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Normal enzyme aids a mutant one to fuel blood cancer's growth

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Reinforcing the need to look beyond genomic alterations to understand the complexity of cancer, researchers from Dana-Farber/Boston Children's Cancer and Blood Disorders Center report that a normal enzyme called SYK pairs with FLT3, the most commonly mutated enzyme found in acute myelogenous leukemia (AML), to promote progression of the disease. This molecular partnership also promotes AML cells' resistance to treatment with FLT3-blocking drugs, potentially explaining the relatively poor showing of FLT3 inhibitors in multiple clinical studies. In an animal model of AML, treatment with a combination of FLT3- and SYK-inhibiting drugs was significantly more effective than treatment with either drug alone.

The findings, published Feb. 10 in the journal *Cancer Cell*, raise hopes that treatment strategies that focus on both enzymes simultaneously could help bring molecularly targeted treatments to AML, a common blood cancer. The study also may have broader implications for how clinicians approach the development of such treatments and understand mechanisms behind resistance to treatment in other cancers.

Approximately 14,600 Americans are expected to be diagnosed with AML this year; children account for about 18 percent of patients. The overall outlook for AML patients is mixed; while the majority of patients with AML achieve remission with treatment, many relapse. The cancer cells of some 20 percent of adult and 15 percent of childhood AML patients harbor a genomic alteration called FLT3-ITD, in which segments of the FLT3 enzyme are duplicated again and again, making

the enzyme overactive.

"Patients whose AML cells express FLT3-ITD are among the highest risk group of patients with AML," says the study's senior author, Kimberly Stegmaier, MD, of Dana-Farber/Boston Children's Hematologic Malignancies Center. "Their AML is particularly difficult to treat."

FLT3 is a kinase, a molecular switch that routs signals for growth, division and other processes within cells. Many cancers harbor mutations or other alterations that leave kinases stuck in the "on" position. This knowledge laid the foundation for the targeted cancer treatment revolution inaugurated by imatinib (Gleevec®), which has made another blood cancer, chronic myelogenous leukemia, a controllable, chronic disease for many patients.

However, patients with AML have not yet benefitted from that revolution. Researchers and pharmaceutical companies are actively working on FLT3 inhibitors, but to date these efforts have been hampered by low efficacy and concerns about drug resistance.

In 2009, Stegmaier's laboratory discovered that SYK, a kinase that had attracted attention for its role in other malignancies, could be a potential drug target in AML. Unlike other cancer-associated kinases, SYK rarely undergoes mutations or other genomic alterations in cancer cells, remaining in its normal or "wild-type" form.

To better understand SYK's role in AML, in the current study, Stegmaier, lead author Alexandre Puissant, PhD, of Dana-Farber/Boston Children's, and their collaborators screened AML cell lines to reveal the full scope of the enzyme's molecular interactions. They found evidence of strong interactions between wild-type SYK and mutated FLT3, in particular FLT3-ITD.

"We wanted to understand the cooperative oncologic effects by which SYK contributes to AML," Stegmaier explains. "The concept of a normal enzyme aiding a mutant one has not yet been widely explored, and so we were both surprised and pleased to see FLT3-ITD come up as a high-priority hit in our screens."

Through experiments in cell lines, primary patient samples and animal models, the research team found that SYK and FLT3-ITD's interactions are a key ingredient in the progression of myeloproliferative disorder, a related blood cell disorder, into AML. AML cells' continued growth after turning malignant also relied on these interactions.

Additionally, the team found that SYK's hyperactivated form can promote resistance to the FLT3-targeting drug quizartinib (AC220, Ambit Biosciences). They could overcome this resistance with a combination of quizartinib and the SYK-blocking molecule PRT062607 (Portola Pharmaceuticals), significantly increasing survival and reducing signs of disease in an FLT3-ITD AML mouse model.

Highlighting their findings' clinical relevance, the researchers found strong SYK activity in cells from FLT3-ITD AML patients. The cells were also highly sensitive to SYK inhibition.

"These data affirm that SYK is an important target in AML," Stegmaier states. "They also suggest that interactions between oncologic kinases and SYK or other wild type enzymes may contribute to resistance of kinase inhibitors more broadly."

Stegmaier notes that over the course of this research, the team has developed a suite of tools that could prove invaluable for future clinical studies of treatments with SYK inhibitors or SYK inhibitors in combination with FLT3 inhibitors.

"We have not only identified SYK as a candidate treatment target in AML, but we have also identified a specific population of patients with AML more likely to respond to SYK inhibitors: patients with FLT3 mutations," she says. "Moreover, we have developed tools for identifying patients with high levels of SYK and FLT3 activation and can monitor these two targets while patients are receiving treatment. Predictive biomarkers of response are becoming increasingly important in the development of effective clinical trials of targeted therapies."

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