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Activation of LYN kinase is associated with imatinib-resistance in CML patients

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Activation of LYN kinase is associated with resistance to imatinib (Gleevec) in patients with chronic myelogenous leukemia (CML), researchers report in the June 24 online issue of the *Journal of the National Cancer Institute*.

Imatinib is the standard therapy for newly diagnosed CML patients. However, some patients develop resistance to the drug over time. In some patients, resistance develops in response to mutations in the BCR-ABL gene. In other cases, though, researchers find no mutations to explain the resistance. Previous work by Nicholas Donato, Ph.D., of the University of Michigan Comprehensive Cancer Center in Ann Arbor and others suggested that one possible mechanism of this mutation-negative resistance is the activation of LYN kinase, which is normally controlled by BCR-ABL in CML cells.

In the current study, Donato and colleagues have expanded that work and examined the impact of overexpression and gene silencing of LYN kinase in CML cell lines treated with imatinib. They also determined the level of LYN activation in samples from 12 imatinib-resistant patients who lacked BCR-ABL mutations and 6 patients whose tumor cells were sensitive to the drug but who were unable to tolerate its side effects.

They found that overexpression and activation of LYN kinase was associated with imatinib resistance in both cell lines and patient samples. Moreover, when they treated these cells with imatinib, they saw that BCR-ABL activity was suppressed as happens in CML cells sensitive to

the drug, but LYN activation was not suppressed. When the researchers blocked expression of the LYN gene in the resistant cells, they restored imatinib responsiveness and triggered cell death.

"These studies expand the spectrum of cellular changes that occur during imatinib therapy beyond outgrowth of cells with BCR-ABL point mutations and support the use of other tyrosine kinase inhibitors to treat a broad spectrum of imatinib-resistant CML patients," the authors write.

In an accompanying editorial, Michael Deininger, M.D., Ph.D., of the Oregon Health and Science University Cancer Institute in Portland and colleagues note that the use of primary patient samples in the current study is particularly important and provides clues as to how consistent LYN activation may occur in CML. Further elucidation of this pathway will be essential, as will surveying a larger patient sample to determine how frequently this type of resistance develops in CML patients.

"The work of [Donato and colleagues] takes us outside of the realm of thoroughly studied kinase domain mutation-based resistance and toward an improved understand¬ing of BCR-ABL–independent disease. In addition to opening new questions for exploration, these results suggest that therapies tar¬geting both BCR-ABL and LYN kinases may prove beneficial in certain circumstances of imatinib-resistant CML," the editorialists conclude.

Source: Journal of the National Cancer Institute