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Newly identified mechanism for silencing genes points to possible anti-cancer strategies

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Genes provide the instructions used by the individual cells to produce the many different proteins that make up the body. Scientists are only beginning to appreciate, however, the extraordinary degree of control exercised over every step of the production process.

Only about 10 percent of human genes, for example, are actively producing proteins in a given cell at a given time. The remaining 90 percent are silenced by a various mechanisms that act to interfere with gene transcription into messenger RNA or translation of messenger RNA into protein.

In a new study published online May 16 in the journal *Nature*, a team of scientists at The Wistar Institute and the University of California, San Diego, report identification of an important new gene-silencing mechanism, one that blocks the cellular machinery responsible for translating messenger RNA into proteins at specific genes.

The findings suggests that small bits of RNA known as microRNAs, known to help regulate genes but not used for protein production, may be operating in a completely novel way to prevent genes from producing proteins. MicroRNAs have been implicated in a number of cancers, and the newly outlined gene-silencing mechanism offers promising potential targets for anti-cancer interventions.

"Some microRNAs closely match their sequences against particular messenger RNA sequences to target them for destruction," explains

Ramin Shiekhattar, Ph.D., a professor in the Gene Expression and Regulation Program and the Molecular and Cellular Oncogenesis Program at Wistar and senior author on the new study. "That's one way we know that microRNAs can silence genes. That mechanism requires extraordinary specificity, however, and we suspected that microRNAs were also acting in some other way to inhibit gene translation into protein. By tracking the associations between molecules involved in generating microRNAs and other molecules in the cell, we uncovered an entirely new pathway, one that led us to a mechanism that blocks the cellular machinery that produces protein from messenger RNA."

In earlier studies, Shiekhattar identified a three-molecule complex known as RISC and showed that it plays a vital role in generating microRNAs. In the current study, Shiekhattar and his colleagues extended those studies to find that RISC also interacts with another complex that includes molecules required to build functional ribosomes. Ribosomes are cellular organelles responsible for translating messenger RNA into protein. Closer investigation showed that the new complex also included a component called eIF6. This molecule is known to interfere with the proper assembly of ribosomes, which prevents them from doing the work of translating messenger RNA into protein.

"We wondered if certain microRNA-responsive genes might be attracting microRNAs that then recruited eIF6 to that location," Shiekhattar says. "If so, the eIF6 would prevent the assembly of a competent ribosome, thus blocking messenger RNA translation at that gene. The result would be to silence that specific gene. We tested this idea in human cells and in worms and found it to be the case in both. Interestingly, this not only supported our hypothesis, but to see it in such different organisms also suggested that the mechanism involved has long been conserved in evolution."

Source: The Wistar Institute