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Cancer's fearsome travelers

By Katherine Hobson

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It's a not-so-fantastic voyage. A single cell somehow breaks off from a tumor and makes its way into the bloodstream, traveling through dark arteries and capillaries until it finds a resting spot in some far reach of the body. Once situated, it might immediately invade the surrounding tissue, replicating itself in a frenzy. Or it might just lie dormant--for as long as a decade, long after the original tumor is gone--until a mysterious signal tells it to start growing.

These cellular ramblings and sojourns are technically known as metastasis, and they are what make cancer a killer. Surgeons can often remove a tumor. That's the easy part. But the invisible spawn of this tumor may have already infiltrated the body. Indeed, much basic cancer research in recent years has focused on these minuscule but deadly cells.

The focus of metastasis inquiry is shifting. As important as these "seeds" are to metastasis, equally as important is what physician Stephen Paget called the "soil"--the varied environments that tumor cells encounter as they travel. Paget's pathbreaking thesis, published in the *Lancet* in 1889, is that metastasis involves a complicated biochemical "conversation" between the seed and soil--cell and host--at every step along the way. Scientists are now taking a harder look at how the body itself can lure, influence, and even hide the errant cell. Though much of the research is still being done in petri dishes and small animals, researchers believe it offers hope for new targets for cancer therapies. "The time has come to put the major emphasis on the soil," says researcher Isaiah Fidler of the M. D. Anderson Cancer Center in Houston.

Traveling long distance through the body is not easy and requires some physiological cleverness. A breakaway tumor cell must invade the surrounding tissue to find either the bloodstream or lymphatic system--the most uncongested avenues of transport. One way to do this is for the cell to cultivate its own lymphatic vessels from the surrounding tissue.

Indeed, research has shown that a malignant cell's ability to commandeer the body's lymph system is a good predictor both of later metastasis--and poor prognosis for survival.

Battered. The cells that actually make it to the bloodstream still face long odds. Like small boats in a storm, they have a good chance of being battered to pieces by the currents in the bloodstream. "A tumor may be releasing millions of cells per day, but we don't see patients with millions of metastases," says Joan Massague, head of Memorial Sloan-Kettering's cancer biology and genetics program. But some do survive. And research published in the *Proceedings of the National Academy of Sciences* in November raises the possibility that these stalwarts are helped in their odyssey by platelets, the saucerlike, clot-forming bodies in the blood. Just how is unknown, but Washington University's Katherine Weilbaecher speculates: "What we think is happening is that the cancer cells actually activate the platelets, get stuck to them, and the platelets form webs over the cancer cells." The platelets might even be nourishing the tumor cells, protecting them from detection or helping them to get a foothold in the blood vessels. This is all based on experimental animal work, but it's promising because there are many anticlotting drugs--including simple aspirin--available right now. Weilbaecher is designing a study to examine the phenomenon in humans.

So how do those circulating tumor cells find the best soil in which to pitch their tent? Researchers from Paget on have noted that certain cancer cells prefer certain organs. Breast cancer cells, for instance, often spread to bone, brain, and liver, while ovarian cancer cells almost never lodge in the lungs. No one knows for sure why this is the case, but research now suggests that it has to do with signaling between the invading cells and the host. A research team at M. D. Anderson has identified what it calls "ZIP codes" on blood vessel walls that may help cellular explorers find a hospitable home. Says M. D. Anderson's Wadih Arap: "Cells in the blood vessels aren't generic. Cancer may be using the vasculature as beacons." If this theory is borne out, ZIP codes might someday offer the hope of delivering drugs in a very targeted way.

Once a wandering cancer cell finds the right address, it still has to infiltrate the organ itself. The thought is that different cancers carry different sets of keys, and they can gain entry only if there's a matching lock. That helps explain why some cancers pass harmlessly through the lungs without lodging there. In 2001, researchers showed that the preferred

lodgings of breast cancer and melanoma were basically "advertising" themselves with chemicals called chemokines. Guest and host, in other words, were on the same wavelength. And once they find each other, the deadly dance begins. Breast cancer cells, for example, stimulate cells that break down bone. The more the bone breaks down, the more the cancer can grow.

So get them on the wrong wavelength; mangle their communication. That's in fact what drugmakers have in mind. Drugs capable of doing that might have to be taken indefinitely, since tumors can lurk undetected in the body for years. Research has even shown that tumor cells can mimic other kinds of cells by taking cues from their environment. Indeed, there is much to be learned about how the tumor's soil influences the progression of metastasis, and few of these discoveries are yet ready to translate to treatment. Thinking of the body as an unwitting but active participant in the process raises the intriguing question: Could our own chemical signals someday be used to block metastasis? After years of trying to crack the seed, many cancer researchers are now sifting through the soil in search of the answer.

Cancer's Itinerary

All metastasizing cells have the same basic plan, though for reasons not known some are picky about where they travel and set up camp. For example, the cells that break off from a primary breast cancer tumor often migrate to the brain.

1 The primary tumor taps into the local blood supply and thrives in the breast tissue.

2 Thousands of cancer cells routinely break off from the tumor and begin traveling through the body's blood and lymph systems. Most of these traveling cells perish, but some arrive in far reaches of the body, where they lodge in a blood vessel wall.

3 Once fortified, the cancer cells vacate the blood vessel and invade healthy organs.

[drawing labels] Tumor, Vessel, Cancer cells, Lymph nodes, Blood vessels

Rod Little--USN&WR

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