It slices, it dices, it silences: ADAR1 as gene-silencing modular RNA multitool

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RNA, once considered a bit player in the grand scheme by which genes encode protein, is increasingly seen to have a major role in human genetics. In a study presented in the April 25 issue of the journal *Cell*, researchers from The Wistar Institute discovered how the RNA-editing protein, ADAR1, also combines with the protein called Dicer to create microRNA (miRNA) and small interfering (siRNA). These varieties of RNA, in turn, play a crucial role in gene regulation—silencing or "switching off" the production of specific proteins.

Upward of 60 percent of mammalian genes are thought to be targeted and regulated by non-coding RNA molecules, researchers say. This aspect of RNA biology is so critical to life, in fact, that the Nishikura laboratory demonstrated how a lack of ADAR1 was lethal in embryonic mice.

"Our evidence suggests that regulation of the microRNA synthesis is critical for life, and we have determined that the regulation is orchestrated by the RNA editing protein ADAR1," said Kazuko Nishikura, Ph.D., a professor in Wistar's Gene Expression and Regulation program and senior author of the study. "We see here this remarkable evolutionary ingenuity, where ADAR1 can combine with other enzymes to serve different roles in RNA functions, like a molecular Swiss army knife."

The genome, in the form of DNA, contains the instructions for both new proteins and the RNA that helps regulate how protein production is

controlled. No longer just seen in the form messenger RNA (mRNA)—delivering transcribed genetic blueprints from DNA to the cellular factories that build proteins. Numerous varieties of RNA, such as non-coding RNA, have been described that hold important roles in many facets of our cellular biology. "Non-coding RNA that do not code for proteins seem to have an overt and pervasive role in overseeing our genome," Nishikura said.

For more than 20 years following the discovery and definition of the ADAR family of proteins, Nishikura's laboratory has been a leader in the study of RNA biology. The ADAR proteins (the acronym stands for "Adenosine deaminases acting on RNA") literally edit RNA molecules, changing the "letters" of RNA from A to I (turning the adenosine subunit of RNA into the inosine subunit). A to I alteration can significantly affect biological function, such as altering brain chemistry, for example, by influencing the production of neurotransmitters.

In response to recent reports that ADAR1 was antagonistic to the chemical pathways that determine how RNA silences genes, Nishikura found, to the contrary, that the protein was a critical part of the process. The ADAR1 molecule operates as a "dimer," where two copies of ADAR1 bind together to form the complete protein. As Nishikura determined, a single copy of ADAR1 binds to the Dicer protein, a protein known to literally chop RNA molecules into miRNA.

This ADAR1-Dicer arrangement has the effect of helping to feed RNA to the enzyme. Additionally, ADAR1 helps load these newly-born miRNAs into RNA-induced silencing complexes (RISCs), large arrangements of multiple proteins that incorporate miRNA or siRNA, in order to target and neutralize specific messenger RNA molecules, thereby preventing a specific gene from producing a protein.

"The RNA regulation of our genome is still a field in its infancy,"

Nishikura explained. "The ability to regulate genetics in this way is amazingly versatile and powerful. It is also a field that has many potential lessons—or direct applications—for human medicine."

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