Researchers uncover 'relocation' plan of metastatic cancer cells

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Few things are as tiresome as house hunting and moving. Unfortunately, metastatic cancer cells have the relocation process down pat. Tripping nimbly from one abode to another, these migrating cancer cells often prove far more deadly than the original tumor. Although little has been known about how these rogue cells choose where to put down roots, researchers at the Stanford University School of Medicine have now learned just how nefarious they are.

"Metastasis is not a passive process," said cancer biologist Amato Giaccia, PhD. "Cells don't just break off the primary tumor and lodge someplace else. Instead the cells actually secrete substances to precondition target tissue and make it more amenable to subsequent invasion."

In other words, the cells plan ahead by first sending molecular emissaries to orchestrate a breach in the body's natural defenses. Blocking this cascade of events in mice hobbled the cells' migration and prevented the metastatic cancer that developed in control animals. The researchers are hopeful that a similar tactic will be equally successful in humans.

Giaccia, the Jack, Lulu and Sam Willson Professor and professor of radiation oncology at Stanford, is the senior author of the research, which will be published in the Jan. 6 issue of *Cancer Cell*. Giaccia is also a member of the Stanford Cancer Center.

Scientists have known for some time that certain primary cancers

metastasize preferentially to other organs — breast cancer often spreads to the lungs, for example. This is in part due to the patterns of blood flow in the body. They also knew that such future colonization sites, called pre-metastatic niches, harbor large numbers of cells derived from the bone marrow that somehow facilitate the cancer cells' entry. What they didn't know is how the bone-marrow-derived cells were summoned, and what, if any, role the primary tumor cells played in site selection.

Giaccia and his colleagues turned their attention to a substance that they had previously shown to be involved in metastasis: a protein called lysyl oxidase, or LOX. In healthy people, LOX works to strengthen developing connective tissue by modifying collagen and elastin, which are components of the extracellular matrix surrounding many organs. LOX expression increases in cancer cells deprived of oxygen — a condition called hypoxia that begins to occur when blood vessels fail to reach the inner cells of a growing tumor mass. Inhibiting LOX expression decreases tumor cell invasion and metastasis in the lungs of mice implanted with human breast cancer cells.

The researchers wanted to know how LOX affected metastasis. In the current study, they found that blocking LOX expression in the mice not only prevented metastases, it also kept the bone-marrow-derived cells necessary for niche formation from flocking to the site. When LOX was present, it accumulated in the lungs of the mice and was associated with one particular type of bone-marrow-derived cell known as a CD11b cell. CD11b cells, in turn, secreted a protein that breaks apart collagen and provides a handy entry point for the soon-to-arrive cancer cells.

"We've never really understood before how normal tissues are modified to allow metastases to target and successfully invade them," said Giaccia, who is hoping to devise a clinical trial to study the effect of blocking LOX activity in humans with primary cancers. "Now we know that LOX goes to the target tissue and attracts CD11b and other bone-derived cells

to the pre-metastatic niche. If the mouse data is transferable to humans, and we have reasons to think it will be, we really believe way may have found an effective way to treat human disease."

Source: Stanford University Medical Center