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Role of CFTR's intrinsic adenylate kinase activity in gating of the Cl^- channel

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Abstract The cystic fibrosis transmembrane conductance regulator (CFTR) is a Cl^-channel in the ATP-binding cassette (ABC) transporter protein family. CFTR features the modular design characteristic of ABC transporters, which includes two membrane-spanning domains forming the channel pore, and two ABC nucleotide-binding domains that interact with ATP and contain the enzymatic activity coupled to normal gating. Like other ABC transporters CFTR is an ATPase ($ATP + H_2O \rightarrow ADP + P_i$). Recent work has shown that CFTR also possesses intrinsic adenylate kinase activity ($ATP + AMP \leftrightarrows ADP + ADP$). This finding raises important questions: How does AMP influence CFTR gating? Why does ADP inhibit CFTR current? Which enzymatic activity gates CFTR *in vivo*? Are there implications for other ABC transporters? This minireview attempts to shed light on these questions by summarizing recent advances in our understanding of the role of the CFTR adenylate kinase activity for channel gating.

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Introduction

The cystic fibrosis transmembrane conductance regulator (CFTR, Fig. 1) belongs to the adenosine triphosphate (ATP)-binding cassette (ABC) transporter family of proteins and contains its defining features, two nucleotide-binding domains (NBDs), and two membrane-spanning domains (MSDs) (Higgins 2001; Riordan et al. 1989). In addition, CFTR has a unique regulatory (R) domain and phosphorylation of this domain is required for normal channel gating (Ostedgaard et al. 2001). In ABC transporters, the NBDs are the most conserved feature. They contain the "ATP-binding cassette" with several highly conserved sequence motifs including a phosphate-binding loop (P-loop or Walker A motif), which is also conserved in other nucleotide-binding proteins including RecA, the F_1-ATPase, Ras, and adenylate kinases (Higgins et al. 1986; Smith and Rayment 1996; Walker et al. 1982), a Walker B motif, and a conserved motif known as the ABC signature (Ames et al. 1992; Kerr 2002; Lewis et al. 2004). In CFTR and other ABC transporters the two NBDs form a head-to-tail dimer that creates two ATP-binding sites (Fig. 1, ATP-site 1 and ATP-site 2) with each ATP molecule sandwiched between the Walker A motif (the P-loop) of one NBD and the signature motif of the other NBD (Higgins and Linton 2004). ABC transporters are remarkably versatile machines that move a wide array of substances, including both hydrophilic and hydrophobic molecules across membranes (Ames et al. 1992; Davidson and Chen 2004; Higgins 2001; Holland and Blight 1999). Some ABC transporters

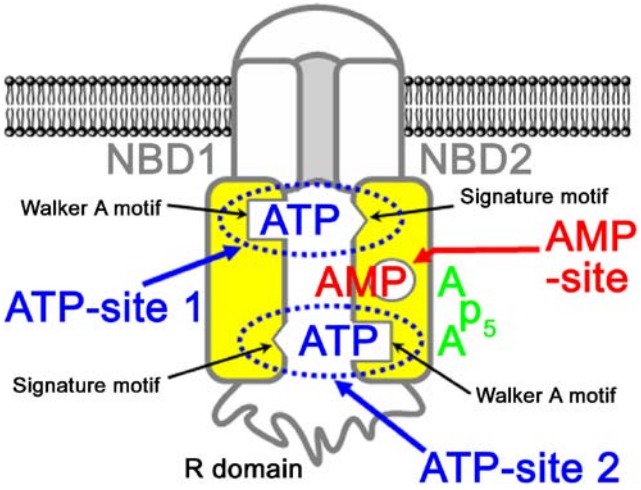

Fig. 1 Simplified model of the CFTR Cl^- channel in the plasma membrane. The channel pore is formed by the membrane-spanning domains. The two homologous NBDs contain the characteristic conserved motifs of ABC transporter NBDs including Walker A, Walker B, and signature motifs. It is thought that the two ATP-sites are formed by head-to-tail NBD dimerization (Callebaut et al. 2004; Mense et al. 2006; Vergani et al. 2005). In the presence of AMP the site 2 ATP is acting as phosphate-group donor in the adenylate kinase reaction . The adenylate kinase inhibitor Ap_5A (P^1,P^5-di(adenosine-5′) pentaphosphate) inhibits CFTR opening by interacting simultaneously with ATP-site 2 and an AMP-site (Randak and Welsh 2003). The physical correlates of the AMP-binding site are unknown

are pumps that create or maintain concentration gradients (Higgins and Linton 2004). CFTR is a Cl^- channel and so far the only known channel protein in the ABC transporter family. Its function and nucleotide dependency can thus be studied by using the patch-clamp technique, a method with sufficient power to study even the activity of single CFTR molecules. Because of this unique experimental approach, progress in CFTR research has often guided research for other ABC transporters.

It has been known for several years that like other ABC transporters CFTR can hydrolyze ATP to adenosine diphosphate (ADP) and inorganic phosphate (P_i) (ATP + H_2O → ADP + P_i) (Anderson et al. 1991; Baukrowitz et al. 1994; Li et al. 1996). Most if not all hydrolysis is carried out at ATP-site 2 (Fig. 1, Aleksandrov et al. 2002; Basso et al. 2003; Berger et al. 2005; Szabo et al. 1999). Recent work with recombinant NBDs (Gross et al. 2006; Randak et al. 1995; 1997; 1999; Randak and Welsh 2003) and with CFTR channels (Randak and Welsh 2003) has shown that CFTR can also interact with adenosine monophosphate (AMP) at a distinct site and possesses readily reversible adenylate kinase activity (ATP + AMP_G ⇆ ADP + ADP). Both enzymatic activities of CFTR, ATPase and adenylate kinase, share an ATP-site (ATP-site 2, Fig. 1). When AMP binds to its site, hydrolytic release of the neighboring ATP γ-phosphate is prevented, and instead the γ-phosphate is transferred to AMP. This minireview focuses on the effects of the adenylate kinase substrates AMP and ADP on CFTR channel gating.

AMP induces an adenylate kinase-dependent gating mechanism

Normal CFTR gating is coupled to ATP binding and ATP-dependent enzymatic activity (Aleksandrov et al. 2007; Gadsby et al. 2006; Hanrahan et al. 2003; Sheppard and Welsh 1999). When ATP is the only nucleotide present, this enzymatic activity is ATPase activity. Several groups have shown that in this case the relationship between ATP concentration and CFTR current shows non-cooperative Michaelis–Menten behavior (Fig. 2 and Csanady et al. 2000; Randak and Welsh 2003; Szellas and Nagel 2003).

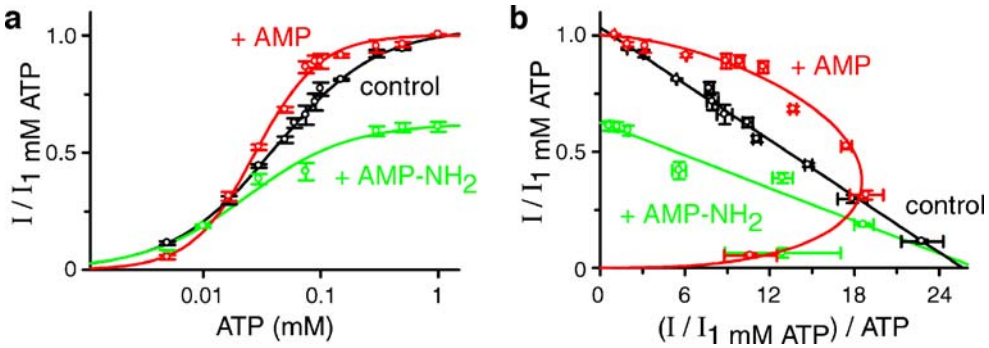

Fig. 2 AMP induces a gating mechanism involving two molecules of ATP and ATP/AMP phosphotransfer (adenylate kinase activity). **a**. Relationship between ATP concentration and Cl^- current (I). For experimental details see Randak and Welsh 2003. Currents were measured in the presence of ATP alone (control) and with 1 mM AMP or 5 mM AMP-NH_2 present. All currents were obtained in the continuous presence of protein kinase A (80 U/ml) and were normalized to the current obtained with 1 mM ATP under control conditions during the same experiment ($I/I_{1\ mM\ ATP}$). Data with AMP-NH_2 are from 23 patches with $n \geq 5$ for each ATP concentration. Control data and data with AMP are from Randak and Welsh 2003, with permission. Line for control data is fit to Michaelis–Menten equation using K_m of 40±2 μM and I_{max} of 1.03±0.01. In presence of AMP, line is fit to Hill equation with K_m of 28±1 μM, I_{max} of 1.00±0.01, and Hill coefficient of 1.60±0.07. In the presence of AMP-NH_2, line is fit to Michaelis–Menten equation using K_m of 23±3 μM and I_{max} of 0.63±0.01. **b**. Eadie–Hofstee plots of data from panel **a**. (Figure adapted from Randak and Welsh 2003, with permission)

AMP alone does not generate Cl^- currents when added to the cytoplasmic surface of phosphorylated CFTR channels (Randak and Welsh 2003; Schultz et al. 1995; Weinreich et al. 1999). When AMP was added in the presence of ATP neither the apparent K_m for ATP increased (Randak and Welsh 2003) nor the maximum current at high ATP concentrations changed significantly (Randak and Welsh 2003; Schultz et al. 1995). However, the relationship between ATP concentration and CFTR current showed a different and more complex pattern than in the absence of AMP, making it impossible to fit the data with a simple Michaelis–Menten equation (Fig. 2, Randak and Welsh 2003): an Eadie–Hofstee plot (Fig. 2b) was no longer linear but fit the data in a curve convex to the right, a shape diagnostic of a positively cooperative effect of ATP to generate current and consistent with a determined Hill coefficient of 1.6. Thus, the effect of adding AMP depended on the ATP concentration. At very low ATP concentrations, AMP reduced current, at intermediate ATP concentrations it increased current, and at high ATP concentrations (above ~10 times K_m) AMP did not significantly influence the magnitude of the current (Fig. 2a). When the effect of AMP on single-channel gating was examined it was found that AMP–like ATP–increased channel opening probability at intermediate ATP concentrations by shortening the mean interburst interval (Randak and Welsh 2003) suggesting that the changes in current seen at different ATP concentrations in the presence and absence of AMP reflect changes in the channel opening rate.

The finding that AMP did not increase the apparent K_m for ATP suggested that it did not compete with ATP. The pattern of positive cooperativity for ATP requiring a Hill coefficient closer to 2 than to 1 to fit the data indicates that the channel interacts with at least 2 molecules of ATP. Taken together, the results with AMP require a model with at least two sites for ATP and one distinct site for AMP to interact with the CFTR channel.

Did the effects of AMP on CFTR current involve ATP:AMP phosphotransfer (adenylate kinase activity)? To answer this question AMP was substituted by AMP-NH_2 (adenosine 5′-monophosphoramidate), an AMP analog that cannot act as a phosphate acceptor (Fig. 2, Randak and Welsh 2003). AMP-NH_2 did not induce the complex changes in the shape of the relationship between ATP concentration and CFTR current. As with ATP alone, the data could be fit to a non-cooperative Michaelis–Menten equation. However, AMP-NH_2 inhibited current partially and non-competitively with ATP by reducing the channel opening rate (Fig. 2a, Randak and Welsh 2003). The addition of AMP reversed AMP-NH_2 inhibition suggesting that both AMP and AMP-NH_2 interacted with the same site, the AMP-binding site (Randak and Welsh 2003). These findings suggested that AMP induced a gating mechanism that was different from the gating mechanism in the presence of ATP alone and involved ATP:AMP phosphotransfer (adenylate kinase activity).

ADP inhibits channel activity involving the reverse adenylate kinase activity

ADP is the substrate of the adenylate kinase reverse reaction, which forms ATP and AMP from two molecules of ADP. Consistent with AMP formation, adding ADP, but not ADP-NH_2 (adenylyl 5′-phosphoramidate, an ADP analog that does not allow phosphotransfer), induced similar complex changes in the shape of the relationship between ATP concentration and CFTR current as did AMP (Fig. 3a–d, Randak and Welsh 2003). However, ADP alone does not produce significant CFTR current (Anderson et al. 1991; Weinreich et al. 1999), even though the reverse adenylate kinase activity should generate ATP. In addition, ADP inhibited ATP-generated CFTR current by reducing the channel opening rate (Randak and Welsh 2003; Schultz et al. 1995; Sheppard et al. 1994; Winter et al. 1994). Some data are consistent with the hypothesis that ADP inhibits by competing with ATP for binding (Aleksandrov et al. 2001; Travis et al. 1993; Zhou et al. 2005). However, knowing that CFTR is an adenylate kinase raised the question of whether this enzymatic activity might be involved in ADP-dependent inhibition. Consistent with this notion, certain missense mutations that disrupted adenylate kinase-dependent gating significantly attenuated the effect of ADP to inhibit CFTR gating (summarized in Randak and Welsh 2005).

At a constant ATP concentration, ADP inhibited current in a dose-dependent manner (Fig. 3e, Anderson and Welsh 1992; Randak and Welsh 2005; Schultz et al. 1995; Weinreich et al. 1999). An Eadie–Hofstee plot of these data revealed a positively cooperative interaction of ADP with CFTR to cause inhibition (Fig. 3f, Randak and Welsh 2005). This result indicated that at least two molecules of ADP interacted with CFTR to inhibit current, which is consistent with the notion that the adenylate kinase reverse reaction is involved in ADP mediated current inhibition.

Further experiments measuring CFTR current inhibition by nucleotide diphosphates under conditions that either permitted or excluded phosphotransfer between diphosphates showed that ADP:ADP phosphotransfer (adenylate kinase activity) contributed to current inhibition (Randak and Welsh 2005). How can the reverse adenylate kinase reaction promote current inhibition and why does the formation of ATP in the reverse reaction not lead to current stimulation? A potential explanation notices ADP interacting with both CFTR ATP sites (Aleksandrov et al. 2001). ADP induces adenylate kinase activity, which leads to the

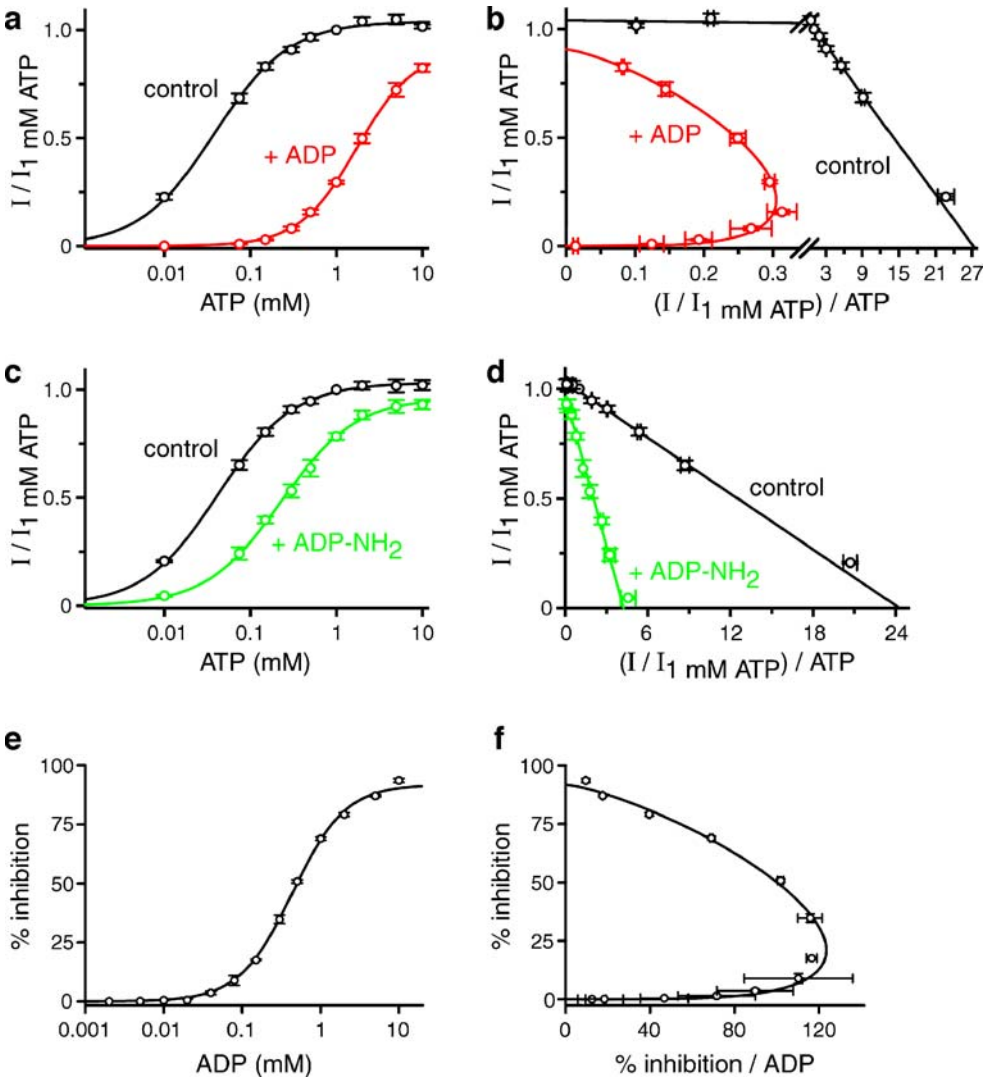

Fig. 3 The effect of ADP and ADP-NH_2 on CFTR Cl^- current. **a**. Effect of ATP concentration on current in absence and presence of 1 mM ADP. For the data in panels **a**–**d**, currents were normalized as in Fig. 2 and they were obtained in the continuous presence of protein kinase A (80 U/ml). Control data were fit to Michaelis–Menten equation using K_m of 38±2 μM and I_{max} of 1.04±0.01. Data in presence of ADP were fit to Hill equation using I_{max} of 0.91±0.03, apparent K_m of 1726±121 μM, and Hill coefficient of 1.30±0.01. Data are from Randak and Welsh 2003, with permission. **b**. Eadie–Hofstee plots of data in panel **a**. **c**. Effect of ATP concentration on current in absence and presence of 1 mM ADP-NH_2. Lines were fit to Michaelis–Menten equation; for control, K_m was 43±3 μM and I_{max} was 1.03±0.01; for ADP-NH_2, I_{max} was 0.96±0.02 and apparent K_m was 228±16 μM. Data are from Randak and Welsh 2003, with permission. **d**. Eadie–Hofstee plots of data in panel **c**. (Panels **a**–**d** are adapted from Randak and Welsh 2003, with permission). **e**. Effect of ADP concentration on CFTR Cl^- current inhibition. ADP was added to the cytosolic surface in the presence of 1 mM ATP and 80 U/ml PKA. Data are percentage inhibition compared to average of current immediately before and after ADP addition. Line is fit to the Hill equation using K_m of 0.43±0.01 mM, maximum inhibition of 91.74±0.90%, and Hill coefficient of 1.30±0.04. Data are from Randak and Welsh 2005, with permission. **f**. Eadie–Hofstee plot of data from panel **e**. (Panels **e**, **f** are adapted from Randak and Welsh 2005, with permission)

formation of ATP at only one of the two ATP-sites, i.e. at ATP-site 2 (Fig. 1). However, the opening mechanism associated with CFTR adenylate kinase activity involves interaction of ATP in a positively cooperative manner (Randak and Welsh 2003), i.e. normal opening involves two molecules of ATP. Thus, ADP bound to ATP-site 1 (Fig. 1) will inhibit channel openings more profoundly than if the opening mechanism was non-cooperative for ATP.

Implications for CFTR gating *in vivo*

Finding that CFTR can function either as an ATPase (if ATP is the only nucleotide present) or as an adenylate kinase (if ATP and AMP or ADP, respectively, are present) raises the question, which enzymatic activity gates the CFTR channel under physiologic conditions? *In vivo* usually all three nucleotides, ATP, ADP and AMP, are

present. Their physiologic concentrations and their relationship to CFTR's nucleotide binding affinities will determine the answer to this important question. Intracellular ATP concentrations have been measured from 1 to ~12 mM in several cells and tissues (Frederich and Balsch 2002; Kennedy et al. 1999). Because these values lie well above the ATP K_m's for gating by both enzymatic activities (Randak and Welsh 2003), ATP will not be the determining factor under basal conditions.

Both enzymatic activities share an ATP binding-site (ATP-site 2, Fig. 1), and most of the enzymatic activity in CFTR is at ATP-site 2. The ATP at site 2 is hydrolysed in the absence of AMP. However, if the channel has interacted with AMP, the ATP at site 2 is used as a phosphate-donor in the adenylate kinase reaction, and its γ-phosphate is transferred to the AMP molecule (Randak and Welsh 2003). Therefore, cytosolic AMP concentrations and CFTR's binding affinity for AMP are critical to determine which enzymatic activity, ATPase or adenylate kinase, will predominate *in vivo*. Intracellular AMP has been measured as 1–6% of the ATP concentration (Bozzi et al. 1994; Malaisse and Sener 1987; Olson et al. 1996; Pucar et al. 2002; Zeleznikar et al. 1995). With intracellular ATP ranging between 1 and ~12 mM the AMP concentration can therefore be estimated to lie between 10 and 700 μM; these concentrations would support adenylate kinase activity as indicated by the AMP K_m of 73±20 μM for CFTR gating (Randak and Welsh 2003), which is very similar to the AMP K_m of recombinant CFTR NBDs containing the adenylate kinase activity (Gross et al. 2006; Randak and Welsh 2003) and to that of physiologic active cytosolic adenylate kinases (Byeon et al. 1995; Font and Gautheron 1980; Ito et al. 1980; Okajima et al. 1993). Of note, the ABC-protein Rad50 has recently been shown to have a similar AMP K_m and to exhibit adenylate kinase activity *in vivo* (Bhaskara et al. 2007). Thus, these measurements suggest that CFTR will also function as an adenylate kinase *in vivo*. Physiologic ADP concentrations also bear on this issue. Intracellular ADP concentrations are reported to be 10–26% of the ATP concentration (Bozzi et al. 1994; Olson et al. 1996; Pucar et al. 2002; Zeleznikar et al. 1995), and therefore may be estimated to lie between 0.1 and 3 mM, concentrations that would affect CFTR currents (Fig. 3e).

Taken together, these arguments suggest that ATP binding to both NBDs influences CFTR gating, but in the presence of physiologic AMP concentrations the predominant enzymatic reaction regulating channel activity is probably adenylate kinase. This conclusion has important energetic implications because the standard transformed Gibbs energy of the ATPase reaction is large (~32 kJ/mole), while that of the adenylate kinase reaction is close to zero, and the equilibrium constant of the adenylate kinase reaction under physiologic conditions never varies far from 1 (Alberty and Goldberg 1992). CFTR forms an anion channel in which Cl^- flows passively in either direction across a membrane, following its electro-chemical gradient. Therefore, in the past, it has seemed difficult to reconcile the huge energy expenditure of ATP hydrolysis with the fact that CFTR transports Cl^- entirely passively and that no other ion channel is known to require the energy of ATP hydrolysis for gating. Because adenylate kinase activity releases little if any energy, our findings bring the energetics of CFTR ion transfer and gating in line with that of other ion channels.

Adenylate kinase activity intrinsic to CFTR may also have physiologic relevance because it couples channel gating with the ATP/ADP/AMP equilibrium or the cellular energy charge (Atkinson 1977), which reflects the metabolic energy stored in the adenine nucleotide system. Under conditions of increased energy demands, rising ADP concentrations would induce the reverse adenylate kinase reaction and reduce CFTR Cl^- currents, which would resume once the cellular energy charge increased again. Similar mechanisms have been proposed for inwardly rectifying K^+ channels (Dzeja and Terzic 1998).

It is also interesting to speculate that CFTR adenylate kinase activity could alter ATP, ADP, and AMP levels in a restricted local environment. Perhaps this activity could account for some of the reported effects of CFTR on other membrane transport processes (Kunzelmann 2003; Schwiebert et al. 1999).

Implications for other ABC transporters

The results with CFTR raise the question whether other members of the ABC transporter family may have AMP-sites and adenylate kinase activity. This possibility has recently been emphasized when Rad50 was shown to have both ATPase and adenylate kinase activities (Bhaskara et al. 2007). Rad50 is part of a DNA repair complex and not a transporter, but it shares the conserved structure of the ABC-NBDs with the ABC transporter superfamily. Its adenylate kinase activity has been found to regulate DNA tethering and to have an essential role in meiosis and telomere maintenance in *S. cerevisiae in vivo*.

Since the NBDs that contain the adenylate kinase activity in CFTR and the catalytic domain of Rad50 represent highly conserved structures within the ABC transporter superfamily, other members of this protein family may contain AMP-sites and utilize adenylate kinase activity to govern transport. This might occur if energy is not required for transport. Because hydrophobic substrates associate with membranes and some substrates are rapidly modified after translocation, it is not clear whether all other ABC transporters accumulate substrate above electrochem-

ical equilibrium. If transport were energetically neutral or downhill, adenylate kinase activity could suffice to control transport. Finally, some ABC transporters, such as the sulphonylurea receptor (SUR) (Matsuo et al. 2003) are not known to perform any transmembrane transport; instead, they regulate other processes. In this context it may be significant, that when the ABC multidrug transporter LmrA of *Lactococcus lactis* was studied in the presence of ADP, downhill substrate transport and ATP formation were demonstrated (Balakrishnan et al. 2004). It would be interesting to determine whether ATP was synthesized from ADP and P_i or from two ADP molecules via adenylate kinase activity. Adenylate kinase activity may provide a physiologic mechanism to couple transport of an ABC transporter to the metabolic state of the cell.

Finally, investigating the structural basis of AMP binding and adenylate kinase activity in CFTR and other ABC transporters may provide a new target for developing agonists and antagonists of potential value for therapy of diseases involving CFTR (cystic fibrosis and secretory diarrheas) as well as other ABC transporters.

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