Study finds drug targets aren't lost in 'translation'

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Irene Ghobrial and Salomon Manier

Traditionally, attacking cancer cells by targeting their "translation" machinery was thought to be as effective as trying to halt a runaway train by uncoupling the caboose.

Translation, the final stage of the process by which genetic information is used to produce proteins in cells, was thought to be a mere tagalong, with little influence over how much of each protein is made. Recently, however, scientists have discovered that in tumor cells, some aspects of translation operate by their own rules, which may be independent of the genetic makeup of the cancer. The discovery suggests that in cancers where protein production is excessive, translation may offer a promising point of attack for new therapies.

That potential is burnished by a recently published study (http://stm.sciencemag.org/content/9/389/eaal2668) by Dana-Farber researchers.

The study, which ran in *Science Translational Medicine*, focused on multiple myeloma, a cancer of the blood-forming cells of the bone marrow. One of the hallmarks of myeloma cells is a hyperactive *MYC* gene, which causes the cells to change from a pre-malignant to malignant state. Among *MYC*'s many jobs is to oversee the construction of ribosomes, tiny structures within the cell that assemble proteins from amino acids.

MYC's central role in myeloma makes it a tantalizing target for drug therapy. Theoretically, putting a damper on overactive *MYC*would slow the production of certain proteins and impede the cancer process. *MYC*, however, has proven exceedingly difficult to target with drug molecules. As a result, researchers have tried a variety of indirect approaches to counter the effects of the overactive gene.

In the new study, researchers led by **Salomon Manier, MD,** and **Irene Ghobrial, MD,** director of the Michele and Stephen Kirsch Laboratory at the Institute, screened nearly 3,000 compounds in myeloma cells to see which had the strongest anti-myeloma effect. The most potent was a compound known as a rocaglate scaffold inhibitor, which hinders the translation process from getting started.

When researchers analyzed the treated cells, they found the agent caused a full reversal of the revved-up translation process driven by overactive *MYC*. The reversal went hand-in-hand with a depletion of five proteins that are critical to the survival of myeloma cells.

"Our work offers the first demonstration of a compound that can interfere with this set of cancer-related proteins, which play a key role in myeloma formation," says Manier, the study's lead author. "The results show we can selectively deplete these proteins while leaving other, non-cancer-related proteins unperturbed."

In follow-up studies involving mouse models of multiple myeloma, researchers found the compound halted the progression of the disease. Researchers plan further pre-clinical studies in animal models, which, if successful, may lead to clinical testing of the compound or similar agent in patients with myeloma, Manier says.

Dana-Farber contributors to the study include Daisy Huynh; Yujia Shen, PhD; Jia Zhou, PhD; Timur Yusufzai, PhD; Karma Salem, MD; Richard Ebright, PhD; Jiantao Shi, PhD; Jihye Park, PhD; Siobhan Glavey, MD; Chia-Jen Liu, MD, PhD; Nathanael Gray, PhD; and James Bradner, MD.

- *Robert Levy*