Genomics of core-binding factor AML

Nicolas Duployez

Lille University Hospital and INSERM UMR-S 1172, France

RUNX1 and *CBFB* encode subunits of the core binding factor (CBF), a heterodimeric transcription factor required for the establishment of definitive hematopoiesis. Acute myeloid leukemia (AML) with t(8;21)/*RUNX1-RUNX1T1* fusion and AML with inv(16)/*CBFB-MYH11* fusion, reported together as CBF AML, account for approximately 25% of pediatric and 15% of adult de novo AML patients. Since the first description of t(8;21) and inv(16) AML in 1973 and 1983 respectively, a great deal has been learned about the molecular consequences of both rearrangements. Experience from murine models as well as clinical observations have demonstrated that the CBF disruption alone is insufficient to induce AML. CBF AML is largely considered as a model of multistep leukemogenes is requiring additional genetic aberrations.

Recently, our group reported the comprehensive genetic profiling in CBF AML patients enrolled in the French trials ELAM02 (0-18 years) and CBF2006 (18-60 years) using both high-throughput sequencing and single nucleotide polymorphism-array[1,2]. We demonstrated that mutations in genes activating kinase signaling were frequent in both subtypes, as previously described by others. Co-occurrence of multiples signaling lesions in independent subclones, named clonal interference, was frequent and conveyed inferior event-free survival[3]. By contrast, we found mutations in genes encoding chromatin modifiers or members of the cohesin complex with high frequencies in t(8;21) AML (41% and 18% respectively) while they were nearly absent in inv(16) AML[1]. Interestingly, such mutations were associated with a higher cumulative incidence of relapse in patients with signaling mutations suggesting synergic cooperation between these events. Other events included *ZBTB7A* and *DHX15* mutations in t(8;21) AML (20% and 6% respectively), *FOXP1* deletions or truncating mutations in inv(16) AML (7%) and *CCDC26* disruption as a possible new lesion associated with aberrant TK signaling in this particular subtype of leukemia (4.5% of CBF AML)[2]. Overall, these findings suggest important pathways that distinguish t(8;21) AML from inv(16) AML leukemogenesis with potential biological and clinical significance[4].

1. Duployez N, Marceau-Renaut A, Boissel N, et al. Comprehensive mutational profiling of core binding factor acute myeloid leukemia. Blood 2016;127(20):2451–2459.
2. Duployez N, Boudry-Labis E, Roumier C, et al. SNP-array lesions in core binding factor acute myeloid leukemia. Oncotarget 2018;9(5):6478–6489.
3. Itzykson R, Duployez N, Fasan A, et al. Clonal interference of signaling mutations holds prognostic relevance in core binding factor acute myeloid leukemia. Blood 2018;blood-2018-03-837781.
4. Kuykendall A, Duployez N, Boissel N, Lancet JE, Welch JS. Acute Myeloid Leukemia: The Good, the Bad, and the Ugly. Am Soc Clin Oncol Educ Book 2018;(38):555–573.