New location found for regulation of RNA fate

July 30 2009

Thousands of scientists and hundreds of software programmers studying the process by which RNA inside cells normally degrades may soon broaden their focus significantly.

That's because University of Wisconsin-Madison researchers have discovered that the RNA degradation, which, when improperly regulated can lead to cancer and other diseases, can be launched in an unexpected location.

"We've been seeing only half the picture," says Vladimir Spiegelman, lead author on the new study and associate professor of dermatology at the UW-Madison School of Medicine and Public Health.

The Wisconsin team also found that CRD-BP, a protein activated in colorectal and other cancers, can prevent RNA from degrading in the newly identified spot.

The finding may have broad implications for cancer research as well as biology in general.

"The finding is important for the proto-oncogenes, or precursor cancer genes, we study, but it may be even more important for the thousands of other genes and proteins that are regulated in a similar way," says Spiegelman.

The study appears in the July 31 issue of *Molecular Cell*.

Spiegelman and his team study proto-oncogenes and other potential "cancer-causers" normally found in cells, analyzing them as they are "converted" from DNA into RNA and ultimately active proteins that can lead to cancer.

It's the same multistep process all genes in a cell — including "cancer-preventers" such as tumor suppressors, anti-inflammatory factors and cell death promoters — go through.

Controls at each step usually keep the process working smoothly, but if a control fails at any number of places along the way, a cancer-promoting gene can tilt the delicately balanced scale toward malignancy.

In their previous work, the Wisconsin researchers found that regulation of some proto-oncogenes occurs after CRD-BP binds to messenger RNA (mRNA). During this intermediary step, mRNA is typically either degraded or goes on unharmed to the next step of translation. The Wisconsin team showed that the mRNA bound by CRD-BP was not degraded, and thus became an active protein — in this case, a full-fledged cancer-causing oncogene.

Until the Spiegelman group's latest study appeared, scientists assumed that the regulation of mRNA fate took place exclusively in an area of the RNA strand called the 3 prime untranslated region, where small regulatory RNAs called microRNAs (miRNA) bind and inhibit mRNAs.

But the Wisconsin team found degradation can also be initiated in an area on the mRNA strand called the coding region.

"This changes the paradigm," says Spiegelman. "Now we can examine this important activity in two places."

The researchers demonstrated that degradation occurs here using a

human mRNA, and described the mechanism by which CRD-BP stabilizes the mRNA and prevents it from degrading and expressing more protein.

"This may be the first example of a negative regulator of an miRNA-dependent RNA-degrading mechanism," Spiegelman says.

The mechanism is relevant to many proteins, he says.

"Understanding this mechanism should also help us in studying cell signaling pathways related to pro-inflammatory and cell death factors that contribute to tumor development," he says.

Source: University of Wisconsin-Madison (news : web)