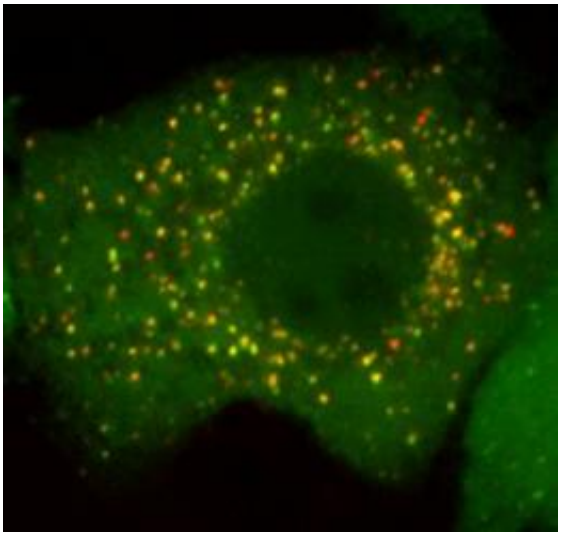
Worm studies shed light on human cancers

April 21 2011



The fusion protein TFG-NTRK-1 may promote the secretion of growth factors that stimulate tumor formation. Here human cells expressing a form of TFG-NTRK-1 (green) localize on ER exit sites, which contain the scaffolding protein Sec16 (red).

(PhysOrg.com) -- Research in the worm is shedding light on a protein associated with a number of different human cancers, and may point to a highly targeted way to treat them.

University of Wisconsin-Madison scientists were studying a worm protein called TFG-1, which is present in many cell types but whose exact role had never been understood. The scientists discovered that the protein controls key aspects of the movement, or secretion, of growth factors out of cells.

"TFG-1 has never been implicated in the secretory process before," says Dr. Anjon Audhya, an assistant professor of biomolecular chemistry in the School of Medicine and Public Health. "It turns out that humans carry a very similar protein, and we think it plays the same role in humans as in worms."

Reviewing the scientific literature, the researchers found that the gene encoding TFG in humans is fused to at least three other genes implicated in anaplastic large cell lymphoma, papillary thyroid carcinoma and extraskeletal chondrosarcoma. The fusions occur when two broken or rearranged pieces of DNA combine to form a "chimeric" gene with completely distinct properties.

Audhya's studies of TFG-1 in the worm led him to develop a model that explains how TFG fusions may stimulate cancer in humans. As reported in the current issue of Nature Cell Biology (Advanced Online Publication), he proposes that abnormal levels of growth factor secretion may produce a rich micro-environment that helps tumors form and thrive.

"We think certain properties of TFG lead it to be a very effective precursor oncogene," he says.

Normally, a growth factor primed to leave a cell is encompassed by a sac, or vesicle, and then transported from one structure inside the cell to another—endoplasmic reticulum (ER) to Golgi—before it leaves the cell and discharges into the extracellular space.

Through their genetic studies, the Wisconsin researchers found that TFG-1 in the worm controls vesicle formation and secretion out of the ER.

"We found TFG-1 lies at the interface between the ER and the Golgi, in

a scaffolding structure called the ER exit site, where it regulates the formation of vesicles carrying their critical cargo," Audhya says.

The research revealed the precise location where TFG-1 does its work and the mechanism by which it spurs unchecked activity.

The scientists demonstrated that human TFG also functions at ER exit sites, which contain a characterized scaffolding protein called Sec16, and likely regulates secretion of multiple cargoes out of cells.

"In the case of one fusion gene, TFG-NTRK-1, the concentrated non-stop activity of NTRK-1 at ER exit sites may cause the first steps that can transform a normal cell into a cancer cell," Audhya says.

The TFG fusions offer a direct target for future "designer" therapies.

"If you identified patients who have fusion genes that express chimeric proteins, you could create a drug that affects only those proteins," he says, adding that TFG fusions leading to chimeric proteins do not exist in healthy people.

Excited about the possibility that their basic science investigations may be applied to several areas of clinical medicine, the researchers have also begun studying TFG as it relates to B-cell development and the secretion of antibodies.

Provided by University of Wisconsin-Madison