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EDITORIAL

Molecular Biology and the Transformation of Protein Science

A new journal is born with trepidation. The intellectual content and quality of the first issues set a tone that begets more of the same, and in time the early pattern becomes institutionalized. The challenge for *Protein Science* is to attract articles that have a substantial emphasis on the methods, concepts, and problems of cell and molecular biology, as they relate to the behavior and properties of proteins. Without these papers, the Journal could be left with a predominantly technical emphasis on methodologies and the theoretical analyses of proteins as chemicals and polymers. This mistake would make *Protein Science* just an average journal for the specialist.

Protein science now depends more on molecular biology than on any of the classical chemical or physical methodologies that characterized the earlier years of the field. Virtually every area has been transformed by the cloning, sequencing, expression, and mutagenesis of genes that encode specific proteins. The character of molecular biology differs sharply from the chemically oriented historical approaches to protein analysis, and for that reason protein science means different things to different people. Should the Journal fail to bridge this dichotomy and to reflect the transformation of protein science by molecular biology, then it cannot hope to be preeminent.

The legacy of molecular biology is pervasive. The greatest impact of molecular biology on protein science has been on the rate of acquisition of new protein sequences. The exponential growth of protein sequences has catalyzed the organization of computer data bases and a myriad of new analytical methods for sequence comparisons. The prediction of protein structures from sequences has advanced significantly because of the large number of sequences available for the same protein and the constraints that the collective comparisons place on possible structures. Similarly, the study of protein evolution has been transformed by the growth in the number of known sequences. In this sense, molecular biology has driven the fields of protein structure prediction, protein design, and protein evolution.

The center of protein science has shifted more toward functional analysis, and it is molecular biology that drives the functional analysis of proteins, including mechanistic enzymology. Functional analysis advanced greatly when site-specific chemical modifications were introduced, as highlighted by the early studies on carboxymethylation of active site histidines in ribonuclease A and the covalent modification of active site serines in serine proteases. These chemical approaches, along with pH-rate profiles, were among the early mainstays of mechanistic enzymology. But today's protein science uses molecular biology to identify active sites, change active sites, alter pH-rate profiles, and distinguish between mechanisms, all by manipulations of the gene for the encoded enzyme. The standards and expectations of the field have been raised sharply, and it is difficult to defend approaches to functional analysis that fail to utilize the obvious advantages of molecular biology.

Molecular biology has also facilitated the rapid acquisition of new information about the forces that stabilize protein structures. Proteins with alternative packing arrangements of hydrophobic cores, interior cavities, reversed salt bridges, and greater thermal stabilities are now available. As much as anything, these creations of molecular biology have taught how much we have yet to learn. But they have also suggested the next experiment, using the same tools of molecular biology. Even X-ray and NMR analyses of protein structures have been affected, in part because of the greater availability of proteins and protein fragments that are produced by gene cloning and expression systems, and in part because of the specific questions about determinants of protein structure that can be addressed with rationally designed mutants. In fact, without the functional analysis made possible by molecular biology, the interpretation of function from structure alone is generally not possible.

New applications of molecular biology will continue to transform protein science. Examples include the further exploitation and development of catalytic antibodies, the design and production of minimalist enzymes, and the replacement of multiple polypeptides with single chains, as exemplified with single chain antibodies and single chain receptors. In another vein, nonnatural amino acids are now placed into specific locations in proteins by the use of in vitro systems that translate a messenger RNA that has an amber codon placed at a predetermined location within the coding sequence. The amber codon is decoded by a tRNA amber suppressor charged with the desired nonnatural amino acid. This approach expands further the power of functional analysis.

Whereas much of what has been done in the past has

focused on the behavior of single proteins, major conceptual advances in the next decade will come from the multiprotein systems of cell biology. Signal transduction pathways, protein trafficking, cell-cell interactions, cytoskeleton assembly, the photosynthetic reaction center, protein-dependent RNA splicing, and histocompatibility complexes illustrate the phenomenal capacity of proteins to assemble sophisticated functional units. For the protein scientists, these systems represent some of the greatest technical and conceptual challenges of the next decade. And just as molecular biology has transformed protein science, protein science is transforming cell biology. The transformation of cell biology by protein science is evident in the structural studies of multiprotein complexes, and in the functional analysis of the assembly of signaling pathways, RNA splicing, transcription complexes, and so on.

As applications of cell and molecular biology grow, new questions will be raised about forces that stabilize proteins at high temperatures or in nonaqueous systems, about the relative contributions of hydrophobic, electrostatic, and solvation forces, and about structure predictions. While these questions fall in the domain of classical protein chemistry, they take on new meaning and rigor because molecular biology offers a reality check on many of the physical and chemical hypotheses that are advanced about protein structure, stability, and function. The properties of just one mutant—the right mutant—can completely change a specific argument or hypothesis. These experimental tests provide a way for the classical areas of protein analysis to be integrated with the protein manipulations of molecular biology.

To be sure, the enabling technology for some of the major applications of molecular biology has its roots in classical chemical analysis. The direct sequencing of 10–20 amino acids of picomole amounts of a scarce protein has provided sufficient information to design oligonucleotide probes to clone the gene or cDNA so that the entire translated DNA sequence can be obtained and the protein can be produced in quantity. Likewise, new chemical methods applied to proteins provide their own reality check on polypeptide sequences that are based on translating DNA sequences, because the translated sequences reveal nothing about posttranslational protein processing. The recent methods for C-terminal protein sequencing and the determination of sequences and molecular weight by mass spectrometry take the analysis and characterization of proteins far beyond the inferred information generated by molecular biology. Still, once the basic facts about a protein are established, the technologies of molecular biology are essential for functional analysis.

For this new Journal, the worry is that, given the pervasive influence of molecular biology, the Journal will grow in a way that fails to reflect that influence. How well a paper is written or how well the science is done is not in itself sufficient to justify publication. Protein science may be different things to different people, but what counts in the end is the impact of the results on the field. This has to be the first criterion by which papers are selected for publication. With this in mind, the transformation of protein science by molecular biology, and the transformation of cell biology by protein science, should be no more evident than in the pages of *Protein Science*. If this happens, then *Protein Science* will make its mark as a leading journal.

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