have evolved independently from unrelated sequences. The FHA domains were first identified by a database screen centred on a conserved region in members of the Forkhead-type transcription factor family[6]. Found mainly in protein kinases, phosphatases and transcription factors, FHA domains consist of roughly 75 amino acids divided into three or four highly conserved sequence blocks. They were identified in proteins from yeast, plants, mammals and bacteria, and in many uncharacterized open reading frames.

But the function of FHA domains remained a mystery. A year before these domains were identified as distinct signalling modules, John Walker's laboratory identified a 239-amino-acid stretch within the kinase-associated protein phosphatase (KAPP) of the tiny weed *Arabidopsis thaliana* that bound a serine/threonine-receptor-like kinase, RLK5. This interaction depended on phosphorylation of RLK5 on serine or threonine residues[7]. Sequence comparisons revealed an FHA domain in the middle of this kinase-interacting domain, and earlier this year Walker and colleagues reported[3] that this FHA domain is critical for the phosphorylation-dependent binding of KAPP to several protein kinases.

A second clue that FHA domains might be phosphoserine/threonine binding modules emerged from studies by David Stern and colleagues. They were searching for proteins that bind to Rad53, a protein kinase involved in controlling cell-cycle checkpoints in the yeast *Saccharomyces cerevisiae*[8]. Rad53 contains two FHA domains flanking a central protein kinase domain, and Stern's group mapped the interaction of Rad53 with another DNA-damage-control protein, Rad9, to the second of these FHA domains. Like the interactions between KAPP and RLK5, the Rad53–Rad9 coupling was specific for the phosphorylated form of Rad9.

Durocher *et al.*[1] now report that, in fact, both of Rad53's FHA domains can bind to Rad9. They show the first direct interaction between the amino-terminal FHA domain of Rad53 and short peptides containing phosphothreonine. Then, using immobilized peptides, they demonstrate that Rad53's carboxy-terminal FHA domain, along with the FHA domains from proteins in *Arabidopsis*, humans, yeast and *Mycobacterium tuberculosis*, also binds sequences that contain phosphothreonine. Although the exact motifs that FHA domains recognize — and the serine/threonine kinases that generate these motifs — are not known, all the data point to the FHA domains as 'SH2-domain equivalents' in the world of phosphoserine/threonine signalling.

But there are other phosphoprotein-binding domains. Some WW domains, for example, bind to phosphoserine. They consist of around 35–40 amino acids folded into a three-stranded β-sheet, and bind to a variety of proline-rich proteins. One such protein, Pin1, regulates entry to and exit from mitosis, presumably by isomerizing phosphoserine–proline bonds[9]. Earlier this year, Lu *et al.*[2] showed that the WW domains from Pin1, the yeast Pin1 homologue Ess1 and the ubiquitin ligase NEDD4, act independently as phosphoserine/threonine-binding modules.

The most highly conserved phosphoserine/threonine-binding proteins identified to date are members of the 14-3-3 protein family[4,5]. In contrast to modular signalling elements (such as FHA and WW domains), which are usually interspersed with other domains in signalling proteins, 14-3-3 molecules are themselves functional dimeric proteins. There are seven different 14-3-3 isotypes in mammalian cells, and at least ten in *Arabidopsis*, allowing them to act in tissue- and organelle-specific ways. When 14-3-3 proteins bind their phosphoprotein prey, they are thought to restrict the bound proteins to the cytosol, either by preventing them from entering the nucleus or by speeding their passage out of it.

Other families of phosphoprotein-binding domains probably remain to be discovered. Those that have been identified so far are unrelated in primary sequence and three-dimensional structure, so must have evolved independently. In some cases — such as phosphotyrosine-binding and WW domains — only one sub-group of the family has phosphopeptide-binding specificity. Perhaps sub-groups of other, previously defined modular domains have evolved phospho-amino-acid specificity. For example, there is evidence that WD40 repeats within F-box proteins mediate the phosphoserine/threonine-dependent binding and ubiquitin-mediated degradation of cyclin-dependent kinase inhibitors[10,11]. The challenge for the future will be to identify the function of each phosphoserine/threonine-binding protein in specific signalling cascades. ■

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Daedalus

Chain in miniature

Microtechnology, even nanotechnology, are popular buzzwords these days. Some of the schemes mustering under these banners may even be feasible. In particular, tiny machines, mass-produced from photo-etched silicon and operating piezoelectrically at kilocycle or megacycle rates under computer control, are already at a pilot stage. Daedalus reckons they are needed in the textile trade.

Weaving is a macrotechnological triumph, but only with continuous fibre. It cannot imitate that mediaeval masterpiece, chain mail. This armoured cloth was made of innumerable interlinked loops of metal wire. Each loop had to be individually threaded into place and closed into a circle by thermal forging. The metal links were hard and rigid; but the mail itself was wonderfully flexible. A silicon micromachine could replicate this structure on the ten- or hundred-micron scale, as rapidly as a conventional loom can weave. It could be fed with normal polymeric fibre, to be chopped into short lengths, bent and melt-welded into linked loops. Fine-gauge tube, slit into rings which are then sliced open, might be even better. After threading, each ring would naturally close again under its own elasticity, ready for its two ends to be melted together. A silicon loom would have thousands of such threading and closing units in a line, each receiving its own feedstock, and linking it into the growing web.

'Micro-chaincloth' will transform the world of fashion. For a start, it will not be limited to a 'warp and weft' structure. Hexagonal or even denser weaves will be feasible, as will three dimensional ones, with several layers of links coupled in thickness. And like chain mail itself, the new cloth will be amazingly tough. It will distribute any load through innumerable linkages, each always capable of a little extra yielding. Yet for all that, micro-chaincloth will be magically soft. With no stiffness above the link scale, it will have a flattering, limpid, almost liquid drape. By the same token, it will be utterly snag-resistant. Having no continuous fibre, it cannot come unravelled; local damage cannot spread. In particular, it will never fray. The edges of a garment will no longer need to be folded over and stitched firm. The widespread worry about visible panty-lines will vanish for ever. **David Jones**