Scientists identify novel inhibitor of human microRNA

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Scientists at The Wistar Institute and their colleagues have identified, for the first time, a molecule that can regulate microRNAs – short strands of RNA that play a vital role in gene expression and are closely associated with cancer. The discovery points the way to the development of a new generation of cancer drugs.

The research team identified a small molecule that blocks the pathway of a particular miRNA, called miR-21, that is implicated in brain cancer, as well as lung, colon, breast, and ovarian cancer. With further development, the molecule has the potential to boost patient response to existing chemotherapies, as well as to become a stand-alone cancer drug, says Wistar's Qihong Huang, M.D., Ph.D., co-senior author of the study.

Although miRNAs were discovered less than two decades ago, their importance in regulating human development and disease is already clear. While the human genome is thought to contain 800 to 1,000 miRNAs, only a few hundred have been described.

Thus, miRNAs represent a largely unexplored class of targets for the development of therapeutics and diagnostics, says Huang, an assistant professor in Wistar's Molecular and Cellular Oncogenesis Program.

"This is a totally novel target," he says. "It's very understudied, and still in its infancy, but its potential is tremendous. Because miRNAs have the ability to shut down genes and prevent their expression, they may ultimately provide a target for therapies that are more selective than

conventional chemotherapy drugs and have fewer side effects."

Alexander Deiters, Ph.D., of North Carolina State University, co-directed the study.

In regulating the molecular mechanisms behind gene expression, miRNAs can control the way in which whole chromosomes, or regions of chromosomes, are activated or deactivated. They are thought to directly regulate the expression of at least 30 percent of all human protein-encoding genes.

miRNAs regulate protein synthesis by binding to the messenger RNAs that provide the recipe for protein construction. In doing so, the miRNAs repress the relevant protein's production. Misregulation of miRNAs can result in genes being over- or under-expressed, leading to cancer and other diseases.

Huang notes that one sizeable hurdle in harnessing the power of miRNAs is getting "the right molecule into the right place at the right time" to regulate their function.

"In terms of developing therapeutic agents for cancer, for example, we need to identify small molecules that can get into the bloodstream and get into the cells," he says. "The problem is, to date, no one had been able to show that such miRNA inhibitors exist."

Huang and his colleagues developed a method to identify inhibitors of miRNA pathways in live human cells. The researchers created screening assays, or tests, to look for small molecules or compounds that selectively repress miRNA. They selected miR-21 as the target agent due to its documented role in preventing cell death – thereby allowing the unchecked cell proliferation associated with cancer – and its elevated levels in various cancers.

The team designed an assay that contained the DNA binding sequence complementary to miR-21, bound to luciferase, the protein fireflies use to create light. Because miRNAs inhibit protein production, when miR-21 is functioning normally, it binds with the complementary sequence and inhibits the translation of luciferase, thus reducing the intensity of the light signal.

"The idea was that when we add small molecules that inhibit the function of miR-21, the light signal will increase," Huang says.

The scientists then screened a "library" of 1,000 compounds and found one molecule that inhibited miR-21 in the assay. The molecule, diazobenzene 2, decreased miR-21 levels by 80 percent and produced a nearly five-fold increase in the intensity of the light signal from the firefly protein. Groups of control cells and untreated cells showed no such signal when treated with the small-molecule inhibitor.

The findings were published in the September 15 issue of the scientific journal *Angewandte Chemie.*

Preliminary data from the researchers' ongoing studies suggest that the inhibitor could be used in combination with other chemotherapy drugs to provide a synergistic effect, Huang says. The researchers also will evaluate its potential as a stand-alone cancer drug. Huang and his colleagues are now conducting studies in mice to assess the inhibitor's effectiveness against brain, breast, and colon tumors, and they are working to modify the molecule to make it even more efficient.

The screening test developed by the researchers provides a unique tool that can be used to advance investigations of miRNAs and their involvement in various diseases, Huang says. "The cell-based assay that we have established can potentially be used to screen for additional small-molecule inhibitors that can block miRNA," he notes.

Source: The Wistar Institute

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