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Molecular mechanism of the *Escherichia coli* maltose transporter

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Abstract

ATP-binding cassette (ABC) transporters are ubiquitous membrane proteins that import and export a large variety of materials across the lipid bilayer. A key question that drives ABC transporter research is how ATP hydrolysis is coupled to substrate translocation. This review uses the maltose transporter of *Escherichia coli* as a model system to understand the molecular mechanism of ABC importers. X-ray crystallography was used to capture the structures of the maltose transporter in multiple conformations. These structures, interpreted in the light of functional data, are discussed to address the following questions: 1. What is the nature of conformational changes in a transport cycle? 2. How does substrate activate ATPase activity? 3. How does ATP hydrolysis enable substrate transport?

Introduction

ATP-binding cassette (ABC) transporters harness the energy from ATP hydrolysis to activate transport of substrates across a membrane [1]. They are highly conserved from bacteria to humans. In prokaryotes, these proteins are critical survival factors, since they function in the uptake of nutrients and in the secretion of toxins and antimicrobial agents. In humans, there are 48 ABC transporters, including the multidrug-resistant transporter (P-glycoprotein), the transporter associated with antigen presentation (TAP), and the cystic fibrosis transmembrane regulator (CFTR) [1]. ABC transporters, both importers and exporters, contain two transmembrane domains (TMDs) that form a substrate translocation pathway and two nucleotide-binding domains (NBDs) that bind and hydrolyze ATP. To achieve active transport, the chemical event of ATP hydrolysis must be coupled to conformational changes that expose an internal substrate-binding site to either side of the membrane.

The maltose transport system of *Escherichia coli* has long been a prototype to investigate molecular mechanisms of ABC transporters. Studies of the maltose system can be traced back to 1948–1950, when Jacques Monod and Annamaria Torriani characterized amylomaltose activity in *E. coli* [2]. In 1981, approximately 80 scientists gathered in Seillac, France, for a workshop on “the maltose system in *E. coli* K12 as a tool in molecular

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Conflicts of interest

The author declares no conflicts of interest.

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genetics". Over the years, the genetics of this transporter have provided a large amount of mutation information [3]. Functional transporter has been reconstituted into proteoliposomes and nanodiscs, and activity assays are well established [4,5]. Fluorescence and electron paramagnetic resonance spectroscopy methods have been developed to probe conformational changes [6–8]. More recently, crystal structures of the maltose transporter have been determined in three functional states [9–11]. The rich genetic, biochemical, and structural data of the maltose transporter enabled detailed analysis of the molecular events that permit the coupling of ATP hydrolysis to substrate translocation.

Structural details of the alternating access model

The maltose transporter (MalFGK₂) is composed of two transmembrane (TM) subunits, MalF and MalG, and two subunits of a cytoplasmic ATPase, MalK. In addition, a periplasmic maltose-binding protein (MBP) is required to initiate the transport cycle [12]. The crystal structure of MalFGK₂, obtained in the absence of MBP and nucleotides, shows an inward-facing, resting state conformation [10]. The maltose-binding site is exposed to the cytoplasm and the NBDs of the MalK subunits are separated (Figure 1a). A pre-translocation complex [11], captured in the presence of the MBP but in the absence of ATP, reveals the initial contacts between MBP and the transporter MalFGK₂ (Figure 1b). MBP binds to the periplasmic surface in a closed conformation, with a maltose molecule bound between the N- and C-lobes. Compared with the resting state, the two TM subunits rotate toward the molecular center, narrowing the opening in the inner leaflet while maintaining a closed periplasmic gate. The large periplasmic P2 loop of MalF, too flexible to be observed in the crystal structure of the resting state, binds and orients MBP for productive interactions with the TMDs. The two NBDs of MalK also rotate inward, forming a semi-open dimer. ATP binding to the pre-translocation state promotes a concerted conformational change involving closure of the NBDs, opening of MBP, and rotation of the TMDs. In the resulting outward-facing state [9], the substrate is transferred from MBP into the TMDs and two ATP molecules are positioned at the closed MalK dimer interface for hydrolysis (Figure 1c).

During the transition between different states in the transport cycle, the subdomains maintain their tertiary structures, but their relative positions are changed through interfacial reorganization, except for the C-terminal regulatory domains of MalK, which maintain the same dimer interface in all three conformations. Preservation of the regulatory domain interfaces in the three conformations defined in the crystal structures is consistent with biochemical studies showing that MBP-stimulated ATPase activity is unaffected by disulfide linking of the regulatory domains [13].

A well-ordered phospholipid binds in a cavity between the first TM helix of MalG and a helical bundle from MalF. Like other annular lipids that stabilize the structure of membrane proteins, this lipid molecule co-purifies with the protein from the *E. coli* membrane and becomes an integral part of the transporter. Despite relative movement of the TM subunits, this lipid molecule resides in the same position on the protein surface in both the pre-translocation and outward-facing state structures. It appears to move in concert with the transporter during its catalytic cycle. This movement also implies that membrane proteins may displace phospholipids away from their normal positions in the bilayer, as suggested in studies of the voltage-dependent K⁺ channel [14].

How does substrate activate ATPase activity?

Given the high intracellular ATP concentration and the abundance ABC transporters, it is necessary to minimize ATP hydrolysis in the absence of substrate. This action is achieved through modulation of ATPase activity by the substrate. The maltose transporter is one of the most tightly regulated ABC transporters. In the absence of MBP, the resting state

transporter has very low ATPase activity [12]. In reconstituted proteoliposomes, maltose-loaded MBP stimulates hydrolysis by more than a 1,000-fold [10]. MBP binds on the periplasmic side of the membrane and ATP hydrolysis is catalyzed by NBDs on the other side of the membrane. How is the signal of MBP binding communicated across the membrane to the NBDs?

Structural and functional data show that the resting-state transporter is a poor catalyst because key residues are absent from the ATP-binding site to orient the γ -phosphate for nucleophilic attack [11]. Binding of MBP to MalFGK₂ induces a partial closure of the MalK dimer, bringing several catalytic residues in contact with the opposite NBD (Figure 1b). The conserved D-loop of one MalK subunit makes H-bonds with the Walker A S38 and the switch H192 of the other subunit. Both S38 and H192 are γ -phosphate sensors, as they interact directly with the γ -phosphate in the outward-facing state (Figure 1c). Binding of ATP to the pre-translocation state would cause rearrangements of the D-loop and switch motif H192, driving the progression to the outward-facing state.

Formation of the outward-facing conformation activates hydrolysis by bringing the conserved LSGGQ motif from the opposing subunit to the ATP-binding site (Figures 1c and 2a). The LSGGQ motif, reminiscent of the “arginine finger” in RecA-like ATPases, plays a key role in orienting the γ -phosphate of ATP for hydrolysis (Figure 2b). In the active site, a network of interactions is formed between ATP, Mg²⁺, the attacking water, and highly conserved catalytic residues (Figure 2c). The ATP β -phosphate forms hydrogen bonds with residues in the Walker A motif. The γ -phosphate interacts with the Walker A, the Q-loop, and the switch H192 of one MalK and the LSGGQ motif of the other MalK, thereby stabilizing the closed NBD interface. The Mg²⁺ ion is coordinated by the Walker A S43, the Q-loop Q82, two water molecules, and the β - and γ -phosphates. In the structure trapped by the transition-state analog ADP-VO₄, a carboxylate oxygen of the Walker B E159 is positioned 2.7 Å away from the hydrolytic water, consistent with the catalytic role of E159 in polarizing water for in-line attack on the γ -phosphorus of ATP (Figure 2c) [15].

For ABC exporters, direct interactions of the transport substrate with the TM subunits stimulate ATP hydrolysis. For importers such as the maltose transporter, the substrate acts through the binding protein. ATPase activity is stimulated by the substrate-loaded binding protein and not the free substrate [12]. Two laboratories have tested whether direct binding of maltose to MalFGK₂ is required for ATP hydrolysis. Shilton and colleagues designed a MBP mutant that binds both maltose and sucrose [16]. Genetic studies have shown that sucrose is a poor competitor for the maltose-binding site in MalFGK₂, suggesting that the maltose-binding site in MalFGK₂ does not recognize sucrose [17,18]. However, the mutant MBP stimulated the ATP hydrolysis equally well with maltose or sucrose, indicating that the closed conformation of MBP is sufficient to initiate the transport cycle [16]. Davidson and colleagues substituted an aspartate for glycine in the maltose-binding site to prevent maltose binding to MalFGK₂. This mutant eliminated maltose transport but retained ATPase activity [19]. These data indicate that, unlike exporters, the binding of free maltose to the transporter does not play a role in ATP hydrolysis.

How does ATP hydrolysis enable substrate transport?

In the maltose transport system, three steps are involved in transferring substrate across the inner membrane of *E. coli*: maltose binds to MBP, transfers from MBP to MalFGK₂, and is finally released from the transporter into the cell. ATP binding is associated with formation of the outward-facing state that transfers maltose from MBP to the membrane, and ATP hydrolysis is required to reset the transporter to the inward-facing state to release maltose.

When maltose diffuses into the periplasm through the outer-membrane channel maltoporin, it binds to MBP with a dissociation constant (K_d) of approximately 3.5 μ M [20]. Yet, the affinity of the maltose binding-site in MalFGK₂ is estimated to be 1–2 mM [21]. How is maltose transferred from the high-affinity site in MBP to the low-affinity site in MalFGK₂? The structure of the outward-facing conformation (Figure 1c) shows that interactions with the transporter abrogate maltose binding to MBP. Maltose binds to MBP in a cleft between two lobes connected by a flexible hinge, where it contacts both lobes [20]. In solution, this closed conformation is in equilibrium with an open conformation where maltose contacts only one lobe and dissociates more readily [22]. In the outward-facing state, MBP is stabilized in the reduced-affinity, open form (Figure 1c). Furthermore, a periplasmic loop of MalG (the scoop loop) inserts into MBP between the two lobes and partially occupies its maltose-binding site (Figure 3). The scoop loop may function as a competitive ligand to prevent maltose from rebinding to MBP. Consistently shortening the scoop loop by four residues resulted in retention of maltose in MBP and futile ATP hydrolysis [19]. In the outward-facing conformation, the two maltose-binding sites are exposed to each other in an enclosed, solvent-filled cavity (Figure 3). The volume of the cavity is approximately 6,500 $\text{\AA}^3$; thus, the effective concentration of maltose would be approximately 260 mM, more than 100-fold higher than the K_d of the binding site in MalFGK₂. These three features—open MBP, scoop loop insertion, and an enclosed cavity—virtually ensure that maltose is transferred from MBP to MalFGK₂.

Transition from the inward- to the outward-facing conformation, allowing substrate entry from the extracellular side, requires the binding energy of both MBP and ATP [23]. The same conformational change also enables ATP hydrolysis. What is the effect of ATP hydrolysis on the structure of the transporter? Although crystallization of the post-hydrolysis state has not been successful, electron paramagnetic resonance studies indicated that ATP hydrolysis would destabilize the closed MalK dimer and reorient the TMDs toward the cytoplasm [24,25]. The two lobes of MBP would move in concert with MalF and MalG to form the closed structure without maltose. Thus, the post-hydrolysis state is a high-energy intermediate [26], resulting in spontaneous dissociation of MBP and resetting the transporter to the resting state. In this conformation, an aqueous channel connects the low-affinity binding site in MalFGK₂ with the cytoplasm and maltose could be released into the cell through diffusion (Figure 4).

Conclusion

ABC transporters, with more than 2000 members identified, constitute one of the largest protein families in nature. It is possible that not all ABC transporters evolved from the same origin [27]. Whereas the structure and sequence of the NBDs are highly conserved among all ABC transporters, the TMDs can be categorized into type I importers, type II importers, and exporters. I believe that the model described in this review (Figure 4) may well apply to other type I importers, which share a common TM core with the maltose transporter [28]. Studies of the vitamin B₁₂ transporter suggest that type II importers function through a distinct mechanism [29–32]. ABC exporters differ from importers in both the architecture of the TMDs and the NBD/TMD interfaces [33–37]. Therefore, how ATP hydrolysis and substrate translocation are coupled in exports will almost certainly differ from that of importers. I look forward to future studies that correlate structure with function and provide molecular understanding of how exporters function.

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Highlights

- Three crystal structures of the maltose transporter are analyzed
- Described the nature of conformational changes in a transport cycle
- A proposed mechanism explains how ATP hydrolysis is coupled to substrate transport

Figure 1. Three structures of the maltose transporter

Ribbon representation and a surface slab view of **(a)** the inward-facing, resting state, obtained in the absence of MBP, maltose, and ATP; **(b)** the pre-translocation state representing the initial complex formed between closed MBP and MalFGK₂; and **(c)** the outward-facing, catalytic intermediate conformation where maltose is delivered to MalFGK₂ and ATP is poised for hydrolysis. Zoom-in views of the corresponding NBD dimer interface are shown in circles. Maltose and nucleotides are shown in ball-and-stick models.

Figure 2. Catalytic center for ATP hydrolysis

(a) The MalK (NBD) dimer viewed from the membrane. LSGGQ and Walker A (WA) motifs are highlighted. ADP-VO₄ is shown in a ball-and-stick model. (b) Comparison of active sites of MalK and F1-ATPase. The structure of the maltose transporter in complex with AMP-PNP and the structure of F1-ATPase in complex with AMP-PNP (PDB code: 2JDI) are aligned on the basis of their Walker A motifs (gray). The LSGGQ motif of MalK and the arginine finger of F1-ATPase are located in similar positions, making contacts with oxygen atoms on the γ -phosphate. Figure modified from [11]. (c) Schematic illustrations showing coordination of ADP-VO₄. Residues from the two MalK subunits are differentiated by color (red and green). Hydrogen bonds and Mg²⁺ coordinations are indicated by dashed lines along with contact distances (in Å). Figure modified from [15].

Figure 3. Enclosed maltose-binding cavity in the transition state complex
Slab view of the cavity, with proteins shown in space-filling models. Maltose is shown in a ball-and-stick model. The scoop loop from MalG is labeled. The viewing angle of this figure differs from that of Figure 1c.

Figure 4. Mechanism of maltose transporter

Maltose binding to MBP stabilizes a closed conformation that interacts with the resting state MalFGK2. Binding of MBP to MalFGK2 brings the NBDs closer so that ATP-binding promotes a concerted motion of MalK closure, reorientation of the TM subunits, and opening of MBP. Formation of the outward-facing conformation transfers maltose from MBP to the TM binding site, while positioning ATP at the catalytic site for hydrolysis. ATP hydrolysis is catalyzed through a general base mechanism. The high-energy post-hydrolysis state may have a conformation similar to that of the pre-translocation state. The transporter resets into the resting state upon dissociation of ADP and MBP.