must have a high therapeutic index. Lestaurtinib was well tolerated in phase 1 and 2 studies, and therefore has already passed its first important test. Nevertheless, inhibition of JAK2 raises concerns, since JAK2 is required for signaling by the receptors for erythropoietin, thrombopoietin, and in part, G-CSF. In this respect, it is encouraging that cells carrying JAK2-V617F were more sensitive to the inhibition of lestaurtinib than cells with WT JAK2. Conversely, cells from MPD patients negative for JAK2-V617F were also inhibited by lestaurtinib. This could be interpreted to mean that activation of JAK2 signaling is a common pathway of pathogenesis in MPDs. Alternatively, lestaurtinib may have additional beneficial “off-target” effects by inhibiting other, as-yet-unknown kinases that act as cooperating cellular signaling pathways.

The work by Hexner and colleagues shows that lestaurtinib can be added to a rapidly growing list of small molecules with inhibitory effects against JAK2. Information about the structure of the complete human kinase, in conjunction with high-throughput screening platforms, may reveal other hidden gems and allow further expansion of targeted cancer therapeutics. The discovery of JAK2 mutations in MPDs has initiated an exciting new phase for clinicians and basic scientists interested in MPDs, and has already substantially improved diagnostics and advanced our knowledge of MPD pathogenesis. In fewer than 3 years since their discovery, there has developed the exciting prospect that patients with MPDs may soon benefit from targeted treatment for their disease.

Conflict-of-interest disclosure: The author is a consultant for Genentech (South San Francisco, CA).

REFERENCES

SNPing away at sickle cell pathophysiology

Martin H. Steinberg  Boston University School of Medicine

In this issue of Blood, Ashley-Koch and coworkers report that, in sickle cell disease–related pulmonary hypertension, SNPs in several genes of the TGF-β/BMP superfamily are associated with this complication.

Sickle cell anemia, a common hemolytic anemia caused by homozygosity for the sickle hemoglobin mutation (glu6val) in the β-globin gene (HBB), is a characteristic Mendelian monogenic disease. Nevertheless, it is clinically heterogenous, resembling a multi-genetic trait. Although environment must account for part of this variability—in developing countries with little access to health care, death in childhood is frequent—even in countries with reasonable health care systems, clinical variability is striking. During the past 5 years, genetic association studies have focused on understanding the basis for this variability by linking single nucleotide polymorphisms (SNPs) in genes that might affect the pathophysiology of disease with disease subphenotypes. As shown in the figure, these subphenotypes include: stroke, priapism, leg ulcers, osteonecrosis, renal failure, bacteremia, and cholelithiasis; many associations, especially with SNPs in genes of the TGF-β/BMP pathway, have been found. The association of these polymorphisms with disease phenotypes is likely to reflect the modulation of sickle vasculopathy.

Now, the first reported study of its kind in sickle cell pulmonary hypertension, an abnormality found in about a third of adults with sickle cell anemia, and one that portends a high risk of very near term mortality,1 adds some SNPs in the TGF-β/BMP pathway to this list. Although the number of patients examined was small, and although one might quibble about the selection of cases and controls and certain analytical issues, it is satisfying that some results recapitulate observations made in other disease subphenotypes like stroke,2 and further implicate the TGF-β/BMP superfamily in the pathophysiology of disease. Other teams are studying larger groups of patients, and we should soon see if the results of these studies are confirmed. The mechanisms by which perturbation of this pathway might modulate the disease remain obscure.

Genetic association studies to date are based on searching for SNPs in candidate genes. That is, each gene was chosen because of its potential importance in this disease. As a result, the positive results are gratifying, but represent a self-fulfilling prophecy. Unraveling the genetic basis for the clinical heterogeneity of sickle cell anemia will require genome-wide association studies in which upwards of a half million SNPs—279 were tested in this

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Proliferation in the presence of lestaurtinib (100 μM) compared to untreated cells was measured in liquid culture.
Conflict-of-interest disclosure: The author declares no competing financial interests.

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