CHAPTER 10

MYOSIN VI: A MULTIFUNCTIONAL MOTOR PROTEIN

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Abstract: Myosins are motor proteins that use the energy derived from ATP hydrolysis to move unidirectionally along actin filament tracks within the cell. Myosin VI appears to be unique, because unlike all the other myosins so far characterised, it moves backwards towards the minus end of actin filaments. Within cells myosin VI is found in distinct locations and has been implicated in a wide range of processes such as endocytosis, exocytosis, maintenance of Golgi morphology and cell migration. Myosin VI’s participation in this diverse array of cellular events is mediated by its interaction with a number of different binding partners, which bind to two specific sites in its C-terminal targeting domain. Within this domain there is also a site which specifically binds the signalling molecule PtdIns(4,5) P_2 (PIP_2) and modulates myosin VI targeting to the plasma membrane. Although it is now generally agreed that myosin VI exists in vitro as a stable monomer and under certain conditions may form a few dimers, it is not known whether myosin VI functions as a monomer and/or dimer in the cell. Understanding the cellular functions of myosin VI has now a greater urgency with the observations that myosin VI is associated with a number of human diseases including deafness and cancers.

Keywords: Actin, cell migration, endocytosis and exocytosis, Golgi complex, myosin VI, myosins

10.1. INTRODUCTION

In eukaryotic cells highly specialised modes of migration and intracellular transport have been developed to safeguard the health of the cell and its survival. In intracellular trafficking pathways cargo such as vesicles, organelles, mRNA and even protein complexes are rapidly moved around the cell between different locations by motor proteins translocating along dynamic networks of microtubules and actin filaments (Langford, 1995; Brown, 1999). For example, at the cell surface endocytosed cargo is first moved through the dense cortical actin filament network lying below the plasma membrane to the ends of the microtubules and is then transported...
further into the cell to its correct intracellular destination along microtubule tracks. Similarly, trafficking of exocytic cargo exiting from internal organelles such as the Golgi complex and on route to the plasma membrane is likely to involve transport along actin filaments and then along microtubules. Kinesin and dynein motor proteins drive the long-range movements along microtubules, whereas the myosins are responsible for the short distance movements along actin filaments. In addition, the steady state localisation and architecture of organelles and membrane compartments also requires holding/tethering functions mediated by the kinesin, dynein and myosin motors. Thus, for intracellular transport, cellular organisation and a whole host of other cellular functions, a vast array of motor proteins, under tight regulatory control, act cooperatively on the microtubule and actin filament networks within the cell.

The myosins, the only known type of actin-based motor protein, are actin-activated Mg\(^{2+}\) ATPases that hydrolyse ATP and convert the released chemical energy into kinetic energy to move unidirectionally along actin filaments. All myosins have a highly conserved domain organisation consisting of an N-terminal ‘motor’ domain with an actin-binding and ATPase site, a regulatory neck region (lever-arm) containing from one to six IQ motifs that bind light chains and/or calmodulin, and a highly variable C-terminal tail domain that binds cargo and defines the function(s) of the myosin. At least 20 different classes of myosins have been identified (Berg et al., 2001; Hodge and Cope, 2000), although recently more detailed sequence analysis of newly completed genomes has identified extra more specialised classes of myosin (Foth et al., 2006). The classification of the different myosins is based on variations in their conserved ‘motor’ domain sequences, although when the accompanying C-terminal ‘tail’ domains have been compared, an identical classification is observed. This indicates that the motor and tail domains have evolved together i.e., the mechano-chemical properties of the motor domain have been fine tuned to the unique properties of the tail domain and thus the \textit{in vivo} functional requirements of the myosin (Cope et al., 1996). With the explosion in information regarding the identities of the various myosins and their \textit{in vitro} mechanical and kinetic properties (Vale, 2003; O’Connell et al., 2007), attention has turned to the specific roles of these motor proteins \textit{in vivo}. Although there are fragmentary data available at present, work is moving at pace to improve our current understanding of their cellular functions.

10.2. MYOSIN VI

In this chapter we will focus on the myosin in class VI. This myosin appears to have unique cellular properties and functions because it moves towards the minus end of actin filaments, in the opposite direction to all the other classes of myosins so far studied (Wells et al., 1999). Although the precise polarity of actin filaments in cells is not known, it is believed that actin filaments have their plus ends inserted at or near the plasma membrane and at the surface of intracellular organelles such as the Golgi complex and the phagosome (Cramer, 1999; Defacque et al., 2000). Myosin VI, as