Molecular Medicine 6(7): 555–567, 2000

Molecular Medicine

Review Article

Molecular Defects in Chronic Myeloproliferative Disorders

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Accepted May 8, 2000

Introduction

With the exception of chronic myeloid leukemia (CML), the molecular defects in chronic myeloproliferative disorders (MPDs) have not been elucidated. This poor molecular understanding may contribute to the poor and frequently inaccurate classification of these diseases. MPDs are characterized by clonal proliferation of differentiated myeloid cells, and their manifestation can overlap with those of myelodysplastic syndrome (MDS). For example, various degrees of dysplasia can be seen in chronic myelomonocytic leukemia (CMML), along with significant proliferation in hematopoietic elements in the bone marrow and peripheral blood. Similar proliferation can be seen in some MDS patients, but without effective hematopoiesis leading to pancytopenia. In fact, for this reason, many pathologists and hematologists consider CMML a category independent of MPDs and different from MDS (1).

The traditional MPDs include CML, polycythemia vera (PV), essential thrombocythemia (ET), and agnogenic myeloid metaplasia (AMM) (2,3). However, entities such as chronic neutrophilic leukemia (CNL) (4,5), hypereosinophilic syndrome (6,7), mastocytosis (8,9), and the 8p11 myeloproliferative syndrome (10,11) are also considered MPDs. Discussing these entities alongside classical MPDs is important, because it may provide information on the common biology and molecular abnormalities between these clinically overlapping diseases. Despite the rarity of 8p11 myeloproliferative syndrome, its molecular defects are better characterized than those in most of the MPDs. This is due to its association with a specific cytogenetic abnormality. As molecular techniques improve and genome-wide screening becomes more available, defining the molecular abnormalities underlying other MPDs will become more feasible. Better understanding of molecular abnormalities in CML has lead to significant advances in treatment and management. The hope is that with better understanding of the molecular defects in the rest of the MPDs, better therapies will be developed.

In this review, we discuss the known molecular and biological abnormalities in various MPDs and speculate on a general molecular abnormality or pathway that these diseases may share. We do not discuss the substantial research that has established the clonal nature of primary MPDs, which involve G6PD and X-chromosome activation (12–16). Rather, our discussion will be restricted to acquired primary MPDs. We also do not address hereditary or secondary MPDs.

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Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) has an incidence of 1–2 cases per 100,000 people per year and accounts for 15% of leukemias in adults (17–20). The median age of presentation is 45–50. Fifteen percent of patients with CML

present with an accelerated or blastic acute phase of disease. The blasts can be of myeloid or lymphoid origin. The hallmark of CML is the Philadelphia chromosome, a well-characterized abnormality found in up to 95% of patients. The Philadelphia chromosome represents the addition of a 3′ segment from the Abelson (ABL) gene on chromosome 9q34 to a 5′ segment from the breakpoint cluster region (BCR) gene on chromosome 22q11 (17). This t(9;22)(q34;q11) translocation creates a functional fusion gene (Fig. 1) that can give rise to four different chimeric mRNAs, depending on the breakpoint on chromosome 22 within the BCR gene. Fusion of exon e1 from the BCR gene with a2 from ABL gives rise to a 190-kD BCR-ABL fusion protein. This fusion is commonly seen in acute lymphoblastic leukemia with a Philadelphia chromosome, but also is reported in rare cases of CML (21). Fusion of either BCR exon b2 or b3 and ABL exon a2 gives rise to a 210-kD fusion protein, which is seen in CML. Rare cases of CML are reported to show fusion between BCR exon e19 and ABL exon a2, which gives rise to a 230-kD fusion protein (22,23). Clinical features, prognosis, and response to therapy are similar in patients with b2a2 and b3a2 fusions (24). However, slightly higher platelet counts are reported in patients with the b3a2 fusion. Transcription of both b2a2 and b3a2 also can be seen in some cases of CML. The t(9;22) translocation that leads to the expression of 230 kD e19a2 fusion protein is associated with a clinical presentation similar to chronic neutrophilic leukemia with thrombocytosis. The expression of the 190-kD fusion protein in patients presenting with CML appears to be associated with monocytosis (21).

It is believed that the BCR-ABL fusion protein plays a central role in the leukemogenesis of CML for its ability to transform cells in tissue culture and in transgenic mice (25–27). The ABL protein plays an important role in signal transduction and regulation of cell growth. Its N-terminus contains the sequence of a domain responsible for tyrosine kinase function and the C-terminus contains a DNA binding domain and a nuclear localization sequence (17). It is believed that the added segment of the N-terminus of the BCR gene in the fusion BCR-ABL protein increases its tyrosine kinase activity

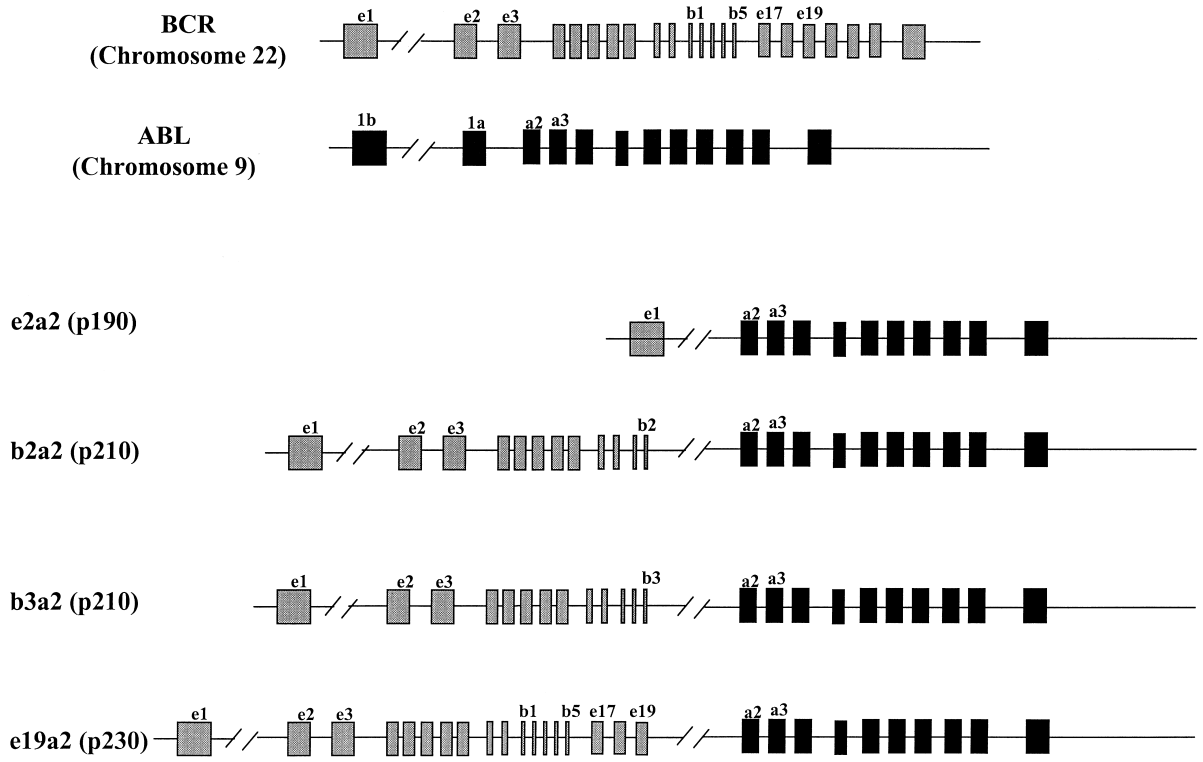

Fig. 1. Schematic map of the BCR, ABL, and BCR-ABL fusion genes. Exons of the ABL gene are shown as solid boxes and exons for the BCR gene are shown as shaded boxes. BCR, breakpoint cluster region; ABL, Abelson.

and leads to constitutive overactivity of its tyrosine phosphokinase. The 190-kD fusion protein has higher tyrosine phosphokinase activity than the 210-kD protein, which may explain its manifestation as acute leukemia, rather than chronic disease (18–19). In addition, the BCR portion of the fusion protein may bind other coregulators, such as the growth factors receptor-bound protein 2 (GRB2), CT-10 regulated kinase (CRK) oncogene-like protein (CRKL), casitas B lineage lymphoma protein (CBL), and Rous sarcoma virus (SRC) homology-2-containing protein (SHC) (17–20). The binding of the GRB2 protein to the BCR portion of the BCR-ABL protein leads to activation of the sarcoma virus (RAS) pathway. This was confirmed by showing that expression of dominant-negative forms of RAS blocks the transforming function of BCR-ABL fusion constructs (28). BCR-ABL fusion protein also activates the c-myelocytomatosis (c-MYC) pathway through E2F1, the just another kinase-signal transducer and activator of transcription (Jak-STAT) pathway, and the protein kinase B (AKT) pathway through the phosphatidylinositol-3 kinase (PI3K; Fig.2) (17,18).

Diagnosis of CML is easily established by the presence of leukocytosis, basophilia, eosinophilia, and the Philadelphia chromosome. However, in approximately 10% of CML patients, the Philadelphia chromosome cannot be detected by standard cytogenetic studies. In these cases, molecular analysis by Southern blots analysis, reverse transcriptase/polymerase chain reaction (RT-PCR), or fluorescent in situ hybridization (FISH) is needed for demonstration of fused BCR-ABL.

Several recent reports demonstrate that the BCR-ABL fusion transcript can be detected in normal individuals who have no evidence of disease and that this detection rate increases with age (29,30). This raises the possibility that the presence of this molecular abnormality, by itself, is inadequate for complete manifestation of the disease and that additional molecular or immunological abnormalities must be present in CML patients.

The progression of CML into the accelerated or blastic acute phase is frequently associated with additional genetic abnormalities, including monosomies of chromosomes 7, 17 and Y, trisomies of chromosomes 8, 17, 19, and 21, translocation t(3;21)(q26;q22), and double Philadelphia chromosomes (Table 1) (17,18, 31,32). These cytogenetic abnormalities are reported in 50%–80% of patients whose disease progresses into acute phase. Specific molecular abnormalities (33–37), including mutations in p53 and RAS genes (32,33,37), mutations and deletions in Rb (34), amplification of MYC (35), deletion of $p16^{INK4a}$ (36), rearrangement of acute myeloid leukemia (AML1) on chro-

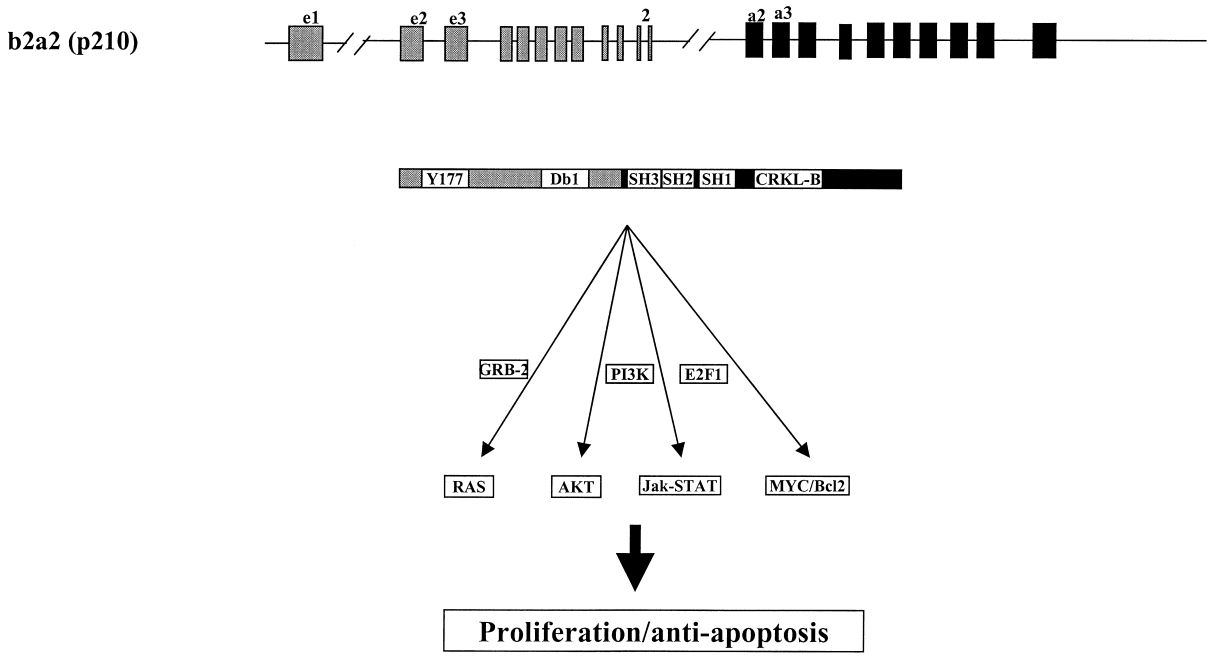

Fig. 2. Schematic representation of various pathways that are activated by the BCR-ABL fusion protein. BCR, breakpoint cluster region; ABL, Abelson.

Table 1. Cytogenetic and molecular abnormalities in MPDs

Disease	Genes	Cytogenetics	References
CML	BCR, ABL P53, Rb, $p16^{ink4a}$, RAS, EVI 1, AML	t(9;22) –7, –17, –Y, +17, +21, t(3:21)(q26:q22)	17–20, 31, 32–38
CNL		del (20q), del (11q14), t(2;2)(q32:p24)	38–40
CMML	RAS, Tel, PDGFR, NF1	t(5;12)(q33:p13), t(5;10) t(5;7)(q33;q11.2), +8, –5, –7, –11, del(14q), t(3;6), t(8;9)	41–49
PV	EPO and EPO-receptor Jak-STAT	+8,+19, del(20q), t(Y;1), t(3;17), del(13q)	50–54, 59–61
ET		+8, t(X;5), inv 3, t(13;14), t(2;3), 11q21	63–67
AMM		del(3q), del(13q), t(1;20), t(1;7), 5q–, 7q–, +9, del(20q), t(4;13), der(1q9p), +8, t(5;17)	83–91
JCML	RAS, NF1	–7,7q–	95–98
Hypereosinophilic Syndrome		Dic(1,7), del(20q), –7, +8	102–105
Mastocytosis	c-kit receptor	+8, +9	110–114
8p11 Myeloproliferative Syndrome	FGFR1, ZNF198 (FIM, RAMP), FOP, MOZ,	t(6;8), t(8;9), t(8;13), t(8;14)	115–120

MPDs, myeloproliferative disorders; CML, chronic myeloid leukemia; CNL, chronic neutrophilic leukemia; CMML, chronic myelomonocytic leukemia; PV, polycythemia vera; ET, essential thrombocythemia; AMM, agnogenic myeloid metaplasia; JCML, juvenile chronic myeloid leukemia.

mosome 21q22 (31), and abnormalities in (EVI-1) ecotropic virus integration site-1 gene on 3q26 (32) are associated with transformation or acceleration of the disease.

Chronic Neutrophilic Leukemia

Chronic neutrophilic leukemia (CNL) is an extremely rare disease, characterized by increased peripheral blood neutrophils and splenomegaly (4,5). Patients' white cell counts are usually higher than 30×10^9/l. Although this disease may overlap with CML, little is known about the molecular defects that drive the abnormal proliferation of the neutrophils. Deletions at 11q14 (38) and on the long arm of chromosome 20 (39) are reported in this disease (Table 1). Hasle et al. (40) reported t(2;2)(q32;p24) trans-location in this disease. Distinguishing CNL from CMML can be very difficult, because both diseases overlap in many aspects. However, CNL is distinguished by the lack of monocytosis and by the relatively higher white cell counts. Our preliminary data suggest that CNL cases show no increases in apoptosis levels; whereas, CMML cases demonstrate significant levels of apoptosis (Fig. 3).

Chronic Myelomonocytic Leukemia

Chronic myelomonocytic leukemia (CMML) is generally classified as MDS, however, all cases of CMML show several proliferative features,

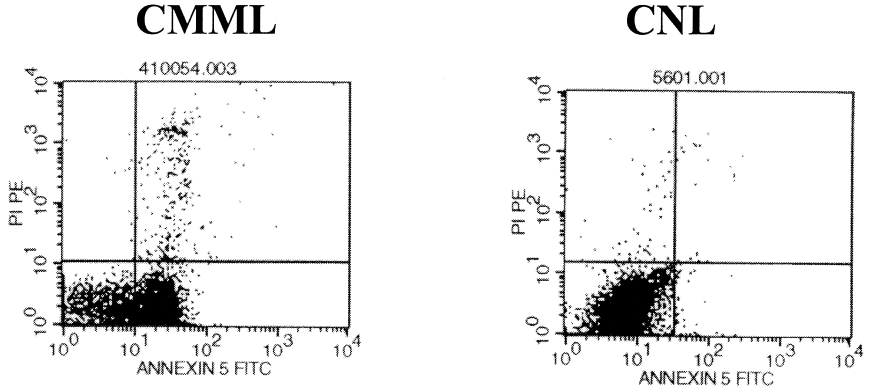

Fig. 3. Difference in apoptosis between CMML and CNL, as demonstrated by the cell surface expression of Annexin V. CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia; FITC, fluorescein isothiocyanate; PI, propidium iodide; PE, phychoerythrin.

in addition to apoptosis, that distinguish this disease from MDS. The proliferative nature of CMML recently was recognized in the new World Health Organization classification (1), where CMML was separated from MDS and classified as a separate proliferative disease. Monocytosis ($>1000 \times 10^6$/l), sometimes with mild eosinophilia and basophilia, is characteristic of CMML. In most cases, the morphology of the monocytes is normal, with little or no dysplasia. However, some cases show abnormal dysplastic morphology. Using loss of heterozygosity (LOH) in patients with –7 and –5 chromosomal abnormalities or X-chromosome activation, we can demonstrate the clonal nature of the monocytes in this disease (Fig. 4). Mutations and activation of the RAS oncogene are the most consistent findings in this disease. Our data indicates that approximately 35% of CMML patients carry mutations in RAS (41–43). However, it is believed that in most cases in which the RAS oncogene is not mutated, defects in related genes in the RAS pathway cause activation of the RAS pathway. Abnormalities in the neurofibromatosis 1 (NF1) gene are reported in this disease (44). Chromosomal t(5;12) (q33;p13) translocation involving the tel gene (chromosome 12) and the platelet-derived growth factor receptor β (PDGFRβ) gene (chromosome 5) are reported in some cases of CMML (45–48). In this translocation, the tel gene, which is a member of the Ets family and contains a helix-loop-helix (HLH) domain, is believed to be responsible for dimerization and activation of the PDGFRβ. This leads to increased kinase activity and localization of PDGFRβ to the nucleus in a fashion similar to activation of the BCR-ABL and RAS oncogene pathway. Activation of PDGFRβ in CMML also is reported in similar translocations involving chromosome 5 (Table 1) translocation (46). Abnormalities in chromosomes 5, 6, 7, 8, and 14 also are reported in CMML (Table 1) (47–49). Adult CMML is clinically and biologically similar to the juvenile chronic myeloid leukemia (JCML), which is seen in children and is reported to have high incidence of deletion of the NF1 gene (see below).

Polycythemia Vera

Polycythemia vera (PV) is a clonal disease characterized by excessive production of all bone marrow elements, including red blood cells, granulocytes, and megakaryocytes (2,3). The disease starts in a proliferative phase and usually ends with marrow fibrosis. The diagnosis of PV is usually established by the presence of specific clinical and laboratory criteria, including increased red blood cell mass, but normal arterial oxygen saturation, splenomegaly, thrombocytosis, leukocytosis, increased neutrophil alkaline phosphatase levels, and increased serum vitamin B12 levels (2). The disease is relatively rare (5–10 cases per million people). The most common cytogenetic abnormalities reported in PV are +8, +9, and del(20q) (50–52), but abnormalities involving chromosome 3 and 13 also are reported (53–55). The molecular defects in this disease are not known. However, it is believed that the major abnormality in this disease lies in the erythroid lineage and is due to the disproportional increase in proliferation of the erythroid cells. Several investigators reported increased sensitivity of erythroid cells to interleukin (IL) 3 and granu-

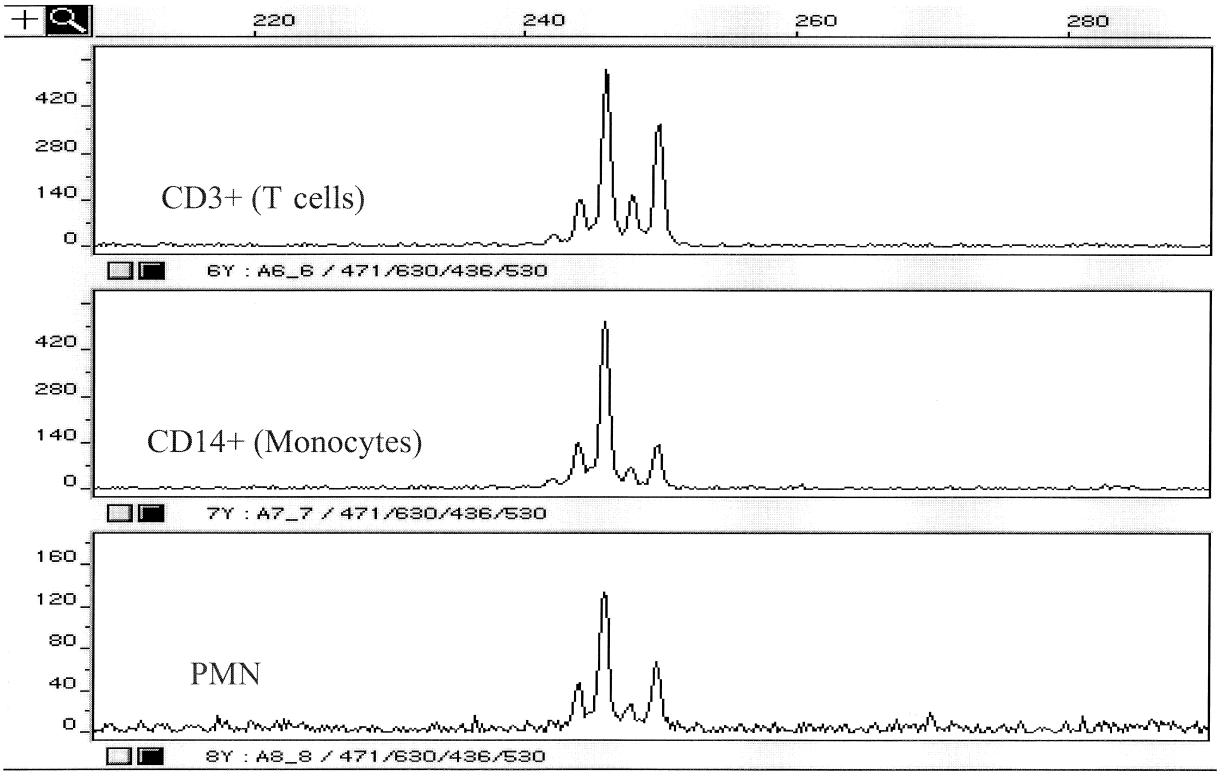

Fig. 4. Example of an electropherogram showing loss of heterozygosity (LOH) in monocytes and polymorphonuclear (PMN) cells and not in T-cells from a patient with CMML. CMML, chronic myelomonocytic leukemia.

locyte-macrophage colony-stimulating factor (GM-CSF) in these patients (56). Axelrad et al. (56) showed that erythroid cells in PV patients were also highly sensitive to insulin-like growth factor-1 (IGF-1). It was demonstrated that the IGF-1 receptor was hyperphosphorylated in the erythroid cells of PV patients. Erythropoietin (EPO) levels are reduced and the EPO receptor levels are downregulated in PV patients, but the cells are no longer dependent on EPO for maturation (57). Mutations in the EPO receptor are described in cell lines, but studies in PV patients did not demonstrate genetic alteration in the EPO receptor (58). However, Chepa, et al. (59) detected an alternatively spliced, truncated EPO receptor mRNA in some PV patients and believed that the truncated mRNA translated into a truncated receptor that was cytoplasmic. This truncated EPO receptor may become constitutively active, triggering intracellular signaling and overgrowth of erythroid progenitor cells. De La Chapelle et al. (60) described mutations in the EPO receptor gene in some cases of hereditary PV that activated the EPO receptor leading to STAT kinase pathway activation and transcription of several growth-and proliferation-regulating genes. It appears that the growth and proliferation of the erythroid cells in PV patients is driven by dimerization of the receptor and activation of the Jak-STAT pathway, which leads to activation of several genes that block apoptosis and promote proliferation (61).

Essential Thrombocythemia

Essential thrombocythemia (ET) is a clonal disease that involves multipotent stem cells and manifests as a persistent thrombocytosis in patients who have normal iron levels, have not undergone splenectomy, and have normal levels of serum C reactive proteins (62). The disease is relatively rare (7 cases per million people) and affects males and females equally. Patients' platelet counts are usually higher than $1{,}000 \times 10^9$/l. Despite the increase in counts, the platelets may function poorly, producing a tendency for hemorrhagic or thrombotic events.

The molecular mechanisms responsible for ET are unknown at present. Although the disease involves mutipotent stem cells, the major abnormalities in this disease involve the path-

way responsible for the proliferation and differentiation of megakaryocytes. Cytogenetic abnormalities are rare in ET, though the presence of +8, inv3, t(13;14), t(2;3), 13q deletions, and 11q21 deletions are reported (Table 1) (63–67). The recent cloning of the *c-mpl* oncogene, which is a tyrosine kinase receptor expressed mainly in megakaryocytes and considered a receptor for thrombopoietin (TPO), has made it possible to investigate the role of the TPO/receptor system in ET disease (68–70). Overexpression of TPO in mice leads to thrombocytosis and myelofibrosis. Expressing a truncated *c-mpl* protein in mice leads to acute myeloproliferative disease (71). However, recent publications suggest that there is no evidence of c-mpl mutation in ET patients, and growth and differentiation of megakaryocytes appear unrelated to TPO or its receptor in ET patients (72).

Agnogenic Myeloid Metaplasia

Chronic idiopathic myelofibrosis, or agnogenic myeloid metaplasia (AMM), is a clonal disease that involves multipotent stem cells and manifests by marked proliferation of megakaryocytes, bone marrow fibrosis, extramedullary hematopoiesis, and peripheral blood panmyelosis (2,3,73). In addition to bone marrow fibrosis and proliferation of megakaryocytes, leukocyte counts vary between 1×10^9/l and 25×10^9/l with left-shift, and platelet counts vary from 150×10^9/l to 500×10^9/l. The characteristic feature of this disease is the presence of tear-drop erythroid cells in peripheral blood (73). The proliferating fibroblasts in this disease are not clonal and appear reactive (74). It is believed that several growth factors, some of which are secreted by megakaryocytes, are responsible for the proliferation of fibroblasts and synthesis of fibronectin and collagen (75). The most studied factor is platelet-derived growth factor (PDGF)(76,77). In addition, transforming growth factor-β (TGFβ), TPO, epidermal growth factor, and IL-6 are expressed at high levels in patients with AMM (78–80). Our recent data suggest that the levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are markedly high in AMM patients with increased vascularity, which suggests that angiogenesis is a major factor in the pathogenesis of this disease (Albitar et al., unpublished data). The TPO and c-mpl were also thought to play a role in this disease (81), but recent studies demonstrated that growth and differentiation of megakaryocytes in AMM were independent of the TPO/c-mpl pathway (82).

Comprehensive cytogenetic studies are not available on this disease. However, abnormalities in chromosome 3q, 5q, 7q, 13q, and 20q are reported (83–86). Translocations, including t(1;20), t(1;7), t(4;13), and t(5;17), in addition to trisomies 8 and 9 also are reported without involvement of specific genes (Table 1) (86–91). However, it appears that the most commonly detected cytogenetic abnormality in this disease is del (20q)(83). A recent study mapped the commonly deleted region (CDR) on chromosome 20, between 20q11.2 and 20q13.1, a region containing several important genes, including adenosine deaminase (ADA) and genes associated with topoisomerase I and PI3K (83).

Juvenile Chronic Myeloid Leukemia

Juvenile chronic myeloid leukemia (JCML) is a rare disease that is different from adult CML and shows clinical and molecular features similar to those of adult CMML (92). The disease usually affects patients under 4 years of age and affects twice as many boys as girls. Monocytosis and mild leukocytosis are common features shared between JCML and adult CMML. However, one unique feature of JCML is the increased levels of fetal hemoglobin (Hb F) in patients (93,94). These high levels of Hb F are believed to result from activation of the expression of the γ-globin genes as a result of expression of trans-acting factors that are activated in the leukemic process. JCML cases lack the Philadelphia chromosome. Monosomy 7 or 7q- are frequent cytogenetic abnormalities in this disease (95,96). As in adult CMML, there is increased incidence of RAS mutations (30%) (97) and NF1 deletions (98). Young children with neurofibromatosis type 1 show a high incidence of JCML and the majority have deletions in both alleles, leading to constitutive activation of the RAS oncogene pathway.

Idiopathic Hypereosinophilic Syndrome

Hypereosinophilic syndrome is a rare disease defined by the presence of at least 1.5×10^9 eosinophils/l for at least 6 months, in the absence of any etiology (6,7). The disease is

usually associated with some evidence of organ involvement, including hepatosplenomegaly, heart murmurs, congestive heart failure, diffuse or focal central nervous system abnormalities, marrow fibrosis or anemia, and weight loss (99). The disease is nine times more frequent in males than in females. Clonality of the eosinophils was demonstrated with and without the presence of cytogenetic abnormalities. Hypereosinophilic syndrome is considered a chronic proliferative disease and some investigators report that it can evolve into acute myeloid leukemia or acute lymphoblastic leukemia in a fashion similar to other MPDs (100,101). Reported chromosomal abnormalities in this disease include dic(1;7), 20q-, monosomy 7, and trisomy 8 (102–105). Eosinophilic leukemia is usually a term reserved for cases where the blasts counts in peripheral blood and bone marrow are elevated. Several cytokines, including IL-5, IL-6, IL-3, and GM-CSF are implicated in the proliferation and stimulation of eosinophils (106–108). IL-5 transgenic mice develop massive eosinophilia and the IL-5 levels are usually increased in hypereosinophilic syndrome patients (109). The organ damage in hypereosinophilic syndrome is caused by secretion of several cytokines from the eosinophils, leading to significant fibrosis in various organs.

Systemic Mastocytosis

Systemic mastocytosis is a term used for collective disorders characterized by abnormal growth and accumulation of mast cells. The disease can manifest as a myeloproliferative or myelodysplastic features (8,9). Mast cells are believed to be derived from multipotent hematopoietic cells. The most commonly reported abnormality in this disease is an Asp816Val mutation in the c-kit receptor (110–112), a tyrosine kinase characterized by the presence of 5 immunoglobulin-like repeats in the extracellular domain and cytoplasmic kinase domain. Stem cell factor (SCF) is the ligand for the c-kit receptor, but the Asp816Val mutation is believed to lead to constitutive activation and to uncontrolled proliferation of mast cells. Recent studies show this mutation in the peripheral blood mononuclear cells from a significant number of patients with mastocytosis, suggesting that early stem cells are involved in the neoplastic process in some patients with mastocytosis (112). Association between mastocytosis and trisomies 9 and 8 also are reported (113–114).

Myeloproliferative Disease Associated with 8p11 Chromosomal Abnormality

The 8p11 MPD is distinct and unusual in its clinical course (10,11). It is characterized by myeloid hyperplasia, eosinophilia, and T cell or B cell lymphoblastic lymphoma that may progress to acute myeloid leukemia. This unusual phenotype is believed to be due to molecular abnormalities involving hematopoietic stem cells that can differentiate to various lineages. Several translocations are reported in this disease, including t(8;16)(p11;p13), t(8;14)(p11;q11.1), t(8;19)(p11;q13), t(8;22)(p11;q13), and t(8;13)(p11;q11–12) (115–120). The fibroblast growth factor receptor 1 (FGFR1) gene on chromosome 8p11 is involved in all these translocations. FGFR1 is a member of the fibroblast growth factors receptors family (FGFR1-4). These genes are tyrosine kinase receptors involved with mediating cellular responses to 17 fibroblast growth factors (FGF1-17). They are involved in cell growth and migration, angiogenesis, organ formation, and bone growth. The tyrosine kinase domain coding sequence of FGFR1 is retained in almost all translocations and presumably activated by the fused partner genes through dimerization. These partner genes include zinc finger protein ZNF198 (FIM fused in myeloproliferative disorders) on chromosome 13, FGFRI oncogene partner (FOP) on chromosome 6, and monocytic leukemia zinc finger (MOZ) on chromosome 16.

In summary, activation of a tyrosine kinase signal transduction pathway appears to be the most common molecular abnormality in the pathogenesis of chronic myeloproliferative disorders. Further studies are needed to identify specific genes involved in most of these diseases. However, the recent introduction of several tyrosine kinase inhibitors as therapeutic agents in some of these diseases represents a promising new therapeutic tool for this group of diseases.

References

1. Harris NL, Jaffe ES, Diebold J. (1999) World Health Organization classification of neoplas-

tic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee-Airlie House. *Clinical Oncology* **17:** 3835–3849.
2. Tefferi A. (1999) Introduction: overview of chronic myeloproliferative disorders. *Semin. Hematol.* **36:** 1–2.
3. Terreri A. (1998) The Philadelphia chromosome negative chronic myeloproliferative disorders: a practical overview. *Mayo Clin. Proc.* **73:** 1177–1184.
4. Montefusco E, Alimena G,L Coco F, et al. (1992) Ph-negative and bcr-negative atypical chronic myelogenous leukemia: biological features and clinical outcome. *Ann. Hematol.* **1:** 17–21.
5. Bennett JM, Catovsky D, Daniel MT, et al. (1994) The chronic myeloid leukaemia: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. *Brit. J. of Hematology* **87:** 746–754.
6. Weller PF, Bubley GJ. (1994) The idiopathic hypereosinophilic syndrome. *Blood* **83:** 2759–2779.
7. Hardy WR, Anderson RE. (1968) The hypereosinophilic syndrome. *Ann. Intern. Med.* **68:** 1220.
8. Metcalfe DD. (1991) Classification and diagnosis of mastocytosis: current status. *J. Invest. Dermatol.* **96:**25–45.
9. Tharp MD. (1995) Mast cell disease and its diagnosis. *J. Invest. Dermatol* **104:** 885.
10. Macdonald D, Aguiar RCT, Mason PJ, Goldman JM, Cross NCP. (1995) A new myeloproliferative disorder associated with chromosomal translocations involving 8p11: a review. *Leukemia* **9:** 1628–1630.
11. Aguiar RCT, Chase A, Coulthard S, et al. (1997) Abnormalities of chromosome band 8p11 in leukemia: two clinical syndromes can be distinguished on the basis of MOZ involvement. *Blood* **90:** 3130–3135.
12. Raskind WH, Steinmann L, Najfeld V. (1998) Clonal development of myeloproliferative disorders: clues to hematopoietic differentiation and multistep pathogenesis of cancer. *Leukemia* **2:** 108–116.
13. Blanchard KL, Gililand DG, Bunn HF. (1992) Clonality in myeloproliferative disorders. *Am. J. Med. Sci.* **304:** 125–130.
14. Gilbert HL, Acharya J, Pearson TC. (1998) Implications for the use of X-chromosome inactivation patterns and their relevance to the myeloproliferative disorders. *Eur. J. Haematol.* **4:** 282–283.
15. Fialkow PJ, Jacobson RJ, Papayannopoulou T. (1977) Chronic myelocytic leukemia: clonal origin in a stem cell common to the granulocyte, erythrocyte, platelet and monocyte/macrophage. *Amer. J. Med.* **63:** 125–130.
16. Raskind WH, Steinmann L, Najfeld V. (1997) Clonal development of myeloproliferative disorders: clues to hematopoietic differentiation and multistep pathogenesis of cancer. *Leukemia* **12:** 108–116.
17. Faderl Stefan, Talpaz Moshe, Estrov Zeev, et al. (1999) The biology of chronic myeloid leukemia. *New Eng. J. Med.* **341:** 164–172.
18. Warmuth M, Danhauser-Riedl S, Hallek M. (1999) Molecular pathogenesis of chronic myeloid leukemia: implications for new therapeutic strategies. *Ann Hematol.* **78:** 49–64.
19. Kantarjian HM, Smith TL, O'Brien S, Beran M, Sherry P, Talpaz M. (1995) Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-α therapy. *Ann. Intern. Med.* **122:** 254–261.
20. Melo J. (1996) Overview: the molecular biology of chronic myeloid leukemia. *Leukemia* **10:** S4–S9.
21. Ravandi F, Cortes J, Albitar M, et al. (1999) Chronic myelogenous leukaemia with p185 (BCR/ABL) expression: characteristics and clinical significance. *Br. J. Haematol.* **3:** 581–586.
22. Pane F, Frigeri F, Sindona M, et al. (1996) Neutrophilic-chronic myeloid leukemia: a distinct disease with a specific molecular marker. *Blood* **88:** 2410–2414. [Erratum, Blood (1997) 89:4244.]
23. Melo JV, Myint H, Galton DAG, Goldman JM. (1994) P190 BCR-ABL chronic myeloid leukaemia: the missing link with chronic myelomonocytic leukaemia. *Leukemia* **8(1):** 208–211.
24. Zaccaria Alfonso, Martinelli Giovanni, Testoni Nicoletta, et al. (1995) Does the type of BCR/ABL junction predict the survival of patients with Ph1-positive Myeloid Leukemia? *Leuk. and Lymph.* **16:** 231–236.
25. Daley GQ, Van Etten RA, Baltimore D. (1990) Induction of chronic myelogenous leukemia in mice by the p210bcr/abl gene of the Philadelphia chromosome. *Science* **247:** 824–830.
26. Heisterkamp N, Jenster G, ten Hoeve J, Zovich D, Pottengale PK, Groffen J. (1990) Acute leukaemia in bcr/abl transgenic mice. *Nature* **344:** 251–253.
27. Honda H, Fujii T, Takatoku M, et al. (1995) Expression of p210bcr/abl by metallothionein promoter induced T-cell leukemia in transgenic mice. *Blood* **85:** 2853–2861.
28. Cortez D, Stoica G, Pierce JH, Pendergast AM. (1996) The BCR-ABL tyrosine kinase inhibits apoptosis by activating a Ras-dependent signaling pathway. *Oncogene* **13:** 2589–2594.
29. Biernaux C, Loos M, Sels A, Huez G, Stryckmans P. (1995) Detection of major *bcr-abl* gene expression at a very low level in blood cells of some healthy individuals. *Blood* **86:** 3118–3122.
30. Bose S, Deninger M, Gora-Tybor J, Goldman JM, Melo JV. (1998) The presence of typical

and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. *Blood* **92**: 3362–3367.
31. Faderl S, Kantarjian MH, Talpaz M. (1999) Chronic myelogenous leukemia: update on biology and treatment. *Oncology* **13**: 2.
32. Mitani K, et al. (1994) Generation of the AML1-EVI1 fusion gene in the t(3;21)(q26;q22) causes blastic crisis in chronic myelocytic leukemia. *EMBO J.* **13**: 504–510.
33. Feinstein E, Cimino G, Gale RP, Alimena G, Berthier R, et al. (1991) p53 in chronic myelogenous leukemia in acute phase. *Proc. Natl. Acad. Sci. U.S.A.* **88**: 6293–6297.
34. Towatari M, Adachi, Kato H, Saita H. (1991) Absence of the human retinoblastoma gene product in the megakaryoblastic crisis of chronic myelogenous leukemia. *Blood* **78**: 3259–3268.
35. Nieborowska-Skorska M, Ratajczak MZ, Calabretta B, Skorski T. (1994) The role of c-Myc protooncogene in chronic myelogenous leukemia. *Folia Histochem. Cytobiol.* **4**: 231–234.
36. Sill H, Goldman JM, Cross NC. (1995) Homozygous deletions of the p16 tumor-suppressor gene are associated with lymphoid transformation of chronic myeloid leukemia. *Blood* **85**: 2013–2016.
37. Gow J, Hughes D, Farr C, et al. (1988) Activation of Ha-ras in human chronic granulocytic and chronic myelomonocytic leukaemia. *Leuk. Res.* **10**: 805–810.
38. Negrini M, Cuneo A, Nakamura T, et al. (1995) A novel t(9;11)(p22;q23) with ALL-1 gene rearrangement associated with progression of a myeloproliferative disorder to acute myeloid leukemia. *Cancer Genet. Cytogenet.* **83**: 65–70
39. Turhan AG, Solary E, Vainchenker W, Dusanter-Fourt I. (1998) Molecular pathophysiology of chronic myelogenous leukemia. *Hematol. Cell Ther.* **5**: 217–221.
40. Hasle H, Olesen G, Kerndrup G, Philip P, Jacobsen N. (1996) Chronic neutrophil leukaemia in adolescence and young adulthood. *Br. J. Haematol.* **4**: 628–630.
41. Albitar M, Wu Wi, Feltz E, et al. (1997) Simplified reverse dot blot analyses for detecting of ras oncogene mutations. *Mol. Diag.* **3**: 169–176.
42. Cogswell PC, Morgan R, Dunn M, et al. (1989) Mutations of the ras protooncogenes in chronic myelogenous leukemia: a high frequency of ras mutations in bcr/abl rearrangement-negative chronic myelogenous leukemia. *Blood* **8**: 2629–2633.
43. Gaidano G, Guerrasio A, Serra A, Rege-Cambrin G, Saglio G. (1994) Molecular mechanisms of tumor progression in chronic myeloproliferative disorders. Leukemia. **8** (Suppl 1): S27–29.
44. Ludwig L, Janssen JW, Bartram CR. (1995) Exon trap analysis of a NF1 splice site mutation in a chronic myelomonocytic leukemia patient. *Leukemia* **5**: 922–924.
45. Carroll M, Tomasson MH, Barker GF, Golub TR, Gilliland DG. (1996) The TEL/platelet-derived growth factor B receptor (PDGF BR) fusion in chronic myelomonocytic leukemia is a transforming protein that self-associates and activates PDGF BR kinase-dependent signaling pathways. *Proc. Natl. Acad. Sci.* **93**: 14845–14850.
46. Golub TR, Barker GF, Lovett M, Gilliland DG. (1994) Fusion of PDGF receptor B to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. *Cell* **77**: 307–316.
47. Ritchie KA, Aprikayan AA, Bowen-Pope DF, et al. (1999) The Tel-PDGFRβ fusion gene produces a chronic myeloproliferative syndrome in transgenic mice. *Leukemia* **13**: 1790–1803.
48. Sambani C, Trafalis DT, Vessalas G, et al. (1998) Trisomy 6 and double minute chromosomes in a case of chronic myelomonocytic leukemia. *Cancer Genet. Cytogenet.* **106**: 180–181.
49. Sawyers CL, Denny CT. (1994) Chronic myelomonocytic leukemia: tel-a-kinase what ets all about. *Cell* **77**: 171–173.
50. Diez-Martin JL, Graham DL, Petitt RM, Dewald GW. (1991) Chromosome studies in 104 patients with polycythemia vera. *Mayo Clinic Proc.* **66**: 287–299.
51. Amiel A, Gaber E, Manor Y, et al. (1995) Fluorescence in situ hybridization for the dectection of trisomy 8 and trisomy 9 in polycythemia-vera. *Cancer Gen. and Cytogen.* **79**: 153–156.
52. Asimakopoulos FA, Holloway TL, Nacheva EP, et al. (1996b) Detection of chromosome 20q deletions in bone marrow metaphases but not peripheral blood granulocytes in patients with myeloproliferative disorders or myelodisplastic syndromes. *Blood* **87**: 1561–1570.
53. Lawler SD, Millard RE, Kay HEM. (1970) Further cytogenetical investigations in polycythaemia vera. *Eur. J. Cancer* **6**: 223–233.
54. Miller JB, Testa JR, Lindgren V, Rowley JD. (1985) The pattern and clinical significance of karyotypic abnormalities in patients with idiopathic and postpolycythemic myelofibrosis. *Cancer* **55**: 582–591.
55. Fernandez-Luna JL, Silva M, Richard C, Sanz C, Adalberto B. (1998) Pathogenesis of plycythemia vera. *Heamatologica* **83**: 150–158.
56. Correa PN, Axelrad AA. (1991) Production of erythropietic bursts by progenitor cells from adult human peripheral blood in an improved serum-free medium: role of insulin-like growth factor-I. *Blood* **78**: 2823–2833.
57. Yoshimura A, Longmore G, Lodish HF. (1990) Point mutation in the exoplasmic domain of the erythropoietin receptor resulting in hor-

mone-independent activation and tumorigenicity. *Nature* **348**: 647–649.
58. Hess G, Rose P, Gamm H, Papadileris S, Huber C, Seliger B. (1994) Molecular analysis of erythropoietin receptor system in patients with polycythemia vera. *Br. J. Haematol.* **88**: 794–802.
59. Chiba S, Takahashi T, Takeshita K, et al. (1997) Selective expression of mRNA coding for the truncated form of erythropoietin receptor in hematopoietic cells and its decrease in patients with polycythemia vera. *Blood* **90**: 97–104.
60. De La Chapelle A, Sistonen P, Lehvaslaiho H, Ikkala E, Juvonen E. (1993) Familial erythropoiten receptor gene. *Lancet* **341**: 82–84.
61. Zhuang H, Niu Z, He TC, Pastel SV, Wojchowski DM. (1995) Erythropoietin-dependent inhibition of apoptosis is supported by carboxyl-truncated receptor forms and blocked dominant-negative forms of Jak2. *J. Biol. Chem.* **270**: 14500–14504.
62. El-Kassar N, Hetet G, Brie're J, Grandchamp B. (1997) Clonality analysis in essential thrombocythaemia. *Blood* **90**: 347a.
63. Third International Workshop on Chromosomes in Leukemia. (1981) Report on essential thrombocythemia. *Cancer Gen. and Cytogen.* **4**: 138–142.
64. Elis A, Amiel A, Manor Y, Tangi I, Fejgin M, Lishner M. (1996) The detection of trisomies 8 and 9 in patients with essential thrombocytosis by fluorescence in situ hybridization. *Cancer Genet. Cytogenet.* **92**: 14–17.
65. Mitev L, Georgiev G, Petrov A, Manolova Y. (1996). Unusual chromosome aberration, t(13; 14)(q32; q32.3), in a case of essential thrombocythemia with extreme thrombocytosis. *Cancer Genet. Cytogenet.* **91**: 68–70
66. Killick S, Matutes E, Swansbury J, Catovsky D. (1998). Case 17: essential thrombocythaemia with inversion 3 terminating in acute leukaemia. *Leuk. Lymphoma.* **30**: 661–664.
67. Rios R, Sole F, del Mar Perez M, Gascon F, Garcia F, Gonzalez PM. (1996) t(2; 3) in a case of blastic transformation of essential thrombocythaemia. *Br. J. Haematol.* **92**: 769–770.
68. Horikawa Y, Matsumura I, Hashimoto K, et al. (1997) Markedly reduced expression of platelet c-mpl receptor in essential thrombocythaemia. *Blood* **90**: 4031–4038.
69. Kiladjian JJ, El-Kassar N, Hetet G, et al. (1997) Study of thrombopoietin receptor in essential thrombocythaemia. *Leukemia* **11**: 1821–1826.
70. Li Y, Hetet G, Kiladjian J-J, et al. (1996) Proto-oncogene *c-mpl* is involved in spontaneous megakaryocytopoiesis in myeloproliferative disorders. *Br. J. Haemat.* **92**: 60–66.
71. Zhou W, Toombs CF, Zou T, Guo J, Robinson MO. (1997) Transgenic mice overexpressing human c-mpl ligand exhibit chronic thrombocytosis and display enhanced recovery from 5-fluorouracil or antiplatelet serum treatment. *Blood* **89**: 1551–1559.
72. Taksin AL, Le Couedic JP, Dusanter-Fourt I, et al. (1999) Autonomous megakaryocyte growth in essential thrombocythemia and idiopathic myelofibrosis is not related to an autocrine stimulation by Mpl-L. *Blood* **93**: 125–139.
73. Cripe LD, Hromas R. (1998) Malignant disorders of megakaryocytes. *Sem. in Hemat.* **35**: 200–209.
74. Jacobson RJ, Salo A, Fialkow PJ. (1978) Agnogenic myeloid metaplasia: a clonal proliferation of hematopoietic stem cells with secondary myelofibrosis. *Blood* **51**: 189–194.
75. Martyre MC, Le Bousse-Kerdiles MC, Romquin N, et al. (1997) Elevated levels of basic fibroblast growth factor in megakaryocytes and platelets from patients with idiopathic myelo-fibrosis. *Br. J. Haematol.* **2**: 441–448.
76. Ross RRE, Bowen-Pope DF. (1986) The biology of platelet-derived growth factor. *Cell* **46**: 155–169.
77. Reilly JT. (1998) Pathogenesis and management of idiopathic myelofibrosis. *Baillieres Clin. Haematol.* **4**: 751–767.
78. Folkman J, Klaesburn M. (1987) Angiogenic factors. *Science* **235**: 442–447.
79. Wang JC CC, Lou L-H, Mora M. (1997) Blood thrombopietin, IL-6 and IL-11 levels in patients with agnogenic myeloid metaplasia. *Leukemia* **11**: 1827–1832.
80. Rameshwar P, Denny TN, Stein D, Gascon P. (1994) Monocyte adhesion in patients with bone marrow fibrosis is required for the production of fibrogenic cytokines. Potential role for interleukin-1 and TGF-β. *J. Immunol.* **153**: 2819–2830.
81. Yan XQ, Lacey D, Hill D, et al. (1996) A model of myelofibrosis and osteosclerosis in mice induced by overexpressing thrombopoietin (mpl ligand): reversal of disease by bone marrow transplantation. *Blood* **88**: 402–409.
82. Yan XQ, Lacey D, Fletcher F, et al. (1995) Chronic exposure to retroviral vector encoded MGDF (mpl-ligand) induces lineage-specific growth and differentiation of megakaryocytes in mice. *Blood* **86**: 4025–33.
83. Bench AJ, Aldred MA, Humphray SJ, et al. (1998) A detailed physical transcriptional map of the region of chromosome 20 that is detected in myeloproliferative disorders and refinement of the common deleted region. *Genomics* **49**: 351–362.
84. Borgström GH, Knuutila S, Ruutu T, et al. (1984) Abnormalities of chromosome 13 in myelofibrosis. *Scand. J. Haemat.* **33**: 15–21.
85. Dewald GW, Wright PI. (1995) Chromosome abnormalities in the myeloproliferative disorders. *Semi. in Oncol.* **22**: 341–354.

86. Donti E, Tabilio A, Bocchini F, et al. (1990) Partial trisomy 1q in idiopathic myelofibrosis. *Leuk. Res.* **14:** 1035–1040.
87. Geraedts JPM, den Ottolander GJ, Ploem JE, Muntinghe OG. (1980) An identical translocation between chromosome 1 and 7 in three patients with myelofibrosis and myeloid metaplasia. *Br. J. Haemat.* **44:** 569–575.
88. Hsu LYF, Pinchiaroli D, Gilbert HS, et al. (1997) Partial trisomy of the long arm of chromosome 1 in myelofibrosis and polycythemia vera. *Amer. J. Hemat.* **2:** 375–383.
89. Reilly JT, Snowden JA, Spearing RL, et al. (1997) Cytogenetic abnormalities and their prognostic significance in idiopathic myelofibrosis: a study of 106 cases. *Br. J. Haemat*. **98:** 96–102.
90. Smadja N, Krulik M, de Gramont A, et al. (1987) Cytogenetic studies in twelve patients with myelofibrosis and myeloid metaplasia. *Cancer Gen. and Cytogen.* **24:** 151–158.
91. Whang-Peng, J, Lee E. Knutsen T, et al. (1978) Cytogenetic studies in patients with myelofibrosis and myeloid mataplasia. *Leuk. Res.* **2:** 41–56.
92. Cambier N, Baruchel A, Schlageter MH, et al. (1997) Chronic myelomonocytic leukemia: from biology to therapy. *Hemat. and Cell Ther.* **39:** 41–48.
93. Passamore SJ, Hann IM, Stiller CA, et al. (1995) Pediatric myelodysplasia: a study of 68 children and a new prognostic scoring system. *Blood* **85:** 1742–1750.
94. Papayannopoulou T, Nakamoto B, Anagnou NP, Chui D, Dow L, Sanders J. (1991) Expression of embryonic globins by erythroid cells in juvenile chronic myelocytic leukemia. *Blood* **12:** 2569–2576.
95. Butcher M, Frenck R, Emperor J, et al. (1995) Molecular evidence that childhood monosomy 7 syndrome is distinct from juvenile chronic myelogenous leukemia and other childhood myeloproliferative disorders. *Genes Chromo. Cancer* **1:** 50–57.
96. Shannon KM, Watterson J, Johnson P, et al. (1992) Monosomy 7 myeloproliferative disease in children with neurofibromatosis, type 1: epidemiology and molecular analysis. *Blood* **79:** 1311–1318
97. Miyauchi J, Asada M, Sasaki M, Tsunematsu Y, Kojima S, Mizutani S. (1991) Mutations of the N-ras gene in juvenile chronic myelogenous leukemia. *Blood* **8:** 2248–2254.
98. Savasan S, Zulfikar B, Ozgeneci A, Ozbek U, Sengun Z. (1996) Monosomy 7 myeloproliferative disease associted with neurofibramatosis type I: a case report. *J. Chemother.* **3:** 243–246.
99. Chang HW, Leong KH, Koh DR, Lee SH. (1999) Clonality of isolated eosinophils in the hypereosinophilic syndrome. *Blood* **5:** 1651–1657.
100. Fishel RS, Farnen JP, Hanson CA, Silver SM, Stephen GE. (1990) Acute lymphoblastic leukemia with eosinophilia. *Medicine* **69:** 232–243.
101. Troxell M, Mills G, Allen R. (1984) The hypereosinophlic syndrome in acute lymphocytic leukemia. *Cancer* **54:** 1058–1061.
102. Forrest DL, Horsman DE, Jensen CL, et al. (1998) Myelodysplastic syndrome with hypereosinophilia and a nonrandom chromosomal abnormality dic(1;7): confirmation of eosi-nophil clonal involvement by fluorescencein in situ hybridization. *Cancer Genet. Cytogenet.* **1:** 65–68.
103. Brigaudeau C, Liozon E, Bernard P, Trimoreau F, Bordessoule D, Praloran V. (1996) Deletion of chromosome 2Oq associated with hypereosinophilic syndrome. A report of two cases. *Cancer Genet. Cytogenet.* **1:** 82–84.
104. Maibrain ML, Van den Bergh H, Zachee P. (1996) Further evidence for the clonal nature of the idiopathic hyperosinophilic syndrome: complete haematological and cytogenetic remission induced by interfon-α in case with with a unique chromosal abnormality. *Br. J. Haematol.* **1:** 176–183.
105. Brigaudeau C, Liozon E, Bernard P, et al. (1996) Deletion of chromosome 20q associated with hypereosinophilic syndrome. A report of two cases. *Cancer Gene. and Cytogen.* **87:** 82–84.
106. Fermand JP, Mitjavila MT, Le Couedic JP, et al. (1993) Role of granulocyte-macrophage colony-stimulating factor, interleukin-3 and interleukin-5 in the eosinophilia associated with T cell lymphoma. *Br. J. Haematol.* **83:** 359.
107. Chang H, Jamal N, Wang XH, Minden MD, Messner HA. (1992) Constitutive production of the interlukins IL-5 and IL-6 by the lymphoma cell line OCI-Ly 17 derived from a patient with malignant lymphoma and hypereosinophilia. *Leuk. Lymphoma* **8:** 97.
108. Schrezenmeier H, Thome SD, Tewald F, Fleischer B, Raghavachar A. (1993) Interlukin-5 is the predominant eosinophilopoietin produced by cloned T lymphocytes in hypereosinophilic syndrome. *Exp. Hematol.* **21:** 358.
109. Strath M, Dent L, Sanderson C. (1992) Infection of IL5 transgenic mice with *Mesocestoides corti* induces very high levels of IL5 but depressed production of eosinophils. *Exp. Hematol.* **20:** 229.
110. Longley BJ, Tyrrell L, Lu SZ, et al. (1996) Somatic c-kit activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat. Genet.* **12:** 312–314.

111. Nagata H, Worobec AS, Oh CK, Chowdhury, et al. (1995) Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc. Natl. Acad. Sci.* **92:** 10560–10564.
112. Worobec AS, Semere T, Nagata H, Metcalfe DD. (1998) Clinical correlates of the presence of the Asp816Val c-kit mutation in the peripheral blood mononuclear cells of patients with mastocytosis. *Amer. Cancer Soc.* **83:** 2120–2129.
113. Lishner M, Confino-Cohen R, Mekori YA, et al. (1996) Trisomies 9 and 8 detected by flourescence in situ hybridization in patients with sytemic mastocytosis. *J. Allergy Clin. Immunol.* **98:** 199–204.
114. Shekhter-Levin S, Ball E, Swerdlow SH, et al. (1998) A near-haploid bone marrow karyotype in systemic mast cell disease: is it characteristic of the disease or an incidental finding? *Cancer Genet. Cytogenet.* **103:** 124–129.
115. Xiao S, Nalabolu SR, Aster JC, et al. (1998) FGFR1 is fused with a novel zinc-finger gene, ZNF198, in the t(8;13) leukemia/lymphoma syndrome. *Nature Genetics* **18:** 84–87.
116. van den Berg H, Kroes W, van der Schoot CE, et al. (1996) A young child with acquired t(8;9)(p11;q34):additional proof that 8p11 is involved in mixed myeloid/T lymphoid malignancies. *Leukemia* **10:** 662–668.
117. Chaffanet M, Popovici C, Leroux D, et al. (1998) t(6;8), t(8;13) translocations associated with stem cell myeloproliferative disorders have close or identical breakpoints in chromosome region 8p11–12. *Oncogene* **16:** 945–949.
118. Elsner S, Martin H, Rode C, et al. (1994) An uncommon chromosomal translocation *t*(6;8) associated with atypical acute myelogeneous leukaemia/myeloproliferative disease detected by fluorescence in situ hybridization. *Br. J. Haemat.* **87** (Suppl. 1): 124.
119. Fagan K, Hyde S, Harrison P. (1993) Translocation (8;13) and T-cell lymphoma. *Cancer Gene. and Cytogen.* **65:** 71–73.
120. Xu X, Weinstein M, LI C, Deng C-X. (1999) Fibroblast growth factor receptors (FGRs) and their roles in limb development. *Cell and Tissue Res.* **296:** 33–43.