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Team finds new genetic target for a different kind of cancer drug

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Researchers from the UNC School of Medicine have discovered that the protein RBM4, a molecule crucial to the process of gene splicing, is drastically decreased in multiple forms of human cancer, including lung and breast cancers. The finding, published today in the journal *Cancer Cell*, offers a new route toward therapies that can thwart the altered genetic pathways that allow cancer cells to proliferate and spread.

"Historically, scientists haven't targeted the proteins in cancer cells that are involved in gene splicing," said Zefeng Wang, PhD, associate professor in the department of pharmacology and senior author of the *Cancer Cell* paper. "This is a whole new ballgame in terms of gene regulation in cancer."

There are approximately 25,000 genes in the human genome – the same amount as in a fruit fly. But in humans, these genes are spliced together in different ways to create various kinds of messenger RNA to produce the many different proteins humans require. It's like a filmmaker splicing together bits of movie scenes to create alternative cuts of a movie. In genetics, this process is called alternative splicing.

Wang's lab found that RBM4 is an important film editor.

Wang, a member of the UNC Lineberger Comprehensive Cancer Center, studies how alternative splicing happens in normal cells and in cancer cells. Through a series of biochemical experiments and high-throughput screening methods, his team identified about 20 proteins that

are involved in regulating alternative splicing. Then his team conducted further experiments to pinpoint changes in the activity of these proteins in various kinds of human cancer cells and in mouse models. Such "misregulated" protein expression would provide evidence that the proteins are involved in cancer development or metastasis.

Wang found that the protein RBM4 was decreased, as compared with normal tissue. In lung and breast cancer patients, RBM4 was drastically "down regulated."

"In normal cells, RBM4 inhibits alternative splicing," Wang says. "It makes genes splice from a long form into a short form. For one of the genes we study, which is called Bcl-x, we want the short form because it has anti-cancer properties."

When RBM4 is low, the longer form of Bcl-x is produced, which plays a role in promoting cancer development and metastasis. "In mouse models, we showed that activating RBM4 can reverse cancer progression," Wang said.

Wang's group also found that RBM4 played a role in controlling another splicing regulator called SRSF1, which is highly expressed in some cancer cells. "What's interesting is that RBM4 actually inhibits the expression of SRSF1 and therefore controls the splicing of many SRSF1 targets in an opposite fashion. This again showed us why RBM4 has activity as a tumor suppressor.

Wang said that RBM4 is needed in the proper amount so that these genes are spliced properly and don't contribute to cancer development and metastasis. This means that the level of RBM4 in cancer patients can actually be used to predict their chances of survival.

"Where we go from here is trying to find out what shuts down RBM4,"

Wang said. "We want to find out if we can target RBM4 and manipulate it. We will probably have to target more than one thing to treat cancer patients, but we think RBM4 could be a very important one."

Provided by University of North Carolina Health Care

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