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Novel riboswitch measures glycine

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RNA self-regulation is as complex and sophisticated as protein-based gene regulation, according to a report in Science this week. A novel *Bacillus subtilis* riboswitch as described by the authors is an efficient and highly sophisticated on or off control mechanism, with a key regulatory role of switching between burning glycine for energy and using it for protein synthesis.

The riboswitch is the first example of a riboswitch that involves complex binding interactions comparable to multiple protein interactions, according to Ronald R. Breaker's group at Yale University, and is the only one so far discovered that switches on gene expression if activated instead of responding in a simple negative-feedback fashion to levels of their target compound.

The riboswitch has two domains that bind to glycine, while all other riboswitches only have one binding domain, Breaker said. "Binding of one ligand at one binding site improves the binding affinity of the second ligand to the second binding site," he told us. "This allows the riboswitch to sense much smaller changes in ligand concentration." Most riboswitches will significantly change the expression of the genes over about a 100-fold change in concentration of ligand, but this one requires only about a tenfold change in concentration of the ligand, making it very sensitive, Breaker said.

In addition the aptamer - the part of the RNA sequence that binds the ligand - is exquisitely sensitive and specific, according to David M.J. Lilleyat the University of Dundee. "Glycine is a pretty small undistinguished molecule, and it is quite remarkable that RNA constantly surpasses its ability to act as a recognition macromolecule in a similar way to protein," Lilley told us.

The riboswitch differentiates between glycine and alanine, in which "the only difference there is CH2. In one case its side group is a proton, and in the other case it's a methyl group. That's a remarkable feat of distinguishing in terms of molecular recognition," said Lilley, who was not involved in the study.

But scientists cannot agree whether the riboswitch represents an ancient or modern form of genetic control. "I'm not as eager to buy into the point of view [that] this is a literal fossil of the RNA world but as a proof of principle of the kind of function of RNA that one could have seen," Gerald F. Joyce, professor at The Scripps Research Institute, told us. He said Breaker had done a lot of bioinformatics analysis to suggest they might be present in mammals, "but the burden of proof is so high in the field now, one has to actually show this ligand binding domain does control gene expression, that it's a live player."

Joyce, who is Breaker's former supervisor but was not involved in the study, added, "That's a tougher goal in eukaryotic cells, but that's the next big thing that people are waiting for."

While acknowledging the jury was still out, Breaker said he favored the idea of the switch being a version of a fossil mechanism dating from the RNA world. "This switch might have come from those earliest organisms that did not have proteins to serve as molecular switches, and in fact observing this switch in modern cells is precisely what the RNA world hypothesis is predicting. RNA should have been sophisticated enough to do this kind of thing four billion years ago," Breaker said.

"In my opinion, riboswitches are the oldest regulatory system we know," said Mikhail Gelfand, a professor at the Institute for Information Transmission Problems in Moscow, who was also not involved in the study. "There are examples of riboswitches in all three domains of life," and their discovery in fungi, plants and archean bacteria suggested their antiquity, he told us. In addition, it pointed to the possibility that such riboswitches would also be found in mammals. "We are not that very different from fungi and plants," he quipped.

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