Drug strategy makes cancer genes get lost in translation

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A new strategy for fighting cancer aims to make its genes get lost in translation, according to a report in the January 26, 2007, issue of the journal *Cell*, published by Cell Press.

According to the researchers, such a therapy would essentially take advantage of a weakness of the disease: that the majority of growth- and proliferation-related proteins, which cancer depends upon, are encoded by "weak" messenger RNAs (mRNAs). Transcribed from DNA, mRNAs serve as templates for the synthesis of proteins through a process known as translation.

The researchers now report the discovery of a small molecule that targets such weak mRNA, preferentially interrupting its translation into active proteins. As a result, the molecule, called 4EGI-1, effectively silences oncogenes, which have links to cancer. They also found evidence that the small molecule inhibitor exhibits activity against multiple cancer cell lines, including lung and blood cancer cells.

While cancer-promoting proteins may be lost as a result of such treatment, more readily translated "housekeeping" genes--those encoded by "strong" mRNAs that cells need on a regular basis--might continue their activities, said Gerhard Wagner of Harvard Medical School. Therapies targeted at translation might have general use in tackling many forms of cancer, regardless of its genetic origin, given that the uncontrolled growth of cells is a general characteristic of the disease, he added.

The new findings establish a "possible new strategy for cancer therapy," the researchers said. However, they cautioned, the newly described inhibitor is not strong enough for use as a drug in itself. The researchers will next work to chemically modify the inhibitor to enhance its action and screen additional chemical libraries in search of more potent molecules before tests of such a drug in animals could ensue.

Weak mRNAs are translated into proteins less efficiently as a result of long and highly structured, "untranslated regions" at their so-called 5' end, the researchers explained. The lengthy region of weak mRNAs serves as an obstacle for the ribosomal machinery that does the translating, making it a challenge to determine where to begin, he added.

In contrast, strong mRNAs have only short 5' untranslated regions that allow for easier protein formation. The successful translation of weak mRNAs therefore depends more heavily on other protein factors, called initiation factors, to help the process along.

In the current study, the researchers sought to capitalize on the weakness of cancer-related mRNAs by disrupting the interaction between two protein initiation factors, eIF4E and eIF4G.

Assembly of the eIF4E/eIF4G complex is known to have a central role in controlling genes at the level of translation initiation. The complex is normally kept under wraps by still other proteins, the 4E-BPs, which compete with the initiation factors for binding and have tumor-suppressor activity.

The researchers screened thousands of available small molecules for their ability to interfere with the initiation proteins' interaction in a manner similar to the 4E-BPs. The most potent compound identified, 4EGI-1, binds one of the proteins, eIF4E, thereby disrupting the ability of the eIF4E/eIF4G complex to do its job. That interference, in turn,

blocked the formation of proteins that require assistance from initiation factors.

"Surprisingly, this compound does not inhibit binding of [the tumor suppressor] 4E-BP1 to eIF4E and instead causes a significant apparent increase in the amount of this protein that is bound," the researchers reported.

Treatment of mammalian cancer cells with the compound had a similar effect on the translation of weak mRNAs to that seen in the initial in vitro tests, they show. What's more, the level of a classic housekeeping gene remained unaffected in treated cells, while expression of two oncogenes, c-Myc and Bcl-xL, declined significantly.

"Our results demonstrate that it is possible to inhibit the protein-protein interaction between eIF4E and eIF4G using small molecules and to establish a methodology that can readily be used to identify new classes of such inhibitors through the screening of compound libraries," the researchers concluded.

The method could lead to new forms of stand-alone or combination cancer therapies, Wagner said, noting that the strategy is "unusual in that it targets a protein-protein interaction, which has not typically been considered a good drug target."

In addition, they added, small-molecule inhibitors of the eIF4E/eIF4G interaction might serve as a useful chemical genetic tool. They noted that such a tool could be used in researchers' investigation of the translational control of gene expression in various cellular processes, such as cell growth and embryonic development.

Source: Cell Press