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Forum Editorial

Organic Redox Cofactors

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REDOX-ACTIVE COFACTORS, including quinones and flavins, are important components in biological systems. Together with the apoprotein, they perform complex redox chemistry, provide an important link in signal transduction, and participate in crucial electron transfer pathways, aspects that are often inefficiently carried out by the proteins themselves. These apoprotein–cofactor assemblies are essential in all aspects of cellular function, making them important targets for chemical and biochemical investigations. Although there is enormous diversity in the processes mediated by organic cofactors, the fact that the same redox unit is utilized to perform a multiplicity of functions provides common ground for researchers from a wide variety of fields. It is this multi- and interdisciplinary approach that we have focused on for this issue, bringing together chemists, biochemists, and molecular biologists that explore key issues of cofactor-mediated processes.

Unlike many metal centers, the chemistry of organic cofactors can be studied outside of the apoenzyme environment using synthetic and computational model systems as powerful tools for the understanding of their more complex enzymatic prototypes. In a broader sense, redox proteins (and the systems that model them) provide a unique milieu for the study of enzymatic processes. The cofactor provides an "active site" with relatively few structural differences relative to most other enzymatic systems. This greatly simplifies the catalytic event, allowing the role of individual effects to be explored using both molecular and supramolecular methods.

The relatively small size of organic cofactors allows for the application of high-level computational methods in the modeling of biological systems. In this issue, a communication by Rizzo describes the use of *ab initio* computational methods to explore the structure of an $FADH_2$ analog. Also, O'Malley describes the correlation of density functional calculations and electron paramagnetic spectroscopic studies of quinone cofactors.

In the area of cofactor chemistry, Carson, Tam-Chang, and Beck illustrate the use of surface-immobilized flavins to study microenvironmental effects on the redox properties of flavin cofactors. Supramolecular chemistry provides an additional tool for the modeling of cofactor-mediated processes. Reviews by Yano as well as Fukuzumi and Itoh describe applications of this approach in the modeling of flavoenzymes and quinoenzymes, respectively. Spectroscopy provides a bridge between chemistry and biochemistry, allowing information transfer between the simpler model systems and their more complex biological prototypes. In this issue, Stanley provides an up-to-date review of the application of a number of spectroscopic techniques to the study of flavins and flavoenzymes.

The structural attributes of cofactor-containing proteins make them particularly good candidates for in-depth studies of structure and

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function. Not surprisingly, the large number of protein systems that have and continue to be investigated has yielded a wealth of biochemical information, the comprehensive review of which is beyond the scope of this forum. Several diverse examples are included that illustrate both the versatility of the cofactors and the experimental approaches in their study. Sampson reviews the use of mutagenesis and cofactor replacement to probe the behavior of cholesterol oxidase. This concise approach has been applied to the biomedically significant monoamine oxidases as discussed in a review by Edmondson and Newton-Vinson on the role and mechanism of covalent flavin attachment. Studies by Sablin and Ramsay compare the effects of inhibitors and substrates on the redox potentials of the monoamine oxidases, providing insight into the perplexing properties of these systems. Anthony provides an in-depth review of pyrroloquinoline quinone and quinoprotein enzymes, whereas Tu presents a discussion of the roles of reduced flavins in biological systems. Rounding out the diverse array of articles in this special issue, we have a research communication by Koder, Oyedele, and Miller exploring the evolution of a flavin-dependent nitroreductase. Finally, the emerging role of the flavin as a biosensor is explored in a review by Briggs, Christie, and Salomon on the phototropins, plant blue-light receptors, whereas the review of Taylor, Rebbapragada, and Johnson discusses the role of the FAD-PAS domain as a biosensor for regulating chemotaxis.

The articles in this issue in no way present a comprehensive view of the field of cofactor research. We hope, however, that the vitality and multidisciplinary nature of the field are conveyed in this special "Forum" edition of *Antioxidants & Redox Signaling*.