Table 13-10 Major Subtypes of AML in the WHO Classification

Class	Prognosis	Morphology/Comments
I. AML with Genetic Aberrations		
AML with t(8;21)(q22;q22); *RUNX1/ETO* fusion gene	Favorable	Full range of myelocytic maturation; Auer rods easily found; abnormal cytoplasmic granules
AML with inv(16)(p13;q22); *CBFB/MYH*11 fusion gene	Favorable	Myelocytic and monocytic differentiation; abnormal eosinophilic precursors with abnormal basophilic granules
AML with t(15;17)(q22;11-12); *RARA/PML* fusion gene	Intermediate	Numerous Auer rods, often in bundles within individual progranulocytes; primary granules usually very prominent, but inconspicuous in microgranular variant; high incidence of DIC
AML with t(11q23;v); diverse *MLL* fusion genes	Poor	Usually some degree of monocytic differentiation
AML with normal cytogenetics and mutated *NPM*	Favorable	Detected by immunohistochemical staining for NPM
II. AML with MDS-like Features		
With prior MDS	Poor	Diagnosis based on clinical history
AML with multilineage dysplasia	Poor	Maturing cells with dysplastic features typical of MDS
AML with MDS-like cytogenetic aberrations	Poor	Associated with 5q-, 7q-, 20q-aberrations
III. AML, therapy-related	Very poor	If following alkylator therapy or radiation therapy, 2- to 8-year latency period, MDS-like cytogenetic aberrations (e.g., 5q-, 7q-); if following topoisomerase II inhibitor (e.g., etoposide) therapy, 1- to 3-year latency, translocations involving *MLL* (11q23)
IV. AML, Not Otherwise Specified		
AML, minimally differentiated	Intermediate	Negative for myeloperoxidase; myeloid antigens detected on blasts by flow cytometry
AML without maturation	Intermediate	>3% of blasts positive for myeloperoxidase
AML with myelocytic maturation	Intermediate	Full range of myelocytic maturation
AML with myelomonocytic maturation	Intermediate	Myelocytic and monocytic differentiation
AML with monocytic maturation	Intermediate	Nonspecific esterase-positive monoblasts and pro-monocytes predominate in marrow; may see monoblasts or mature monocytes in the blood
AML with erythroid maturation	Intermediate	Erythroid/myeloid subtype defined by >50% dysplastic maturing erythroid precursors and >20% myeloblasts; pure erythroid subtype defined by >80% erythroid precursors without myeloblasts
AML with megakaryocytic maturation	Intermediate	Blasts of megakaryocytic lineage predominate; detected with antibodies against megakaryocyte-specific markers (GPIIb/IIIa or vWF); often associated with marrow fibrosis; most common AML in Down syndrome

AML, Acute myeloid leukemia; DIC, disseminated intravascular coagulation; MDS, myelodysplasia; NPM, nucleophosmin; vWF, von Willebrand factor.

therapy. A fourth "wastebasket" category includes AMLs lacking any of these features. These are classified based on the degree of differentiation and the lineage of the leukemic blasts. Given the increasing role of cytogenetic and molecular features in directing therapy, a further shift toward genetic classification of AML is both inevitable and desirable.

Pathogenesis. **Many of the recurrent genetic aberrations seen in AML disrupt genes encoding transcription factors that are required for normal myeloid differentiation.** For example, the two most common chromosomal rearrangements, t(8;21) and inv(16), disrupt the *RUNX1* and *CBFB* genes, respectively. These two genes encode polypeptides that bind one another to form a RUNX1/CBF1β transcription factor that is required for normal hematopoiesis. The t(8;21) and the inv(16) create chimeric genes encoding fusion proteins that interfere with the function of RUNX1/CBF1β and block the maturation of myeloid cells. However, experiments in mouse models indicate that genetic lesions that merely block the maturation of myeloid progenitors are not sufficient to cause AML. Thus other genetic changes (discussed next) are also essential.

There is increasing evidence that mutations that lead to activation of growth factor signaling pathways collaborate with transcription factor aberrations to produce AML. One example is found in AML with the t(15;17), acute promyelocytic leukemia. The t(15;17) creates yet another fusion gene encoding a chimeric protein consisting of the retinoic acid receptor-α (RARα) fused to a portion of a protein called PML (after the tumor). As discussed in Chapter 7, this fusion protein interferes with the terminal differentiation of granulocytes, an effect that can be overcome by treatment with either all-trans retinoic acid or arsenic trioxide. However, expression of the PML-RARa fusion protein in the bone marrow cells of mice produces disease only in aged mice, suggesting that PML-RARα is not sufficient. Indeed, AMLs with the t(15;17) (a subtype referred to as acute promyelocytic leukemia) also have frequent activating mutations in FLT3, a receptor tyrosine kinase that transmits signals that mimic normal growth factor signaling, thereby increasing cellular proliferation and survival. As might be predicted, the combination of PML-RARα and activated FLT3 is a potent inducer of AML in mice. Other similar observations in human AML and in mouse models indicate that aberrant activation of growth factor signaling pathways is a common feature of AML.

Deep sequencing of AML genomes has also revealed unexpectedly frequent mutations affecting factors that impact the state of the "epigenome," suggesting the epigenetic alterations have a central role in AML.

www.PTools.ir