

JAK2V617F mutations as cooperative genetic lesions in t(8;21)-positive acute myeloid leukemia

Significant progress has been made in identifying genetic lesions that are causally implicated in the pathogenesis of acute myeloid leukemia (AML). These insights improve our understanding of the genetic basis of the disease, a prerequisite for the development of novel therapeutic approaches.

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Based on the broad spectrum of mutations identified a model comprising two complementation groups has been proposed: mutations that activate signal transduction pathways, resulting in enhanced proliferation and/or survival of hematopoietic progenitors and mutations affecting transcription factors or components of the transcriptional coactivation complex, resulting in impaired hematopoietic differentiation and/or aberrant acquisition of self-renewal properties by hematopoietic progenitors.¹

Studies using murine models demonstrated that the fusion genes *RUNX1-CBFA2T1* or *CBFB-MYH11*, resulting from the translocation t(8;21) or inv(16)/t(16;16) respectively, are not sufficient to cause AML. Instead, they are characterized by a differentiation block without developing of the leukemic phenotype, whereas constitutively activated signaling molecules such as *FLT3*, *KIT* or *RAS* family members induce a myeloproliferative disease.¹

Recently, Schessl *et al.* showed that *RUNX1-CBFA2T1* and the *FLT3* internal tandem duplication (ITD) mutation collaborate in inducing acute leukemia in a murine bone marrow transplantation model.² Moreover, they identified additional *FLT3* (ITD), *KIT* and *NRAS* mutations in 28% of 135 t(8;21)-positive leukemias supporting the concept of oncogenic co-operation between *RUNX1-CBFA2T1* and activating gene mutations.

These findings prompted us to screen³ a large series of t(8;21) (n=64) or inv(16)/t(16;16)-positive AML (n=99) for the presence of the activating JAK2V617F mutation that has recently been discovered as a single-site, clon-

al, gain-of-function mutation in myeloid cells from the majority of patients with chronic myeloproliferative disorders.⁴ Heterozygous JAK2V617F mutations were identified in 4 (6%) of t(8;21) AML whereas none of the inv(16)/t(16;16)-positive cases showed sequence variations at codon 617. Interestingly, two of the four mutated leukemias revealed additional gain-of-function mutations in the genes encoding for *FLT3* and *NRAS* (Table 1).

To date, analysis of AML patients has shown that the JAK2V617F mutation is not a common event in the pathogenesis of AML and predominantly occurs in patients with a preceding myeloproliferative disorder.⁵⁻⁷ However, these studies did not include a significant number of t(8;21) or inv(16)/t(16;16)-positive leukemias. In our analysis, JAK2V617F mutations were identified in 6% of t(8;21)-positive AML; in analogy to other activating gene mutations that have been described within this subgroup of AML, these findings sustain the model of co-operating gene mutations.

However, the pathogenic role of JAK2V617F mutations in t(8;21) AML has not been determined yet and it is unclear whether a single or several gene mutations contribute to a specific phenotype. The four mutated leukemias in our series had no distinct biological or clinical features compared to the unmutated t(8;21) group. Nevertheless, conclusive results on the prognostic impact of such additional gene mutations need to be obtained by meta-analysis since the number of patients in single prospective AML trials is too low. Since the *JAK2* tyrosine kinase represents a potential target for pharmacologic inhibition, mutation screening might be of therapeutic importance in the future.

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Table 1. *FLT3* [ITD and TKD (D835)], *NRAS*, *KRAS* and *KIT* mutation status in JAK2V617F-mutated t(8;21) AML.

Patient no.	<i>FLT3</i>		<i>NRAS</i>		<i>KRAS</i>			<i>KIT</i>		
	ITD	D835	exon1	exon2	exon1	exon2	exon8	exon10	exon11	exon17
HO-446	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt
98A-40	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	poly/wt	wt/wt	wt/wt
98A-418	ITD/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt	wt/wt
98A-931	wt/wt	wt/wt	G12S	wt/wt	wt/wt	wt/wt	wt/wt	poly/poly	wt/wt	wt/wt

wt: wild-type sequence; ITD: internal tandem duplication; D835: tyrosine kinase domain mutations at D835; poly: polymorphism 1642A→C.

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