Structure watch

DNMT1 SPECIFICITY

Mammalian CpG methylation must be faithfully reproduced when DNA is replicated to ensure that gene expression patterns are accurately inherited when cells divide. Maintenance DNA methylation is catalysed by DNA methyltransferase 1 (DNMT1), which has high affinity for hemi-methylated DNA; this allows it to recognise methylation on the parent DNA strand and copy it to the newly synthesized daughter strand. Now, Song *et al.* have used X-ray crystallography to show that unmethylated DNA is occluded from the active site of DNMT1, thus explaining how DNMT1 is specific for hemi-methylated DNA.

They solved a crystal structure of mouse DNMT1 in complex with unmethylated DNA at 3 Å resolution and showed that when the CXXC domain of DNMT1 binds to unmethylated DNA the protein conformation is altered such that the CXXC–bromo-adjacent homology 1 (BAH1) linker blocks access of the methyltransferase active site to the DNA. In addition, the target recognition domain of DNMT1 becomes stabilized in a retracted position, preventing it from interacting with the unmethylated DNA. This autoinhibitory mechanism prevents DNMT1 from introducing aberrant *de novo* methylation and thereby promotes accurate replication of DNA methylation patterns.

ORIGINAL RESEARCH PAPER Song, J. *et al.* Structure of DNMT1-DNA complex reveals a role for autoinhibition in maintenance DNA methylation. *Science* 16 Dec 2010 (doi:10.1126/science.1195380)

DOCKING APC SUBSTRATES

The anaphase-promoting complex (APC; also known as the cyclosome) controls the separation of sister chromatids and mitotic exit by promoting the ubiquitylation of cell cycle proteins, including securin and cyclin B, thereby targeting them for degradation by the proteasome. The recruitment of substrates to APC has been proposed to occur in the 'inner cavity' surface of the complex, but detailed structural insight into this has been lacking, and the location of Destruction of cyclin B 1 (Doc1), an APC subunit that regulates processive ubiquitylation of substrates, was unclear.

Buschhorn *et al.* used photo-crosslinking experiments to show that Doc1 associates with three other APC subunits: Cdc16, Cdc27 and Apc1. They then compared a three-dimensional structure of yeast APC (determined by electron microscopy) with that from vertebrates and found that the overall structure of the two complexes is similar and that APC can form 36S homodimers that might be able to support two ubiquitylation reactions. Analysis of different forms of the APC revealed that Doc1 associates with the inner cavity surface of the complex adjacent to the co-activator Cdh1, which is also important for substrate recognition. Substrates are recruited close to this site in-between the two factors, suggesting that Doc1 and Cdh1 together form a 'bipartite substrate receptor' that promotes processive ubiquitylation of the substrate.

ORIGINAL RESEARCH PAPER Buschhorn, B. A. *et al.* Substrate binding on the APC/C occurs between the coactivator Cdh1 and the processivity factor Doc1. *Nature Struct. Mol. Biol.* **18**, 6–13 (2011)