Medical Xpress

Neuronal regulators offer potential targets for cancer

March 19 2008

Being too brainy can be a bad thing in a junior high cafeteria, where the social hierarchy favors other traits. "Braininess" also causes problems for cells. When a breast cell begins making the proteins normally produced in neurons, for example, it can acquire cancerous properties.

Now, researchers in Stephen Elledge's laboratory at Harvard Medical School (HMS) have identified some of the switches that control this transformation, providing promising new therapeutic targets in some types of cancer. Their results appear in the March 20 issue of *Nature*.

"These switches play an important physiologic role in neural development and pathologic role in cancer," says first author Thomas Westbrook, who is now an assistant professor at Baylor College of Medicine. "I'm optimistic that we can use small molecules to control them."

In a previous study, Westbrook showed that a protein called REST--which keeps neural programs silent in most parts of the body--serves as a tumor suppressor.

"He's now identified a protein that promotes tumor growth by tagging REST for destruction, thereby activating neural programs," says Elledge, who holds primary appointments in the HMS Department of Genetics and at Brigham and Women's Hospital.

If the protein REST worked at a club, he would be a bouncer, preventing

dozens of rowdy patrons from causing trouble. REST serves as a "master repressor," keeping numerous neural genes silent in breast cells, lung cells, etc, where they could wreak havoc. When REST disappears, these genes roar to life, pushing cells to become more like neuron precursor cells.

But cells outside the nervous system keep neural genes silent for a reason. When neural genes get switched on in breast cells anchored to surfaces, for example, they acquire the ability to live without the anchoring that is essential for normal cells to survive. That is, they can grow in suspension, which is a classical characteristic of cancer cells.

After uncovering this role, Westbrook used a technique called RNA interference (RNAi) to search for proteins that reduce REST levels. He reasoned that these proteins might promote tumor formation if expressed outside the nervous system.

The RNAi screen netted a known tumor promoter called Î²-TRCP. Further genetic tests revealed that Î²-TRCP binds directly to REST, tagging it for destruction. But REST must be primed with a particular molecule called phosphate for this interaction to occur.

"If we can prevent Î²-TRCP from binding to REST, we may be able to treat certain tumors that display neuronal gene expression profiles," says Elledge, who is also a member of the HMS-Partners HealthCare Center for Genetics and Genomics and investigator with the Howard Hughes Medical Institute. "Such profiles are remarkably common in epithelial cancers, such as breast cancer and ovarian cancer."

"This discovery is particularly exciting because the scientific community knows how to target enzymes that add and remove phosphate groups from proteins with small molecules," says Westbrook. "Big pharmaceutical companies have devoted lots of resources to

accomplishing this task."

Information about the interaction between Î²-TRCP and REST might also aid researchers in the embryonic stem cell field.

"It's hard to control the differentiation of embryonic stem cells into specialized cells such as neurons," says Westbrook. "If one could prevent Î²-TRCP from tagging REST for destruction, one could potentially keep embryonic stem cells from turning into neurons. Alternatively, one might be able to make neurons more efficiently by quickening REST destruction."

Source: Harvard Medical School