INO80 and SWR1 complexes: the non-identical twins of chromatin remodelling

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The INO80 family of chromatin remodellers are multisubunit complexes that perform a variety of tasks on nucleosomes. Family members are built around a heterohexamer of RuvB-like protein, an ATP-dependent DNA translocase, nuclear actin and actin-related proteins, and a few complex-specific subunits. They modify chromatin in a number of ways including nucleosome sliding and exchange of variant histones. Recent structural information on INO80 and SWR1 complexes has revealed similarities in the basic architecture of the complexes. However, structural and biochemical data on the complexes bound to nucleosomes reveal these similarities to be somewhat superficial and their biochemical activities and mechanisms are very different. Consequently, the INO80 family displays a surprising diversity of function that is based upon a similar structural framework.

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Chromatin remodelling complexes facilitate access to nuclear DNA by altering the chromatin landscape, which is packaged into a repeating unit known as the nucleosome. Structures of the nucleosome first began to populate the Protein Data Bank in 1997 [1] and revealed how 145–147 base pairs (bp) of DNA wrap around the core histone octamer. This wrap can be divided into waypoints at superhelical locations across the surface of the histone octamer, which are mirrored on opposing faces. Of these waypoints, superhelical location 2 (SHL2), which is two DNA turns removed from the nucleosomal dyad, and SHL6, which is nearer the nucleosomal entry/exit site, are more readily distorted through protein:DNA interactions, making them the canonical sites for remodeller binding [2].

All remodelling enzymes, whether single or multi-sub-unit, utilise a superfamily II translocase motor [3] to mobilise nucleosomal DNA via ATP hydrolysis. This motor is the centrepiece of all remodellers and loss of its enzymatic activity results in a loss of remodelling *in vivo* and *in vitro*. High resolution cryo-electron micros-copy (cryoEM) structures have been determined for members in each of the four remodelling families [4] in complex with a mononucleosome (Snf2 [5,6••], ISWI [7,8•], Chd1 [9••,10•], Chd4 [11], INO80 [12••,13••], SWR1 [14••], RSC [15–17] and SWI/SNF [18]), providing insight into how their motors interact with their substrate. Beyond the highly conserved motor, however, each remo-deller carries unique accessory domains and variable subunit compositions that differentiate remodelling mechanisms from one another.

This is particularly evident in the INO80 family (Table 1). These large, multi-subunit complexes have crucial roles in double-strand break repair [19] and were first characterised in the early 2000s [20–22]. While the activity of other remodeller families appears to be limited to nucleosome sliding, members of the INO80 family perform additional functions with differ-ent outcomes on chromatin structure (Table 1). Conse-quently, whether these enzymes utilise a similar mech-anism for remodelling or exhibit adaptations in line with these differences is currently unknown, but struc-tural and biochemical studies have begun to address this question.

Structural similarities between INO80 and SWR1

INO80 family complexes share common core architec-tural features including several subunits of overlapping function (Table 1). A prominent unique and ubiquitous feature of INO80 family members is the hexameric ring of RuvB-like proteins (RuvBL1/2 or pontin/reptin in humans, Rvb1/2 in yeast) (Figure 1a). Even though ATPase activity of these AAA+ proteins is not required for remodelling by INO80 [12••] or SWR1 [14••], the hexameric structure acts as a linchpin for the motor subunit by enveloping a polypeptide insertion that extends from the second motor domain (Figure 1). Although the insertion is an INO80 family specific struc-tural element, there is only ~15% sequence identity (22% similarity) in this region between yeast INO80 and SWR1 (Figure 1b), and only 20% identity between human and yeast INO80. In turn, there are no obvious recurring sequence motifs that might drive the formation of the

Table 1

Subunit composition of INO80 family chromatin remodelling complexes

Complex	INO80	INO80	SRCAP	SWR1	TIP60	NuA4
Organism	*Human*	*Yeast*	*Human*	*Yeast*	*Human*	*Yeast*
Cellular role	DNA repair and Transcription	DNA repair and Transcription	DNA repair	DNA repair and Transcription	DNA repair	DNA repair
Biochemical activity	Nucleosome sliding		Histone exchange		Histone acetylation	Histone acetylation
	Histone exchange				Histone exchange	
Function	Subunits					
Motor	Ino80	Ino80	SRCAP	Swr1	TRRAP	Tra1
Scaffolding	RuvBL1	Rvb1	RuvBL1	Rvb1	RuvBL1	Eaf1
	RuvBL2	Rvb2	RuvBL2	Rvb2	RuvBL2	Epl1
					Epc1	
Regulation	Ino80B (Ies2)	Ies2			Tip60	Esa1
Coupling	Actr5 (Arp5)	Arp5	Actr6 (Arp6)	Arp6	Actl6a (Arp4)	Arp4
	Ino80C (Ies6)	Ies6	YL1	Swc6	Actin	Actin
	Actl6a (Arp4)	Arp4	DMAP1	Swc2		
	Actr8 (Arp8)	Arp8	Gas42	Swc5		
	Actin	Actin	Cfdp1 (Swc5)	Arp4		
			Actl6a (Arp4)	Actin		
			Actin			
Undefined	Amida	Ies1		Yaf9	Eaf6	Eaf6
	Ino80D & E	Ies3		Bdf1	Gas41	Yaf9
	MCRS1	Ies4		Swc3	ING3	Yng2
	NFRKB	Ies5		Swc4	Mrg15	Eaf7
	UCH37	Nhp10		Swc7	MrgBP	Eaf3
	YY1	Taf14			MrgX	Eaf5
					Eaf2	Swc4
					Brd8	
					YL-1	
Available structural information						
PDB IDs	5OAF, 6HTS	5NBN, 6FHS, 6FML	6IGM	6GEJ, 6GEN		5J9Q, 5Y81, 5J9T, 5J9U, 5J9W, 5OJS,
EMDB IDs (EMD-XXXX	3954, 3772, 3773, 3774, 3775	2385, 2386, 4264, 4277, 4278, 4280, 6924, 8696	9668, 9669	4395, 4396, 3607, 5626, 5638		

'spoked wheel' architecture [23•]. By contrast, the flanking motor domain has significant sequence identity (about 50%) and structural overlap (RMSD 1.9 Å). The differences within the insert region impose a necessary asymmetry on the AAA+ ring, which enforces subunit interactions that are unique to each complex [23•]. For example, the asymmetry results in the association of only one Arp5 in INO80, despite there being two otherwise identical sites on the other RuvBL2/Rvb2 protomers. Therefore, the simplest description of the role of the hexameric ring is as an architectural scaffold upon which other subunits are assembled.

All members of the INO80 family also contain actin in combination with actin-related proteins (Arps) (Table 1). Two Arps (Arp7 and Arp9) are also found in yeast RSC [24] and SWI–SNF complexes [25]. Early studies showed that Arps are essential to remodelling by INO80 family enzymes [26] and are involved in histone recognition, with distinct preferences for certain histone types. Arp4, for example, interacts with unmodified [27] and phosphorylated H2A (γ-H2AX in humans) [28]. Arp8, in contrast, has a

preference for H3/H4 tetramers [26,29,30], and Arp5 interacts with H2A:H2B histone dimers [12••,31].

To accommodate some of these Arps, all Arp-containing remodellers have a helical region known as the HSA (helicase-SANT-associated) domain, which precedes the motor domain (Figure 2a). Structures of the HSA regions of a number of systems have been determined including INO80 bound to Arp4, Arp8 and actin (Figure 2a) [32••], RSC with Arp7 and Arp9 [33,34] and SWR1 complexed with Arp4 and actin [35]. These structures reveal that the HSA domain adopts an extended α-helical conformation with the actin/Arps sitting astride this in a staggered configuration via interactions with a hydrophobic groove at the base of the actin fold. In addition, the HSA domain has DNA-binding activity in both RSC [36] and INO80 [32••,37•].

Despite the contribution of actin and Arps to chromatin remodelling, a feature missing in all high resolution INO80 family remodeller cryoEM structures is the Arp-HSA module [12••,13••,14••]. Evidence suggests that

Figure 1
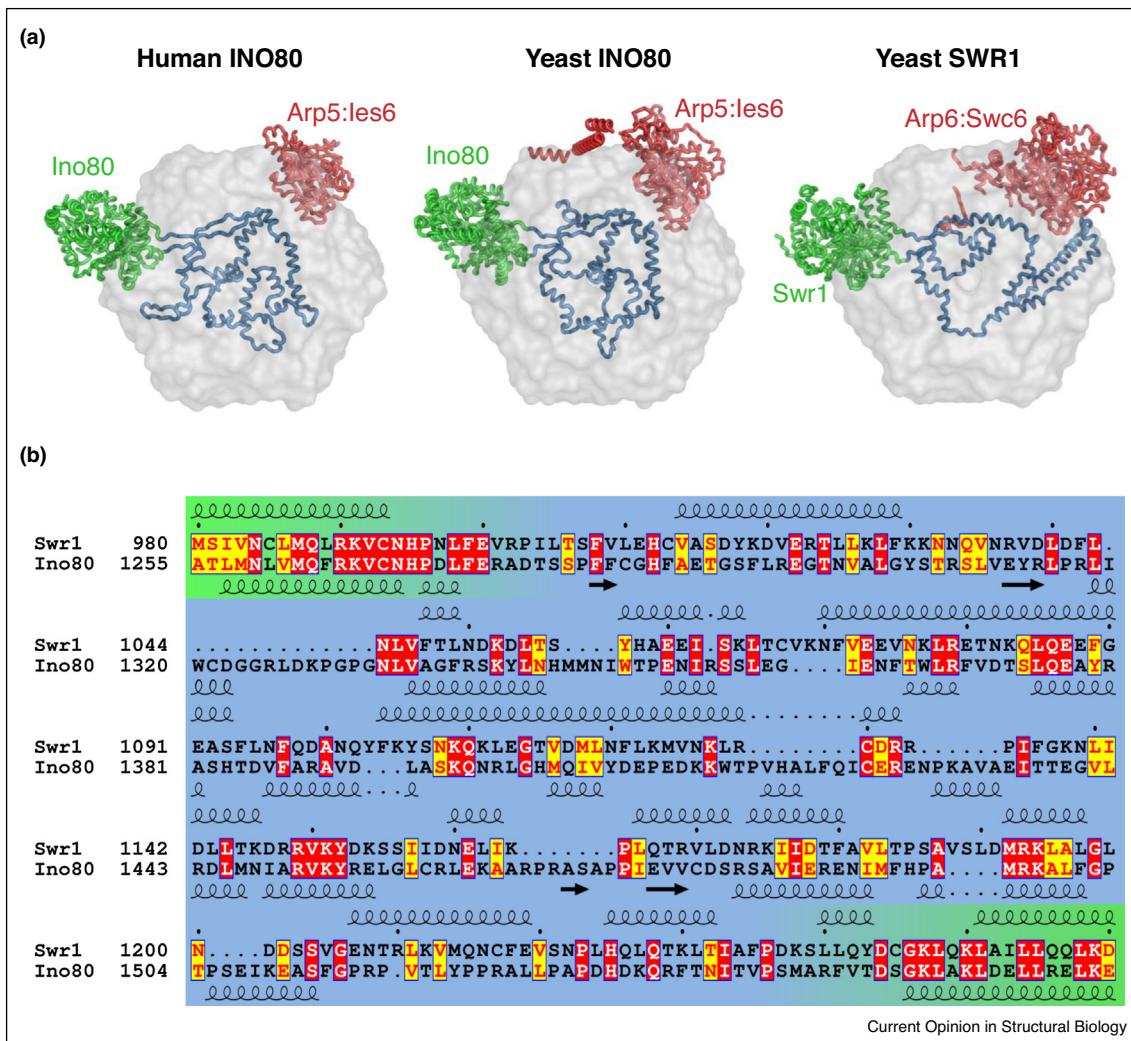
A. Top view of yeast and human INO80, and yeast SWR1 core components. All motor subunits (green) of INO80 family members contain a large polypeptide insertion (blue) that is encapsulated by a heterohexamer of RuvBL1 and RuvBL2 subunits (Rvb1 and Rvb2 in yeast) (grey). This asymmetry facilitates the incorporation of some complex-specific subunits (red). B. Sequence alignment of yeast Swr1 and Ino80 motor domain insertion. The motor domain (flanking region, highlighted green) is highly conserved in all INO80 family members, but the interspersed insertion is highly variable. Red denotes sequence identity, yellow sequence similarity. Secondary structure of Swr1 and Ino80 are respectively shown above and below the alignment.

this module resides on nucleosomal linker DNA in these structures [13**,32**] (Figure 2b), but it is unclear whether this is its only location. Low resolution structures of INO80 in the absence of a nucleosome [23*,38] show this module is tucked under the RuvBL1/2 ring and motor domain, implying that a dramatic conformational change occurs upon binding the substrate.

Mechanisms of translocation and coupling to chromatin remodelling

Recent structures have begun to determine how translocation is coupled to the nucleotide-binding and hydrolysis cycle of the main motor subunit of all remodellers [6**,8*], which share significant structural and sequence similarity even between families. This occurs in a 3' to 5' direction [39] via a cycle of discrete steps [40*] on the so called 'tracking strand'. Binding of the motor creates a single base bulge in the direction of translocation. Nucleotide binding induces movement of a base on the opposing strand (the 'guide strand'), thereby resetting the geometry of base pairing. Following hydrolysis and release of the nucleotide, the cycle repeats and produces a shuffle-like movement along the nucleosomal wrap.

This series of movements is self-contained, but can only result in productive movement of DNA relative to the

Figure 2
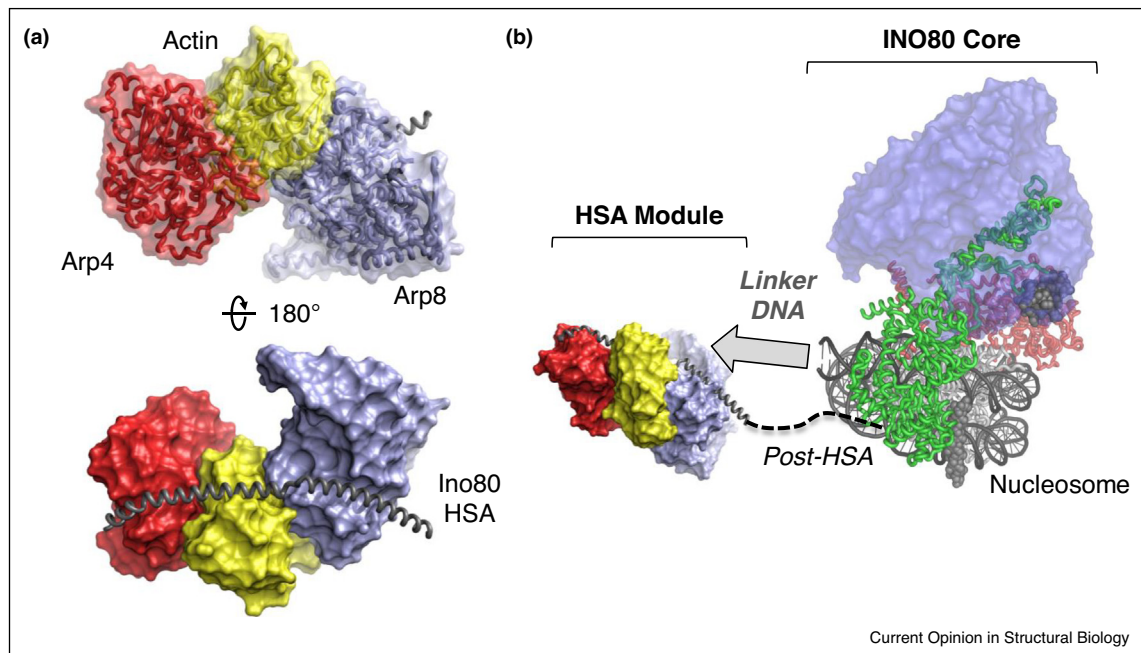
A. Cartoon representation of the INO80 HSA domain (grey) bound by Arp4 (red), actin (yellow) and Arp8 (light blue). The HSA domain forms an extended alpha-helical structure which accommodates Actin and Actin-related subunits in all INO80 family remodellers. B. Proposed location of the HSA-containing module relative to the motor and Rvb1/2 heterohexamer in Ino80. Based on biochemical work and 2D analysis of electron microscopy data, the HSA module is thought to reside on linker DNA projecting from the nucleosomal entry site. In this way it acts as a sensor of extranucleosomal DNA and can, presumably, regulate the function of the motor. For SWR1, the location of this module relative to the motor is still unclear.

histone core if the remodeller is physically tethered to one or multiple histones during translocation. Evidence from the structures of nucleosome-bound INO80 [12••,13••] and SWR1 [14••] suggests that Arp5:Ies6 and Arp6:Swc6, respectively, are in a prime position to fulfil this role. Support for this comes from recent biochemical interrogations of Arp5 and Ies6, which revealed a role for coupling the motor ATPase to productive nucleosome sliding [41–43]. In this way, Arp5 is not just important for recruitment [44,45] but directly involved in determining the extent of sliding *in vivo*, thereby explaining the dysfunction observed upon deletion of the gene [46–48]. In similar fashion, Snf2, the motor of SWI/SNF complexes, uses its SnAC (<u>Sn</u>f2 <u>A</u>TP <u>c</u>oupling) domain to remain tethered to the histone surface [49]. Deletion of Arp6 in SWR1 also leads to a loss of multiple subunits and histone exchange activity [50,51]. These tethers, therefore, support both structure and function of different chromatin remodellers.

Differences in a conserved bidentate interaction with the nucleosome

Even though INO80 and SWR1 share a common core architecture and features in line with other remodellers, their differences become apparent through their interaction with a nucleosome. Both INO80 [12••,13••] and

SWR1 [14••] have a bidentate interaction with the nucleosomal wrap that is likely to be central to the mechanism of INO80 family enzymes (Figure 3). One contact is made at SHL6/7, where the entry/exit DNA is peeled away from the histone octamer, and a second occurs at SHL2/3. In both remodellers, this involves the motor and the aforementioned tether (Figure 3a). However, the motor–tether arrangement is inverted between INO80 and SWR1: while Ino80 and Arp5:Ies6 are bound at SHL6/7 and SHL3, respectively, the Swr1 motor binds at SHL2 with Arp6:Swc6 at SHL6 (Figure 3). The position of Swr1 at SHL2 is more in-line with that observed for nucleosome sliding enzymes such as Chd1 [9••], ISWI [7,8•] and Snf2h [52,53•], even though its biochemical activity is not nucleosome sliding, but histone exchange. Footprinting studies are consistent with the position of the INO80 and SWR1 motors within their respective structures [54,55•].

This opposing arrangement of INO80 and SWR1 on the nucleosome means that they cannot employ the same mechanism for moving DNA across the octamer surface. In both cases ATP-dependent translocation likely occurs between SHL6/7 and SHL2/3, but the position of INO80 means that it would *push* entry side DNA against the Arp5:Ies6 anchor, while SWR1 would *pull* from Arp6:Swc6. As a result, the conformational state of the tether

Figure 3
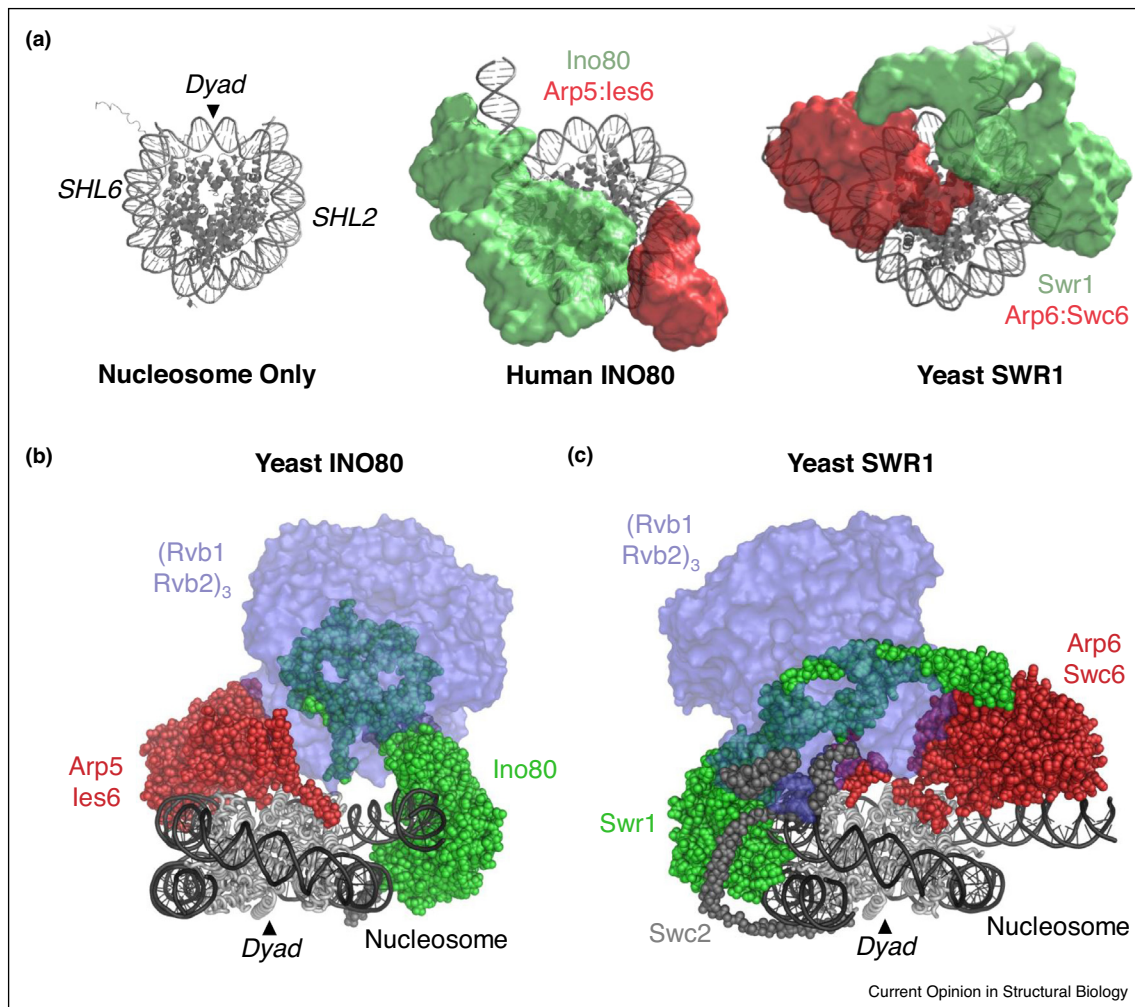
A. (Left) Top view of the nucleosome, showing the locations of SHL2 and SHL6. The nucleosome view is the same in the middle and right panels. (Middle) Bidentate interaction of INO80 with the nucleosome. The motor (green) is bound at SHL6/7 and the tether (Arp5:Ies6, red) at SHL3. (Right) Bidentate interaction of SWR1 with the nucleosome. The motor (green) is bound at SHL2 (+1) and the tether (Arp5:Ies6, red) at SHL6. B. View of yeast INO80 complex down the dyad axis. The motor (green) is positioned at SHL6/7, while Arp5 and Ies6 (red) sit over the histone core and make contacts with SHL3. C. View of yeast SWR1 complex down the dyad axis. The motor (green) is engaged at SHL2 and has rotated by 35-degrees as a consequence of a 1 bp translocation. The Arp6:Swc6 heterodimer resides at SHL6 near the entry site, where the DNA has been peeled away.

could play a crucial role in regulating DNA movement. Some evidence for this comes from a comparison of the nucleosome-bound human [12$^{\bullet\bullet}$] and yeast [13$^{\bullet\bullet}$] INO80 structures. The yeast complex shows a significant contact with the histone core via Arp5, which are absent in the human complex. These differences can be explained by the conditions used for the *in vitro* reconstitution of the nucleosome-bound complex: the human complex was formed in the presence of the non-hydrolysable ATP analogue ADP-beryllium fluoride (ADP-BeF$_3$), whereas the yeast complex was not, suggesting that supplementation with ADP-BeF$_3$ has favoured a conformation different to the yeast enzyme. Conversely, the SWR1-nucleosome complex shows a definitive engagement with the histone

core via Swc6 (which forms a tight interaction with Arp6) in the presence of ADP-BeF$_3$. Therefore, while the nucleotide-state of the tether is clearly important, identical states have opposite outcomes in INO80 and SWR1.

SWR1 and INO80 are distinguished further by their oligomeric states for remodelling. SWR1, like several other remodellers, acts as a monomer [51], whereas two human INO80 complexes are required for nucleosome sliding [56$^{\bullet\bullet}$]. This 'functional dimerisation' has also been observed for Snf2h [53$^{\bullet}$,57,58] and forms the basis for the proposed spacing mechanism of human ISWI complexes. For INO80, however, this finding is particularly surprising given the substantial size of a single complex relative to a

nucleosome, let alone two complexes. Importantly, this means that neither structure of nucleosome-bound INO80 paints a complete picture of the remodelling mechanism.

The requirement for one or two complexes, as well as the opposing setup on the nucleosome, may ultimately relate to the outcome of chromatin remodelling by INO80 and SWR1. Continuous movement of DNA across the octamer surface is an integral part of nucleosome sliding by INO80 [59]. By contrast, SWR1 appears to perform histone exchange via limited translocation (six or seven base pairs) between the entry site and the motor with no net change in nucleosome position [54]. Consistent with these observations, a single base pair translocation is observed towards the dyad in the SWR1-nucleosome structure but only as far as the motor bound DNA segment [14••]. Therefore, the configuration of SWR1 is tightly linked to the region of DNA that wraps around the canonical H2A:H2B or the incoming replacement HTZ:H2B dimer.

Although histone exchange by yeast INO80 has been reported [60,61], it remains a contentious issue [62,63]. Nevertheless, recent experiments show that INO80 also exhibits a mode of limited translocation at the H2A:DNA interface in aid of histone exchange [55•]. High cooperativity of binding *in vitro* implies that INO80 interacts with the nucleosome almost exclusively in pairs [56••], but a condition may exist that favours a monomeric interaction and regulates a switch from continuous (sliding) to limited translocation (exchange). A significant proportion of ATPase activity is uncoupled from sliding and it may be that this has a role in histone exchange instead. Further work is needed to reveal a role for such a regulatory mechanism for INO80 *in vivo*.

Regulation of INO80 and SWR1

Nucleosomes undergo extensive post-translational modifications (PTMs) that can affect recruitment of effector proteins as well as the structure of chromatin itself [64]. Both TIP60 (another INO80 family member) and NuA4 complexes (Table 1), acetylate H4 and H2A.Z/HTZ histones [65], in an early stage of DNA repair [66]. Acetylation of H4 stimulates the incorporation of HTZ: H2B histone dimers by SWR1 although this appears to be an effect on affinity of binding rather than catalysis *per se* [67]. It is noteworthy that this mirrors the activating effects of H4 on nucleosome sliders Chd1 [68] and ISWI [7,69,70], which are also positioned at SHL2. However, despite the functional consequences on SWR1 activity, a direct interaction between SWR1 and the H4 N-terminal tail has not been demonstrated.

Histone tails also regulate the ATPase and nucleosome sliding activity of INO80 [71,72], with H3 tails inhibiting the complex [12••]. This is consistent with the location of the INO80 motor at SHL6/7 (Figure 3b), where the H3 tail trajectory follows the path of linker DNA, which is unpeeled in the nucleosome-bound structure. The H3 N-terminus is itself crucial to the stability of the nucleosomal entry/exit DNA and regulates release of the H2A: H2B dimer near the start of the wrap [73]. This suggests that INO80 overcomes the inherent stability conferred by the H3 N-terminal tail in order to loosen the DNA from the H2A:H2B dimer surface and perform its nucleosome sliding activity.

Furthermore, there are self-contained mechanisms of regulation in different remodellers, that act in addition to regulation by PTMs. For example, regions adjacent to the HSA domain are thought to regulate activities of both INO80 and SWR1, as well as RSC: under certain circumstances, a region C-terminal to the HSA (the post-HSA) interacts with the motor to control translocation [28••,74], while in Swr1 a region adjoining the HSA (referred to as the 'Z-domain' [75]) is responsible for binding the variant HTZ:H2B dimer, which in turn stimulates the ATPase activity of the motor [76]. As such, the HSA module and its complementary features regulate the motor depending on whether histones or DNA are engaged.

Future perspectives

Since their discovery, research on INO80 family enzymes over the last two decades has taken significant steps towards understanding the mechanistic basis for their biological functions, even though the role of accessory subunits remains largely unclear. In particular, the disorder of the essential HSA module in all current structures is a limitation that must be overcome to understand the remodelling mechanism in full. Furthermore, in contrast to SWR1 and all nucleosome sliders, the human INO80 complex functions as a dimer [56••] and the corresponding remodelling mechanism must also account for this observation.

One final note of caution is that these systems operate on chromatin and will never encounter isolated nucleosomes within the cell. This leads to the possibility that the evolution of accessory domains and multi-subunit architectures is in fact linked to higher order functions that cannot be described by studies centred on mono-nucleosome substrates alone. It would be prudent, therefore, to shift focus to poly nucleosome substrates that are more chromatin-like. In doing so, the field may reveal functionality for complexes beyond simple translocation.

Conflict of interest statement

Nothing declared.

Acknowledgements

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