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Synthesis of proteins containing unnatural amino acids using reengineered bacterial ribosomes

While the bacterial ribosome is remarkable for its facility of polypeptide synthesis, it has been optimized for α -L-amino acid incorporation; other types of amino acids are incorporated poorly. To expand the repertoire of amino acids capable of being incorporated into protein, we have considered strategies for ribosome modification. Since the ribosome is a ribozyme, i.e. peptide bond formation is actually mediated by ribosomal RNA rather than protein, we have focused on rRNA modification. We have created libraries of *E. coli* each harboring a plasmid with the operon for 23S rRNA; these plasmids have been randomized in rRNA regions important for peptide bond formation. The antibiotic puromycin consists of a modified adenosine attached to an amino acid via an amide bond; it binds to the ribosomal A-site by virtue of its resemblance to the 3'-end of aminoacyl-tRNA. Puromycin accepts growing polypeptide chains from the P-site peptidyl-tRNA, thereby terminating protein synthesis. Puromycin is internalized by bacteria; these cells are killed by protein synthesis inhibition. In the belief that a structurally modified ribosomal A-site, having a geometry conducive to recognition of an unnatural (e.g. beta) amino acid, would also bind a puromycin analogue having the same type of amino acid, we surveyed our *E. coli* containing ribosomal RNA libraries for colonies sensitive to puromycins containing modified amino acids. The colonies so identified make normal proteins of good quality, but also exhibit enhanced incorporation of modified amino acids. Examples of the incorporation of D-amino acids, β -amino acids, modified dipeptides and dipeptidomimetics will be discussed.

Biography

Sidney Hecht obtained his PhD in Chemistry at the University of Illinois. He was an MIT Chemistry faculty member (1971-79) and was John Mallet Professor of Chemistry at UVa (1978-2008). He is Director of the Center for BioEnergetics in ASU's Biodesign Institute. He was an Alfred P. Sloan Fellow, a John Simon Guggenheim Fellow and an ACS Cope Scholar Awardee. Hecht was selected as Virginia's Outstanding Scientist for 1996. He received the 2011 ASU Faculty Achievement Award in Defining Edge Research: Innovation. He is Associate Editor of the *Journal of the American Chemical Society* and has published 440 research papers.

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