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A Broken Stress Response System Can Contribute to Gleevec Resistance

New clues to why some kinds of leukemia are more aggressive and deadly than others are coming from research examining the types of genetic damage that allow some blood cells to grow out of control, scientists report.

According to Charles J. Sherr, a Howard Hughes Medical Institute researcher at the St. Jude Children's Research Hospital in Memphis, Tennessee, his team's new findings may help doctors understand why some cancers can be controlled with drugs, at least temporarily, while others somehow resist treatment.

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— Charles J. Sherr

Sherr and colleagues Richard T. Williams, the lead author, and Martine F. Roussel reported their research findings on April 17, 2006, in an advance online publication in the *Proceedings of the National Academy of Sciences*.

The investigators studied two types of leukemia: CML—chronic myelogenous leukemia, which can now be alleviated to a large extent with a drug called Gleevec (imatinib), and a subtype of ALL—acute lymphoblastic leukemia, which does not respond well to this drug. The hallmark of both diseases is a genetic alteration in an enzyme (BCR-ABL) whose activity is specifically blocked by Gleevec treatment. The work reveals that loss of a gene known as *Arf*, which is frequently mutated in patients with ALL, but not CML, can cause some leukemias to resist Gleevec treatment.

Patients with CML who are taking Gleevec readily go into remission, and their cancer cells stop growing while they are maintained on drug therapy. Sherr explained that Gleevec's impact has been truly revolutionary. It's a targeted therapy that works; the results have been miraculous.

Unfortunately, there is still a small relapse rate—about five percent per year—that doctors would like to erase. Other researchers have found that patients who fail while on therapy have developed subsequent mutations in

the BCR-ABL enzyme that alter Gleevec's effectiveness, Sherr said.

Further clinical trials are now under way, he said, with drugs that block these mutated forms of BCR-ABL, building upon the benefit that is offered by Gleevec and keeping CML under better control.

CML is caused by a genetic change that scientists call the Philadelphia chromosome. It results when chromosomes 9 and 22 break and reattach themselves to one another. At the point where the chromosomes meet, the joined DNA creates the *BCR-ABL* gene, which has the unfortunate property of causing abnormal growth of the white blood cells that leads to leukemia.

This misarranged chromosome is also seen in a subset of patients with ALL. Unfortunately, Gleevec is much less effective against this more aggressive form of the disease. Sherr's team is studying why that is true, focusing especially on a way to re-sensitize the tumor cells to Gleevec treatments.

Chromosomes are the long, coiled molecules on which genes—life's blueprints—reside. So when chromosomes and genes are disrupted, the damage can lead to diseases, including cancer. Nature has equipped cells with repair systems that recognize genetic damage and try to correct it. But if the damage cannot be fixed, one alternative is to kill the sickened cell by activating a built-in cell suicide system.

Trouble ensues when normal growth-control mechanisms go awry and normal repair and cell suicide mechanisms also fail. Thus cancer cells gain immortality—not dying when they should—and begin growing without restraint to form tumors. In leukemia, the problem is a severe over-supply of one type of white blood cell or another.

In their experiments with mice, Sherr and his colleagues found evidence that a mutation in one of the cell's stress response systems can contribute to tumor growth even in the presence of Gleevec. The mutation disables or erases the function of a gene called *Arf*, which normally helps suppress the growth of cancer cells. Mutations in the *Arf* gene are found in the cells of more than 30 percent of patients with ALL, whereas they have not been observed in patients with CML.

The researchers found that when the *Arf* gene was inactivated, BCR-ABL induced a much more aggressive form of ALL in mice. These mice do not achieve remission on high doses of oral imatinib (Gleevec), and succumb to leukemia, Sherr said. In other words, the drug doesn't work and the mice die soon. The combination of the two [genetic abnormalities] makes the tumors almost 1,000 times more aggressive in terms of their ability to induce disease, he explained.

Although the biological mechanism that underlies this form of drug resistance isn't well understood, tumor cells removed from the drug-resistant mice remained sensitive to Gleevec treatment in cell cultures, Williams said, so there must be a host signaling system in the mice that makes the cells drug resistant. The investigators provide proof of principle that additional drugs

might reverse this form of drug resistance, thereby restoring Gleevec's power to control this type of leukemia.