Chapter 9

Role of Genetic Analysis in New Treatments of Acute Myeloid Leukemia

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Abstract

Genetics has an important role in the risk stratification and management of the patients with acute myeloid leukemia (AML). Molecular testing can't take the place of cytogenetic testing results, but has complementary role to help refine prognosis of the disease, especially within specific AML subgroups. Molecular genetic analysis of CEBPA, NPM1, and FLT3 is already the standard of care in AML patients, and mutations in several additional genes are assuming increasing importance. The French-American-British (FAB) classification and the World Health Organization (WHO) classification are the most classifications for AML. The aim of this chapter is a review on the role of genetic analysis in new treatments of AML.

Keywords: acute myeloid leukemia, genetics, mutation, classification, treatment

1. Introduction

Acute myeloid leukemia is the most common acute leukemia in adults and highly heterogeneous disease, characterized by gene mutations, chromosome abnormalities, changes in expression of multiple genes, and microRNAs [1]. In 2008, World Health Organization (WHO) categorized acute myeloid leukemia into four groups; AML with genetic abnormalities, AML with myelodysplasia, treatment-dependent AML, and AML not categorized. In the first group, prognosis depends on cytogenetic findings, so patients with acute myeloid leukemia were divided into different prognostic groups. For example, the translocations t(8;21), t (15;17), and inv(16) indicate a favorable prognosis, whereas 11q23 abnormalities indicate intermediate or worse prognosis. In the last group, 40–50% of AML cases were included, and

Type	Name	Cytogenetics	Percentage of adults with AML (%)
M0	Acute myeloblastic leukemia, minimally differentiated		5 [3]
M1	Acute myeloblastic leukemia, without maturation		15 [3]
M2	Acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(q22;q22), t(6;9)	25 [3]
M3	Promyelocytic, or acute promyelocytic leukemia (APL)	t(15;17)	10 [3]
M4	Acute myelomonocytic leukemia	inv (16)(p13q22), del(16q)	20 [3]
M4eo	Myelomonocytic together with bone marrow eosinophilia	inv (16), t(16;16)	5 [3]
M5	Acute monoblastic leukemia (M5a) or acute monocytic leukemia (M5b)	del (11q), t(9;11), t(11;19)	10 [3]
M6	Acute erythroid leukemia, including erythroleukemia (M6a) and very rare pure erythroid leukemia (M6b)		5 [3]
M7	Acute megakaryoblastic leukemia	t(1;22)	5 [3]

Table 1. French-American-British (FAB) classification of acute myeloid leukemia (AML).

no chromosomal abnormalities were detected by conventional karyotyping. Almost these patients located into the intermediate prognostic group [2]. The French-American-British (FAB) classification system divides AML into eight subtypes, M0 through to M7, based on the morphological and cysto-chemical characteristics of the leukemic cells as shown in **Table 1**. This is done by examining the appearance of the malignant cells with light microscopy and/or by using cytogenetics to characterize any underlying chromosomal abnormalities [4]. In AML, somatic genetic changes are often thought to contribute to leukemogenesis through a "two-hit" process: (1) mutations that activate signal transduction pathways and thereby increase the proliferation or survival, or both, of hematopoietic progenitor cells (class I; Mutations in KIT, FLT3, and N-RAS) and (2) mutations that affect transcription factors or components of the cell-cycle machinery and cause impaired differentiation (class II; RUNX1, CBFβ, CEBPA, NPM1, PU1, MLL, and RARA) [5]. Genes that were significantly mutated in AML were organized into several functional categories (**Figure 1**) [6]. The purpose of AML genetic testing and classification at diagnosis is mainly to risk-stratify patients with AML, and thus determine proper treatment modalities.

2. Class I mutations

2.1. KIT mutations

KIT is a member of the type III RTK family, encodes a receptor tyrosine kinase and ligand-independent activation of KIT. KIT mutations are detected mostly in association with core binding factor (CBF) AML, and correlated with t(8;21), inv (16), and t(16;16) [7, 8].

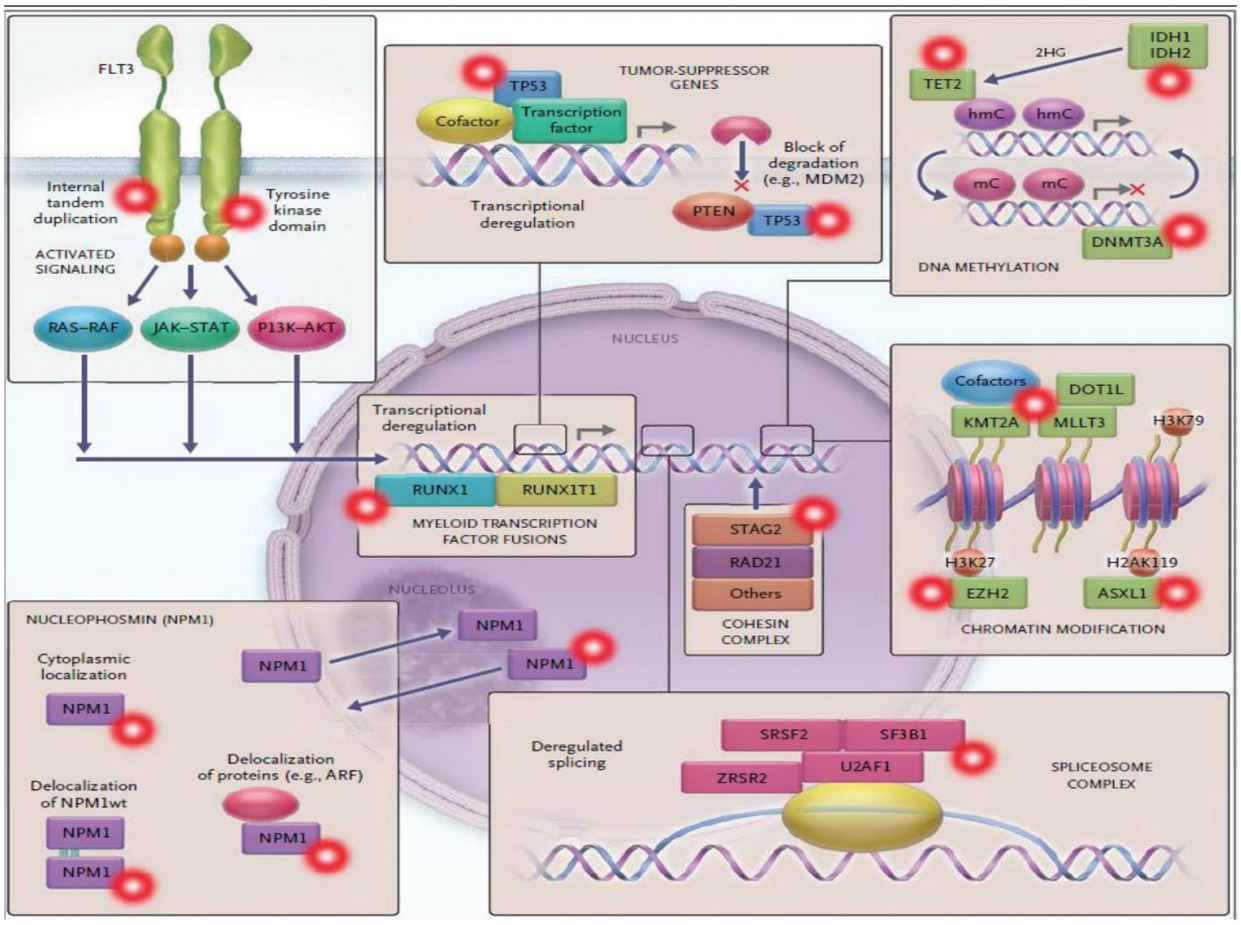

Figure 1. Acute myeloid leukemia and commonly mutated genes. Upper-left box shows mutations in *FLT3* signaling that confer a proliferative through the RAS–RAF, PI3K–AKT, and JAK–STAT signaling pathways. Upper-middle box shows *TP53* mutations, can lead to deregulation of transcription and impaired degradation through the phosphatase and tensin homolog (PTEN) and the mouse double minute 2 (MDM2) homolog. Upper-right box shows *DNMT3A* and *TET2* mutations, also *IDH1* and *IDH2* mutations, can lead to the deregulation of DNA methylation. Center-right box shows mutations of *ASXL1* and *EZH2* genes, cause deregulation of chromatin modification, also *KMT2A-MLLT3* gene fusion, can impair other methyltransferases such as DOT1L. In center-right box shows *RUNX1* and *RUNX1-RUNX1T1* mutations, result in reduced hematopoietic differentiation and transcriptional deregulation. Center-middle box shows mutations in the *RAD21* and *STAG2*, might impair accurate chromosome segregation and transcriptional regulation. Lower-right box shows mutations of *U2AF1*, *ZRSR2*, *SF3B1*, *SRSF2* are involved in deregulated RNA processing. Lower-left box shows *NPM1* gene mutations, resulting in the aberrant cytoplasmic localization of NPM1 and NPM1-interacting proteins.

2.2. FLT3 mutations

Fms-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase involved in proliferation, cell survival, and differentiation of hematopoietic progenitor stem cells. FLT3 mutations are one of the most common genetic changes in AML that occur in about 30% of these cases and confer a poor prognosis [9, 10]. Internal tandem duplications (ITD) mutations in the juxtamembrane (JM) domain and missense point mutations in the second tyrosine kinase domain (TKD) of the FLT3 gene are the molecular abnormalities that have been found in 20% of all AML patients [11].

2.3. RAS mutations

Mutations in N-RAS and K-RAS occur in AML as well as solid Tumors in about 10 and 5% of AML patients, respectively [12].

3. Class II mutations

In addition to class I mutations, in AML patients, mutations in brain and acute leukemia gene (BAAL), MLL-MLLT3 gene fusion created by the t(9;11)(p22;q23) translocation is associated with intermediate prognosis in AML, nucleoplasmin 1(NPM1), CCAAT/enhancer-binding protein α (CEBPα), and Wilms tumor gene (WT-1) have also been detected. Lately, mutations in DNMT3A, encode DNA methyltransferases that catalyze the addition of a methyl group to the cytosine residue of CpG dinucleotides, have been recognized in one-third of de novo AML patients with intermediate-risk cytogenetics. Genomes with DNMT3A mutations commonly harbored extra mutations in NPM1, IDH1, and FLT3. The incidence of any DNMT3A mutation, alone or in combination with FLT3 ITD mutation, is related with lower overall survival (OS) [12, 13].

4. Molecule analysis of mutations in AML

The single most important prognostic factor in AML is cytogenetic testing of bone marrow samples. Results are highly predictive of response to induction chemotherapy, relapse risk, and overall survival (OS). Approximately 50–60% of newly diagnosed AML patients can be detected by cytogenetic abnormalities [14]. To recognize cytogenetic abnormalities,

Risk	Cytogenetics	Molecular
Favorable	inv (16) or t(16;16) t(8;21) t(15;17)	Normal cytogenetics with: Isolated biallelic *CEBPA* mutation *NPM1* mutation without *FLT3* ITD
Intermediate	Normal cytogenetics Isolated +8 t(9;11) Other non-good and non-poor changes	*KIT* mutation in core binding factor leukemia: inv (16) or t(16;16) t(8;21)
Poor	Complex (≥3 clonal abnormalities) Monosomal karyotype −5/−5q or − 7/−7q 11q23 rearrangements other than t(9;11) inv (3) or t(3;3) t(6;9) t(9;22)	Normal cytogenetics with: *FLT3* ITD

Table 2. Genetic risk classification of acute myeloid leukemia.

fluorescence in-situ hybridization technique (FISH) and DNA analysis should be done as well routine cytogenetics. Results of these tests are used for patient-risk stratification and to guide patient management. In **Table 2**, most of the prognostic cytogenetic abnormalities are listed, grouped by risk category [15]. AML Patients with the t(8;21)(q22;q22), t(15;17)(q22;q12), and inv (16)(p13.1;q22) are associated with longer survival and remission, whereas alterations of chromosomes 7, 5, complex karyotype, and 11q23 are associated with poor response to therapy and shorter overall survival [16]. The vital chromosomal abnormalities in AML include deletions in chromosomes 5 or 7 or monosomies and trisomy 8 [17]. Furthermore, other abnormalities consist of the balanced translocations between chromosomes 15 and 17 (t (15;17)); long arm of chromosome 11 (11q); chromosomes 8 and 21 (t(8;21)); (q22;q22), (q31; q22), and t(9;11); and inversion for instance inv (16) [18].

5. Oncofusion proteins related with AML

In total, 749 chromosomal aberrations have been recorded in AML [19]. **Table 3** shows the common chromosomal aberrations and their corresponding Oncofusion Proteins in AML [12].

In conclusion, AML is a highly aggressive heterogeneous malignant disease, classified by genetic abnormalities that define subgroups of distinct biological and clinical features. Despite best efforts at targeted therapy, therapeutic approaches have stuck to "one-size fits all" conventional chemotherapy because of lack of targeted therapeutic options.

Translocations	Oncofusion protein	Frequency of occurrence (% of AML)
t(8;21)	AML1-ETO	10
t(15;17)	PML-RARα	10
inv(16)	CBFβ-MYH11	5
der(11q23)	MLL-fusions	4
t(9;22)	BCR-ABL1	2
t(6;9)	DEK-CAN	1
t(1;22)	OTT-MAL	<1
t(8;16)	MOZ-CBP	<1
t(7;11)	NUP98-HOXA9	<1
t(12;22)	MN1-TEL	<1
inv(3)	RPN1-EVI1	<1
t(16;21)	FUS-ERG	<1

Table 3. Acute myeloid leukemia (AML)-associated Oncofusion proteins.

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