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Riboswitch Flips to Control Magnesium

Magnesium, essential for energy-production and structural integrity, is critical to cell survival. Researchers have now found that cells use specialized segments of RNA called riboswitches to ensure that there is an adequate supply of the mineral. The newly described riboswitch can both sense magnesium levels and respond directly by regulating production of a magnesium transport protein.

Riboswitches are a recently discovered class of gene expression regulators. They control gene expression through a segment of messenger RNA (mRNA)--the copy of a gene that is used to produce a protein--that interacts with a target molecule to regulate its own translation into protein. Usually, the protein regulated by the riboswitch is part of the cellular machinery that regulates the levels of the target molecule.

In this case, the riboswitch lies on an mRNA that the cell uses to produce a transporter protein that carries magnesium into the cell. When the switch detects that magnesium has dropped to too low a level, it can boost the translation of the RNA--meaning the cell produces more of the transporter protein, thereby correcting the magnesium deficiency.

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- Eduardo A. Groisman

The discovery, which was described in an article published in the April 7, 2006, issue of the journal *Cell*, is important for two reasons, said Howard Hughes Medical Institute investigator Eduardo A. Groisman. First, the finding solves a biological puzzle about one of the cell's most important--albeit underappreciated--substances, he said.

Every energy-producing reaction in the cell depends on magnesium as an accompanying cofactor for the cell's main energy molecule, ATP.

Magnesium is also essential for the stability of the cell's membranes and its protein-producing ribosomes. Nevertheless, almost nothing was known about how the cell senses low magnesium levels, said Groisman, who is at the Washington University School of Medicine.

The finding also helps advance understanding of how riboswitches regulate gene expression, which is quite different from the more familiar regulation by proteins called transcription factors. The discovery is also important because, while riboswitches are known to respond to many substances in the cell, such as amino acids and sugars, this is the first that has been found to sense a charged atom, called an ion, Groisman said. "This is the first example of an ion-regulated riboswitch, and I am sure there will be others," Groisman noted. "And they will likely be involved in similar sensing mechanisms."

The proteins that transport magnesium into the cell--MgtA and MgtB--had been known for decades, Groisman said. And he and his colleagues discovered a decade ago that a regulatory system they called PhoP/PhoQ switches the genes for the transporters on or off in response to changing magnesium levels. "But before this work, it wasn't suspected at all that a riboswitch might sense magnesium levels in the cell," Groisman said.

"Although there was no reason to think there should be any additional regulation, we found evidence that there was, indeed, an independent magnesium sensor in the cell," he said. One piece of evidence came in the form of a mutation in the *Salmonella* bacterium that the researchers studied. That mutation in the PhoQ protein should have rendered the cell unable to respond to low magnesium levels, but the transporter genes remained sensitive to fluctuations in the mineral, said Groisman.

So, the researchers decided to analyze in detail how the mRNA molecule for mgtA responded to magnesium, in hopes of discovering a basis for magnesium-sensing. To do so, they dissected the function of the components of the *Salmonella* bacterium's mRNA for mgtA by systematically altering those parts' function and observing the results.

Their studies revealed that a region at one end of the mRNA molecule--which is not translated into the MgtA protein--responded to levels of magnesium. A specific structure in this untranslated region, they showed, adopted different shapes depending on the level of magnesium in the bacterium.

"Although we still have much work to do to understand the system, our analysis indicates that, in response to different magnesium levels, these different structures either allow or prevent the full-length messenger RNA from being translated," said Groisman. He noted that the sequence of the untranslated region is conserved across many organisms, which indicates that it has a critical regulatory role.

In further studies, Groisman and his colleagues hope to understand in greater structural detail how the riboswitch senses magnesium levels--pinpointing the particular part of the molecule influenced by magnesium. Also, he said, the researchers will seek to understand how this magnesium sensor applies the brakes on translation of the mRNA into the magnesium transporter protein, MgtA.