Combination microRNA therapy shown to suppress non-small-cell lung cancer

September 5 2014

Micro RNAs (miRNA) have recently emerged as key therapeutic agents against cancers and are actively being evaluated in pre-clinical models of various cancers as well as in human clinical trials.

Now, new findings show that a combination therapy of two miRNAs, let-7 and miR-34, suppressed tumor growth in an animal model of non-small-cell lung cancer, offering a promising therapeutic avenue for this extremely aggressive malignancy.

Currently reported online in the journal *Oncogene*, the study provides two important examples of basic science discoveries making their way to the clinical setting and offers the possibility of a less toxic and more direct method to target multiple biologically relevant pathways to which tumor cells have become addicted.

"Targeted cancer therapies are often used in combinations to help offset primary or secondary resistance," explains co-senior author Frank Slack, PhD, Director of the Institute for RNA Medicine (iRM) in the Cancer Center at Beth Israel Deaconess Medical Center (BIDMC) who conducted the work while at Yale University, together with Andreas Bader, PhD, and colleagues at Mirna Therapeutics, Austin, Texas. "We know that miRNAs target many oncogenes. We, therefore, hypothesized that a combination of two miRNAs could similarly offset resistance."

Lung cancer is the leading cause of cancer-related deaths worldwide, and non-small-cell lung cancer (NSCLC) makes up the bulk of newly

identified lung-cancer cases.

"NSCLC is extremely aggressive, owing to an accumulation of mutations that affect the cancer pathways RAS and p53," says Slack. The K-RAS mutation is found in about 25 percent of NSCLC patients, and the p53 mutation is in about 50 percent of these individuals. There are no currently approved drugs that are effective for these patients.

Previous work by Slack and Bader found that the let-7 and miR-34 miRNAs function as tumor suppressors.

"Our research groups and others have found that both of these miRNAs can inhibit tumor growth in a variety of cell and animal model systems when used as therapeutic agents," says Slack. "Because tumor formation in this NSCLC model depends on two or more signaling pathways, and because let-7 and miR-34 repress distinct oncogenes, we explored whether combining let-7 and miR-34 into a single therapeutic could be even more effective."

Slack co-discovered let-7 with Gary Ruvkun, PhD, in a model of C. elegans in 2000 and showed that rather than coding for a typical protein-coding gene, let-7 coded for a micro RNA. With the sequencing of the human genome, it didn't take the investigators long to find a homologue of the gene in the human genome, and let-7 became the first known human miRNA.

"We realized early on that a reduced expression of let-7 was causing stem cells to divide out of control, which is one of the hallmarks of cancer," he explains. When Slack's laboratory at Yale University conducted a genetic screen looking for suppressors of the let-7 mutant phenotype, one of the genes that emerged was RAS, a well-known oncogene that promotes the proliferation of cells. Together with scientists at Mirna Therapeutics, Slack's group tested therapeutic

miRNA formulations provided by the company in genetically engineered animal models of lung cancer. In this new paper, they report that intravenous administration of let-7 by a liposomal nanoparticle can directly deliver the miRNA to tumors in the lung.

The miR-34 micro RNA, also first discovered in C. elegans, is known to be a downstream effector of p53, the so-called "guardian of the genome."

"Because p53 loss is prevalent in many different types of cancer, we examined the role of miR-34 in lung cancer," says Slack. The investigators used the same liposomal nanoparticles to deliver the miR-34 by intravenous administration to the lung tumor model, and once again, demonstrated efficacy in cancer suppression.

"So, we thought, 'What if we tried both of these microRNAs together?'" says Slack. The investigators took half the dose of each and showed that it was effective, demonstrating that a combination of these two biologically relevant, tumor-suppressive miRNAs is superior in its ability to repress oncogene expression, prevent proliferation and invasion of cancer cells in culture, inhibit tumor proliferation in a mouse model of NSCLC and confer a survival advantage.

"Half the dose of each of these miRNAs was capable of repressing relevant biological targets in cells and in vivo, and was well tolerated by the animals," notes Slack. "We have performed these timely in vivo studies using a liposomal microRNA delivery agent already in clinical trials, which could accelerate the translation of this combinatorial miRNA therapeutic approach into the clinic."

Provided by Beth Israel Deaconess Medical Center