Cargo binding and regulation of kinesins

Sophie Hesketh and Joe Cockburn

Introduction

The long-range transport of material through the cytoplasm is crucial for cellular function and defects in this process are associated with a number of diseases. Molecular motors (kinesins and dyneins) harness ATP hydrolysis to power movement of cellular cargoes along microtubules. Although these motors vary profoundly in the their molecular organisation, broadly speaking they contain (i) a motor module, which hydrolyses ATP to generate movement along microtubules, and (ii) a cargo receptor, which attaches to cellular cargoes. The cargo receptors must bind to their cognate cargoes with high specificity to ensure that only the correct molecules are transported, and must also allosterically regulate the ATPase activity of the motors to ensure that they hydrolyse ATP only when transporting cargo along microtubules. Whilst the mechanochemical cycles of motor modules are now quite well understood, we know far less about how the cargo receptors work.

Results

We aim to understand the cargo receptor of kinesin-1 family motors. Kinesin-1 transports a wide variety of cellular cargoes such as proteins, mRNPs, vesicles, organelles and viruses. When not bound to cargo, kinesin-1 folds into a compact, autoinhibited conformation. Cargo binding induces a large-scale conformational change, allowing the motor domains to bind to microtubules, hydrolyse ATP, and move. We will answer three fundamental questions about the kinesin-1 cargo receptor: What is its molecular organisation? How do ligands bind? And how does ligand binding trigger a response, in this case motility? We will use a multidisciplinary approach to tackle these fundamental questions. A complex macromolecular machine such as kinesin-1 can only be understood using structural biology, but we will use in vitro and cell biology assays to integrate this knowledge into the *in vivo* context.

Funding

Funding from a Royal Society Research Grant & startup funding from the University of Leeds is gratefuly acknowledged.

Collaborators

University of Leeds: M. Peckham, A. Breeze, N. Ranson, A. Ashcroft