MedicalXpress

Molecule common in some cancers, rheumatoid arthritis leads to potential therapy for both

November 14 2013

A molecule that helps cells stick together is significantly over-produced in two very different diseases—rheumatoid arthritis and a variety of cancers, including breast and brain tumors, concludes a new study. The scientists who made the discovery also found candidate drugs to inhibit the molecule, cadherin-11, one of which is already in a clinical trial.

The study, published in *Oncotarget*, was led by investigators at Georgetown University Medical Center, and included collaborators from Harvard and Columbia Universities, Mayo Clinic and Queen's University in Belfast, Northern Ireland.

"Our findings suggest that cadherin-11 is important for cancer progression as well as rheumatoid arthritis—for reasons we do not fully understand. Nevertheless, we are rapidly translating this discovery for use in the clinic," says the study's senior investigator, Stephen Byers, PhD, a professor and molecular oncologist at Georgetown Lombardi Comprehensive Cancer Center.

Byers and his Georgetown colleagues, Shahin Assefnia DVM, Siva Dakshanurthy PhD, and Jaime Guidry Auvil, PhD, have found that cadherin-11 is over-expressed in 15 percent of breast cancers, and in many glioblastomas. He believes the molecule also contributes to pancreatic cancer.

"What most of these cancers all have in common is cadherin-11 and a poor prognosis, with no effective therapies," Byers says. "Cadherin-11 expression is required for tumors to grow. If it is blocked, the cancers in cell line studies and in animals just stop growing—which is really quite striking."

The Georgetown team has developed a small molecule agent to shut down cadherin-11 in cancer, and, by screening drugs now on the market, found that the well known arthritis drug Celebrex acts in a similar way. While it is unlikely that Celebrex could be used as a single agent against cancer because it would be too toxic at the level needed to impair cadherin-11, a Celebrex-related molecule works the same way, and may potentially be less toxic.

Co-author Michael Brenner, MD, at Harvard University, has designed an antibody that can shut down cadherin-11 in rheumatoid arthritis. The *Oncotarget* study demonstrated that Brenner's antibody worked in animal models of tumors that made cadherin-11.

It was chance that he and Brenner were working on the same molecule at the same time and came to know of each other's work. Coincidentally, co-author Lawrence Shapiro, PhD, at Columbia, was building a crystal structure of cadherin-11 and is now working with Byers and Brenner to show how the molecule binds to Celebrex and other small molecule drug cadherin-11 inhibitors.

This close collaboration led Byers, Brenner and Shapiro to apply for a grant last year from the National Cancer Institute's Provocative Questions project. They proposed answering the question related to the connection between drugs, such as anti-inflammatory agents, that can protect against cancer and other conditions.

Medical Xpress

Provided by Georgetown University Medical Center

Citation: Molecule common in some cancers, rheumatoid arthritis leads to potential therapy for both (2013, November 14) retrieved 13 May 2024 from https://medicalxpress.com/news/2013-11-molecule-common-cancers-rheumatoid-arthritis.html

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