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Counting Proteins

Proteomics: Single-molecule methods quantify bacterium's proteome

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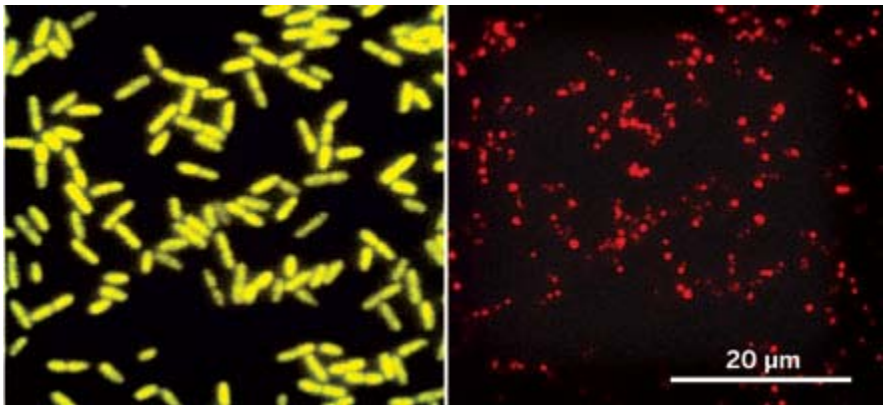

Science

At a given time, the levels of a YFP-labeled protein (yellow) and its corresponding mRNA (red) are uncorrelated, as shown in these fluorescence microscopy images of E. coli cells.

Researchers have quantified a significant fraction of the *Escherichia coli* proteome with single-molecule sensitivity in single cells (*Science* **2010,** *329,* 533). Such sensitivity allows quantification of proteins present at low abundance.

"It's the first time any proteome has been characterized with single-molecule sensitivity," says team leader X. Sunney Xie, a chemistry professor at Harvard University. "This allows us to evaluate protein levels across the entire range of protein expression." Xie likens the analysis to counting people in a census.

Paul J. Choi and Huiyi Chen, graduate students in Xie's lab, constructed a library of *E. coli* strains, with each strain containing genetic instructions to tag a different *E. coli* protein with yellow fluorescent protein (YFP). Using single-molecule fluorescence microscopy, postdoc Yuichi Taniguchi counted the YFP-tagged proteins to determine how protein expression differed across a population of genetically identical cells. The team found that 20% of *E. coli* proteins are expressed at extremely low levels, averaging less than one copy per cell. So far, they have measured the levels of more than 1,000 different *E. coli* proteins.

When they analyzed the cell-to-cell variation, or "noise," in protein production, the researchers found that the randomness of single-molecule biochemical processes dominates at low protein-expression levels. The statistical distribution of protein abundance depends on the messenger RNA production rate and the number of proteins generated per mRNA. At high expression levels, however, other factors such as heterogeneity of the mRNA production rate from cell to cell can account for the variation.

Jeff Hasty, a bioengineering professor at the University of California, San Diego, calls the work "a milestone in the ongoing efforts to understand how cells function when their constituent molecules exhibit a large degree of randomness." He notes that "the finding that a large number of intracellular proteins are present at extremely low copy numbers implies that stochastic effects are ubiquitous and highlights the importance of incorporating random fluctuations into quantitative descriptions of cellular function."

In addition, Gene-Wei Li of Xie's team simultaneously measured proteins and their corresponding mRNA. This analysis revealed that at any given time the amounts of a protein and its corresponding mRNA are uncorrelated. Xie and coworkers attribute this finding to differences in the lifetimes of mRNA and protein, with mRNA counts representing the most recent history, a minute or two before the measurement, and protein counts reflecting the distant past, time periods comparable to the cell cycle.

"The authors' approach is likely to be most reliable at low protein numbers, where noise effects are the strongest," says Terence T. Hwa, a biophysicist at UCSD. "It will be interesting to apply this approach to study some relevant biological problems in depth."

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