Study identifies one of the mechanisms behind breast cancer metastasis

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Several years ago, scientists at Beth Israel Deaconess Medical Center (BIDMC) and other laboratories made a paradoxical discovery regarding the Akt molecular pathway, a popular target for cancer drug therapies. They discovered that while one Akt protein - Akt1 - was actively preventing cancer cells from spreading, another closely related family member - Akt2 - was actually promoting breast cancer cell migration. And, indeed, subsequent studies in mouse models of breast cancer revealed that blocking the Akt pathway resulted in enhanced metastasis to the lungs.

This left scientists and clinicians faced with a troubling situation: Would the drugs actively being developed to inhibit Akt activity and halt breast cancer survival mechanisms be simultaneously enhancing cancer cells' abilities to metastasize to other organs?

Now, BIDMC scientists Alex Toker, PhD, and Rebecca Chin, PhD, have identified the first direct Akt1 target, a protein called palladin, providing an explanation for how Akt1 can function as a suppressor of breast cancer invasion and metastasis. This new finding, reported in the May 14, 2010 issue of the journal *Molecular Cell*, reveals another key piece of information as scientists continue their development of targeted cancer therapies, and underscores the importance of dissecting the precise mechanisms by which tumor cells invade and metastasize to distant organs.

"In 2005, after our lab had made the discovery that Akt was acting as something of a double agent, we wanted to delve into the mechanism that was accounting for opposing functions of these proteins during breast cancer progression," explains Toker, an Associate Professor of Pathology at BIDMC and Harvard Medical School (HMS). "We reasoned that identifying the specific molecular mechanisms by which Akt proteins either inhibit or promote cancer invasion and metastasis would be instrumental for developing more efficient targeted breast cancer therapies."

As with many proteins in cancerous cells, Akt actually exists as a "family" of related proteins, consisting of Akt1, Akt2 and Akt3, explains Chin, an Instructor of Pathology at BIDMC and HMS. "In breast cancer, Akt1 and Ak2 are found, and are frequently hyperactivated due to genetic mutations in the pathway. But we now know that the two family members have opposing functions such that Akt1 inhibits, while Akt2 enhances invasion into the local tumor stroma, leading to metastasis."

To identify novel downstream targets of Akt proteins in breast cancer, the scientists used a discovery-based proteomics approach, coupled with analyses of breast cancer cell lines derived from patients with aggressive metastatic disease. This widely used approach led the authors to identify palladin, a protein known to regulate cell motility and named after the Italian Renaissance architect Andrea Palladio and the Palladian style of architecture.

"Palladin's normal function is to inhibit cell migration and keep cells in place," explains Toker. "By organizing the cellular cytoskeleton at the molecular level, palladin maintains the architecture of the cell in a highly organized manner." But, he adds, because Akt1 regulates palladin in an exclusive manner (by blocking cell motility) when palladin is lost, cells become disorganized, leading to a marked increase in cell migration. "It is believed that the end result is enhanced metastasis, a hypothesis that our lab is continuing to investigate using mouse models of disease progression," notes Toker.

Since the mid-1990s, scientists have known that there exist more than 100 targets of Akt proteins. "But among all of these, only a handful have been shown to be specific to either Akt1 or Akt2," adds

Toker. "Our discovery really is the first example of this type of specific mechanism in the Akt pathway, and understanding specific targets is of enormous importance for pharmacological purposes."

Provided by Beth Israel Deaconess Medical Center