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RESEARCH

Antibiotic Corrects Genetic Glitch

By Ricki Lewis

Antibiotics that enable ribosomes to "read through" premature stop codons (nonsense mutations), which truncate proteins, may kick-start a new approach to gene therapy. A team of researchers from the University of Alabama at Birmingham and from the Women's and Children's Hospital in South Australia applied a long-ago observation about the antibiotic gentamicin on ribosomes to correct the enzyme deficiency that causes Hurler syndrome, in cultured fibroblasts from patients.¹ The antibiotic apparently enables ribosomes to zip past nonsense mutations, in which a single base substitution converts an amino-acid encoding codon into a stop codon, shortening the protein product. "It's been known since the early 1960s that aminoglycoside antibiotics bind the 16S bacterial ribosomal RNA subunit, affecting translational fidelity, causing read-through of stop codons in bacteria. In mammalian ribosomes, the region is similar but it has a lower binding affinity, and that's why these antibiotics kill bacteria before they kill people. We show that the concentrations of antibiotic used clinically to kill bacteria are tweaking mammalian ribosomes," explains **David M. Bedwell**, associate professor of microbiology at the University of Alabama.^{2,3}

The symptoms of Hurler syndrome--mental retardation, dwarfism, hearing loss, enlarged liver and spleen, and cardiac and respiratory problems--stem from deficiency of alpha-L-iduronidase, which normally breaks down glycosaminoglycans (a type of mucopolysaccharide) in the lysosomes of fibroblasts and white blood cells. Just a modest boost in enzyme production can lessen the severity of symptoms, but attempts at enzyme replacement therapy have failed. The researchers focused on Hurler syndrome because nearly two-thirds of the known mutations are nonsense. However, the investigators and others have also used the antibiotic to suppress nonsense mutations in cells from patients with cystic fibrosis,⁴ and in mice with muscular dystrophy.⁵ "This approach has tremendous potential. Aminoglycosides are just one type of antibiotic, and it works," says Bedwell. PTC Therapeutics of South Plainfield, NJ, is one step ahead--they are using high throughput assays to discover variations on the gentamicin theme that do not bring the side effects of kidney and ear toxicity.

Bedwell likens this new use for an old drug to the Viagra saga, where "a funny side effect led to a huge new market. You have to keep your eyes open and if you know the molecular mechanism, you can zero in on a treatment."

References

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