The 5q− Syndrome

By Jacqueline Boultonwood, Sian Lewis, and James S. Wainscoat

THE 5q− SYNDROME was first described by Van den Berghe et al1 in 1974 in three patients with refractory anemia and an interstitial deletion of the long arm of chromosome 5. This review discusses the clinical features of the 5q− syndrome and the role of candidate genes in the pathogenesis of the syndrome, taking into account recent evidence on the critical region of gene loss. The cytogenetic deletion of the cytogenetic enhancer gene in patients with myelodysplasia provides circumstantial evidence for the existence of tumor-suppressor loci, but the size of these deletions makes the identification of tumor-suppressor genes difficult.2 Similarly, the pathogenetic mechanism underlying the 5q− syndrome most probably involves the deletion of a tumor-suppressor gene on the long arm of chromosome 5. There is particular interest in the 5q− syndrome because of the large number of genes coding for hemopoietic growth factors or their receptors that are localized to the long arm of chromosome 5.

CLINICAL FEATURES

A detailed description of the clinical and hematologic features of patients with refractory anemia (RA) and a chromosome 5q deletion was published by Sokal et al.3 The patients were predominantly female and had macrocytic anemia, modest leukopenia, normal or high platelet counts, bone marrow erythroid hypoplasia, hypolobulated megakaryocytes, and bone marrow blast counts of less than 20%. The constellation of features described by these investigators has been termed the 5q− syndrome, which is now recognized as a distinct clinical entity with a favorable prognosis and a low risk of transformation to acute leukemia.4,5

The mean age of patients at presentation is 66 years,5,7 with patients less than 50 years of age making up only 15% of cases.5 There is a female preponderance that is more marked for patients classified as RA than as RA with excess blasts (RAEB) according to the French-American-British (FAB) classification.6 In the study of Van den Berghe et al,5 the female to male ratio in previously unpublished cases with RA and a 5q deletion as the sole karyotypic abnormality was 3:1, whereas, in RAEB, the incidence was equal. A similar result was obtained in the series of Mathews et al,6 with a female to male ratio of 2:1 in RA and a ratio of 4:3 in RAEB. The majority of patients with myelodysplastic syndrome (MDS) and a 5q− as a sole abnormality are RA at diagnosis.5

Thrombopoiesis. Platelet counts in the 5q− syndrome are typically normal or increased. Approximately half of all patients with the 5q− syndrome have platelet counts greater than 350 × 109/L. However, normal platelet counts are not uncommon in the MDS generally and high platelet counts are a feature of MDS with structural abnormalities of the long arm of chromosome 5.7 Monolobular megakaryocytes are a consistent finding in all reports of the 5q− syndrome,4,5,10,11 although they are not specific to the 5q− syndrome and have been reported in patients with MDS associated with normal or abnormal karyotypes.11 Despite these well-documented abnormalities of thrombopoiesis, hemorrhagic or thrombotic complications are not a prominent feature of this syndrome.

Erythropoiesis. A macrocytic anemia is a consistent feature of the 5q− syndrome. Dyserythropoiesis and erythroid hypoplasia are inconsistent findings. Patients who otherwise have the classical features of the syndrome may have decreased, normal, or increased erythroid activity.5,6 Sideroblasts are identified in the bone marrows of 25% of patients with the 5q− syndrome and are more commonly identified in RAEB than in RA.4,5,12,13 Approximately 10% of cases will fulfill the FAB criteria of RA with ringed sideroblasts (RARS). The majority of patients require regular blood transfusions, although a minority remain transfusion-independent for many years.

Myelopoiesis. Typically, patients with the 5q− syndrome have modest leukopenia. In the series of Van den Berghe,3 the mean white blood cell count (WBC) was 4.3 × 109/L, with a range of 1.9 to 7.4 × 109/L. A detailed morphologic analysis of the myeloid series in the 5q− syndrome has not been published although in our experience dysplastic changes in neutrophils are not marked. This pres-
ervation of relatively normal myelopoiesis appears to be reflected in the low rate of infection in these patients.

**DEFINITION**

The specificity of a combination of hematologic indicators for the 5q− syndrome in patients with MDS was examined in a study by Teerenhovi et al, in which 83 patients with MDS were analyzed for the presence of the following three hematologic features: (1) macrocytic anemia, (2) normal or high platelet count, and (3) megakaryocytic hypolobulation in most megakaryocytes. Nine of the 83 patients displayed all three features, with 8 of these 9 patients having the 5q− syndrome; there were 2 additional patients with the 5q− syndrome who did not possess all three features. None of the 6 patients with additional karyotypic abnormalities in the same clone as the 5q− abnormality fulfilled all three criteria. This study shows that the 5q− syndrome can be predicted with a high degree of certainty using these three simple criteria.

However, the criteria that have been applied to the diagnosis of the 5q− syndrome have varied, and published series have included patients with thrombocytopenia, severe leukopenia, or a normocytic anemia. An imprecise definition of the 5q− syndrome limits the prognostic value of the diagnosis and hinders comparison between published series. We propose a simple definition of the 5q− syndrome to be primary MDS of the FAB-type RA with a 5q deletion as the sole karyotypic abnormality. Patients with the 5q− syndrome so defined possess the following features: female preponderance, macrocytic anemia, modest leukopenia, a normal or high platelet count, hypolobular megakaryocytes, a low risk of transformation to acute leukemia, and a favorable prognosis. Although our proposed definition includes the majority of cases previously described in the literature as 5q− syndrome, it does exclude two groups of cases with a less-favorable prognosis that are sometimes included in the diagnosis, i.e., (1) those with RAEB and (2) those with additional karyotypic abnormalities.

**PROGNOSIS**

The determination of median survival in patients with the 5q− syndrome is problematic for several reasons: the early reports predate the FAB classification, the patients are elderly so that unrelated causes of death may be significant, and, finally, in many studies, the median survival time is greater than that of the period of observation. The reported median survival in patients with RA was 28 months in a study by Teerenhovi et al, in which 16 of 26 previously unpublished cases alive at the end of follow-up. Mathews et al reported a median survival of 81 months. In our series, median follow-up was 40 months, with 8 of 10 patients alive at the end of the study. Estimates of survival of patients with 5q deletion and RAEB vary widely, which may reflect the small number of patients in these groups. Van den Berghe et al reported an overall median survival of 28 months in RAEB, although median follow-up of previously unpublished cases was only 6 months. In the series of Mathews et al, a median survival of 51 months was reported in patients with either RAEB and RAEB(t). In the latter study, a number of patients were treated with chemotherapy, which may have influenced the prognosis of some patients. In our own group of patients, who received supportive treatment only, the survival of those with a 5q− chromosome as the sole karyotypic abnormality and RAEB was 16 months. The presence of karyotypic abnormalities in addition to the 5q− chromosome is well recognized to be associated with a comparatively poor survival. The favorable prognosis of the 5q− syndrome appears to reflect both a low rate of transformation to acute leukemia and preservation of peripheral blood counts with a low incidence of infective and hemorrhagic episodes. Van den Berghe et al estimated that 11% of patients with the 5q− syndrome transform to acute leukemia; none of the 10 patients in our series of 5q− syndrome (as defined above) has transformed to acute leukemia and other studies have been reported with no cases having transformed to acute leukemia.

**THERAPY**

A number of treatment modalities have been tried in the 5q− syndrome, but the results have been disappointing. Steroids have been shown to result in a transient improvement in a small number of cases. Pyridoxine, androgens, and therapy with danazol and cis-retinoic acid have not been shown to have any consistent beneficial effect. The low rate of transformation to acute leukemia and favorable prognosis in this elderly group of patients suggests that, in the majority of cases, supportive therapy is most appropriate. A majority of patients require regular blood transfusions, but, nevertheless, some patients remain transfusion-independent for many years. Clinical symptoms of iron overload are common; 16% will develop heart failure, 10% will develop diabetes, and approximately 5% will die of hemosiderosis. Iron chelation therapy should be considered in patients who would otherwise have a prolonged survival. Patients whose disease transforms to acute leukemia should be treated as considered appropriate for their age and performance status, although it should be recognized that such patients respond poorly to current regimes of intensive chemotherapy. A number of trials of the use of erythropoietin (EPO) in a range of MDS have now been performed and the results have been generally disappointing, with an overall response rate of 23%. There are no clearly defined clinical characteristics that are predictive of a good clinical response and no evidence to suggest that patients with the 5q− syndrome are more likely to respond than patients with other MDS. Neogrim et al treated the anemia of MDS using recombinant human granulocyte colony-stimulating (G-CSF) factor in combination with EPO. Three patients in this study had the 5q− abnormality (2 cases of RA and 1 case of RAEB), 1 patient had a partial erythroid response, and 2 patients had no erythroid response.

**CELLULAR BIOLOGY**

The nature of the progenitor cell affected in MDS has been the subject of several investigations, with some studies indicating that a common myeloid-lymphoid stem cell is
involved in the disorder,\textsuperscript{17,18} whereas others have suggested that the disease originates in a progenitor cell committed to the myeloid lineage.\textsuperscript{19} It seems probable that both disease heterogeneity and also technical problems, particularly of X-inactivation studies, account for these differences.\textsuperscript{20} However, for patients with the 5q\textsuperscript{−} syndrome, there is agreement from two reports that myeloid cells, but not lymphoid cells, carry the 5q\textsuperscript{−} deletion. The study of Abrahamson et al\textsuperscript{21} included four patients with the 5q\textsuperscript{−} syndrome and all showed chromosome 5q gene loss by Southern blotting in granulocyte but not in T-lymphocyte fractions. The same conclusion was reached in a study using polymerase chain reaction (PCR) analysis for loss of heterozygosity using mini-repeat sequences on highly purified cell fractions, including neutrophils, monocytes, T lymphocytes, and B lymphocytes.\textsuperscript{22} In addition, the cell fractions of patients in these two studies were examined by X-linked restriction fragment length polymorphism (X-RFLP) analysis for evidence of monoclonality; both studies showed that only granulocyte cell fractions were monoclonal.

Several groups have cultured bone marrow from patients with the 5q\textsuperscript{−} syndrome in vitro. Cytogenetic studies have confirmed that the 5q\textsuperscript{−} chromosome is present in both erythroid and myeloid progenitor cells.\textsuperscript{23} These studies show that cultures of colony-forming unit-granulocyte-macrophage (CFU-GM) exhibit normal colony growth, whereas erythroid progenitor cells show a decrease or even absence of colony growth.\textsuperscript{23,24}

**ETIOLOGY**

One of the most striking aspects of the 5q\textsuperscript{−} syndrome is the female preponderance, which is unusual, not only for MDS and leukemia, but for malignancies in general. There seems to be a relationship in published reports between a more stringent definition of the 5q\textsuperscript{−} syndrome adopted and a higher female to male sex ratio for the patients. The preponderance of elderly females led Van den Berghe et al\textsuperscript{20} to suggest the possibility of a toxic agent in the home environment.

A complex issue is the relationship between the 5q\textsuperscript{−} syndrome and the other myeloid disorders associated with the 5q\textsuperscript{−} abnormality, particularly the secondary leukemias.\textsuperscript{25} The frequent association of abnormalities of chromosome 5 and/or 7 with these malignancies was first reported by Rowley et al.\textsuperscript{26} Much of the high frequency of these karyotypic abnormalities is caused by the high incidence of monosomy 7, and the incidence of 5q\textsuperscript{−} in secondary leukemia is relatively modest, eg, 10\% and 15\% in studies of Whang-Peng et al\textsuperscript{27} and Pederson et al,\textsuperscript{28} respectively. The overall proportion of patients with 5q\textsuperscript{−} and/or secondary MDS is not greater than the proportion of patients with 5q\textsuperscript{−} and primary MDS. Furthermore, the 5q\textsuperscript{−} chromosome in secondary leukemias usually occurs as part of a complex karyotype, eg, only 2 of 300 cases from 4 large series were shown to have the 5q\textsuperscript{−} deletion as a sole abnormality.\textsuperscript{29-30}

Therefore, there is no circumstantial evidence to suggest that the 5q\textsuperscript{−} syndrome is a form of secondary leukemia. The poor prognosis of patients with secondary leukemias associated with the 5q\textsuperscript{−} abnormality also contrasts with that of the 5q\textsuperscript{−} syndrome. Interestingly, monosomy 5 is extremely rare as a sole karyotypic abnormality\textsuperscript{31} and therefore it is not possible to compare its phenotypic effects to the 5q\textsuperscript{−}. It may be tempting to propose a multistep model for the 5q\textsuperscript{−} syndrome through to acute nonlymphocytic leukemia (ANLL), but there is little supportive evidence for this model in patients with the classic 5q\textsuperscript{−} syndrome as defined above.

**CYTOGENETICS**

The 5q\textsuperscript{−} is one of the most frequent karyotypic abnormalities observed in MDS and ANLL.\textsuperscript{31} Terminal as well as interstitial deletions of 5q\textsuperscript{−} have been reported; all 13 bands between 5q11 and 5q35 have been implicated as breakpoints in both MDS and ANLL. However, most reviews have concluded that the 5q\textsuperscript{−} is interstitial; the breakpoints most frequently cited are 5q12-14 (proximal breakpoint) and 5q31-33 (distal breakpoint).\textsuperscript{32} Some of the variability in the reported deletion breakpoints may result from the difficulties of interpretation of some leukemic chromosomal preparations. Mitelman et al\textsuperscript{32} reported identical breakpoints del(5)(q13;q33.1) in 15 patients with MDS using high-resolution techniques, raising the possibility that this particular deletion was common to all cases of the 5q\textsuperscript{−} syndrome. The del(5)(q13.3;q33) was found in 36 of 96 patients in the study by Pederson and Jensen\textsuperscript{33} and was reported as the most common deletion in secondary ANLL and MDS.\textsuperscript{34} It was suggested by Pederson and Jensen\textsuperscript{33} that this particular deletion is associated with a greater female sex preponderance, older age, and longer survival and may represent a distinct clinical subgroup; further studies are needed to corroborate this proposal. Pederson and Jensen\textsuperscript{33} reported several other deletion breakpoints in addition to those in the common del(5)(q13;q33). Although the 5q deletion is generally large, typically encompassing most of the long arm, cases with smaller 5q deletions have been reported.\textsuperscript{35} As noted in the large reviews, there appears to be no difference in the patterns of reported breakpoints of the 5q deletion between MDS and ANLL.

The critical region of gene loss in tumorigenesis is operationally defined as the minimum region of common loss of genetic material. The cytogenetic reports have given rise to a number of different putative critical regions: q21-q22\textsuperscript{19}; q22\textsuperscript{22}; and q31\textsuperscript{32,35}. It should be noted that, in these studies, the patients have had the 5q\textsuperscript{−} abnormality associated with a spectrum of myeloid malignancies rather than the 5q\textsuperscript{−} syndrome.

**MOLECULAR BASIS**

The molecular basis for the 5q\textsuperscript{−} syndrome has been the subject of extensive investigation. In general, there are two major classes of tumor-associated genes: the proto-oncogenes and the tumor-suppressor genes. There is now substantial evidence for the model of chromosomal translocations leading to the abnormal activation of oncogenes or to the creation of novel oncogenes by gene fusion in leukemia.\textsuperscript{37} Theoretically, this might also be the consequence of a large interstitial chromosome deletion whereby the juxtaposition of specific sequences is the important pathogenetic event.
The hypothesis of a two-step mechanism\textsuperscript{4} was confirmed by the discovery that mutational inactivation or deletion occurs successively at both alleles of the gene, leading to loss of gene activity.\textsuperscript{5} Other tumor-suppressor genes, including p53\textsuperscript{6} and APC,\textsuperscript{7} have now been identified,\textsuperscript{8} but no tumor-suppressor functions have yet been definitively identified from the study of chromosome deletions in leukemias. However, intriguing data on 9p deletions in acute lymphocytic leukemia (ALL) shows that hemizygous and homozygous deletions of the interferon (IFN) genes exist, indicating that either the IFN genes or a gene closely linked to them may have tumor-suppressor functions.\textsuperscript{9} Most recently, data have been published on the NF1 gene in the childhood MDS suggesting that it acts as a tumor-suppressor gene.\textsuperscript{10}

In recent years, much excitement has been generated by the discovery that mutational inactivation or deletion occurs successively at both alleles of the gene, leading to loss of gene activity. The consistent loss of genetic material in association with rearrangements/deletions. The determination of the critical region is dependent on the analysis of a small number of exceptional cases for the molecular delineation of the critical region. Figure 1 illustrates the proposed critical regions from four studies. The study of Boulton et al.\textsuperscript{11} is based on the molecular mapping of the chromosome deletion in two patients with classic 5q\textsuperscript{−} syndrome whose karyotypic analysis showed that they had relatively small chromosome 5 deletions del(5)(q31;q33). The allelic loss of 11 genes localised to q23-qter was investigated using gene dosage and in situ hybridization analysis and the deletion breakpoints were mapped using pulsed field electrophoresis.\textsuperscript{12-15} The critical region established from this study is an approximately 5-Mb region between the genes for FGFA and NKSFl (including CSF-1R). The study of Le Beau et al,\textsuperscript{16} was based on FISH analysis using a panel of DNA markers in a group of 17 patients with overlapping deletions and reported a more centromeric 2.8-Mb region between IL9 and D5S166 (including EGR-1). It should be noted that most of the patients in this latter study did not have the classic 5q\textsuperscript{−} syndrome (5 patients had therapy-related MDS or ANLL, 8 patients had primary ANLL, and 1 patient had ALL with 3 cases of primary

Table 1. Genes Localized to Chromosome Region 5q13-q33

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEXB</td>
<td>Hexosaminidase β</td>
</tr>
<tr>
<td>DHFR</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td>RASA</td>
<td>Ras p21 protein activator</td>
</tr>
<tr>
<td>FER</td>
<td>Fer (fps/tes-related) tyrosine kinase</td>
</tr>
<tr>
<td>APC</td>
<td>Adenomatous polyposis coli</td>
</tr>
<tr>
<td>MCC</td>
<td>Mutated in colorectal cancer</td>
</tr>
<tr>
<td>IL-4</td>
<td>Interleukin-4</td>
</tr>
<tr>
<td>IL-5</td>
<td>Interleukin-5</td>
</tr>
<tr>
<td>IRF1</td>
<td>Interleukin regulatory factor 1</td>
</tr>
<tr>
<td>IL-3</td>
<td>Interleukin-3</td>
</tr>
<tr>
<td>CSF-2</td>
<td>Colony-stimulating factor 2 (granulocyte/macrophage)</td>
</tr>
<tr>
<td>TCF7</td>
<td>T-cell-specific transcription factor 7</td>
</tr>
<tr>
<td>IL-9</td>
<td>Interleukin-9</td>
</tr>
<tr>
<td>EGR-1</td>
<td>Early growth response 1</td>
</tr>
<tr>
<td>CD14</td>
<td>Myeloid antigen CD14</td>
</tr>
<tr>
<td>FGFA</td>
<td>Fibroblast growth factor, acidic (endothelial growth factor)</td>
</tr>
<tr>
<td>GRL</td>
<td>Glucocorticoid receptor</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Adrenergic, β1 receptor, surface</td>
</tr>
<tr>
<td>CSF-IR</td>
<td>CSF1 receptor formely FMS)</td>
</tr>
<tr>
<td>SPARC</td>
<td>Secreted protein, acidic, cysteine-rich (osteonectin)</td>
</tr>
<tr>
<td>GLUH1</td>
<td>Glutamate receptor</td>
</tr>
<tr>
<td>NKSFl</td>
<td>Subunit of interleukin 12</td>
</tr>
<tr>
<td>GABRA1</td>
<td>γ-Aminobutyric acid (GABA) A receptor, α1</td>
</tr>
</tbody>
</table>

The genes are listed top (HEXB) to bottom (GABRA1) in their respective order, centromere to telomere.\textsuperscript{17-20} Resulting from the deletion, the marked variability in the reported proximal and distal breakpoints of the 5q deletion would argue against this model for the 5q\textsuperscript{−} chromosome, although it remains a theoretical possibility for the common del(5)(q13;q33). The mechanism for generating large chromosome deletions such as the 5q\textsuperscript{−} is unknown. It is possible that the losses represent abnormal forms of lineage-specific gene rearrangements/deletions.\textsuperscript{21} The determination of the sequence at the breakpoints of several examples of the 5q\textsuperscript{−} might be instructive in this regard.

The consistent loss of genetic material in association with a specific syndrome suggests that the paradigm offered by the RBL gene in retinoblastoma may be a relevant model.\textsuperscript{22,23} The hypothesis of a two-step mechanism\textsuperscript{24} was confirmed by the discovery that mutational inactivation or deletion occurs successively at both alleles of the RBL gene, leading to loss of gene activity.\textsuperscript{25} Other tumor-suppressor genes, including p53\textsuperscript{26} and APC,\textsuperscript{27} have now been identified,\textsuperscript{28} but no tumor-suppressor functions have yet been definitively identified from the study of chromosome deletions in leukemias. However, intriguing data on 9p deletions in acute lymphocytic leukemia (ALL) shows that hemizygous and homozygous deletions of the interferon (IFN) genes exist, indicating that either the IFN genes or a gene closely linked to them may have tumor-suppressor functions.\textsuperscript{29} Most recently, data have been published on the NF1 gene in the childhood MDS suggesting that it acts as a tumor-suppressor gene.\textsuperscript{30}

In recent years, much excitement has been generated by the large number of hematopoietic growth factor and growth factor receptor genes localized to 5q.\textsuperscript{31-33} A large number of genes encoding other growth factors and neurotransmitter

Fig 1. Schematic diagram of chromosome 5 illustrating critical regions.
MDS). Similarly, an anonymous DNA marker D5S89, mapping within the critical region as defined by Le Beau et al., has been shown to be deleted in four MDS patients with 5q- and in one ANLL patient with monosomy 5 by Nagarajan et al. Willman et al. identified a more centromeric region of critical gene loss encompassing the IRFl gene using gene dosage and FISH in 11 patients with 5q-, comprising 2 cases of therapy-related ANLL, 4 cases of primary ANLL, 4 cases of primary MDS, and 1 case of ALL. Therefore, a number of distinct critical regions of the 5q– chromosome in malignant myeloid disorders have been reported that localize to a relatively small region of approximately 10 to 15 Mb, predominantly mapping within the chromosome band 5q31. The explanation for these mutually exclusive critical regions is unknown. In the study by Willman et al., example, three patients were identified who showed loss of IRF1 but retained loci immediately distal. Similarly, the critical regions identified by Willman et al. and Le Beau et al. were shown to be retained in the 5q– patients in the Boulwood et al. study and vice versa. The presence of more than one critical region of the 5q– chromosome suggests that there may be more than one myeloid-specific tumor-suppressor gene localized to distal 5q, possibly reflecting the different patient populations included in these studies. By way of comparison, it is interesting to note the evidence for multiple tumor-suppressor genes on chromosome 17.

Many genes have been proposed as candidate genes for the 5q– syndrome. The granulocyte-macrophage colony-stimulating factor (CSF-2) has been shown to be deleted from the 5q– chromosome in some patients. Many of the interleukin genes, a group of cytokines that stimulate the proliferation and differentiation of leukocytes, have also been localized to the long arm of chromosome 5. The interleukin genes interleukin-3 (IL-3), IL-4, IL-5, and IL-9 have all been shown to be deleted from the 5q– chromosome in some patients. Other genes assigned to distal 5q possessing a hematologic function include the myeloid surface antigen CD14 and the T-cell-specific transcription factor (TCF7). More recently, the thrombin receptor has been localized to 5q13, a common site for the proximal breakpoint of the 5q deletion. The familial adenomatous polyposis coli (APC) gene and the mutant in colorectal cancer gene (MCC) gene were identified as a result of their frequent rearrangement or mutation in colorectal cancer. They are the only known tumor-suppressor genes to map to the long arm of chromosome 5, although it is not known whether these genes are mutated in the 5q– syndrome. It is not clear how the deletions of any of the above genes could give rise to the 5q– syndrome, particularly as many are not expressed in the myeloid cells known to acquire 5q deletions in MDS.

In addition, the recent molecular delineation of the critical region within 5q31 now excludes many candidate genes, including CSF-2, IL-3, IL-4, IL-5, APC, and MCC.

The three candidate genes that have been the subject of most discussion are EGR-1, IRF1, and CSF-1R. EGR-1 is encoded by an immediate early gene that is induced by mitogens, suggesting that EGR-1 is a positive regulator of cell growth. The DNA-binding region of the WT-1 protein is closely related to the corresponding region of the EGR-1 transcriptional activator, and the two proteins can bind the same DNA target sequences. EGR-1 is expressed in myeloid cells and plays a role in the differentiation of myeloid blasts. The functional nature of this gene has led to the suggestion that loss of EGR-1 is important in the development of myeloid malignancies with a 5q deletion. Le Beau et al. have shown EGR-1 to be consistently deleted in a large group of patients with primary and secondary MDS and ANLL. However, no evidence for mutations of EGR-1 has yet been found in patients with the 5q– syndrome or ANLL.

The IRF1 gene is a transcriptional activator of type 1 IFN (IFNα and IFNβ) and other IFN-inducible genes. The IRF1 protein possesses growth-inhibitory and antioncogenic activities and is a candidate tumor-suppressor gene. The allelic loss of the IRF1 gene has been shown in a group of patients with MDS and ANLL and a 5q– chromosome by Willman et al. A proportion of the patients showed the deletion of both alleles in a subpopulation of cells when analyzed by gene dosage and FISH analysis, although no mutations of IRF1 were reported. The study by Boulwood et al. showed the loss of one allele of the IRF1 gene in most patients with a 5q– chromosome, but no there was no evidence for homozygous loss of the IRF1 gene. The CSF-1R gene encodes the receptor for CSF-1 and as such plays a central role in the growth regulation of myeloid cells. CSF-1 is a hematopoietin promoting the proliferation and differentiation of monocyte progenitors. Macrophages may be stimulated by CSF-1 to release other pluripoietins such as IL-1 and CSF-3 (G-CSF), illustrating the pleiotropic effects of the growth factor on the control of myeloid hematopoiesis. Several studies have reported the loss of CSF1R from the 5q– chromosome. Boulwood et al. reported the loss of a CSF1R allele from the 5q– chromosome together with the loss of the second allele in a subpopulation of cells in some patients with MDS. The properties of the CSF-1R gene do not suggest it has a role as a tumor-suppressor gene, and it is unlikely that the CSF-1R gene is the critical gene in the 5q– syndrome. However, these observations point towards a tumor-suppressor gene being localized close to CSF1R, as our data on the critical region of gene loss in the 5q– syndrome would also suggest.

SUMMARY AND FUTURE PROSPECTS

Little is known about the relationship between the 5q– syndrome and the other subtypes of MDS, primary ANLL, or therapy-related MDS and ANLL with 5q-. The natural history of these disorders is very different to the 5q– syndrome, suggesting the presence of different underlying abnormalities. In particular, the good prognosis of the 5q– syndrome and rare transformation to ANLL contrasts with the poor prognosis and clinically aggressive course of RAEBt and therapy-related MDS and ANLL. It has previously been postulated by others that the disease genes causing the 5q– syndrome and therapy-related MDS and ANLL may be distinct. The recent molecular delineation of the different critical regions of the 5q– chromosome in malignant myeloid disorders supports this view.

From www.bloodjournal.org by guest on October 22, 2017. For personal use only.
ever, it remains possible that different mutations of a single gene localized to 5q31 or additional mutations elsewhere in the genome are responsible for some of the different phenotypic manifestations of the 5q− in myeloid disorders. Whether there are different disease genes implicated in the development of the 5q− syndrome and the other malignant myeloid disorders with a 5q− will only be finally resolved by the identification and cloning of these genes.

In the absence of a fortuitous discovery it now seems probable that the identification of the 5q− syndrome gene will be achieved by an approach analogous to that recently used in the cloning of the APC gene in colorectal cancer.43 In these studies, a yeast artificial chromosome (YAC) contig was constructed encompassing the entire 5-Mb critical region and novel coding sequences mapping to the deleted region identified by screening the YAC clones against cDNA libraries. These candidate genes were then examined for rearrangements and/or mutations in patient material. The identification of small nested deletions in two patients with familial APC57 considerably reduced the complexity of the task, and the APC gene was identified as a result of its frequent mutation.44 Similarly, any candidate genes mapping to the critical region of the 5q− syndrome will need to be closely examined for rearrangements or mutations on the normal chromosome 5 homolog. The number of genes contained within the approximately 10-Mb region encompassing the proposed critical regions is unknown; some regions are relatively rich in genes and others are relatively depleted. A recent study that gives some insight into this question examined the number of genes found in one megabase of the HLA class I region.86 cDNA selection was applied to three overlapping YACs spanning 1 Mb of this region. In addition to the recognized class I genes, 20 additional anonymous cDNA clones were identified. Similarly, YAC coverage of 880 kb of the Huntington disease region (2.2 mb) has allowed for the isolation of 13 cDNA clones.87 Therefore, based on these analyses of gene-rich regions, the approximate 10 Mb encompassing the putative critical regions in 5q31 may possess up to 200 genes. It is probable that most of the genes in this region will be identified over the next 5 years or so, given the progress of the Human Genome Mapping project. Such comprehensive information on chromosome 5 should enable the resolution of the genetic basis of the 5q− syndrome.

REFERENCES

35. Hubecker K, Inobe M, Croce CM, Golde DW, Kaufman SE, Gasson JC: The human gene encoding GM-CSF is at 5q21-q32, the chromosome region deleted in the 5q− anomaly. Science 230:1282, 1985
37. Sutherland GR, Baker E, Callen DF, Campbell HD, Young IC: Molecular organization of the cytokine gene cluster, involving the GM-CSF and FMS in the deletion (5q) in myeloid disorders. Blood 73:1142, 1989


The 5q-syndrome

J Boulwood, S Lewis and JS Wainscoat