

Protein predicts Gleevec resistance in gastrointestinal tumors

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Excess amounts of a protein called IGF-1R in patients with gastrointestinal stromal tumors (GISTs) could indicate that the patient would be less responsive to the drug imatinib mesylate (known as Gleevec), according to Andrew K. Godwin, Ph.D., a researcher at the Fox Chase Cancer Center in Philadelphia.

Preliminary studies have shown that GIST cells, especially Gleevec-resistant cells, might respond well to agents in development for treatment-resistant breast cancer, a form of breast cancer also marked by excessive production of the IGF-1R protein. IGF-1R could also serve as a marker to identify this subset of GIST patients before therapy begins, when alternative treatments would be most effective, the researcher says.

Godwin presents his findings at the 2008 Annual Meeting of the American Society of Clinical Oncology, held May 30 through June 3 in Chicago.

“A small percentage of adult gastrointestinal stromal tumors – and most pediatric cases – are often less responsive to Gleevec,” says Godwin, Director of Fox Chase's Clinical Molecular Genetics Laboratory. “We have found that tumors in many of these cases coincide with an overabundance of the IGF-1R protein.”

In most occurrences, GISTs develop through a mutation in the genes c-KIT or PDGFR α , both of which are targets of Gleevec. GISTs without those mutations, known as “wild type,” as well as pediatric GISTs, do not

often respond well to treatment with Gleevec.

The Fox Chase researchers found that, when compared to mutant GISTs, the DNA of wild type and pediatric GISTs exhibited more copies of the IGF1R gene. These tumors also produced many more copies of the IGF-1R protein, which serves to promote cell survival, proliferation and growth in normal cells. In tumors, an excess of IGF-1R allows cancer cells to grow out of control, breaking the normal control mechanisms that are an inherent part of cell function. In the laboratory, the researchers found that drugs that decrease IGF-1R activity induced the death of tumor cells.

According to Godwin and his colleagues, their studies are the first to reveal that the development of wild type GISTs could be related to abnormal expression of IGF-1R.

“IGF-1R overproduction seems to be a common factor in a number of different cancers, and there are several IGF-1R-targeted therapeutic agents in development and in clinical trials that might also be effective against GISTs,” Godwin says. “As is often the case with targeted therapies, we need to find the right patient for the drug as much as we need to find the right drug for the disease.”

Godwin and his colleagues will soon publish the full results of their studies and have begun investigating the possibility of testing for IGF-1R in clinical trials at Fox Chase.

Source: Fox Chase Cancer Center

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