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REVIEW

Unique features of myosin VI: a structural view

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Abstract Myosin VI is the only known molecular motor for the transportation of cargo vesicles from the plus end to the minus end of actin filaments. Thus, myosin VI possesses several unique features to distinguish it from other myosin family motors, such as the ability to move in a reverse direction, the unusual large walking step size, and the cargo-mediated dimerization. Recent structural studies of myosin VI have provided mechanistic insights into these unique features. On the basis of the resolved structures of myosin VI each domains (i.e., the structures of the N-terminal motor domain, the C-terminal cargo binding domain, and the region in the middle), the unique features of myosin VI will be reviewed here from a structural perspective. The structural studies of myosin VI definitely provide some answers about the unique features of myosin VI, but also raise significant questions on how myosin VI functions as a special motor both for directional cargo transport and for structural anchoring.

Keywords molecular motor, myosin VI, cargo transport, cargo binding, walking step size

1 Introduction

Myosin family proteins are actin-based molecular motors essential for a variety of cellular processes ranging from muscle contraction to directional cargo transport (Sellers, 2000; Foth et al., 2006; O'Connell et al., 2007). Among them, myosin VI is the only known unconventional myosin (with respect to the conventional myosin for muscle contraction) to date that can transport cargo vesicles from the plus end to the minus of actin filaments (Buss et al., 2004; Sweeney and Houdusse, 2007; Buss and Kendrick-Jones, 2008). Myosin VI was originally discovered as a member of actin-filament-associated proteins (Kellerman and Miller, 1992; Hasson and Mooseker, 1994), and the following motor-walking studies showed that myosin VI walks efficiently along actin-filaments with high duty ratio, ideally functioning as a processive transporter (Wells et al., 1999; Rock et al., 2001; Nishikawa et al., 2002; O'Connell et al., 2007). Being a transporter, myosin VI has been discovered to play critical roles in the control of various transport-based cellular activities (Fig. 1B), e.g., clathrin-coated/uncoated vesicle-mediated endocytosis (Buss et al., 2001; Morris et al., 2002; Aschenbrenner et al., 2004; Dance et al., 2004;), leading edge protrusion during cell migration (Geisbrecht and Montell, 2002; Chibalina et al., 2009), and asymmetric distribution of cellular components in epithelial cells (Au et al., 2007). As the active functions in collective cell migrations, overexpression of myosin VI ultimately leads to severe disorders, such as ovarian and prostate cancers (Yoshida et al., 2004; Dunn et al., 2006).

In addition to being a transporter, myosin VI was also intriguingly discovered to function as a non-processsive anchor, linking cellular components and membranes to the cytoskeletons and thus stabilizing a number of cellular structures (Fig. 1B), such as the trans-Golgi network, the stereo-cilia of inner hair cells, the apical junctions of epithelial cells, and the transcription machinery in the nucleus (Hasson et al., 1997; Warner et al., 2003; Seiler et al., 2004; Sahlender et al., 2005; Vreugde et al., 2006; Maddugoda et al., 2007). Due to the significant structural anchoring roles, genetic mutations of myosin VI result in the severe hearing loss, Snell's waltzer deafness (Avraham et al., 1995; Melchionda et al., 2001). Therefore, based on current studies, myosin VI could function both as a transporter and as an anchor, and the switch between these two functions might be controlled by cargo-loading (Altman et al., 2004; Iwaki et al., 2006).

As a processive transporter, distinct from other myosin motors, myosin VI possesses several unique features on its own. Firstly, myosin VI is the only known myosin motor for reverse cargo transportation (opposite to the conventional myosin transportation direction), i.e., transporting cargo vesicles toward the minus end of actin-filaments (Wells et al., 1999). Secondly, the specific dimerization of

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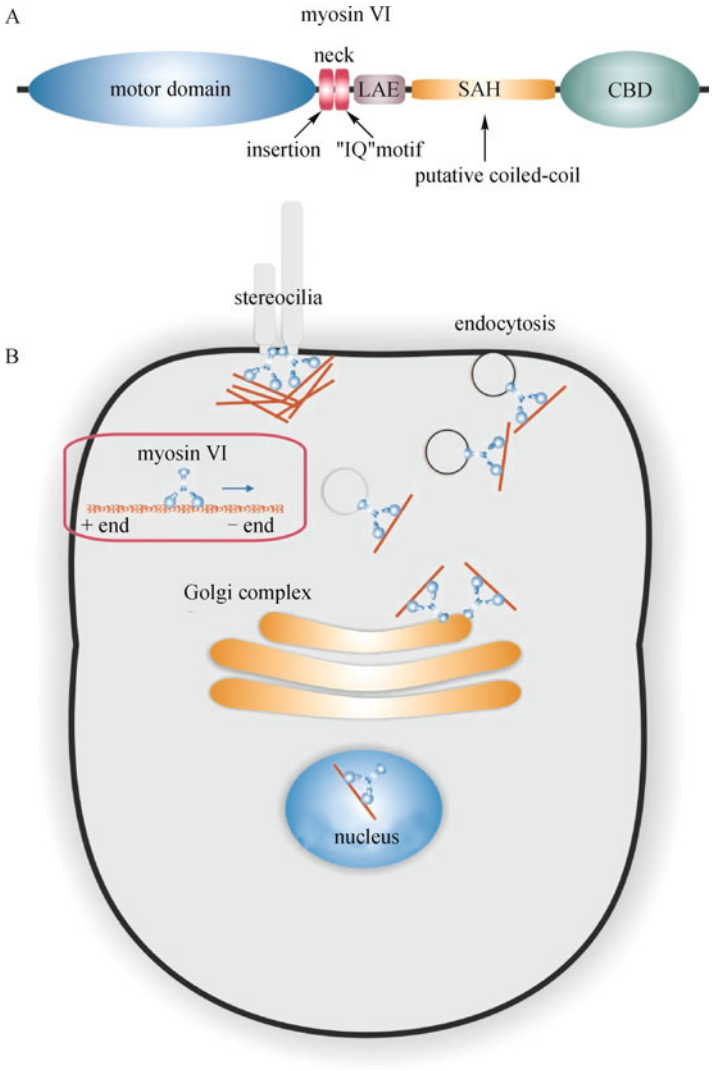

Fig. 1 Myosin VI is a unique molecular motor playing diverse roles in a variety of cellular processes. **A**: Domain organization of myosin VI. Myosin VI contains an N-terminal motor domain, a short neck region/lever arm (including a unique insertion and one "IQ" motif), a lever arm extension (LAE) and a single α-helix (SAH) (a putative coiled-coil domain) in the middle, and a C-terminal cargo-binding domain (CBD). **B**: Myosin VI is an actin-filament minus-end-orientated myosin motor and plays diverse roles in a variety of cellular processes, including clathrin-coated/uncoated vesicle-mediated endocytosis and stabilization of the basal region of stereo-cilia, the trans-Golgi complexes, and the nuclear transcription machinery. Myosin VI is shown in a dimeric state with two motor heads attaching to actin-filaments.

molecular motors is required for them to walk along the cytoskeletons like "two legs"; however, myosin VI has been found to exist as a monomer in solution (Lister et al., 2004). Recent studies of myosin VI also demonstrated that it indeed could form a specific dimer but only during vesicle transportation (after the cargo-loading) (Park et al., 2006; Altman et al., 2007). Therefore, myosin VI can exist both as a monomer and as a dimer. Finally, according to the "lever arm hypothesis" for molecular motors, the walking step size is directly correlated with the length of the neck region/lever arm (i.e., the longer the lever arm, the bigger the step size) (Spudich, 2001). Interestingly, myosin VI only contains a small lever arm (three times shorter than myosin V) (Fig. 1A), but still walks along actin-filaments with much larger than expected step sizes, thus challenging the classical swigging lever arm hypothesis (Rock et al., 2001; Nishikawa et al., 2002). All these unique features distinguish myosin VI from other myosin motors and might endow myosin VI with a distinct walking mechanism.

Myosin VI is composed of an N-terminal motor domain, a short neck region and a single α-helix (SAH) domain in the middle, and a C-terminal cargo binding domain (CBD) (Fig. 1A). Recently, structural studies of these isolated domains of myosin VI have largely uncovered the molecular basis of its unique features (i.e., the reverse transport direction, the monomer/dimer conversion, and the large step size with short lever arm) with a clear

structural picture (Menetrey et al., 2005; Spink et al., 2008; Mukherjea et al., 2009; Phichith et al., 2009; Yu et al., 2009). Here, these unique features of myosin VI will be reviewed from a structural view, thus providing mechanistic insights for the understanding of myosin VI as a processive molecular motor.

2 Reverse transport direction of myosin VI

Compared with other myosin family motors, myosin VI was originally discovered as a processive motor but with the ability to move in the reverse direction (i.e., from the plus end to the minus end of actin-filaments) (Mermall et al., 1994; Wells et al., 1999). The studies further showed that the reverse-direction movement of myosin VI might be achieved by rotating its lever arm in the opposite direction to the conventional myosin lever arm movement (Wells et al., 1999). Interestingly, unlike other myosin motors, myosin VI has a large unique insertion between its motor domain and its single "IQ" motif (the specific apo-calmodulin (CaM) binding sequence) (Fig. 1A). The studies of this unique insertion unexpectedly demonstrated that it can specifically bind to Ca^{2+}-CaM and act as an integral part of the myosin VI "converter" region, and thus might reposition the myosin VI "lever arm" for reverse transportation (Bahloul et al., 2004).

The crystal structure of the motor domain together with the unique insertion and the IQ motif (both in complex with the CaM) in the nucleotide-free form (the post-powerstroke/rigor-like status) has been solved (Menetrey et al., 2005). As expected, the structure revealed that, in addition to the classical "IQ" motif for the apo-CaM binding, the large unique insertion between the motor domain and the "IQ" motif is indeed a specific Ca^{2+}-CaM binding site (Fig. 2B). This unique insertion continuously integrates the "converter" region with the "IQ" motif and thus keeps the lever arm orientated in a direction (pointing to the minus end of actin-filaments) opposite to that of the conventional myosin lever arm, thus contributing to the reverse transport direction (Menetrey et al., 2005) (Fig. 2B).

The structural basis for the reverse transport direction was further explained by the crystal structure of the motor domain in the ADP/Pi-bound form (the pre-powerstroke status) (Menetrey et al., 2007). The structure revealed that, compared with the structure in the post-powerstroke state, the "converter" region and the following unique insertion region undergo large conformational rearrangement, which fixes the lever arm in an orientation pointing to the plus end

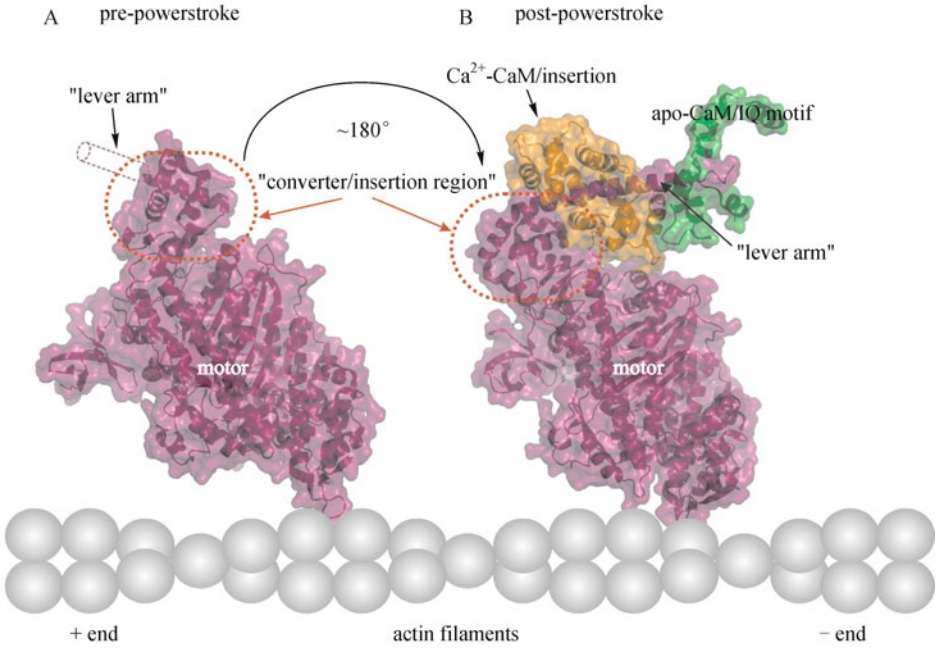

Fig. 2 Structural basis of the reverse transport direction of myosin VI. **A**: A ribbon diagram combined with surface representation of the myosin VI motor domain in the ADP/Pi-bound state (the pre-powerstroke state) (PDB code: 2V26). The lever arm not included in the structure is represented by a dash cylinder. **B**: A ribbon diagram combined with surface representation of the motor domain together with the lever arm (including the unique insertion and the "IQ" motif both in complex with the CaM) in the nucleotide-free state (the post-powerstroke state) (PDB code: 2BKI). The motor domain (including the converter/insertion region and the lever arm), the Ca^{2+}-CaM, and the apo-CaM are colored in purple, orange, and green respectively. From the pre-powerstroke state to the post-powerstroke state, the "converter/insertion" region of the motor undergoes significant conformational changes and the lever arm rotates about 180° re-pointing from the plus end to the minus end of actin-filaments.

of actin-filaments (Fig. 2A). On the basis of the crystal structures of the motor domain (together with the lever arm region) both in the pre-powerstroke and the post-powerstroke stages, the molecular mechanism of the reverse transport direction is more defined (Menetrey et al., 2005; Menetrey et al., 2007). Upon tightly binding to actin-filaments, the "converter" region together with the unique insertion of myosin VI largely determine the lever arm orientation. Before ADP/Pi release (the pre-powerstroke state), the lever arm orientates to the plus end of actin-filaments (Fig. 2A). When myosin VI transits from the pre-powerstroke state to the post-powerstroke sate, the "converter" and the insertion regions undergo large conformational changes, and the lever arm rotates about 180° re-pointing from the plus end to the minus end of actin-filaments, therefore, allowing myosin VI to walk along actin-filaments in a reverse direction (Fig. 2B). But unfortunately, the molecular mechanism for such extreme conformational rearrangements during the pre/post-powerstroke transitions is unclear yet (Menetrey et al., 2007).

3 Cargo-mediated dimerization of myosin VI

According to the classical myosin working model, dimerization of the motor via the C-terminal coiled-coil domain is critical for the processive walking of myosin along the actin-filaments (Spudich, 2001). Distinct from other myosin motors, the purified native myosin VI was surprisingly found to exist as a monomer *in vitro* in the electron microscopy (EM) studies (Lister et al., 2004). However, additional EM studies of myosin VI showed that the purified myosin VI can form dimers but only at high concentrations through clustering-induced dimerization (Park et al., 2006). The fluorescence resonance energy transfer-based (FRET) assay *in vivo* also demonstrated that myosin VI indeed forms dimers on the surface of transport vesicles, although the molecular mechanism is unknown (Altman et al., 2007).

Actually, myosin VI also contains a putative coiled-coil domain in the C-terminus supposedly for the dimerization of myosin VI (Fig. 1A). However, recent studies of the coiled-coil domain found that this domain only forms an extended monomeric helix that defines the stepping space and does not contribute to dimer formation (Spink et al., 2008). The studies immediately raise an important question regarding the dimerization mechanism of the motor: which part of myosin VI is responsible for the dimerization? The *in vivo* FRET studies of myosin VI have already revealed that the CBD is essential for the dimerization of myosin VI (Park et al., 2006). Furthermore, cargo-binding is also essential, as myosin VI moves along the actin-filaments processively only upon cargo-binding (Iwaki et al., 2006). Hence, both the myosin VI CBD and the related cargo-binding are essential for the dimerization of myosin VI.

We first determined the solution structure of the CDB in the apo-form. Before cargo-binding, the CBD is a monomer at low concentrations, but can form large aggregates at high concentrations (Yu et al., 2009). However, the CBD alone cannot form a specific dimer. We further determined the crystal structure of the CBD in complex with a cargo adaptor Dab2. Unexpectedly, the CBD/Dab2 complex forms a specific dimer with the two continuous helices of Dab2 tethering two CBD together (Fig. 3). Therefore, upon cargo adaptor binding, the CBD together with the cargo adaptors form specific dimers, and myosin VI undergoes the cargo-mediated dimerization, i.e., the synergetic bindings between the CBD and its cargo adaptors dimerize myosin VI for cargo transportation (Yu et al., 2009). The results were further confirmed by EM studies. Without cargo adaptors such as Dab2 or optineurin, myosin VI only exits in a monomeric form. However, after adding the cargo adaptors, myosin VI forms specific dimers with two clearly observed "heads" (motors) under EM (Phichith et al., 2009). Hence, all the studies uncovered the unique dimerization mechanism of myosin VI, i.e., the cargo-binding-mediated dimerization.

4 Large step sizes of myosin VI

On the basis of the lever arm hypothesis, binding of CaM to the "IQ" motifs of each motor causes the motifs to form rigid extended α-helices, which function as the two "legs" for each myosin dimer to walk along actin-filaments (Spudich, 2001) (Figs. 2 and 3). Therefore, the length of the lever arms is directly correlated to the step size of each myosin motor, i.e., the longer the lever arm, the larger the step size. Compared with other myosin family motors, myosin VI has a very short lever arm, containing only two "IQ" motifs (including the unique insertion) (Fig. 1A), and hence, the theoretic step size of myosin VI should be much smaller than other myosin motors, such as myosin V (six "IQ" motifs with a ~36 nm step size) (Mehta et al., 1999; Walker et al., 2000). However, the stepping studies of myosin VI surprisingly discovered that myosin VI still walks along actin-filaments with a large step size of 30–36 nm (Rock et al., 2001), and the discovery somewhat challenges the classical lever arm hypothesis for myosin motor stepping (Spudich and Sivaramakrishnan, 2010).

The structural studies of the C-terminal putative coiled-coil domain have already found that the domain does not form the coiled-coil dimer, but only forms one long extended rigid helix that can lengthen the short lever arm and ideally provide much space for myosin VI to walk with large step sizes (Spink et al., 2008). There is a small region closely linked to the lever arm, namely lever arm extension (LAE in short) (Fig. 1A). Initial studies of this region showed that it is highly flexible and can extend the short lever arm for large step sizes (Rock et al., 2005). However, further small angle X-ray scattering (SAXS) studies of this

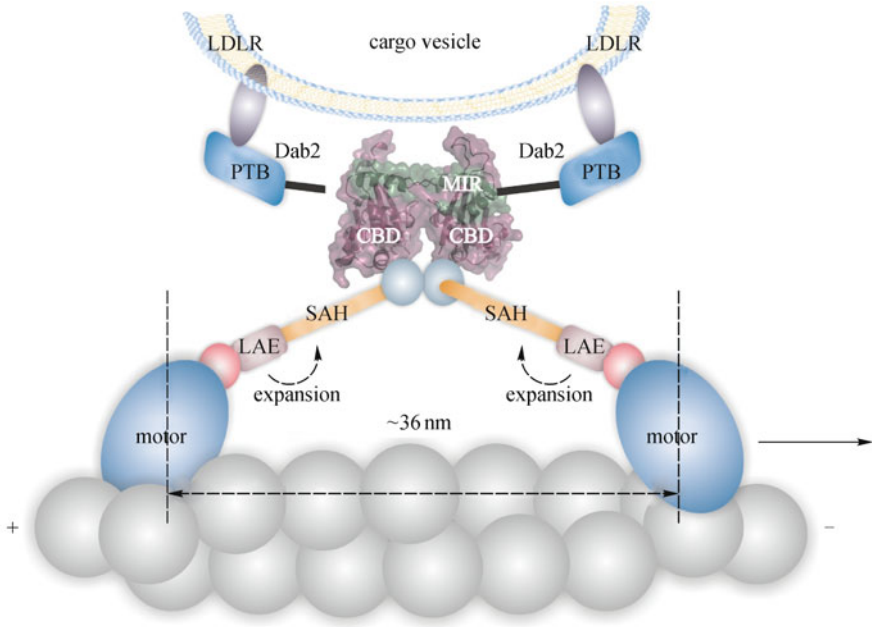

Fig. 3 Structural insights into the cargo-binding-mediated dimerization and the large step size of myosin VI. A schematic model showing the dimeric myosin VI walks along actin-filaments with a ~36 nm step size. The synergistic binding between the CBD and the Dab2 (i.e., two continuous helices of Dab2 C-terminal tail tether the two CBD together) results in the dimerization of myosin VI. Interestingly, both the isolated CBD and the isolated Dab2 are monomers, and therefore, myosin VI forms specific dimers only upon cargo-binding. The large ~36 nm step size of myosin VI might be contributed by both the SAH and the LAE expansion (indicated by the dash arrows). The myosin VI CBD/Dab2 complex structure (PDB code: 3H8D) is in the combined surface and ribbon representations; other domains of myosin VI, the cargo adaptor Dab2, and the cargoes, are all in the cartoon representations for simplicity.

region demonstrated that it forms a well-folded structure and cannot account for the large stepping (Spink et al., 2008). Interestingly, recent studies of this region showed that it can be unfolded/expanded, and the unfolding of the LAE is triggered by myosin VI dimerization (Mukherjea et al., 2009). Therefore, the myosin VI LAE undergoes dimerization-mediated lever arm expansion to allow a large walking step size; however, the molecular mechanism for its opening is still an open question. In summary, the regions after the original lever arm including the LAE and the SAH regions might be both critical for the large stepping (Spink et al., 2008; Mukherjea et al., 2009), and myosin VI employs these unique structural components hidden in the C-terminus to achieve the large step size required for efficient cargo transportation (Fig. 3).

5 Concluding remarks

The unique features of myosin VI (i.e., the reverse transport direction, the cargo-mediated dimerization, and the large step size) endow it as a special myosin motor for the efficient transportation of cargos from the plus end to the minus end of actin-filaments. Recent structural studies of the isolated domains of myosin VI provide mechanistic insights underlying these unique features, but also raise more significant questions regarding the conformational change mechanism of "converter"/insertion regions during the pre/post-powerstroke transitions, the regulation mechanism of cargo-binding (e.g., how are cargoes unloaded from the motor, and how does cargo-unloading further control the dimer-monomer switch potentially for structural anchoring?) and the lever arm expansion mechanism (e.g., how does the LAE expand itself during the cargo transportation?). All of these questions are worthwhile for further investigations. Furthermore, the current structural studies of myosin VI are limited to each isolated domains, and the overall structural picture of myosin VI in detail is still required for the complete understanding of myosin VI as a unique myosin motor. We believe that, using a combination of different structural biology methods, the complete picture of how myosin VI functions will emerge in the near future.

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