Protein-dependent 'switch' regulates intracellular trafficking in epithelial cells

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With findings highlighted on a recent cover of Developmental Cell, researchers at Weill Cornell Medical College in New York City have shed important new light on key trafficking mechanisms within epithelial cells. Epithelial cells line the outside of nearly all organs.

Specifically, the team has discovered a molecular "switch" in developed epithelial cells that selects from a large family of "motor proteins," called kinesins. Each kinesin facilitates the transport of specific surface markers from production sites inside the cell to their ultimate home on the cell's surface.

"Not only are many more kinesins present in cells than previously thought, but their selectivity helps direct which packages of surface proteins are transported, as well as their ultimate destinations," explains lead researcher Dr. Geri Kreitzer, assistant professor in the department of cell and developmental biology at Weill Cornell Medical College.

"Breakdown in these types of intracellular trafficking pathways is a serious contributing factor to many diseases ranging from cystic fibrosis to cancer," Dr. Kreitzer continues. "So, a better understanding of processes directed by the specific kinesin family members marks a big step forward in developing therapeutics that might someday treat or cure these illnesses. By targeting the individual motors rather than the tracks along which they all move (a current approach used to treat some types of cancer), we could bypass some of the effects on global cellular function that affect patients adversely."

Scientists have long understood the importance of kinesins in the life of the cell, she notes.

"These proteins are essentially 'trains' pulling packets (vesicles) of essential proteins and lipids from production sites in the heart of the cell up to areas on the outer surface, where the cell interacts with its environment," Dr. Kreitzer explains.

These kinesin "trains" work by moving their cargoes along filamentous tracks, known as microtubules. "When everything is working right, appropriate surface markers end up where they need to go. However, in rare cases, mix-ups occur, and they can be devastating -- causing sickness not only of cells but of the organ of which those cells are a part," Dr. Kreitzer explains.

Scientists have spent decades investigating vesicular trafficking. But the exact role for each of the 41 members of the kinesin family has remained unclear.

In their study, Dr. Kreitzer's team focused on four different cell membrane proteins. They knew these proteins were destined to be packed up and transported via microtubules to key spots on the surface of the epithelial cell.

"We knew kinesins played a role in all that -- but did it matter which kinesin?" Dr. Kreitzer says.

To find out, her team inhibited specifically the activity of a series of different kinesins, in turn, then watched to see what happened.

"We discovered something exciting: that the journey a particular surface marker makes depends on a specific member of the kinesin family. What worked for one protein did not work for the others," Dr. Kreitzer

says. "That tells us that there's real 'selectivity' going on. It also tells us that the type of kinesin selected is a key piece of information determining where a particular surface protein will go."

"That's great news for drug development, because it means that we might use this selectivity to target the appropriate motor protein whenever a specific pathway goes wrong," Dr. Kreitzer says. "That could potentially mean more effective, targeted therapies with fewer side effects."

The team also discovered that selectivity of the motor for its cargo (passenger) switches after the epithelial cell has differentiated and fully matured. "When we worked with immature, developing cells, the type of kinesin used is clearly different," Dr. Kreitzer points out.

But how does the mature cell decide which kinesin to put to work on a particular transport mechanism"

"Right now, we just don't know," Dr. Kreitzer said. "Figuring out that molecular 'switch' is the next great frontier in this research."

For now, the study's findings hold promise for the study of devastating illnesses caused by defective placement of surface proteins, such as in cystic fibrosis, and even cancer.

"Right now, most chemotherapy targets the whole microtubule 'track' -- that's a really heavy-handed approach that typically affects the cell as a whole and causes serious side effects," notes Dr. Kreitzer.

"Imagine, though, that we could use what we now know about kinesins to target only the specific trafficking machinery that's gone awry," she says. "The result could be better, safer cancer care. And that paradigm holds true for a myriad of other diseases, as well."

Source: New York- Presbyterian Hospital