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Molecular embrace

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We take our three dimensional architecture for granted. Yet, were it not for biological scaffoldings of different kinds, all living entities would probably be quite flat. Besides acting as something from which muscles and internal organs can hang, skeletons bestow on humans a characteristic shape. As they do on giraffes. On a far smaller scale, any specific cell also has a distinctive contour, given to it by what is known as the cytoskeleton. The cytoskeleton is made up – for the most part – of actin filaments, which are themselves assemblies of thousands of globular actin monomers. Cytoskeletons – like any scaffolding – need builders to be erected, and the protein twinfilin is one such builder. Twinfilin is intimately involved in actin filament dynamics, and without it there is not much that living entities could do.

Actin is at the heart of many essential cellular processes such as endocytosis, motility, cell division, secretion and intracellular signal transduction. Take any of these functions away, and a cell can hardly be called a cell at all. And life loses its crutch. Actin filaments have a dynamic of their own, and spend a lot of energy growing on one end whilst diminishing on the other. What may sound like some form of 'bio-indecision' is in fact a means of lengthening, shortening, or regenerating vital structures as a cell lives. And such processes are continuously checked by a host of accessory proteins. Indeed, a cell cannot have a filament growing too long, or no filament growing at all, or no pool of spare actin monomers awaiting their destiny. Actin dynamics are fine-tuned, and twinfilin is part of the fine-tuning.

From yeast to mosquitoes, and frogs to orang-utans, twinfilin is found in all eukaryotes save plants. It is a small protein with two distinctive globular domains followed by a linear C-terminal domain, and looks a little like a pair of sunglasses that have lost an arm. The globular domains are known as ADF-H domains, or actin depolymerizing factor homology domains. ADF-H domains are responsible for grabbing hold of the actin monomers. But not any old monomers. The ones twinfilin proteins are attracted to most are ADP-actin monomers, i.e. those which drop off the end of an actin filament. Characteristically, a growing actin filament has a pointed end from which monomers are severed, and a barbed end onto which novel actin monomers are added. Twinfilin does not promote actin filament shortening at the pointed end but instead recuperates the monomers once they have dropped off it.

Embrace, Jeannette Jarville

Courtesy of the artist

Surprisingly, though both ADF-H domains bind ADP-actin monomers, the C-terminal domain has a higher affinity for the monomers than does the N-terminal domain. It is thought that actin is first bound to the N-terminal domain which then passes it onto the C-terminal domain which takes a more secure grasp on it. In this way, ADP-actin is sequestered in the cell's cytoplasm by way of a molecular embrace before it is re-

integrated in the form of ATP-actin at the barbed end of a growing filament.

The mechanism by which sequestered actin is subsequently released from twinfilin in order to be phosphorylated and then – if need be – added to an actin filament is still unclear. Twinfilin can bind to capping protein via its C-terminal linear end. Capping proteins are located on the barbed ends of actin filaments where they cap – precisely – the extremity of the growing actin filament thereby hindering any further elongation. It is thought that in docking to capping protein, twinfilin is urged to release its ADP-actin monomer, which is then free to be phosphorylated and added to a growing actin filament.

Sequestration is not twinfilin's only trick. Recently, it has been suggested that twinfilin also has the power to act as a capping protein, which would make it yet a stronger decider in actin filament dynamics. Researchers believe that twinfilin performs capping at the barbed ends of filaments by way of its ADF-H domains, in the same way it sequesters ADP-actin.

However, while actin sequestration is performed essentially by the C-terminal ADF-H domain, capping is fulfilled by both. So twinfilin would cling onto the ends of filaments thanks to the embrace of both its ADF-H domains! What is more, this additional gift is relatively recent in evolutionary terms since it seems to be found only in vertebrates.

Actin is vital. Yet – like all cellular activities – it must be harnessed, which is why discovering proteins such as twinfilin that are at the heart of filament fine-tuning are of great interest. A twinfilin mutation in Drosophila, for instance, produces undersized adults and aberrant bristle morphology. Mutations in human twinfilin would certainly bring on similar distortions, bristles apart... Twinfilin has much more to reveal. It sequesters and it caps, and it may well sever too, according to some. And it is yet another example of how delicate and fragile the fabric of life is.

Cross-references to Swiss-Prot

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Twinfilin, *Saccharomyces cerevisiae* (Baker's yeast): P53250
Twinfilin, *Xenopus laevis* (African clawed frog): Q68F50
Twinfilin, *Gallus gallus* (Chicken): Q5ZM35

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