

Pathobiology of acute myeloid leukemia

Authors

Wendy Stock, MD
Michael J Thirman, MD

Deputy Editors

Rebecca F Connor, MD

Editor in Chief

Richard A Larson, MD

Section Editors

Richard A Larson, MD

INTRODUCTION — Acute myeloid leukemia (AML) develops as the consequence of a series of genetic changes in a hematopoietic precursor cell. These changes alter normal hematopoietic growth and differentiation, resulting in an accumulation in the bone marrow and peripheral blood of large numbers of abnormal, immature myeloid cells. These cells are capable of dividing and proliferating, but cannot differentiate into mature hematopoietic cells (ie, neutrophils).

Similar to other malignancies, the genetic alterations in AML include mutation of oncogenes as well as the loss of tumor suppressor genes. In contrast to most solid tumors, many hematologic malignancies are associated with a single characteristic cytogenetic abnormality (eg, the Philadelphia chromosome [t(9;22)] in chronic myelogenous leukemia and t(15;17) in acute promyelocytic leukemia).

Advances in the identification of recurring chromosomal abnormalities and translocations have provided major insight into the pathobiology of AML. (See "Cytogenetic and molecular genetic diagnostic tools").

The focus of this topic review will be on the various molecular genetic events involved in the pathogenesis of AML [1]. More general discussions of genetic events in hematologic malignancies are presented separately. (See "Genetic abnormalities in hematologic and lymphoid malignancies" and see "General aspects of cytogenetics in hematologic malignancies").

NATURE OF THE LEUKEMIC DEFECT — Cells in AML exhibit maturation defects that correspond to stages in hematopoietic differentiation; thus, it will be useful here to review the stages of normal hematopoiesis. (See "Overview of hematopoiesis and stem cell function"). In order to sustain hematopoiesis, stem cells are part of a developmental hierarchy capable of three basic functions:

- Maintenance in a non-cycling state
- Self-renewal capacity, allowing production of additional stem cells
- Production of committed progenitor cells

These progenitor cells commit to subsets of myeloid and lymphoid lineages, and ultimately to single developmental pathways, resulting in the expression of the terminally differentiated stage of each cell type ([show figure 1](#)) [2,3].

Normal hematopoiesis is a dynamic, highly regulated process controlled by the combined effects of growth factors that permit cellular proliferation, and nuclear transcription factors that activate specific genetic programs, resulting in commitment to a specific lineage and in terminal differentiation ([show figure 2](#)). Many of the regulatory growth factors and a number of specific transcription factors have been identified that play critical roles in lineage commitment, and in the subsequent development of the mature lymphoid and myeloid (erythroid, granulocytic/monocytic, and megakaryocytic) lineages [4,5].

A number of genes encoding these transcription factors are involved in recurring chromosomal translocations seen in AML, suggesting that the AML variants arise because the translocations result in significant alterations in regulatory processes controlling growth and differentiation programs [6]. The novel fusion genes created by these translocations will be reviewed in detail below.

Single cell origin of AML — A great deal of evidence supports the concept that acute leukemia develops from a single transformed hematopoietic progenitor cell. For example, studies of isoenzyme restriction in leukemic myeloblasts of females heterozygous for the A and B isoforms of glucose 6-phosphate dehydrogenase (G6PD) have demonstrated the clonal origin of AML [7,8] . The G6PD locus is on a portion of the X chromosome that undergoes inactivation in XX somatic cells (Lyonization). Approximately one half of the cells in normal somatic tissue will have randomly inactivated one or the other of the X chromosomes, allowing expression of the A and B isoforms in approximately equal amounts. Cells of clonal origin, however, express only one type of G6PD.

In each of the G6PD heterozygous females with AML, both types of enzyme were found in normal tissues, but only a single type was observed in the leukemic myeloblasts [7-9] . Similar conclusions were reached using X-linked recombinant DNA probes, standard cytogenetics, and fluorescence in situ hybridization (FISH) [10-12] . (See "Cytogenetic and molecular genetic diagnostic tools" and see "Cytogenetics in acute myeloid leukemia" and see "General aspects of cytogenetics in hematologic malignancies", section on Definition of clonality).

Leukemic transformation — Two models have been proposed to explain the heterogeneity of AML observed at the molecular, cytogenetic, phenotypic, and clinical level.

Transformation at one of several developmental stages — This model proposes that any cell type within the stem cell/progenitor cell hierarchy, from primitive multipotent stem cell to lineage-committed progenitor cell, is susceptible to leukemic transformation, resulting in the expansion of abnormal cells that exhibit different stages of differentiation. For AML, this model predicts that the phenotype of the leukemic stem cells restricted to the granulocytic-monocytic series differs from that of cells with involvement of erythroid, megakaryocytic, and granulocytic-monocytic lineages ([show figure 1](#)).

The correlation between specific cytogenetic and molecular genetic aberrations and the morphologic appearance of leukemic cells might suggest that the transforming event occurs at different stages of myeloid differentiation. This hypothesis is underscored by the French-American-British (FAB) classification for AML, which distinguishes different subtypes of AML based upon the stage of apparent differentiation ([show table 1](#) and [show table 2](#)). Additional supporting evidence comes from studies of clonal hematopoiesis in AML, which indicate that, although the majority of cells derived from the leukemic clone can undergo differentiation to cells of the granulocytic-monocytic lineage, they also may differentiate into cells of the erythroid and/or megakaryocytic pathways [10-13] . Such multi-lineage involvement has been noted more frequently in elderly patients, in those whose AML arose following a documented prior myelodysplastic disorder, or following treatment for another malignancy [12,13] .

Transformation within primitive multipotent cells — A second model proposes that mutations responsible for leukemic transformation and progression occur only in primitive multipotent stem cells, with disease heterogeneity resulting from a variable ability of these primitive stem cells to differentiate and acquire specific phenotypic lineage markers [14,15] .

Hematopoietic stem cells express a characteristic cell surface antigen (CD34), and can be further subdivided by the expression of additional cell surface antigens, including CD38 and HLA-DR ([show figure 3](#)) [16,17] :

- CD34+/CD38-/HLA-DR- cells are multipotential hematopoietic stem cells, give rise to mixed-lineage granulocytic-erythroid- megakaryocytic colonies in culture, can repopulate immune deficient mice with normal hematopoietic cells in vivo, and demonstrate self-renewal capacity, as assessed by their ability to be serially transplanted into secondary recipient mice. There are data to suggest that, in some cases of AML, the leukemic stem cell may be quite similar to normal hematopoietic stem cells [18] .

- CD34+/CD38+/HLA-DR+ cells define a committed population of myeloid progenitor cells [19] . (See "Overview of hematopoiesis and stem cell function").

Cytogenetic and FISH studies of sorted stem cell compartments from patients with AML evolving from a prior myelodysplastic syndrome and patients with de novo AML have shown that the characteristic cytogenetic abnormality from both groups was present in the CD34+/CD38- multipotential stem cell compartment [20-22] . Similar findings were noted in patients with the 5q- syndrome [23] and monosomy 7 [24] , myelodysplastic disorders with differing risks of leukemic transformation. (See "Clinical manifestations and diagnosis of the myelodysplastic syndromes", section on The 5q- syndrome).

More compelling evidence comes from studies in which purified stem cell subpopulations from normal subjects and those with AML were transplanted into mice with severe combined immunodeficiency disease (SCID) [25] . These experiments have detected approximately one SCID mouse leukemia-initiating cell (SL-IC) in 10(5) AML cells, which can repopulate immune deficient mice with leukemic cells phenotypically identical to those of the AML patient from which they were derived [22,25,26] .

Using a non-obese diabetic (NOD)/SCID mouse [27] , SL-ICs were found to reside only in the CD34+/CD38- fraction [28] . This was consistent regardless of the FAB subtype, lineage markers, or percentage of leukemic blast cells expressing the CD34 antigen. The SL-ICs also demonstrated self-renewal capacity, a requirement for maintenance of the leukemic clone. The uniformity of the leukemic stem cell phenotype strongly suggests that the leukemia initiating transformation and progression-associated genetic events occur in primitive cells and not in committed progenitors. Similar conclusions about the site of the leukemia initiating transformation have been made in acute lymphoblastic leukemia [29] .

Additional evidence for the second model derives from the use of a retroviral gene transfer system to express AML1/ETO, a fusion gene linked to the pathogenesis of AML, in normal human hematopoietic stem and progenitor cells (see "AML1/ETO in t(8;21)" below) [30] . When this fusion gene was expressed in more mature progenitor cells, the result was growth arrest and abrogated colony formation in primary clonogenic assays. On the other hand, AML1/ETO expression in stem cells resulted in their preferential expansion and/or self-renewal [31] .

An exception to these findings may occur in acute promyelocytic leukemia (APL), an AML subset (FAB-M3) not examined in the NOD/SCID mouse studies, but in which flow cytometric/molecular analysis of patient samples suggest that the leukemic cell arises in a committed lineage-restricted, CD34+/CD38+ progenitor cell [32] .

MULTISTEP AND MULTICAUSAL PATHOGENESIS OF AML — Progression to acute leukemia may require a series of genetic events beginning with clonal expansion of a transformed leukemic stem cell [33] . The specific mutational event(s) required for this progression are not currently well defined, although the "two-hit hypothesis" of leukemogenesis implies that AML is the consequence of at least two mutations, one conferring a proliferative advantage and another impairing hematopoietic differentiation [34] .

Important insights have been obtained from human leukemias and mouse models:

- In chronic phase chronic myeloid leukemia (CML), all leukemic cells contain t(9;22), resulting in formation of the BCR/ABL fusion gene [35] , whose product is of critical significance in the pathogenesis of CML [36] . (See "Cellular and molecular biology of chronic myelogenous leukemia", section on Properties of the fusion protein). As the disease progresses, additional cytogenetic abnormalities are acquired [37] , which are often accompanied by loss of important tumor suppressor genes such as p53 [38] . (See "Molecular genetics of chronic myelogenous leukemia", section on Progression to blast crisis).

- A variety of clonality studies have shown that patients with AML in clinical remission may still have clonal, rather than polyclonal, hematopoiesis [10,39-41] . Such clonal remission may represent the presence of a "preleukemic stem cell", that has undergone an initial transforming event but has not acquired the additional mutation(s) essential to progression to overt leukemia. In these cases, it is presumed that the transformed, overtly leukemic cell probably represented a subclone of the original "preleukemic stem cell" which secondarily acquired the additional genetic mutations required for the definitive block in differentiation and manifestation of the leukemic phenotype.

Although some studies suggest that "clonal" remissions may be the result of skewed Lyonization (preferential inactivation of one X chromosome over another) [42,43] , more carefully controlled studies suggest that clonal remissions do occur following treatment for AML [44,45] .

AML1/ETO fusion transcript — Data suggest that expression of a chimeric protein represents only one of the genetic modifications necessary for the development of cancer and leukemia, and that the affected cell requires additional mutational events in order to express the transformed phenotype. A number of examples indicate that the presence of cells with the AML1/ETO fusion transcript may not be sufficient, in itself, to result in AML:

- Transgenic mice expressing AML1/ETO were healthy throughout their lifespan, developing AML only after exposure to an alkylating mutagen [46] , or in cooperation with Wilms tumor gene (WT1) overexpression [47] .
- Remission bone marrow samples from patients with de novo AML (FAB -M2) with t(8;21)(q22;q22) and the AML1/ETO fusion transcript (described below) have been found to harbor the aberrant fusion transcript for as many as eight years following cessation of all chemotherapy [48] .
- The AML1/ETO fusion transcript has been detected in bone marrow samples from patients in remission following allogeneic bone marrow transplantation for AML [49] .
- In five children who developed AML with t(8;21) at 3 to 12 years of age, in whom archived blood samples for metabolic studies (Guthrie cards) were available, AML1/ETO sequences were detected at birth [50] . Of interest, similar observations were made in three children developing acute lymphoblastic leukemia at ages 3 to 5 years of age with t(12;21) [51] .

As noted above, AML1/ETO is not immediately leukemogenic in either animals or man, and may require a "second hit" for the development of AML [52,53] . However, the presence of an alternatively spliced isoform AML1/ETO9a has been shown to be present in the majority of patients with t(8;21) [54] . Expression of this alternative isoform leads to rapid development of leukemia in a mouse model, and coexpression of AML1/ETO and AML1/ETO9a results in the substantially earlier onset of AML and blocks myeloid cell maturation at a more immature stage. These early results suggest that fusion proteins from alternatively spliced isoforms resulting from a chromosomal translocation may work together to induce this malignancy.

Chemotherapy induced AML — The development of MDS and AML following chemotherapy for a variety of malignancies (eg, breast cancer, Hodgkin lymphoma) is an unfortunate complication of curative treatment strategies [55] , such as dose-intensive therapy with or without hematopoietic cell transplantation and growth factor support [55-59] . This identification of an increasing incidence of therapy-related AML (t-AML) in an attempt to improve cure rates emphasizes the critical importance of understanding the underlying pathogenetic mechanisms for development of t-AML [60,61] . (See "Malignancy after hematopoietic cell transplantation" and see "Second malignancies after treatment of Hodgkin lymphoma", section on Acute leukemia and see "Side effects of adjuvant chemotherapy for early stage breast cancer", section on Leukemia and myelodysplastic syndromes).

T-AML typically develops following alkylating agent-induced damage, at a median of three to five years following therapy for the primary malignancy and is usually associated with an antecedent myelodysplastic disorder [62]. This latency period suggests that multiple mutational events are involved in the development of the malignant phenotype [33].

- Clonal chromosomal abnormalities have been reported in the majority of cases of t-AML. (See "Cytogenetics in acute myeloid leukemia", section on Therapy-related MDS/AML). The most frequently reported abnormalities involve complete loss or interstitial deletions of the long arm of chromosomes 7 and/or 5.
- Other therapy-related leukemias are associated with rearrangements of the MLL gene in chromosome band 11q23 [63] (see "involvement of the MLL locus" below). AML associated with 11q23 often develops after treatment with drugs that target DNA-topoisomerase II (eg, epipodophyllotoxins, anthracyclines) with a very short latency of 12 to 18 months following treatment, and are not typically associated with an antecedent myelodysplastic syndrome [64-66]. (See "Cytogenetics in acute myeloid leukemia", section on Following DNA topoisomerase II inhibitors).

Genetic polymorphisms of a number of drug-metabolizing enzymes may alter the risk of t-AML [61,67,68]. As an example, polymorphisms in genes that encode glutathione S-transferases (GST), which detoxify potentially mutagenic chemotherapeutic agents, may alter susceptibility to t-AML [67]. In one study, relative to de novo AML, the GSTP1 codon 105 Val allele occurred more often among patients with t-AML with prior exposure to chemotherapy, particularly those with exposure to known GSTP1 substrates (odds ratio 4.3; 95% CI 1.4-13), and not among those t-AML patients with prior exposure to radiotherapy alone.

Ionizing radiation — Ionizing radiation shares with alkylating agents the ability to damage DNA, usually by inducing double strand breaks that may cause the mutations, deletions, or translocations required for hematopoietic stem cell transformation [55,69]. As examples, an increased incidence of AML, which may have been directly proportional to the radiation exposure [70], has been noted in atomic bomb survivors [71] as well as in radiologists and radiologic technologists chronically exposed to high levels of radiation in the period before 1950 [72].

Ionizing radiation used in the treatment of malignancies (eg, Hodgkin lymphoma, breast cancer, uterine cancer, lung cancer) has also been linked to the development of AML [73]. This risk appears to be quite low when radiation alone is used as treatment, and is associated with age of the patient, and doses of more than 20 Gy [74,75]. Whether irradiation adds to the risk of t-AML associated with chemotherapy remains controversial. Although some studies suggest that the risk of development of AML is significantly increased when the two modalities are combined, other studies demonstrated that high doses of radiotherapy confined to small volumes in combination with chemotherapy did not significantly increase leukemogenic risk [76-79].

Chemical exposure — Exposure to organic solvents such as benzene and other petroleum products has been associated with a higher risk of developing AML [80,81]. However, case-control studies of leukemia have demonstrated only a slight increase in risk of disease for persons with occupational or chemical exposures. Except for special groups exposed to high levels of benzene or radiation, the reported risks associated with occupation and chemicals have generally been less than twofold, making these exposures of questionable pathogenetic significance [82].

The presence of RAS mutations in patients with AML has been associated with specific occupational exposure to chemicals, suggesting that these exposures may induce genetic damage culminating in acute leukemia [83]. In a case-control study, cigarette smoking was associated with only a modest increase in leukemic risk; however, a twofold increase in risk for AML was noted in study subjects over the age of 60 [84].

Polymorphisms resulting in inactivation of NAD(P)H:quinone oxidoreductase 1 (NQO1, originally called DT-diaphorase), an enzyme which detoxifies quinones and reduces oxidative stress, have been associated with an increased risk of de novo [85] and therapy-related acute leukemia [86], as well as a greater risk of benzene-induced hematotoxicity and leukemia [87]. For de novo AML, the most significant effect of low or null NQO1 activity was observed among patients with chromosomal translocations and inversions (odds ratio: 2.4), and was especially high for those with inv(16) (odds ratio: 8.1) [85].

Genetic polymorphisms in the microsomal epoxide hydrolase (HLY1) gene, an enzyme involved in benzene metabolism, have also been associated with an increased incidence of AML. Data from one study suggest that smoking and/or exposure to a carcinogen which is activated by HYL1, such as benzene, may be important in subsets of patients with AML, such as males with t(8;21) or -7/del(7q) [88,89].

Retroviruses — In a number of animal models, retroviruses have been demonstrated to play an important role in leukemogenesis (see "Animal models of AML" below), and the human T-lymphotropic virus type I (HTLV-I) is associated with adult T-cell lymphoma/leukemia [90]. (See "Clinical and pathologic features of adult T cell lymphoma/leukemia"). In AML, however, despite extensive investigation, there has been no clear association of a retrovirus with leukemogenesis [91].

Familial leukemia — Familial leukemia can occur in the context of a medical syndrome in which AML is one component of the overall disease, or it can occur as an isolated leukemia not specifically associated with co-morbid conditions [92,93]. These include:

- A rare constitutional trisomy 8 syndrome associated with a characteristic facial and skeletal muscle dysmorphism, and the development of hematologic disorders, including aplastic anemia, myelodysplasia, and acute and chronic myeloid leukemia [94]. Potential chromosome 8 genes associated with the development of AML are reviewed in detail in subsequent sections of this topic review, and include the ETO gene, involved in the t(8;21)(q22;q22) translocation and the MOZ gene, involved in FAB M4/M5 leukemias with a t(8;16)(p11;p13) translocation [95,96].
- In Down syndrome (trisomy 21) there is a 10- to 18-fold increased risk for leukemia [97-99]. In individuals under the age of three, the leukemia is most frequently AML of the FAB-M7 (megakaryoblast) subtype. In studies of children with Down syndrome-associated transient myeloproliferative disorder or acute megakaryoblastic leukemia, almost all had acquired mutations in GATA-1, a transcription factor which, among other functions, plays an important role in megakaryocyte development [100-106]. (See "Megakaryocyte biology and the production of platelets", section on GATA-1 transcription factor and see "Clinical features and diagnosis of Down syndrome", section on Hematologic disorders).

Over the age of three, the development of ALL is more common. From the study of atypical karyotypes, it has been possible to narrow down the critical region for leukemia. This region includes the AML1 locus on 21q22.3, which encodes the alpha subunit of core-binding factor (CBF), and is the site of recurrent t(8;21)(q22;q22) translocations in AML [95,107] (see "Involvement of core binding factor" below).

Familial disorders leading to AML — Inherited disorders associated with defective DNA repair have also been associated with a high incidence of hematologic malignancies, including AML. These and other familial disorders include (see "Familial platelet disorder with predisposition to AML" below) [93]:

- Bloom's syndrome, in which AML, ALL, lymphoma or other malignancies occur in about 25 percent of affected individuals [108,109].

- Fanconi's anemia, in which approximately 52 percent of patients develop AML or myelodysplasia by the age of 40 [110] . (See "Inherited aplastic anemia in children", section on Fanconi anemia).
- Neurofibromatosis, which results from mutations in the neurofibromin tumor suppressor gene on chromosome 17q11.2 and is associated with the development of juvenile CML, ALL, lymphomas, and a disproportionately high rate of MDS evolving into AML in young patients [111,112] .
- Li-Fraumeni syndrome, which occurs as a consequence of dominantly inherited germline mutations of the p53 tumor suppressor genes, and is associated with the development of multiple types of tumors, occasionally including leukemia.
- Wiskott-Aldrich syndrome, an X-linked immunodeficiency syndrome associated with the occasional development of lymphomas, AML, and ALL [113] . (See "Combined immune deficiencies", section on Wiskott-Aldrich syndrome).
- Kostmann's syndrome (infantile agranulocytosis), which has been associated with mutations in the G-CSF receptor on chromosome 1p35-p34.3 [114,115] . (See "Congenital neutropenia", section on Acute myeloid leukemia and myelodysplasia).
- Diamond Blackfan anemia (congenital hypoplastic anemia) and growth retardation [116] .

Several families have been reported in which multiple siblings have developed childhood onset of myelodysplasia with bone marrow monosomy for chromosome 7, followed by evolution to AML [117] . The inheritance pattern is autosomal recessive. Autosomal dominant patterns of inheritance of leukemia have also been reported, with a variety of morphologic and cytogenetic subtypes [118-121] . Some are associated with an antecedent myelodysplastic syndrome, while others appear to arise as de novo AML.

While the environmental and hereditary conditions described above serve as excellent models for obtaining insights into the molecular pathogenesis of AML, it must be emphasized that the vast majority of patients with de novo AML show no evidence of any of these risk factors, and the etiologic factors contributing to the development of AML remain unknown. Interestingly, in a series of 127 patients with a previous primary malignancy and secondary AML, 30 percent did not receive any chemotherapy or radiation treatment prior to the development of AML [122] .

ROLE OF HEMATOPOIETIC GROWTH FACTORS — Using in vitro clonogenic assays, leukemic cells have been shown to proliferate in response to many of the endogenous hematopoietic growth factors critical for normal hematopoiesis, including granulocyte, granulocyte-monocyte, macrophage, and stem cell colony-stimulating factors (G-CSF, GM-CSF, M-CSF, SCF), interleukin 3, and Flt3 ligand (flt3-L) [123-127] , with combinations of these factors producing a synergistic growth response.

Mutations in the G-CSF receptor gene — Mutations in the granulocyte colony-stimulating factor (G-CSF) receptor gene have been described in patients with severe congenital neutropenia [115] . A number of patients with severe congenital neutropenia with documented nonsense mutations in the G-CSF receptor have developed AML, supporting the notion that defective signaling function by the aberrant receptor increased the susceptibility to AML [128] . It is also possible that mutations in the G-CSF receptor predispose to the myelodysplastic syndrome [129] , or to AML via a resistance to apoptosis [130] , allowing more time for a "second hit" mutation to occur. (See "Congenital neutropenia", section on Acute myeloid leukemia and myelodysplasia).

In a substantial number of patients with AML, autonomous growth has been reported to occur as a result of autocrine or paracrine stimulation by a number of factors, including G-CSF, GM-CSF, IL-1b, and IL-6 [131,132] . Several investigators have noted that the presence of autonomous growth

characteristics by AML cells grown in vitro correlates with lower remission rates, and poor survival [133,134] . In a multivariate analysis, expression by leukemic blasts of c-mpl, the receptor for thrombopoietin, correlated with a significantly decreased remission duration in patients with AML [135] .

Several explanations for these observations have been proposed. One possibility is that the acquisition of autonomous growth capability allows AML cells to become more aggressive, by making them independent of stromal cell production of essential growth factors [134] . Others have suggested that autonomous production of growth factors, such as GM-CSF, may reduce the cytotoxicity of chemotherapy agents, by altering intracellular drug metabolism [136] . Some data suggest that exogenously administered, as well as endogenously produced, hematopoietic growth factors not only stimulate in vitro growth and proliferation, but also inhibit apoptosis of AML cells [137,138] .

As a result of in vitro data demonstrating the growth-promoting effects of a variety of cytokines on AML cells, one of the controversies in the treatment of AML has centered on the use of hematopoietic growth factors during or following induction chemotherapy. The desired goal of reducing the toxicity of treatment and the duration of cytopenia with exogenous administration of G-CSF or GM-CSF has been tempered by concerns about their leukemogenic potential. A number of large, randomized clinical trials in AML demonstrate variable clinical efficacy of these growth factors with respect to significant decreases in morbidity and mortality [139] . While different conclusions have been reached regarding clinical efficacy, there is consensus about the safety and lack of increased leukemogenic potential of these growth factors when they are administered following induction or consolidation chemotherapy. (See "Treatment of acute myeloid leukemia in younger adults", section on Use of hematopoietic growth factors). Although similar theoretical arguments have been made against the use of growth factors in MDS, they appear to be safe and have a role in the treatment of selected patients. (See "Treatment and prognosis of the myelodysplastic syndromes", section on Hematopoietic growth factors).

HETEROGENEITY AMONG THE ACUTE MYELOID LEUKEMIAS — The current classification of AML relies on the morphological and cytochemical criteria of the French-American-British (FAB) classification, which assigns a single lineage to each leukemia (eg, AML FAB M0 through M7, [show table 1](#) and [show table 2](#)) [140] . This standardization has greatly improved the reproducibility of traditional AML diagnosis and classification [141,142] .

Some FAB AML subgroups correlate with selected pathologic or clinical features, such as [140,143] :

- Megakaryoblastic differentiation with marrow fibrosis — FAB M7
- Monocytic differentiation with soft tissue infiltrates — FAB M4
- Promyelocytic differentiation with disseminated intravascular coagulation — FAB M3

However, these features give few insights into the pathobiology of AML, and do not necessarily correlate with treatment outcome. Several modifications have been proposed to make the AML classification scheme more relevant to clinical decision-making, by incorporation of biologic and genetic data, including sophisticated immunophenotyping and the recurring chromosomal abnormalities which characterize subgroups of AML. As an example, one comprehensive classification system subdivides AML into two groups not recognized by traditional classification: AML evolving from prior myelodysplastic syndromes and de novo AML, and incorporates pathogenetic mechanisms and treatment responses, in addition to morphology and cytogenetics [144,145] .

Correlation between specific AML morphologic subtypes and recurring chromosome translocations that result in the creation of novel fusion genes has provided great insight into potential mechanisms of leukemogenesis and has led to important clinical observations ([show table 3](#)). Examples include:

- The association of FAB-M3 morphology in acute promyelocytic leukemia (APL) with t(15;17)(q22;q11-12) and the PML-RAR fusion gene involving the retinoic acid receptor gene on chromosome 17 ([show bone marrow 1](#)). This observation provided an explanation for the

highly effective treatment of APL with all-trans retinoic acid. (See "Molecular biology of acute promyelocytic leukemia").

- A subgroup of FAB-M2 AML with prominent Auer rods, vacuoles, and myeloblast granules has t(8;21)(q22;q22) and the AML1/ETO fusion gene ([show bone marrow 2](#)).
- A subgroup of FAB-M4 AML with atypical eosinophilic myeloblast granules (M4Eo) has inv(16)(p13q22) and the CBFb/MYH11 fusion gene ([show bone marrow 3](#)).

These three AML variants are associated with a favorable prognosis ([show table 4](#)), with the latter two responding well to consolidation treatment containing high doses of cytarabine [[146](#)]. (See "Cytogenetics in acute myeloid leukemia", section on Use for prognosis). The fusion genes created as a result of the latter two translocations contain components of the core-binding factor complex (AML1 and CBFb), which may render these leukemia cells more sensitive to the effect of cytarabine. These fusion genes, and other AML-associated chromosomal translocations are reviewed in detail below. Since specific recurring chromosomal abnormalities have prognostic relevance [[142,147,148](#)], some current AML trials stratify treatment based on the presenting cytogenetic abnormalities and known response to treatment of a specific subtype.

MOLECULAR GENETICS OF ACUTE MYELOID LEUKEMIA

Tumor suppressor genes — Abnormalities within several of the known tumor suppressor genes have been well characterized in myeloid leukemias:

- Progression to blast crisis in CML is commonly associated with p53 mutations [[149-151](#)]. (See "Molecular genetics of chronic myelogenous leukemia", section on Progression to blast crisis). In AML, only about 7 percent of cases have known p53 mutations at the time of diagnosis, although the incidence of p53 abnormalities may be slightly higher in patients with AML evolving from a prior myelodysplastic syndrome [[152](#)], and in cases with 11q23 translocations [[153,154](#)].
- The p16INK4 gene is a critical cell cycle regulatory gene which is frequently deleted in acute lymphoblastic leukemia but only very rarely in AML [[155](#)].
- Overexpression of the BCL-2 gene occurs in a wide variety of lymphoid malignancies as a result of t(14;18) which juxtaposes BCL-2 with the Ig heavy chain locus. (See "Clinical and pathologic features of follicular lymphoma", section on Oncogenes). BCL-2 overexpression in AML has been reported only rarely; however, in one study of patients with newly diagnosed AML, a multivariate analysis showed that BCL-2 overexpression was associated with lower complete remission rates and a significantly shorter survival [[156](#)].
- Patients with neurofibromatosis and mutations of the NF-1 tumor suppressor gene have a high rate of developing neoplasms, including progression of MDS into AML [[111,157](#)].
- The Wilms tumor suppressor gene (WT-1) is overexpressed in the leukemic blasts of approximately 75 percent of cases of newly diagnosed AML [[158,159](#)]. The WT-1 gene, located in the 11p13 region, encodes a transcription factor normally expressed in a time and tissue-dependent manner mainly in kidneys and gonads [[160,161](#)], although it is also expressed in normal CD34+/CD38- hematopoietic progenitor cells [[162](#)]. In AML, high WT-1 levels at diagnosis have, in some studies, been shown to correlate with lower remission rates and overall survival [[158,159](#)].
- Certain genetic alterations are specific to AML. These include the loss of the long arms of chromosomes 5, 7, and 20, which occur commonly in therapy-related AML and AML associated with prior MDS, and are associated with a poor prognosis ([show table 4](#)) [[62,65,75](#)]. The

involved genes have not yet been cloned, although novel tumor genes are likely to be identified at these loci.

RAS oncogene mutations — Mutations of three closely related RAS (H-RAS, K-RAS, N-RAS) proto-oncogenes occur in human malignancies. Each of these genes encodes a structurally similar 21 kilodalton protein which localizes to the inner plasma membrane and plays an important role in signal transduction [163]. Specific point mutations occur characteristically in each of the three genes, although no consistent karyotypic abnormalities have been associated with RAS mutation and activation [164].

Mutations of RAS have been identified in approximately 25 percent of cases of AML [164,165], and are observed with higher frequency in MDS (35 percent) [166,167]. The majority of the mutations in AML and MDS are in the N-RAS gene; K-RAS and H-RAS mutations occur less frequently. In both AML and MDS, RAS mutations have been reported more frequently in cases with a monocytic morphology (eg, FAB M4 and chronic myelomonocytic leukemia) [168]. An association between AML in patients with a variety of occupational exposures and RAS mutations has also been observed [83].

The significance of RAS mutations in AML remains unclear. RAS mutations have been reported at diagnosis, but not at relapse in some AML cases [169]. Conversely, RAS mutations have been acquired at the time of relapse or disease progression [168,170]. However, the presence of RAS mutations has been associated with improved survival [165], possibly related to a lower leukemic cell burden at presentation, or an increased sensitivity to chemotherapy with cytarabine [171].

Chromosomal translocations — Chromosomal translocations can affect the cell by one of two mechanisms [6]:

- Juxtaposition of an intact transcription unit from one chromosome to an enhancer element from a gene on another chromosome. As an example, in t(14;18), the BCL-2 gene translocates into the immunoglobulin heavy chain (IgH) locus, leading to the inappropriate expression of a normal BCL-2 gene product. (See "Clinical and pathologic features of follicular lymphoma", section on Oncogenes).
- Formation of chimeric fusion proteins. Chromosomal translocations can disrupt two different genes within their coding sequences, leading to the creation of a chimeric protein. For example, the t(9;22) in CML results in the formation of a chimeric BCR/ABL fusion protein. (See "Cellular and molecular biology of chronic myelogenous leukemia", section on Properties of the fusion protein).

In AML, the vast majority of chromosomal translocations result in the generation of chimeric fusion genes that are never expressed in wild type cells. Characterization of the genes involved in these translocations has led to the elucidation of many transcriptional regulatory pathways in hematopoiesis [5,172-174]. For example, the alpha and beta subunits of core-binding factor have been found to be required for definitive hematopoiesis; both of these subunits are involved in chromosomal translocations in AML.

The involvement in chromosomal translocations of several other classes of transcription factors has been recognized, including those that contain zinc fingers, ring fingers, leucine zippers, basic helix-loop-helix motifs, and ETS domains [175]. Homologues of these transcription factors have been well characterized in animal models such as *Drosophila*, including the AML1 homologue "runt", and the MLL homologue "trithorax". Several other proteins with well-defined hematopoietic functions have been recognized at chromosomal translocation breakpoints, including retinoic acid receptors and Hox genes. However, structural proteins that do not appear to be specific to myeloid cells have also been identified, including members of the nuclear pore complex and nucleolar phosphoproteins. The functions of many other genes involved in chromosomal translocations remain to be elucidated.

Many genes are capable of participating in translocations that involve multiple alternative partner genes. For example, the MLL gene forms chimeric fusion genes with at least 18 known partners and an additional 10 to 15 that have not yet been cloned. These alternative fusions provide an opportunity to contrast the contributions of each component of the fusion gene and thus dissect the motifs within these genes that are critical to tumorigenesis. The fusion of nucleophosmin (NPM) to ALK is a frequent recurring abnormality in anaplastic large cell lymphoma. (See "Clinical and pathologic features of anaplastic large cell lymphoma T/null cell type", section on 2;5 translocation). NPM also fuses to RARA in acute promyelocytic leukemia and to MLF1 in other subtypes of AML.

In the following sections, we will discuss specific fusion genes in the context of families of fusions that share common features. The recurring involvement of the same genes in multiple different translocations has two important implications:

- The genomic structure of these genes may contain "hot spots" for chromosomal breakage.
- Disruption of the pathways regulated by these genes results in malignant transformation, rather than cell death.

Involvement of core binding factor — Chromosomal aberrations in AML commonly involve subunits of the core-binding factor (CBF) group of transcription factors [176,177]. Members of the CBF group function as heterodimeric complexes regulating diverse target genes involved in tissue differentiation [178]. CBF factors consist of an alpha subunit that binds DNA, and a beta subunit that does not bind DNA directly but enhances binding by the alpha subunit. Three alpha subunits have been identified: AML1/CBFA2/PEBP2aB, AML2/CBFA3/PEBP2aC, and AML3/CBFA1/PEBP2aA. In view of its pivotal role in both normal hematopoiesis and leukemia, we will refer to AML1/CBFA2/PEBP2aB as AML1. As will be described below, both the alpha and beta subunits of CBF are disrupted in common subtypes of AML and form chimeric fusion transcripts with genes not normally expressed in hematopoietic cells [179].

In hematopoietic cells, CBF binding sites have been observed in genes specific to both the lymphoid lineage (T-cell receptor enhancers, CD3e, and LCK proximal promoter) and myeloid lineage (M-CSF receptor, IL-3, GM-CSF, myeloperoxidase, granzyme B, and neutrophil elastase) [5,180].

The AML1 subunit has been studied extensively in hematopoiesis. Multiple splice variants have been identified; AML1B contains the runt domain and a transactivation domain, whereas AML1A lacks the transactivation domain [181]. Disruption of AML1 by gene targeting in embryonic stem cells results in embryonic lethality due to an absence of fetal liver hematopoiesis and to central nervous system hemorrhage [182]. The knockout of CBFbeta results in a similar phenotype, indicating that both the alpha and beta subunits of CBF are essential for definitive but not primitive hematopoiesis [176,183]. The role of CBF in later stages of hematopoietic differentiation is not yet clear.

Familial platelet disorder with predisposition to AML — Familial platelet disorder with predisposition to acute myelogenous leukemia (FPD/AML) is an autosomal dominant disorder characterized by qualitative and quantitative platelet defects, a decrement in megakaryocyte colony formation, and an approximately 37 percent incidence of acute myelogenous leukemia (AML) [93,184]. In six pedigrees with this disorder and evidence of linkage to markers on chromosome 21q, nonsense mutations or intragenic deletion of one allele of AML1 (also called RUNX1 or CBFA2) were seen in four and missense mutations in two [185].

In a three-generation family with FPD/AML, a missense mutation in the Runt DNA-binding domain of the CBFA2 gene (RUNX1/AML1) was found [186], three residues away from the one noted above [185]. One family member with AML underwent successful transplantation with cells from his HLA-matched sister. Subsequently, he developed MDS progressing to AML, with malignant cells of donor origin. Concurrently, the donor, who had the same genetic defect as her brother, developed MDS progressing to AML, and was successfully transplanted using a matched unrelated donor.

Of interest, a mouse model heterozygous for the RUNX1 null mutation, considered to be genetically comparable to human FPD/AML patients, was not associated with the development of leukemia, suggesting the requirement for additional genetic or epigenetic alterations. Insertion of a RUNX1 mutation into BXH2 mice, which develop myeloid leukemia following random integration of a murine retrovirus, resulted in a shortening of the latency period for the development of leukemia [187] .

Other causes of familial AML — A family has been described in which three members were affected by AML associated with an identical mutation in CEBPA, the gene that encodes CCAAT enhancer binding protein alpha, a granulocytic differentiation factor [93,188] . Acquired mutations of this gene have also been described in sporadic, nonfamilial AML [189] .

AML and MDS — Point mutations of AML1 (RUNX1) have been infrequently reported in de novo AML or MDS, at incidences varying from zero to 12 percent [190-192] . In one study of 132 patients with primary MDS, the presence of these mutations was associated with a significantly higher frequency of chromosome 7/7q deletion as well as shortened overall survival [192] .

In a study from Japan, such mutations were found in 6 of 13 Atom-bomb survivors who developed MDS, and in 5 of 13 patients who developed AML/MDS following alkylating agent treatment with or without supplementary radiation [190] .

AML1/ETO in t(8;21) — The t(8;21)(q22;q22) is associated with the FAB-M2 subtype of AML ([show bone marrow 2](#)), and was the first recurring chromosomal translocation in AML to be identified [95] . The clinical and morphologic correlations of this subtype of AML include a high propensity to develop extramedullary collections of leukemic blasts (granulocytic sarcomas). Another hallmark of t(8;21) leukemia is the relatively high rate of responsiveness to chemotherapy, particularly to high dose Ara-C [146] .

Leukemic myeloblasts in this subtype have a characteristic morphology, including prominent Auer rods, large cytoplasmic granules, and vacuoles. When the characteristic histologic appearance of these cells is identified in AML blasts that do not contain a t(8;21), the AML1/ETO fusion can be identified by polymerase chain reaction techniques, indicating that the formation of the molecular fusion is responsible for the morphologic and clinical features of this subtype of AML [193] .

In t(8;21), AML1 fuses to the ETO gene on the der(8) chromosome to form a chimeric fusion protein [194] . The chimeric protein fuses the N-terminus of AML1 including the runt homology domain, but excluding the transactivation domain, to nearly all of ETO. The AML1/ETO fusion gene has pleiotropic effects in reporter gene assays as it appears to repress several AML1 target genes [195,196] , but to activate the M-CSF receptor promoter [197,198] . (See "Regulation of myelopoiesis", section on Transcription factors).

By engineering a "knock-in" of the ETO cDNA into the murine AML1 locus, a mouse model of t(8;21) has been generated. These mice exhibit a mid-gestation embryonic lethality with an absence of fetal liver hematopoiesis and central nervous system hemorrhage that is similar to the AML1 and CBFb knockout mice [199] . This result suggests that the AML1/ETO fusion gene can act as a dominant negative of normal AML1 function.

AML1/EAP, MDS1, EVI1 in t(3;21) — The t(3;21)(q26;q22) has been observed in the blast crisis of CML and therapy-related MDS and AML [200] . The AML1 gene has been found to be rearranged in these cases, leading to the formation of alternative fusion transcripts involving the EAP, MDS1, and EVI1 genes [201,202] . These fusions contain the N-terminus of AML1, including its runt homology domain, fused to alternative C-terminal sequences derived from partner genes on 3q26. EVI1 is also involved in the inv(3)(q21q26) and t(3;3)(q21;q26) in AML [203] . However the consequence of these chromosome aberrations is the inappropriate expression of the EVI1 transcription unit, whereas in the t(3;21), EVI1 participates in the formation of a fusion gene with AML1. Sequences from another transcription unit, MDS1, are also observed in t(3;21). Although mapping data indicate that the exons of MDS1 and EVI1 are separated by several hundred kilobases, they have been found to be spliced

together not only in cases with the t(3;21), but also in normal tissues. The AML1-MDS1 fusion has been shown to transform the Rat1A fibroblast cell line [204] .

TEL(ETV6) and AML1 in t(12;21) — AML1 is involved in the t(12;21)(p13;q22), resulting in the generation of a chimeric protein with the TEL(ETV6) gene [205] . The t(12;21) fusion is observed commonly in pre B-cell ALL. The TEL(ETV6) gene was originally cloned from a t(5;12)(q33;p13) in CMML where it fuses to the PDGFR β gene and it has also been found to fuse to the ABL gene in t(12;22) in AML [206,207] .

CBF β /MYH11 in inv(16) and t(16;16) — The inv(16)(p13q22) and t(16;16)(p13;q22) are observed primarily in the FAB-M4Eo subtype of AML ([show bone marrow 3](#)). These patients, similar to those with the t(8;21), have a relatively good prognosis and a high likelihood to respond to high dose Ara-C-containing chemotherapy regimens [208] . The beta subunit of CBF located at 16q22 is disrupted as a result of either the chromosomal inversion or translocation, leading to the formation of a fusion transcript with the gene for smooth muscle myosin heavy chain, MYH11, located at 16p13 [209] .

A mouse model for inv(16) leukemia has been generated through a "knock-in" approach [210] . These mice exhibit a mid-gestation embryonic lethality, an absence of fetal liver hematopoiesis, and central nervous system hemorrhage. The chimeric mice generated from embryonic stem cells containing the CBF β /MYH11 did not develop leukemia. However, there was no contribution by the embryonic stem cells to hematopoiesis. Thus, a striking similarity has been observed for the knockouts of AML1 and CBF β , as well as the AML1/ETO and CBF β /MYH11 "knock-in" mice. This convergence in phenotypes from seemingly disparate gene targeting experiments indicates that AML1 and CBF β are both essential for definitive hematopoiesis, and that both are required for the function of the CBF heterodimer.

Involvement of the retinoic acid receptor — The cytogenetic hallmark of acute promyelocytic leukemia (APL, FAB-M3), is a translocation involving the RAR α locus on chromosome 17 [211] . (See "Molecular biology of acute promyelocytic leukemia"). The vast majority of these cases contain a t(15;17)(q22;q11-12), although several variant translocations involving RAR α have been identified. These include PLZF in t(11;17)(q23;q11-12) and NPM in t(5;17)(q35;q11-12). These translocations lead to the formation of chimeric fusion transcripts from each of the derivative chromosomes. The pathobiology of APL is discussed in detail separately. (See "Molecular biology of acute promyelocytic leukemia").

Involvement of the MLL locus — Translocations involving chromosome band 11q23 occur frequently in both AML and ALL, and have several unique features compared to other subtypes of leukemia. There are at least 51 different partner chromosomes involved in recurring reciprocal 11q23 translocations [63,212,213] . This exceeds the number of known translocations affecting the immunoglobulin loci, suggesting that the 11q23 breakpoint region may contain genomically unstable sequences leading to recombination events.

Translocations involving 11q23 are the single most common cytogenetic abnormality in infants with acute leukemia, regardless of phenotype, and occur in approximately 70 to 80 percent of cases. 11q23 translocations are also observed frequently in therapy-related leukemias in patients who have previously been treated with drugs that inhibit topoisomerase II, especially the epipodophyllotoxins. (See "Cytogenetics in acute myeloid leukemia", section on Therapy-related MDS/AML). This syndrome differs from the therapy-related myeloid leukemias that occur in patients exposed to alkylating agents, which are commonly associated with deletional events on chromosomes 5 and 7.

The chromosomal partners in 11q23 translocations are usually lineage specific. In AML, t(9;11)(p22;q23), t(11;19)(q23;p13.1) and t(6;11)(q27;q23) are the most common, and in ALL, t(4;11)(q21;q23) and t(11;19)(q23;p13.3) occur predominantly. Translocations at 11q23 have been observed in several FAB subtypes, but occur most commonly in the FAB-M4 myelomonocytic and FAB-M5 monoblastic leukemias [212,214,215] . Myeloid leukemias with 11q23 translocations often coexpress lymphoid markers, whereas 11q23 lymphoid leukemias often express myeloid or monocytoid markers in addition to B-cell markers. These observations suggest that rearrangements of

MLL may affect a pluripotent stem cell or, alternatively, that disruption of MLL may affect a common differentiation pathway shared by lymphoid and myeloid progenitor cells.

The MLL gene was isolated from the 11q23 breakpoint by several groups and is referred to by other names including HRX, ALL-1, and Htrx [216-219]. MLL encodes a large protein, with a predicted molecular weight of 430 kD, that contains two regions of extensive homology to the *Drosophila* trithorax gene [220].

In a subset of patients with AML and either trisomy 11 or a normal karyotype, a unique pattern of rearrangement of the MLL gene has been observed. As in the translocations that affect MLL, a fusion occurs involving one of the exons in its breakpoint cluster region. However, rather than fusing to a partner gene, the fusion is to 5' sequences from MLL itself [221,222]. These partial duplications of MLL appear to occur primarily in older patients, and are infrequent in childhood and therapy-related leukemias. The morphology of the leukemias also differs in that the partial duplication patients usually are classified as FAB M1 or M2, rather than the M4 or M5 typically observed in cases with MLL translocations.

To create an MLL-AF9 "knock-in" mouse model of 11q23 leukemias, the AF9 cDNA was targeted into the murine MLL locus by homologous recombination in embryonic stem cells [223]. The chimeric mice generated from these embryonic stem cells all developed acute myeloid leukemia within 6 to 9 months.

Retroviral bone marrow infection has been used to express another 11q23 fusion gene, MLL-ENL, in hematopoietic cells [224]. After transplantation of MLL-ENL transduced bone marrow, recipient mice developed acute myeloid leukemia. These models have established the proof of principle that the expression of MLL fusion genes contributes to leukemogenesis, and that the MLL partner genes are essential to this process [213,225].

OTHER FUSION GENES IN AML

DEK/CAN in t(6;9) and SET-CAN — The t(6;9)(p23;q34) is observed usually in the M2 and M4 subtypes of AML, but has also been identified in the M1 subtype and MDS. This translocation is associated with a younger age and a poor prognosis. The CAN gene was also found to be rearranged in a patient with acute undifferentiated leukemia and a normal karyotype. A chimeric transcript containing an alternative CAN partner gene, named SET, was isolated in this case [226]. The SET gene was also localized to 9q34, suggesting that this fusion results from an inversion of chromosome 9 or a cryptic translocation.

TLS/FUS/ERG and t(16;21) — The t(16;21)(p11;q22) has been observed in several FAB subtypes of AML, blast crisis of CML, and MDS [227,228]. In this translocation, the TLS/FUS gene at 16p11 fuses to the ERG gene at 21q22 to generate a chimeric protein. Both TLS/FUS and ERG are involved in chromosomal translocations with other partner genes in sarcomas [229-231]. The striking similarity of the TLS/FUS/ERG fusion gene in AML to the sarcoma associated fusion genes suggests that disruption of a common differentiation pathway may lead to transformation in multiple cell types.

NPM/MLF1 in t(3;5) — The t(3;5)(q25.1;q35) has been observed in several FAB subtypes of AML, especially in M6 and MDS [232]. The NPM gene at 5q35 was found to be rearranged in patients with this translocation, resulting in the formation of a fusion gene with the MLF1 (myelodysplasia-myeloid leukemia factor 1) gene at 3q25.1. Previously, the involvement of NPM had been identified in the t(2;5)(p23;q35) in anaplastic large cell lymphoma, where it fuses to the ALK gene [233]. NPM is also rearranged in the t(5;17)(q35;q21) in APL, where it fuses to RAR α , as discussed above.

The MLF1 protein normally localizes to the cytoplasm, whereas in leukemia cells with t(3;5), the NPM-MLF1 fusion protein is observed primarily in nucleoli. The involvement of NPM in chromosome translocations involving three different partner genes, resulting in three discrete types of hematologic malignancies, suggests that NPM plays an important role in normal hematopoietic differentiation.

EVI1 in inv(3) and t(3;3) — EVI1 (Ecotropic Virus Integration 1) was initially cloned as the gene at a common site of retroviral integration in murine myeloid leukemia. The EVI1 gene is normally expressed only in kidney and ovary. In mice, the retroviral integration at the murine Evi-1 locus leads to its inappropriate expression in hematopoietic cells. A similar phenomenon occurs in human AML with inv(3)(q21q26) and t(3;3)(q21;q26). As a result of these cytogenetic aberrations, the EVI1 gene is juxtaposed to enhancer elements of the Ribophorin gene leading to inappropriate activation of the EVI1 transcription unit, a component of the complex fusion transcripts that involve the AML1 gene in t(3;21).

MOZ/CBP in t(8;16) — The t(8;16)(p11;p13) has been recognized in the M4 and M5 subtypes of AML that exhibit a characteristic erythrophagocytosis [234]. This translocation has been observed in both de novo and therapy-related leukemias. Several variant translocations involving 8p11 have been recognized in monocytic leukemias with erythrophagocytosis, but the genes involved in these translocations have not yet been cloned. CBP is also involved with a fusion to MLL in t(11;16)(q23;p13) [235].

CALM/AF10 in t(10;11) — The t(10;11)(p13;q14) has been recognized in both ALL and AML. In AML, the cases are primarily of the M0 and M1 subtypes.

NUP98/HOXA9 in t(7;11) and NUP98/DDX10 in inv(11) — The t(7;11)(p15;p15) is observed in the M2 and M4 subtypes of AML and CML. The HOXA9 gene was identified at the 7p15 breakpoint and the NUP98 gene at the 11p15 break [236]. In BXH-2 mice, the Hoxa9 gene has been implicated in myeloid leukemia as a result of its activation via proviral insertion. NUP98 has been found to be involved in the inv(11)(p15q22) in AML. This cytogenetic aberration has been recognized in both de novo and therapy-related MDS and AML.

ANIMAL MODELS OF AML — There are several examples of naturally occurring animal models of AML that are caused by retroviruses via one of two mechanisms. The retrovirus can:

- Encode for an oncogene that leads to transformation, or
- It can inappropriately activate the expression of a gene adjacent to its integration site

The characterization of these processes has revealed a number of genes critical to normal hematopoiesis and myeloid leukemias. These animal models have also demonstrated the multistage nature of the evolution of leukemia.

Myb leukemias — The v-Myb gene is involved in two different avian retroviruses that induce leukemia in chickens. The v-Myb gene was originally identified as the transforming element in the avian myeloblastosis virus (AMV). In the E26 retrovirus, a fusion gene consisting of gag, v-Myb, and v-Ets has been identified [237]. The formation of a fusion gene containing sequences of two transcription factors is reminiscent of the fusions that result from chromosomal translocations in human acute leukemia. In chickens, AMV causes monoblastic leukemias and transforms only myelomonocytic cells in vitro, whereas E26 induces erythroleukemias, but is capable of transforming myeloid, erythroid, and megakaryocytic lineages in vitro [238].

C-Myb, the normal cellular counterpart of v-Myb, is essential for definitive hematopoiesis [239]. Promonocytic leukemias have been induced by priming mice with intraperitoneal injections of pristane, followed by infection with the Moloney murine leukemia virus [240]. The majority of the mice that develop leukemia have undergone insertional mutagenesis at the c-Myb locus [241]. The role of pristane is unknown, but it appears to promote leukemogenesis by mediating an inflammatory response. At this time, there is no evidence for the rearrangement of c-Myb in human leukemias.

Friend virus/SFFV erythroleukemia — The erythroleukemia induced by infection with the Friend viral complex is the culmination of a three step process that has become a paradigm for multistage neoplastic transformation [242]:

- Polyclonal proliferation induced by a cytokine
- Inactivation of a tumor suppressor gene
- Oncogenic activation of a gene involved in normal hematopoiesis

Infection of susceptible mice with the Friend murine leukemia virus/spleen focus-forming virus (SFFV) complex induces a polyclonal proliferation of erythroid progenitors within 48 hours. This expansion of erythroid precursors is secondary to the SFFV envelope gene product, the gp55 glycoprotein, that has the capacity to bind and activate the erythropoietin receptor. These erythroid cells are not transformed, and retain the ability to undergo terminal differentiation.

After approximately two weeks, a clonal population of transformed erythroblasts emerges which depends on two additional independent genetic events. One of these is the inactivation of the p53 tumor suppressor gene by deletion, mutation, or proviral insertion [243,244]. In addition, the activation of either the PU.1 gene, also referred to as Spi-1 (SFFV proviral integration 1), or the Fli-1 gene occur as a result of proviral integration adjacent to these loci [245,246]. PU.1 and Fli-1 are members of the ETS family of transcription factors; PU.1 is essential for both myeloid and lymphoid development [247].

BXH-2 leukemias — BXH-2 mice are derived from a cross of C57BL/6J and C3H/He mice. Although the parental strains have a low incidence of leukemia, more than 95 percent of BXH-2 mice develop myeloid leukemia by one year of age, caused by expression of a horizontally transmitted Ecotropic murine leukemia virus [248]. These retroviruses induce leukemia by insertional activation or mutation of proto-oncogenes adjacent to the viral integration site. One of the most frequent viral integration sites is Evi-2 (Ecotropic viral integration site 2), localized to a large intron within the Nf1 tumor suppressor gene [249]. The consequence of this integration event is the disruption of the normal expression of Nf1 in the affected mice.

In humans, the neurofibromatosis type I autosomal dominant disorder is caused by mutation of the NF1 gene [250]. In addition to neurofibromas, patients have an increased risk of developing several types of solid tumors and malignant myeloid disorders, especially juvenile chronic myelogenous leukemia (JCML) and the monosomy 7 syndrome [251].

Mice heterozygous for the Nf1 allele develop myeloid leukemia with loss of the wild type allele, indicating that Nf1 acts as a tumor suppressor gene [252]. In JCML patients without neurofibromatosis, activating RAS mutations are frequently identified. The consequence of either the disruption of NF1 or the activation of RAS has been shown to be an inability to negatively regulate GM-CSF signalling in hematopoietic cells [253,254].

Because viral integration within the Nf1 gene has been observed in only 15 percent of BXH-2 mice, the identification of additional mutations within other genes associated with myeloid leukemias has been pursued. A proviral tagging approach has been used to identify additional viral integration sites that alter the expression of three genes, Hoxa7, Hoxa9, and Meis-1 [255,256]. The HOXA9 gene is involved in t(7;11)(p15;p15) in AML, resulting in the formation of a fusion gene with NUP98. PBX1 is involved in t(1;19) in ALL, where it fuses to the E2A gene. This underscores a recurring theme of the involvement of similar families of genes in both human and spontaneous animal models of AML.

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