1: frequency and impact on clinical outcome. *Leukemia*. 2014;28(7):1449-1458.

5. Micol JB, Duployez N, Boissel N, et al. Frequent ASXL2 mutations in acute myeloid leukemia patients with t(8;21)/RUNX1-RUNX1T1 chromosomal translocations. *Blood*. 2014; 124(9):1445-1449.

6. Yin JA, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. *Blood*. 2012;120(14): 2826-2835.

7. Zhu HH, Zhang XH, Qin YZ, et al. MRD-directed risk stratification treatment may improve outcomes of t(8;21) AML in the first complete remission: results from the AML05 multicenter trial. *Blood*. 2013;121(20): 4056-4062.

8. Höllein A, Jeromin S, Meggendorfer M, et al. Minimal residual disease (MRD) monitoring and mutational landscape in AML with RUNX1-RUNX1T1: a study on 134 patients. *Leukemia*. 2018;32(10):2270-2274.

9. Stephens ZD, Lee SY, Faghri F, et al. Big data: Astronomical or genomical? *PLoS Biol*. 2015; 13(7):e1002195.

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Torsten Haferlach and Manja Meggendorfer

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