SnapShot: Acute Myeloid Leukemia

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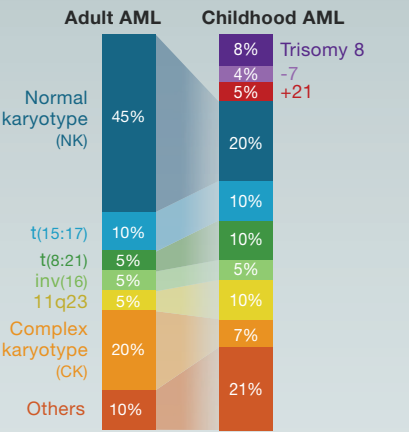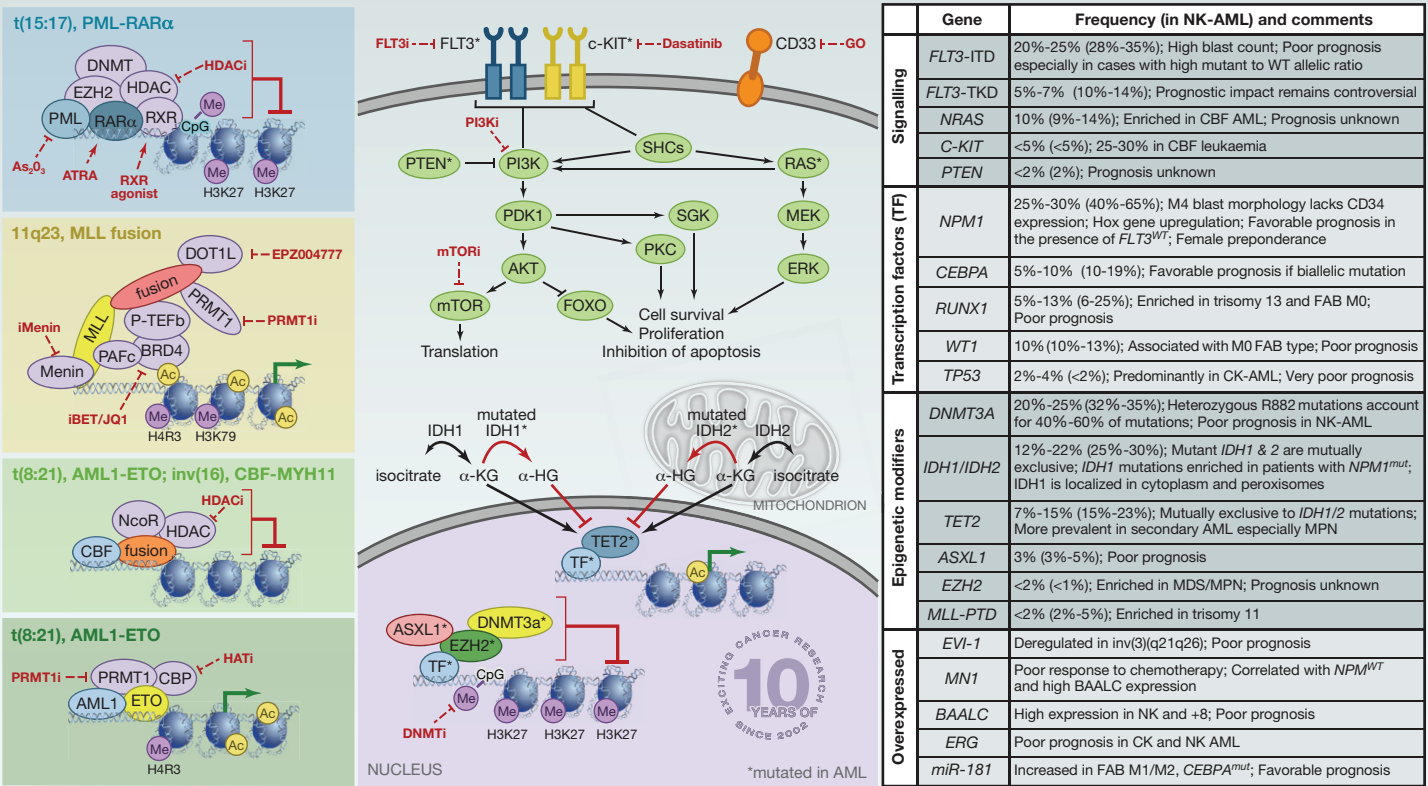
Cancer Cell

Clinical Features and Risk Stratification of AML

Prognostic category	Favorable risk (5 yr OS: 45%-80%)		Intermediate risk (5 yr OS: 20%-40%)		Adverse risk (5 yr OS: 5%-20%)	
	40%-45% of AML cases		25%-35% of AML cases		25%-30% of AML cases	
	Aberration	Frequency (%)	Aberration	Frequency (%)	Aberration	Frequency (%)
	• t(15:17)	7-12	• NK with $FLT3$-ITD	15-20	• 11q23,	3-5
	• t(8:21)	5-8	• NK with NPM^{WT} & no $FLT3$-ITD	10-17	• inv(3)/t(3;3)/EVI-1	~1
	• inv(16)	5-8	• t(9;11)	2-3	• t(6;9)/DEK-$NUP214$	~1
	• NK with NPM^{mut} & no $FLT3$-ITD	18-25	• Other cytogenetic abnormalities not included elsewhere	5-8	• -7/7q-	3-5
	• NK with biallelic $CEBPA^{mut}$	6-12			• -5/5q-	2-3
					• 17p deletions	~2
					• CK	10-12
Current therapies	Standard induction cytotoxic therapy ("3+7"), followed by postremission therapy with high dose cytarabine. ATRA as a differentiating agent with anthracycline based chemotherapy in t(15;17)		Standard induction cytotoxic therapy ("3+7"), followed by postremission consolidation. Allogeneic HSCT should be considered as main modality of consolidation, especially in patients with $FLT3$-ITD		Standard induction cytotoxic therapy ("3+7"), although dismal outcome with chemotherapy alone. Allogeneic HSCT should be offered in clinical remission 1. Consider use of investigational and novel agents	

Cytogenetic Aberrations in AML

Adult AML / Childhood AML

- Trisomy 8: 8%
- -7: 4%
- +21: 5%
- Normal karyotype (NK): Adult 45%, Childhood 20%
- t(15:17): Adult 10%, Childhood 10%
- t(8:21): Adult 5%, Childhood 10%
- inv(16): Adult 5%, Childhood 5%
- 11q23: Adult 5%, Childhood 10%
- Complex karyotype (CK): Adult 20%, Childhood 7%
- Others: Adult 10%, Childhood 21%

Molecular Mechanisms, Recurrent Gene Mutations, and Emerging Targeted Therapies in AML

	Gene	Frequency (in NK-AML) and comments
Signalling	$FLT3$-ITD	20%-25% (28%-35%); High blast count; Poor prognosis especially in cases with high mutant to WT allelic ratio
	$FLT3$-TKD	5%-7% (10%-14%); Prognostic impact remains controversial
	$NRAS$	10% (9%-14%); Enriched in CBF AML; Prognosis unknown
	C-KIT	<5% (<5%); 25-30% in CBF leukaemia
	$PTEN$	<2% (2%); Prognosis unknown
Transcription factors (TF)	$NPM1$	25%-30% (40%-65%); M4 blast morphology lacks CD34 expression; Hox gene upregulation; Favorable prognosis in the presence of $FLT3^{WT}$; Female preponderance
	$CEBPA$	5%-10% (10-19%); Favorable prognosis if biallelic mutation
	$RUNX1$	5%-13% (6-25%); Enriched in trisomy 13 and FAB M0; Poor prognosis
	$WT1$	10% (10%-13%); Associated with M0 FAB type; Poor prognosis
	$TP53$	2%-4% (<2%); Predominantly in CK-AML; Very poor prognosis
Epigenetic modifiers	$DNMT3A$	20%-25% (32%-35%); Heterozygous R882 mutations account for 40%-60% of mutations; Poor prognosis in NK-AML
	$IDH1/IDH2$	12%-22% (25%-30%); Mutant $IDH1$ & 2 are mutually exclusive; $IDH1$ mutations enriched in patients with $NPM1^{mut}$; $IDH1$ is localized in cytoplasm and peroxisomes
	$TET2$	7%-15% (15%-23%); Mutually exclusive to $IDH1/2$ mutations; More prevalent in secondary AML especially MPN
	$ASXL1$	3% (3%-5%); Poor prognosis
	$EZH2$	<2% (<1%); Enriched in MDS/MPN; Prognosis unknown
	MLL-PTD	<2% (2%-5%); Enriched in trisomy 11
Overexpressed	EVI-1	Deregulated in inv(3)(q21q26); Poor prognosis
	$MN1$	Poor response to chemotherapy; Correlated with NPM^{WT} and high BAALC expression
	$BAALC$	High expression in NK and +8; Poor prognosis
	ERG	Poor prognosis in CK and NK AML
	miR-181	Increased in FAB M1/M2, $CEBPA^{mut}$; Favorable prognosis

*mutated in AML

Cell of Origin and Clonal Evolution Model of Leukemic Stem Cells

Self-renewal pathways		
Loss of function	Impact on HSC	Impact on LSC
PTEN	–	+
β-catenin	NS	–
BMI	–	–
HOX	NS	–

LSK	Lineage⁻, Sca-1⁺, c-KIT⁺ population
CMP	Common myeloid progenitor
GMP	Granulocyte macrophage progenitor
+	Positive impact
–	Negative impact
NS	Not significant
	Colors represent different clones
	Indicates (epi)genetic mutations
LSC	Leukemic stem cell
	Other Leukemic (non-stem) cells
LSC-SC	Leukemic subclone originating from LSC
SC	Leukemic subclone originating from non-LSC
↻	Self-renewal

NORMAL HEMATOPOIESIS — PRE-LEUKEMIA — OVERT LEUKEMIA — CLINICAL REMISSION — RELAPSE

Initiating event e.g., MLL fusion/ PML-RARα — Cooperating event e.g., FLT3 — Founding AML clone — Other cooperating event — CHEMOTHERAPY

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Clinical Features and Risk Classification of AML

Acute myeloid leukemia (AML) is a heterogeneous clonal disorder of hematopoietic stem/progenitor cells characterized by the rapid growth of abnormal white blood cells (blasts) that accumulate in the bone marrow and interfere with the production of normal blood cells. In contrast to the classical French-American-British (FAB) classification based on morphological appearance of blasts and their cytochemistry, the 2008 revised WHO classification of AML incorporates cytogenetic/genetic data that help to define biologically homogenous entities with prognostic and therapeutic relevance. Based on (cyto)genetic features of the AML, patients can be broadly classified into three risk groups, although patient-specific factors (age, performance status, comorbidity, etc.) are also key predictors of outcome. The "3+7" combination of daunorubicin and cytarabine is routinely used as induction chemotherapy for adult patients with AML, except PML-RARα leukemia, whereas molecular profiling is currently guiding postinduction therapeutic strategies. Comparison between adult and childhood AML shows that children have a higher incidence of chromosomal translocation, whereas normal (NK) and complex karyotype (CK)—the latter includes monosomal karyotype (MK) and is associated with dismal prognosis—are more prevalent in adults. While risk classification has advanced in the last decades, treatment of AML, except for t(15;17) leukemia, is only marginally improved, mainly by better supportive care, highlighting the need for novel therapies.

Molecular Mechanisms, Recurrent Gene Mutations, and Emerging Targeted Therapies in AML

PML-RARα from t(15;17) that exclusively associates with FAB-M3 (acute promyelocytic leukemia, APL) forms transcriptionally repressive complexes with retinoic X receptor (RXR), histone deacetylases (HDACs), enhancer of zeste (EZH2), and DNA methyltransferase (DNMT). All-trans retinoic acid (ATRA), which dissociates repressor complexes from PML-RARα and mediates its subsequent degradation, can effectively induce differentiation of APL cells. In combination with chemotherapy, ATRA achieves a 5 year overall survival of approximately 80%. While As_2O_3, which degrades PML-RARα, is commonly employed to treat relapsed patients, other targeted therapeutic agents, including HDAC inhibitors and RXR agonists, are being developed.

The MLL gene located at 11q23 has over 60 different fusion partners in AML. Wild-type MLL encodes a SET domain containing H3K4 histone methyltransferase but the SET domain is invariably replaced by the partner proteins in MLL fusions. All MLL fusions retain MLL's N terminus that recruits Menin and the polymerase associated factor complex (PAFc), which are critical for DNA binding, gene expression, and cellular transformation. Importantly, the fusion partners themselves recruit a variety of protein complexes involved in transcriptional elongation (p-TEFb) and/or histone methylation, e.g., DOT1L (H3K79) or PRMT1 (H4R3), resulting in aberrant transcriptional activation. Several novel targeted strategies are emerging for 11q23 AML, including inhibition of Menin, DOT1L, PRMT1, the histone acetylation reader BRD4, and LSD1 (although the mechanisms underlying the efficacy of LSD1 inhibition remain unclear).

Genes encoding core binding factors including AML1/RUNX1 and CBFβ are the most frequently rearranged ones in AML. Both core binding factor fusions complex with transcriptional repressors, such as HDACs and NCoR, to suppress expression of downstream targets, thus prompting HDAC inhibitors as potential therapeutic agents. AML1-ETO fusions may also recruit transcriptional coactivators such as PRMT1 and histone acetyltransferase (HAT) CBP that are critical for transformation.

Going beyond microarray analyses, next-generation sequencing has been unravelling the vast genetic heterogeneity in AML and improving risk stratification, especially for NK-AML. This has led to the discovery of not only several candidate genes that could be classified under the conventional two-hit model (e.g., signaling and transcription factors) of myeloid leukemogeneis but also those involved in epigenetic regulation, spliceosome machinery, and the cohesin complex. Interestingly, some of the mutations identified in NK-AML such as those in FLT3 and c-KIT are also recurrent in AML with translocations. Several kinase inhibitors (e.g., FLT3i and dasatinib), anti-CD33 antibody conjugate gemtuzumab ozogamicin (GO), and hypomethylating agents are currently in clinical trials. The role of epigenetic modulation in AML has only started to be unraveled, even though the therapeutic benefit of hypomethylating agents in low blast AML predates our knowledge of the existence of these epigenetic regulator mutations.

Cell of Origin and Clonal Evolution Model of Leukemic Stem Cells

The cell of origin for AML stem cells is still unclear. However, studies using mouse models have shown that both hematopoietic stem cells (HSCs) and progenitor cells can be targeted by initiating events, such as MLL fusions and PML-RARα, to generate preleukemic stem cells (pre-LSCs) and, subsequently, LSCs with acquisition of additional cooperative events (e.g., FLT3). The origin of LSCs can influence the leukemia type and lineage, although the cellular origin's role in treatment response remains to be determined. LSCs possess self-renewal ability and can give rise to short-lived progenies, which form the bulk of the leukemic population in the patient. LSCs and leukemic progenies can further evolve into different subclones by acquiring additional mutations, leading to multiple (epi)genetically different leukemic clones with various clone sizes in the patient at the time of diagnosis. After chemotherapy, the bulk of leukemic cells is eradicated, leading to clinical remission; however, chemoresistant LSCs persist in the patient at low levels. With time, LSCs, which may be shaped by the treatment, can give rise to different progenies again, reinitiating the disease. Thus, the dominant clone at the time of relapse may not necessarily be the same as the one at diagnosis. Self-renewal is a common feature shared by LSCs and HSCs. Pathways such as β-catenin and PTEN, which have differential effects on LSCs versus normal HSCs, may be key targets to eradicate LSCs.

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