

From a lowly yeast, researchers divine a clue to human disease

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Working with a common form of brewer's yeast, University of Wisconsin-Madison researchers have uncovered novel functions of a key protein that allow it to act as a master regulatory switch -- a control that determines gene activity and that, when malfunctioning in humans, may contribute to serious neurological disorders.

The work, published in the Dec. 8 issue of the journal *Molecular Cell*, shows how a mutation in a single gene can have widespread effects on regulation of the genetic program in a cell, causing some genes to be read more than normal and others less than normal.

While nearly every cell in an organism contains a complete set of DNA, each individual cell uses only a small fraction of that information at any given moment, explains David Brow, the senior author of the new study and a professor of biomolecular chemistry in the UW School of Medicine and Public Health. A host of proteins are responsible for controlling which genetic messages are read and how much of the information is used. Working with yeast, Brow and his colleagues show that a protein called Sen1 plays an important early role in this process.

Mutations in the human version of Sen1 are linked to neurological diseases, including a rare form of amyotrophic lateral sclerosis, also known as ALS or Lou Gehrig's disease, and movement disorders. By exploring how Sen1 works in yeast, Brow provides a powerful tool other researchers can use to better understand the interplay of the protein and gene regulation in human disease.

"This work gives a method to start examining what the defect is in humans," he says.

In the past, says Brow, researchers looked at regulation of individual genes but not the whole genome at once. Using yeast, a small and relatively simple organism, the Wisconsin group developed a method to get a broad view of how Sen1 works and what happens when it doesn't work properly.

Normally, Sen1 acts like a molecular stop sign, telling another protein called RNA polymerase II when to stop transcribing genetic information from DNA into related threads of RNA. The polymerase reads along DNA strands, building RNA as it goes. Multiple genes strung along a single length of DNA are separated by gaps to mark boundaries. As the polymerase reaches the end of a gene, Sen1 flips a switch and knocks it off the DNA track.

The group, led by Brow and Eric Steinmetz, compared normal yeast to a strain with a mutated form of Sen1 that does not see the stop signal. "The Sen1 mutant reads right through the stop sign and keeps going," Brow says.

Without a properly functional Sen1, RNA polymerase II "reads through" the end of the gene and builds longer and longer RNA messages. "In some cases it doesn't have a big effect," Brow says. "Other times, it's a big problem," like when another important gene is right next-door on the same piece of DNA.

Like run-on sentences, long RNAs from multiple genes are confusing and hard or impossible for the cell to use. "It really messes up a lot of things, not just the read-through gene but also adjacent genes," Brow says.

In other cases, Sen1 stop signs near the beginning of some genes normally prevent RNA polymerase II from making RNA from those genes. Sen1 mutations, on the other hand, allow access to these messages, triggering genes that normally aren't operational.

These garbled genetic messages -- whether with too much or too little genetic information -- can disrupt the normal functions of cells and, in some cases, lead to disease. Sen1 mutations are likely to have similar effects in humans, says Brow. By adapting his approach, other researchers may be able to identify specific genes affected in the human Sen1-linked neurological disorders.

Source: University of Wisconsin-Madison

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