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An Introduction to the Mitochondrial Anion Carrier Family

Peter L. Pedersen[1]

There are three major classes of proteins that comprise the mitochondrial inner membrane. These include the electron transport chain complexes and the ATP synthase complex which are responsible for oxidative phosphorylation, and the mitochondrial anion carriers. Previous volumes of this journal have featured minireview series on the electron transport chain complexes (Vol. 25, Nos. 2, 3, and 4) and the ATP synthase complexes (Vol. 24, No. 5). Therefore, the series featured here will focus exclusively on the mitochondrial anion carriers. (For excellent reviews that summarize the importance of mitochondrial carriers and their early history, see Refs. 1–4, and for more recent reviews, see Refs. 5–8.)

There are at least nine anion carrier proteins located in the mitochondrial inner membrane (Fig. 1). In intact mitochondria the ADP/ATP carrier (AAC) and the phosphate carrier (PIC) are absolutely essential for the process of oxidative phosphorylation that generates most of the cellular ATP. The remaining anion carriers frequently play a dual role, participating in two or more metabolic processes.[7,8] Thus, the pyruvate carrier (PYC) supplies pyruvate to the mitochondrial matrix during the catabolic phase of cell metabolism to fuel the citric acid cycle, and during the anabolic phase to initiate glucose synthesis. The aspartate/glutamate carrier (AGC) and the oxoglutarate carrier (OGC) play a vital role in glucose catabolism in cytosolic-mitochondrial shuttle systems responsible for regenerating NAD^+ for glycolysis. They also participate in glucose synthesis and in nitrogen metabolism. The dicarboxylate carrier (DIC) is best known for its role in glucose synthesis but also participates in urea synthesis, whereas the citrate carrier (CIC) plays an essential role in fatty acid and lipid biosynthesis. The glutamate carrier (GC) plays a role in urea synthesis and in some other processes related to nitrogen metabolism. Finally, the $ATPMg/P_i$ carrier (APC) is evidently responsible for "charging" the mitochondrial matrix with adenine nucleotides during early stages of development, thus inducing a variety of processes including ATP and glucose synthesis.[9]

In addition to the nine anion carriers noted above, the mitochondrial inner membrane may contain additional anion carriers whose function remains unclear or unknown.[7,8] Also of metabolic or physiological importance are several cation carriers (Fig. 1). These include the ornithine carrier (ORC) and the carnitine carrier (CC) involved, respectively, in urea synthesis and fatty acid oxidation and the uncoupling protein (UC) responsible for the proton translocation that results in thermogenesis in newborn and hibernating animals. Mitochondria of some tissues contain also a glutamine carrier involved in the degradation of glutamine.

Progress to date in the study of the mitochondrial anion carrier family is summarized in Table I. Despite the fact that progress has been painfully slow at times, the persistence and hard work of a relatively few laboratories operating with minimal support have succeeded in bringing this area to the molecular level. Thus, it will be noted in the minireviews presented here that three of the anion carriers, the ATP/ADP carrier,[10–12] the phosphate carrier,[5,13–15] and the oxoglutarate carrier[11,14,15] have proceeded through the purification, reconstitution, cloning, sequencing, and functional expression stages. In addition, progress on the closely related uncoupler binding protein has proceeded also through these stages,[10] while work on the citrate carrier,[16,17] of which there are two different isoforms, has proceeded through all of the same stages except functional expression.

Because of their relative simplicity, the mitochondrial anion carriers are certain to provide some of the

[1] Laboratory of Molecular and Cellular Bioenergetics, Department of Biological Chemistry, Johns Hopkins University, School of Medicine, 725 North Wolfe Street, Baltimore, Maryland 21205.

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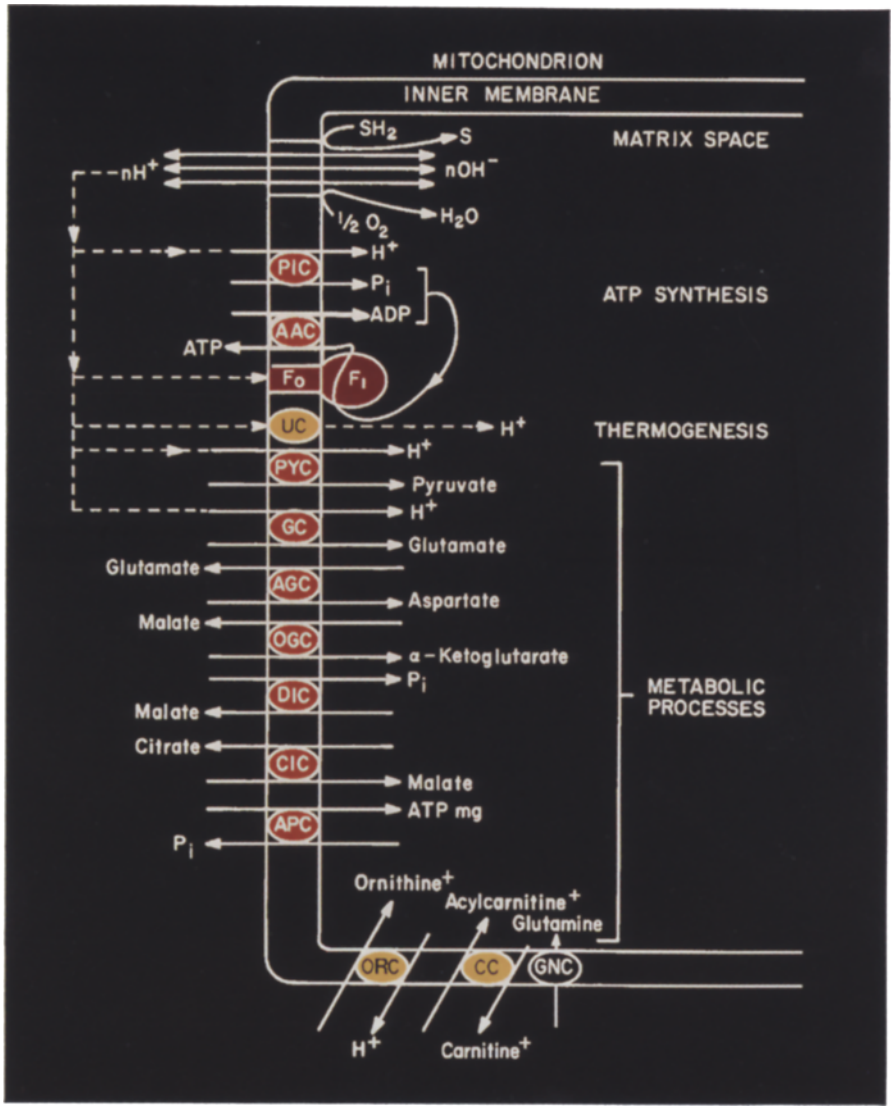

Fig. 1. Mitochondrial metabolite carriers. Depicted are nine anion carriers (orange), three cation carriers (yellow), and a carrier for glutamine. See text for a brief description of their major metabolic roles. This minireview series focuses on the anion carriers. Abbreviations for the anion carriers: PIC, phosphate carrier; AAC, ATP/ADP carriers; PYC, pyruvate carrier; GC, glutamate carrier; AGC, aspartate/glutamate carrier; OGC, oxoglutarate carrier; DIC, dicarboxylate carrier; CIC, citrate carrier; APC, ATPMg/P_i carrier. Abbreviations for the cation carries: UC, uncoupler binding protein (a proton carrier); ORC, ornithine carrier; and CC, carnitine carrier. The glutamine carrier is designated as GNC. [*Note*: Some of the transport systems are tissue specific and are not present in all mitochondria. Also, note that the PYC and the GC are usually depicted in the literature with a hydroxyl group leaving the matrix space rather than as a proton entering. To avoid controversy, charges are not shown on the ligands transported by the anion carriers.]

most popular models for understanding the molecular mechanism of biological transport in the future. These carriers are all small molecules (28–38 kDa) and most are related in their primary structures. Of particular interest are the nonhomologous regions of these carriers, as these are likely to contain those amino acids that distinguish one anion species from another and therefore determine anion specificity. Although several intriguing models depicting transport mechanisms have been published,[7,8,18,19] the unpleasant but

Table I. Mitochondrial Anion Carriers and Progress made to date in their Study[a]

Progress	Mitochondrial carrier									
	AAC	PIC	OGC	(UC)[b]	CIC	AGC	DIC	PYC	APC	GC
Purification	+	+	+	+	+	+	+	±	–	–
Functional reconstitution	+	+	+	+	+	+	+	±	–	–
Kinetic analysis	+	+	+	+	+	+	+	±	±	±
Cloning and CDNA	+	+	+	+	+	–	–	–	–	–
Topology (exp. data)	±	±	–	±	–	–	–	–	–	–
Functional expression	+	+	+	+	–	–	–	–	–	–
Functional overexpression	–	–	+	+	–	–	–	–	–	–
Crystallization	–	–	–	–	–	–	–	–	–	–
3D structure	–	–	–	–	–	–	–	–	–	–
Gene regulation	±	–	–	–	–	–	–	–	–	–
Human Chromosomal Location	+	+	–	–	–	–	–	–	–	–

[a] A positive sign (+) indicates that either this aspect of the problem has been completed or that much work has been done. A negative sign (–) indicates that much more work needs to be done to complete this aspect of the problem. A ± sign indicates that significant progess has been made, but that additional work is in order. (See Fig. 1 legend or text for meaning of the abbreviations.)

[b] The uncoupler binding protein is a proton carrier but is included here because of its striking primary structural similarity to the anion carriers.

challenging reality is that the mitochondrial anion transport field, like every other field of membrane biology, will not advance appreciably in understanding basic mechanisms until the three-dimensional structures of these proteins are known. As a number of investigators working on the mitochondrial anion carriers have either reached the mutational analysis stage, or are rapidly approaching this stage, the need for "real" 3-dimensional structures is imminent. It seems extremely important that agencies funding work on membrane proteins in general, and biological transport specifically, also recognize this problem. Thus, should an established membrane biochemist be penalized for proposing to functionally overexpress and crystallize a membrane protein that constitutes his/her life's work, or be encouraged to make every attempt possible?

Finally, it should be emphasized that in our quest, or perhaps "zeal" to understand the basic mechanisms of transport catalyzed by the mitochondrial anion carrier family, we must recognize that other important research needs to be conducted on these proteins. For example, very little is known about how the genes encoding these carriers are regulated. Also, the roles that these carriers play in a variety of physiological functions, in development, and in certain diseased states is poorly understood, although several of the minireviews presented here do touch upon these areas.[9,11,16,17]

As briefly summarized in Table I, and in detail in the accompanying minireview series, we have made tremendous progress in acquiring knowledge about the mitochondrial anion carrier family, but some of the most challenging and important work has yet to be done.

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