SYNTHETIC BIOLOGY

A genetic code for phosphoprotein production

Engineering the genetic code of bacteria and worms opens up new possibilities.

Phosphoproteins are abundant in eukaryotic cells and essential for their regulation. However, because phosphate groups are added post-translationally, phosphoproteins have been difficult to produce in quantities convenient for study. Now, researchers at Yale University and New England Biolabs have made such proteins by expanding the genetic code of *Escherichia coli* such that the amino acid phosphoserine can be incorporated site-specifically (Park *et al.*, 2011).

The researchers began with a transfer RNA (tRNA) and RNA-synthetase pair specific to *O*-phosphoserine, identified through basic research in methanogenic archaea. After engineering the tRNA to recognize a new codon, UAG (usually a stop codon), the researchers transferred genes coding for the tRNA and RNA-synthetase

into *E. coli* and added *O*-phosphoserine to the nutrient medium. They also had to engineer a bacterial protein known as EF-Tu, which monitors protein quality. EF-Tu was necessary to bind the introduced components, allowing the synthesis of proteins incorporating *O*-phosphoserine.

The researchers produced the constitutively active form of a kinase, MEK1, that contains *O*-phosphoserine on two residues. Although they isolated only 25 micrograms of protein from one liter of culture medium, the researchers expect the use of engineered *E. coli* strains that do not pause synthesis at the UAG stop codon to boost protein production tremendously, says Dieter Söll of Yale University, one of the corresponding authors. Researchers will also be able to study how the placement of the modified amino acid affects protein function. “You can make proteins with phospho-

serine in places where nature would not put it,” he says.

In separate work, researchers at the Medical Research Council Laboratory of Molecular Biology in Cambridge reported the first expansion of the genetic code in a multicellular organism (Greiss & Chin, 2011). They used translation machinery imported from *E. coli* to incorporate unnatural amino acids in proteins produced throughout *Caenorhabditis elegans*. This should allow the introduction of proteins primed for properties such as photomodification and purification.

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RESEARCH PAPERS

Greiss, S. & Chin, J.W. Expanding the genetic code of an animal. *J. Am. Chem. Soc.* **133**, 14196–14199 (2011).

Park, H.-S. *et al.* Expanding the genetic code of *Escherichia coli* with phosphoserine. *Science* **333**, 1151–1154 (2011).