

REVIEW

Tyrosine kinase fusion genes in chronic myeloproliferative diseases

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With the exception of chronic myeloid leukemia (CML), chronic myeloproliferative disorders (CMPDs) are a heterogeneous spectrum of conditions for which the molecular pathogenesis is not well understood. Most cases have a normal or aneuploid karyotype, but a minority present with a reciprocal translocation that disrupts specific tyrosine kinase genes, most commonly PDGFRB or FGFR1. These translocations result in the production of constitutively active tyrosine kinase fusion proteins that deregulate hemopoiesis in a manner analogous to BCR-ABL. With the advent of targeted signal transduction therapy, an accurate clinical and molecular diagnosis of CMPDs has become increasingly important. Currently, patients with PDGFRB or ABL fusion genes are candidates for treatment with Imatinib (STI571), but it is likely that alternative strategies will be necessary for the treatment of most other patients.

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Introduction

The chronic myeloproliferative diseases (CMPD) are clonal disorders characterized by excess proliferation of cells from one or more myeloid lineages. Proliferation is accompanied by relatively normal maturation, resulting in increased numbers of granulocytes, red blood cells and/or platelets in the peripheral blood. Some patients also show dysplastic features and are considered to have a related condition termed myelodysplastic/myeloproliferative disease (MDS/MPD).¹ Below we use the term 'MPD' to encompass all patients with myeloproliferative features, ie either CMPD or MDS/MPD.

The most common CMPD is chronic myelogenous leukemia (CML), a disease that has been reviewed in detail recently.^{2,3} CML is characterized by the presence of the BCR-ABL fusion gene in all myeloid lineage cell types, as well as in some lymphoid cells. The BCR-ABL chimeric protein is a deregulated, constitutively active tyrosine kinase that is believed to be the primary, and possibly the only driving force behind the disease. Bone marrow-derived metaphases from approximately 90% of CML cases harbor the t(9;22)(q34;q11.2), the smaller derivative of which is known as the Philadelphia (Ph) chromosome. The remaining patients either have a cryptic translocation between BCR and ABL that cannot be detected by routine cytogenetic analysis, or they have a complex translocation that involves a third or more chromosomes in addition to chromosomes 9 and 22.⁴ The chimeric BCR-ABL protein activates multiple signal transduction pathways, although the detailed mechanisms by which it

causes the phenotypic features of CML have only been partially unravelled.⁵

BCR-ABL negative diseases

Overview

Whereas a small number of cases with a BCR-ABL-negative CMPD appear to be indistinguishable from CML in terms of clinical and laboratory findings, the majority present with atypical, heterogeneous clinical features.^{1,6,7} Some of these cases have an elevated monocyte count and thus overlap with chronic myelomonocytic leukemia (CMML), an entity now considered as a subtype of MDS/MPD. The molecular pathogenesis of BCR-ABL negative MPDs is poorly understood but a minority of cases present with an acquired reciprocal chromosomal translocation that is amenable to molecular analysis (Figure 1). Whilst many of these translocations are apparently unique, ie, they exist as single case reports in the literature, there are two clear breakpoint clusters, at 5q31–33 and 8p11.

Clinical features of patients with translocations that target 5q31–33 or 8p11

The term '8p11 myeloproliferative syndrome (EMS)' or 'stem cell leukemia-lymphoma syndrome (SCLL)' has been suggested for the distinctive disease associated with 8p11 translocations.^{8,9} The clinical phenotype of EMS, and also that associated with 5q rearrangements, has been reviewed in detail elsewhere.^{10,11}

Briefly, patients with a 5q31–33 rearrangement present at a median age of between 50 and 60 years and, remarkably, virtually all patients are male. Patients with EMS present at a

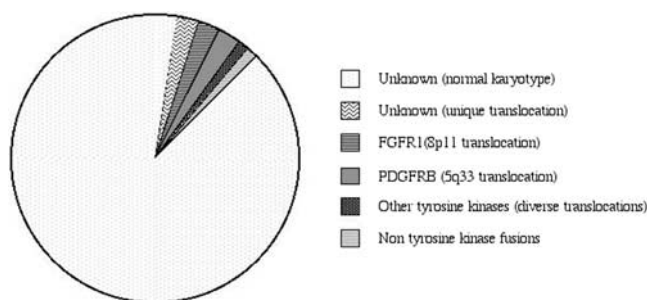


Figure 1 Approximate proportions of CML/CMML-like MPDs for which the molecular pathogenesis is unknown (karyotype shows no translocation or a unique, uncharacterized translocation) or known (FGFR1 fusion, PDGFRB fusion, other tyrosine kinase fusion, non-tyrosine kinase fusion).

median age of 32 years with a slight male predominance of 1.5:1. Of interest, both 5q and 8p rearrangements are associated with splenomegaly and marked eosinophilia in the peripheral blood and/or bone marrow. Thrombocytosis and basophilia are uncommon but 5q patients typically present with a variable degree of monocytosis and thus have features that are suggestive of both CML and CMML. EMS can also resemble CMML, but the distinguishing feature of this condition is the strikingly high incidence of co-existing non-Hodgkin's lymphoma that may be either of B or, more commonly, T cell phenotype. In many cases lymphadenopathy is present at diagnosis, whereas in others it appears during the course of the disease. Transformation to acute leukemia occurs in a minority of 5q cases with a highly variable latency from 9 months to 12 years. EMS is much more aggressive disease and rapidly transforms to acute leukemia, usually of myeloid phenotype, within 1 or 2 years of diagnosis. The median time to transformation is only 6 to 9 months and thus far the only effective treatment for this condition appears to be allogeneic bone marrow transplantation.

The molecular consequences of 5q and 8p translocations

Involvement of tyrosine kinases

Cloning of 5q31–33 and 8p11 translocations in patients with MPDs revealed that they each disrupt genes encoding tyrosine kinases, specifically the platelet-derived growth factor receptor B (PDGFRB) on chromosome 5 and the fibroblast growth factor receptor 1 (FGFR1) on chromosome 8. As a consequence, constitutively active fusion proteins are produced that are functionally and structurally analogous to BCR-ABL (Table 1). To date, four partner genes for both PDGFRB and FGFR1 have been described, but FISH analysis has indicated that several other partners remain to be identified.

FGFR1 partner genes

The t(8;13)(p11;q12), t(8;9)(p11;q33), t(6;8)(q27;p11) and t(8;22)(p11;q22) fuse ZNF198 (also known as RAMP or FIM), CEP110, FOP and BCR to FGFR1, respectively.^{12–19} Disruption

of FGFR1 has also been described in patients with a t(8;12)(p11;q15), ins(12;8)(p11;p11p21), t(8;17)(p11;q25) or t(8;19)(p12;q13), but the partner gene in these cases remains to be identified.^{20,21}

Although the numbers of patients in the literature are small, there are suggestions that different FGFR1 partner genes are associated with subtly different disease phenotypes. For example, two patients with a t(6;8) and a FOP-FGFR1 fusion were diagnosed initially as having polycythemia vera.¹⁶ Thrombocytosis and monocytosis have been described relatively frequently in patients with a t(8;9), and thus the disease with this translocation resembles CMML but without major dysplastic signs in either lineage.^{11,22} The incidence of T-NHL appears to be considerably higher in cases that present with a t(8;13) compared to patients with variant translocations. For example, in a recent survey 13/16 patients with a t(8;13) had T-NHL compared to 3/11 patients with a t(6;8) or t(8;9).¹⁰

Strikingly, the three patients that have been described with a t(8;22) and a BCR-FGFR1 fusion had a clinical and morphological picture that was very similar to typical, BCR-ABL positive CML.^{18,19} All three patients had basophilia, a feature that is uncommon in BCR-ABL-negative MPDs and, as noted above, is rare in EMS with other FGFR1 partner genes. It is possible, therefore, that the BCR moiety of the fusion might directly contribute to the specific clinical features that are characteristic of CML. However, in common with other EMS patients, disease progression in BCR-FGFR1 cases appears to be rapid.

PDGFRB partner genes

To date, four gene fusions in association with a MPD have been described: the t(5;12)(q31q33;p12), t(5;7)(q33;q11), t(5;10)(q33;q21.2) and t(5;17)(q33;p13) fuse ETV6/TEL, HIP1, H4/D10S170 and RAB5 to PDGFRB.^{23–27} Of these, the t(5;12) is by far the most common. A fifth fusion, CEV14-PDGFRB, has been described in a patient who acquired a t(5;14)(q33;q32) as a secondary abnormality at relapse in a patient who initially presented with AML.²⁸ Since the number of cases reported with variant translocations is so small, it is not possible to discern if there are any phenotypic differences between patients with different PDGFRB fusions.

Normal activation of tyrosine kinases

Tyrosine kinases are normally tightly regulated signalling proteins that impact on proliferation, apoptosis and differentiation.²⁹ FGFR1 and its relatives FGFR2–4 play important roles in early development, in conjunction with their ligands, the fibroblast growth factors (FGFs), of which there are currently more than 20 members.³⁰ The FGF/FGFR systems may also impact on hemopoiesis, although their role in this context has not been clearly defined. PDGFRB is normally expressed on fibroblasts and endothelial cells and plays an important role in wound healing and vascular repair. In the hemopoietic system PDGFRB is normally expressed in erythroid and myeloid precursors in the bone marrow. In addition, it is expressed by mature monocytes, megakaryocytes, and osteoblasts.³¹ Expression of PDGFRB in monocytes suggests a role in monocytic differentiation, possibly in the activation of macrophages once they have matured.

In their inactive state, receptors such as FGFR1 and PDGFRB are thought to exist as monomeric proteins embed-

Table 1 Tyrosine kinase fusion genes in chronic myeloproliferative disorders

<i>Fusion gene</i>	<i>Translocation</i>
BCR-ABL	t(9;22)(q34;q11)
ETV6-ABL	t(9;12)(q34;p13)
ZNF198-FGFR1	t(8;13)(p11;q12)
FOP-FGFR1	t(6;8)(q27;p11)
CEP110-FGFR1	t(8;9)(p11;q33)
BCR-FGFR1	t(8;22)(p11;q22)
ETV6-PDGFRB	t(5;12)(q33;p13)
HIP1-PDGFRB	t(5;7)(q33;q11)
H4-PDGFRB	t(5;10)(q33;q21)
RAB5-PDGFRB	t(5;17)(q33;p13)
ETV6-JAK2	t(9;12)(p24;p13)
BCR-JAK2	t(9;22)(p24;q11)
ETV6-SYK2	t(9;12)(q22;p12)

ded in the plasma membrane. They consist of an extracellular ligand binding domain, a transmembrane domain and a cytoplasmic domain that harbors the catalytic element, plus other components necessary for signal transduction and response to negative feedback processes. Binding of FGF or PDGF ligands induces dimerization of the cognate receptor, which juxtaposes the two catalytic domains, inducing a conformational change which partially activates the enzymatic activity. This leads to transphosphorylation of a key tyrosine residue in the activation loop, resulting in an increase in enzymatic activity, autophosphorylation of additional tyrosines and subsequently phosphorylation and/or recruitment of target substrates. Ligand-stimulated tyrosine kinases activate multiple signalling pathways including those involving STATs, Ras/MAPK, PI3K and PLC γ .^{22,29,32} These pathways are also activated by the derivative fusion proteins.^{3,33,34}

Aberrant activation of tyrosine kinases by gene fusion

Chromosomal translocations that target genes encoding tyrosine kinases generate fusion proteins in which the partner protein is joined to the entire catalytic domain of the tyrosine kinase. Although mRNA encoding the reciprocal fusion is detectable in many (but not all) cases, there is no evidence to suggest that these products play any important role in the disease process. Partner proteins are unrelated in sequence and function, but they have two features in common. First, homotypic interaction between specific domains of the partner protein leads to dimerization or oligomerization of the fusion protein. This mimics the normal process of ligand-mediated dimerization and results in constitutive activation of the tyrosine kinase moiety. Motifs of the partner gene that serve as dimerization/oligomerization interfaces include the BCR coiled-coil domain, the ETV6 pointed (helix-loop-helix) domain and a proline-rich domain in ZNF198.³⁵⁻³⁷ Second, since the elements that control the expression of the partner gene will almost certainly control expression of the tyrosine kinase fusion gene, the partner gene must be normally expressed in hemopoietic stem cells. In fact, most partner genes appear to serve a housekeeping role in that they universally or widely expressed. The partner proteins may also provide additional functions, for example tyrosine 177 of BCR serves as a Grb2 binding site when it is phosphorylated, an

interaction that plays an important role in BCR-ABL-mediated transformation.³⁸

In mouse models, the ETV6-PDGFRB fusion gene induces an MPD that is characterized by an excess of neutrophils and megakaryocytes in the marrow and splenomegaly due to extramedullary hemopoiesis. Transformation is dependent on a functional PDGFRB tyrosine kinase domain, the presence of the dimerization motif encoded by the partner gene, PDGFRB tyrosines 579/581 and involves both STAT5-dependent and independent pathways.³⁹⁻⁴²

Involvement of other tyrosine kinases

Other fusion genes

Sporadic MPD cases have been reported in association with other tyrosine kinase fusion genes such as ETV6-ABL and ETV6-JAK2.^{43,44} These fusion genes, that have also been reported in other malignancies, notably acute lymphoblastic leukemia, and ETV6-JAK2 have been shown to induce a fatal mixed myelo- and T cell lymphoproliferative disorder in a murine model.⁴⁵ In addition, a single patient with a CML-like disease and a BCR-JAK2 fusion has been described and an ETV6-SYK fusion has been reported in an MDS patient who appeared to have a disease with a myeloproliferative component.^{46,47} In the great majority of cases tyrosine kinase fusion genes is associated with relatively aggressive, CML-like diseases rather than the more indolent MPDs.

Overwhelmingly then, translocations that have been cloned from patients with MPDs have been shown to result in tyrosine kinase fusion genes. However, the association is not absolute and a few cases of CML-like diseases have been reported in conjunction with translocations that are normally associated with AML, for example the t(6;9)(p23;q24) and the t(7;11)(p15;p15), which result in DEK-CAN fusion and NUP98-HOXA9 fusions, respectively.⁴⁸⁻⁵³ Also, it is important to emphasize that the great majority of MPDs do not present with a reciprocal chromosomal translocation and consequently their molecular pathogenesis is almost completely obscure (Figure 2).

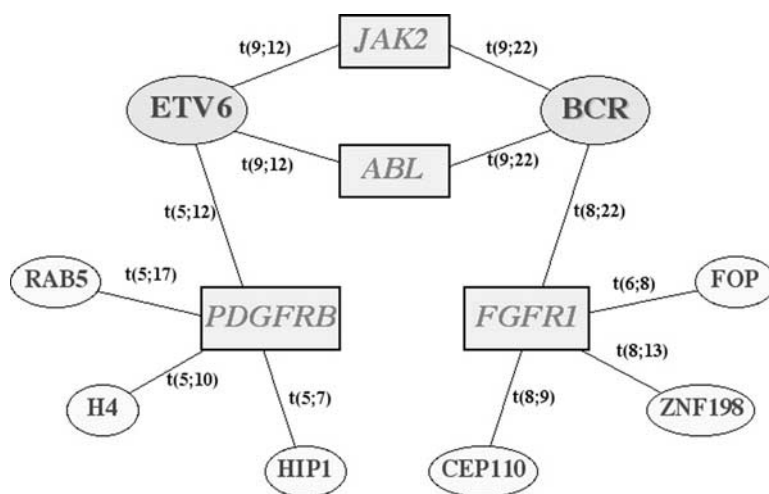


Figure 2 Network of tyrosine kinase fusion genes in MPDs.

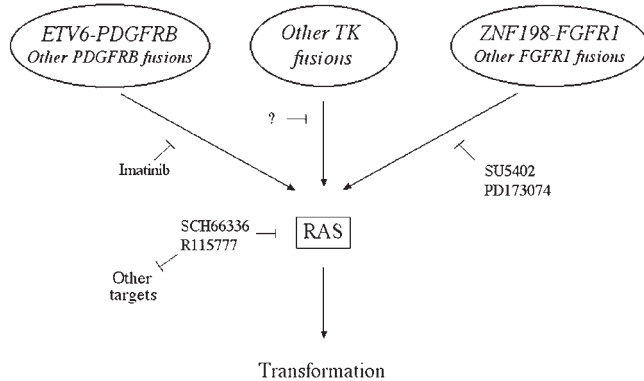


Figure 3 Possible therapeutic strategies for BCR-ABL-negative MPDs with tyrosine kinase fusion genes.

Targeted therapy of activated tyrosine kinases

Imatinib, a 2-phenylaminopyrimidine molecule, occupies the ATP binding site and inhibits tyrosine phosphorylation of ABL, c-KIT and PDGFRB. Recent data have shown impressive clinical benefits from treatment in patients with BCR-ABL-positive CML with an incidence of complete cytogenetic responses in the order of 60%. It is not yet completely understood if inhibition of BCR-ABL alone is responsible for the anti-leukemic activity (and the relatively mild side-effects) or whether inhibition of additional tyrosine kinases might also play a role. Severe side-effects are rare but nothing is yet known about possible long-term sequelae and whether Imatinib actually prolongs life compared to standard IFN α treatment. In addition, acquired resistance might be problematic.^{54–56} Several mechanisms of resistance have been identified thus far, notably overexpression of BCR-ABL as a result of gene amplification and mutations within the ATP binding domain that reduce the affinity of Imatinib binding.

Imatinib has also shown anti-leukemic activity in a murine model of ETV6-PDGFRB-positive disease and early results suggest that t(5;12) patients respond well to treatment with this compound. However, Imatinib is inactive against FGFR1 and so it is very unlikely that it will benefit patients with EMS.¹⁸ In contrast, other compounds have been developed, eg SU5402 and PD173074 that also function as ATP binding site blockers and which possess anti-FGFR activity.^{18,57} These compounds are inactive against BCR-ABL but can specifically inhibit the growth of ZNF198-FGFR1 and BCR-FGFR1 transformed cells. FGFR inhibitors are therefore good candidates for treatment of EMS patients.¹⁸

Tyrosine kinases, including the derivative fusion proteins, activate multiple, common sets of overlapping signalling pathways. Some of these pathways are believed to be essential for transformation mediated by tyrosine kinase fusion proteins and therefore they are also attractive targets for therapeutic intervention. Currently, the most promising agents are farnesyl transferase inhibitors (FTIs), which inhibit the activation of RAS, plus a large number of largely uncharacterized farnesylated proteins. Somewhat surprisingly given the fundamental role played by RAS and other targets, FTIs appear to be well tolerated in phase I/II studies. FTIs have significant *in vitro* (SCH66366) and *in vivo* (R115777) anti-leukemic activity in diverse hematological malignancies.^{58–60} In addition, they seem to be active against CML cells that have acquired resistance to Imatinib and also cell lines transformed by FGFR1 fusions. Overall then it is likely that targeted therapy of a

wider subset of BCR-ABL negative MPDs will become a reality in the near future (Figure 3).

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