frontiers | Frontiers in Chemical Biology

TYPE Editorial
PUBLISHED 07 February 2025
DOI 10.3389/fchbi.2025.1565931

OPEN ACCESS

EDITED AND REVIEWED BY
Mi Hee Lim,
Korea Advanced Institute of Science and Technology (KAIST), Republic of Korea

*CORRESPONDENCE
Justin M. Miller,
justin.miller@mtsu.edu

RECEIVED 23 January 2025
ACCEPTED 27 January 2025
PUBLISHED 07 February 2025

CITATION
Miller JM and Offenbacher A (2025) Editorial: Structure-function relationship of enzymes through a chemical lens.
Front. Chem. Biol. 4:1565931.
doi: 10.3389/fchbi.2025.1565931

Editorial: Structure-function relationship of enzymes through a chemical lens

Justin M. Miller[1]* and Adam Offenbacher[2]

[1]Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN, United States,
[2]Department of Chemistry, East Carolina University, Greenville, NC, United States

KEYWORDS

enzyme structure and function, enzyme, editorial, biophysics, special issue

Editorial on the Research Topic
Structure-function relationship of enzymes through a chemical lens

The relationship between molecular or biomolecular structure and function remains an active area of investigation within the life sciences. As fields like biotechnology, drug discovery, or genetic engineering push the boundaries of what is possible, advancing our understanding of molecular processes becomes increasingly important. On the other hand, an array of technologies may not even exist without the knowledge that basic science research in these areas has provided. For example, the COVID-19 vaccines would not exist in the absence of the foundational insights provided by research into mRNA biology, synthesis, and related lipid nanoparticle delivery systems (Brenner et al., 1961; Cobb, 2015; Dounce, 1952; Work and Campbell, 1953; Gros et al., 1961; Jacob and Monod, 1961; Watson, 1963; Kowalski et al., 2019; Guan and Rosenecker, 2017; Xiong et al., 2018; Hajj and Whitehead, 2017; Pardi et al., 2018). Another, often overlooked, example is that of restriction enzymes, which were originally studied by researchers seeking to understand bacterial immune systems (Roberts, 2005; Loenen et al., 2014). Indeed, the Nobel Prize in Physiology or Medicine was awarded in 1978 to Werner Arber, Daniel Nathans, and Hamilton O. Smith for their discovery of restriction enzymes, which enabled applications to molecular genetics that set the stage for modern biotechnology as we know it today (Raju, 1999). These examples serve to highlight how basic knowledge of chemical and biochemical processes, gleaned from fundamental studies, can enable and inspire scientific applications that seem to be distant from the original goals of a research project. This special issue makes this point a centerpiece by bringing together cutting-edge research that illuminates the complex interplay between enzyme structure, dynamics, and function, viewed through a distinctly chemical lens.

With methods ranging from electron paramagnetic resonance (EPR) spectroscopy to *in silico* high-throughput screening, this special issue is structured to provide a glimpse into approaches presented with the goal of reflecting the multifaceted nature of enzymology as a field. We hope that by bridging advanced structural and functional studies with the "classic" methods, such as modeling enzyme activity through the methods of Michaelis and Menten, readers will observe how diverse technical methodologies can converge to deepen our understanding of enzyme-catalyzed processes. This special issue features a blend of research and review articles, showcasing how diverse methodologies drive scientific progress while highlighting the importance of drawing insights from past discoveries to move a field forward.

Consider the investigation by Xu and colleagues into the catalase activity of KatG, a heme-dependent enzyme (Xu et al.). The work illustrates the complexity of enzyme regulation by conformational dynamics. An in-depth examination of the interplay between an "Arg Switch" and the oxidizable "proximal Trp" has revealed how conformationally dynamic structural elements can cooperate to maintain efficient hydrogen peroxide degradation. Their findings highlight how subtle structural features can have profound effects on enzyme function and stability–a theme that resonates throughout this special issue.

In contrast, Sosa and colleagues highlight how a knowledge of basic chemical details underlying enzyme function can be leveraged to the pursuit of practical applications through their work on ketoreductases (Sosa et al.). Their work made use of computational tools to test 16 enzymes identified as top hits from a screening library of approximately half a million candidate enzymes. The ideal candidate enzyme would serve as a biocatalyst capable of efficient reaction catalysis and producing the desired enantiomeric excess. Their use of computational tools to identify and characterize enzymes capable of synthesizing optically pure compounds demonstrates how a fundamental understanding of structure-function relationships can be leveraged for industrial applications. Their high-resolution structural studies, combined with computational analysis and site-directed mutagenesis, provide insight into how substrate specificity is achieved at the molecular level.

The exploration of bifunctional enzymes by Zhu et al. adds another layer to our understanding of structure-function relationships. Their review of glutamine-hydrolyzing synthetases demonstrates how nature has evolved elegant solutions for coordinating multiple catalytic activities within a single protein structure. These enzymes, crucial for various biosynthetic pathways, showcase the sophistication of molecular machinery that enables efficient substrate channeling and coupled reactions. Similarly, a review by Richards and Naismith describing C-nucleoside biosynthesis (Richards and Naismith), along with the characterization of dual-specific phosphatases by Imhoff et al. , provides further emphasis of how diverse analytical techniques can be combined to unravel complex enzymatic mechanisms. These works demonstrate the power of integrating structural, spectroscopic, and chemical biology approaches to understand enzyme function.

Looking ahead, several key challenges and opportunities emerge from this collection that point to where enzymology is heading as a field. The dynamic nature of enzymes, including conformational changes and protein dynamics, is recognized as integral to their function, which demands attention to mechanisms of conformational regulation, catalysis, and substrate specificity. The integration of computational and experimental approaches is becoming ever more powerful, enabling both prediction and validation of structure-function relationships. Technological advances—such as advanced structural techniques, sophisticated spectroscopic methods, and powerful computational tools—have unveiled unprecedented insights into enzyme mechanism and function, pushing the boundaries of our understanding. The papers in this special issue document significant progress while highlighting the exciting future directions of enzyme engineering, drug design, and fundamental biological catalysis. Serving as both a milestone and a springboard, this collection emphasizes the critical role of new technologies and approaches in driving forward our understanding of these molecular machines.

Author contributions

JM: Writing–original draft, Writing–review and editing. AO: Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

References

Brenner, S., Jacob, F., and Meselson, M. (1961). An unstable intermediate carrying information from genes to ribosomes for protein synthesis. *Nature* 190, 576–581. doi:10.1038/190576a0

Cobb, M. (2015). Who discovered messenger RNA? *Curr. Biol.* 25 (13), R526–R532. doi:10.1016/j.cub.2015.05.032

Dounce, A. L. (1952). Duplicating mechanism for peptide chain and nucleic acid synthesis. *Enzymologia* 15 (5), 251–258.

Gros, F., Hiatt, H., Gilbert, W., Kurland, C. G., Risebrough, R. W., and Watson, J. D. (1961). Unstable ribonucleic acid revealed by pulse labelling of *Escherichia coli*. *Nature* 190, 581–585. doi:10.1038/190581a0

Guan, S., and Rosenecker, J. (2017). Nanotechnologies in delivery of mRNA therapeutics using nonviral vector-based delivery systems. *Gene Ther.* 24 (3), 133–143. doi:10.1038/gt.2017.5

Hajj, K. A., and Whitehead, K. A. (2017). Tools for translation: non-viral materials for therapeutic mRNA delivery. *Nat. Rev. Mater* 2, 17056. doi:10.1038/natrevmats.2017.56

Jacob, F., and Monod, J. (1961). Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.* 3, 318–356. doi:10.1016/s0022-2836(61)80072-7

Kowalski, P. S., Rudra, A., Miao, L., and Anderson, D. G. (2019). Delivering the messenger: advances in technologies for therapeutic mRNA delivery. *Mol. Ther.* 27 (4), 710–728. doi:10.1016/j.ymthe.2019.02.012

Loenen, W. A., Dryden, D. T., Raleigh, E. A., Wilson, G. G., and Murray, N. E. (2014). Highlights of the DNA cutters: a short history of the restriction enzymes. *Nucleic Acids Res.* 42 (1), 3–19. doi:10.1093/nar/gkt990

Pardi, N., Hogan, M. J., Porter, F. W., and Weissman, D. (2018). mRNA vaccines - a new era in vaccinology. *Nat. Rev. Drug Discov.* 17 (4), 261–279. doi:10.1038/nrd.2017.243

Raju, T. N. K. (1999). The Nobel chronicles. *Lancet* 354 (9189), 80. doi:10.1016/s0140-6736(05)75353-8

Roberts, R. J. (2005). How restriction enzymes became the workhorses of molecular biology. *Proc. Natl. Acad. Sci.* 102 (17), 5905–5908. doi:10.1073/pnas.0500923102

Watson, J. D. (1963). Involvement of RNA in the synthesis of proteins. *Science* 140 (3562), 17–26. doi:10.1126/science.140.3562.17

Work, T. S., and Campbell, P. N. (1953). Nucleic acid template hypotheses. *Nature* 172 (4377), 541–542. doi:10.1038/172541b0

Xiong, Q., Lee, G. Y., Ding, J., Li, W., and Shi, J. (2018). Biomedical applications of mRNA nanomedicine. *Nano Res.* 11 (10), 5281–5309. doi:10.1007/s12274-018-2146-1