Novel mechanism for control of gene expression revealed

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Dr. David Levin, Professor of Molecular & Cell Biology at Boston University Henry M. Goldman School of Dental Medicine and Professor of Microbiology at Boston University School of Medicine discovered recently a novel, evolutionarily conserved mechanism for the regulation of gene expression. The study describing this work titled, "Mpk1 MAPK Association with the Paf1 Complex Blocks Sen1-Mediated Premature Transcription Termination," appears in the March 4 issue of *Cell*.

Normal cell growth, embryonic development, and responses to stress, require proper spatial and temporal control of gene expression. Studies on control of transcription (RNA biosynthesis) are typically centered on understanding how the RNA polymerase is recruited to the promoter, the control region of a gene. However, new work from Levin and postdoctoral fellow, Ki-Young Kim, has revealed the existence of a second level of control in a yeast model system.

They found that genes expressed solely under certain stress conditions are normally maintained in a silent state by a process called transcriptional attenuation. In attenuation, the RNA polymerase initiates transcription of the gene, but its progress is terminated prematurely by a termination complex that binds to the polymerase. Attenuation occurs commonly in bacteria, but was not previously known to operate in eukaryotic cells (those with a nucleus).

"In response to an inducing stress signal, attenuation must be overcome so that a target gene can be expressed," said Levin. "The way that works

in this instance is that an activating transcription factor, called Mpk1, serves double duty—it is first responsible for recruitment of the RNA polymerase to the promoter, but Mpk1 then binds to the transcribing polymerase to block association of the termination complex."

Mutations in a human protein, called Senataxin, which is related to a component of the yeast termination complex, are responsible for causing juvenile-onset forms of ALS and ataxia, two neuromuscular degenerative diseases.

In their newest research, Levin and Kim show that the discovered attenuation mechanism is evolutionarily conserved in humans. "The findings of this research have broad implications that translate to human cells," said Levin. "We know that when the key yeast proteins are replaced by their human counterparts, they are able to engage in the same interactions to exert control over attenuation."

Levin believes that attenuation is actually a widespread phenomenon. "Approximately 10% of yeast genes appear to be under attenuation control, which suggests that it may also be common in humans," said Levin. "This opens the door to the possibility of new approaches to therapeutic gene silencing, now that we know transcriptional attenuation operates in eukaryotic cells and that it's a regulated process."

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