Biochemistry matters

Arthur Kornberg

Fashions prevail in science as in all human affairs. In recent years, biochemistry has become less fashionable, but there is no doubt that the discipline is important for the full understanding of biology.

A recent editorial in this journal, "In praise of biochemistry"[1], made the case for the classic biochemical approach of fractionating and isolating enzymes from a cell-free system toward understanding a biological event. Is it simply semantics that the title of this journal does not contain biochemistry but, rather, its extension to the structures and biological functions of enzymes? Biochemistry matters because it does something that genomics, proteomics and other 'omics' cannot yet do.

Examples abound in which assays in a cell-free system, followed by isolation of discrete proteins, have given us our major insights into fermentation, bioenergetics, transcription, translation, intracellular trafficking and the replication, repair and recombination of DNA. What naturally followed was to determine how the structure of these proteins could account for their functions and fit them in the biology of growth, development and senescence.

In our everyday lives, we are asked to choose the ten best among destinations, movies, albums and so on. For some years, I have played this game with the more compelling title "The Ten Commandments of Enzymology"[2]. Such a list, dictated by personal experience and taste, requires periodic amendments[3] and reordering but, the first commandment, reaffirmed over many years, has remained: "Thou shalt rely on enzymology to resolve and reconstitute biologic events." The universality of biochemistry, manifested in the conservation of the functions and sometimes even the structures of these proteins in the billion-year evolution from bacteria to humans, is one of the greatest revelations in the history of science.

Enzymes have three faces. Most thoroughly examined, in atomic detail, is the 'catalytic face' as seen in the isolated state. How the enzyme catalyzes reactions in a cell must be inferred with insights provided by genetic and environmental manipulations. Reaching farther is a view of the 'regulatory face' of an enzyme, exquisitely controlled in rate and range by other proteins, allosteric effectors and a large variety of covalent modifications. Still beyond and of great importance is the third face, the 'social face' of an enzyme. Few, if any, enzymes are freely diffusible in a cell. Rather they are organized in a tight community of 'somes' attached to nucleic acids, polysaccharides, lipids and polyphosphate on membranes and cytoskeletons. Every detail of these associations is essential for the efficient performance of an oriented multistep pathway.

My own odyssey to track the social faces of enzymes was the 30-subunit replisome machine of DNA replication moving at an error-free rate in excess of 1,000 base pairs per second. After a happy, 40-year marriage to this venture, I turned some dozen years ago to an older but far less glamorous polymer than DNA. It is inorganic polyphosphate (poly-P), a chain of hundreds of phosphate residues linked by ATP-like bonds.

Conserved from prebiotic times and abundant in every bacterial, fungal, plant and animal cell, it had for lack of assigned functions been regarded as a 'molecular fossil'[4]. Obeying the First Commandment, I sought the enzymes that made and used poly-P. With their isolation and the cloning, overexpression and mutation of their genes, we showed that poly-P is essential for bacterial responses to stresses and starvation and for bacterial survival[4]. In many of the serious pathogens, mutants lacking the conserved poly-P kinase (PPK1), the enzyme responsible for the synthesis of poly-P, are deficient in growth, motility, biofilm formation and virulence in animal models[5].

We have sought and isolated a novel PPK (PPK2) from the eukaryote *Dictyostelium discoideum*. Astonishingly, this PPK proved by every criterion to be an actin, one of the wide number of cytoskeletal tracks essential for a variety of cellular movements. This 43-kDa polypeptide assembles and disassembles the two polymers at once: actin filaments and poly-P in a tightly linked fashion (M.R. Gomez-Garcia and A.K, unpublished results). Now we wonder how the social activities of such an enzyme employing poly-P may be involved in the myriad, motor-based activities of a cell.

F.G. Hopkins, one of my favorites of all time, who did more than any one to make nutrition a science, said of the biochemist in 1931 (ref. 6), "He should be bold in experiment but cautious in his claims. His may not be the last word in the description of life, but without his help, the last word will never be said." Sydney Brenner, one of the founders of molecular biology, said as much in "Biochemistry strikes back"[7]. Having mused that both communism and biochemistry had disappeared by 1990, Brenner explained that "protein interactions will not be solved by proteomics or protein chips but by protein biochemistry… [which] provides the only experimental basis for causal understanding of biological mechanisms."

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