New synthetic form of protein holds promise to stop cancer spread

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Researchers at the Medical College of Wisconsin in Milwaukee have a pending patent on a new synthetic form of a protein involved in certain types of cancers and immune system diseases.

The protein, CXCL12, is known as a chemokine. Chemokines are proteins that regulate the movement of cells into tissues and recruit infection-fighting white blood cells to infected and injured sites. They essentially act as homing beacons for the immune system.

New information on the structure of the protein was discovered in the lab of Brian Volkman, Ph.D., associate professor of biochemistry at the Medical College. The findings were based on seminal reports by Michael Dwinell, Ph.D., associate professor of microbiology and molecular genetics, who initially inspired Dr. Volkman to look into the properties of CXCL12 in 2001. (See sidebar)

"We hope that stable synthetic versions of CXCL12 will allow us to conduct proof-of-concept studies about cancer prevention," Dr. Volkman says. "It's clear that CXCL12 is an important molecule for designing new ways to treat cancer."

The new findings from the Medical College are published in the September issue of *Science Signaling*, a new online journal published by *Science* magazine. Christopher Veldkamp, Ph.D., a biochemistry graduate of the Medical College's Graduate School of Biomedical Sciences, who was awarded a postdoctoral research fellowship by the

American Cancer Society earlier this year, is lead author of the study.

It had been previously established that CXCL12 and its target cellular receptor, CXCR4, played an important role in the migration of cancer cells to common sites of tumor formation, such as bone marrow, lymph nodes, liver and lung tissue. Dr. Dwinell's laboratory established that CXCL12 expression was key to interfering with the progression of cancer.

To discover the new inhibitor, Dr. Volkman's lab created a new three-dimensional model of how the CXCL12 protein interacts with a portion of the CXCR4 receptor. Because previous research on the CXCL12 structure failed to resolve these details, a key step in the spread of metastatic cancer remained poorly understood.

To complete the molecular model for CXCL12 binding to CXCR4, Drs. Volkman and Veldkamp discovered that it was necessary to link two CXCL12 molecules, in effect locking it into a form that could not be chemically separated. This locked form of the protein, known as a dimer, could still bind to the CXCR4 receptor.

However, the locked protein displayed different behavior than the unlocked form. A normal CXCL12 protein strongly induces cell migration, but the locked form of the protein caused no cells to migrate at all.

The researchers then ran another experiment to see what would happen if the normal CXCL12 and locked CXCL12 dimer were combined. The combined molecule had the opposite effect of the single molecule, and it resulted in a near elimination of cell migration. This meant they had discovered that it was possible to convert CXCL12 into a protein that inhibits cell migration.

"This was exciting because it was genuinely unexpected," says Dr. Volkman. "It was the strongest suggestion yet that chemokine dimers might really be active participants in directing the migration of white blood cells and possibly other kinds of cells."

Dr. Volkman says the next step is establishing if the CXCL12 dimer could be effective in inhibiting the spread of cancer. He again turned to the assistance of Dr. Dwinell, who had filed an earlier patent application on the use of CXCL12 in limiting cancer progression. This pending patent also involved a graduate student, Michael Wendt.

"While we were focused on understanding details of the molecular structure of CXCL12, Dr. Dwinell's research group had developed a sophisticated method for measuring breast cancer metastasis," he says. "So we asked him to help us design experiments to find out if his CXCL12 dimer could interfere with the spread of cancer."

While it's not clear yet if the CXCL12 dimer will have the effect Dr. Volkman hopes for, he says that this discovery is just the beginning of his lab's experiments with the properties of this molecule.

Dr. Volkman's lab will also investigate if CXCL12 has any protective effects on the heart following a traumatic event, such as a heart attack. While these experiments are also in their early phases, he is hopeful and acknowledges that this breakthrough would not have been possible without the collaborations of Dr. Veldkamp, Dr. Dwinell and others.

"Collaborations promote the exchange of ideas between scientists from different backgrounds and often lead in completely unanticipated directions," he says. The study was funded by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Source: Medical College of Wisconsin