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Study suggests which glioblastoma patients may benefit from drug treatment

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Clinicians testing the drug dasatinib, approved for several blood cancers, had hoped it would slow the aggressive growth of the deadly brain cancer glioblastoma; however, clinical trials to date have not found any benefit. Researchers at Mayo Clinic, who conducted one of those clinical trials, believe they know why dasatinib failed—and what to do about it.

In the online issue of *Molecular Oncology*, investigators report finding that dasatinib inhibits proteins that promote cancer growth as expected but also suppresses proteins that protect against cancer.

The findings suggest that pretesting patient glioblastoma biopsies will help identify who may respond well to dasatinib and who should avoid using the drug, says the study's senior author, Panos Z. Anastasiadis, Ph.D., chair of the Department of Cancer Biology at Mayo Clinic in Florida.

Dasatinib is a general Src-family kinase (SFK) inhibitor. It shuts down all members of the Src family of protein kinases, which are believed to activate proteins that essentially give tumors "legs" upon which to crawl through tissue to seek blood nutrients.

In the study, the investigators teased apart dasatinib's effect on individual Src family members—Src, Fyn, Yes and Lyn—using laboratory glioblastoma cell lines and mouse models of the brain cancer.

In the cell lines, inhibiting Src, Fyn and Yes generally reduced growth

and migration. So did Lyn, but to a lesser degree.

But, there were significant differences in mice, depending on which Src family member was experimentally inhibited. Mice with glioblastoma tumors lacking functioning Src or Fyn showed no difference in survival, compared to untreated mice. In contrast, inhibiting Yes in mice increased survival, while inhibiting Lyn resulted in shorter survival and accelerated tumor growth.

"These findings were very surprising to us for two reasons," Dr. Anastasiadis says. "One is the difference between lab and animal findings. The other is that, together with the bad, dasatinib inhibited the good, as well."

"Yes promotes cancer growth, so it should be inhibited," he says. "Unexpectedly though, Lyn protects against cancer growth, and, so, it should not be deactivated by use of dasatinib."

Researchers found that not all human tumors express all members of the Src family, and that expression of Yes and Lyn differed among tumors.

The research team is examining tumor biopsies from the patients who participated in Mayo Clinic's clinical trial testing the use of dasatinib combined with bevacizumab (Avastin), an agent that restricts blood flow to tumors. They will match expression of Lyn and Yes with clinical outcomes.

"We hope these results will affirm our conclusion that patients with high levels of Lyn should not be treated with dasatinib," says Dr. Anastasiadis. "Instead, dasatinib may prove to work well in select patients whose tumors express Yes, but not Lyn.

"The last thing we want to do is target both the good and the bad with

dasatinib," says Dr. Anastasiadis. "In the long run, developing a drug that targets Yes, but has no effect on Lyn could prove a much more effective therapy for gliomas."

Provided by Mayo Clinic