hot off the press

Remodelling without a power stroke

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DNA within eukaryotic organisms is packaged into chromatin, which helps organization and compaction of the genetic material in the limited space within the nucleus. However, for efficient transcription, nucleosome positioning must be dynamically regulated, either allowing access to the transcription machinery or to block spurious gene expression [1]. Nucleosomes are inherently stable structures, with multiple contacts between DNA and the histone octamer. To perturb nucleosomes, eukaryotes have molecular machines called chromatin remodellers. These bind to DNA and the octamer core and harness the energy of ATP hydrolysis to disrupt DNA–histone contacts [2]. Swi/Snf-like chromatin remodellers slide or evict nucleosomes exposing DNA segments, which allows binding by transcription factors [2,3]. By contrast the ISWI and CHD family of remodellers slide and space nucleosomes to form ordered nucleosomal arrays that are refractory to transcription [2,3]. Nucleosomes are made up of a histone octamer core, with the DNA wrapped one-and-three-quarter turns around it. DNA enters the nucleosome through a distinct entry site and extrudes out of the exit site (Fig 1). Unlike Snf2, ISWI and CHD remodellers contain accessory DNA-binding domains, HAND-SANT SLIDE, at their carboxyl termini, in addition to the conserved helicase domain [2,3]. The helicase domain of ISWI and CHD enzymes binds to nucleosomal DNA at super helical location2 (SHL2), a region that is two helical turns away from the centre of the nucleosome (dyad axis), whereas the DNA-binding domain contacts super helical location 7 (SHL7) near the DNA entry site (Fig 1). Single-molecule studies show that remodelling ensues when the helicase domain bound to SHL2, uses ATP hydrolysis to translocate DNA in 1 bp increments [4]. These steps of translocation allow 7 bp to extrude from the exit site, simultaneously resulting in a strain on the nucleosomal DNA. For movement

of DNA into the nucleosome, it has been hypothesized that an ATPase-dependent power stroke generates force between the helicase and DNA-binding domains, which allows entry of 3 bp of DNA into the nucleosome and releases the strain on the DNA (Fig 1A). Subsequent exit of DNA happens in 3 bp increments that are coupled with entry of DNA of similar length. However, studies have shown that the introduction of nicks or single-stranded gaps, which work to release strain on the nucleosomal DNA, does not significantly affect remodelling [5]. Also, deleting or mutating the DNA-binding domain of these proteins only partly reduces remodelling [6]. These observations argue against a strict requirement for a power stroke.

“These results [...] argue against a need for strong coupling between the two domains and generation of a power stroke needed to dissipate the torsional force on the DNA strand”

The question remains, therefore, of whether a power stroke is needed for efficient remodelling by ISWI and CHD remodellers. In this issue of EMBO reports, two studies, one on yeast Chd1 and the other on *Drosophila* ISWI, address this very question [7,8]. A power stroke necessitates the rigid coupling between helicase and DNA-binding domains, which suggests that the linker between the two domains should be of a defined length. Both research groups have focused on studying how altering the length of this linker region affects remodelling of nucleosomes. Deletion of the HAND-SANT SLIDE domain of ISWI or shortening of the linker region of Chd1 to around 150 amino acids significantly affected remodelling activities of the proteins [7,8]. These results are in accordance with previous studies, which suggests that a linker of sufficient

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length connecting the two domains is critical for simultaneous engagement of the DNA-binding domain to SHL7 and the helicase domain to SHL2 [6]. However, if a fixed length of linker were needed for remodelling, increasing the length would be expected to decrease the efficiency of coupling between the helicase and DNA-binding domains. Such an effect would in turn alter communication of the power stroke generated by the helicase domain to the DNA-binding domain, thus disrupting movement of DNA into the nucleosome from the entry site. Interestingly, introduction of additional flexible stretches of amino acids between the helicase and the DNA-binding domains of Chd1 or ISWI had no significant effect on their remodelling [7,8]. In ISWI, the HAND-SANT domain regulates ATPase activity of the helicase domain, and it should be also important for communicating the force generated by the helicase domain to the DNA-binding SLIDE domain [6]. Introduction of short amino acid stretches between the helicase and HAND-SANT or the HAND-SANT and SLIDE domains had only minor effects on remodelling [8]. Also, a mutant Chd1 protein in which the nonspecific DNA-binding domain was replaced with a sequence-specific one, efficiently remodelled nucleosomes on templates with sequence-specific binding sites when the linker region was long enough to allow for contacts of the DNA-binding domain with the sequence-specific site [7]. These results suggest that the important function of the DNA-binding domain is to anchor the helicase domain onto the nucleosome for effective remodelling. Furthermore, they argue against a need for strong coupling

Fig 1 | Mechanisms of chromatin remodelling. (A) Power stroke model. The helicase domain of ISWI or Chd1 binds to nucleosomal position SHL2. The DNA-binding domain contacts position SHL7. A rigid linker region connects the two domains. The ATPase activity of the helicase domain allows for translocation of 7 bp of DNA, causing an equal length of DNA to extrude out of the exit site, which results in a torsional strain on the DNA wrapped around the nucleosome (represented as dashed red arrow). In order to release the strain on the DNA, the next step of ATP hydrolysis generates a power stroke that transduces from the helicase domain, along the rigid linker (shown as maroon arrow along the linker region), to the DNA binding domain. This allows scrunching of 3 bp of DNA into the nucleosome from the entry site. Subsequently, remodelling proceeds in 3 bp steps of exit and entry of DNA into the nucleosome. **(B) Remodelling without a power stroke.** As for the power stroke model, remodellers bind the nucleosome and the first step of remodelling extrudes 7 bp from the exit site of the nucleosome resulting in strain on the DNA. However, unlike the power stroke model, where a rigid linker carries the force of a power stroke to the DNA-binding domain, the main function of the linker, which may be flexible, is to keep both the helicase and DNA-binding domains productively engaged with the nucleosome. The strain on the DNA is most likely relaxed by a conformational change of the DNA-binding domain, which causes it to temporarily disengage from the DNA at the entry site, allowing for 3 bp of DNA to be pulled into the nucleosome. Nucleosome remodelling then proceeds in 3 bp increments of movement of DNA into and out of the nucleosome. The positions of the centre of the nucleosome (dyad axis) and positions from which DNA is pulled into the nucleosome (entry site) and extruded out during remodelling (exit site), super helical location 2 (SHL2) and super helical location 7 (SHL7) are shown with arrows. The dashed lines show direction of movement of DNA along the octamer surface during remodelling.

between the two domains and generation of a power stroke needed to dissipate the torsional force on the DNA strand. Instead the strain on the DNA can be relaxed by conformational changes of the DNA-binding domain, causing it to temporarily release DNA, which then allows 3 bp to be ratcheted into the nucleosome (Fig 1B).

So what roles do the DNA-binding domains of ISWI and CHD play in remodelling nucleosomes? The answer may lie in the inherent differences in how the Snf2-like family of chromatin remodellers disrupts DNA–histone contacts. In Swi/Snf-like complexes that do not contain accessory DNA-binding domains, the catalytic subunit remodels nucleosomes by intercalating between the histone core and DNA gyre, thereby breaking DNA–histone contacts [9]. This results in the formation of loops of around 50bp that can propagate around the nucleosome. By contrast, ISWI remodellers translocate by binding to DNA on the outer surface of nucleosomes and causing only small disruptions in the

DNA–histone contacts [9]. DNA-binding domains may function to correctly position the helicase domain on SHL2, and keep it productively engaged with the nucleosome so that each ATPase cycle allows for small but continuous translocation on the DNA. Furthermore, since ISWI and CHD remodellers work by spacing nucleosomes [2], the DNA-binding domain may recognize and bind to DNA, which would allow directional sliding by the helicase domain, while simultaneously acting as a sensor of precise linker lengths between nucleosomes and preventing collision with neighbouring nucleosomes. This allows for well-positioned arrays of nucleosomes around 15–20bp apart, as observed in *Saccharomyces cerevisiae* [10]. The activity of chromatin remodellers can be modulated by either members of the specific remodelling complexes or by other factors. The DNA-binding domains are attractive candidates for interaction with regulatory proteins that can influence localization and function of these enzymes.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

- Li B, Carey M, Workman JL (2007) *Cell* **128**: 707–719
- Narlikar GJ, Sundaramoorthy R, Owen-Hughes T (2013) *Cell* **154**: 490–503
- Mueller-Planitz F, Klinker H, Becker PB (2013) *Nat Struct Mol Biol* **20**: 1026–1032
- Deindl S et al (2013) *Cell* **152**: 442–452
- Langst G, Becker PB (2001) *Mol Cell* **8**: 1085–1092
- Hota SK et al (2013) *Nat Struct Mol Biol* **20**: 222–229
- Nodelman IM, Bowman GD (2013) *EMBO Rep* [Epub ahead of print] doi:10.1038/embor.2013.158
- Ludwigsen J, Klinker H, Mueller-Planitz F (2013) *EMBO Rep* [Epub ahead of print] doi:10.1038/embor.2013.160
- Dechassa ML et al (2012) *Nucleic Acids Res* **40**: 4412–4421
- Gkikopoulos T et al (2011) *Science* **333**: 1758–1760

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