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"Remote Control" for Expression of Human Growth Hormone Gene

Mistakes in expression implied in growth disorders

Researchers at the University Of Pennsylvania School Of Medicine recently discovered a novel mechanism that works over an extensive genomic distance and controls the expression of human growth hormone (hGH) in the pituitary gland. This mechanism involves a newly discovered set of "non-coding RNAs" expressed in the vicinity of the hGH gene. By examining the relationship between these non-coding RNAs and the hGH gene, researchers hope to understand how these remote regions impact hGH gene expression and dysfunction. Such insight may aid researchers in the development of therapeutics for growth hormone defects and lead to a greater understanding of the causes of other genetic disorders. The human genome is comprised of both non-coding DNA and coding regions, or genes. While researchers once believed that only genes were transcribed into messenger RNA (mRNA), investigators have recently discovered that non-coding DNA is copied into mRNA as well. Unlike coding mRNAs, which are translated into functional proteins and peptides, the function of most non-coding RNAs is unclear. Although non-coding RNAs fail to produce functional proteins, researchers believe that in some cases these RNAs may control gene expression. Using a genetically modified mouse model, Nancy E. Cooke, MD, Stephen A. Liebhaber, MD, Professors of Genetics and Medicine, and colleagues, demonstrated a critical role of two non-coding regions on the activation of the hGH gene. They described their recent findings in the August issue of *Molecular Cell*. Synthesized by the pituitary gland, human growth hormone activates growth and cell reproduction. In addition to serving as a major contributor to height growth during childhood, hGH plays a role in strengthening bones and increasing muscle mass throughout life. While mutations to the hGH gene often lead to abnormal growth in children and adults, these mutations have provided researchers with key clues regarding the genomic areas that appear to control expression of the hGH gene. Previous work in the laboratories of Cooke and Liebhaber found that the hGH gene is controlled by a non-coding DNA region, or locus control region. Remarkably, this region is located more than 14,000 base pairs away from the hGH gene. At the genomic level, a 14,000 base-pair separation is equal to the size of 10 growth hormone genes lined end to end. "The effects of the locus control region on human growth hormone expression is as if you turn a key in the lock of a house at one end of your street, and find that this action opens the lock and door of a house a block away," notes Liebhaber. By carefully analyzing the 14,000 base pairs separating the hGH gene and its locus control region, co-authors Yugong Ho, PhD, an Instructor of Genetics at Penn and a Cooke/Liebhaber lab member, and Felice Elefant, PhD, Assistant Professor at Drexel University and former member of the Cooke/Liebhaber lab, found that the locus control region was copied into RNA, and discovered a gene called CD79b within this region. Remarkably this CD79b gene was also copied into RNA in the pituitary. While the CD79b gene normally codes for a protein in blood lymphocytes, researchers discovered that CD79b appears to play a very different role in the pituitary gland. Here, CD79b was actively transcribed into mRNA, but this mRNA failed to translate into a functional protein. Instead, the non-coding RNA was suspected to play a role in hGH gene regulation. In order to determine whether the CD79b RNA in the pituitary gland served a function, Ho inserted a segment of human DNA that included hGH, the hGH locus control region, and CD79b into a group of mice. As a result, the transgenic mice expressed high levels of human growth hormone in the pituitary as well as mouse growth hormone. To test whether the transcription of the locus control region and CD79b played a significant role in hGH expression in transgenic mice, Ho then inserted a special piece of DNA into the locus

control region. This DNA insertion specifically blocked the copying of the CD79b gene into RNA in the pituitary. This blockade led to the five-fold repression of hGH gene expression. These findings confirm that the CD79b non-coding DNA actively contributes to hGH expression. The relationship between CD79b, the hGH locus control region, and the hGH gene may aid researchers in the development of treatments for patients suffering from hGH deficiency. "Our data predict that a subset of children with short stature and low growth hormone may be suffering from a mutation in the hGH locus control region, which blocks full levels of hGH gene activity," explains Ho. "We are now actively screening the appropriate clinical populations for such genetic defects." In the future, Cooke, Liebhaber, and Ho will continue to search for how transcription contributes to long-range activation of hGH gene expression through the development of new transgenic mouse models and the biochemical analysis of the hGH locus. "By understanding how non-coding DNA functions at the human growth hormone locus, researchers may be able to identify similar situations at other genetic loci," says Liebhaber. "With every step forward in understanding how genes are expressed, we increase our awareness of how naturally occurring and acquired mutations interfere with this process," adds Cooke. "Our research sets the groundwork for advances in diagnosis and eventual treatment of genetic diseases." These studies were funded by the National Institutes of Health.