Notorious cancer gene may work by destroying messenger

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A new study suggests how a notorious cancer gene may contribute to tumor growth.The insight emerged from a long-running study of a protein called PMR1, the key player in an unusual mechanism that cells use to quickly stop production of certain important proteins.

Researchers discovered that PMR1 is activated – or "turned on – by another molecule, an energy-packing protein called Src (pronounced "sark").

Discovered in 1977, Src became the first "oncogene" – mutated genes that help make cells cancerous. Oncogenes are altered forms of genes that control cell growth and cell division.

These findings provide insight into how Src might contribute to cancer development.

The study by researchers with the Ohio State University Comprehensive Cancer Center is published in the March 9 issue of the journal *Molecular Cell*.

"The link between Src and cancer was discovered 30 years ago, but to this day, we still don't know its exact role in tumor development," says principal investigator Daniel R. Schoenberg, professor of molecular and cellular biochemistry.

"Our data suggest that Src may promote cancer by causing PMR1 to halt

production of proteins that normally put the brakes on cell growth – tumor-suppressor proteins, for example, or other growth-regulating proteins."

In healthy cells, Src helps control cell proliferation, differentiation, survival and movement. Mutated Src is found in about half of all colon, liver, lung, breast and pancreatic tumors, and the amount of Src can be significantly higher in cancer cells compared to normal cells.

Earlier research led by Schoenberg found that PMR1 helps control protein production by destroying particular messenger RNAs (mRNAs), molecules that carry the information used to assemble a protein.

That work showed that PMR1 attaches to the mRNAs and remains there as a silent passenger. If it receives the proper signal, however, the protein chops up and destroys the mRNA, which instantly stops production of that protein.

Cells use that mechanism to control the production of proteins such as growth factors, which activate genes in response to a hormone or other signal.

PMR1 also plays a key role in Cooley's anemia, which causes the loss of red blood cells in infants and children.

For the present study, Schoenberg and coauthor Yong Peng, a research associate in Schoenberg's laboratory, wanted to learn how PMR1 is activated to attach to mRNAs.

They found that activation occurs when PMR1 is momentarily joined by an unidentified enzyme. Contact with this enzyme changes the properties of PMR1, and this enables it to join with, or bind to, its target mRNA.

Peng then used monoclonal antibodies to isolate PMR1 and the enzyme while the two were bound together, capturing both. After separating the two, the investigators identified the enzyme as Src, which is a member of a large family of molecules called tyrosine kinases. These molecules act like switches that turn other molecules on and off, including PMR1.

“That's the real excitement about this paper,” Schoenberg says. “We came at this with an interest in mRNA decay, and we may have stumbled across a fundamental mechanism of cancer.”

Next, Schoenberg and his associates Xiaoqiang Liu and Elizabeth Murray will use three cancer-cell lines to try to identify what messenger RNAs – which will also tell them what proteins – are targeted and destroyed by PMR1.

“That will help tell us whether Src works through PMR1 to contribute to cancer,” Schoenberg says.

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Source: Ohio State University