Researchers describe function of key protein in cancer spread

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Research led by David Worthylake, PhD, Assistant Professor of Biochemistry and Molecular Biology at LSU Health Sciences Center New Orleans, may help lay the groundwork for the development of a compound to prevent the spread of cancer. The research will be published in the May 29, 2009 issue of the *Journal of Biological Chemistry*.

During the transition from a localized tumor to metastatic disease, cancer cells acquire the ability to detach from their neighboring cells and move to and invade tissue at distant points in the body.

"Because tumor metastasis leads to a poor prognosis and tremendously complicates treatment, it is of utmost importance that we understand, at a molecular level, the processes that regulate cell adhesion, migration and invasion," notes Dr. Worthylake.

He and his colleagues studied a protein in cells that is involved in regulating cell structure, cell-to-cell contact, and cell movement. When too much of this protein, called IQGAP1, is produced, it can weaken cell-to-cell contacts and promote cell migration and invasion - processes that occur during tumor metastasis.

The research team focused on the area of IQGAP1 that interacts with two smaller proteins Cdc42 and Rac which, when activated, contribute to cell destabilization, cell movement, and invasion. This region on IQGAP1 is related to proteins that accelerate deactivation of another

small protein similar to Cdc42 and Rac. However, IQGAP1 does not deactivate Cdc42 and Rac - in fact, IQGAP1 prolongs their activated states. The researchers determined the atomic structure of this region of IQGAP1 and furthermore, built a model of their IQGAP1 structure bound to the previously determined structure of Cdc42 in order to understand why IQGAP1 does not deactivate Cdc42. The model provides detailed information about the (likely) specific contacts made between IQGAP1 and Cdc42. The model also shows that IQGAP1 is missing a key component required to rapidly deactivate Cdc42, and that binding to IQGAP1 likely disturbs the positions of components of Cdc42 that are required for even normal rates of deactivation, explaining how IQGAP1 prolongs the activated state of Cdc42.

"This knowledge could serve as a guide for further studies to define IQGAP1 function and perhaps the design of a small molecule to regulate Cdc42/IQGAP1 interaction to prevent cancer cells from moving to and invading other parts of the body," concludes Dr. Worthylake.

According to the American Cancer Society, metastatic cancer is a cancer that has spread from its primary site (the part of the body in which it developed) to other parts of the body. If cells break away from a cancerous tumor, they can travel to other areas of the body. There, they may settle and form "colony" tumors. In their new location, the cancer cells continue growing. The spread of a tumor to a new part of the body is called metastasis. Most people who die of cancer have metastases at the time of their death, and metastatic disease is directly responsible for the majority of cancer deaths. This year, about 562,340 Americans are expected to die ofcancer, more than 1,500 people a day. Cancer is the second most common cause of death in the US, exceeded only by heart disease. In the US, cancer accounts for nearly 1 of every 4 deaths.

Source: Louisiana State University Health Sciences Center