International Man of Enzymology: Vince Massey’s Work on Flavin Catalysis

The Mechanism of Action of Xanthine Oxidase
(Olson, J. S., Ballou, D. P., Palmer, G., and Massey, V. (1974) J. Biol. Chem. 249, 4363–4382)

Activation of Molecular Oxygen by Flavins and Flavoproteins
(Massey, V. (1994) J. Biol. Chem. 269, 22459–22462)

The Mechanism of high Mr Thioredoxin Reductase from Drosophila melanogaster
(Bauer, H., Massey, V., Arscott, L. D., Schirmer, R. H., Ballou, D. P., and Williams, C. H., Jr. (2003) J. Biol. Chem. 278, 33020–33028)

From humble beginnings as the son of a fisherman in a small village in New South Wales, Australia, Vincent Massey became one of the leading enzymologists in the world. Massey was particularly interested in the enzymology of flavins, which are organic compounds that undergo oxidation-reduction reactions. An example of a flavin is vitamin B2. Massey’s early work helped to pave the way for other flavin enzymologists.

According to Dave Ballou and Charles Williams, former research associates of Massey’s, his greatest asset was his firm belief in collaboration. “He believed that if you were going to ask the hard questions, you were going to need more brains than you had in your own head,” says Williams. “And for a guy who had a big brain in his head, I think that was a really humble attitude.”

Ballou describes how Massey’s dedication to collaboration and his outgoing personality stimulated a global network among researchers working in the flavin field. “It was a remarkable community—a worldwide community—that he fostered,” says Ballou.

Ballou and Williams both worked with Massey at the University of Michigan in Ann Arbor, where the former two remain to this day. Massey’s life, like his work, was international in scale. He grew up and attended college in Australia, where he met and married his wife, Margot, a German refugee who had survived the Holocaust. Massey earned his doctorate at the University of Cambridge in the UK. He moved to Ann Arbor in 1963, where he was a professor at the University of Michigan for almost 40 years. During that time, he collaborated with colleagues all over the world and took sabbaticals in Germany and Japan. Massey died in 2002.

Flavins can be components of flavoproteins, which are required in biological processes such as electron transfer reactions, signaling, photosynthesis, bioluminescence, and DNA repair. An early work of Massey’s, performed in collaboration with Ballou and others, appeared in the
Journal of Biological Chemistry (JBC) in 1974. The paper focused on the flavoprotein xanthine oxidase.

Xanthine oxidase catalyzes the oxidation of hypoxanthine to a purine base called xanthine and of xanthine to uric acid, a compound that can cause gout. The enzyme forms hydrogen peroxide and superoxide as side products; both are reactive species of oxygen that can be harmful to the body if not removed.

Xanthine oxidase contains four redox moieties: a flavin-adenine dinucleotide (FAD), a cofactor known as a molybdopterin, and two iron-sulfur centers. The 1974 paper examined how the enzyme transmits electrons through these redox units to oxygen. The paper’s description of the enzyme’s catalytic mechanism has served as a model for understanding the activities of other proteins involving multiple redox groups, such as cytochrome P450 reductase and nitrogenase.

In 1994, Massey published a minireview in the JBC that organized flavoproteins into definable categories. Some flavoproteins do not contain metals. Among them, some react rapidly with oxygen while others react slowly. The minireview describes an intermediate that can be detected spectrally: Flavoprotein oxidases can produce red semiquinones, whereas flavoprotein reductases can yield blue semiquinones. “It seems that every recent paper on flavins and oxygen references that one,” says Ballou.

Massey published close to 400 papers throughout his lifetime. His last paper, published in the JBC a few months after his death, describes the mechanistic behavior of thioredoxin reductase, one of three crucial antioxidant enzymes in most cells. Small differences between the enzyme isolated from humans and that found in certain parasites make it an attractive drug target.

Thioredoxin reductase cycles between a four-electron state and a two-electron reduced state. The need for the greater reductive power of the four-electron reduced enzyme is not fully understood. However, the processes described in the 2003 paper have implications for the understanding of redox control in various systems.

The papers presented here as JBC Classics are snapshots of a long and fruitful career in enzymology. “The amazing thing is the collection of all of the papers he published in the JBC,” says F. Peter Guengerich at Vanderbilt University, who was a postdoctoral fellow with a different group at Ann Arbor during Massey’s tenure. “It wasn’t just one single paper that drove everything.”

As a researcher, Massey had hands-on involvement in nearly all of the studies he published. “He was very active in the lab,” says Guengerich. “I think he sort of competed with his post-docs and students. He dared them to beat him.”

This level of involvement made Massey unusual by contemporary standards. “The experiments were all in his hands,” says Ballou. “I think that distinguishes him from virtually all other biochemists since 1970.”

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