required for Swallow-mediated localization within the oocyte.

The interaction between Swallow and Dlc is a significant finding and provides the basis for a model in which the dynein-motor complex is responsible for the anterior localization of *bicoid* RNA within the oocyte. Interestingly, the transient localization of Swallow to the oocyte anterior occurs at a time when most of the dynein-motor subunits are concentrated at the posterior of the oocyte[13]. This raises the possibility that at least two distinct dynein complexes are present within the oocyte cytoplasm and are targeted to different locations. However, it is possible that Dlc may associate with Swallow in a complex other than the dynein motor. A precedent for such a model is provided by the association of Dlc with the myosin-V-motor complex[14]. Thus, it will be important to investigate directly whether dynein-motor activity is actually required for the anterior localization of *bicoid* mRNA.

Cytoplasmic dynein is implicated in many biological processes, including vesicle and organelle transport, mitotic-spindle function and orientation, and now RNA transport and localization. It is important to emphasize that a single isoform of the dynein-motor subunit is known to be targeted to several cellular functions and molecular cargoes within individual cells. Thus it is those molecules with adaptor functions, such as those proposed here for Swallow, that must account for the functional specificity of dynein, and which are therefore the current targets of molecular searches. More detailed examination of Swallow's adaptor function and the mechanisms that regulate the 'swallowing of dynein' should provide clues as to how motor function is controlled both spatially and temporally in the localization of mRNAs and the generation of cell asymmetry. □

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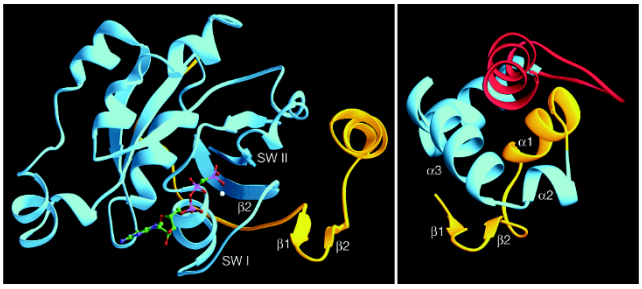
Unsheathing WASP's sting



The Wiskott-Aldrich Syndrome Protein (WASP) family lie at a signalling node. A wide variety of upstream signals cause activation of WASP family members which then bind to the ARP2/3 actin-nucleating complex and thereby alter cytoskeletal architecture. Activation of ARP2/3 is achieved by a domain, close to the WASP carboxy terminus, known as the VCA region (for Verprolin homology, Cofilin homology, Acidic), which is separated from the amino terminus by a proline-rich region. It is with this more variable N terminus, which normally binds to the VCA region to autoinhibit ARP2/3 binding, that upstream signalling molecules interact.

In the archetypal protein, WASP, and its closely related neuronal cousin, N-WASP, the N terminus contains a region that binds to the small GTPases Rac and Cdc42. Last year, Michael Rosen and colleagues at the Memorial Sloane Kettering Cancer Center reported the structure of this GTPase binding domain (GBD) of WASP in complex with Cdc42 (left panel, WASP in yellow, Cdc42 in blue), showing how changes in Cdc42 upon hydrolysis of GTP were responsible for the establishment of this complex (*Nature* **399,** 379–383; 1999). Now, in a recent issue of *Nature* (**404,** 151–158; 2000), the same group provide the other side of the story. They illustrate the extensive structural changes undertaken by WASP to accommodate Cdc42 binding, and show how these changes release the autoinhibition of WASP's ARP2/3 binding ability.

On its own, the WASP GBD has little inherent structure, at least in aqueous solution. However, Rosen and colleagues found that a construct containing both the GBD and the VCA region was much more stable than the GBD alone. The reason for this is clear from the structure (right panel, GBD in yellow and blue, VCA region in red), as a helix from the C terminus fits snugly into a groove on the opposite side of the domain to its β-strands, locking the structure in place like the pin of a hand grenade.

Comparison of the two WASP structures pictured reveals why the auto-inhibitory binding of the C terminus to the VCA region is incompatible with WASP's interaction with a small GTPase. When bound to Cdc42, only the β-hairpin and first α-helix of the WASP GBD remain (yellow in both panels), while the third and fourth helix have been supplanted by the Switch I and II regions of Cdc42. This can only be achieved by the destruction of almost half of the GBD including the cleft into which the C-terminal helix nestles. The VCA region is thus free to interact with ARP2/3.

Thus WASP's biological usefulness is rooted in its flexibility and the instability of its GBD. Other examples of inherently unstructured protein domains exploring a number of induced structures dependent on the presence of particular molecular locking pins will doubtless emerge. But for WASP at least, any such analogy to a hand grenade is turned on its head. Rather than the pulling of a locking pin resulting in the explosion of the GBD grenade, destruction of the GBD by Cdc42 or Rac allows the release of the active part of the WASP molecule, the VCA pin itself.

CHRISTOPHER SURRIDGE is a senior editor at *Nature*