STRUCTURE WATCH

How to reach targets

Polo-like kinases (Plks) have important roles in cell-cycle progression and mitosis. They comprise an amino-terminal kinase domain and a non-catalytic, carboxy-terminal Polo-box domain (PBD), which contains two Polo-box motifs. Recently, the PBD of human Plk1 has been implicated in the phosphodependent targeting of this kinase to mitotic structures and substrates. Now, in *Cell*, Yaffe, Smerdon and colleagues show that the PBDs of human, *Xenopus* and yeast Plks all recognize the same core sequence (S-[pS/pT]-P/X), and provide further insights by describing the 1.9-Å X-ray structure of a human Plk1 PBD–phosphopeptide complex.

In this structure, each Polo box is composed of a $\beta_6\alpha$ motif, and these motifs pack together to form a 12-stranded β-sandwich in the PBD. The phosphopeptide binds to one end of a conserved, positively charged cleft at the interface between the two Polo boxes and, interestingly, most of the phosphoryl-group contacts involve a lattice of water-mediated hydrogen bonds (such solvent-bridged interactions have not been seen in other protein–phosphopeptide complexes). Using site-directed mutagenesis, the authors showed that phosphodependent substrate recognition by the PBD is essential for Plk targeting to substrates and for proper mitotic progression. In addition, they showed that the kinase activity of full-length Plk1 is stimulated by phosphopeptide binding to the PBD. This led them to propose that intramolecular inhibition of the kinase by the PBD is relieved by phosphopeptide binding.

REFERENCE Elia, A. E. H. *et al.* The molecular basis for phosphodependent substrate targeting and regulation of Plks by the Polo-box domain. *Cell* **115**, 83–95 (2003)

Untangling knots

Desmosomes and adherens junctions are intercellular adhesion junctions that maintain cell shape and tissue integrity. Although they each have a distinct molecular composition, both junctions rely on interactions between cadherin molecules. The types of cadherin in these junctions are closely related and are characterized by the presence of five, tandem extracellular domains (EC1–EC5). There are, however, many models for how cadherins interact with one another, and this topic has remained controversial. So, to clarify which model is most physiologically relevant, Stokes and colleagues visualized the molecular interactions in an intact junction.

In *Science*, they describe the use of electron tomography on plastic sections from neonatal mouse skin to obtain three-dimensional reconstructions of desmosomes. The reconstructions showed that cadherin molecules cluster in groups of 10–20 with their amino-terminal domains forming a series of knots at the midline between the membranes. When they fitted the X-ray structure of classical cadherin to these reconstructions, they identified three distinct geometries for the interacting molecules in the knots and these were all consistent with a model in which the EC1 domains interact through the exchange of amino-terminal tryptophan residues. In addition, as this exchange can occur in *cis* or *trans*, two of the geometries provided a way to propagate this interaction. The observation of three different geometries indicates flexibility in cadherin extracellular domains, and the authors propose that this flexibility highlights a new way to generate *cis* and *trans* interactions and to propagate these adhesive interactions along the junction.

REFERENCE He, W. *et al.* Untangling desmosomal knots with electron tomography. *Science* **302**, 109–113 (2003)