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A model of processive movement of dimeric kinesin

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ABSTRACT

Dimeric kinesin can move processively on microtubule filaments by hydrolyzing ATP. Diverse aspects of its movement dynamics have been studied extensively by using various experimental methods. However, the detailed molecular mechanism of the processive movement is still undetermined and a model that can provide a consistent and quantitative explanation of the diverse experimental data is still lacking. Here, we present such a model, with which we study the movement dynamics of the dimer under variations of solution viscosity, external load, ATP concentration, neck linker length, effect of neck linker docking, effect of a large-size particle attached to one kinesin head, etc., providing consistent and quantitative explanations of the available diverse experimental data. Moreover, predicted results are also provided.

1. Introduction

Kinesins are a class of motor proteins capable of moving on microtubule (MT) filaments by hydrolyzing ATP (Howard, 1996; Hirokawa, 1998; Vale, 2003; Cross, 2004; Asbury, 2005; Kikkawa, 2008). According to their structures, they fall into two forms—monomers and dimers. In this work, we focus on the dimer such as conventional kinesin [kinesin-1 family (Lawrence et al., 2004)] that consists of two identical N-terminal motor domains or heads that are connected together by a rod-shaped, coiled-coil stalk through their neck linkers.

Since its discovery (Vale et al., 1985), the movement dynamics of kinesin-1 has been studied extensively by using various experimental methods. It has been well determined that the dimer can advance stepwise over the MT surface lattice and towards the plus end in about 8 nm increments—the MT tubulin dimer repeat distance, with a run length in the order of micrometers. The processive movement is in a hand-over-hand manner (Yildiz et al., 2004): a given head is displaced in discrete steps with a size of about 16 nm, resulting in the step size of the dimer of about 8 nm. In particular, by using single-molecule optical trappings, many aspects of dimer's dynamics such as the mean movement velocity, stall force, backward stepping, etc., under various loads and ATP concentrations have been studied elaborately (Howard et al., 1989; Svoboda and Block, 1994; Visscher et al., 1999; Nishiyama et al., 2002; Carter and Cross, 2005). Recently, Yildiz et al. (2008) and Clancy et al. (2011) studied in detail the effects of the extension of the neck linkers on the processive movement of the dimeric kinesin. They found that the extension decreases greatly the movement velocity and the mechanochemical coupling ratio (i.e., the ratio of the mean number of forward steps to the mean number of ATP molecules hydrolyzed), and also has a substantial effect on the stall force (Clancy et al., 2011). Khalil et al. (2008) found that nullifying the neck linker docking reduces its movement velocity and stall force. More recently, Sozański et al. (2015) revealed that the increase in solution viscosity has a major deterious effect on the movement of the dimer although it does not affect ATPase activity.

It is puzzling that while the extension of the neck linkers has nearly no effect on the ATPase activity (Yildiz et al., 2008), it decreases greatly the movement velocity and the mechanochemical coupling ratio (Yildiz et al., 2008; Clancy et al., 2011). Since the extension has no effect on the neck linker docking and the interaction of the head with MT, it is puzzling that how the extension can have a substantial effect on the stall force. Since the mechanical stepping is very fast and the ATPase rate that is independent of solution viscosity is the rate-limiting factor to the movement of the dimeric kinesin (Carter and Cross, 2005), it is puzzling how the increase in the solution viscosity can affect significantly the movement velocity (Sozański et al., 2015). Moreover, considering that the increase in the solution viscosity by only several-fold can reduce greatly the movement velocity (Sozański et al., 2015), it is more puzzling that attaching a particle of size of 40 nm to one head of the dimer has only a slight effect on the movement velocity (Mickolajczyk et al., 2015; Isojima et al., 2016), and attaching a bead of size of micrometer to the coiled-coil stalk of the dimer has little effect on the movement velocity and in addition the dimer can even undergo a backward load of as large as 6–7.5 pN (Visscher et al., 1999; Carter and Cross, 2005; Khalil et al., 2008).

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To understand the molecular mechanism of the processive movement of dimeric kinesin, a lot of models have been proposed in the literature. Generally, these models can be classified into two types [see, e.g., review paper (Xie, 2010a)]. In the first and prevailing type of the model, after ATP hydrolysis and then Pi release the trailing head detaches from the MT and the detached trailing head is not allowed to rebind the MT until the ATP-binding-induced neck linker docking in the leading head drives the detached head moving to the leading position and then binding the nearest MT-binding site, triggering ADP release. Since in this model the neck linker docking provides the driving force to facilitate the forward movement of the detached trailing head, the model was called neck-linker-docking (NLD) model. In the second type of model, there are two pivots. The first one is that the strong interaction of the kinesin head in ATP and ADP.Pi states with the MT induces the local conformational change of the MT-binding site (Hoenger et al., 1995; Hoenger and Milligan, 1997; Hirose et al., 1997; Krebs et al., 2004; Gigant et al., 2013; Morikawa et al., 2015). Upon the interaction between the head and MT becoming weak induced by Pi release, the locally changed conformation of the MT-binding site relaxes to its normally unperturbed conformation with a delayed time relative to the Pi-release-induced conformational change of the kinesin head. Thus, after Pi release the binding energy of the ADP-head with the local MT-binding site is temporally weaker than that with other unperturbed MT-binding sites. The other pivot is that there exists an interaction between the two heads. This type of model was thus called two-heads-interacting (THI) model (Xie, 2010a). It is noted that in this type of model, the MT plays a crucial active role in the kinesin movement due to the first pivot, in contrast to the NLD model where the MT acts only as a passive track. Combining the two types of model, another model has also been proposed in the review paper (Xie, 2010a), where besides the interaction between the two heads, the neck linker docking in the MT-bound head also prevents the detached head from moving backwards to rebind the previous binding site. This model was thus called two-heads-interacting plus neck-linker-docking (THI-NLD) model.

In this work, we improve the THI-NLD model. With the improved model, we try to explain quantitatively the diverse experimental data on moving dynamics of the dimeric kinesin. To illustrate this, here we make comparisons of our calculated results with some typical experimental results that seem difficult to explain consistently with a model. In particular, our model gives a consistent and quantitative explanation of the puzzling experimental results mentioned above.

2. Methods

2.1. The model

As done in the THI-NLD model (Xie, 2010a), we make following three assumptions to build up the model used in this work.

(i) As done before (Xie et al., 2007; Xie, 2008, 2010a), we assume that after Pi release the binding energy of the ADP-head with the local MT-binding site is temporally weaker than that with other unperturbed MT-binding sites. This can be understood as follows. The strong binding of nucleotide-free, ATP- or ADP.Pi-head leads to a conformational change of the local MT-tubulin heterodimer (Hoenger et al., 1995; Hoenger and Milligan, 1997; Hirose et al., 1997; Krebs et al., 2004; Gigant et al., 2013; Morikawa et al., 2015), resulting in the local tubulin having a further weaker interaction with the ADP-head than other unperturbed tubulins during a short time period after the kinesin head changes its conformation from ADP.Pi to ADP form but before the local tubulin heterodimer relaxes to its normally unperturbed conformation. In a time of t_r, the local tubulin heterodimer relaxes to its normally unperturbed conformation, with the interaction energy of the local tubulin with the ADP-head becoming the same as other tubulins.

(ii) To be consistent with the available experimental data (Rice et al., 1999; Asenjo et al., 2006), we assume that the neck linker docking of a head is dependent on its nucleotide state: when the head is in ATP or ADP.Pi state there is a *small* free energy to facilitate its neck linker docking into the motor domain, while when the head is in nucleotide-free or ADP state no such free energy is present to facilitate the neck linker docking.

(iii) In the THI and THI-NLD models (Xie, 2008, 2010a), it was proposed that the binding energy between the two heads is independent on the nucleotide states of the two heads. Here, in the improved model we assume that the binding energy between the two heads is dependent on the nucleotide states of the two heads. Considering that during stepping the detached head is in ADP state and the MT-bound head can be in ATP or ADP.Pi or nucleotide-free state, it is argued that when the MT-bound head is in ATP or ADP.Pi state and the other head is in ADP state the two heads have a low binding energy, while when the MT-bound head is in nucleotide-free state and the other head is in ADP state the two heads have a high binding energy. In addition, when both heads are in ADP state the two heads also have a high binding energy. Alternatively, it is assumed that the neck linker docking in one head weakens the interaction between the two heads. The structural data of dimeric kinesin with both heads bound by ADP (Kozielski et al., 1997) are consistent with this assumption. The biochemical data of Hackney (1994), showing that upon the dimer with both heads bound by ADP mixing with MT only half fraction of ADP molecules are released, are also consistent with this assumption.

2.2. Potential of interaction between a kinesin head and MT

Based on assumption (i) (see above section), we take the interaction potential of a kinesin head with MT as described as follows. In nucleotide-free state the kinesin head binds strongly to MT, with the interaction potential being written as $V_S(x, y, z, \alpha, \theta) = V_{Sx}(x)V_y(y)V_z(z)V_\alpha(\alpha)V_\theta(\theta)$, where coordinate *oxyz* is defined in Fig. 1a, α is the nutational angle of the kinesin head and θ is the rotational angle (when the kinesin head is in the MT-binding site, α and θ correspond to the angles of rotations in *xoz* and *xoy* planes, respectively). Since the flexible neck linker, which is stretchable and bendable easily, is incompliant to make a torsional rotation, we do not consider here the *precession* motion of the head by twisting the neck linker (i.e., the rotation around the direction of its neck linker), which corresponds to the rotation in the *yoz* plane when the head is in the MT-binding state. Term $V_{Sx}(x) < 0$ (with the maxima equal to zero) represents the interaction potential between the kinesin head and MT along a MT protofilament and is approximately shown in Fig. 1a. The period of $V_{Sx}(x)$, d =8 nm, is equal to the distance between two successive binding sites on MT. To be consistent with that for the monomeric KIF1A (Xie et al., 2007), we take $V_{Sx}(x)$ in one periodicity having an asymmetric form here, with asymmetric ratio d_1/d_2 =3/5. It should be mentioned that taking other forms for $V_{Sx}(x)$ (including the symmetric form) has little effect on our results presented in this work for the dimer. Terms $V_y(y) \equiv \exp[-(y - y_0)/A_y]$ and $V_z(z) \equiv \exp(-|z - z_0|/A_z)$ denote the potential changes in the vertical and horizontal directions, respectively, with A_y and A_z characterizing the interaction distances. Note that, due to the steric restriction of MT, the position of the kinesin head is confined to the region $y \geq y_0$. Terms $V_\alpha(\alpha) \equiv \exp(-|\alpha - \alpha_0|/A_\alpha)$ and $V_\theta(\theta) \equiv \exp(-|\theta - \theta_0|/A_\theta)$ denote the potential changes resulting from the head rotations, with A_α and A_θ characterizing the interaction distances. Here, we define $y_0 = z_0 = \alpha_0 = \theta_0 = 0$ in the MT-binding state. These potential changes $V_y(y)$, $V_z(z)$, $V_\alpha(\alpha)$ and $V_\theta(\theta)$ are similar to the Morse potential form that describes the van der Waals interaction. To be consistent with the Debye length that is in the order of 1 nm in solution, we take $A_y = A_z$