Meeting report

Determining the cellular function of myosin VI

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The myosin superfamily of actin-based molecular motor proteins comprises an ever growing number of subfamilies (15 or more classes to date). These have been identified biochemically, genetically and by cloning technology. An exciting development in the myosin field is the discovery that *in vitro* myosins of class VI are a 'reverse' actin motor (Wells AL *et al. Nature,* 1999, 401:505-508 [PMID: 10519557]). This new information, combined with the already established importance of myosin VI in cells, will aid interpretation of the cellular function of this myosin.

For a myosin to move 'backwards', theoretical, structure-based considerations either require the redesigning of the actin-binding interface on myosin so that the myosin head domain faces the minus end of the actin filament, or the repositioning of the lever arm (light chain binding domain) such that the myosin head moves in the opposite direction. Redesigning the actin-binding interface would require huge changes to myosin protein structure, and if such a protein exists, it is more likely to be a member of a distinct family of actin motors than a recognisable myosin. Discovering such a new protein family in the future remains a possibility, considering that there are already two known distinct families of microtubule-based motor proteins. In contrast, repositioning the lever arm is plausible with only minor structural modifications, placing the protein within the myosin superfamily.

Myosin VI is the only known subfamily of myosins with a repositioned light chain binding domain (IQ motif), due to an extra 50 amino acids inserted in the 'converter domain' (domain between the catalytic head and light chain binding domain). Interestingly this does not appear to change the predicted protein structure of this region, remaining α-helical as observed for other classes of myosins. Potentially there are important amino acid changes in this insert sufficient to cause minus-end directionality: cryo-electron microscopy of myosin bound to actin at different nucleotide states reveals that the converter domains of myosin VI and myosin V, a myosin class experimentally shown to have plus-end directed activity, swing in opposite directions. Motility assays carried out *in vitro*, using chimeric myosin II and VI proteins, show that the myosin VI converter domain is sufficient to drive minus-end directed movement. Similarly, in the kinesin family of microtubule-based motors, which includes plus- and minus-end-directed motors, a functionally related domain - the neck region - is required for directionality. So, converter domains in myosin motors and neck regions in kinesin motors may be conserved at the functional level.

In cells, myosin VI is required for several types of cell shape change and cell motility, ranging from large-scale membrane remodelling events during stereocilia development (T Self, MRC Institute of Hearing Research, Nottingham), spermatid formation in *Drosophila* (JL Hicks, Washington University of St Louis), to smaller-scale particle motility (V Mermall, Washinton University of St Louis). In fish photoreceptor cells, myosin VI is sandwiched between longitudinal actin filaments and an interconnected array of mitochondria, both spatially polarized to one location in the cell (Jennifer Breckler, San Francisco State University). In *Caenorhabditis elegans*, formation of spermatids is defective in myosin VI null cells, correlating with defects in required partitioning of organelles and other particles into forming spermatids (Joseph Kelleher, University of Minnesota). Whether these data implicate myosin VI as an organelle transport motor, or in tethering/retention of organelles, has not yet been investigated; a similar question remains concerning the role of myosin VI function.

In larger-scale surface membrane remodelling events, the available data cannot distinguish between surface remodelling due to myosin VI-dependent membrane recycling, and tethering of emergent surface features to underlying actin

filaments in the cell cortex. The existence of alternatively spliced forms of a single myosin VI gene in *Drosophila*, and of two distinct myosin VI genes in fish (Breckler) opens the possibility that distinct myosin VI isotypes may have different cell functions - as are apparent for class V yeast myosins (Thein Win, University College London). There are clues that myosin VI activity is regulated by phosphorylation in tissue culture cells (Buss F *et al. J Cell Biol*: 1998, 143:1535-1545 [PMID: 9852149]) and in inner ear development (Tama Hasson, University of California San Diego). Clearly, a variety of genetic, biochemical and cell-biological studies in cells of a variety of types will contribute to unravelling the functions of this 'reverse' actin motor.