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Surprising origin of cell's internal highways

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Scientists have long thought that microtubules, part of the microscopic scaffolding that the cell uses to move things around in order to hold its shape and divide, originated from a tiny structure near the nucleus, called the centrosome.

Now, researchers at Vanderbilt University Medical Center reveal a surprising new origin for these cellular "highways." In the June issue of *Developmental Cell*, Irina Kaverina, Ph.D., and colleagues report that the Golgi apparatus -- a stack of pancake-shaped compartments that sorts and ships proteins out to their cellular destinations -- is the source of a particular subset of these microscopic fibers. The findings point to a novel cellular mechanism that may guide cell movement and possibly cancer cell invasion.

Microtubules are the largest of the three main types of filaments that make up the cytoskeleton -- a web of microscopic fibers inside the cell.

They form when two globular proteins, alpha- and beta-tubulin, polymerize into long chains, which then assemble into long, hollow tubes. In order to gain a foothold, nascent microtubule "seeds" must be anchored at a structure near the cell's nucleus called the centrosome or microtubule-organizing center (MTOC).

From the MTOC, the growing microtubules launch out in all directions to the cell's periphery. Their rapid assembly and disassembly helps transport proteins throughout the cell and generate polarized (directional) signal distribution that causes cells to move.

While microtubules in some specialized cells can originate from non-centrosomal structures, the centrosome has been considered the main origination point for microtubule "nucleation" in most cells. Until now.

"I've seen that there are lots of microtubules not attached to the centrosome," said Kaverina, assistant professor of Cell and Developmental Biology and senior author on the paper. "So I am trying to look at their origins."

The Golgi has been suspected to function as an MTOC, explained Kaverina. However, conclusively demonstrating this was impossible before the advent of live-cell imaging techniques that could reveal the true origins of these structures.

"The Golgi apparatus is very close to the centrosome," said Kaverina. "So if you're not looking at it precisely, it is hard to distinguish between the centrosome and Golgi."

To get a close look, Kaverina and colleagues tagged the growing ("plus") ends of microtubules in human retinal epithelial cells with a fluorescent molecule, videotaped their growth and carefully followed the tracks back to their origin.

"We show that not only the centrosome, but the Golgi also makes microtubules," Kaverina said. "And unlike centrosomal microtubules, which are radial and symmetric, these microtubules are directional."

They found that microtubules originating at the Golgi are directed toward the cell "front," or the leading edge, of motile cells. Since such an orientation is needed for directional migration, Kaverina hypothesizes that this subset of microtubules may influence cell motility by facilitating the transport of proteins needed for movement to the cell front.

"This new microtubule subset that we discovered directly connects the Golgi to the cell front, so it would be very logical if these microtubules act as 'tracks' for this delivery," she said.

In addition to identifying this novel site of microtubule nucleation, Kaverina and colleagues also examined the molecular mechanisms governing the process. They found that proteins normally associated with the plus ends of microtubules, called CLASPs, localize to a specific compartment of the Golgi (the Trans Golgi Network) and stabilize the microtubule "seeds" at the Golgi.

Golgi-originating microtubules could also be an important factor influencing how cancer cells invade distant tissues.

Because microtubules play a central role in cell division, cancer drugs like colchicine, vincristine and paclitaxel (Taxol) can block cell division by altering microtubule dynamics.

"Many classic chemotherapy strategies affect microtubules, although it's not quite clear how these drugs influence cancer cells differently than normal cells," said Kaverina. "Both microtubule regulation of proliferation and microtubule regulation of migration and invasion probably contribute to the therapeutic effects."

Therefore, further study of this new subset of microtubules might offer insight into how the invasion of cancer cells into surrounding tissues could be halted.

Source: Vanderbilt University