The Discovery and Characterization of Molybdopterin: the Work of K. V. Rajagopalan

Hepatic Sulfite Oxidase. A Functional Role for Molybdenum

Characterization of the Molybdenum Cofactor of Sulfite Oxidase, Xanthine, Oxidase, and Nitrate Reductase. Identification of a Pteridine as a Structural Component

The Structure of the Molybdenum Cofactor. Characterization of Di(carboxamidomethyl)molybdopterin from Sulfite Oxidase and Xanthine Oxidase

K. V. Rajagopalan was born in 1930 in Udupi, a town in South India. He attended Presidency College in Madras (now called Chennai) and graduated with a B.Sc. in Chemistry in 1951. He then enrolled at the University of Madras to do graduate work in the biochemistry department and earned his Ph.D. in 1957. After graduating, Rajagopalan served as an assistant research officer at the Indian Council of Medical Research. Two years later, he started a postdoctoral fellowship in the biochemistry department at Duke University, working with Journal of Biological Chemistry (JBC) Classic author Philip Handler (1).

Rajagopalan’s initial research project at Duke, carried out in collaboration with JBC Classic author Irwin Fridovich (2), dealt with the competitive inhibition of several enzymes by urea and guanidine. Next, Rajagopalan moved on to studies of aldehyde oxidase and xanthine oxidase and noticed that both enzymes had unusual absorption spectra. Further investigation revealed that they both contained a molybdenum cofactor, something that had not been seen in any other mammalian proteins. Some of Rajagopalan’s electron paramagnetic resonance (EPR) studies on aldehyde oxidase can be found in the JBC Classic on Helmut Beinert (3).

These early findings led to an interest in proteins containing molybdenum and formed the basis of Rajagopalan’s future research. In the first JBC Classic reprinted here, Rajagopalan,
Fridovich, and Harvey J. Cohen report the discovery of another molybdenum-containing enzyme, sulfite oxidase. The paper documents the presence and function of molybdenum in sulfite oxidase and describes some aspects of its EPR signal. The paper was published along with two other papers (4, 5), which discussed the purification and properties of sulfite oxidase from bovine liver and the nature of its heme prosthetic group.

By 1980, several more molecules had been added to the list of molybdenum-containing proteins, but the nature of the cofactor still remained elusive. This was, in part, due to the fact that the activated cofactor was extremely labile in the presence of oxygen and thus very hard to characterize. To circumvent this problem, Rajagopalan developed a method to isolate the oxidized, inactive form of the molybdenum cofactor from sulfite oxidase, xanthine oxidase, and nitrate reductase. His procedure and initial characterization are reported in the second JBC Classic reprinted here. In the paper, Rajagopalan and his colleagues also provided evidence that a pteridine moiety acted as a structural component of the cofactor.

Continuing with this work, Rajagopalan was able to isolate two additional stable degradation products (6) and confirm that the molybdenum cofactor consisted of a complex between molybdenum and a unique pterin which he named molybdopterin.

In the final JBC Classic reprinted here, Rajagopalan describes the successful isolation of a stable alkylated derivative of molybdopterin, camMPT, from sulfite oxidase and xanthine oxidase by a procedure involving treatment with iodoacetamide under mild denaturing conditions. Structural studies on the product confirmed that molybdopterin is a 6-alkylpterin with a 4-carbon side chain, which has an enedithiol at carbons 1′ and 2′, a hydroxyl at carbon 3′, and a terminal phosphate group.

Today, Rajagopalan remains at Duke as James B. Duke Professor of Biochemistry, a position he assumed in 1995. It is interesting to note that, in 1969 when Handler left Duke to become the President of the National Academy of Sciences, he designated Rajagopalan as PI of his National Institutes of Health (NIH) grant. This has subsequently become the longest continuously funded NIH grant, currently in its 62nd year.

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REFERENCES