nature reviews genetics

https://doi.org/10.1038/s41576-023-00666-x

Review article

Check for updates

Context-specific functions of chromatin remodellers in development and disease

Sai Gourisankar[1,2], Andrey Krokhotin[1,3], Wendy Wenderski[1,3] & Gerald R. Crabtree[1,3]

Abstract

Chromatin remodellers were once thought to be highly redundant and nonspecific in their actions. However, recent human genetic studies demonstrate remarkable biological specificity and dosage sensitivity of the thirty-two adenosine triphosphate (ATP)-dependent chromatin remodellers encoded in the human genome. Mutations in remodellers produce many human developmental disorders and cancers, motivating efforts to investigate their distinct functions in biologically relevant settings. Exquisitely specific biological functions seem to be an emergent property in mammals, and in many cases are based on the combinatorial assembly of subunits and the generation of stable, composite surfaces. Critical interactions between remodelling complex subunits, the nucleosome and other transcriptional regulators are now being defined from structural and biochemical studies. In addition, in vivo analyses of remodellers at relevant genetic loci have provided minute-by-minute insights into their dynamics. These studies are proposing new models for the determinants of remodeller localization and function on chromatin.

Sections

[1]Department of Pathology, Stanford University, Stanford, CA, USA. [2]Department of Chemical Engineering, Stanford University, Stanford, CA, USA. [3]Department of Developmental Biology, Stanford University, Stanford, CA, USA.
e-mail: crabtree@stanford.edu

Introduction

In eukaryotes, gene expression is regulated by chromatin organization and transcriptional regulators. The former category includes the arrangement of nucleosomes along DNA and histone post-translational modifications, which, together with the three-dimensional structure of chromatin, define the physical accessibility of DNA to various factors. The latter category includes transcription factors (TFs), co-activators or co-repressors, chromatin modifiers such as 'readers', 'writers' and 'erasers' of histone post-translational modifications, and ATP-dependent chromatin remodellers. Notably, chromatin remodellers hydrolyse ATP to alter nucleosome structure and regulate chromatin accessibility. They additionally biochemically interact with various other transcriptional regulators, ultimately having an integral role in facilitating the activation and repression of gene expression programmes at the right time and place in an organism.

Chromatin remodellers are composed of an ATPase protein and can have multiple associated subunits. SWI/SNF (switch/sucrose non-fermenting) was the first ATP-dependent chromatin remodeller to be discovered in yeast studies in the 1980s (Box 1). Since then, homology searches based on the sequence conservation of the Snf2-like ATPase domain[1] have expanded the repertoire of remodellers to encompass 32 different proteins and/or protein complexes in *Homo sapiens* (Fig. 1a). The four canonical families are SWI/SNF, ISWI (imitation SWI), CHD (chromodomain helicase DNA-binding) and INO80/SWR (SWI2/SNF2-related) (Fig. 1b). In general, ATP-dependent chromatin remodellers are present in increasing diversity in higher-order species[1].

Despite some commonalities in structure and biochemical function, chromatin remodellers have specific and distinct biological activities in mammals. Recent human genetic data have revealed that remodellers are widely but characteristically mutated in human developmental diseases and cancers, and efforts are underway to find therapeutic avenues to target remodellers in these pathologies[2]. Therefore, a major research question is understanding how remodellers confer very specific and diverse functions in gene expression, physiology and disease.

Here we review the distinct, non-redundant and dosage-sensitive biological roles of chromatin remodellers and the mechanisms underlying their specificity, such as the combinatorial assembly of subunits, interactions with TFs, and how remodellers localize on chromatin. We discuss evidence from large-scale genetic studies of developmental disorders and cancer that have led to insights into the multiple, context-specific mechanisms of remodeller function, focusing on the mammalian complexes. For additional discussions that complement these areas, we refer readers to several excellent recent reviews[3–9].

General features of chromatin remodellers

Commonalities and differences in remodeller structure and function

Recent structural studies of remodellers in complex with nucleosomes have greatly contributed to understanding the commonalities and differences in their core remodelling function. Cryogenic electron microscopy (cryo-EM) structures that highlight structure–function relationships have been reported for 11 human chromatin remodellers (reviewed in refs. 8,10; listed in Supplementary Table 1) and a representative structure from each remodeller family are shown in Fig. 1c. The common feature of each of the structures of chromatin remodellers defined to date is the binding of a nucleosome. A direct nucleosomal interaction was in fact predicted by early genetic studies in yeast that identified suppressor mutations in histones[11–13] as well as in vitro nucleosome remodelling studies with purified remodellers[14–18].

The nucleosome is bound predominantly by the ATPase subunit, with additional contact provided sometimes by accessory subunits, such as BAF47 (encoded by the gene *SMARCB1*) in the BAF (mSWI/SNF) complex or ARP5 (*ACTR5*) and IES6 (*INO80C*) in INO80 (ref. 19) (Fig. 1c). (See Box 1 for an explanation of the nomenclature of chromatin remodellers.) Accessory subunits can assemble with the ATPase subunit into megadalton-sized macromolecular machines. Interestingly, BRM and BRG1 (*SMARCA2* and *SMARCA4*) in BAF seem to be the only ATPases to have a SnAC domain (Fig. 1c), which anchors histone contacts in a 'C' clamp-like structure and could have a role in BAF-specific functions. The nucleosome can also be engaged without additional subunits, as demonstrated by the structures of CHD (Fig. 1c), in which amino-(N-)terminal chromodomains interact with methylated histone tails to mediate nucleosome association[7]. However, many of the human remodellers described as functioning without accessory subunits are far less well studied and may associate biochemically with as yet unidentified dedicated protein partners that confer upon them additional functions. In addition, many of the cryo-EM structures have coverage of only around 40% of the remodelling complex, with electron density not observed or unable to be resolved for many subunits. In Supplementary Table 1, we provide detail on the resolved structures of remodelling complexes.

The fundamental steps in nucleosome remodelling are powered by the binding and hydrolysis of ATP to the ATPase domain, which forces a translocation of DNA along the nucleosome of approximately one base pair (bp) per molecule of ATP and breaks histone–nucleotide contact in a mechanism that is usually referred to as 'inch-worming' the DNA along the nucleosome[8,20]. The general term 'nucleosome remodelling' or 'nucleosome turnover' describes several different outcomes: linear nucleosome translation along the DNA, nucleosome eviction, histone variant deposition into the nucleosome octamer and/or nucleosome exchange. Specific remodellers have distinct roles in nucleosome dynamics. For example, ISWI-family remodellers slide nucleosomes along DNA[21,22]. ATRX cooperates with death-domain-associated protein DAXX to deposit H3.3 over repetitive DNA[23–25], whereas LSH (*HELLS*) inserts the histone variant macroH2A[26], and BAF can evict either H3K27me3-modified nucleosomes or directly evict Polycomb repressive complexes[27,28]. In some cases, these differences in remodelling type are facilitated by accessory domains on the remodeller ATPase subunit, as in the case of the HAND–SANT–SLIDE domains of ISWI ATPases, which bind extra-nucleosomal DNA[29]. Auxilliary subunits of remodelling complexes that bind DNA and modified histones also contribute to differences in nucleosome remodelling activity.

The molecular and genetic basis of multitasking by chromatin remodellers

In mammals, most remodellers have evolved to have multiple non-catalytic auxiliary subunits and different functional protein domains. That suggests the potential for a diversity of complexes with a diversity of function, based on the combinatorial assembly of subunits, many of which are paralogous with each other[30]. For example, a recent estimate suggests that 1,452 different BAF complexes can be assembled, composed of around 16 subunits encoded by 29 genes[31]. This is probably a lower bound, because almost all BAF subunits have multiple isoforms caused by alternative splicing. Another example is the NuRD complex, composed of one of CHD3, CHD4 or CHD5, and one of various paralogous subunits such as MBD2/MBD3, GATAD2A/B, HDAC1/2 and

Box 1

The discovery of ATP-dependent chromatin remodellers

Independent and concurrent yeast genetic studies in the laboratories of Marion Carlson at Columbia, and Ira Herskowitz at the University of California San Francisco (UCSF), led to the first realization that chromatin could be regulated by the actions of large protein complexes containing ATPases. Coincidentally, both groups were interested in genetically defining components of cellular signalling pathways. Marion Carlson's group was studying the response of yeast to nutrient signalling and sugar use. They called their mutant strains sucrose-non-fermenting, or SNF, and found that the genes involved were ones that might be expected, such as kinases[185]. However, one of their mutant strains was unexpected, implicating a gene called *SNF2*, which encoded a large ATPase[185]. Parallel and independent studies in the Herskowitz laboratory at UCSF were defining the requirements for mating type switching in response to pheromones. Here again, a series of informative genes were discovered in their screens and one encoded an ATPase that they called SWI2[186]. In a second screen for genes that might reverse part or all of the SWI2 phenotype, they and others found genes encoding histones and realized that these discoveries might reflect functions in the nucleus at the termination of a signalling pathway[12,13,187]. When the two groups compared their results, they found that SWI2 was identical to SNF2 (reviewed in ref. 188; sequences of SNF2 determined in ref. 189). Work by Craig Peterson in the Herskowitz laboratory demonstrated that several of the genes they discovered were part of a large complex that came to be known as the SWI/SNF complex[190].

Genetic studies continued to provide insight into remodeller function when Tamkum, Scott and Kennison found that phenotypes in flies with mutations in Pc (and Pc-like), which was later shown to be a subunit of the *Drosophila* orthologue to Polycomb repressive complex 1 (PRC1), could be rescued by another mutation in a protein called Brahma[191]. Cloning of Brahma (also called BRM) revealed that it encoded an ATPase similar to the SWI2 and SNF2 proteins[191]. Within the protein, a conserved domain was discovered of approximately 60 amino acids that was the first bromodomain identified. Additional biochemical studies also revealed that Brahma was part of a large protein complex (reviewed in ref. 192). However, mutations in only some of the subunits could rescue the phenotypes caused by Polycomb complex mutations[64].

In mammalian cells, studies of genomic DNase accessibility had revealed that during development, genetic regulatory regions became accessible so that they could receive a signal from the cell membrane before they expressed the receptors that would trigger the activation of the gene[193]. Somehow, the nucleus was prepared to receive signals from the cell membrane during development, as though developmental transitions involved the coordinated preparation of the chromatin accessibility with the expression of the receptors that would send signals into the nucleus, a conclusion that was reinforced by genetic receptor-switch experiments performed later in several laboratories[194–196]. Purification of the proteins that bound to these tissue-specific DNase-sensitive sites[193,197] and positional cloning led to the identification of mammalian homologues of the proteins discovered in yeast and flies[18,33,34,198,199] as well as several new proteins not present in these organisms. Further biochemical, proteomic and next-generation-sequencing studies have since identified 16 subunits encoded by 29 different genes in humans[31,180], forming a family of mammalian BAF (Brahma-associated factor) or mSWI/SNF complexes (Fig. 2a). Many other remodellers with homologous Snf2-like-ATPase domains have now been characterized (Fig. 2).

A note on chromatin remodeller complex subunit gene and protein names

In part owing to contributions from diverse research groups in discovering the genes and protein components of remodeller complexes, many alternative names have entered the literature. We choose to present the HUGO Gene Nomenclature Committee gene name in italics, and related names commonly used to refer to the human genes or the protein products in upright text, writing both at first mention. Subsequently, we refer to only the protein or gene, depending on which was being discussed. For example, *ARID1B* is the gene responsible for encoding the protein BAF250B. For BAF complex subunits such as BAF250B, the numerical suffix after 'BAF' refers to the molecular weight in kilodaltons of the subunit observed on a SDS–PAGE gel, and the capital letter refers to the paralog, making the names of subunits easy to recall. Confusingly, different names for complexes are also used in the literature, such as BAF, also known as mSWI/SNF (mammalian SWI/SNF). Supplementary Table 1 lists each remodeller and common alternative names that one might encounter.

MTA1/2/3 (ref. 5) (Fig. 2). In the ISWI complex, a core ATPase, SNF2H or SNF2L (*SMARCA5* or *SMARCA1*) is paired with one of six different regulatory subunits that are important for histone and nucleosomal DNA substrate recognition[32] (Fig. 2).

These observations raise the question of whether a single cell contains each possible complex or whether a unique assembly is solely present in a single cell type. Early studies using immunofluorescence showed that within a single cell, the position of the BAF complex ATPase could be occupied by either BRG1 or BRM[33,34]; yet both ATPases are expressed within most cell types. Consistent with these earlier studies, recent single-cell RNA sequencing (RNA-seq) studies of mammalian tissues have shown that each cell type examined has the potential (in terms of expressed mRNAs for subunit families) to form a diversity of possible complexes[35]. Conceptually, these studies suggest the first model whereby each cell contains a diversity of complexes predicted by combinatorics, creating a range of different complexes with distinct composite surfaces capable of interacting with ambient TFs and other nuclear proteins. Such a model could explain how these complexes carry out multiple different functions within a single cell. Whereas chromatin remodeller complexes such as BAF are present at about 300,000–500,000 complexes per cell[36], most of the TFs that they interact with are present in numbers of the order of 10,000 molecules per cell[37]. Thus, if a TF or a DNA repair or recombination protein binds to one subset of BAF remodelling complexes within a specific cell,

other combinatorial assemblies are free to interact with different TFs at the same time, illustrating how biochemical multitasking is accomplished. This 50-fold or more abundance over TFs leads to a technical difficulty in immunoprecipitation studies, as antibodies against a TF often co-immunoprecipitate the remodeller, but antibodies against the remodeller often fail to reveal the relevant, functionally linked TF[36,38,39].

Support for the second model, that certain cells contain unique remodeller assemblies, stems from the observation that certain paralogous subunits (and/or isoforms) have been found to be tissue-specific in expression. These include BAF45A, BAF45B, BAF45C and BAF45D (encoded by *PHF10*, *DPF1*, *DPF3* and *DPF2*, respectively), or BAF53A and BAF53B (*ACTL6A* and *ACTL6B*) in BAF complexes[40], or CHD3, CHD4 and CHD5 in NuRD complexes[41,42]. Since many TFs are also cell-type-specific in their actions and/or expression patterns, the combinatorial use of subunits could permit remodellers to bring lineage specificity to their functions. Indeed, as we discuss in the later section about remodellers in development, switches in complex subunit composition can be necessary and sufficient for directing differentiation, and direct reprogramming experiments that induce certain remodeller subunits' expression or downregulate paralogous subunits have successfully converted cell types[43,44].

A noteworthy recent example illustrating the importance of asymmetric, cell-specific expression of specific subunits in the earliest stages of development was observed in studies examining the role of the mouse embryonic-stem-cell-specific esBAF complex in determining cell fate[45]; this specialized BAF complex includes BRG1 but not BRM, and BAF155 (encoded by *SMARCC1*) but not its paralog BAF170 (*SMARCC2*)[46]. During early embryogenesis, the formation of the trophectoderm, which gives rise to the placenta, arises from initial asymmetry in the four-cell or eight-cell embryo. Hippo signalling by the TFs YAP and TEAD have a critical role in the designation of trophoblast and results in the activation of the homeobox factor CDX2, a major determinant of the formation of trophoblastic cells. One of the first hallmarks of early trophoblastic differentiation is the asymmetric expression of cytoplasmic keratins 8 and 18. The asymmetric expression of keratin 8 and 18 in mouse and human four-cell or eight-cell blastomeres resulted from differential expression of BAF155 in the vegetal blastomere[45]. By manipulating the cells in which BAF155 was more highly expressed at the two-cell state, the authors could increase both YAP–TEAD signalling as well as keratin expression, indicating that heterogeneities at the cellular level in BAF complexes in the developing embryo have a critical role in defining the first steps in designating the placenta and embryo.

Dosage-sensitivity of chromatin remodellers in mammals

Chromatin remodellers were once thought to be dosage-insensitive with largely redundant activity. This hypothesis originated from early genetic studies of chromatin remodelling genes in yeast, which found that RSC/Sth1 was the only remodeller essential for yeast viability[47–49]. Furthermore, deletion of any individual yeast remodeller had only modest effects on nucleosome positioning, as characterized both by MNase-sequencing in cells and in recombinant preparations of purified complexes, and the effects of deleting a single remodeller could be compensated for by related remodellers[50–54]. However, recent human genetics studies have revealed both a surprising intolerance to the loss of function (LoF) and dosage sensitivity of chromatin remodelling genes. From a therapeutic development perspective, dosage sensitivity could define targets at which a drug might exert a maximum effect without having to remove all the activity of the gene product.

Analysis of the genomes of 141,456 individuals has permitted estimates of both intolerance to LoF and constraint on missense variants for every human gene[55]. Remodeller complexes are remarkable in that the estimated intolerance of their subunits to LoF (as well as constraint on missense variants) are among the most severe of all human genes (Fig. 3a). The copy numbers of many genes encoding remodeller subunits are conserved across 13 mammalian genomes from mice to humans (Fig. 3b). Remodeller subunit genes, compared to all other genes, are statistically significantly enriched (Fisher's exact $P < 10^{-23}$) in regions specific to human pathogenic copy number variation (CNV)[56]. Subunits of remodellers may show triplosensitivity, when an extra gene copy produces a phenotype. For example, triplosensitivity for *Brwd1*, a bromodomain histone 'reader' that assembles substoichiometrically into BAF complexes in the mammalian brain, was found to be responsible for Down-syndrome-related molecular and behavioural phenotypes in a Down syndrome mouse model[38]. A separate analysis of all variants in DECIPHER[57], a database of genetic information on individuals with developmental disorders, found that almost 50% of the variants in the four major remodeller families were copy number losses[58]. Tight regulation of gene expression across evolution is a characteristic of haploinsufficient genes, which are defined as those intolerant to the loss of a single allele (often classified by a probability of intolerance to LoF (pLI) score ≥ 0.9 (ref. 59)).

Intriguingly, subunits within the same complex often do not show the same intolerance to LoF or constraint as their neighbours. Analysis of the differences between subunit intolerance to LoF and constraint on missense variation can thus generate informative structural and functional hypotheses. Compare the vastly different intolerance to loss of function (pLI scores) between integral members of the BAF complex such as *SMARCA4* or *SMARCA2* (encoding the ATPases) (Fig. 2a), and other BAF subunits such as *PHF10* (BAF45A) (Fig. 2b). Subunits tolerant to LoF (pLI ~0) may be tangential in structure for remodeller function; for example, BAF45A is the last subunit to be added to the pBAF complex during its assembly, and it may not be integral to a semi-functional pBAF complex[31]. Paralogous subunits, such as the BAF subunits *BCL7A*, *BCL7B* and *BCL7C*, are often tolerant to LoF variation, perhaps because one can be substituted for another. In other cases, tolerance to LoF variation may tell us about subunits that are only expressed in or have important functions in adult life (when these metrics are less influenced by selective pressure) or specific tissue types. An example of such a subunit is the neuron-specific BAF subunit *ACTL6B*[43], in which deleterious recessive mutations cause autism spectrum disorder[60] but the subunit is specific in function and expression to postmitotic neurons. Other remodellers found to be tolerant to loss might truly be redundant in humans; for example, *CHD1L* and *ZRANB3* have both been found with high-confidence homozygous LoF variants in at least one individual[61] (Fig. 2j, Fig. 3a). From a therapeutic development perspective, the identification of individuals with homozygous LoF variants in a gene can often indicate the tolerability of pharmacologically targeting the encoded protein[62].

The multitasking potential of remodellers, through different protein surfaces or by cell-specific subunit expression, could also explain the disparities in mutational burden among adjacent subunits within the same complex. For example, deleterious mutations in the core *ARID1B* (encoding the largest BAF subunit, BAF250B) are the most common de novo mutations in human intellectual disability[63], indicating a critical and LoF-sensitive role in human neurodevelopment. Yet, adjacent subunits known to be part of neuronal BAF complexes, such as *BCL7A* or *SMARCD2* (BAF60B) (see Fig. 1c), seem to be LoF-insensitive and are not implicated in neurodevelopmental disorders, as defined

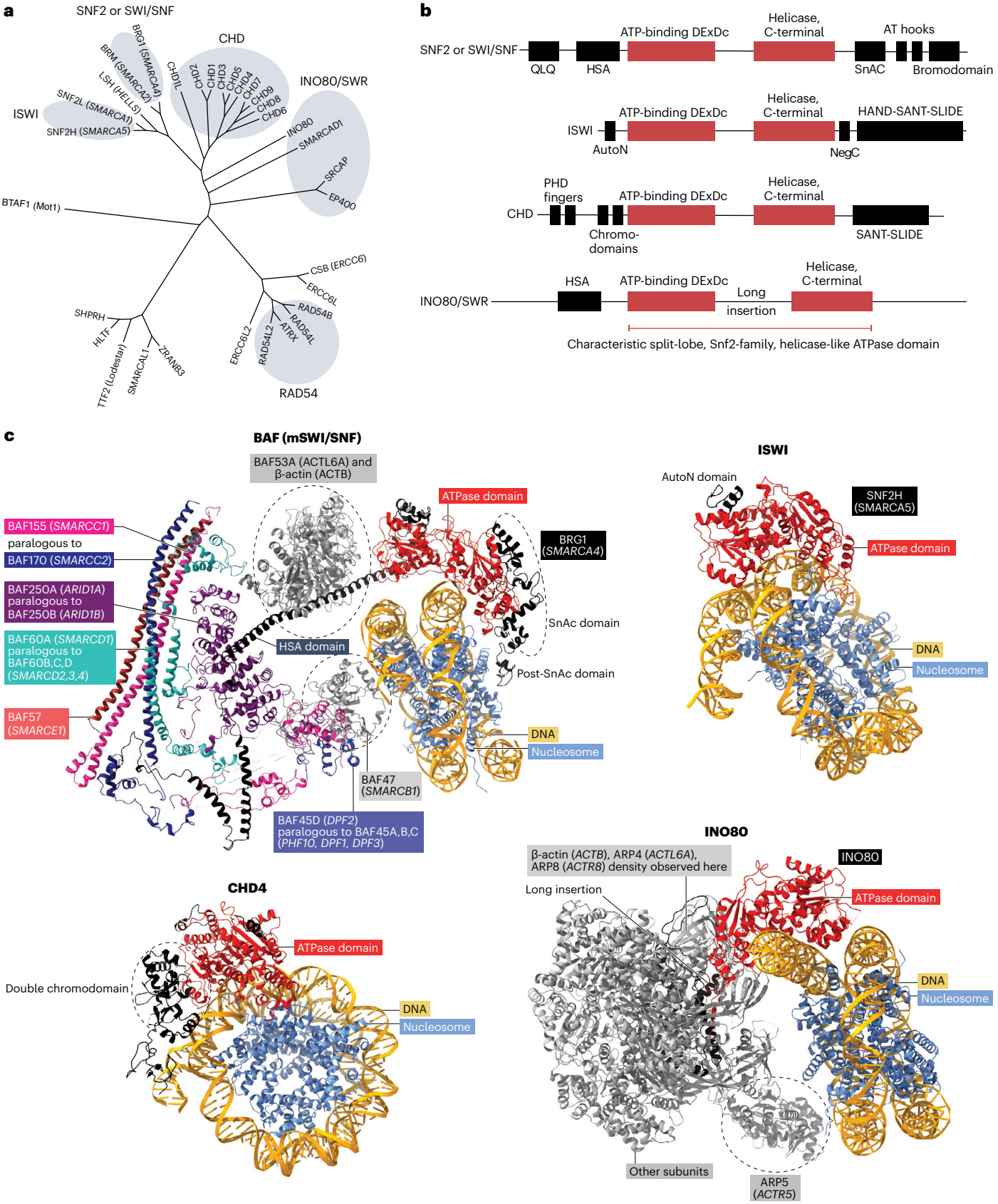
a
SNF2 or SWI/SNF
CHD
INO80/SWR
ISWI
BRG1 (SMARCA4)
BRM (SMARCA2)
LSH (HELLS)
SNF2L (SMARCA1)
SNF2H (SMARCA5)
CHD1L
CHD2
CHD1
CHD3
CHD5
CHD4
CHD7
CHD9
CHD8
CHD6
INO80
SMARCAD1
SRCAP
EP400
BTAF1 (Mot1)
CSB (ERCC6)
ERCC6L
RAD54B
RAD54L
ATRX
RAD54L2
ERCC6L2
SHPRH
HLTF
TTF2 (Lodestar)
SMARCAL1
ZRANB3
RAD54
b
SNF2 or SWI/SNF
QLQ
HSA
ATP-binding DExDc
Helicase, C-terminal
AT hooks
SnAC
Bromodomain
ISWI
AutoN
ATP-binding DExDc
Helicase, C-terminal
HAND-SANT-SLIDE
NegC
CHD
PHD fingers
Chromo-domains
ATP-binding DExDc
Helicase, C-terminal
SANT-SLIDE
INO80/SWR
HSA
ATP-binding DExDc
Long insertion
Helicase, C-terminal
Characteristic split-lobe, Snf2-family, helicase-like ATPase domain
c
BAF (mSWI/SNF)
BAF53A (ACTL6A) and β-actin (ACTB)
ATPase domain
BRG1 (SMARCA4)
BAF155 (SMARCC1)
paralogous to
BAF170 (SMARCC2)
BAF250A (ARID1A) paralogous to BAF250B (ARID1B)
BAF60A (SMARCD1) paralogous to BAF60B,C,D (SMARCD2,3,4)
BAF57 (SMARCE1)
HSA domain
SnAc domain
Post-SnAc domain
DNA
Nucleosome
BAF47 (SMARCB1)
BAF45D (DPF2) paralogous to BAF45A,B,C (PHF10, DPF1, DPF3)
ISWI
AutoN domain
SNF2H (SMARCA5)
ATPase domain
DNA
Nucleosome
CHD4
ATPase domain
Double chromodomain
DNA
Nucleosome
INO80
β-actin (ACTB), ARP4 (ACTL6A), ARP8 (ACTR8) density observed here
Long insertion
INO80
ATPase domain
DNA
Nucleosome
Other subunits
ARP5 (ACTR5)

Fig. 1 | The family of human chromatin remodellers. a, The 32 human chromatin remodellers cluster into families based on sequence similarity of their ATPase domains. The tree was constructed from a multiple sequence alignment of only the ATPase domains of human chromatin remodellers. **b**, The four canonical sub-families of chromatin remodellers are shown with their defining Snf2-family helicase-like ATPase domain highlighted along with distinguishing auxiliary domains often present in sub-family members. **c**, The structure of remodellers from each of the major families: the BAF or mSWI/SNF complex (Protein DataBase (PDB): PDBDEV_00000056), *SMARCA5* or SNF2h (ISWI complexes) (PDB: 6ne3), CHD4 (PDB: 6ryr) and INO80 (PDB: 6hts). Each displays an example of how the ATPase domain, in red, of remodellers contacts the nucleosome, assisted by non-ATPase domains such as the SnAC (Snf2 ATP coupling), and/or by auxiliary subunits. An example of other subunits in the BAF complex is labelled. Other subunits in grey are not labelled for simplicity; see Fig. 2 and Supplementary Table 1 for a detailed list of subunits. DExDc, Asp, Glu, X, Asp motif and DEAD-like helicases superfamily; HAND, secondary structure of four α-helices, three of which are in an L-shape configuration; HSA, helicase/SANT-associated; PHD, plant homeodomain; QLQ, Gln, Leu, Gln motif; SANT, switching-defective protein 3 (Swi3), adaptor 2 (Ada2), nuclear receptor co-repressor (N-CoR), transcription factor (TF)IIIB; SLIDE, SANT-like ISWI domain.

by the same genome-sequencing efforts (Fig. 2a). This parsing out of functions probably reflects specific interactions between the subunits of the remodeller and lineage-specific TFs or epigenetic regulators found within a given cell type and developmental stage. Testing this hypothesis will almost certainly require analysis of the hotspot mutations within a given subunit and identification of the interactions lost in these mutated complexes.

Loss of remodellers or their subunits may also inhibit their ability to balance global processes in the cell. Studies using chemical inducers of proximity and degron tags (Box 2) suggest that the BAF complex can regulate the distribution of Polycomb repressive complexes 1 and 2 (PRC1 and PRC2) by direct, ATP-dependent eviction of PRC1[27], or, by evicting nucleosomes that have repressive modifications. Polycomb repression is known to be dosage-sensitive[64], and BAF or other remodellers may titrate the dosage of other epigenetic complexes.

There is a possibility of redundant remodelling functions in mammals. The high rate of nucleosome exchange – several times per cell cycle[65] – could be due to a redundant function of remodellers over the large majority of the genome where nucleosomes are not positioned, but rather rapidly randomized after cell division[66]. At these largely intergenic regions, containing critical, developmentally active enhancers, several remodellers might contribute to nucleosome mobility or the rapid rate of exchange at a specific genomic region. A LoF- or dosage-sensitive, non-redundant function of a specific remodeller does not preclude redundant functions governing rapid rates of nucleosome mobility and exchange over other parts of the genome. Teasing out these redundant functions from the critical, context-specific functions of remodellers will be key to understanding the roles individual remodellers have in epigenetic, metabolic or other pathways during human development and disease.

Genomic localization of remodellers

A critical mechanism underlying the biological specificity of chromatin remodellers is probably their intrinsic localization. In part, remodeller localization arises from the domains or subunits that bind at least one of three substrates: TFs, histone modifications and extra-nucleosomal DNA. Some examples are the CHDs, which have chromodomains that bind methylated histone tails[7] or NuRD complex methyl-binding-DNA (MBD) subunits[67]. However, remodeller biological function seems specific enough that chromatin-binding domains alone cannot predict targeting. One of the most well studied roles of remodellers has been their assistance of TFs[68]. Interactions with TFs are particularly intriguing, not only because of their DNA-sequence-specific binding capability, but also because TF expression and/or activity is often lineage-specific, which might then impart biological specificity to remodeller function. Here we provide a perspective on recent models that have emerged concerning the interaction between remodellers and TFs.

Models of cooperation between remodellers and TFs

Three models of remodeller–TF cooperation are commonly evoked (Fig. 4). In the first, TFs use their sequence-specific binding sites to initiate the process of nucleosome remodelling, then recruit remodellers (Fig. 4a). In some cases, these TFs are 'pioneer' TFs, such as FOXA1, and/or pluripotency factors, such as OCT4 or SOX2, that can bind to nucleosomal DNA[69,70] and remodel nucleosomes on their own and recruit other TFs and remodellers. But the relatively limited sequence specificity of nearly all mammalian TFs seems to be incompatible with a pure version of such a 'TF-first' model, given that most TFs have thousands or even millions of potential recognition sequences but bind only a fraction of them[71]. Also, kinetic recruitment studies in which the remodeller or the TF is brought to an endogenous locus within minutes using chemically induced proximity[72], and conditional knockout studies in mouse embryonic stem cells, have showed that some pioneer factors such as OCT4 and SOX2 require recruitment by the BAF complex for creating genomic accessibility to support binding[73,74].

In another model, genome-wide ATP-dependent remodelling of nucleosomes establishes an accessible landscape for the TF to exploit and bind to a specific site (Fig. 4b). This model is supported by the observation that nucleosome turnover occurs many times per cell cycle across most of the genome[65]. The vast majority of the genome does not have stably positioned nucleosomes[66], presumably as a result of the rapid nucleosome turnover and the relative lack of stably bound chromatin-binding proteins that could exert a phasing (regular, arrayed positioning) effect. Therefore, a TF could find an opportunity for binding a specific locus within a few hours even if it could not bind to nucleosomal DNA. Also supporting this model are recent studies applying degron tags or PROTACs (Box 2) that degrade BRG1 and/or BRM in human cancer cell lines that found that acute degradation results in loss of TF binding at thousands of lineage-specific enhancers[75].

Localization specificity in the second model would come from remodeller subunits that recognize histone modifications and often subunits that bind features of DNA without absolute sequence specificity, such as ARID domains (which bind AT-rich regions), HMG domains (which bind kinked DNA) or the MBD1/2/3 methylated-DNA-binding domains. In BAF, subunits such as BAF57 bind to topologically restricted DNA in the form of a cruciform structure[76]. Remarkably, this cruciform-binding domain is a hotspot for mutations in diffuse malignant meningiomas[77]. Recent ATAC-seq studies in mouse embryonic stem cells have suggested that the binding of certain TFs relies selectively on specific chromatin remodelling pathways[78]. For example, in mouse embryonic stem cells, CTCF binding is dependent on SNF2H, the ATPase of the ISWI complex, but not BRG1 (BAF complex), whereas REST binding is BAF but not ISWI-dependent[78]. It remains to be investigated whether this specificity arises from specific remodeller function

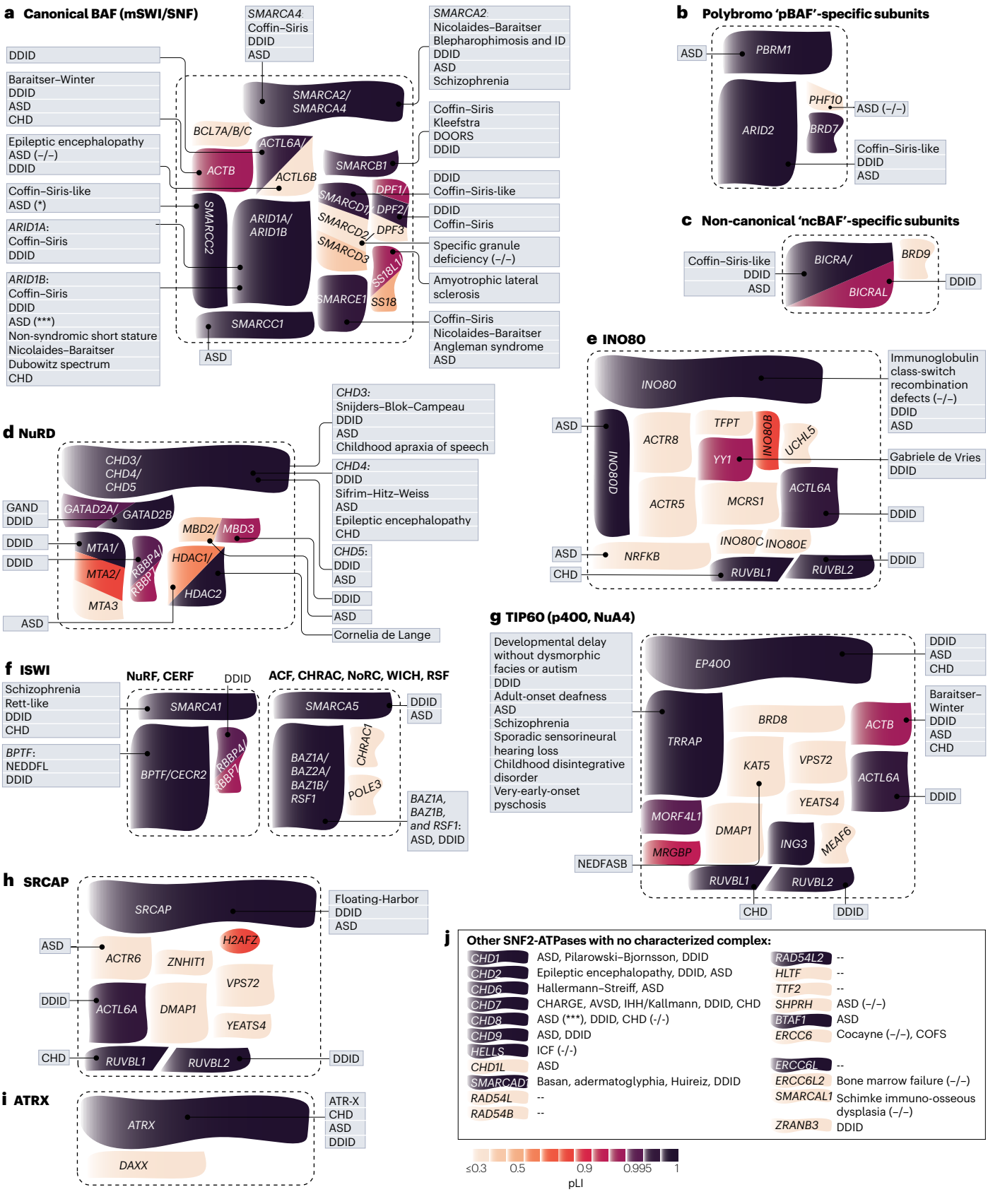
a Canonical BAF (mSWI/SNF)
SMARCA4:
Coffin–Siris
DDID
ASD
SMARCA2:
Nicolaides–Baraitser
Blepharophimosis and ID
DDID
ASD
Schizophrenia
DDID
Baraitser–Winter
DDID
ASD
CHD
Epileptic encephalopathy
ASD (–/–)
DDID
Coffin–Siris-like
ASD (*)
ARID1A:
Coffin–Siris
DDID
ARID1B:
Coffin–Siris
DDID
ASD (***)
Non-syndromic short stature
Nicolaides–Baraitser
Dubowitz spectrum
CHD
SMARCA2/
SMARCA4
BCL7A/B/C
ACTL6A/
ACTB
ACTL6B
SMARCB1
SMARCC2
ARID1A/
ARID1B
SMARCD1
SMARCD2/
SMARCD3
DPF1/
DPF2/
DPF3
SS18L1
SS18
SMARCE1
SMARCC1
ASD
Coffin–Siris
Kleefstra
DOORS
DDID
DDID
Coffin–Siris-like
DDID
Coffin–Siris
Specific granule deficiency (–/–)
Amyotrophic lateral sclerosis
Coffin–Siris
Nicolaides–Baraitser
Angleman syndrome
ASD
b Polybromo ‘pBAF’-specific subunits
ASD
PBRM1
ARID2
PHF10
BRD7
ASD (–/–)
Coffin–Siris-like
DDID
ASD
c Non-canonical ‘ncBAF’-specific subunits
Coffin–Siris-like
DDID
ASD
BICRA/
BICRAL
BRD9
DDID
d NuRD
CHD3:
Snijders–Blok–Campeau
DDID
ASD
Childhood apraxia of speech
CHD4:
DDID
Sifrim–Hitz–Weiss
ASD
Epileptic encephalopathy
CHD
CHD5:
DDID
ASD
DDID
ASD
Cornelia de Lange
CHD3/
CHD4/
CHD5
GAND
DDID
GATAD2A/
GATAD2B
DDID
MTA1/
MTA2/
MTA3
RBBP4/
RBBP7
DDID
MBD2/
MBD3
HDAC1/
HDAC2
ASD
e INO80
Immunoglobulin class-switch recombination defects (–/–)
DDID
ASD
Gabriele de Vries
DDID
DDID
DDID
ASD
CHD
INO80
ASD
INO80D
ACTR8
TFPT
INO80B
UCHL5
YY1
ACTR5
MCRS1
ACTL6A
INO80C
INO80E
NRFKB
RUVBL1
RUVBL2
f ISWI
NuRF, CERF
DDID
ACF, CHRAC, NoRC, WICH, RSF
Schizophrenia
Rett-like
DDID
CHD
BPTF:
NEDDFL
DDID
SMARCA1
BPTF/CECR2
RBBP4/
RBBP7
SMARCA5
BAZ1A/
BAZ2A/
BAZ1B/
RSF1
CHRAC1
POLE3
DDID
ASD
BAZ1A, BAZ1B, and RSF1:
ASD, DDID
g TIP60 (p400, NuA4)
Developmental delay without dysmorphic facies or autism
DDID
Adult-onset deafness
ASD
Schizophrenia
Sporadic sensorineural hearing loss
Childhood disintegrative disorder
Very-early-onset pyschosis
EP400
TRRAP
BRD8
KAT5
VPS72
YEATS4
ACTB
ACTL6A
MORF4L1
MRGBP
DMAP1
ING3
MEAF6
NEDFASB
RUVBL1
RUVBL2
CHD
DDID
DDID
ASD
CHD
Baraitser–Winter
DDID
ASD
CHD
DDID
h SRCAP
Floating-Harbor
DDID
ASD
SRCAP
ASD
ACTR6
H2AFZ
ZNHIT1
VPS72
DDID
ACTL6A
DMAP1
YEATS4
CHD
RUVBL1
RUVBL2
DDID
i ATRX
ATR-X
CHD
ASD
DDID
ATRX
DAXX
j
Other SNF2-ATPases with no characterized complex:
CHD1 ASD, Pilarowski–Bjornsson, DDID
CHD2 Epileptic encephalopathy, DDID, ASD
CHD6 Hallermann–Streiff, ASD
CHD7 CHARGE, AVSD, IHH/Kallmann, DDID, CHD
CHD8 ASD (***), DDID, CHD (-/-)
CHD9 ASD, DDID
HELLS ICF (-/-)
CHD1L ASD
SMARCAD1 Basan, adermatoglyphia, Huireiz, DDID
RAD54L --
RAD54B --
RAD54L2 --
HLTF --
TTF2 --
SHPRH ASD (–/–)
BTAF1 ASD
ERCC6 Cocayne (–/–), COFS
ERCC6L --
ERCC6L2 Bone marrow failure (–/–)
SMARCAL1 Schimke immuno-osseous dysplasia (–/–)
ZRANB3 DDID
≤0.3 0.5 0.9 0.995 1
pLI

Fig. 2 | Chromatin remodelling complexes in human development and disease. a–j, The human chromatin remodelling complexes are shown with their composition of subunits. Subunits, where possible, reflect the actual position and relative size in the available structures of remodeller complexes. Paralogous subunits that can be substituted for one another are displayed as A/B/C, and subunits are coloured according to their probability of intolerance to loss-of-function (pLI) scores for their encoding genes in the human genome[55,61]. Developmental disorders associated by protein-truncating variants and predicted deleterious missense mutations found in the genes encoding remodeller subunits are labelled, compiled from large-scale sequencing studies of de novo mutations in individuals with autism spectrum disorder (ASD) and developmental delay and/or (idiopathic) intellectual disability (DDID)[91,175–178], congenital heart disease (CHD)[179], as well as manual curation of variants in the literature from case studies (Supplementary Table 2). *.**.***: false discovery rate (FDR) < (0.05, 0.01, 0.001) of association with ASD from the Autism Sequencing Consortium[91]; −/−, homozygous mutation; ATR-X, X-linked alpha-thalassaemia/mental retardation; AVSD, atrioventricular septal defect; CHARGE, coloboma, heart defect, atresia choanae, growth retardation, genital abnormality, and ear abnormality; COFS, cerebro-oculo-facio-skeletal; DOORS, deafness, onychodystrophy, osteodystrophy, mental retardation, seizures; GAND, GATAD2B-associated neurodevelopmental disorder; ICF, immunodeficiency, centromeric instability facial anomalies spectrum; IHH, idiopathic hypogonadotropic hypogonadism; NEDDFL, neurodevelopmental disorder with dysmorphic facies and distal limb anomalies; NEDFASB, neurodevelopmental disorder with dysmorphic facies, sleep disturbance and brain abnormalities.

dictated by the chromatin landscape, or selective TF–remodeller biochemical interactions.

'Assisted loading' or 'dynamic assisted loading'[79] is a third model that proposes a synthesis of the two more parsimonious mechanisms proposed above (Fig. 4c). This model accounts for the fact that different TFs exist on a continuum of ability to bind nucleosomal DNA, as illustrated by recent large-scale analyses of TF positional binding bias[80]. Here, the observation is made that some TFs and remodellers have comparable on and off rates for binding to chromatin, and act simultaneously to open nucleosome-occluded DNA. Recent single-molecule studies of the dynamics of chromatin remodellers[81] and TFs[82] have reported short (1–10 s) residence times of each, supporting this observation, which implies that binding of any individual remodeller or TF is too transient to create a stable, accessible state on its own. Studies using small-molecule inhibitors of the BAF ATPases BRG1 and BRM found rapid (within 10 min) losses in accessibility genome-wide in mouse embryonic stem cells[83,84], albeit by using high (10 μM) concentrations of a low-nanomolar inhibitor (IC_{50} < 5 nM; Box 2), which may have resulted in off-target inhibition. Other, less finely detailed kinetic studies have also suggested a co-dependent assisted-loading model, as in the case of BAF and OCT4 (ref. 73), BAF and the glucocorticoid receptor[85], BAF and YAP–TEAD[36], or BAF and ASCL1 (ref. 86).

Questions about these three localization models have motivated structural studies to define the interfaces responsible for remodeller–TF interactions. Recent work has mapped out a structured hinge region in OCT4 that is responsible for the interaction with BRG1 and CHD4 (ref. 87). The region is not homologous to the hinge regions in the other OCT4-related POU family of TFs and possibly explains how OCT4 is able to act as a pioneer factor in concert with the BAF complex. GATA3, another pioneer TF, was also shown to co-immunoprecipitate BRG1 and co-bind on chromatin in a manner correlated with its pioneer activity[88]. Further structural work defining critical remodeller–TF interfaces will help to elucidate mechanisms of remodeller–TF cooperation.

Localization as a determinant of function

Genomic distributions of remodelling complexes are presumed to reflect their sites of involvement. However, a different model is suggested by the fact that their sites of occupancy do not always associate with their sites of action, as determined by rapid conditional deletion, degradation or inhibition of the remodellers and subsequent measurement of transcription, nucleosome positioning[89], redistribution of interacting regulators such as Polycomb[90], or chromatin accessibility. In a recent study, upon BAF ATPase inhibition in induced human neural cultures, only 69% of loci that changed in chromatin accessibility were bound by BAF[86]. These investigations have in some cases revealed a potential gap in our understanding. The disparity between the localization of the remodeller and regions of remodeller function suggests that some or many of the sites occupied by remodellers, as determined by ChIP, might be sites where they are resting or in storage, and that sites where accessibility is regulated by the remodeller might be the product of a rapid 'hit and run' mechanism that can only be captured by rapidly acting chemical probes over timescales of seconds. Another interpretation of these observations is that remodellers of different compositions stand in reserve to be made use of to respond to environmental signalling such as steroid hormones[85], metabolic or developmental events. The use of new fast-acting probes and tools to study remodeller kinetics in living cells (Box 2), as well as single-molecule imaging studies and related assays to track remodellers inside cells, will probably be required to elucidate the contribution of localization to function.

Chromatin remodellers in developmental disease

Deleterious, de novo and/or inherited mutations in genes encoding chromatin remodellers and their associated subunits have been implicated in dozens of human developmental diseases (Fig. 2, Supplementary Table 2). Genes encoding members of CHD, INO80, SWI/SNF, ATRX and ISWI complexes were mutated in almost 1 in 10 cases in DECIPHER[57,58]. In keeping with the themes of non-redundancy, biological specificity and multitasking explored earlier, the mutational burden of remodellers in developmental disorders is distinctive to particular subunits and disorders.

Genetic perturbations to remodellers in animal and cellular models have revealed how they control critical, rate-limiting processes in developmental progression. Remodellers maintain pluri- or multi-potency and self-renewal capacity in stem cells and progenitors, and direct differentiation and lineage commitment. They also prepare chromatin to help the cell respond to environmental signals as well as directly respond to environmental stimuli, helping to maintain plasticity throughout the adult life of an organism. At a molecular level, these processes are mediated by the biophysical mechanisms discussed above, including interactions with TFs and ATP-dependent nucleosome remodelling. Here, we review these prototypical functions of remodellers in development and what we know about how the mutations found in human individuals might cause disease. We focus particularly, but not solely, on neurodevelopment, an area in which recent human genetics studies have led to fundamental mechanistic insights through new structural and systems approaches.

Remodellers implicated in neurodevelopmental disorders

Pathogenic mutations in remodellers are over-represented in human neurodevelopmental and psychiatric disorders, including

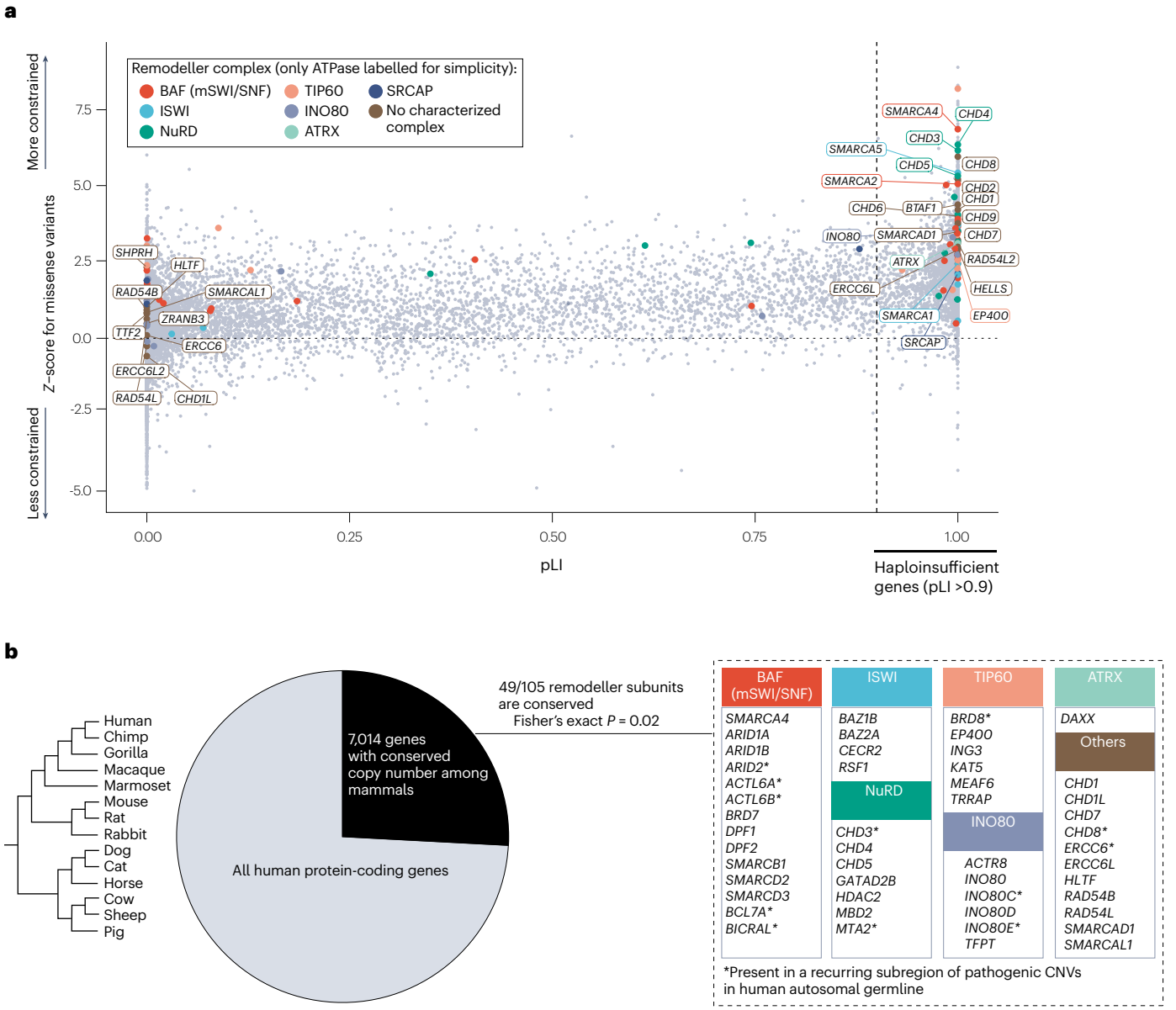

Fig. 3 | The dosage sensitivity of human remodellers. a, Remodeller genes are among the most sensitive to loss in human individuals. The constraint against missense variation and the intolerance to loss-of-function are plotted for all human genes. Genes encoding remodeller ATPase subunits are labelled and coloured by complex if applicable. Other complex subunits are coloured but left unlabelled for simplicity. All data is from gnomAD[55,61]. **b**, Remodelling complex genes are enriched among all genes conserved in copy number across mammals and enriched in known pathogenic copy number variants (CNVs), suggesting strong selective pressure on their dosage. The tree in part **b** is adapted from ref. 56, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

autism spectrum disorder (ASD), intellectual disabilities, epilepsy and schizophrenia. Indeed, in a recent analysis of missense and protein-truncating de novo variants in individuals with various neurodevelopmental disorders, genes encoding the BAF complex and CHD-family chromatin remodellers ranked first and fourth, respectively, in frequency of mutations[58]. In a targeted, large-scale exome sequencing study of 11,986 individuals with ASD, the CHD-family remodeller *CHD8* had the second-highest rate of disruptive (truncating or deleterious missense) de novo variation among any gene[91]. In this same cohort, *ARID1B* had the third-highest rate of disruptive variants in ASD and, in an older study examining 1,333 children with severe, idiopathic developmental disorders[63], *ARID1B* was the most significantly enriched for de novo mutations. Mutations in remodellers are predominantly heterozygous, reflecting their dosage-sensitive roles, and in most cases de novo, suggesting that they are disease-causing.

The BAF complex is particularly implicated in a set of rare syndromic and non-syndromic intellectual disabilities—the BAFopathies, such as Coffin–Siris syndrome and Nicolaides–Baraitser

Box 2

Understanding remodeller function using fast-acting, cell-permeable small molecules

Chemically induced proximity for in vivo kinetic biochemical studies

Chemically induced proximity (CIP) is a fundamental mechanism underlying the role of post-translational modification, allostery and subcellular localization[200]. CIP-regulated phenomena appear to be all-or-nothing events, because the probability of an effective collision between two molecules is inversely related to the cube of the distance between them. Bromodomain proteins that bind acetylated histones and bring along large co-activator complexes to contribute to transcription elongation are an example of CIP and its regulatory effects on chromatin. Efforts to understand the complexities of in vivo chromatin remodelling have led to the development of approaches that use bifunctional ligands, acting via CIP[200] to recruit a chromatin regulator or TF to a precise position in the genome, and studying the minute-by-minute consequences within the natural chromatin state of a living cell. This approach allows analysis of long-range interactions, phase transitions, topology, complex combinations of histone modifications as well as of epigenetic memory not assayed by conventional approaches. In addition, this system operates at the physiological effective molarity of the various molecules contributing to transcriptional and epigenetic regulation. An example is the chromatin in vivo assay (CiA), consisting of mice with arrays of DNA-binding sites (GAL4 or ZFHD1) inserted by homologous recombination into a gene of interest, such as *Oct4* (ref. 201). Chromatin regulators of interest can then be reversibly localized to these sites upon addition of a cell-permeable, bifunctional small molecule, which binds to ligand-binding tags on the chromatin regulator and an expressed DNA-binding domain. The gene of interest could be studied in a variety of developmental timepoints in an animal, and be compared to the unmodified second allele, serving as a control. The ability to wash out localization using competitor small molecules and the rapid permeability of the bifunctional molecule allows measurement of the orderly sequence of biochemical events following recruitment of the remodeller (or another chromatin or transcriptional regulator) to the locus. Washout studies also allow the assay of chromatin-based memory across cell passages. CIP has been extended to use with nuclease-dead Cas9 (dCas9) tagged to a small-molecule-binding domain, as a way to localize chromatin remodellers or other transcriptional regulators to any locus of interest that would be targetable with a guide RNA (gRNA). Finally, efforts to develop molecules that induce proximity of entirely endogenous, untagged, chromatin regulators and sequence-specific transcription factors, which could have therapeutic implications, have recently been reported[202].

Several molecular mechanisms of chromatin remodellers have been investigated effectively using CIP (see the Box 2 table). For example, the opposition between BAF and Polycomb was found to involve direct interaction with Polycomb complexes and ATP-dependent eviction[27,28]. Directly targeting the BAF complex to bivalent gene promoters was found to induce transcription and cause loss of H3K27me3 levels in as little as 15 minutes[203]. In other studies, the remodeller HELLS (LSH) was found to insert the histone variant macroH2A[26,204] at sensitive loci. As these examples illustrate, chemical induced proximity tools can shed light on the multiple ATP-independent and ATP-dependent actions of remodeller complexes on native chromatin substrates, which is important in light of the context-specific functions of remodellers in development and disease.

Chemical inhibitors and degraders

A rapidly growing area of interest in both academic and pharmaceutical drug development is the optimization of cell-permeable, nanomolar-affinity small-molecule inhibitors to ATPase, bromodomains, and other subunits in different remodellers[205–208]. In addition, degrons[84,90] and PROTACs (proteolysis targeting chimeras), which work on the basis of CIP[169,209,210], can quickly (within hours) degrade remodeller subunits. Many more are unpublished but in the patent literature owing to their obvious therapeutic applications. These have been used to inactivate remodellers and measure downstream consequences on chromatin and cell biology. For example, BAF ATPase inhibitors, degraders and degron tags have been used to measure the minute-scale effects of BAF inhibition or loss on genome-wide accessibility, TF binding[83,211], and Polycomb complex redistribution in mouse embryonic stem cells[90]. A small molecule identified as a BAF250A inhibitor in a screen for inhibitors of BAF-mediated gene repression has been used to study the BAF250A-containing complex's activity in de-repressing the HIV long terminal repeat in T lymphocytes[205], killing cancer cells in synergy with ATR inhibitors[207], and promoting BAF-mediated memory T cell formation in mice to enhance the efficacy of chimeric antigen receptor T cell (CAR-T) immunotherapy[149]. We note that BAF ATPase inhibition in cancers has been of particular recent interest[212] and BAF-targeting chemical inhibitors and degraders have been reviewed previously[139].

DNA-barcoded nucleosome arrays

Recently, high-throughput DNA-barcoded nucleosome arrays have enabled analysis of interactions between purified remodellers (ISWI[213] and BAF[214]) and modified nucleosomes. By coupling binding assays with in vitro chromatin accessibility measurements based on restriction enzyme cutting, the effects of complex nucleosome modifications on activity versus binding can be measured. Despite informative results, in vitro approaches are unable to discern the effects of long-range in vivo interactions, topological features, effective intranuclear molarity, and other aspects of chromatin structure yet to be defined.

(continued from previous page)

Name	Chromatin regulator targeted	Approach
Chemical inducer of proximity (CIP)-based		
CiA (chromatin in vivo assay)	SS18 (BAF complex)[27,72] HELLS (LSH)[26] Hp1 (ref. 201) DOT1L[215]	Zinc-finger and GAL4-binding site arrays knocked-in upstream of *Oct4-eGFP* to create a CiA:OCT4 mouse. FKBP12-ZFHD1 or GAL4-ABI1 expressed with chromatin regulator fused to FRB or PYL1. Addition of a cell-permeable CIP ligand, rapamycin or abscisic acid, that dimerizes FRB and FKBP12 or ABI1 and PYL1, respectively, recruits the chromatin regulator to the locus immediately (<5 min).
FIRE–Cas9 (FKBP/FRB inducible recruitment for epigenome editing by Cas9)	SS18 (BAF complex)[203]	FRB-fusion chromatin complex (HP1, BAF, VPR) recruited with rapamycin to MCP–FKBP with a double-MS2 loop gRNA that binds MCP, associated with dCas9 at a locus.
Chemical epigenetic modifiers	HDAC-containing complexes[216] BRD4, BRPF1, and CBP and EP300[217]	FKBP-binding compound, FK506, covalently linked to a binder of a chromatin modifier, such as an HDAC inhibitor, and recruited to FKBP–dCas9.
Inhibitors		
ATPase subunit inhibitors	BRG1 and BRM (BAF complex)[83,84,206] CHD4 (NuRD complex) and SMARCA5 (ISWI complex)[208] CHD1L[218,219]	Allosteric inhibitors of ATPase activity, selective to paralogs (BRM014 (ref. 206) is a selective, IC_{50} < 5 nM allosteric inhibitor of BRG1 and BRM ATPase activity) or with characterized off-targets (ED2-AD101 (ref. 208) is a micromolar allosteric inhibitor of both CHD4 and SMARCA5 ATPase activity). Micromolar IC_{50} inhibitors of CHD1L ATPase activity have also been reported with anti-colorectal cancer cell and xenograft activity[218,219].
Bromodomain inhibitors	BRG1, BRM and PBRM1 (BAF including pBAF complex)[220] BRD9[221], (non-canonical ncBAF complex) BRD8[222] (TIP60 complex) BAZ2A/B[223], BPTF[224,225] and CECR2[226] (ISWI complex) PBRM1-specific (pBAF complex)[227]	Various inhibitors have been optimized for binding of remodeller bromodomains with K_D values of ~1–200 nM, with different specificities. For example, PFI-3 is a BRG1, BRM and PBRM1 bromodomain inhibitor with K_D of ~89 nM (ref. 220). BI-7273 and BI-9564 are selective inhibitors of BRD9 with K_D values ~15 nM (ref. 221). DN02 is a selective inhibitor of bromodomain 1 of BRD8 with K_D of 34 nM (ref. 222). GSK2801 is semi-selective for BAZ2A/B at ~ 200 nM but also binds BRD9 (ref. 223). DC-BPi-11 has a ~25 nM K_D (ref. 224). BZ1 has 6.3 nM K_D for the bromodomain of BPTF[225]. NVS-CECR2-1 binds the CECR2 bromodomain with a K_D ~ 80 nM (ref. 226). Compound 16 is selective to bromodomain 2 of PBRM1 over BRG1/BRM with a K_D ~ 290 nM (ref. 227).
BAF modulators	BAF250A or a spatially associated surface (BAF complex)[205]	Modulator of BAF250A-containing BAF-complex-mediated transcription (BRD-K98645985 or BD98) with EC_{50} of ~2.4 μM (ref. 205).
YEATS domain inhibitor	YEATS4[228] (TIP60 complex)	Compounds **4d** and **4e** are selective YEATS4 binders with K_D of 33 nM and 37 nM (shown in ref. 228).
Acetyltransferase activity inhibitor	KAT5[229] (TIP60 complex) HDAC1/2 (NuRD complex)	NU9056 is a 2 μM inhibitor of histone acetyltransferase activity of TIP60 (ref. 229). Various HDAC1 and HDAC2 inhibitors reported[230].
Degrons/degraders		
PROTAC (proteolysis targeting chimera)	BRG1 and BRM[75,210] or BRM-specific[231] (BAF complex) BRD9 (ncBAF complex)[169,209] BRD7 and BRD9[232] (pBAF and ncBAF complexes)	PROTACs degrade their respective protein by recruiting an endogenous E3 ligase and then the proteosomal machinery.
Degron tag	BRG1 (human BAF complex)[84] BRG1 (mouse BAF complex)[90]	A dTAG[233] degron, in which the gene is tagged with *FKBP12* and then a synthetic ligand that binds FKBP12 and an endogenous E3 ligase degrades the protein, was engineered with *SMARCA4* (BRG1) in HAP1 cells. An auxin-inducible degron[234], with a similar concept where the gene is tagged with an IAA17 degron along with overexpression of the plant F-box protein TIR1, which co-localizes upon addition of auxin, was engineered with *Smarca4* (Brg1) in mouse embryonic stem cells.

syndrome. Patients with these syndromes have some phenotypic overlap, characterized by intellectual disability, microcephaly, seizures, stunted growth, agenesis of the corpus callosum and digit abnormalities[92]. Recently, BAF was also implicated in Down syndrome through its assembly of BRWD1 as a putative subunit in mammalian brains; this protein is encoded within the triplicated region of human chromosome 21 causal for Down syndrome[38]. Heterozygous mutations in the CHDs, including *CHD1*, *CHD2*, *CHD3*, *CHD4*, *CHD5*, *CHD6*, *CHD7*, and *CHD8* are all implicated in related neurodevelopmental disorders with many phenotypes shared with BAFopathies, such as intellectual disability, but with subtle differences in presentation that may inform their mechanisms of action. For example, individuals with *CHD3* mutations[93] and those with *CHD8* mutations present with macrocephaly[7,94], in contrast to the microcephaly associated with BAFopathies. This is a general theme: the disorders tabulated in Fig. 2 and Supplementary Table 2 have imperfectly overlapping phenotypes related to developmental delays and intellectual disabilities.

Cell biological and molecular roles of remodellers in development

The clinical phenotypes connected to mutations in remodellers arise from the critical roles that they have in directing the stereotyped development of the brain and other organs. Genetic perturbations in mice have revealed essential roles for most major remodelling complexes in maintaining embryonic-stem-cell self-renewal and pluripotency, and in many cases, pre-implantation development[9]. Conditional knockout studies in specific tissues have also identified complexes that are essential for lineage-specific progenitor cell proliferation, such as CHD8 in neural progenitors[95–97], INO80 in embryonic endocardial progenitors[98], or specialized BAF complexes containing BAF53A[39] and BAF170 in neural progenitors[46,99]. The microcephaly phenotypes observed in patients with BAF complex mutations may be related to the essential functions of BAF in regulating progenitor proliferation.

Switches in subunit composition within a complex often dictate lineage commitment. For example, in neurogenesis, the mammalian BAF complex undergoes sequential developmental changes in subunit composition from an embryonic-stem-cell-specific complex (esBAF), required for pluripotency, to a neural-progenitor complex (npBAF),

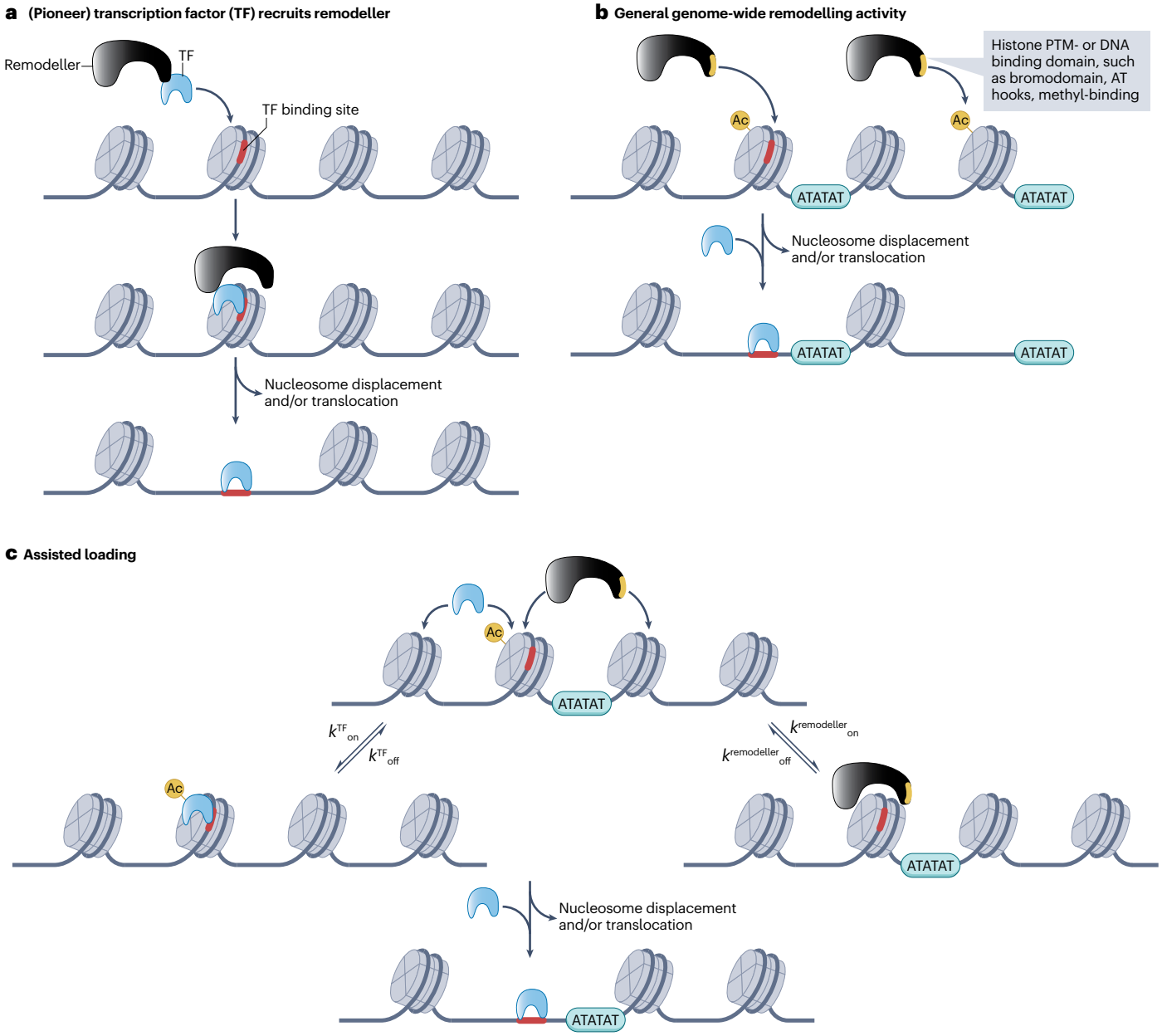

Fig. 4 | Models of remodeller–TF interactions. Three models of remodeller–transcription factor (TF) interactions are shown. **a**, A pioneer TF that can bind a motif on nucleosomal DNA recruits remodellers to a nucleosome via a biochemical interaction. **b**, Remodeller activity and genome-wide localization, constrained modestly by histone post-translational modifications (PTM) and/or DNA sequences that remodeller domains or complex subunits can recognize, creates accessibility for TF binding. **c**, Remodeller and TF activity cooperate based on their respective on- and off-rates *k* to nucleosomal DNA.

Glossary

Assay for transposase-accessible chromatin with sequencing (ATAC-seq)
An assay to measure accessible (open) chromatin that uses the transposase Tn5, which preferentially targets open chromatin sites to insert sequencing primers.

Chromatin immunoprecipitation (with sequencing)
An assay to measure chromatin–protein interactions by immunoprecipitating the DNA bound to a protein (ChIP) and sequencing it (ChIP-seq).

Constraint on missense variants
A transcript is more intolerant of variation (more constrained) if there are fewer rare missense variants per transcript observed than expected (as predicted by a sequence-context-based mutational model)[61].

Dosage sensitivity
Genetic dosage sensitivity defines steps in a biological pathway in which a reduction in functional protein or a gain in protein copy leads to a phenotypic effect.

Haploinsufficiency
Haploinsufficient genes are a subset of dosage-sensitive genes where loss of function of a single allele produces a phenotype, defining a rate-limiting role for a gene in a biological process.

Micrococcal nuclease digestion with sequencing (MNase-seq)
An assay to determine nucleosome structure where genomic DNA is treated with micrococcal nuclease, which digests open DNA, leaving sequences bound by nucleosomes and other chromatin-bound proteins.

required for progenitor proliferation, and finally to an exquisitely specific neuronal complex (nBAF), found only in postmitotic neurons and required for dendritic morphogenesis[40,43]. The switch from npBAF to nBAF subunits, such as from BAF53A (npBAF-specific) to BAF53B (nBAF-specific), is governed by microRNAs, repressed in progenitors by the transcription factor REST, that bind to the 3′ untranslated region of *Actl6a* (encoding BAF53A)[43]. A similar switch is found in myogenesis, where mir-133 and miR1/206 repress *Smarcd1* (BAF60A) and *Smarcd2* (BAF60B), required for stem cell proliferation, causing a switch to *Smarcd3* (BAF60C)-containing complexes that turn on muscle-specific transcription[100,101]. In the ISWI family, *Smarca5* (SNF2H) is essential for early mouse embryo development and enriched in embryonic stem cells and proliferating neural progenitors; its close homologue *Smarca1* (SNF2L) is dispensable for survival but active in differentiated cells and required for neurogenesis[102]. Similar changes in activity and/or patterns of expression are present for CHD family members, including CHD3/4/5 of the NuRD complex[7].

Social behaviour and chromatin remodelling: from flies to mammals

A critical contribution of remodellers to development is their role in mediating the response of a cell or organism to experience, to stimulus and to signals from the environment. This is reflected in part in the frequency of mutations in remodelling complexes connected to disorders of learning, memory and social behaviour, such as ASD. De novo transcription is critical for formation of long-term memory, synaptic plasticity, and the construction of neural circuitry[103], and remodellers both prepare accessible chromatin to receive a signal from the membrane and respond biochemically by post-translational modifications (for example)[104]. For example, the NuRD complex has been shown to respond to neuronal activity (resulting from, for example, a mouse running on a rotarod), by depositing the histone variant H2A.Z at cerebellar granule-cell gene promoters and inactivating them. The core NuRD ATPase Chd4 is thus essential for sensorimotor encoding and dendrite architecture[105]. The neuronal-specific nBAF complex is also required for connecting neurons through dendritic outgrowth and synaptic specificity. Early studies in mice found that several nBAF subunits, including BAF53B, BRG1, BAF57, BAF45B and CREST were required for activity-dependent dendritic outgrowth in hippocampal and cortical neurons[106,107].

The broader relationship between behaviour and chromatin remodelling has perhaps been most studied with the nBAF complex. Recently, characterization of the nBAF-specific BAF53B subunit in Mendelian recessive autism[60] found that ASD-associated missense mutations in *ACTL6B* (encoding BAF53B) produced social and learning defects in adult mice. In the olfactory system of flies, which is important for social communication, deletion of the orthologue of BAF53B, Bap55, had been found to cause a perfect dendritic retargeting phenotype, in which dendrites project to the wrong glomerulus with 100% penetration[108]. The retargeting defect could be rescued with wild-type human BAF53B but were reproduced by human BAF53B with ASD mutations[60]. Then, specific deletion of another ASD-linked BAF subunit, *Arid1b*, in only the serotonergic neurons of the adult mouse brain was also shown to produce deficits in social behaviour[109]. Social and hyperactive behaviours in mice bearing *Actl6b* or *Arid1b* mutations could be rescued with a selective serotonin receptor 1b receptor agonist, which inhibits neural activity[109]. This finding suggests that an excess of neural activity might underly social impairments in mice with BAF mutations. These studies have raised questions about which BAF target genes are responsible for this rapid change in social behaviour and what circuit-specific roles the BAF complex, or other remodellers, could have. Remodeller complexes such as BAF may act not just cell-specifically but also circuit-specifically, by mediating the response to experience and governing neuronal plasticity.

Structural genetics elucidates critical mechanistic roles

The mutations in remodellers in developmental disorders are often missense and cluster in regions. This has provided an opportunity for mechanistic dissection, by mapping hotspot regions of mutations onto recent structural data on remodeller complexes. One study examined carboxy- (C-)terminal mutations in *SMARCB1* (ref. 92) in Coffin–Siris syndrome that mapped to key nucleosome–remodeller contacts[110]. Parallel investigations had shown that cancer mutations in the *SMARCA4* SnAC domain defined an interaction site with the nucleosomal acidic patch[111]. Mapped together on the BAF structures, these two groups of human mutations defined a ‘C’ clamp for the nucleosome unique to the nucleosome remodelling mechanism of the BAF complex[110]. As suggested by this study of a specific set of mutations, a recent large-scale genotype-to-phenotype map of neurodevelopmental disorder mutations onto the BAF complex structure highlighted perturbations to ATPase activity and nucleosome engagement as correlating with severe clinical phenotypes[58]. Characterization of the mutational landscape can also raise new questions about the specific roles of remodeller subunits. For example, missense variants in the ATPase domains of *SMARCA4* and *SMARCA2*, which can compensate for one another and are co-expressed in the brain, have been found in two related intellectual disabilities, Coffin–Siris syndrome and Nicolaides–Baraitser syndrome. Interestingly, there are no *SMARCA4* mutations reported in

Nicolaides–Baraitser syndrome and no *SMARCA2* mutations reported in Coffin–Siris syndrome[92], suggesting distinct neurodevelopmental roles related to ATPase subunit function that have yet to be elucidated.

A long-standing question has been the role of β-actin and actin-like proteins in ATP-dependent chromatin remodelling. β-actin, once considered solely cytoskeletal, is a subunit of the BAF as well as the TIP60 and INO80 complexes[112]. De novo heterozygous missense[113] and LoF[114] mutations in *ACTB*, encoding β-actin, are associated with rare intellectual disabilities such as Baraitser–Winter syndrome and other developmental disorders that have very similar phenotypic characteristics to the disorders linked to chromatin remodellers (Fig. 2). Cryo-EM structures have shown that actin binds adjacent to the ATPase domain of the remodeller[111,115] (Fig. 1c), suggesting coupling, as in myosin, to the ATPase exchange mechanism[116]. β-actin binds adjacent to an actin-related protein (ARP), such as BAF53A or BAF53B (both homologous to the yeast protein ARP4) in BAF complexes, or BAF53A and ARP8 (*ACTR8*) in INO80[8]. Deletion of the *ACTB* gene in mouse fibroblasts caused genome-wide increases in H3K27me3, dissociation of BRG1 from chromatin, and disruption of neuronal reprogramming, phenotypes that were dosage-dependent[117]. Other work discovered that β-actin deletion in mouse fibroblasts affects three-dimensional genome structure through a mechanism involving both the BAF complex and EZH2, the catalytic subunit of PRC2 (ref. 118). However, the deletion of β-actin also led to genome-wide increases in H3K9me3, and the mechanistic origin of some of the gene-expression phenotypes might include roles unrelated to chromatin remodelling. These investigations highlight how subunits important in development can contribute to functions beyond nucleosome remodelling activity.

Just as the emerging studies of developmental disease hotspot mutations in BAF complex subunits have led to mechanistic understanding[92], mutations in other remodellers can provide insight into or validate their unique biological roles during development. An example is *ATRX*, which was discovered through profiling of genetic lesions in patients with alpha-thalassemia, mental retardation, X-linked syndrome; it was named for this intellectual disability[119] and was originally best known for depositing H3.3 in heterochromatin, including at telomeres[23,24,120]. However, recent biochemical studies in postmitotic mouse neurons have revealed that ATRX also responds to neuronal activity, by repressing spurious transcription of minor satellite regions by recognizing the combination of activity-dependent H3S10 phosphorylation and H3K9me3 (ref. 121). Similarly, we consider the remodeller *SMARCAD1*, which is commonly mutated in syndromes where patients lack fingerprints (Basan syndrome and adermatoglyphia) (Fig. 2). SMARCAD1 has been shown to have a critical role in silencing genes by promotion of H3K9me3 deposition coincident with reducing histone acetylation at these sites[122]. The Basan syndrome and adermatoglyphia mutations in *SMARCAD1* suggest a link to an as yet uncharacterized biological role in epithelial development, underlining the remarkable non-redundancy and biological specificity encoded in chromatin remodelling complexes.

Chromatin remodellers in cancer

Analogous to the unique roles of remodellers in human development, recent large-scale tumour sequencing studies have showed that remodellers have biologically specific functions in human cancers. Cell- and context-specific function is reflected in the mutation rates of genes encoding the subunits of remodeller complexes across cancers of different origins: different complexes and subunits of even the same complex can have vastly different mutational burdens in different cancers (Fig. 5). Many remodellers are statistically significantly mutated above the background mutation rate of a tumour (Fig. 5), suggesting that these mutations confer a growth advantage to the cancer cell.

The BAF complex, as a whole, is the most frequently mutated chromatin remodelling complex in cancer. Indeed, around 20% of all malignancies have BAF-subunit alterations (reviews in refs. 3,4,123), and the mutation rate of BAF subunits in almost all cancers (32/34 surveyed by The Cancer Genome Atlas) is far above background rates (Fig. 5). *ARID1A* is the most frequently mutated subunit, but mutation rates differ substantially between other BAF subunits and certain cancers are much more likely to have particular subunits mutated, suggesting that BAF subunit mutations are not all equivalent at promoting tumorigenesis. That observation is in line with the metaphor of chromatin remodellers as a combinatorial assembly of complexes, whereby different surfaces formed by different subunits have specific roles in certain cell types, thereby defining specific targets for drug development. Other remodellers, such ATRX, are mutated particularly frequently in only certain cancers (such as pancreatic neuroendocrine tumours, gliomas and sarcomas), and a few complexes, such as INO80, are less frequently mutated in cancer. Remodellers appear to act like the function keys on your computer keyboard, showing different activity or essentiality depending on the cellular genetic context.

Given cancer-context-dependent genetic lesions, a primary area of investigation is in understanding the unique contributions of different remodelling complexes to cancer progression. Many excellent reviews on the contributions of specific chromatin remodellers in cancer have been published[3–5,7,8,123]. One stimulating observation that has motivated research is that remodellers can act as tumour suppressors or as oncogenes, depending on cellular genetic context. The molecular mechanisms by which remodellers suppress tumour progression or activate oncogenesis can involve modulation of chromatin accessibility at lineage-specifying regulatory regions such as enhancers, interactions with other chromatin modifiers and TFs, and regulation of chromatin-templated processes such as DNA damage response and overall genome maintenance. From a therapeutic standpoint, remodeller mutations can also result in vulnerabilities in other genes, producing synthetic lethal pathways amenable to therapeutic targeting. Mutations in remodellers can also sensitize or de-sensitize the tumour to cancer therapies. In the following section we focus on these overarching mechanistic themes of how remodellers can both suppress tumour progression or contribute to it.

Remodellers as tumour suppressors

The first studies implicating remodellers as tumour suppressors came from observations that many cancer cell lines appeared to have lost, or had highly repressed, alleles of *SMARCA4* (refs. 124,125). Classic tumour suppressors are characterized by inactivation of both alleles[126], and conclusive evidence that BAF functions as a tumour suppressor came later in studies examining biallelic inactivating mutations in *SMARCB1*, a core subunit of the BAF complex, in patients with malignant rhabdoid tumours[127] and atypical teratoid rhabdoid tumours[128–130]. In those tumour types, the first allele of *SMARCB1* is often lost in the germline and followed by a loss of the second allele somatically in tumour tissue. Advances in tumour genome sequencing studies have since uncovered deleterious mutations in almost every BAF subunit. Some mutations are very specific to particular tumours, such as *PBRM1* losses in 41% of clear cell renal carcinoma[131], whereas others are among the most mutated genes across tumours categorized by The Cancer Genome Atlas, such as *ARID1A*, altered (mostly by truncating mutations) in 8% of all patients[132]

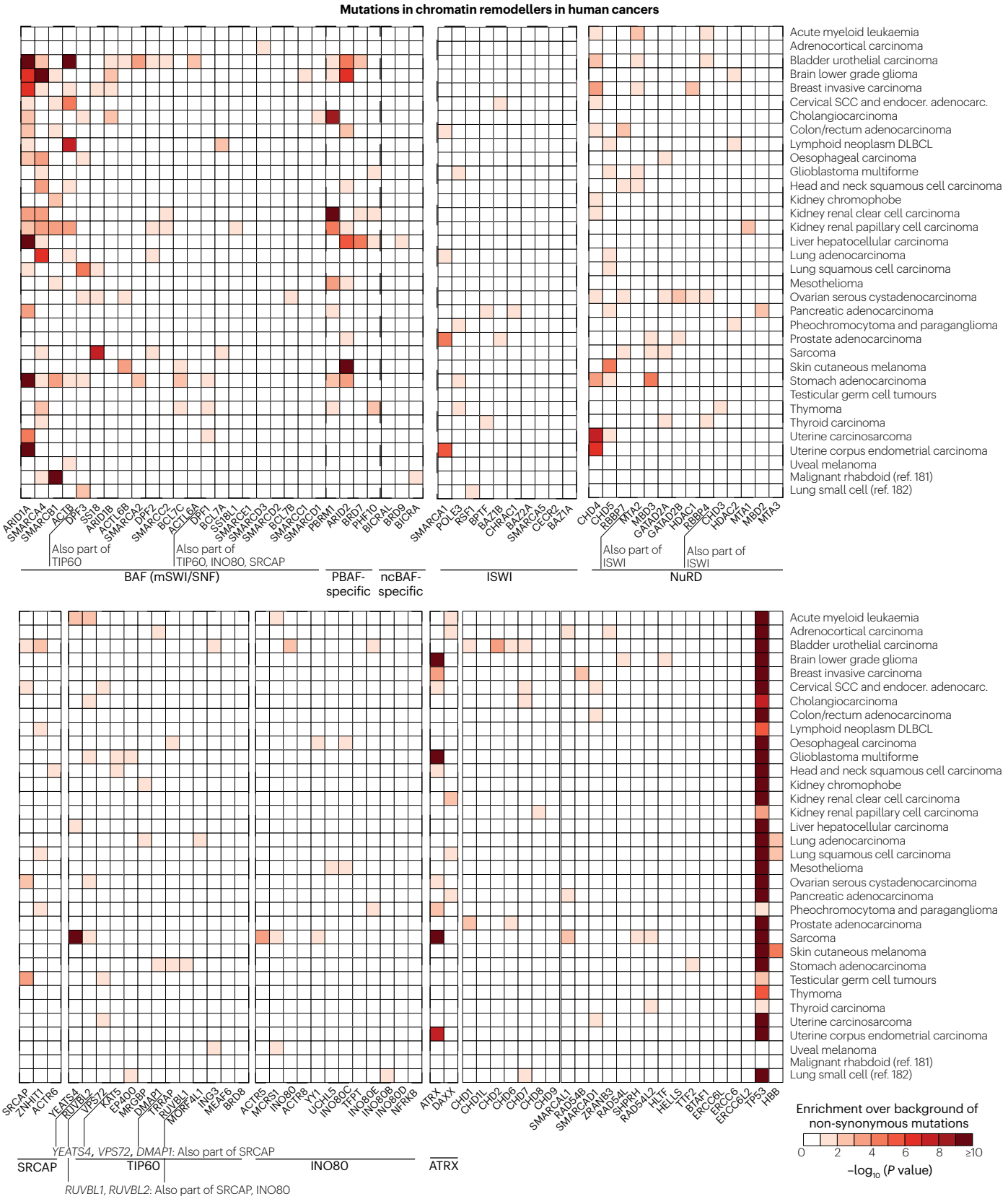
Mutations in chromatin remodellers in human cancers
Acute myeloid leukaemia
Adrenocortical carcinoma
Bladder urothelial carcinoma
Brain lower grade glioma
Breast invasive carcinoma
Cervical SCC and endocer. adenocarc.
Cholangiocarcinoma
Colon/rectum adenocarcinoma
Lymphoid neoplasm DLBCL
Oesophageal carcinoma
Glioblastoma multiforme
Head and neck squamous cell carcinoma
Kidney chromophobe
Kidney renal clear cell carcinoma
Kidney renal papillary cell carcinoma
Liver hepatocellular carcinoma
Lung adenocarcinoma
Lung squamous cell carcinoma
Mesothelioma
Ovarian serous cystadenocarcinoma
Pancreatic adenocarcinoma
Pheochromocytoma and paraganglioma
Prostate adenocarcinoma
Sarcoma
Skin cutaneous melanoma
Stomach adenocarcinoma
Testicular germ cell tumours
Thymoma
Thyroid carcinoma
Uterine carcinosarcoma
Uterine corpus endometrial carcinoma
Uveal melanoma
Malignant rhabdoid (ref. 181)
Lung small cell (ref. 182)
ARID1A SMARCA4 SMARCB1 ACTB DPF3 SS18 ARID1B ACTL6B SMARCA2 DPF2 SMARCC2 BCL7C ACTL6A DPF1 BCL7A SS18L1 SMARCE1 SMARCD3 SMARCD2 BCL7B SMARCC1 SMARCD1 PBRM1 ARID2 BRD7 PHF10 BICRAL BRD9 BICRA
SMARCA1 POLE3 RSF1 BPTF BAZ1B CHRAC1 BAZ2A SMARCA5 CECR2 BAZ1A
CHD4 CHD5 RBBP7 MTA2 MBD3 GATAD2A GATAD2B HDAC1 RBBP4 CHD3 HDAC2 MTA1 MBD2 MTA3
Also part of TIP60
Also part of TIP60, INO80, SRCAP
Also part of ISWI
Also part of ISWI
BAF (mSWI/SNF)
PBAF-specific
ncBAF-specific
ISWI
NuRD
SRCAP ZNHIT1 ACTR6 YEATS4 RUVBL2 VPS72 KAT5 EP400 MRGBP DMAP1 TRRAP RUVBL1 MORF4L1 ING3 MEAF6 BRD8
ACTR5 MCRS1 INO80 ACTR8 YY1 UCHL5 INO80C TFPT INO80E INO80B INO80D NFRKB
ATRX DAXX
CHD1 CHD1L CHD2 CHD6 CHD7 CHD8 CHD9 SMARCAL1 RAD54B SMARCAD1 ZRANB3 RAD54L SHPRH RAD54L2 HLTF HELLS TTF2 BTAF1 ERCC6L ERCC6 ERCC6L2 TP53 HBB
YEATS4, VPS72, DMAP1: Also part of SRCAP
SRCAP
TIP60
INO80
ATRX
RUVBL1, RUVBL2: Also part of SRCAP, INO80
Enrichment over background of non-synonymous mutations
0 2 4 6 8 ≥10
−log10 (P value)

Fig. 5 | Enrichment of non-synonymous cancer mutations in chromatin remodelling complexes. Non-synonymous mutations include missense mutations, nonsense mutations, fusions, frameshifts, in-frame deletions and splice site mutations. The enrichment of mutations in a gene observed above those expected is adjusted for gene length and the calculated background mutation rate in the cancer. *P* values were computed as in ref. 180 by, for a given cancer, comparing the observed number of mutations *k* with the cancer's background mutation rate *r*, adjusted for gene length, with the assumption that *k* could be approximated by a Poisson distribution. The background rate was calculated from the total number of mutations per gene length for all genes in that cancer. All data was from The Cancer Genome Atlas Project (TCGA Research Network) plus refs. 181,182 accessed from the cBioPortal[183,184] using the R package 'cgdsr'. *TP53*, an important tumour suppressor, and *HBB*, rarely mutated in cancer, are plotted as comparisons. Adenocac., adenocarcinoma; DLBCL, diffuse large B cell lymphoma; endocer., endocervical; SCC, squamous cell carcinoma.

and ranked fourth in a recent study of tumour-suppressor genes[133]. That study also nominated multiple other BAF subunits as tumour suppressors as well as *ATRX* (18th) and CHD8 (87th). Further, targeted sequencing studies continue to identify remodellers as tumour suppressors such as CHD5 (in gliomas and neuroblastomas)[134] and CHD1 (prostate cancer)[135].

Why particular subunits are mutated in only particular cancers is an important question. One answer may be in the cell-of-origin of the cancer, in which a particular remodeller may be critical for developmental processes discussed earlier, such as lineage specification or regulation of pluripotency. A recent study sought to identify the cellular origin of rhabdoid tumours by single-cell transcriptomics and genetically engineered mouse models[136]. The researchers generated various genetically engineered mouse models with five different cell-type-specific and inducible losses of *Smarcb1*, finding that only selective *Smarcb1* loss in *Sox2*-positive, embryonic day 6.5 precursor cells was sufficient to result in rhabdoid tumour growth. Further cell-specific knockout of one allele of *Smarcb1* in primordial germ cells led to tumours resembling the MYC subtype of atypical teratoid rhabdoid tumours. Although these studies nominated primordial germ cells as one potential cell of origin for MYC-subtype atypical teratoid rhabdoid tumours, tumour penetrance was not 100% and there may also be other cells of origin. The work suggests a critical role for *Smarcb1* in the development of Sox2-positive embryonic precursors and primordial germ cells.

Consistent with a dosage-dependent mechanism, many tumours have remodeller LoF mutations in only one allele. For example, *ARID1A* mutations in many ovarian clear cell carcinoma, gastric cancer, primary breast tumours and nearly all hepatocellular carcinomas are heterozygous[137]. Cancer cellular and mouse models of *ARID1A* heterozygosity further suggested that it acts in a haploinsufficient manner[137]. In separate studies, *Smarca4* heterozygosity also caused mammary tumours in mice by a haploinsufficient mechanism[138]. Given the statistical enrichment of mutations in several other dosage-dependent remodellers across tumour types (Figs. 3 and 5), it may be likely that their haploinsufficiency mediates a role in tumour progression as well.

Synthetic lethal pathways involving remodellers. The high rates of inactivation of remodellers in tumours has raised the question of how they can be targeted therapeutically. A growing area of research is in identifying synthetic lethal pathways involving remodellers, in which inactivation of the remodeller sensitizes the cell to alterations in another gene, or vice versa. Recent efforts using functional genomics and chemical screens has uncovered a variety of such synthetic lethal interactions involving remodellers. These efforts have nominated many kinases, epigenetic modifiers, DNA damage response factors and receptor signalling pathways as therapeutic vulnerabilities in particular tumours. The BAF complex, again, has been well studied in this regard; a compiled table of synthetic lethal interactions is provided in ref. 139 and includes many targets of already FDA-approved therapies such as the Abl kinase (dasatinib), PARP (olaparib), and CDK4/6 (palbociclib). Synthetic lethality has also nominated and/or validated remodeller biological mechanisms of action; for example, ATRX knockout in glioma cells and immortalized astrocytes sensitized these cells to PARP inhibition[140], consistent with its role in responding to DNA damage. The synthetic lethal genes may also be the paralogs of the subunits altered in the cancer. For example, *ARID1B* is a vulnerability in *ARID1A*-deficient tumours, and *SMARCA2* (BRM) is a synthetic lethal vulnerability in *SMARCA4* (BRG1)-deficient tumours[141,142]. The latter finding suggests that developing BRM-specific inhibitors could be therapeutic in cancers that have lost BRG1. Both those vulnerabilities were found by searching recent data from large-scale knockout and knockdown studies mapping dependencies in hundreds of cancer cell lines[143] and ongoing expansion of such data will probably yield further context-specific therapeutic targets.

Remodellers and cancer immunotherapy. Remodeller mutations can also promote responses to other cancer therapies by more complex mechanisms. One of the major areas of current investigation is understanding how tumour mutations can contribute to sensitivity or resistance to immunotherapies. Immune checkpoint inhibitors and CAR-T therapies have had transformative, curative outcomes for many patients with cancer, but many patients do not respond, and most tumour types cannot currently be targeted with immunotherapies. A recent set of preclinical studies in mice[144] and clinical retrospective analyses[145] showed that *ARID1A* loss improves tumour responses to checkpoint inhibitors, and related studies have also nominated other BAF subunits such as *PBRM1* (refs. 146,147) in having similar sensitizing roles. BAF loss is hypothesized to sensitize cells to interferon-gamma signalling, resulting in increased recruitment of tumour-killing effector T cells[148]. In other studies, inhibiting BAF during the activation and generation of CAR-T cells promoted T effector cell memory and efficacy against osteosarcoma and glioma tumour mouse models[149]. Given the critical roles remodellers have in both oncogenesis and in development, we anticipate that further investigation of their roles in promoting antitumour immune response will yield fresh therapeutic targets.

Molecular mechanisms of remodeller contributions to tumour suppression. One molecular mechanism of how remodellers may function as tumour suppressors is in regulating chromatin accessibility at regulatory regions. In rhabdoid tumours, for example, *SMARCB1* loss destabilizes the BAF complex and diminishes its ability to maintain enhancer activity at critical differentiation genes and to oppose Polycomb-mediated repression at bivalent promoters[150,151]. *CHD1*, usually deleted (~10%) in prostate cancer[152], normally co-enriches on chromatin at lineage-specific enhancers with the androgen receptor. CHD1 loss redistributes androgen receptor to other accessible chromatin to promote tumour progression[153]. CHD5, a tumour suppressor often deleted in neuroblastomas, is part of the NuRD complex, and

facilitates Polycomb repression along with the NuRD complex histone deacetylases (HDACs)[154]. One critical point is that remodeller tumour suppressor function is often lineage-specific; for example, CHD1 is rarely deleted in non-prostatic cancers despite ubiquitous expression in normal tissue. In keeping with the theme of multifunctionality, these transcription-regulatory roles are not mutually exclusive with other mechanisms detailed below.

A second molecular mechanism of how remodellers may function as tumour suppressors is in genome maintenance. A hallmark of cancer is genome instability and many studies have shown that remodellers have a role in the normal maintenance of DNA integrity. As an example, during cell division, topoisomerase II enzymes function in DNA decatenation by a complex mechanism involving single-strand cleavage of DNA, pass-through and ligation. Simple observations of cells in which *SMARCA4* was deleted led to the finding that many cells failed to complete mitosis and were characterized by anaphase bridges: strands of DNA remaining between chromosomes attempting to separate[155]. Biochemical studies revealed that BAF complexes interact with and are essential for the binding of topoisomerase II across the genome[155]. Furthermore, using non-small-cell lung cancer cell lines and mouse models, researchers found that *SMARCA4* mutations are genetic biomarkers that predict enhanced sensitivity to topoisomerase II inhibitors in response to EZH2 inhibition[156]. In tumours from breast cancer patients, mutations in BAF subunits, Polycomb subunits, and the lysine demethylase KDM4B emerged as predictive of responses to treatment with topoisomerase II inhibitors (anthracyclines)[157]. Thus, chromatin remodelling via BAF complexes appear to be a major determinant of the function of topoisomerase II in maintaining DNA integrity.

Remodellers have also been implicated directly in the repair of double-strand breaks. The pBAF complex containing *PBRM1* (BAF180) was found to be important for double-strand-break-induced transcriptional silencing[158], promoting repair of a subset of DNA double-strand breaks at early time points after DNA damage. An ATM kinase phosphorylation site on BAF180 is required for silencing. Cancer-associated BAF180 mutants are unable to restore the silencing functions, suggesting that the role of pBAF in repressing transcription near double-strand breaks may contribute to its tumour-suppressor activity.

Maintenance of telomeres is important for genomic stability and cancer cell immortality. The ATRX/DAXX complex, which facilitates the incorporation of histone variant H3.3 into telomeric chromatin[120], is frequently mutated in cancer, particularly in glioma, sarcoma and pancreatic neuroendocrine tumours[159]. Cancer-associated mutations in *ATRX* are found throughout the gene body, and mostly lead to loss of protein expression, unlike mutations found in patients with the intellectual disability ATRX syndrome (alpha-thalassemia X-linked), which are localized in the N-terminal or helicase domains[25]. Loss of ATRX, or its partner DAXX, has been correlated with the alternative lengthening of telomeres mechanism that maintains telomeres without the use of telomerase, in paediatric glioblastomas and in pancreatic neuroendocrine tumours[160,161]. The histone variant H3.3 was also found to be recurrently mutated (K27M or G34R) in these glioblastomas, suggesting a common pathological mechanism of action involving dysregulation of the known function of ATRX/DAXX in depositing H3.3 at telomeres[24], although these histone mutations may also dysregulate Polycomb repression through H3K27me3 or other H3 post-translational modifications.

Remodellers as oncogenes

Remodellers function as oncogenes by virtue of regulating activating and repressive chromatin, often in cooperation with other chromatin modifiers (such as Polycomb complexes). For example, just as in promoting tumour suppression by regulating repressive chromatin (above), NuRD complexes (containing CHD3, CHD4 or CHD5, as well as HDACs) can promote many pro-oncogenic transcriptional programmes by silencing tumour-suppressor genes[5,7,162]. Examining structural alterations in remodeller genes can also suggest where they act to promote oncogenesis. Perhaps the most straightforward role of a remodeller as an oncogene is found in synovial sarcoma, where almost 100% of the cells in every case have the same genetic lesion, with few other mutations in the genome[3,123]. In these cancers, the gene encoding the SS18 subunit of BAF is translocated to the SSX family locus, resulting in the addition of exactly 89 amino acids of SSX to the C-terminus of SS18 (refs. 163–165). The alteration is constrained to only one allele and the resulting fusion protein retargets the BAF complex to evict Polycomb complexes and de-repress genes such as *SOX2* and other targets, which then drive cancer progression[166–168]. The fusion protein generates a large unstructured region that has been resistant to drug development because of its lack of structure but approaches that degrade BAF complexes containing these fusion proteins are promising[169]. Certain other soft-tissue sarcomas contain similar translocations of the gene encoding the histone acetylation reader protein YEATS4 (ref. 170), part of the TIP60 complex, although the mechanism by which this contributes to cancer progression is not yet known.

Genomic amplifications specific to cancers can also nominate oncogenes. Approximately 30 to 50% of squamous cell carcinoma tumours have amplification of *ACTL6A* (BAF53A). This subunit is normally sub-stoichiometric with respect to the rest of the BAF complex in normal keratinocytes, and amplification at a very early point in carcinogenesis leads to the formation of fully stoichiometric BAF complexes[36]. The fully stoichiometric, supercharged complex directly interacts with the YAP-TEAD transcriptional activators and leads to the activation of YAP-TEAD target genes[36]. The BAF53A-containing BAF complex evicts Polycomb more robustly, derepressing genes that have critical roles in squamous cell carcinoma proliferation. These two molecular processes act like a Boolean AND gate in allowing the cancer to be initiated and maintained[36]. Interestingly, BRD9, a member of the non-canonical ncBAF complex, is also usually amplified in a number of patient tumours including bladder cancer, ovarian cancer, lung squamous cell carcinoma, oesophageal carcinoma and lung adenocarcinoma[171].

Examining the genetic exclusivity of mutational burden can also identify context-dependent oncogenic roles, as in the case of CHD1 in prostate cancer. Recent genomic analyses showed that *CHD1* deletion is almost always mutually exclusive with *PTEN* deletion[172] and in *PTEN*-deleted contexts, CHD1 maintains and promotes an immunosuppressive transcriptional program[172,173]. This suggests that CHD1 degradation or inhibition might be a targeted therapeutic strategy in *PTEN*-null prostatic cancers.

Another oncogenic possibility occurs when some remodeller subunits are inactivated by mutation, but the remaining residual complexes acquire a gain-of-function, and are aberrantly targeted to activate oncogenic gene expression. In cellular models of malignant rhabdoid tumours, *SMARCB1* loss leads to altered enhancer targeting that inactivates differentiation programs, but residual complexes maintain super-enhancer controlled oncogenic expression[151]. Alternatively, aberrant targeting may be a result of mutations in a TF that normally cooperates with the remodeller. An example of this phenomenon is in the interaction of BAF complexes in many normal cell types with the protein EWSR1. In Ewing's sarcomas, EWSR1 is often genetically fused

to ETS family TFs such as FLI1. BAF becomes re-localized by EWS–FLI fusions to tumour-specific enhancers and contributes to oncogene activation[174].

Conclusions

A theme that emerges from both genetic studies and biochemical work in mammals is that remodellers have characteristic, biologically non-redundant and specific functions. Recent human genetic studies have discovered hundreds of new alleles that define mutational hotspots within the subunits of complexes and have identified their genetic dosage sensitivity. Remodellers are mutated in a large percentage of cancers and developmental disorders. These findings are motivating efforts to define precise targets for therapeutic modulation of specific biological functions while excluding the subunits and domains with general viability functions.

Many mechanistic questions remain about the activities of remodellers in living cells on their native chromatin substrates and their contribution to biological phenotypes. One is the contribution of each remodeller to nucleosome exchange rates, and preferences for modified nucleosomes. A second question is in understanding the remarkable specificity of the phenotypes produced by mutations in remodelling complexes. Structural studies have called attention to the formation of varied composite surfaces, which are thought to drive the engagement and functional modulation of a wide variety of nuclear proteins. Another set of questions revolves around mechanisms of recruitment and targeting. These questions inherently demand time-resolved studies to be conducted in living cells, and therefore we anticipate that further development of tools and chemical probes for remodellers will aid investigative efforts. The contributions of various remodellers to disease progression and the possibility of pharmacological interventions motivates these efforts.

Published online: 24 November 2023

References

1. Flaus, A. Identification of multiple distinct Snf2 subfamilies with conserved structural motifs. *Nucleic Acids Res.* **34**, 2887–2905 (2006).
2. Centore, R. C., Sandoval, G. J., Soares, L. M. M., Kadoch, C. & Chan, H. M. Mammalian SWI/SNF chromatin remodeling complexes: emerging mechanisms and therapeutic strategies. *Trends Genet.* **36**, 936–950 (2020).
3. Hodges, C., Kirkland, J. G. & Crabtree, G. R. The many roles of BAF (mSWI/SNF) and PBAF complexes in cancer. *Cold Spring Harb. Perspect. Med.* **6**, a026930 (2016).
4. Pulice, J. L. & Kadoch, C. Composition and function of mammalian SWI/SNF chromatin remodeling complexes in human disease. *Cold Spring Harb. Symp. Quant. Biol.* **81**, 53–60 (2016).
5. Bracken, A. P., Brien, G. L. & Verrijzer, C. P. Dangerous liaisons: interplay between SWI/SNF, NuRD, and Polycomb in chromatin regulation and cancer. *Genes. Dev.* **33**, 936–959 (2019).
6. Ho, P. J., Lloyd, S. M. & Bao, X. Unwinding chromatin at the right places: how BAF is targeted to specific genomic locations during development. *Development* **146**, dev178780 (2019).
7. Alendar, A. & Berns, A. Sentinels of chromatin: chromodomain helicase DNA-binding proteins in development and disease. *Genes Dev.* **35**, 1403–1430 (2021).
8. Clapier, C. R. Sophisticated conversations between chromatin and chromatin remodelers, and dissonances in cancer. *Int. J. Mol. Sci.* **22**, ijms22115578 (2021).
9. Hota, S. K. & Bruneau, B. G. ATP-dependent chromatin remodeling during mammalian development. *Development* **143**, 2882–2897 (2016).
   Hota and Bruneau comprehensively review genetic and functional studies showing the unique roles of chromatin remodellers during mammalian development.
10. Sundaramoorthy, R. & Owen-Hughes, T. Chromatin remodelling comes into focus. *F1000Res* **9**, https://doi.org/10.12688/f1000research.21933.1 (2020).
11. Hirschhorn, J. N., Brown, S. A., Clark, C. D. & Winston, F. Evidence that SNF2/SWI2 and SNF5 activate transcription in yeast by altering chromatin structure. *Genes. Dev.* **6**, 2288–2298 (1992).
12. Sternberg, P. W., Stern, M. J., Clark, I. & Herskowitz, I. Activation of the yeast *HO* gene by release from multiple negative controls. *Cell* **48**, 567–577 (1987).
13. Nasmyth, K., Stillman, D. & Kipling, D. Both positive and negative regulators of HO transcription are required for mother-cell-specific mating-type switching in yeast. *Cell* **48**, 579–587 (1987).
14. Mizuguchi, G. et al. ATP-driven exchange of histone H2AZ variant catalyzed by SWR1 chromatin remodeling complex. *Science* **303**, 343–348 (2004).
15. Hota, S. K. et al. Nucleosome mobilization by ISW2 requires the concerted action of the ATPase and SLIDE domains. *Nat. Struct. Mol. Biol.* **20**, 222–229 (2013).
16. Hamiche, A., Sandaltzopoulos, R., Gdula, D. A. & Wu, C. ATP-dependent histone octamer sliding mediated by the chromatin remodeling complex NURF. *Cell* **97**, 833–842 (1999).
17. Langst, G., Bonte, E. J., Corona, D. F. & Becker, P. B. Nucleosome movement by CHRAC and ISWI without disruption or trans-displacement of the histone octamer. *Cell* **97**, 843–852 (1999).
18. Kwon, H., Imbalzano, A. N., Khavari, P. A., Kingston, R. E. & Green, M. R. Nucleosome disruption and enhancement of activator binding by a human SW1/SNF complex. *Nature* **370**, 477–481 (1994).
19. Ayala, R. et al. Structure and regulation of the human INO80-nucleosome complex. *Nature* **556**, 391–395 (2018).
20. Narlikar, G. J., Sundaramoorthy, R. & Owen-Hughes, T. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. *Cell* **154**, 490–503 (2013).
    This is a clear and concise review of the basic biochemical mechanisms of nucleosome remodelling.
21. Deuring, R. et al. The ISWI chromatin-remodeling protein is required for gene expression and the maintenance of higher order chromatin structure in vivo. *Mol. Cell* **5**, 355–365 (2000).
22. Längst, G. & Becker, P. B. Nucleosome mobilization and positioning by ISWI-containing chromatin-remodeling factors. *J. Cell Sci.* **114**, 2561–2568 (2001).
23. Drane, P., Ouararhni, K., Depaux, A., Shuaib, M. & Hamiche, A. The death-associated protein DAXX is a novel histone chaperone involved in the replication-independent deposition of H3.3. *Genes Dev.* **24**, 1253–1265 (2010).
24. Lewis, P. W., Elsaesser, S. J., Noh, K. M., Stadler, S. C. & Allis, C. D. Daxx is an H3.3-specific histone chaperone and cooperates with ATRX in replication-independent chromatin assembly at telomeres. *Proc. Natl Acad. Sci. USA* **107**, 14075–14080 (2010).
25. Dyer, M. A., Qadeer, Z. A., Valle-Garcia, D. & Bernstein, E. ATRX and DAXX: mechanisms and mutations. *Cold Spring Harb. Perspect. Med.* **7**, a026567 (2017).
26. Ni, K. et al. LSH mediates gene repression through macroH2A deposition. *Nat. Commun.* **11**, 5647 (2020).
27. Kadoch, C. et al. Dynamics of BAF–Polycomb complex opposition on heterochromatin in normal and oncogenic states. *Nat. Genet.* **49**, 213–222 (2017).
28. Stanton, B. Z. et al. Smarca4 ATPase mutations disrupt direct eviction of PRC1 from chromatin. *Nat. Genet.* **49**, 282–288 (2017).
29. Clapier, C. R. & Cairns, B. R. Regulation of ISWI involves inhibitory modules antagonized by nucleosomal epitopes. *Nature* **492**, 280–284 (2012).
30. Wu, J. I., Lessard, J. & Crabtree, G. R. Understanding the words of chromatin regulation. *Cell* **136**, 200–206 (2009).
31. Mashtalir, N. et al. Modular organization and assembly of SWI/SNF family chromatin remodeling complexes. *Cell* **175**, 1272–1288 e1220 (2018).
32. Erdel, F. & Rippe, K. Chromatin remodelling in mammalian cells by ISWI-type complexes—where, when and why? *FEBS J.* **278**, 3608–3618 (2011).
33. Wang, W. et al. Diversity and specialization of mammalian SWI/SNF complexes. *Genes. Dev.* **10**, 2117–2130 (1996).
34. Wang, W. et al. Purification and biochemical heterogeneity of the mammalian SWI–SNF complex. *EMBO J.* **15**, 5370–5382 (1996).
35. Ren, J. et al. Single-cell transcriptomes and whole-brain projections of serotonin neurons in the mouse dorsal and median raphe nuclei. *eLife* **8**, e49424 (2019).
36. Chang, C. Y. et al. Increased ACTL6A occupancy within mSWI/SNF chromatin remodelers drives human squamous cell carcinoma. *Mol. Cell* **81**, 4964–4978 e4968 (2021).
37. Biggin, M. D. Animal transcription networks as highly connected, quantitative continua. *Dev. Cell* **21**, 611–626 (2011).
38. Fulton, S. L. et al. Rescue of deficits by Brwd1 copy number restoration in the Ts65Dn mouse model of Down syndrome. *Nat. Commun.* **13**, 6384 (2022).
39. Braun, S. M. G. et al. BAF subunit switching regulates chromatin accessibility to control cell cycle exit in the developing mammalian cortex. *Genes. Dev.* **35**, 335–353 (2021).
40. Lessard, J. et al. An essential switch in subunit composition of a chromatin remodeling complex during neural development. *Neuron* **55**, 201–215 (2007).
    Lessard and colleagues describe a neuron-specific remodelling complex (neuronal BAF or nBAF) with subunits expressed only in the nervous system.
41. Goodman, J. V. & Bonni, A. Regulation of neuronal connectivity in the mammalian brain by chromatin remodeling. *Curr. Opin. Neurobiol.* **59**, 59–68 (2019).
42. Nitarska, J. et al. A functional switch of NuRD chromatin remodeling complex subunits regulates mouse cortical development. *Cell Rep.* **17**, 1683–1698 (2016).
43. Yoo, A. S., Staahl, B. T., Chen, L. & Crabtree, G. R. MicroRNA-mediated switching of chromatin-remodelling complexes in neural development. *Nature* **460**, 642–646 (2009).
44. Takeuchi, J. K. & Bruneau, B. G. Directed transdifferentiation of mouse mesoderm to heart tissue by defined factors. *Nature* **459**, 708–711 (2009).
    These two studies defined switches in BAF complex subunit composition that are instructive for maturation of neurons (Yoo et al., 2009) or the cardiomyocytes (Takeuchi et al., 2009), and the groups have continued to study the cell-type-specific remodeller complexes.
45. Lim, H. Y. G. et al. Keratins are asymmetrically inherited fate determinants in the mammalian embryo. *Nature* **585**, 404–409 (2020).

46. Ho, L. et al. An embryonic stem cell chromatin remodeling complex, esBAF, is essential for embryonic stem cell self-renewal and pluripotency. *Proc. Natl Acad. Sci. USA* **106**, 5181–5186 (2009).
47. Cairns, B. R. et al. RSC, an essential, abundant chromatin-remodeling complex. *Cell* **87**, 1249–1260 (1996).
48. Laurent, B. C., Yang, X. & Carlson, M. An essential *Saccharomyces cerevisiae* gene homologous to SNF2 encodes a helicase-related protein in a new family. *Mol. Cell Biol.* **12**, 1893–1902 (1992).
49. Tsuchiya, E. et al. The *Saccharomyces cerevisiae* NPS1 gene, a novel CDC gene which encodes a 160 kDa nuclear protein involved in G2 phase control. *EMBO J.* **11**, 4017–4026 (1992).
50. Tsukiyama, T., Palmer, J., Landel, C. C., Shiloach, J. & Wu, C. Characterization of the imitation switch subfamily of ATP-dependent chromatin-remodeling factors in *Saccharomyces cerevisiae*. *Genes. Dev.* **13**, 686–697 (1999).
51. Alén, C. et al. A role for chromatin remodeling in transcriptional termination by RNA polymerase II. *Mol. Cell* **10**, 1441–1452 (2002).
52. Gkikopoulos, T. et al. A role for Snf2-related nucleosome-spacing enzymes in genome-wide nucleosome organization. *Science* **333**, 1758–1760 (2011).
53. Kubik, S. et al. Opposing chromatin remodelers control transcription initiation frequency and start site selection. *Nat. Struct. Mol. Biol.* **26**, 744–754 (2019).
54. Krietenstein, N. et al. Genomic nucleosome organization reconstituted with pure proteins. *Cell* **167**, e712 (2016).
55. Karczewski, K. J. et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* **581**, 434–443 (2020).
56. Rice, A. M. & McLysaght, A. Dosage sensitivity is a major determinant of human copy number variant pathogenicity. *Nat. Commun.* **8**, 14366 (2017).
57. Firth, H. V. et al. DECIPHER: database of chromosomal imbalance and phenotype in humans using Ensembl resources. *Am. J. Hum. Genet.* **84**, 524–533 (2009).
58. Valencia, A. M. et al. Landscape of mSWI/SNF chromatin remodeling complex perturbations in neurodevelopmental disorders. *Nat. Genet.* **55**, 1400–1412 (2023).
59. Morrill, S. A. & Amon, A. Why haploinsufficiency persists. *Proc. Natl Acad. Sci. USA* **116**, 11866–11871 (2019).
Morill and Amon provide an insightful perspective on how genetic dosage and haploinsufficiency contribute to cellular fitness.
60. Wenderski, W. et al. Loss of the neural-specific BAF subunit ACTL6B relieves repression of early response genes and causes recessive autism. *Proc. Natl Acad. Sci. USA* **117**, 10055–10066 (2020).
The authors identified recessive missense variants in a neuron-specific subunit of the BAF complex in individuals with autism spectrum disorder, and mapped their biochemical contributions to autism-spectrum-disorder-related phenotypes in flies, human organoids and mouse models, finding that these mutations produce specific defects in social behaviour and neuronal-activity-dependent responses.
61. Lek, M. et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* **536**, 285–291 (2016).
62. Minikel, E. V. et al. Evaluating drug targets through human loss-of-function genetic variation. *Nature* **581**, 459–464 (2020).
63. The Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. *Nature* **519**, 223–228 (2015).
64. Kennison, J. A. & Tamkun, J. W. Dosage-dependent modifiers of Polycomb and Antennapedia mutations in *Drosophila*. *Proc. Natl Acad. Sci. USA* **85**, 8136–8140 (1988).
In this study, Kennison and Tamkun identified the ATPase Brahma (part of the BAF complex) and its role in opposing Polycomb complexes; the opposition between Polycomb and BAF complexes is a crucial underlying mechanism that has been observed in many human malignancies and developmental disorders.
65. Deal, R. B., Henikoff, J. G. & Henikoff, S. Genome-wide kinetics of nucleosome turnover determined by metabolic labeling of histones. *Science* **328**, 1161–1164 (2010).
Deal, Henikoff and Henikoff develop a chemical biological method to measure rates of nucleosome turnover and find that turnover occurs faster than a cell cycle across most of the genome, implying that nucleosome remodelling itself can regulate active or repressive gene expression states simply by modulating local DNA accessibility.
66. Lai, B. et al. Principles of nucleosome organization revealed by single-cell micrococcal nuclease sequencing. *Nature* **562**, 281–285 (2018).
67. Yildirim, O. et al. Mbd3/NURD complex regulates expression of 5-hydroxymethylcytosine marked genes in embryonic stem cells. *Cell* **147**, 1498–1510 (2011).
68. Narlikar, G. J., Fan, H.-Y. & Kingston, R. E. Cooperation between complexes that regulate chromatin structure and transcription. *Cell* **108**, 475–487 (2002).
69. Cirillo, L. A. et al. Opening of compacted chromatin by early developmental transcription factors HNF3 (FoxA) and GATA-4. *Mol. Cell* **9**, 279–289 (2002).
70. Soufi, A. et al. Pioneer transcription factors target partial DNA motifs on nucleosomes to initiate reprogramming. *Cell* **161**, 555–568 (2015).
71. Barozzi, I. et al. Coregulation of transcription factor binding and nucleosome occupancy through DNA features of mammalian enhancers. *Mol. Cell* **54**, 844–857 (2014).
72. Miller, E. L. et al. TOP2 synergizes with BAF chromatin remodeling for both resolution and formation of facultative heterochromatin. *Nat. Struct. Mol. Biol.* **24**, 344–352 (2017).
73. King, H. W. & Klose, R. J. The pioneer factor OCT4 requires the chromatin remodeller BRG1 to support gene regulatory element function in mouse embryonic stem cells. *eLife* **6**, e22631 (2017).
74. Friman, E. T. et al. Dynamic regulation of chromatin accessibility by pluripotency transcription factors across the cell cycle. *eLife* **8**, e50087 (2019).
75. Xiao, L. et al. Targeting SWI/SNF ATPases in enhancer-addicted prostate cancer. *Nature* **601**, 434–439 (2021).
76. Wang, W. et al. Architectural DNA binding by a high-mobility-group/kinesin-like subunit in mammalian SWI/SNF-related complexes. *Proc. Natl Acad. Sci. USA* **95**, 492–498 (1998).
77. Smith, M. J. et al. Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas. *Nat. Genet.* **45**, 295–298 (2013).
78. Barisic, D., Stadler, M. B., Iurlaro, M. & Schubeler, D. Mammalian ISWI and SWI/SNF selectively mediate binding of distinct transcription factors. *Nature* **569**, 136–140 (2019).
Barisic and colleagues use functional genomic and epigenomic analyses to identify the unique contributions of different remodellers to the binding of different transcription factors in mouse embryonic stem cells.
79. Swinstead, E. E., Paakinaho, V., Presman, D. M. & Hager, G. L. Pioneer factors and ATP-dependent chromatin remodeling factors interact dynamically: a new perspective. *BioEssays* **38**, 1150–1157 (2016).
80. Grossman, S. R. et al. Positional specificity of different transcription factor classes within enhancers. *Proc. Natl Acad. Sci. USA* **115**, E7222–E7230 (2018).
81. Kim, J. M. et al. Single-molecule imaging of chromatin remodelers reveals role of ATPase in promoting fast kinetics of target search and dissociation from chromatin. *eLife* **10**, e69387 (2021).
Kim and colleagues measure rates of remodeller association with chromatin and find very fast residence times (less than ten seconds), proposing a 'tug-of-war' model between many remodellers and other regulators and loci on chromatin.
82. Erin et al. Steroid receptors reprogram FoxA1 occupancy through dynamic chromatin transitions. *Cell* **165**, 593–605 (2016).
83. Iurlaro, M. et al. Mammalian SWI/SNF continuously restores local accessibility to chromatin. *Nat. Genet.* **53**, 279–287 (2021).
84. Schick, S. et al. Acute BAF perturbation causes immediate changes in chromatin accessibility. *Nat. Genet.* **53**, 269–278 (2021).
85. Johnson, T. A. et al. Conventional and pioneer modes of glucocorticoid receptor interaction with enhancer chromatin in vivo. *Nucleic Acids Res.* **46**, 203–214 (2018).
86. Paun, O. et al. Pioneer factor ASCL1 cooperates with the mSWI/SNF complex at distal regulatory elements to regulate human neural differentiation. *Genes. Dev.* **37**, 218–242 (2023).
87. Esch, D. et al. A unique Oct4 interface is crucial for reprogramming to pluripotency. *Nat. Cell Biol.* **15**, 295–301 (2013).
88. Takaku, M. et al. GATA3-dependent cellular reprogramming requires activation-domain dependent recruitment of a chromatin remodeler. *Genome Biol.* **17**, 36 (2016).
89. Zentner, G. E., Tsukiyama, T. & Henikoff, S. ISWI and CHD chromatin remodelers bind promoters but act in gene bodies. *PLoS Genet.* **9**, e1003317 (2013).
90. Weber, C. M. et al. mSWI/SNF promotes Polycomb repression both directly and through genome-wide redistribution. *Nat. Struct. Mol. Biol.* **28**, 501–511 (2021).
91. Satterstrom, F. K. et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell* **180**, 568–584.e523 (2020).
92. Son, E. Y. & Crabtree, G. R. The role of BAF (mSWI/SNF) complexes in mammalian neural development. *Am. J. Med. Genet. C* **166**, 333–349 (2014).
93. Snijders Blok, L. et al. CHD3 helicase domain mutations cause a neurodevelopmental syndrome with macrocephaly and impaired speech and language. *Nat. Commun.* **9**, 4619 (2018).
94. Ronan, J. L., Wu, W. & Crabtree, G. R. From neural development to cognition: unexpected roles for chromatin. *Nat. Rev. Genet.* **14**, 347–359 (2013).
95. Sood, S. et al. CHD8 dosage regulates transcription in pluripotency and early murine neural differentiation. *Proc. Natl Acad. Sci. USA* **117**, 22331–22340 (2020).
96. Breuss, M. W. & Gleeson, J. G. When size matters: CHD8 in autism. *Nat. Neurosci.* **19**, 1430–1432 (2016).
97. Durak, O. et al. Chd8 mediates cortical neurogenesis via transcriptional regulation of cell cycle and Wnt signaling. *Nat. Neurosci.* **19**, 1477–1488 (2016).
98. Rhee, S. et al. Endothelial deletion of Ino80 disrupts coronary angiogenesis and causes congenital heart disease. *Nat. Commun.* **9**, 368 (2018).
99. Tuoc, T. C. et al. Chromatin regulation by BAF170 controls cerebral cortical size and thickness. *Dev. Cell* **25**, 256–269 (2013).
100. Goljanek-Whysall, K. et al. myomiR-dependent switching of BAF60 variant incorporation into Brg1 chromatin remodeling complexes during embryo myogenesis. *Development* **141**, 3378–3387 (2014).
101. Saccone, V. et al. HDAC-regulated myomiRs control BAF60 variant exchange and direct the functional phenotype of fibro-adipogenic progenitors in dystrophic muscles. *Genes. Dev.* **28**, 841–857 (2014).
102. Goodwin, L. R. & Picketts, D. J. The role of ISWI chromatin remodeling complexes in brain development and neurodevelopmental disorders. *Mol. Cell Neurosci.* **87**, 55–64 (2018).
103. Alberini, C. M. & Kandel, E. R. The regulation of transcription in memory consolidation. *Cold Spring Harb. Perspect. Biol.* **7**, a021741 (2014).
104. Kim, B. et al. Neuronal activity-induced BRG1 phosphorylation regulates enhancer activation. *Cell Rep.* **36**, 109357 (2021).
105. Yang, Y. et al. Chromatin remodeling inactivates activity genes and regulates neural coding. *Science* **353**, 300–305 (2016).
106. Wu, J. I. et al. Regulation of dendritic development by neuron-specific chromatin remodeling complexes. *Neuron* **56**, 94–108 (2007).

107. Aizawa, H. et al. Dendrite development regulated by CREST, a calcium-regulated transcriptional activator. *Science* **303**, 197–202 (2004).
Aizawa and colleagues discovered that CREST (a subunit of the BAF complex) is required for activity-dependent dendritic outgrowth; these findings initiated further studies by this group and many others to understand the contributions of remodellers to activity-dependent neuronal processes.
108. Tea, J. S. & Luo, L. The chromatin remodeling factor Bap55 functions through the TIP60 complex to regulate olfactory projection neuron dendrite targeting. *Neural Dev.* **6**, 5 (2011).
109. Walsh, J. J. et al. Systemic enhancement of serotonin signaling reverses social deficits in multiple mouse models for ASD. *Neuropsychopharmacology* **46**, 2000–2010 (2021).
110. Valencia, A. M. et al. Recurrent SMARCB1 mutations reveal a nucleosome acidic patch interaction site that potentiates mSWI/SNF complex chromatin remodeling. *Cell* **179**, 1342–1356.e1323 (2019).
Valencia and colleagues used hotspot disease mutations in a BAF subunit to elucidate its biochemical interactions with the nucleosome; the study provides a roadmap for how human genetics data can be used for studies of remodeller mechanisms.
111. Mashtalir, N. et al. A structural model of the endogenous human BAF complex informs disease mechanisms. *Cell* **183**, 802–817 e824 (2020).
112. Zhao, K. et al. Rapid and phosphoinositol-dependent binding of the SWI/SNF-like BAF complex to chromatin after T lymphocyte receptor signaling. *Cell* **95**, 625–636 (1998).
113. Riviere, J. B. et al. De novo mutations in the actin genes *ACTB* and *ACTG1* cause Baraitser-Winter syndrome. *Nat. Genet.* **44**, 440–444 (2012).
114. Cuvertino, S. et al. ACTB loss-of-function mutations result in a pleiotropic developmental disorder. *Am. J. Hum. Genet.* **101**, 1021–1033 (2017).
115. He, S. et al. Structure of nucleosome-bound human BAF complex. *Science* **367**, 875–881 (2020).
116. Clapier, C. R. et al. Regulation of DNA translocation efficiency within the chromatin remodeler RSC/Sth1 potentiates nucleosome sliding and ejection. *Mol. Cell* **62**, 453–461 (2016).
117. Xie, X., Jankauskas, R., Mazari, A. M. A., Drou, N. & Percipalle, P. β-actin regulates a heterochromatin landscape essential for optimal induction of neuronal programs during direct reprograming. *PLoS Genet.* **14**, e1007846 (2018).
118. Mahmood, S. R. et al. β-actin dependent chromatin remodeling mediates compartment level changes in 3D genome architecture. *Nat. Commun.* **12**, 5240 (2021).
119. Gibbons, R. J., Picketts, D. J., Villard, L. & Higgs, D. R. Mutations in a putative global transcriptional regulator cause X-linked mental retardation with α-thalassemia (ATR-X syndrome). *Cell* **80**, 837–845 (1995).
120. Goldberg, A. D. et al. Distinct factors control histone variant H3.3 localization at specific genomic regions. *Cell* **140**, 678–691 (2010).
121. Noh, K. M. et al. ATRX tolerates activity-dependent histone H3 methyl/phos switching to maintain repetitive element silencing in neurons. *Proc. Natl Acad. Sci. USA* **112**, 6820–6827 (2015).
122. Sachs, P. et al. SMARCAD1 ATPase activity is required to silence endogenous retroviruses in embryonic stem cells. *Nat. Commun.* **10**, 1335 (2019).
123. Kadoch, C. & Crabtree, G. R. Mammalian SWI/SNF chromatin remodeling complexes and cancer: mechanistic insights gained from human genomics. *Sci. Adv.* **1**, e1500447 (2015).
124. Dunaief, J. L. et al. The retinoblastoma protein and BRGI form a complex and cooperateto induce cell cycle arrest. *Cell* **79**, 119–130 (1994).
This paper describes the first evidence that remodellers can act as tumour suppressors.
125. Wong, A. K. C. et al. BRG1, a component of the SWI–SNF complex, is mutated in multiple human tumor cell lines. *Cancer Res.* **60**, 6171–6177 (2000).
126. Knudson, A. G. Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc. Natl Acad. Sci. USA* **68**, 820–823 (1971).
127. Versteege, I. et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature* **394**, 203–206 (1998).
128. Biegel, J. A. et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. *Cancer Res.* **59**, 74–79 (1999).
129. Sevenet, N. et al. Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. *Am. J. Hum. Genet.* **65**, 1342–1348 (1999).
130. Biegel, J. A. et al. Germline INI1 mutation in a patient with a central nervous system atypical teratoid tumor and renal rhabdoid tumor. *Genes Chromosomes Cancer* **28**, 31–37 (2000).
131. Varela, I. et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene *PBRM1* in renal carcinoma. *Nature* **469**, 539–542 (2011).
132. Sanchez-Vega, F. et al. Oncogenic signaling pathways in the Cancer Genome Atlas. *Cell* **173**, 321–337.e310 (2018).
133. Davoli, T. et al. Cumulative haploinsufficiency and triplosensitivity drive aneuploidy patterns and shape the cancer genome. *Cell* **155**, 948–962 (2013).
134. Kolla, V., Zhuang, T., Higashi, M., Naraparaju, K. & Brodeur, G. M. Role of CHD5 in human cancers: 10 years later. *Cancer Res.* **74**, 652–658 (2014).
135. Burkhardt, L. et al. CHD1 is a 5q21 tumor suppressor required for ERG rearrangement in prostate cancer. *Cancer Res.* **73**, 2795–2805 (2013).
136. Graf, M. et al. Single-cell transcriptomics identifies potential cells of origin of MYC rhabdoid tumors. *Nat. Commun.* **13**, 1544 (2022).
137. Wu, J. N. & Roberts, C. W. ARID1A mutations in cancer: another epigenetic tumor suppressor? *Cancer Discov.* **3**, 35–43 (2013).
138. Bultman, S. J. et al. Characterization of mammary tumors from *Brg1* heterozygous mice. *Oncogene* **27**, 460–468 (2008).
139. Wanior, M., Kramer, A., Knapp, S. & Joerger, A. C. Exploiting vulnerabilities of SWI/SNF chromatin remodelling complexes for cancer therapy. *Oncogene* **40**, 3637–3654 (2021).
140. Garbarino, J., Eckroate, J., Sundaram, R. K., Jensen, R. B. & Bindra, R. S. Loss of ATRX confers DNA repair defects and PARP inhibitor sensitivity. *Transl. Oncol.* **14**, 101147 (2021).
141. Hoffman, G. R. et al. Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers. *Proc. Natl Acad. Sci. USA* **111**, 3128–3133 (2014).
142. Helming, K. C. et al. ARID1B is a specific vulnerability in ARID1A-mutant cancers. *Nat. Med.* **20**, 251–254 (2014).
143. Meyers, R. M. et al. Computational correction of copy number effect improves specificity of CRISPR–Cas9 essentiality screens in cancer cells. *Nat. Genet.* **49**, 1779–1784 (2017).
144. Shen, J. et al. ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. *Nat. Med.* **24**, 556–562 (2018).
145. Okamura, R. et al. ARID1A alterations function as a biomarker for longer progression-free survival after anti-PD-1/PD-L1 immunotherapy. *J. Immunother. Cancer* **8**, e000438 (2020).
146. Pan, D. et al. A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing. *Science* **359**, 770–775 (2018).
147. Miao, D. et al. Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma. *Science* **359**, 801–806 (2018).
148. Krishnamurthy, N., Kato, S., Lippman, S. & Kurzrock, R. Chromatin remodeling (SWI/SNF) complexes, cancer, and response to immunotherapy. *J. Immunother. Cancer* **10**, e004669 (2022).
149. Guo, A. et al. cBAF complex components and MYC cooperate early in $CD8^+$ T cell fate. *Nature* **607**, 135–141 (2022).
150. Nakayama, R. T. et al. SMARCB1 is required for widespread BAF complex-mediated activation of enhancers and bivalent promoters. *Nat. Genet.* **49**, 1613–1623 (2017).
151. Wang, X. et al. SMARCB1-mediated SWI/SNF complex function is essential for enhancer regulation. *Nat. Genet.* **49**, 289–295 (2017).
152. Liu, W. et al. Identification of novel CHD1-associated collaborative alterations of genomic structure and functional assessment of CHD1 in prostate cancer. *Oncogene* **31**, 3939–3948 (2012).
153. Augello, M. A. et al. CHD1 loss alters AR binding at lineage-specific enhancers and modulates distinct transcriptional programs to drive prostate tumorigenesis. *Cancer Cell* **35**, 603–617.e608 (2019).
154. Egan, C. M. et al. CHD5 is required for neurogenesis and has a dual role in facilitating gene expression and Polycomb gene repression. *Dev. Cell* **26**, 223–236 (2013).
155. Dykhuizen, E. C. et al. BAF complexes facilitate decatenation of DNA by topoisomerase II α. *Nature* **497**, 624–627 (2013).
156. Fillmore, C. M. et al. EZH2 inhibition sensitizes BRG1 and EGFR mutant lung tumours to TopoII inhibitors. *Nature* **563**, E27 (2015).
157. Seoane, J. A., Kirkland, J. G., Caswell-Jin, J. L., Crabtree, G. R. & Curtis, C. Chromatin regulators mediate anthracycline sensitivity in breast cancer. *Nat. Med.* **25**, 1721–1727 (2019).
158. Kakarougkas, A. et al. Requirement for PBAF in transcriptional repression and repair at DNA breaks in actively transcribed regions of chromatin. *Mol. Cell* **55**, 723–732 (2014).
159. Chan, C. S. et al. ATRX, DAXX or MEN1 mutant pancreatic neuroendocrine tumors are a distinct α-cell signature subgroup. *Nat. Commun.* **9**, 4158 (2018).
160. Heaphy, C. M. et al. Altered telomeres in tumors with ATRX and DAXX mutations. *Science* **333**, 425 (2011).
161. Schwartzentruber, J. et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* **482**, 226–231 (2012).
162. Xia, L. et al. CHD4 has oncogenic functions in initiating and maintaining epigenetic suppression of multiple tumor suppressor genes. *Cancer Cell* **31**, 653–668.e657 (2017).
163. Clark, J. et al. Identification of novel genes, *SYT* and *SSX*, involved in the t(X;18)(p11.2;q11.2) translocation found in human synovial sarcoma. *Nat. Genet.* **7**, 502–508 (1994).
164. de Leeuw, B., Balemans, M., Olde Weghuis, D. & Geurts van Kessel, A. Identification of two alternative fusion genes, *SYT-SSX1* and *SYT-SSX2*, in t(X;18)(p11.2;q11.2)-positive synovial sarcomas. *Hum. Mol. Genet.* **4**, 1097–1099 (1995).
165. Skytting, B. et al. A novel fusion gene, *SYT-SSX4*, in synovial sarcoma. *J. Natl Cancer Inst.* **91**, 974–975 (1999).
166. McBride, M. J. et al. The nucleosome acidic patch and H2A ubiquitination underlie mSWI/SNF recruitment in synovial sarcoma. *Nat. Struct. Mol. Biol.* **27**, 836–845 (2020).
167. McBride, M. J. et al. The SS18–SSX fusion oncoprotein hijacks BAF complex targeting and function to drive synovial sarcoma. *Cancer Cell* **33**, 1128–1141.e1127 (2018).
168. Kadoch, C. & Crabtree, G. R. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18–SSX oncogenic fusion in synovial sarcoma. *Cell* **153**, 71–85 (2013).
These two studies provide an example of how a remodeller may function directly as an oncogene; in this case, by virtue of a genetic translocation in a subunit creating a fusion protein that then drives aberrant remodelling activity.
169. Brien, G. L. et al. Targeted degradation of BRD9 reverses oncogenic gene expression in synovial sarcoma. *eLife* **7**, e41305 (2018).
170. Barretina, J. et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. *Nat. Genet.* **42**, 715–721 (2010).
171. Sima, X. et al. The genetic alteration spectrum of the SWI/SNF complex: the oncogenic roles of BRD9 and ACTL6A. *PLoS One* **14**, e0222305 (2019).

172. Zhao, D. et al. Synthetic essentiality of chromatin remodelling factor CHD1 in PTEN-deficient cancer. *Nature* **542**, 484–488 (2017).
173. Zhao, D. et al. Chromatin regulator CHD1 remodels the immunosuppressive tumor microenvironment in PTEN-deficient prostate cancer. *Cancer Discov.* **10**, 1374–1387 (2020).
174. Boulay, G. et al. Cancer-specific retargeting of BAF complexes by a prion-like domain. *Cell* **171**, 163–178.e119 (2017).
175. The Deciphering Developmental Disorders Study. Prevalence and architecture of de novo mutations in developmental disorders. *Nature* **542**, 433–438 (2017).
176. Lelieveld, S. H. et al. Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. *Nat. Neurosci.* **19**, 1194–1196 (2016).
177. Rauch, A. et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. *Lancet* **380**, 1674–1682 (2012).
178. de Ligt, J. et al. Diagnostic exome sequencing in persons with severe intellectual disability. *N. Engl. J. Med.* **367**, 1921–1929 (2012).
179. Jin, S. C. et al. Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. *Nat. Genet.* **49**, 1593–1601 (2017).
180. Kadoch, C. et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat. Genet.* **45**, 592–601 (2013).
This study extensively surveyed Cancer Genome Atlas data and found that BAF complexes were mutated in almost 20% of all human cancers.
181. Chun, H. E. et al. Genome-wide profiles of extra-cranial malignant rhabdoid tumors reveal heterogeneity and dysregulated developmental pathways. *Cancer Cell* **29**, 394–406 (2016).
182. George, J. et al. Comprehensive genomic profiles of small cell lung cancer. *Nature* **524**, 47–53 (2015).
183. Gao, J. et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* **6**, pl1 (2013).
184. Cerami, E. et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* **2**, 401–404 (2012).
185. Neigeborn, L. & Carlson, M. Genes affecting the regulation of *SUC2* gene expression by glucose repression in *Saccharomyces cerevisiae*. *Genetics* **108**, 845–858 (1984).
186. Stern, M., Jensen, R. & Herskowitz, I. Five *SWI* genes are required for expression of the *HO* gene in yeast. *J. Mol. Biol.* **178**, 853–868 (1984).
These papers discovered SWI/SNF from screens in yeast for defects in sucrose fermentation and pheromone-dependent mating-type switching.
187. Kruger, W. et al. Amino acid substitutions in the structured domains of histones H3 and H4 partially relieve the requirement of the yeast SWI/SNF complex for transcription. *Genes. Dev.* **9**, 2770–2779 (1995).
188. Laurent, B. C., Treich, I. & Carlson, M. Role of yeast SNF and SWI proteins in transcriptional activation. *Cold Spring Harb. Symp. Quant. Biol.* **58**, 257–263 (1993).
189. Laurent, B., Treitel, M. A. & Carlson, M. Functional interdependence of the yeast SNF2, SNF5, and SNF6 proteins in transcriptional activation. *Proc. Natl Acad. Sci. USA* **88**, 2687–2691 (1991).
190. Peterson, C. L. & Herskowitz, I. Characterization of the yeast *SWI*, *SW2*, and *SW13* genes, which encode a global activator of transcription. *Cell* **68**, 573–583 (1992).
191. Tamkun, J. W. et al. Brahma: a regulator of *Drosophila* homeotic genes structurally related to the yeast transcriptional activator SNF2/SWI2. *Cell* **66**, 561–572 (1992).
192. Kingston, R. E. & Tamkun, J. W. Transcriptional regulation by trithorax-group proteins. *Cold Spring Harb. Perspect. Biol.* **6**, a019349 (2014).
193. Siebenlist, U. et al. Promoter region of interleukin-2 gene undergoes chromatin structure changes and confers inducibility on chloramphenicol acetyltransferase gene during activation of T cells. *Mol. Cell Biol.* **6**, 3042–3049 (1986).
194. Goldsmith, M. A., Desai, D. M., Schultz, T. & Weiss, A. Function of a heterologous muscarinic receptor in T cell antigen receptor signal transduction mutants. *J. Biol. Chem.* **264**, 17190–17197 (1989).
195. Socolovsky, M., Dusanter-Fourt, I. & Lodish, H. F. The prolactin receptor and severely truncated erythropoietin receptors support differentiation of erythroid progenitors. *J. Biol. Chem.* **272**, 14009–14012 (1997).
196. Brisken, C., Socolovsky, M., Lodish, H. F. & Weinberg, R. The signaling domain of the erythropoietin receptor rescues prolactin receptor-mutant mammary epithelium. *Proc. Natl Acad. Sci. USA* **99**, 14241–14245 (2002).
197. Northrop, J. P. et al. NF-AT components define a family of transcription factors targeted in T-cell activation. *Nature* **369**, 497–502 (1994).
198. Khavari, P. A., Peterson, C. L., Tamkun, J. W., Mendel, D. B. & Crabtree, G. R. BRG1 contains a conserved domain of the SWI2/SNF2 family necessary for normal mitotic growth and transcription. *Nature* **366**, 170–174 (1993).
199. Muchardt, C. & Yaniv, M. A human homologue of *Saccharomyces cerevisiae SNF2/SWI2* and *Drosophila brm* genes potentiates transcriptional activation by the glucocorticoid receptor. *EMBO J.* **12**, 4279–4290 (1993).
200. Stanton, B. Z., Chory, E. J. & Crabtree, G. R. Chemically induced proximity in biology and medicine. *Science* **359**, aa05902 (2018).
201. Hathaway, N. A. et al. Dynamics and memory of heterochromatin in living cells. *Cell* **149**, 1447–1460 (2012).
202. Gourisankar, S. et al. Rewiring cancer drivers to activate apoptosis. *Nature* **620**, 417–425 (2023).
203. Braun, S. M. G. et al. Rapid and reversible epigenome editing by endogenous chromatin regulators. *Nat. Commun.* **8**, 560 (2017).
204. Ren, J., Hathaway, N. A., Crabtree, G. R. & Muegge, K. Tethering of Lsh at the *Oct4* locus promotes gene repression associated with epigenetic changes. *Epigenetics* **13**, 173–181 (2017).
205. Marian, C. A. et al. Small molecule targeting of specific BAF (mSWI/SNF) complexes for HIV latency reversal. *Cell Chem. Biol.* **25**, 1443–1455.e1414 (2018).
206. Papillon, J. P. N. et al. Discovery of orally active inhibitors of Brahma homolog (BRM)/SMARCA2 ATPase activity for the treatment of Brahma related gene 1 (BRG1)/SMARCA4-mutant cancers. *J. Med. Chem.* **61**, 10155–10172 (2018).
207. Chory, E. J. et al. Chemical inhibitors of a selective SWI/SNF function synergize with ATR inhibition in cancer cell killing. *ACS Chem. Biol.* **15**, 1685–1696 (2020).
208. Kishtagari, A. et al. A first-in-class inhibitor of ISWI-mediated (ATP-dependent) transcription repression releases terminal-differentiation in AML cells while sparing normal hematopoiesis. *Blood* **132**, 216 (2018).
209. Remillard, D. et al. Degradation of the BAF complex factor BRD9 by heterobifunctional ligands. *Angew. Chem. Int. Edn Engl.* **56**, 5738–5743 (2017).
210. Farnaby, W. et al. BAF complex vulnerabilities in cancer demonstrated via structure-based PROTAC design. *Nat. Chem. Biol.* **15**, 672–680 (2019).
211. Schick, S. et al. Systematic characterization of BAF mutations provides insights into intracomplex synthetic lethalities in human cancers. *Nat. Genet.* **51**, 1399–1410 (2019).
212. Rago, F. et al. Exquisite sensitivity to dual BRG1/BRM ATPase inhibitors reveals broad SWI/SNF dependencies in acute myeloid leukemia. *Mol. Cancer Res.* **20**, 361–372 (2022).
213. Dann, G. P. et al. ISWI chromatin remodellers sense nucleosome modifications to determine substrate preference. *Nature* **548**, 607–611 (2017).
214. Mashtalir, N. et al. Chromatin landscape signals differentially dictate the activities of mSWI/SNF family complexes. *Science* **373**, 306–315 (2021).
215. Chory, E. J. et al. Nucleosome turnover regulates histone methylation patterns over the genome. *Mol. Cell* **73**, 61–72 e63 (2019).
216. Butler, K. V., Chiarella, A. M., Jin, J. & Hathaway, N. A. Targeted gene repression using novel bifunctional molecules to harness endogenous histone deacetylation activity. *ACS Synth. Biol.* **7**, 38–45 (2018).
217. Chiarella, A. M. et al. Dose-dependent activation of gene expression is achieved using CRISPR and small molecules that recruit endogenous chromatin machinery. *Nat. Biotechnol.* **38**, 50–55 (2020).
218. Abbott, J. M. et al. First-in-class inhibitors of oncogenic CHD1L with preclinical activity against colorectal cancer. *Mol. Cancer Ther.* **19**, 1598–1612 (2020).
219. Prigaro, B. J. et al. Design, synthesis, and biological evaluation of the first inhibitors of oncogenic CHD1L. *J. Med. Chem.* **65**, 3943–3961 (2022).
220. Vangamudi, B. et al. The SMARCA2/4 ATPase domain surpasses the bromodomain as a drug target in SWI/SNF-mutant cancers: insights from cDNA rescue and PFI-3 inhibitor studies. *Cancer Res.* **75**, 3865–3878 (2015).
221. Martin, L. J. et al. Structure-based design of an in vivo active selective BRD9 inhibitor. *J. Med. Chem.* **59**, 4462–4475 (2016).
222. Remillard, D. et al. Chemoproteomics enabled discovery of selective probes for NuA4 factor BRD8. *ACS Chem. Biol.* **16**, 2185–2192 (2021).
223. Chen, P. et al. Discovery and characterization of GSK2801, a selective chemical probe for the bromodomains BAZ2A and BAZ2B. *J. Med. Chem.* **59**, 1410–1424 (2016).
224. Lu, T. et al. Discovery of high-affinity inhibitors of the BPTF bromodomain. *J. Med. Chem.* **64**, 12075–12088 (2021).
225. Zahid, H. et al. New design rules for developing potent cell-active inhibitors of the nucleosome remodeling factor (NURF) via BPTF bromodomain inhibition. *J. Med. Chem.* **64**, 13902–13917 (2021).
226. Park, S. G., Lee, D., Seo, H. R., Lee, S. A. & Kwon, J. Cytotoxic activity of bromodomain inhibitor NVS-CECR2-1 on human cancer cells. *Sci. Rep.* **10**, 16330 (2020).
227. Shishodia, S. et al. Selective and cell-active PBRM1 bromodomain inhibitors discovered through NMR fragment screening. *J. Med. Chem.* **65**, 13714–13735 (2022).
228. Londregan, A. T. et al. Discovery of high-affinity small-molecule binders of the epigenetic reader YEATS4. *J. Med. Chem.* **66**, 460–472 (2023).
229. Coffey, K. et al. Characterisation of a Tip60 specific inhibitor, NU9056, in prostate cancer. *PLoS One* **7**, e45539 (2012).
230. Li, Y. & Seto, E. HDACs and HDAC inhibitors in cancer development and therapy. *Cold Spring Harb. Perspect. Med.* **6**, a026831 (2016).
231. Kofink, C. et al. A selective and orally bioavailable VHL-recruiting PROTAC achieves SMARCA2 degradation in vivo. *Nat. Commun.* **13**, 5969 (2022).
232. Zoppi, V. et al. Iterative design and optimization of initially inactive proteolysis targeting chimeras (PROTACs) identify VZ185 as a potent, fast, and selective von Hippel–Lindau (VHL) based dual degrader probe of BRD9 and BRD7. *J. Med. Chem.* **62**, 699–726 (2019).
233. Nabet, B. et al. The dTAG system for immediate and target-specific protein degradation. *Nat. Chem. Biol.* **14**, 431–441 (2018).
234. Nishimura, K., Fukagawa, T., Takisawa, H., Kakimoto, T. & Kanemaki, M. An auxin-based degron system for the rapid depletion of proteins in nonplant cells. *Nat. Methods* **6**, 917–922 (2009).
These two papers describe two chemical biological tools that use chemically induced proximity to recruit endogenous proteins to the proteosome in order to rapidly delete them in living cells and organisms and have been increasingly deployed to define the direct functions of remodellers.

Acknowledgements
The authors apologize to all co-workers who have contributed to this large field whose work we have been unable to cite for want of space.

Author contributions
G.R.C., S.G., A.K. and W.W. researched data for the article. G.R.C., S.G. and A.K. wrote the article. All authors contributed substantially to discussion of the content. All authors reviewed and/or edited the manuscript before submission.

Competing interests
G.R.C. is a founder and scientific adviser for Foghorn Therapeutics and a founder of Shenandoah Therapeutics. The other authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41576-023-00666-x.

Peer review information *Nature Reviews Genetics* thanks Jerry Workman and the other, anonymous, reviewers for their contribution to the peer review of this work.