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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

The RAS proteins are a large superfamily of low molecular-weight guanine nucleotide-binding proteins, which are activated by cytokine receptors in response to ligand stimulation and therefore control cell proliferation and survival of hematopoietic progenitors.(Downward 2003, Reuther and Der 2000, Shields, *et al* 2000, Wittinghofer 1998) Three members of the RAS family, HRAS, KRAS and NRAS, are found to be activated by mutations in human cancers.(Bos 1989, Downward 2003) Almost all RAS mutations occur by single nucleotide substitutions in codons 12, 13 and 61.(Bos, *et al* 1987, Farr, *et al* 1988, Senn, *et al* 1988, Toksoz, *et al* 1989) *NRAS* and *KRAS* mutations are found in approximately 12-30% and 9-14%, respectively, of AML patients. In a large cohort study of 2502 AML patients, the mutations were found much prevalent in patients with inv(16)/t(16;16) and inv(3)/t(3;3), but seldom found in those with t(15;17) and complex karyotype.(Bacher, *et al* 2006)

The prognostic relevance of *RAS* mutation in AML has not been firmly established. Some studies showed *RAS* mutation predicted poor prognosis(De Melo, *et al* 1997, Kiyoi, *et al* 1999, Meshinchi, *et al* 2003), some showed no impact on clinical outcome,(Bacher, *et al* 2006, Bowen, *et al* 2005, Radich, *et al* 1990, Ritter, *et al* 2004) whereas others found *RAS* mutations were associated with a favorable prognosis.(Coghlan, *et al* 1994, Neubauer, *et al* 1994) However, higher dose of cytarabine may decrease the relapse rate in *RAS*-mutated AML patients.(Neubauer, *et al* 2008)

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

Hunter 2001, Bowen, *et al* 2005, Radich, *et al* 1990) High expression of *KIT* (CD117) is a common finding in AML,(Ikeda, *et al* 1991, Reuss-Borst, *et al* 1994) and activation mutations of *KIT*, most commonly affecting exons 8 and 17 can be identified in 20–45% of AML with inv (16) and 12.8–46.8% of AML with t(8;21), but infrequently found in other AML types.(Beghini, *et al* 2000, Beghini, *et al* 2004, Care, *et al* 2003) Most, though not all, studies,(Boissel, *et al* 2006, Care, *et al* 2003, Schnittger, *et al* 2006) showed *KIT* mutation was associated with inferior outcome in the core binding factor (CBF) AML, especially *KIT*-D816 mutations in t(8;21)/*RUNX1-RUNX1T1*–positive AML.

2.4 *JAK2* mutations

JAK2 is a nonreceptor tyrosine kinase. The *JAK2* V617F mutation induces the activation of JAK2-STAT5 signal transduction pathway and then substantially alters the proliferation and self-renewal of hematopoietic precursors.(Liu, *et al* 1999, Walz, *et al* 2006) Although the *JAK2* V617F mutation is a common genetic event in the patients with myeloproliferative neoplasms (MPN),(Baxter, *et al* 2005, Goldman 2005, Kralovics, *et al* 2005, Levine, *et al* 2005b) it is seldom found (<1%-2%) in *de novo* AML patients.(Frohling, *et al* 2006, Illmer, *et al* 2007, Lee, *et al* 2006, Levine, *et al* 2005a) Illmer et al showed 3.6% of patients with CBF AML had *JAK2* V617F mutation and these patients had an aggressive clinical course and poor outcome.(Illmer, *et al* 2007)

2.5 *PTPN 11* mutations

SHP-2 is encoded by *PTPN11* which is located on chromosome 12q24. The protein is a non-receptor tyrosine phosphatase participating in intracellular signaling elicited by a number of growth factors, cytokines, hormones and adhesion molecules.(Neel, *et al* 2003, Tartaglia, *et al* 2004) Germline *PTPN11* mutations were first reported by Tartaglia *et al* in patients afflicted with Noonan syndrome.(Tartaglia, *et al* 2002, Tartaglia, *et al* 2001) Subsequently, somatic *PTPN11* mutations were also found in patients with juvenile myelomonocytic leukemia, and myelodysplastic syndrome (MDS).(Chen, *et al* 2006, Loh, *et al* 2004b, Tartaglia, *et al* 2003) The *PTPN11* mutation is not a frequent molecular event (4-5%) in AML.(Hou, *et al* 2008, Loh, *et al* 2004a, Tartaglia, *et al* 2005) In a study of 272 primary AML patients, we found this gene mutation was closely associated with older age, French-American-British (FAB) M4/M5 subtype, CD14 expression, normal karyotype and *NPM1* mutation.(Hou, *et al* 2008) Loh *et al* and Tartaglia *et al* revealed that the *PTPN11* mutation had no prognostic implication for pediatric patients with AML;(Loh, *et al* 2004a, Tartaglia, *et al* 2005) however, this mutation may be a poor-risk factor for OS in adult AML patients without *NPM1* mutations.(Hou, *et al* 2008)

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*

mutations are observed in 7% to 18% of patients with AML.(Frohling, *et al* 2004, Lin, *et al* 2005, Pabst, *et al* 2001b, Preudhomme, *et al* 2002) Two major types of *CEBPA* mutations have been identified; one alters COOH terminal bZIP of *CEBPA*, resulting in decreased DNA-binding and/or dimerization activity and the other disrupts translation of the C/EBPα NH2 terminus, thereby up-regulates an alternative 30-kDa isoform with dominant-negative effect on the full-length wild-type C/EBPα.(Koschmieder, *et al* 2009, Lin, *et al* 1993, Pabst, *et al* 2001b) Most patients with *CEBPA* mutations harbored biallelic mutations involving both the NH2-terminal TAD region and the COOH-terminal bZIP domain.(Hou, *et al* 2009, Lin, *et al* 2005, Pabst, *et al* 2009, Renneville, *et al* 2009a) *CEBPA* mutations occur most frequently in patients with FAB subtype M2, and are closely associated with CD7, CD15, CD34, and HLA-DR expression on the leukemic cells, higher circulatory blasts and normal cytogenetics.(Frohling, *et al* 2004, Lin, *et al* 2005, Pabst, *et al* 2001a, Zhang, *et al* 1997) This mutation seems quite stable during AML evolution and may be a potential marker to monitor MRD. The fact that none of the AML patients who do not have *CEBPA* mutations at diagnosis acquire the mutation at relapse suggests that this mutation may not play a major role in the progression of AML.(Lin, *et al* 2005, Tiesmeier, *et al* 2003) Several studies have shown mutant *CEBPA* predicts favorable outcome in AML patients with intermediate or normal cytogenetics.(Barjesteh van Waalwijk van Doorn-Khosrovani, *et al* 2003, Bienz, *et al* 2005, Frohling, *et al* 2004, Preudhomme, *et al* 2002) The favorable impact of *CEBPA* mutations in the AML patients is only observed in the absence of *FLT3*/ITD or other associated cytogenetic abnormalities.(Renneville, *et al* 2009a) Moreover, only double *CEBPA* mutations, but not single *CEBPA* mutation, are associated with better prognosis and define a distinct genetic entity.(Dufour, *et al* 2010, Hou, *et al* 2009, Pabst, *et al* 2009, Wouters, *et al* 2009)

3.2 *MLL* -PTD

The *MLL* partial tandem duplication (*MLL*-PTD) most commonly results from a duplication of a genomic region encompassing exon 5 through exon 11/12 and insertion of the duplicated segment into intron 4 of the full-length *MLL* gene.(Caligiuri, *et al* 1994, Schichman, *et al* 1994, Whitman, *et al* 2005) The duplication involves a portion of the gene corresponding to the amino terminus of the MLL protein which contains the AT hook and a region of homology to DNA methyltransferase motifs.(Schichman, *et al* 1995) The mechanism by which *MLL*-PTD contributes to leukemic phenotype is not clear, but may be through silencing of the wild-type *MLL* by epigenetic mechanisms.(Dimartino and Cleary 1999, Whitman, *et al* 2005) This mutation is found in 5-12% of patients with cytogenetically normal AML (CN-AML),(Dohner, *et al* 2002, Munoz, *et al* 2003, Schnittger, *et al* 2000, Shiah, *et al* 2002) and up to 54% of AML patients with trisomy 11.(Rege-Cambrin, *et al* 2005) Compared with patients without *MLL*-PTD, patients with this mutation more often have FAB M2 subtype, CD11b expression, wild-type *NPM1* and high *BAALC* expression, but lower WBC counts, less frequently extramedullary involvement and FAB M4/M5 subtype at diagnosis.(Shiah, *et al* 2002, Whitman, *et al* 2007) The presence of *MLL*-PTD predicts shorter remission duration and worse OS;(Dohner, *et al* 2002, Munoz, *et al* 2003, Shiah, *et al* 2002) however, more intensive consolidation therapy that includes hematopoietic stem cell transplantation (HSCT) during first complete remission (CR) may reverse the poor prognosis conferred by this mutation.(Whitman, *et al* 2007)

3.3 *AML1/RUNX1*

The *AML1/RUNX1* gene(Ito 2008), consisting of 10 exons (exons 1-6, 7A, 7B, 7C and 8), is one of the most frequently deregulated genes in leukemia through chromosomal translocations and point mutations.(Friedman 2009, Niebuhr, *et al* 2008, Osato 2004, Yamagata, *et al* 2005) Monoallelic germ-line mutation of the *RUNX1* gene occurs in rare cases of familial platelet disorder with predisposition to AML (FPD/AML).(Michaud, *et al* 2002) Acquired *RUNX1* mutation was frequently reported in therapy-related MDS or MDS/AML.(Harada, *et al* 2004) The incidence of *RUNX1* mutation in AML varies from 2.9% to 46% depending on the population selected, the regions of *RUNX1* screened, and the methods used.(Dicker, *et al* 2007, Preudhomme, *et al* 2000, Tang, *et al* 2009) In a large cohort study of 470 adult patients with *de novo* non-M3 AML, we detected *RUNX1* mutation in 13.2% of cases. The *RUNX1* mutation is closely associated with older age, immature FAB subtypes (M0/M1) and specific cytogenetic abnormalities such as trisomy 8 (+8), +13, or +21.(Dicker, *et al* 2007, Schnittger, *et al* 2011, Tang, *et al* 2009) None of the patients with t(8;21), inv(16), t(15;17) or 11q23 translocation shows *RUNX1* mutation.(Tang, *et al* 2009) One half of *RUNX1*-mutated patients have concurrently other gene mutations, mostly (83.9%) Class I mutations, especially *FLT3*/ITD, *FLT3*/TKD and *N-RAS* mutations(Tang, *et al* 2009) which all result in hyperactivation of the receptor tyrosine kinase (RTK)-RAS signalling pathways.(Niimi, *et al* 2006) This finding is consistent with the two-hit model of leukemogenesis.(Frohling, *et al* 2005, Gilliland 2002) Further, the *RUNX1* mutation is mutually exclusive with *CEBPA* and *NPM1* mutations, but closely associated with *MLL*/PTD.(Schnittger, *et al* 2011, Tang, *et al* 2009) The mutation may be lost at relapse in *RUNX1*-mutated patients, but none of the patients who do not harbor *RUNX1* mutation at diagnosis acquire novel mutation at relapse.(Tang, *et al* 2009) *RUNX1* mutation is an independent poor-risk factor for DFS and OS in *de novo* AML patients.(Gaidzik, *et al* 2011, Schnittger, *et al* 2011, Tang, *et al* 2009) In addition, HSCT seems to ameliorate the poor survival impact of *RUNX1* mutations.(Gaidzik, *et al* 2011, Tang, *et al* 2009)

4. Other mutations

4.1 *NPM1* mutations

NPM1 mutation in AML was first identified by Dr. Falini's group, who noticed that some AML patients' leukemia cells exhibited aberrant cytoplasmic localization of NPM1 protein, which normally located in nucleoli in non-mitotic cells.(Falini, *et al* 2005) Subsequent investigation revealed a tetra-nucleotide insertion near the C-terminal end of the coding sequence of *NPM1*. The most frequent form of mutation is duplication of TCTG (type A, c.860_863dupTCTG), resulting in alteration of the peptide sequence from DLWQWRKSL* to DLCL AVEEVSLRK*. *NPM1* mutation occurs in about 30% of AML, more frequently in elder patients,(Falini, *et al* 2011, Falini, *et al* 2005) and is highly associated with normal karyotype, and *FLT3*/ITD, but significantly exclusive with *CEBPA* mutation, favorable karyotype, and expression of CD34 and HLA-DR.(Boissel, *et al* 2005, Chou, *et al* 2006, Dohner, *et al* 2005, Falini, *et al* 2005, Schnittger, *et al* 2005, Suzuki, *et al* 2005, Verhaak, *et al* 2005) *NPM1* mutation generally renders better prognosis,(Falini, *et al* 2005) especially when *FLT3*-ITD is absent.(Schlenk, *et al* 2008, Thiede, *et al* 2006) Further refinement of patient groups disclosed 3 groups with distinct prognosis: good (*NPM1*$^+$/*FLT3*-ITD$^-$), intermediate (*NPM1*$^+$/*FLT3*-ITD$^+$ or *NPM1*$^-$/*FLT3*-ITD$^-$), and poor (*NPM1*$^-$/*FLT3*-ITD$^+$).(Gale, *et al* 2008) *NPM1* mutation seems quite consistent with disease status.(Chou, *et al* 2007, Schnittger, *et al*

2009) 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

The *Wilms' Tumor 1* (*WT1*) gene, encoding a zinc-finger transcription factor, is physiologically expressed in hematopoietic stem cells and involved in regulation of cellular growth and differentiation.(Baird and Simmons 1997, Ellisen, *et al* 2001) *WT1* was initially identified as a tumor suppressor gene,(Haber, *et al* 1990) but was later found to be overexpressed in AML as well as other cancers and thus was suggested to be an oncogene.(Bergmann, *et al* 1997, King-Underwood, *et al* 1996, Miwa, *et al* 1992) Mutations in *WT1* gene are found in about 7-13% of CN-AML patients with hotspots in the four Cys-His zinc finger domains on exons 7 and 9.(Gaidzik, *et al* 2009, Hou, *et al* 2010, King-Underwood, *et al* 1996, Paschka, *et al* 2008, Virappane, *et al* 2008) The precise role of WT1 mutations in the leukemogenesis remains to be defined. The majority of *WT1* mutations are frame-shift mutations occurring in exon 7, followed by single amino acid substitutions in exon 9; whereas frame-shift mutations in exon 9 are rare. *WT1* mutations occur with similar frequencies in patients with normal karyotype and those with abnormal cytogenetics.(Hou, *et al* 2010) Chromosomal abnormality t(7;11)(p15;15), a translocation resulting in *NUP98/HOXA9* fusion, is closely associated with *WT1* mutation.(Hou, *et al* 2010) *WT1* mutations are positively associated with *FLT3*/ITD and *CEBPA* mutations.(Gaidzik, *et al* 2009, Renneville, *et al* 2009b) Paschka *et al* showed patients with *WT1* mutations had higher expression of *ERG* and *BAALC* than patients without.(Paschka, *et al* 2008) *WT1* mutation is an independent poor prognostic factor in CN-AML as well as total AML patients.(Hou, *et al* 2010, Paschka, *et al* 2008, Renneville, *et al* 2009b, Virappane, *et al* 2008), though different results have been reported.(Gaidzik, *et al* 2009, Santamaria, *et al* 2009)

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

Recently, mutations in exon 12 of *Additional sex comb-like 1* (*ASXL1*) gene were found in various types of myeloid malignances, including MDS, MPN, MDS/MPN, and AML.(Abdel-Wahab, *et al* 2010, Boultwood, *et al* 2010, Carbuccia, *et al* 2009, Carbuccia, *et al* 2010, Gelsi-Boyer, *et al* 2009) *ASXL1*, a human homologue of the *Additional sex combs* (*Asx*) gene of *Drosophila*, mapped to chromosome 20q11, a region commonly involved in cancers.(Fisher, *et al* 2003) It consists of an N-terminal *ASX* Homology (ASXH) domain and a C-terminal plant homeodomain (PHD) zinc finger region.(Fisher, *et al* 2003, Fisher, *et al* 2006) In human, the exact function of *ASXL1* mutation remains to be defined, but it is involved in regulation of histone methylation by cooperation with heterochromatin protein-1 (HP1) to modulate the activity of LSD1, a histone demethylase for H3K4 and H3K9.(Dange and Colman 2010, Wang, *et al* 2009) *ASXL1* mutations in exon 12 are found with an incidence of 10.8%, 8.9% and 12.9% among total cohort of patients with *de novo* AML, those with normal karyotype and abnormal cytogenetics, respectively.(Chou, *et al* 2010b) Most of the mutations appear to be either non-sense or frame-shift mutations, leading to disruption of the plant hoemodomain (PHD) at the C terminal of ASXL1, which is well conserved among different species and can recognize methylated H3K4.(Abdel-Wahab, *et al* 2010, Fisher, *et al* 2003, Pena, *et al* 2006, Shi, *et al* 2006, Wysocka, *et al* 2006) Up to two thirds of mutations occurred at c.1934dupG (an extra G after 1934th nucleotide of the coding sequence of *ASXL1*) causing G646WfsX12 (change of glycine to tryptophan at amino acid 646, with a

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-harboring 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.(Chou, *et al* 2007, Schnittger, *et al* 2009) 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) Another stable marker is *IDH* mutation. *IDH1* and *IDH2* mutations are stable and highly consistent with disease status.(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.(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,(Chou, *et al* 2011b, Shih, *et al* 2002) although this length mutation can be readily and sensitively detected by GeneScan-based method.(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.(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.(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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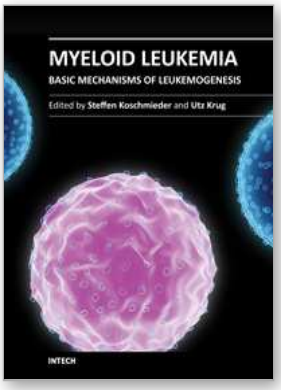

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The current book comprises a series of chapters from experts in the field of myeloid cell biology and myeloid leukemia pathogenesis. It is meant to provide reviews about current knowledge in the area of basic science of acute (AML) and chronic myeloid 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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