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Editorial

# Introduction to flavoproteins: Beyond the classical paradigms

Flavin-dependent enzymes have been the subject of intense biophysical and biochemical research since the discovery of the first enzymes in this class in the mid 1930's [1,2]. Initial biochemical studies focused on flavin-dependent enzymes that were from sources easily accessible to scientists, such as cow's milk (xanthine oxidase) and pig's heart (succinate dehydrogenase) [3,4]. For more than 80 years, the study of flavin-dependent enzymes has flourished to the point of being its own discipline: flavoenzymology. Some of the early studies focused on understanding the chemical and biophysical properties of flavin cofactors [5–8]. For example, major efforts were made to understand the mechanism of activation of molecular oxygen and formation of the C4a-(hydro)peroxyflavin, an intermediate essential for oxygenation reactions [9,10]. Similarly, the mechanism of C-H bond cleavage in amino acids, alpha-hydroxyl acids, and in fatty acid oxidation was extensively studied [11–13]. These mechanistic studies, in combination with elucidation of the structures of enzymes in complex with substrates, products, analogs, and inhibitors, as well as in different redox states, have provided a clear understanding of the role of the flavin cofactor in redox reactions such as the transfer of electrons, dehydrogenation, and oxygenation reactions. Recently, the flavoenzymology field has entered a new era where novel roles for flavin cofactors have been demonstrated. This renaissance is fueled, in part, by the post-genome era, which has enabled identification of many flavoenzymes in the biosynthetic pathways of natural products.

This special issue of *Archives of Biochemistry and Biophysics*: "Flavoenzymes: Beyond the classical paradigms" highlights a collection of enzymes that either utilize the flavin cofactor in a novel fashion or have had their mechanistic and structural properties extensively studied but are not part of the flavoenzymology mainstream. The direct role of the flavin-N5 atom in covalent catalysis in several redox reactions is presented. Adak and Begley describe the role of the flavin-N5-oxide in three known enzyme systems and provide insights into the chemical requirements for the formation of this intermediate [14]. Karunaratne et al., provide a summary of the mechanistic, structural, and inhibitor design studies of flavin-dependent thymidylate synthase. Formation of thymidylate by flavin-dependent thymidylate synthase, provides an example of the flavin-N5 atom as a methyl transfer in nucleotide biosynthesis [15]. The role of oxygenated flavin species, including the N5-oxide, in halogenation, nitroso and nitrone formation, carbonate formation, and hydroxylation-induced cascade reactions in natural products biosynthesis, including intriguing mechanistic perspectives, is eloquently described by Teufel [16]. Lombard and Hamdane summarize the various RNA modifications catalyzed by several flavoenzymes including methylation by a flavin-N5-methelene carrier, hydride transfer, and other reactions that are not well-understood, such as the biosynthesis of hydroxybutosine [17]. Formation of a flavin-N5 adduct in the reaction of carbanions with oxidized FAD in nitroalkane oxidase is reviewed by Fitzpatrick [18]. The flavin in this reaction also facilitates elimination of the nitrite group via a proton shuttle through the 2′OH ribityl group. Thibodeaux and Liu describe the current understanding of the function of reduced flavin in the redox neutral reaction of type II isopentenyl diphosphate:dimethylallyl diphosphate isomerase. The experimental data is consistent with the reduced flavin being involved in acid/base catalysis; however, the exact mechanism is currently not well-established [19]. Another redox neutral reaction, described by Sobrado and Tanner, is catalyzed by UDP-galactopyranose mutase, which also requires the reduced flavin for activity. In this reaction, the reduced flavin functions as a nucleophile forming a flavin-N5-galactose adduct. In addition, the flavin is involved in proton transfer steps that are essential for activating reaction intermediates [20].

In addition to covalent catalysis, the function of flavoenzymes in metabolite repair is described in the review by Moran and Hoag. They present the mechanistic and structural data that properly describes renalase as a 2- and 6-dihidronicotinamide isomerase and the biochemical, structural, and inhibition studies that support its function in detoxification of metabolic enzymes that utilize $NAD(P)^+$ [21]. Sun et al. describe the mechanism of dehalogenation by iodotyrosine deiodinase and its structural relationship with nitroreductases [22]. The versatility of bi-covalent flavins in the berberine bridge family, which catalyze oxidation reactions in natural product biosynthesis, is described by Daniel et al. They review the structure and mechanism of berberine bridge enzymes and the diverse reactions catalyzed by members of this subfamily of flavoproteins [23]. The classification of the vanillyl alcohol oxidase/*para*-cresol methylhydroxylase (VAO/PCMH) family of flavoenzymes is presented by Ewing et al. They identify and discuss the properties of 11 subgroups within this family, which include several enzymes covered in this issue [24]. Vanoni reviews the structural and mechanistic data on the controversial NADPH-dependent F-actin depolarization mechanism catalyzed by the multidomain enzyme MICAL (from Molecule Interacting with CasL) [25]. Liu et al. summarize the structure and function of another multidomain enzyme, protein utilization A (PutA), with a focus on substrate channeling, enzyme hysteresis, transcriptional repressor function, and redox-dependent cellular localization mechanism [26]. The unifying mechanism for electron hopping, bifurcation, and tunneling routes that take place in DNA repair reactions catalyzed by photolyases are presented by Zhang et al. [27]. Reis and colleagues provide a chronological summary of the structure and mechanism of dihydroorotate dehydrogenases, with emphasis on drug discovery [28]. The structural and mechanistic knowledge recently acquired on D-arginine dehydrogenase is

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presented by Ouedraogo et al. D-arginine dehydrogenase exhibits broad substrate specificity with marked preference for cationic D-amino acids, is one of a few flavoenzymes that show an absolute lack of reactivity with molecular oxygen, and is a model for loop dynamics in relation to substrate capture and catalysis [29]. Speranzini et al. demonstrate that the p53 C-terminal domain inhibits the activity of LSDI histone demethylase and that formation of the complex between these proteins involves non-specific electrostatic interactions [30]. Marshall et al. present the mechanism of formation of a recently identified prenylated flavin. The high resolution structural and mechanistic data for cofactor biogenesis and its utilization in decarboxylation reactions is presented [31].

"Flavoproteins: Beyond the classical paradigms" continues a long tradition of *Archives of Biochemistry and Biophysics* in publishing review articles on flavoenzymes [32–56]. Flavoenzymology has witnessed a new, vibrating renaissance and its future looks as yellow (i.e., $\lambda_{max} = 450$ nm) as it can be, with new structures and mechanisms that will likely be discovered and new paradigms established. We would like to thank all the authors for their fantastic contributions, Prof. Paul F. Fitzpatrick for his invitation to be the Guest Editors for this Special Issue, and the staff at Elsevier for their expert, kind, and professional assistance. Finally, special thanks go to all the reviewers for their expert comments and suggestions.

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