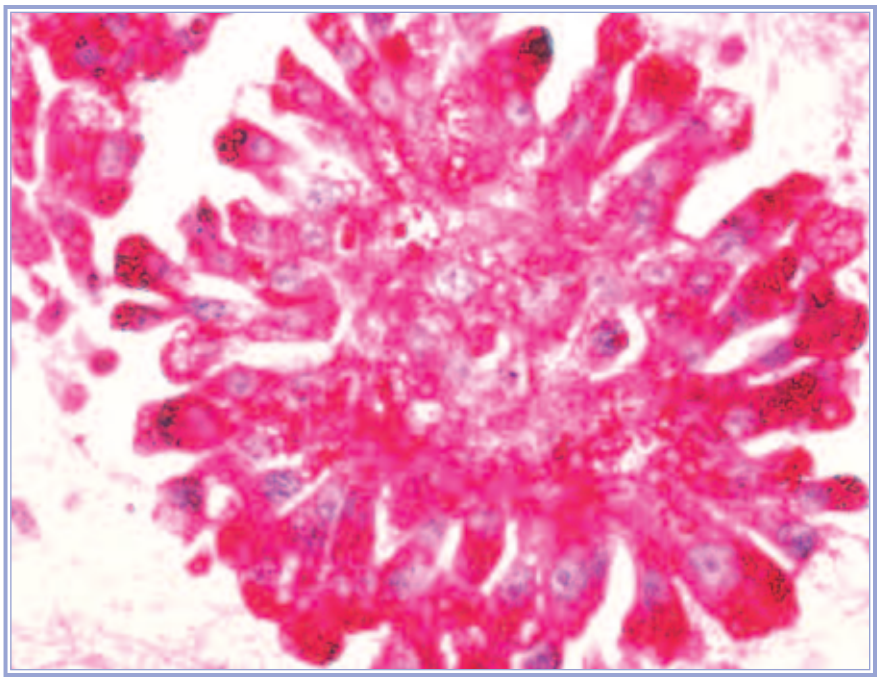
New Clues to Blocking Metastasis in Sarcoma



(*Image:* L. Liotta, CCR)

Suppressing a metastasis-suppressing protein, called KAI1, by tagging it for degradation by the proteasome may be one factor in a sarcoma cell's development of the ability to spread.

Cancer's wanderlust can be its most fatal feature. Metastasis—the spread of cancer cells to sites far from the original tumor—is the cause of death for approximately 90 percent of cancer patients. It is not a simple, one-step process: To metastasize, cancer cells must escape the original tumor, enter and exit the bloodstream or lymphatic system, and establish themselves in a new target organ or tissue. All told, the process requires the activation of several genes and the deactivation of several others.

Findings from a team of CCR researchers suggest that for at least some sarcomas (a group of cancers of the connective and supportive tissues, such as bone, cartilage, fat, muscle, or blood vessels), cancer cells may get the green light to metastasize not because of genomic changes but because a protein important for suppressing this process is tagged for destruction. This insight has come about because the CCR researchers—led by Allan M. Weissman, M.D., Chief of the Laboratory of Protein Dynamics and Signaling, and Chand Khanna, D.V.M., Ph.D., of the Pediatric Oncology Branch—chose to study not genomic mechanisms of metastasis but rather the fate of the proteins produced from these genes.

Weissman and Khanna focused their attention on gp78, one of many proteins whose job it is to mark other proteins with a small protein called ubiquitin. The cell normally uses this molecular tag to flag excess or damaged proteins for destruction by a complex cellular machine called the proteasome.

Using RNA interference (RNAi) in an animal model of sarcoma, the researchers turned down gp78 expression, finding that metastasis was similarly reduced. Looking at gp78's interactions, they found that it tags a protein called KAI1—one of about 10 known metastasis suppressors—for degradation by the proteasome. In their laboratory sarcoma models, the team found that reducing levels of gp78 caused KAI1 levels protein to rise and the survival of metastatic sarcoma cells to diminish. Subsequently, turning gp78 expression back up reversed the situation: KAI1 was tagged more for destruction more frequently, and metastatic cancer cells with the rejuvenated gp78 expression had better survival.

To establish the clinical relevance of their findings, the scientists looked at archived clinical samples of sarcoma tumors. There, too, they found evidence for an inverse relationship between the two proteins: When levels of gp78 were low, KAI1 levels were high, and vice versa.

The structure of gp78 makes it a potential candidate for targeted therapeutics. Spurred on by the findings, the CCR team, as well as other scientists, is now beginning to look for similar relationships between gp78 and metastasis in other cancers. The results also open the door to exploring the use of available proteasome inhibitors, such as bortezomib (Velcade®), to treat metastatic cancers. Bortezomib is already successfully used to treat the blood cancer multiple myeloma and has been widely studied in other cancers.