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Protein May Be Target for New Cancer Drugs

During development of multicellular organisms, cells are bombarded by signals from their environment. The repertoire of receptors that cells display on their surfaces often determines whether or not individual cells respond to environmental cues.

Researchers have now found that a protein that oversees the transport of receptors from the surface to the interior of the cell also tags receptors for degradation. This finding is important because cells turn off their response to external growth signals by decreasing the number of receptors available to bind signals.

"The image shows a Garland cell which functions as a kidney cell in the fruit fly, *Drosophila*. The Hrs protein delivers receptors from endosomes (green) to lysosomes (red) where they are degraded. In the absence of Hrs, activated receptors for growth signals cannot be turned off -- a defect also seen in cancer cells."

In an article published in the January 25, 2002, issue of *Cell*, Howard Hughes Medical Institute investigator Hugo J. Bellen and colleagues at Baylor College of Medicine report that the activity of the protein Hrs may regulate cell proliferation and could be an important new target for anticancer drugs.

A process called endocytosis regulates the cell-surface expression of many receptors. During endocytosis, a patch of the cell membrane containing the receptor is internalized by the cell and forms small vesicles that later fuse into a large vesicle called the endosome. From the endosome, growth factor receptors and other cargo may be recycled back to the cell surface, or they may be sent to another compartment, called the lysosome, where they can be degraded.

According to Bellen, experiments in yeast by other researchers — including HHMI investigator Scott D. Emr at the University of California, San Diego — suggested that Hrs might be involved in endocytosis, but its specific function remained unknown. Bellen's group analyzed mutant fly larvae that lacked functional Hrs in order to try to understand the protein's role in endocytosis during development.

Using electron microscopy, the researchers revealed how specific cells in the flies' stomachs absorbed a fluid tracer. The studies showed that the mutant flies had enlarged endosomes. They found that the abnormalities were due to defects in the endosome's ability to form "multi-vesicular bodies," specialized endosomes that contain vesicles inside them that carry cargo to the lysosome.

"What's exciting in this finding is that we now understand one reason why multi-vesicular bodies form," said Bellen. "Our later studies showed that these bodies are needed to turn off signals from key receptors involved in cellular communication."

The scientists demonstrated that epidermal growth factor receptor (EGFR) and Torso tyrosine kinase receptor remained switched on constantly in the mutant flies, because they depend on Hrs for inactivation. When they analyzed the Hrs protein, the scientists determined that it could bind specifically to a chemical tag that targets receptors to the lysosome for degradation.

A receptor may receive an external chemical signal such as a growth hormone at the cell surface, but that may not necessarily activate the cell's growth machinery, Bellen explained. "The signaling may not occur from most receptors at the cell membrane," Bellen noted. "For example, signaling may occur in the cytoplasm after the receptor has been taken in by endocytosis. When Hrs attaches to the receptor and pushes it inside the vesicle, this process would end its access to the cytoplasm and thus its signaling."

Receptors such as EGFR control cell proliferation, so their over-activity (caused by an absence of Hrs to guide them to the lysosome for degradation) might underlie many cancers, said Bellen. In fact, a protein called TSG101 that is missing in some forms of cancer has also been shown to play a role in forming multi-vesicular bodies.

"We know that Hrs is involved in regulating key signaling proteins that have been implicated in numerous cancers because they control cell proliferation and cell differentiation," he said. "Hrs should be studied in detail, not only to determine whether there are mutations in the protein that cause cancer, but also as a drug target. One could potentially use drugs to affect this protein's activity — either to eliminate it or overexpress it — to modify a signaling pathway."