Nature Reviews Molecular Cell Biology | AOP, published online 8 April 2009; doi:10.1038/nrm2681

Structure watch

CYCLIN D–CDK4 FINDS FORM

Cyclin-dependent kinase 4 (CDK4) forms a complex with D-type cyclins (D1, D2 or D3) to promote progression through the G1 phase of the cell cycle. In addition to being regulated by cyclin binding, CDK4 must be phosphorylated at residue Thr172 for full activation. Despite the fact that deregulation of CDK4 activity promotes tumourigenesis, which suggests that it is a promising drug target, its structure has remained elusive. Now, Day *et al.* report the crystal structure of phosphorylated CDK4 in complex with cyclin D1 at 2.3 Å resolution, and Takaki *et al.* describe the structure of non-phosphorylated CDK4 in complex with cyclin D3 at 3.0 Å resolution. In both studies, and regardless of CDK4 Thr172 phosphorylation, binding of a D-type cyclin to CDK4 is not sufficient to trigger rearrangement of the CDK4 active site into an active conformation. By contrast, in all other resolved crystal structures of CDK–cyclin complexes, cyclin binding and phosphorylation of the conserved Thr residue converts the CDK into an active form. Thus, phosphorylated CDK4 that is bound to cyclin D may be in a state that is permissive for activation, but it requires an additional event for activation to occur.

ORIGINAL RESEARCH PAPERS Day, P. J. *et al.* Crystal structure of human CDK4 in complex with a D-type cyclin. *Proc. Natl Acad. Sci. USA* **106**, 4166–4170 (2009) | Takaki, T. *et al.* The structure of CDK4/cyclin D3 has implications for models of CDK activation. *Proc. Natl Acad. Sci. USA* **106**, 4171–4176 (2009)

STRUCTURAL CHECKPOINT

The anaphase-promoting complex/cyclosome (APC/C) is a ubiquitin ligase that promotes the degradation of proteins that arrest mitosis. APC/C is activated by cell division cycle 20 (CDC20), a protein that is inhibited by the mitotic checkpoint complex (MCC) until chromosomes are properly aligned on the mitotic or meiotic spindle. The structure of human APC/C, in three distinct functional states, has recently been solved.

Herzog and colleagues used single-particle electron microscopy to obtain three-dimensional models of human APC/C in the absence of MCC proteins and CDC20, in complex with MCC proteins and CDC20, and bound to CDC20 alone. Comparison of the APC/C forms reveals that MCC and CDC20 bind to the front side of APC at partially overlapping sites. Thus, the authors propose that MCC binding may inhibit APC/C by causing APC/C-bound CDC20 to change its position. In addition, antibody labelling experiments were performed to assess the topology of APC/C. Data show that MCC binding also switches APC/C to a closed conformation, which restricts the binding of substrate proteins, providing further clarification of the structural basis for APC/C inhibition by mitotic checkpoint proteins.

ORIGINAL RESEARCH PAPER Herzog, F. *et al.* Structure of the anaphase-promoting complex/cyclosome interacting with a mitotic checkpoint complex. *Science* **323**, 1477–1481 (2009)