Metastasis, the process that allows some cancer cells to break off from their tumor of origin and take root in a different tissue, is the most common reason people die from cancer. Metastatic brain tumors are ten times more common than primary brain cancers.

Yet most tumor cells die before they can take root in the brain, which is better protected than most organs against colonization by circulating tumor cells. To seed in the brain, a cancer cell must dislodge from its tumor of origin, enter the bloodstream, and cross densely packed blood vessels called the blood-brain barrier. Until now, little research has been done into how metastatic brain tumors develop, but previous mouse experiments that imaged metastatic breast cancer cells over time have shown that of those cancer cells that do make it to the brain, fewer than one in 1,000 survive.

“We didn’t know why so many of these cells die,” says Joan Massagué, PhD, Director of the Sloan Kettering Institute and senior author of the study. “What kills them? And how do occasional cells survive in this vulnerable state — sometimes hiding out in the brain for years — to eventually spawn new tumors? What keeps these rare cells alive and where do they hide?”

In the Cell study, Dr. Massagué, with Fellow Manuel Valiente, PhD, and other team members, found that in

mouse models of breast and lung cancer — two tumor types that often spread to the brain — many cancer cells that enter the brain are killed by astrocytes. These killer cells, the most common type of brain cell, secrete a protein called Fas ligand.

When cancer cells encounter this protein, they are triggered to self-destruct. The exceptional cancer cells that escape the astrocytes do so by producing a protein called Serpin, which acts as a sort of antidote to the death signals fired at them by nearby astrocytes.

After imaging defiant metastatic cells in the brains of mice, researchers noticed that the cells that were able to survive grew on top of blood capillaries, each cell sticking closely to its vessel "like a panda bear hugging a tree trunk," Dr. Massagué says. They found that the tumor cells produce a protein that acts like Velcro to attach the cells to the outer wall of a blood vessel.

"This hugging is clearly essential," Dr. Massagué explains. "If a tumor cell detaches from its vessel, it gets killed by nearby astrocytes. By staying on, it gets nourished and protected, and may eventually start dividing to form a sheath around the vessel."

Under the microscope, the researchers watched these sheaths of cancer cells around the blood capillaries grow into tiny balls, which eventually became tumors. "Once you've seen it, you can never forget this image," Dr. Massagué says.

The tumor-cell survival factors uncovered by this study might one day be targeted with drugs to further diminish people's risk of metastasis. Dr. Massagué is particularly interested in the ability of tumor cells to hug blood vessels, as he suspects this behavior may be essential for the survival of metastatic cancer cells not only in the brain but also in other parts of the body where metastatic tumor growth can occur.

"Most cancer patients are actually at risk of having their tumor spread to multiple sites," Dr. Massagué notes. For example, breast cancers can metastasize to the bones, lungs, and liver, as well as to the brain. "What we may be looking at," he adds, "is a future way to prevent metastasis to many organs simultaneously" using drugs that make tumor cells let go of the blood vessels they cling to.

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