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Cancer's break-in tools possibly identified (w/ Video)

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A single cell in a 1-millimeter nematode worm is providing valuable new clues into cancer's deadliest behavior -- its ability to put down roots in new tissues after spreading throughout the body.

Duke University biologist David Sherwood has spent the last several years studying the mechanics of a single cell in the developing body of a worm called Caenorhabditis elegans. It's called the anchor cell and one of its jobs is to connect the developing animal's uterus with its vulva, a crucial step in ensuring the worm's fertility.

To establish this slender connection, the anchor cell must work its way through two layers of basement membrane, a dense, sheet-like barrier structure lining most tissues, including the epithelial cells in humans that are the hosts of many cancers.

In a paper appearing online Aug. 17 in the journal *Developmental Cell*, Sherwood and colleagues describe how the nematode's anchor cell uses a series of molecular signals to create a stretched opening in the membrane. They believe the process is essentially the same as the one cancer cells use to invade new tissues.

Together, these molecules, called integrin and netrin, may be a valuable new target in the efforts to halt cancer's spread via metastasis.

"Metastasis accounts for most of cancer's lethality," said Sherwood, who is an assistant professor of biology at Duke. "It's the most essential step

in cancer progression, but it's the least understood."

To push a hole through the basement membranes, the worm's anchor cell forms several lancet-like points, called puncta. They look remarkably like a structure seen in cancer cells called invadopodia that are believed to have the same function, but modeling this part of metastasis in the lab has proven impossible so far because nobody has figured out how to make a basement membrane in a dish.

The abundant, cheap, rapidly multiplying worms -- and their basement membranes -- have enabled Sherwood to do a variety of experiments to narrow down the genes and molecular signals in play. And, with newly developed imaging technologies, they can actually watch as the cell invasion occurs.

"In vivo, you're dealing with individual cancer cells moving around the body. It is very hard to watch that,." Sherwood said. "And then asking the cancer cell 'what genes are you using to do that?' is even more difficult."

From the latest set of findings with the model organism, Sherwood believes that integrin helps the anchor cell orient itself toward the basement membranes, and that it also directs netrin to build the puncta in the proper place to ease an opening through. Interestingly, netrin is also the signal that encourages developing neuron cells to branch out and make new connections.

What's even more encouraging about both of these molecules is that they're outside the cell, Sherwood said, making them easier to target with possible drug therapy.

There are about 100 genes that seem to prevent cell invasion, and Sherwood's team is searching for those that might be the most effective.

A gene called SPARC, for example, is known to be over-active in cancer cells, enabling easier penetration of the basement membrane. They are currently examining how this gene helps the anchor cell invade.

He said they would like to know how the cell turns on "invasiveness" to understand the best way to interrupt this potentially lethal behavior.

Sherwood's research was supported by a Basil O'Connor Award, Pew Scholars Award and a grant from the National Institutes of Health.

Source: Duke University (news : web)