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Molecular marker predicts patients most likely to benefit longest from two popular cancer drugs

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Johns Hopkins scientists have identified a molecular marker called "Mig 6" that appears to accurately predict longer survival—up to two years—among patients prescribed two of the most widely used drugs in a class of anticancer agents called EGFR inhibitors.

The U.S. Food and Drug Administration-approved drugs, gefitinib (Iressa) and erlotinib (Tarceva), are prescribed for lung and pancreatic cancer patients but only a few who have mutations in the EGFR gene usually benefit with a prolonged reduction of tumor size. The two drugs block the gene's ramped-up protein production, but patients' response to the drug varies widely – from no survival benefit to several years. The average is several months.

"Clinicians have had no reliable method for distinguishing patients who are not likely to respond to EGFR inhibitors and those who will respond very well," says David Sidransky, M.D., professor of otolaryngology, oncology, pathology, urology, and genetics at Johns Hopkins. Looking at the precise level of protein production from the EGFR gene alone in specific patients was not proven to be a good indicator of patients' response to EGFR-blocking drugs, but the presence or absence of Mig 6 might be, he adds.

In a preliminary study, described July 31 in the online journal, *PLoS ONE*, the Johns Hopkins scientists found the genetic marker in a series

of experiments that began with laboratory-derived lung and head and neck cancer cell lines resistant to EGFR-inhibitor drugs. In the cell lines, the team found very high levels of protein production from the Mig 6 gene—up to three times the level in sensitive cell lines. Mig 6 is one of the molecules that controls the activity of the EGFR protein.

"In the first set of experiments, we found that higher levels of Mig 6 occur often in cells that don't respond to EGFR inhibitors," says Sidransky. "Most tumors are known to have high Mig 6 levels and are not expected to respond to EGFR inhibitors."

Next, the research team studied Mig 6 levels in a variety of tumors that were directly engrafted into mice, a research model known as a xenograft, and treated with an EGFR inhibitor. These new models contain a more complete sampling of the tumor that includes "stromal" cells, which surround and interact with the cancer cells. "These tumors are implanted along with their own microenvironment, into the mice, and we believe this model may be more predictive of what happens in human patients," says Sidransky.

In the xenografts of tumors without EGFR mutations, as Mig 6 levels increased, so did the resistance to EGFR inhibitors, suggesting a correlation between high Mig 6 and lack of response to the drugs. To confirm the correlation, the scientists tested tissue samples of 65 lung cancer patients treated with EGFR inhibitors to compare their Mig 6 levels with outcomes.

Of 18 patients with low Mig 6 levels, five of them survived more than a year without progression of their cancer; four survived more than two years progression-free. Among 16 patients with higher Mig 6 levels, two survived more than one year and none survived, progression-free, beyond two years.

"The beauty of this finding is that it's simple. We're looking for tumors with low levels of Mig 6 to predict clinical benefit, and there aren't many of them," says Sidransky.

Sidransky's team expects to license the Mig 6 marker to a biotechnology or pharmaceutical company and conduct further tests in larger groups of patients.

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