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For Some Metastatic Cancer Cells, There's No Place Like Home

The most dangerous event in cancer is metastasis, when cells break loose from a localized tumor and travel through the circulatory system to spread the disease to vital organs. Now scientists have discovered, contrary to long-held notions, that metastasis can also operate in reverse: That is, a small but aggressive fraction of the renegade cancer cells can circle back through the bloodstream to re-infiltrate the original tumor, boosting its malignant potential.

This newly revealed phenomenon is termed tumor "self-seeding" by Joan Massagué, a Howard Hughes Medical Institute investigator at Memorial Sloan-Kettering Cancer Center (MSKCC), and Larry Norton, an oncologist at MSKCC who led the research being reported December 25, 2009, in the journal *Cell*. Mi-Young Kim, a research fellow in Massagué's lab, was the first author of the paper.

"It has always been strongly believed that metastasis was a one-way street," says Massagué, whose research is revealing how metastatic tumor cells develop the specific traits needed to travel and flourish in a new setting.

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"Now we have found that tumors can recapture some of their most delinquent children, enriching themselves with the most aggressive metastatic cells, enabling them to grow faster and more robustly," he says. "This appears to be a very general feature."

In clinical terms, self-seeding may account for the all-too-frequent reappearance of tumors that seemed to have been completely eliminated by surgery or radiation therapy. Even when the tumor is no longer detectable, the remaining tissue from which it was removed or irradiated “might provide enough of a homing environment for metastatic cells to re-seed,” Massagué suggests. If so, he says, physicians might someday be able to forestall post-treatment recurrences by crippling the tumor’s self-seeding strategy after cancer therapy.

The new insights were spawned by discussions between Massagué and Norton about the striking abilities of metastatic cells to move in and out of the body’s circulation, survive long-distance travel, and adapt themselves to the foreign environment of distant organs. Of the millions of cells that escape from a primary tumor, a small fraction will pass through the tumor again in their journey around the body. Some of these cells—the most wily and aggressive wanderers, Massagué says—are able to slip through the vessel walls and return home.

“We thought, this must be happening abundantly—and we asked, are there consequences?” Massagué says. “Might cancer be a disease that is self-seeding?” He and Norton published an essay in *Nature* in 2006 outlining this concept.

In a series of experiments described in the *Cell* article, the researchers implanted human metastatic breast, colon, and melanoma cells in mice. With labeling and imaging techniques, they demonstrated that these primary tumors could attract and recapture some of their wandering offspring.

The returning metastatic cells don’t simply stumble upon their birthplace, the studies revealed. Rather, homing signals from the tumor attract the vagabond cells, which, in turn, are primed to respond to the signals by escaping from the circulation and rejoining the tumor.

The siren song of attraction is provided by cytokines, called interleukins, IL6 and IL8, the researchers determined. The cytokines are produced by the tumor and its microenvironment, and also by inflammatory cells recruited by the tumor. IL6 and IL8 were previously found to be magnets for cancer cells, and have been implicated in tumor progression.

Corresponding to the “pull” of the cytokines, explains Massagué, is a “push” possessed by the circulating tumor cells—“something that makes them very good at invading tissues and infiltrating the tumor to which they’ve been drawn.”

A search of candidate genes that were active in the tumor cells turned up three that fit that job description. Two of the genes, *collegenase 1*, also known as *matrix metalloproteinase 1 (MMP1)*, and *CXCL1*, produce proteins that are involved in digesting the cellular matrix and enhancing cells’ invasive

abilities. The third, *FASCIN 1 (FSCN1)*, makes a protein that helps adapt the cell's cytoskeleton for movement by "crawling" on small foot-like extensions.

In another series of experiments, the investigators showed in mice that enrichment of breast tumors with metastatic cells caused the tumors to grow faster and expand their networks of small blood vessels (angiogenesis) to support their larger size.

That's not the only clinical implication of the findings. Massagué says that self-seeding "may increase the chances that the tumor will reproduce itself right in the primary site" even after extensive radiation and surgical removal of the mass. Local cancer recurrences generally have been blamed on a small number of hardy cells left behind after treatment.

"Now we are thinking that in some cases, maybe treatment left inflamed tissue that had been a home for those cells that escaped and were residing somewhere temporarily, perhaps in the bone marrow," he suggests. "They may have re-entered the circulation in the weeks and months after surgery, and now, through the self-seeding process, have homed in on this tissue and reproduced the tumor."

If this scenario is an important cause of cancer recurrence, says Massagué, then conceivably the risk could be lowered by giving patients drugs to block the IL6 and IL8 homing signals. "It would make sense to give these drugs for a few weeks or months to decrease the chance of back-seeding."