Killing the messenger RNA -- But which one?

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Tiny molecules called microRNAs, only 19 to 21 nucleotides in length, are able to effectively silence sometimes large sets of genes. They do this by specifically binding to and neutralizing another form of RNA called messenger RNA, responsible for conveying the information from genes to the cellular machinery that uses that information to create proteins, the building blocks of the body. Several hundred species of microRNAs have been identified to date, and increasingly they are being seen as vitally important players in regulating the genome.

Now, a new study led by researchers at The Wistar Institute shows that these microRNAs can undergo a kind of molecular editing with significant physiological consequences. A single substitution in their sequence can redirect these microRNAs to target and silence entirely different sets of genes from their unedited counterparts. Further, errors in the editing can lead to serious health problems. The team's findings appear in the February 23 issue of *Science*.

"What we found was that, in certain cases, edited versions of these microRNAs are being produced that differ from the unedited versions by only a single nucleotide change," says Kazuko Nishikura, Ph.D., a professor in the Gene Expression and Regulation Program at Wistar and senior author on the study. "These edited microRNAs are not encoded in the DNA, which means that at least two versions can being produced by one gene. This was not anticipated – it was something really new.

"Looking more closely, we realized that the substitution we'd identified occurred in a particularly critical region of the molecule, the first 7 or 8

nucleotides – out of a total of only 19 or 21 – that define the molecule's target specificity. This suggested that the change might well redirect these edited microRNAs to silence entirely different sets of genes from the unedited versions."

Using bioinformatics tools to compare the unedited and edited versions of only one species of microRNA against data banks of known gene sequences, the scientists identified two different groups of about 80 genes each likely to be targeted by the two versions of the molecule. They then selected three genes from each group for a closer look, testing to see whether their expression was in fact altered, up or down, by the microRNAs. It was.

Then they chose one potentially affected gene at random to explore the ramifications of microRNA editing in depth. As it turned out, the gene they selected, known as PRPS1, codes for an essential enzyme involved in synthesizing uric acid. If levels of the enzyme are poorly regulated, a number of health problems can arise. For example, too-high levels of the enzyme can cause uric acid levels to rise in the blood, triggering painful episodes of gout. Similarly, in the brain, excess uric acid can damage sensory neurons and cause deafness.

Working with a strain of transgenic mice unable to perform RNA editing and normal control mice, the researchers found that a complete lack of the edited version of the microRNA in question had the effect of driving production of the PRPS1 enzyme to about double its normal levels. This, in turn, drove levels of uric acid up to about two times what they should be.

"This confirmed that our original computer prediction of differential targeting by unedited and edited microRNAs of different sets of genes is likely to be correct," Nishikura says. "And in at least the case of the one gene we investigated, this differential has physiological consequences

seen in the elevated uric acid levels."

Given the fact that the PRPS1 gene was randomly selected for investigation by the researchers, the findings suggest that a number of other as-yet unidentified disorders may also have their roots in this newly identified microRNA editing process.

Source: The Wistar Institute