# Cyclin switch

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Interaction between individual members of two families of proteins—cyclins and the cyclin-dependent kinases (CDKs)—is vital for progression through the cell cycle. The CDKs modulate the activity of proteins responsible for the biomechanics of the cell cycle and the activity of the CDKs is positively regulated by their interaction with the cyclins (and by phosphorylation). The structure of the cyclin-A/CDK2 complex (picture taken from P.D. Jeffery, A.A. Russo, K.Polyak, E.Gibbs, J Hurwitz, J. Massagué and N.P.Pavletich, *Nature* **in the press**) now provides insight into the mechanics of this regulation.

The superposition of free CDK2 (grey and green Cα trace; H.L. De Bondt *et al. Nature* **363**, 595–602 (1993)) and CDK2 bound to cyclin-A (blue, red and yellow Cα trace) reveals that cyclin-A prises open the CDK2 catalytic cleft, which is located between the N-terminal β-sheet domain (left) and the C-terminal α-helical domain (right).

Cyclin-A interacts with the upper surface of CDK2 in the picture (the cyclin-A molecule is not shown), and in particular with the α1, or PSTAIRE, helix (red/green) and the T-loop (yellow/green). On binding cyclin-A the PSTAIRE helix undergoes a large translation and rotation down into the catalytic cleft, thereby positioning the side chain of Glu 51 in close proximity to the two other members of the suggested catalytic triad of CDK2.

The movement of the PSTAIRE helix is facilitated by a series of conformational changes in CDK2 on binding cyclin-A.The T-loop, which in the structure of free CDK2 blocks the entrance to the active site, is pulled back and away from the catalytic cleft by cyclin-A. The short L12 α-helix, found at the start of the loop (green) in free CDK2, is transformed into a short stretch of β-sheet (yellow) in the complex. The movement, and transformation of helix to sheet, allows the PSTAIRE helix to gain access to the cleft. This access is also facilitated by the movement of the N-terminal β-sheet domain back and away from the C-terminal α-helix, which widens the cleft still further

The threonine-160 phosphorylation site on the descending arm of the T-loop, which is buried in the free CDK2 structure, is exposed to solvent in the complex. Addition of a phosphate here may cause a further adjustment to the conformation of the loop, allowing the protein substrate of the cyclin-A/CDK2 complex to bind with high affinity. Indeed, the authors can identify a pocket lined with arginine residues which may act as a binding site for the phosphate moiety. Insights gleaned from the structure of this complex should provide an outline of the mechanism of activation of all the cyclins/CDK complexes, given their high sequence similarity.

**GR**