Researcher Discovers Molecules That Inhibit Important Gene Regulators

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A North Carolina State University chemist has discovered a molecule that can potentially stop the production of cancer cells at the very beginning of the process by switching off the gene regulators responsible for turning healthy cells into cancer cells. The discovery could lead to the development of drugs that can treat some of the deadliest forms of cancer, including brain cancer.

Dr. Alex Deiters, assistant professor of chemistry at NC State, and colleagues at the Wistar Institute of Philadelphia believed that genetic regulators known as microRNAs would be an excellent target for cancer therapies, based on their importance in the process of "programming" a gene, also known as gene regulation.

MicroRNAs, or miRNAs, are small, single-stranded molecules of about 20 nucleotides – like miniature strands of DNA – that reside in every cell in the human body. These molecules are involved in more than 30 percent of all gene regulatory processes, and direct the translation of genes. When miRNAs are misregulated – either overrepresented or underrepresented – particular genes can be over or under expressed, and cancer can be the result.

The researchers targeted a particular microRNA, called miRNA-21, linked to cancers such as glioblastoma, an aggressive, hard-to-treat form of cancer which is responsible for 52 percent of all brain tumors. MiRNA-21 is responsible for the cancer cells' rapid growth, because it prevents the cancer cells from undergoing apoptosis, or cell death. By

stopping the production of miRNA-21, the researchers hoped, they would induce cell death in the glioblastoma cells.

Deiters and colleagues tested more than 1,200 separate compounds before finally coming up with a molecule that decreased miRNA-21 levels by 80 percent. Not only did the compound work to decrease the level of miRNA-21, it presumably worked by inhibiting the transcription of the miRNA itself, without affecting any other miRNAs. While the compound doesn't destroy glioblastoma cells outright, decreasing the level of miRNA-21 removes the cells' anti-apoptotic factor, potentially making them more susceptible to traditional cancer therapy.

The results appear online in the journal *Angewandte Chemie*.

"Essentially we have discovered the first small molecule that inhibits miRNA function. Moreover, our inhibitor of miRNA-21 is specific to that particular miRNA and disrupts the transcription of that specific miRNA" Deiters says. "The work represents a real paradigm change in the way we approach cancer drug discovery."

Citation: "Small-Molecule Inhibitors of MicroRNA miR-21 Function", Dr. Alexander Deiters, North Carolina State University, Dr. Qihong Huang, Wistar Institute, online in *Angewandte Chemie*

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