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Introduction

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The three major classes of ion-motive ATPases are the P, V, and F type (Pedersen and Carafoli, 1987a, b). The P-type ATPases are distinguished from the other two classes by the fact that they form a covalent phosphorylated intermediate during their reaction cycle. The distinctive characteristic of the V-type ATPases is their vacuolar location, and that of the F-type ATPases is their direct participation in ATP synthesis. The previous two issues in this series (Vol. 24, Nos. 3 and 4) have focused on the P- and V-type ATPases, respectively. Therefore, it is the purpose of this volume to provide a recent synopsis of work on the F-type ATPases.

F-type ATPases are also referred to in the literature as ATP synthases, ATP synthase/H^+-ATPase complexes, F_0F_1-ATPases, and more simply as just F_0F_1. As the latter name implies, these enzymes are comprised of two major units, one called F_0 and the other F_1. During ATP synthesis F_0 directs the coupling of an electrochemical gradient of protons across a biological membrane to the net synthesis of ATP on the F_1 unit. For comprehensive reviews see Hatefi (1985), Senior (1988), Futai *et al.* (1989), Fillingame (1990), and Penefsky and Cross (1991).

Both the F_0 and F_1 units have been extensively studied and each is known to consist of a complex substructure. In most species studied the F_1 unit consists of five subunit types called α, β, γ, δ, and ε, which are present in the stoichiometric ratio $\alpha_3\beta_3\gamma\delta\varepsilon$. In *E. coli* the F_0 unit consists of three subunit types called "a", "b", and "c", but in higher eukaryotes more than five additional subunit types are present. All F_0 and F_1 subunits have been sequenced either chemically or by molecular biological techniques. Significantly, the α, β, and "c" subunits are highly conserved throughout the phylogenetic scale, and for this reason have been subjected to more intensive investigation than the other subunits of the F_0F_1 complex.

During the past decade investigators working with F-type ATPases from a variety of sources have used a number of different approaches to extract from these complicated enzymes valuable secrets about their three-dimensional structure, the location and function of their nucleotide binding domains, and the role of conserved amino acids. Significantly, investigators now agree that F-type ATPases from most species examined exhibit an $\alpha_3\beta_3\gamma\delta\varepsilon$ subunit composition; that the α and β subunits each contain at least one nucleotide-binding domain of more than 100 amino acids; that these domains contain the Walker A and B consensus motifs (Walker *et al.*, 1982); and that α and β subunits must interact to achieve maximal catalytic activity. Considerable progress has been made also on the three-dimensional structure of the F_1 unit of F-type ATPases. As emphasized in this issue, the quaternary structure of the rat liver enzyme, as it relates to the relative positions of the α and β subunits, has been elucidated by X-ray crytallography (see cover figure), and image reconstruction analysis on the *E. coli* enzyme has provided valuable information about the location of the smaller subunits (see Capaldi *et al.*, this issue).

Despite this progress, however, there remains much to be done. The precise location of nucleotide-binding domains within a high-resolution structure must be obtained. A better understanding of the roles of these nucleotide domains must be forthcoming, particularly as it relates to their relative role(s) in ATP synthesis, and its regulation. Knowledge of the chemical details of how F_0 interacts with F_1 is essential to understanding the mechanism by which the F_0 unit participates in the coupling of an electrochemical gradient to the F_1 unit, and whether this coupling is direct or delivered through conformational changes. If, in fact, the coupling event also entails movement of the

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small subunits from one $\alpha\beta$ pair to the other as suggested by an earlier model (Williams *et al.*, 1987), it becomes critical to define in chemical detail how this movement is initiated and how it occurs. Finally, the mechanism by which ATPase inhibitor proteins regulate F-type ATPases at a molecular/chemical level remains to be solved. For recent reviews, see Schwerzmann and Pedersen, 1986, and Rouslin, 1991.

In this minireview series which focuses exclusively on the F-type ATPases, the reader should obtain a good flavor for some of the recent developments in this area, and some ideas about how F-type ATPases work. Hopefully, the information presented in this series of lucid minireviews will stimulate all of us to design new experiments which will help answer the many important questions that remain about this important class of enzymes.

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