

Scientists determine how precursors of gene-regulating small RNAs are sorted by cellular machinery

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A team of scientists at Cold Spring Harbor Laboratory (CSHL) has determined a hierarchical set of criteria that explain how the molecular precursors of gene-regulating small RNAs are sorted by the cellular machinery.

Led by Benjamin Czech, a group working in the laboratory of CSHL Professor Gregory Hannon posed the question: can distinct patterns be observed in the process that unfolds when double-stranded RNAs enter the RNAi pathway? Shorthand for [RNA interference](#), RNAi is a biological response to double-stranded RNA that can culminate in the regulation of [gene expression](#). It has been observed in a vast range of organisms ranging from plants to worms to flies to man.

An enzyme called Dicer cuts double-stranded RNAs into smaller double-stranded pieces called duplexes. Czech, Hannon and colleagues propose rules governing the next step in the RNAi pathway, in which duplexes are sorted to proteins called Argonautes which are at the core of a molecular complex called RISC (the RNA-Induced Silencing Complex).

"Only one strand of each duplex is chosen," explains Czech, "and which one makes all the difference. In the fruit flies that we used as models for this series of experiments, the selection of one or another strand effectively determines whether the short [RNA](#) will seek out and regulate a gene, or whether it will perform another function such as protecting a

cell against a viral invader."

The rules determining how a duplex is processed and sorted are discussed in a paper the team published recently in *Molecular Cell*. These include the overall arrangement of the [nucleotides](#) in the duplex; how many bases are paired; where they're paired and unpaired; and how tightly the ends of the duplex are stuck together.

"These rules for sorting are important for two reasons," according to Hannon, who is also an Investigator of the Howard Hughes Medical Institute. "One is that since small RNAs play critical biological roles in nearly every process, understanding which strands of the small RNAs entering RISC act as regulators of gene expression is critical for our fundamental understanding.

"The rules are also important because scientists are hoping to use small RNAs one day as therapeutics. By understanding the rules by which small RNAs are processed and sorted, we move closer to the goal of being able to manipulate the RNAi pathway, bend it to the purpose of addressing disease."

More information: "Hierarchical Rules for Argonaute Loading in *Drosophila*" appeared in *Molecular Cell*, Vol. 36, No. 3. The authors are: Benjamin Czech, Rui Zhou, Yaniv Erlich, Julius Brennecke, Richard Binari, Christians Villalta, Assaf gordon, Norbert Perrimon and Gregory J. Hannon.

Provided by Cold Spring Harbor Laboratory

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