Experimental agent reduces breast cancer metastasis to bone

November 3 2009

Researchers have reduced breast cancer metastasis to bone using an experimental agent to inhibit ROCK, a protein that was found to be over-expressed in metastatic breast cancer. In a study in mice, the team of researchers from Tufts University School of Medicine, the Sackler School of Graduate Biomedical Sciences at Tufts, and Tufts Medical Center report that inhibiting ROCK, or Rho-associated kinase, in the earliest stages of breast cancer decreased metastatic tumor mass in bone by 77 percent and overall frequency of metastasis by 36 percent. The results suggest that ROCK may be a target for new drug therapies to reduce breast cancer metastasis.

"While the primary tumor causes significant illness and requires treatment, metastasis accounts for over 90 percent of breast cancer-related deaths. There are no treatments to eradicate metastasis. Establishing ROCK's role in the spread of breast cancer and identifying agents to inhibit ROCK brings us one step closer to an approach that might reduce metastasis in the future," said senior author Michael Rosenblatt, MD, professor of physiology and medicine at Tufts University School of Medicine and member of the cellular and molecular physiology program faculty at the Sackler School of Graduate Biomedical Sciences at Tufts. Rosenblatt is also dean of Tufts University School of Medicine.

"We also found that using shRNA - short hairpin RNA - to knock down ROCK expression slowed metastasis. In order for cancer cells to migrate, an extensive transportation apparatus is required. ROCK directs

the formation of this apparatus, but use of the ROCK inhibitor as well as shRNA rendered the cells' transportation mechanism ineffective, significantly reducing breast cancer metastasis to bone," said first author Sijin Liu, PhD, research instructor and member of the Rosenblatt Laboratory at Tufts.

"This study also revealed that a specific microRNA cluster, 17 through 92, is associated with ROCK expression and breast cancer metastasis. The microRNA cluster responded to ROCK inhibition, which provides insight into the mechanism driving metastasis and is a finding that will be of particular interest to researchers focused on the role of microRNAs in gene expression," continued Liu.

Rosenblatt, Liu, and colleagues used luminescent imaging to observe ROCK's effect on breast cancer metastasis. The researchers found that inserting high levels of ROCK in non-metastatic cancer cells caused the cells to metastasize to several secondary sites, while cells with no ROCK exposure remained localized. The researchers then used an experimental agent (Y27632) or shRNA to reduce ROCK activity in seven mice with metastatic tumors, finding a significant decrease in metastasis to bone compared to six untreated mice.

Breast cancer is the second leading fatal cancer in women, and affects just under one in eight women in the United States. Bone is the most common site of breast cancer metastasis, affected three times more often than the lungs or liver.

Source: Tufts University, Health Sciences