Team demos safety of RNA therapy

26 September 2007

Researchers from MIT, Alnylam Pharmaceuticals and other institutions have demonstrated the safety of a promising type of genetic therapy that could lead to treatments for a wide range of diseases such as cancer.

The work, which will be published in the Sept. 27 issue of *Nature*, describes a new approach to conducting the therapy. A paper in *Nature* last year reported that another commonly used approach caused fatalities in mice.

The research focuses on RNA interference, or RNAi, a key part of the body's genetic machinery. RNAi works by using short strands of RNA to block the expression of specific genes.

“RNAi has huge potential as a therapeutic agent,” said Daniel Anderson, a research associate at MIT's Center for Cancer Research and one of the authors of the new paper.

However, a paper published in *Nature* last year by a different team showed that large doses of one type of RNA used for RNAi, short hairpin RNA, disrupted another key RNA pathway, the microRNA pathway, and caused the mice in the study to die. That result worried some RNAi researchers, said Anderson.

“That first paper demonstrated that short hairpin RNA could lead to mouse fatality,” he said. “Researchers were concerned that a second type of RNA, small interfering RNA (siRNA), would induce the same toxicity.”

In the current study, the researchers demonstrated that siRNA did not have the same toxic effects as large doses of shRNA because it does not interfere with the microRNA pathway. Further, they achieved 80 percent silencing of target genes in mice and hamster liver cells.

“Using chemically synthesized siRNA, you can deliver sufficient siRNA to achieve therapeutically valuable gene silencing, without interfering with the cell's endogenous microRNA,” said David Bumcrot, a director of research at Alnylam (an MIT startup) and one of the authors of the paper.

The research team used a new RNA delivery system developed at MIT, the details of which will be published in another upcoming paper, to perform the RNA interference.

In many RNAi studies, including the one that the MIT/Alnylam team was following up on, researchers use retroviruses to deliver genes that code for short hairpin RNA, which is a precursor to siRNA. Once the gene is incorporated into the cell's DNA, short hairpin RNA is synthesized and transported from the cell nucleus to the cytoplasm for further processing.

The earlier study showed that large amounts of short hairpin RNA blocked the cell's ability to export microRNA, which uses the same export pathway. Without normally functioning microRNA, the mice died. Low doses of short hairpin RNA were not toxic, but the dosage is difficult to control because once the shRNA gene is incorporated into the DNA of the host cells, it is expressed for long periods of time, said Bumcrot.

In the current MIT/Alnylam study, siRNA was delivered directly to the cell cytoplasm, so it did not compete with the export of microRNA.

“We wanted to demonstrate that if you go downstream of that (export) step in the pathway, you don't get interference with the microRNA pathway,” said Bumcrot. “With synthetic siRNAs, we deliver a defined dose and we know how long the effect lasts. If toxicity issues arise, dosing can be stopped at any time. It's much easier to control and, therefore, safer.”

Source: Massachusetts Institute of Technology

APA citation: Team demos safety of RNA therapy (2007, September 26) retrieved 17 November 2019 from https://medicalxpress.com/news/2007-09-team-demos-safety-rna-therapy.html

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