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Genetic Alterations and Their Clinical Implications in Acute Myeloid Leukemia

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1. Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy with great variability in the pathogenesis, clinical features, and treatment outcomes. Advances in molecular research have greatly improved our understanding of the leukemogenesis in AML. A two-hit model proposes that the development of AML requires the cooperation between at least two classes of gene mutations. (Frohling, et al 2005, Gilliland 2002) Class I mutations, such as RAS, FLT3, KIT, PTPN11 and JAK2 mutations, involve genes in the kinase signaling pathways leading to cell survival and proliferation and Class II mutations, such as t(15;17)/PML-RARA, inv(16)/CBFB-MYH11 and t(8;21)/RUNX1-RUNX1T1 fusions, and MLL/PTD, and CEBPA and AML1/RUNX1 mutations, involve transcription factors or cofactors resulting in impaired hematopoietic differentiation. In addition to genetic abnormalities, increasing evidences show that epigenetic deregulations are also critical to the pathogenesis of AML. (Chen, et al 2010) Compatible with these findings, several novel mutations involving genes related to epigenetic modifications, such as isocitrate dehydrogenase 1 (IDH1), IDH2, ten-eleven translocation 2 (TET2), additional sex comb-like 1 (ASXL1), and DNA methyltransferase 3A (DNMT3A) were detected in AML recently. (Chou, et al 2010b, Delhommeau, et al 2009, Gelsi-Boyer, et al 2009, Ley, et al 2010, Mardis, et al 2009, Metzeler, et al 2011)

Risk-adapted treatment may not only improve the prognosis, but also reduce the toxicity from the therapy in patients with AML. In addition to the conventional risk factors, such as age, white blood cell (WBC) counts and cytogenetics, molecular genetic alterations, such as mutations of NPM1, CEBPA, AML1/RUNX1, WT1, FLT3, TET2, and DNMT3A etc., are also important prognostic factors in AML patients. Furthermore, the gene mutations which are stable during treatment courses can also be used as biomarkers to monitor minimal residual disease (MRD). Herein, we will review the gene mutations in AML and discuss their clinical implications.

2. Class I mutations that lead to cell survival and proliferation

2.1 FLT3 mutations

FMS-like tyrosine kinase 3 (FLT3), mapped at 13q12, encodes a receptor tyrosine kinase. (Kiyoi, et al 1998) FLT3-internal tandem duplication (FLT3-ITD) mutation, one of the
most common mutations in AML, was found by Nakao et al in 1996. (Nakao, et al. 1996) The mutation occurs as a duplication of nucleotide sequences of variable lengths in exons 14 and 15, leading to addition of repeated peptide in the juxtamembrane domain in the cytoplasm. Another activating FLT3 mutation occurs in tyrosine kinase domain (FLT3-TKD), causing point mutations, small deletions or insertions mainly at codon 835 or 836 within the activation loop of the second kinase domain. (Bacher, et al 2008, Yamamoto, et al. 2001) The FLT3 mutant protein constitutively activates the cascade of FLT3 signaling in the absence of FLT3 ligand promoting cell proliferation and decreased apoptosis.

FLT3-ITD occurs in about 25% of adult AML and shows association with normal karyotype and NPM1 mutation. The patients with this mutation have higher WBC counts, shorter disease-free survival (DFS) and overall survival (OS), and increased relapse rate. (Kottaridis, et al. 2001, Kottaridis, et al. 2002) While mutant size may not be related to prognosis, higher mutant levels are associated with higher relapse rate and shorter survival. (Gale, et al. 2008) Absence of FLT3-ITD combined with NPM1 mutation is regarded as a favorable prognostic genotype. (Gale, et al. 2008, Schlenk, et al. 2008) Up to one third of AML patients with FLT3-ITD can lose the mutation at disease relapse, indicating that this mutation is much less stable than NPM1 mutation, and is not a good marker for disease monitoring. (Chou, et al 2011b, Kottaridis, et al 2002, Palmisano, et al 2007, Shih, et al 2002) FLT3-TKD occurred in about 4%-10% of AML patients. (Yamamoto, et al. 2001, Bacher, et al. 2008) AML with this mutation also shows specific clinical and biologic features, such as elevated WBC counts at diagnosis, higher frequency of normal karyotype and mutations in NPM1, CEBPA, and NRAS. However, the prognostic significance is still inconclusive. (Bacher, et al. 2008, Whitman, et al. 2008)

2.2 RAS mutations

2.3 KIT mutations
KIT, a member of type III receptor tyrosine kinase family, is important for the development of hematopoietic progenitor cells and also crucial in leukemogenesis. (Blume-Jensen and
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2.4 JAK2 mutations

2.5 PTPN11 mutations

3. Class II mutations that impair hematopoietic differentiation

3.1 CEBPA mutations
CCAAT/enhancer binding protein α (C/EBPα) is a 42-kDa transcription factor that possesses a DNA-binding basic leucine zipper domain (bZIP) in the COOH terminus and two transactivation domains TAD 1 and TAD 2 in the NH2 terminus.(Friedman and McKnight 1990) As a transcription factor, it plays a crucial role in granulocytic differentiation and diminished C/EBPα activity contributes to myeloid progenitor transformation.(Cammenga, et al 2003, Oelgeschlager, et al 1996, Smith, et al 1996) CEBPA

### 3.2 MLL-PTD

3.3 AML1/RUNX1

4. Other mutations
4.1 NPM1 mutations
Serial analyses of NPM1 mutations showed the mutation disappeared at CR, but the same mutation usually reappeared at relapse. This feature makes NPM1 mutation an ideal marker for MRD monitoring. Studies have shown NPM1 mutant levels reflect disease status, predict impending relapse, and bring prognostic implication. (Chou, et al 2007, Gorello, et al 2006, Kronke, et al 2011, Schnittger, et al 2009)

4.2 WT1 mutations

5. Mutations of genes that involve epigenetic modifications
Different from genetic abnormalities which result in DNA sequence changes, epigenetic dysregulation causes aberrant gene expression without alteration of gene sequences. (Baylin and Ohm 2006, Chen, et al 2010, Jones and Baylin 2002) Epigenetic regulation includes DNA methylation, histone modifications, such as methylation, acetylation and phosphorylation, etc, and microRNA expression. (Baylin and Ohm 2006, Chen, et al 2010, Jones and Baylin 2002) The recent findings that mutations of genes related to epigenetic modifications, such as IDH1, IDH2, TET2, ASXL1 and DNMT3A, are detected in AML patients provide new insights into mechanisms of epigenetic deregulation in the leukemogenesis.

5.1 TET2 mutations
TET2 protein can catalyze the conversion of 5-methylcytosine (5-mC) of DNA to 5-hydroxymethylcytosine (5-hmC), with ferrous iron and α-ketoglutarate (α-KG) as cofactors, indicating a role of TET2 in DNA methylation. (Ito, et al 2010) Mutations of TET2 result in global DNA hypermethylation. (Figueroa, et al 2010) TET2 mutation was originally identified in myeloid malignancies via single nucleotide polymorphism and comparative genomic-
hybridization array, which revealed common deletion of this gene in chromosome 4q. (Delhommeau, et al 2009) Subsequent studies confirmed this mutation in MDS, MPN, MDS/MPN, and secondary AML, with frequencies around 10% to 26%, 7% to 13%, 22% to 58% and 24% to 32%, respectively. (Bacher, et al 2010, Couronne, et al 2010, Flach, et al 2010, Jankowska, et al 2009, Kosmider, et al 2009a, Kosmider, et al 2009b, Langemeijer, et al 2009, Saint-Martin, et al 2009, Schaub, et al 2010, Smith, et al 2010, Tefferi, et al 2009a, Tefferi, et al 2009b) TET2 mutation occurs in 18.0% to 23% of CN-AML patients. (Chou, et al 2011a, Metzeler, et al 2011) It is closely associated with older age, higher WBC count, but mutually exclusive with IDH mutation. (Chou, et al 2011a, Metzeler, et al 2011) In our study of AML patients with and without chromosomal abnormalities, TET2 mutation was also found to be positively associated with normal karyotype, intermediate-risk cytogenetics, isolated trisomy 8, NPM1 mutation, and ASXL1 mutation. (Chou, et al 2011a) In European LeukemiaNet (ELN) favorable-risk group (patients with CN-AML with mutated CEBPA and/or mutated NPM1 without FLT3-ITD), (Dohner, et al 2010) but not intermediate-1 risk group (CN-AML with wild-type CEBPA and wild-type NPM1 and/or FLT3-ITD), TET2-mutated patients were found to have a lower CR rate, shorter DFS and OS, compared with TET2-wild type patients. (Metzeler, et al 2011) However, we did not have the same finding, but found that TET2 mutation was an unfavorable prognostic factor in patients with intermediate-risk cytogenetics, and its negative impact was further enhanced when the mutation was combined with FLT3-ITD, NPM1-wild, or unfavorable genotypes (other than ELN favorable-risk group). (Chou, et al 2011a) More studies are needed to clarify the prognostic implication of TET2 mutations in AML.

5.2 IDH mutations

IDH1 and IDH2 genes encode two isoforms of isocitrate dehydrogenase which catalyzes the carboxylation of isocitrate to α-KG. IDH1 and IDH2 mutations were first detected in patients with brain tumors. (Parsons, et al 2008) Later, IDH1 mutations (Mardis, et al 2009) and then IDH2 mutations were discovered in AML patients, too. (Abbas, et al 2010, Marcucci, et al 2010, Ward, et al 2010) IDH1 mutations affect arginine residue in position 132 (R132) and IDH2 mutations, in R140 and R172 of exon 4. IDH mutations occur at low frequencies (3.6% to 5%) in MDS, (Kosmider, et al 2010) and in chronic-phase MPN (about 1.8%) (Pardanani, et al 2010), but obviously increased as these diseases progress to AML (7.5% to 21%). (Kosmider, et al 2010, Pardanani, et al 2010) indicating a role of IDH mutations in leukemogenesis. In de novo AML, IDH2 mutations occur more frequently than IDH1 mutations, with frequencies of 11% vs. 6% in patients younger than 60 years, (Abbas, et al 2010) 15.4% vs. 7.7% in total patients, (Ward, et al 2010) and 19% vs. 14% in adults with normal karyotype. (Marcucci, et al 2010) The underlying mechanism of IDH mutations in the leukemogenesis of AML remains to be determined, but several implications of IDH1/2 mutations in AML have been generated. First, IDH mutations are loss-of-function mutations, as mutant IDH proteins show decreased enzyme activities, (Zhao, et al 2009) and have dominant-negative effects on wild type IDH upon homodimerization. (Zhao, et al 2009) Secondly, IDH mutations are also gain-of-function mutations because the mutant proteins can convert α-KG to 2-hydroxyglutarate (2-HG), a metabolite that may contribute to tumor growth through activating hypoxia-inducing factor-1α (HIF-1α). (Dang, et al 2009, Reitman, et al 2010, Ward, et al 2010) Thirdly, IDH mutations reduce production of α-KG, a cofactor of TET2, thus impair catalytic function of TET2 resulting in global DNA hypermethylation.
similar to the effect of TET2 mutations. 2-HG converted from α-KG in IDH-mutated cells is also shown to inhibit TET2-mediated hydroxymethylation of cytosine, indicating overlapping effects of these two mutations. (Xu, et al 2011) Compatible with this, IDH and TET2 mutations are mutually exclusive in AML patients. (Figueroa, et al 2010, Metzeler, et al 2011)

Studies have shown similar clinical features between AML with IDH1 and IDH2 mutations, including strong association of both mutations with normal karyotype and isolated monosomy 8, but inverse correlation with expression of HLA-DR. However, some differences exist. IDH1 mutation shows strong correlation with NPM1 mutation, and FAB M1 subtype, but is inversely associated with FAB M4 subtype and expression of CD13 and CD14. On the other hand, mutation of IDH2 is associated with higher platelet counts, but is inversely correlated with expression of CD34, CD15, CD7, and CD56, and is mutually exclusive with WT1 mutation and chromosomal translocations involving CBF. While there is no impact of IDH1 mutation on patient survival, multivariate analysis reveals IDH2 mutation as an independent favorable prognostic factor, (Chou, et al 2010a, Chou, et al 2011c,) but different results have also been reported. (Marcucci, et al 2010, Thol, et al 2010) More intriguing are the differences of clinical presentations between patients with R140 and R172 mutations. Compared with IDH2 R140 mutation, IDH2 R172 mutation is associated with younger age, lower WBC count and LDH level, and is mutually exclusive with NPM1 mutation. Recent studies also reported worse prognosis in AML patients bearing IDH2 R172Q, (Boissel, et al 2010, Marcucci, et al 2010) while IDH2 R140Q, in the contrary, conferred a better prognosis. (Green, et al 2010) Why mutations in different isoforms or loci of the same gene render distinct clinical and prognostic features remains to be investigated. Serial analyses of IDH1/2 mutations at both diagnosis and relapse confirmed high stability of these two mutations. (Chou, et al 2010a, Chou, et al 2011c)

5.3 ASXL1 mutations

premature stop codon after another 11 amino acid).(Chou, et al 2010b) The mutation was closely associated with older age, male gender, isolated trisomy 8, RUNX1 mutation, and expression of HLA-DR and CD34, but inversely associated with t(15;17), complex cytogenetics, FLT3-ITD, NPM1 mutations, WT1 mutations, and expression of CD33 and CD15.(Chou, et al 2010b) Patients with ASXL1 mutations had a shorter OS than those without, but the mutation was not an independent adverse prognostic factor in multivariate analysis. Sequential analyses showed that the original ASXL1 mutations could disappear at relapse and/or refractory status in some patients. Moreover, two out of the 109 ASXL1-wild patients acquired a novel ASXL1 mutation at relapse.(Chou, et al 2010b) Thus, the ASXL1 mutation status can change during disease evolution in a few patients.

5.4 DNMT3A mutations
By whole genome sequencing on a single patient with normal cytogenetics, Ley and his colleagues found a mutation in DNMT3A gene, which encodes the enzyme DNA methyltransferase 3A which belongs to the family of DNMTs that catalyze the addition of methyl group to cytosine of CpG dinucleotide.(Ley, et al 2010) In this seminal study, DNMT3A mutation was detected in 22.1% of AML patients. Most of the mutations occurred at R882 amino acid. Others included mis-sense, non-sense and frame-shift mutations. Although DNMT3A is directly related to DNA methylation, the real significance of this mutation to leukemogenesis remains unknown. First, the wide spreading of mutation spots in DNMT3A suggests a loss-of-function mutation, but the remarkable aggregate of mutation at R882 implies a gain of function. Reduction of DNA methylation in 182 genomic areas was noted in R882 mutation-harbori ng AML cells, however, the methylation patterns of vast majority of cytosine methylation regions are the same as wild type.(Ley, et al 2010) DNMT3A mutations are associated with intermediate or normal cytogenetics, higher WBC counts, FAB M4/M5 subtypes, and FLT3-ITD, NPM1, and IDH1 mutations but mutually exclusive with favorable karyotypes.(Ley, et al 2010, Thol, et al 2011) In our study of 500 AML patients, DNMT3A mutations were identified in 14% of total patients and 22.9% of patients with CN-AML. (Hou, et al 2011) In addition to the findings shown in previous reports, (Ley, et al 2010, Thol, et al 2011) we for the first time identified the DNMT3A mutation was positively associated with PTPN11 and IDH2 mutations, but negatively associated with CEBPA mutation.(Hou, et al 2011) Intriguingly, the majority (97.1%) of the DNMT3A-mutated patients showed additional molecular alterations at diagnosis. This mutation renders poor OS among all AML patients, patients with a normal karyotype, and those with FLT3-ITD.(Hou, et al 2011, Ley, et al 2010, Thol, et al 2011) Importantly, DNMT3A mutation is an independent poor prognostic factor. Further, DNMT3A mutation is rather stable during disease progression and can be a potential biomarker for monitoring of MRD.(Hou, et al 2011)

6. Gene mutations as markers to monitor Minimal Residual Disease (MRD)
Since gene mutations are theoretically absent in healthy people and restricted in leukemia cells, it is reasonably to monitor MRD by detection of gene mutations. This is an advantage of leukemia over solid tumors in that leukemia cells are indigenous to blood and marrow, which are easy for access. There are two critical considerations of MRD monitoring by gene mutations: one is the stability of the mutations, and the other is the pattern of mutation. An
ideal MRD marker should be very consistent with disease status, while those that may disappear after disease evolution are not suitable for this purpose. Also, if the mutation appears as a point mutation, probably only qualitative rather than absolute quantitative measurement can be achieved because of inevitable background signals due to minimal sequence differences between wild-type and mutant alleles. Moreover, if the mutation occurs sporadically across the whole coding sequence without a hot spot, the absolute quantification techniques (usually fluorescence-based real-time PCR) would become very cumbersome.

Among the mutations in AML, \( NPM1 \) mutation is perhaps the most useful and intensively studied marker of MRD because this mutation is quite stable, relatively prevalent, highly concentrated at a hot spot, and has 4 nucleotide insertion, which can be clearly discriminated from the wild-type allele in quantitative real-time PCR.\( \)\( (\text{Chou, et al 2007, Schnittger, et al 2009}) \) Studies have shown \( NPM1 \) mutant levels reflect disease status, predict impending relapse, and bring prognostic implication.\( \)\( (\text{Chou, et al 2007, Gorello, et al 2006, Kronke, et al 2011, Schnittger, et al 2009}) \) Another stable marker is \( IDH \) mutation. \( IDH1 \) and \( IDH2 \) mutations are stable and highly consistent with disease status.\( \)\( (\text{Chou, et al 2010a, Chou, et al 2011c}) \) We have developed a single-tube, highly sensitive and specific PCR method to detect all \( IDH1 \) mutations at R132 residue.\( \)\( (\text{Chou, et al 2010c}) \) However, the \( IDH \) mutation is not a good marker for MRD monitoring because the minimal difference between the point mutation and normal allele.

Other gene mutations are not readily applicable in MRD monitoring. \( FLT3 \)-ITD is not stable. This mutation can disappear at disease relapse in a significant proportion of patients,\( \)\( (\text{Chou, et al 2011b, Shih, et al 2002}) \) although this length mutation can be readily and sensitively detected by GeneScan-based method.\( \)\( (\text{Stirewalt and Radich 2003}) \) \( DNMT3A \) mutation at R882, which occurs at a frequency of up to 60% of all \( DNMT3A \) mutation, can be a potential marker for qualitative assessment of MRD, but awaits for further testing.\( \)\( (\text{Ley, et al 2010, Thol, et al 2011, Hou, et al 2011}) \) \( ASXL1 \) and \( TET2 \) mutations do not have hot spots and are not stable during AML evolution. Other mutations have lower incidences and have not been well investigated in MRD monitoring.

7. Risk-adapted treatment according to gene mutations in AML patients

The ultimate goal of risk stratification according to molecular alterations is to explore personalized therapy, thereby reduce the risk of relapse and treatment-related side effects. How to integrate gene mutations into clinical management is a crucial issue. The choice between high-dose Cytarabine (HDAC) and allogeneic HSCT as the post-remission therapy is traditionally based on the cytogenetic risks and the patients’ condition. The meta-analysis showed that allogeneic HSCT resulted in better clinical outcome in younger AML patients with intermediate- and unfavorable-risk cytogenetics in first CR.\( \)\( (\text{Cornelissen, et al 2007, Koreth, et al 2009}) \) Although allogeneic HSCT reduces the risk of relapse and is a curative approach for AML patients, the higher rate of transplantation related morbidity and mortality counterbalances its beneficial effect. Thus, allogeneic HSCT is currently recommended only in those patients with acceptable benefit-risk ratio. Given that AML is a heterogenous disease especially in intermediate-risk cytogenetics and CN-AML, increasing understanding of novel molecular genetic markers in AML leukemogenesis can further help to reassess the value of HSCT in different prognostic groups.
Recently, ELN proposed a new classification to stratify AML patients into different risk groups according to cytogenetics and genetic alterations. (Dohner, et al 2010) In addition to CBF AML, CN-AML with mutated NPM1 without FLT3-ITD and those with mutated CEBPA are categorized as favorable-risk groups; the regimen using repetitive cycles of HDAC as postremission therapy is considered beneficial for this group of patients. Allogeneic HSCT in first CR is not beneficial for CN-AML patients with mutated NPM1 without FLT3-ITD, (Schlenk, et al 2008) and probably neither for those with mutated CEBPA. Allogeneic HSCT is generally not considered in patients with CBF AML in first CR, but may be indicated in those who harbor KIT mutations because such patients did poorly with chemotherapy. For the patients with adverse-risk genotype (other than mutated NPM1 without FLT3/ITD or mutated CEBPA), an allogeneic HSCT from a matched related donor or even unrelated donor in first CR is suggested. (Basara, et al 2009, Cornelissen, et al 2007, Slovak, et al 2000, Suciu, et al 2003, Tallman, et al 2007) Recent studies showed that allogeneic HSCT may be considered in patients with FLT3-ITD even if definite results of prospective trials are not available. (Bornhauser, et al 2007, Gale, et al 2005, Schlenk, et al 2008) Besides, allogeneic HSCT also ameliorates the poor survival impact of RUNX1 mutations on AML patients. (Gaidzik, et al 2011, Tang, et al 2009) The treatment of choice for patients with other recently documented poor-risk mutations, such as WT1, TET2 and DNMT3A mutations is currently unclear.

In addition to chemotherapy and transplantation, targeted therapies aiming to specific molecular pathway are evolving as an adjunctive treatment in AML patients. FLT3/ITD and FLT3/TKD occur in about 20-35% of AML patients. Since FLT3 is a receptor tyrosine kinase and promote cancer phenotypes, it is an ideal target for therapy. Several FLT3 inhibitors, such as sorafenib, PKC-412 (midostaurin), sunitinib, semaxanib, tandutinib, AC220, KW-2449, and CEP701 (lestaurtinib) have been used in clinical trials and some effects were noticed in relapse/refractory setting. (Levis, et al 2002, Metzelder, et al 2009, Stone, et al 2005, Zhang, et al 2008) An ongoing international intergroup trial (10603 RATIFY), incorporating midostaurin into induction, consolidation or maintenance setting is currently underway. All-trans retinoic acid in combination with chemotherapy was found to be beneficial for NPM1-mutated patients (Burnett, et al 2010); however this preliminary result was not confirmed by the other study done on younger patients. (Schlenk, et al 2009) Tyrosine kinase inhibitor, such as imatinib, might be of clinical value in treatment of patients with KIT mutations. (Kindler, et al 2004, Kindler, et al 2003, Kohl, et al 2005) Epigenetic modification through demethylation agent azacitidine or decitibine may play a role in the treatment of patients with MLL rearrangement, (Altucci and Minucci 2009) and those with genetic alterations relating to epigenetic changes, such as TET2 mutations. (Itzykson, et al 2011) Besides, recent report demonstrated that inhibition of glutaminase preferentially killed IDH1-mutated glial cells, which were more dependent on glutaminolysis pathway to supply α-KG, so glutaminase itself could be a potential therapeutical target. (Seltzer, et al 2010) Eventually, it may be reasonable to use combinations of molecularly targeted therapies and chemotherapy to improve the clinical outcome in AML patients.

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The current book comprises a series of chapters from experts in the field of myeloid cell biology and myeloid leukemia pathogenesis. It is meant to provide reviews about current knowledge in the area of basic science of acute (AML) and chronic myeloid leukemia (CML) as well as original publications covering specific aspects of these important diseases. Covering the specifics of leukemia biology and pathogenesis by authors from different parts of the World, including America, Europe, Africa, and Asia, this book provides a colorful view on research activities in this field around the globe.

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