

Cancer biology and NuRD: a multifaceted chromatin remodelling complex

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Abstract | The nucleosome remodelling and histone deacetylase (NuRD; also known as Mi-2) complex regulates gene expression at the level of chromatin. The NuRD complex has been identified — using both genetic and molecular analyses — as a key determinant of differentiation in mouse embryonic stem cells and during development in various model systems. Similar to other chromatin remodellers, such as SWI/SNF and Polycomb complexes, NuRD has also been implicated in the regulation of transcriptional events that are integral to oncogenesis and cancer progression. Emerging molecular details regarding the recruitment of NuRD to specific loci during development, and the modulation of these events in cancer, are used to illustrate how the inappropriate localization of the complex could contribute to tumour biology.

The nucleosome remodelling and histone deacetylase (NuRD; also known as Mi-2) complex is one of four major types of ATP-dependent chromatin remodelling complexes¹. Like other classes of chromatin remodelling complexes, the NuRD complex has important roles in processes such as transcription, chromatin assembly, cell cycle progression and genomic stability. The NuRD complex is highly conserved in plants and animals, and it is broadly expressed in most tissues². It consists of different protein subunits, and the combinatorial assembly of these subunits determines the function of NuRD in genomic targeting and mediating cell type-specific functions. Recent progress in understanding the mechanisms of transcriptional regulation by the NuRD complex in cancer biology, where it has dual roles in promoting and suppressing tumorigenesis, form the focus of this Review. Emerging non-transcriptional roles of this complex in processes such as chromatin assembly and the DNA damage and repair response, and their implications in maintaining genomic integrity, are also discussed.

Biology and function of the NuRD complex

The NuRD complex was first purified about a decade ago in cells from different species^{3–6}, and it contains six core subunits² (TABLE 1). This complex was unique on discovery in that it contained at least two subunits with enzymatic functions: the chromodomain-helicase-DNA-binding protein 3 (CHD3; also known as Mi-2 α) and CHD4 (also known as Mi-2 β) subunits, which have ATP-dependent

chromatin remodelling activity, and histone deacetylase 1 (HDAC1) and HDAC2 that catalyse protein deacetylation. More recently, it has been shown that the lysine-specific histone demethylase 1A (LSD1) can also be associated with the NuRD complex in certain cell types⁷, although this association has not been confirmed independently (see [Cell website comments on REF. 7](#); see Further information). Other non-enzymatic subunits include methyl-CpG-binding domain 2 (MBD2) and MBD3, metastasis-associated gene 1 (MTA1), MTA2 and MTA3, and retinoblastoma-binding protein 4 (RBBP4; also known as RBAP48) and RBBP7 (also known as RBAP46). Several laboratories also report the association of GATAD2A (also known as p66 α) and GATAD2B (also known as p66 β) with the NuRD complex^{8–10}. The RBBP4, RBBP7, GATAD2A and GATAD2B subunits are thought to be structural components of the NuRD complex and have been shown to directly associate with histone tails^{11–13}. The MBD and MTA subunits, conversely, are implicated in targeting the complex to different genomic locations by associating with methylated DNA¹⁴ or with transcription factors¹⁵, respectively.

Combinatorial assembly of the non-enzymatic subunits is proposed to be a fundamental mechanism of conferring functional specificity of the NuRD complex. For example, MBD2 and MBD3 are found in mutually exclusive NuRD complexes¹⁶. Although MBD2 can recognize and bind to methylated DNA, a function that has been conserved throughout evolution, mammalian MBD3 contains an

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doi:10.1038/nrc3091
Published online 7 July 2011

At a glance

- The nucleosome remodelling and histone deacetylase (NuRD; also known as Mi-2) complex is a multisubunit chromatin remodelling complex that contains two core subunits (chromodomain-helicase-DNA-binding protein 3 (CHD3; also known as Mi-2 α) and CHD4 (also known as Mi-2 β), and histone deacetylase 1 (HDAC1) and HDAC2) with enzymatic functions. CHD3 and CHD4 catalyse ATP-dependent chromatin remodelling, and HDAC1 and HDAC2 mediate histone and protein deacetylation.
- All subunits of the complex are encoded by multiple gene paralogues. Combinatorial assembly of these paralogues contributes to the targeting and function of the complex.
- The metastasis-associated gene 1 (MTA1) subunit is widely overexpressed in many types of cancer and is associated with poor prognosis.
- Unlike other chromatin remodelling complexes with well-defined roles in cancer, the NuRD complex can promote or suppress tumorigenesis depending on context.
- NuRD complex recruitment to specific loci is mediated by multiple mechanisms, including recruitment by transcription factors and direct interaction with methylated DNA.
- Emerging evidence suggests non-transcriptional roles of the NuRD complex in the maintenance of genome stability, including DNA replication, chromatin assembly and DNA repair.

amino acid change at the MBD–DNA interface and cannot bind methylated DNA^{17,18}. Instead, the MBD domain in MBD3 may function as a protein–protein interaction domain and has been shown to bind the oncoprotein JUN¹⁹. Analysis of *Mbd2*- and *Mbd3*-knockout mice confirmed the functional difference between the two MBD protein family members — *Mbd3*-knockout mice are embryonic lethal, whereas *Mbd2*-knockout mice are viable and have only mild defects²⁰. Similar to the MBD subunit, MTA family proteins also form exclusive alternative NuRD complexes that associate with different transcription factors and target distinct gene loci. For example, only MTA3 can directly interact with the transcriptional repressor BCL-6 to maintain a germinal centre B cell identity in activated B cells¹⁵. These examples highlight the functional differences between the various family members of the NuRD complex and suggest roles in promoting specialized functions of the complex in different cell types and biological systems.

In addition to their functions within the NuRD complex, some NuRD subunits can also associate with other protein complexes. For example, RBBP4 and RBBP7 are found in several other multisubunit chromatin modification complexes¹². They presumably provide structural support and promote protein–protein interactions, rather than provide functional specificity to protein complexes¹². HDAC1 and HDAC2 are also the core enzymatic subunits of CoREST and SIN3 complexes²¹. Like NuRD, these complexes are also associated with transcriptional repression^{22,23}. It remains unclear whether the different HDAC1 and HDAC2 complexes can function synergistically to repress common downstream targets, or whether the different complexes are specifically targeted to different regions of the genome.

Knockout and transgenic animal models of NuRD complex components reveal that it has functions in normal developmental processes, as well as in tumorigenesis²⁴. The NuRD complex is required at various stages of haematopoietic differentiation, including haematopoietic




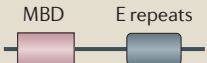
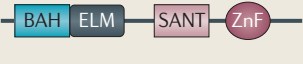
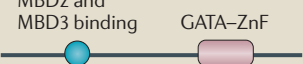

stem cell maintenance and differentiation into lymphoid and myeloid lineage cells²⁵. A NuRD complex containing MTA3 is required for the initiation of haematopoiesis in zebrafish embryos²⁶. The NuRD complex is also involved in the transcriptional regulation of key genes that promote the progression of T and B lymphocyte development^{27–29}. Transcriptional repression of multiple lineage-specific genes by the NuRD complex during haematopoiesis is mediated through friend of GATA1 (FOG1; also known as ZFPM1), which binds MTA family proteins and recruits NuRD to GATA family transcription factors^{30,31}. Other haematopoietic lineage-specific transcription factors that are also associated with the NuRD complex include IKAROS and BCL11B^{32–34}. The MBD3-containing form of the NuRD complex is required for the maintenance of pluripotency in embryonic stem cells and for the initiation of normal differentiation programmes^{35,36}. In the context of cancer, the NuRD complex has been associated with processes such as metastasis and epithelial-to-mesenchymal transition (EMT). The remainder of this Review focuses on the recent progress made in understanding transcriptional regulation by the NuRD complex in promoting tumorigenesis, as well as its involvement in physiological cellular processes that maintain genome stability to prevent the development of cancer.

Gene regulation by NuRD in cancer

Biology of MTA family subunits. Of all the NuRD complex subunits, the MTA family members are the best studied in the context of cancer development. MTA1 was first cloned and characterized as a candidate metastasis-associated gene from a differential cDNA hybridization screen comparing nonmetastatic and highly metastatic rat mammary adenocarcinomas³⁷. Increased levels of MTA1 were subsequently observed in tumours derived from various tissue origins, including breast, colorectal, gastric, oesophageal, endometrial, pancreatic, ovarian, non-small-cell lung and prostate cancer, hepatocellular carcinoma, and diffuse large B cell lymphoma (DLBCL) in humans³⁸. MTA1 overexpression correlates with higher tumour grade, microvascular invasion and poor prognosis in many cancer types³⁸, a result perhaps of MTA1 being a downstream target of the MYC oncoprotein³⁹. Silencing of MTA1 was found to abrogate the ability of MYC to transform mammalian cells³⁹.

In the context of breast cancer, MTA1 and MTA2, but not MTA3, have been shown to repress oestrogen functions⁴⁰. Although MTA1 promotes breast tumour progression, MTA3 has an opposing role by inhibiting EMT⁴¹. EMT is characterized by loss of cell adhesion and increased cellular motility, a process that is thought to be crucial for the initiation of cancer metastasis⁴². Activation of the ERBB2 (also known as HER2) pathway results in the upregulation of MTA1, which in turn physically interacts with oestrogen receptor (ER)-suppressing ER element (ERE)-driven transcription⁴³. Overexpression of MTA1 in ER α -positive (ER α ⁺) breast cancer cells is sufficient to reduce levels of ER target genes, including *BRCA1*, resulting in enhanced invasive growth in an anchorage-independent manner^{43,44}. The initial description of MTA3 revealed further intertwining of the biology of the MTA

Table 1 | Core components of the NuRD complex

Subunit	Protein structure	Functions
CHD3 and CHD4		The CHD3 or CHD4 subunit consists of two PHD fingers, two chromodomains and an ATPase domain. The PHD fingers are required for interaction with HDAC1 (REF. 6) and for modified histone tails ^{96,97} . The chromodomains display DNA-binding activity and are indispensable for ATPase, nucleosome mobilization and nucleosome binding ⁹⁸ . The ATPase domain carries out ATP hydrolysis, which provides the energy necessary for nucleosome remodelling by either histone displacement ^{99,100} or histone octamer sliding ¹⁰¹
HDAC1 and HDAC2		HDAC1 and HDAC2 are class I HDACs that share homology to the yeast <i>RPD3</i> gene and consist of a zinc-containing deacetylase catalytic domain. HDAC1 and HDAC2 uniquely contain an additional carboxy-terminal RB-binding motif ¹⁰²
MBD2		The conserved MBD domain of MBD2 binds methylated DNA ^{17,18} . MBD2 also contains a GR-rich region and a TRD that is involved in recruiting HDACs ^{103,104}
MBD3		The MBD domain of MBD3 does not bind methylated DNA ^{17,18} . MBD3 contains a glutamic acid (E) repeat region near the C terminus
MTA1, MTA2 and MTA3		MTA1, MTA2 and MTA3 share four highly conserved functional domains: BAH domain, ELM domain, SANT domain and a zinc finger DNA-binding domain. The BAH domain is thought to be involved in protein–protein interaction ¹⁰⁵ and the SANT domain seems to contribute to MTA2–HDAC1 interactions ¹⁰⁶ . The zinc finger domain is necessary for interaction with transcription factors or transcriptional co-regulators such as FOG2 (REF. 107). The function of the ELM domain remains undefined
GATAD2A and GATAD2B		GATAD2A and GATAD2B contain two conserved regions. The amino-terminal conserved region directly interacts with MBD2 or MBD3, and the C-terminal conserved region can interact with histone tails and is important for targeting to specific genomic loci ^{10,13}
RBBP4 and RBBP7		Both RBBP4 and RBBP7 contain six WD40 repeats, which fold into a seven-bladed β -propeller structure and bind to histone H4 (REF. 108)

BAH, bromo-adjacent homology; CHD, chromodomain-helicase-DNA-binding protein; ELM, Egl27/MTA1; FOG2, friend of GATA2; HDAC, histone deacetylase; MBD, methyl-CpG-binding domain; MTA, metastasis-associated gene; NuRD, nucleosome remodelling and histone deacetylase; RBBP, retinoblastoma-binding protein; SANT, SW13, ADA2, N-CoR and TFII B; TRD, transcriptional repression domain; ZnF, zinc finger.

gene family with ER^{41–45}. Removal of oestrogen leads to the loss of MTA3 expression, and MTA3 expression positively correlates with ER expression in human primary breast tumours⁴¹. An MTA3-containing NuRD complex has been shown to repress transcription of *SNAIL*, a crucial transcription factor that promotes EMT⁴¹. MTA1 and MTA3 exhibit opposing patterns during tumour progression in a transgenic mouse strain that develops spontaneous breast cancer⁴⁶. MTA3 is highly expressed in epithelial cells in normal ducts, and its expression decreases in the early stages of tumorigenesis and becomes silenced in late-stage invasive carcinoma. By contrast, MTA1 expression progressively increases during breast cancer progression. This opposing pattern of MTA1 and MTA3 expression is in agreement with the molecular connection between MTA1, ER and MTA3, and further supports the model that different MTA family members promote target specificity of the NuRD complex. The biology of the MTA family in breast cancer typifies the current characterization of NuRD complex — the combinatorial assembly of subunits underlies seemingly contradictory biological outcomes. In this sense, the NuRD complex and its roles in cancer are considerably different from those that have been documented for other chromatin remodellers, such as SWI/SNF and Polycomb^{47,48}.

Recruitment of the complex by oncogenes and tumour suppressors. Multiple lines of evidence converge on the conclusion that the NuRD complex associates

with oncogenic transcription factors to promote the transcriptional repression of downstream targets (FIG. 1). Several examples of this mechanism have been observed in different types of malignancies. In B cell lymphomas of germinal centre or post-germinal centre origin, such as DLBCL, the increased expression of MTA3 is commonly observed⁴⁹. As mentioned above, MTA3 can directly interact with BCL-6 (REF. 15), a transcriptional repressor and oncogene that has a causal role in a substantial proportion of DLBCLs⁵⁰. In this system, MTA3 is required for the BCL-6-dependent repression of the transcriptional programme that is associated with plasma cell differentiation¹⁵.

In three cases of aggressive B cell chronic lymphocytic leukaemia, chromosomal translocations involving the immunoglobulin heavy chain locus resulted in the deregulated expression of BCL11A, a Krüppel-like zinc-finger transcriptional repressor⁵¹. As MTA proteins within the NuRD complex directly interact with a closely related protein BCL11B in T cell leukaemia and lymphoma cell lines^{32,33}, it is likely that BCL11A also recruits the NuRD complex to promote B cell-lineage lymphoid malignancies. BCL11A and BCL11B are transcriptional repressors, and knockout mice have indicated that BCL11A and BCL11B are indispensable for early B cell and T cell development, respectively, affecting differentiation, as well as cell survival programmes, in these cells^{52,53}.

TWIST, a basic helix–loop–helix transcription factor, can function as a master regulator of cancer metastasis and EMT in a similar manner to that of SNAIL⁵⁴. Increased expression of TWIST is observed in several types of cancer, including breast, gastric, hepatocellular, prostate, uterine and bladder cancers, and correlates with a poor prognosis⁵⁵. In breast cancer cells, an MTA2-containing NuRD complex was found to associate with TWIST⁵⁶. In this case, TWIST recruits the NuRD complex to the promoter of a target gene, *CDH1* (which encodes E-cadherin), to mediate transcriptional repression and to promote EMT. This finding suggests that the NuRD complex is integral to the prevention⁴¹ and the promotion⁵⁶ of EMT, depending on the cellular context.

The chimeric protein promyelocytic leukaemia (PML)–retinoic acid receptor- α (RAR α), a well-characterized oncogenic transcription factor resulting from a chromosomal translocation in human acute promyelocytic leukemias, also recruits the NuRD complex through direct protein interaction⁵⁷. PML–RAR α recruits NuRD to target genes that include the tumour suppressor retinoic acid receptor β 2 (RAR β 2). The NuRD complex in turn facilitates the recruitment of other epigenetic modifiers, including the Polycomb complex and DNA methyltransferases, to establish the repressive histone methylation mark (H3K27) and DNA methylation and to promote gene-silencing events that result in the blockade of cellular differentiation⁵⁷.

In addition to the association with oncoproteins by the MTA subunits, other components of the NuRD complex can also directly interact with transcription factors. For example, NAB2, a co-repressor of the early growth response (EGR) family of transcriptional transactivators, preferentially binds the carboxy-terminal domain of either CHD3 or CHD4 to co-repress EGR activities that are involved in the progression of prostate cancer⁵⁸. The functions of EGR1 are broad in that it regulates cell growth, differentiation and apoptotic programmes⁵⁹. In prostate cancer, EGR1 targets include insulin-like growth factor 2 (*IGF2*), transforming growth factor β 1 (*TGF β 1*) and platelet-derived growth factor- α (*PDGFA*), which have been implicated in tumour progression⁵⁹. Accordingly, increased EGR1 and reduced levels of NAB2 are frequently observed in prostate cancer⁶⁰.

As mentioned above, the MBD3 subunit can directly interact with JUN¹⁹, which has an important role in regulating intestinal homeostasis and tumorigenesis⁶¹. An MBD3-containing NuRD complex preferentially interacts with an unphosphorylated form of JUN to repress its transcriptional activity. On exposure to extracellular stimuli, such as growth factors and cytokines, JUN is phosphorylated by JUN N-terminal kinase, making its interaction with MBD3 inefficient and relieving the transcriptional repression by the NuRD complex. Inactivation of the *Mbd3* gene in the intestinal crypts of mice leads to increased expression of JUN target genes, resulting in colonic hyperproliferation and increased susceptibility to tumour development¹⁹. These examples indicate that the NuRD complex has a dual role in

promoting, as well as suppressing, tumorigenesis; which of these prevails is probably dependent on cell type, as well as the subunit composition of the complex.

Other examples of the NuRD complex associating with proteins that act as tumour suppressors have also been shown in breast cancer cells. ZIP, a zinc finger and G-patch domain-containing protein, acts as a transcriptional repressor of genes that are involved in cell proliferation, survival and migration⁶². Loss of ZIP results in aggressive tumour growth *in vivo* in mouse xenografts. Like NAB2, ZIP also exclusively interacts with the CHD3 and CHD4 subunits of the NuRD complex.

LSD1 may also associate with the NuRD complex through the MTA subunit in breast cancer cells and was found to repress the transcription of genes that are active in pathways such as TGF β , focal adhesion and MAPK⁷. These pathways are involved in cell migration, invasion and EMT in cancer cells. At the *TGF β 1* promoter, only an MTA3-containing form of the NuRD complex was found to be associated with LSD1 (REF. 7). Depletion of LSD1 led to the upregulation of TGF β 1 expression and increased invasiveness *in vitro* and metastatic potential *in vivo*⁷. These initial results further support the unique role of MTA3 as a tumour suppressor in breast cancer.

It is somewhat surprising that the pattern of association of different proteins with particular subunits that has emerged from the many studies reported to date lacks any unifying features. Most individual subunits of the complex have been reported as key interaction proteins in one system or another, and in many cases different transcription factors are implicated in binding to different regions of individual subunits. This lack of clarity points to a compelling need for additional biochemistry and structural biology findings to ascertain the available protein interaction surfaces within a given NuRD complex and how they are used by transcription factors in diverse biological contexts to elicit a specific biological outcome.

Protein modification and the NuRD complex. Tumour hypoxia, an environmental cue that is known to promote angiogenesis, has also been shown to induce MTA1 expression in breast cancer cells⁶³. MTA1 recruits HDAC1 to deacetylate hypoxia-inducible factor 1 α (HIF1 α), the master regulator of the hypoxia transcriptional programme⁶³ (FIG. 1). The deacetylated form of HIF1 α is stabilized and protected from rapid turnover, thus enhancing the transcriptional activation of downstream targets, including those involved in angiogenesis and cancer metastasis. Similarly, an MTA1- or MTA2-containing NuRD complex can promote the deacetylation of p53 to block p53-dependent transcriptional activation, and can inhibit its function in mediating growth arrest and apoptosis^{64,65} (FIG. 1). Inactivation of p53 by the NuRD complex probably represents another mechanism that facilitates tumour growth and progression.

Subunits of the NuRD complex are also subject to post-translational modification that alters their function. Several recent reports substantiate a role for MTA1 acetylation in gene activation. For example, MTA1 is a transcriptional activator of breast carcinoma-amplified sequence 3 (*BCAS3*), a gene that is overexpressed in

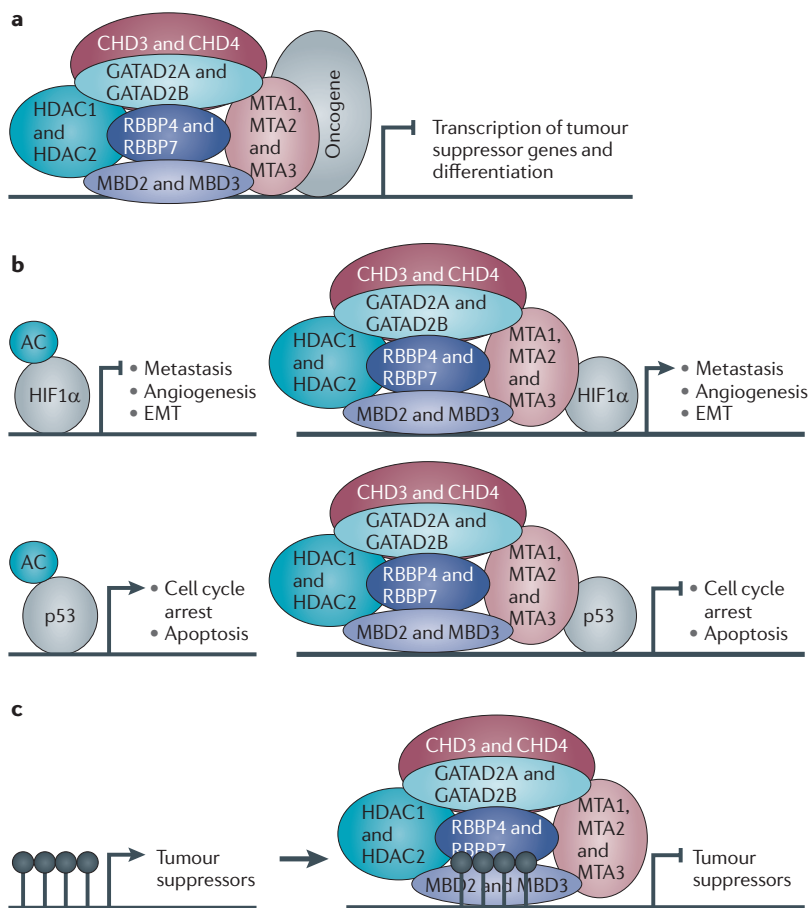


Figure 1 | Mechanisms by which the NuRD complex interacts with different factors to promote cancer development. **a** | The recruitment of the nucleosome remodelling and histone deacetylase (NuRD) complex by a tissue-specific transcription factor to gene promoters to mediate transcriptional repression is shown. Several known oncogenes have been shown to recruit the NuRD complex to suppress the transcription of tumour suppressor genes. **b** | Post-translational modification of a transcription factor by the NuRD complex to modulate downstream transcriptional activities is shown. In hypoxic breast cancer cells, metastasis-associated gene 1 (MTA1) recruits histone deacetylase 1 (HDAC1) to promote the deacetylation of hypoxia-inducible factor 1α (HIF1α), leading to the stabilization of HIF1α and its transcriptional programme⁶³. Conversely, deacetylation of p53 by the NuRD complex results in the inactivation of p53, rendering cells resistant to cell growth arrest and apoptosis^{64,65}. **c** | A methyl-CpG-binding domain 2 (MBD2)-containing NuRD complex targeting hypermethylated promoters (shown by grey lollipops) of tumour suppressor genes to mediate transcriptional silencing is shown^{75–77}. AC, acetylation; CHD, chromodomain-helicase-DNA-binding protein; EMT, epithelial-to-mesenchymal transition.

breast cancer and implicated in enhancing anchorage-independent growth⁶⁶. Only lysine 626-acetylated MTA1 in association with ERα at an intronic enhancer is able to efficiently recruit RNA polymerase II (Pol II) to promote *BCAS3* transcription⁶⁶. In breast cancer cells, only an acetylated form of MTA1 was found to repress *Gai2* transcription, leading to the activation of the RAS–RAF pathway, and only this form was able to transform Rat1 fibroblasts⁶⁷. An acetylated form of MTA1 is also implicated in DLBCL in mice. MTA1 occupies the promoter and an enhancer region in the seventh intron of the *Pax5* gene⁶⁸, a B cell-specific transcription factor. Only acetylated MTA1 efficiently recruits Pol II to the *Pax5*

promoter⁶⁸. Other NuRD complex subunits have also been shown to have post-translational modifications, such as phosphorylation and acetylation^{69–71}. However, functional roles for these modifications have not yet been determined. Regardless, studies of the acetylated form of MTA1 have provided evidence that the NuRD complex can act as a direct transcriptional activator, as well as a transcriptional repressor. Post-translational modifications on NuRD complex subunits probably represent another level through which the biological functions of this complex are regulated.

The recruitment of MBD2 to hypermethylated gene promoters to mediate gene silencing. An aberrant DNA methylation pattern is frequently observed in cancer. Cancer cells often exhibit genome-wide hypomethylation, which is thought to contribute to genome instability⁷². By contrast, promoter CpG islands are frequently hypermethylated in cancer, and are strongly associated with transcriptional silencing⁷³. Promoter hypermethylation is a widespread mechanism in promoting the transcriptional repression of tumour suppressor genes, including *INK4A*, *RB1* and *BRCA1* (REF. 74). In addition to preventing the binding of transcription activators, methylated CpGs can also recruit MBD family proteins and their associated chromatin remodelling enzymes to form repressive chromatin to ensure gene silencing⁷⁵ (FIG. 1). MBD2 has been shown to associate with several hypermethylated promoters in cancer cells, including the *CDKN2A* locus (which encodes *INK4A* and *ARF*) in colon cancer^{76,77}. Although it remains unclear whether MBD2 specifically recruits other NuRD complex subunits to these gene loci, the treatment of colon cancer cells with the HDAC inhibitor trichostatin A resulted in greater expression of *ARF* and *INK4A* than treatment with a DNA methyltransferase inhibitor 5-Aza-cytidine⁷⁷. These data suggest that cooperative actions between MBD2 and HDAC occur at hypermethylated gene loci, which supports an active role for the NuRD complex in gene silencing. Consistent with these observations, *Mbd2* deficiency in tumour-prone *Apc^{min/+}* mice suppresses intestinal tumorigenesis⁷⁸. It remains to be determined to what extent the MBD2-containing NuRD complex promotes gene silencing at hypermethylated promoters in cancer.

Non-transcriptional roles: genome stability

In addition to transcriptional regulation, emerging data indicate that the NuRD complex also has important roles in other processes that ensure proper DNA replication, cellular proliferation and protection of genome integrity^{69,79–82}. Strict regulation of these processes is crucial for protecting cells from malignant transformation. Rapidly proliferating lymphocytes uniquely accumulate a high local concentration of the NuRD complex, or NuRD foci, at pericentromeric heterochromatin on chromosomes 1, 9 and 16 during the S phase of the cell cycle⁷⁹. These NuRD foci colocalize with proteins that are present at active replication forks, such as proliferating cell nuclear antigen (PCNA) and chromatin assembly protein CAF1, suggesting a role for the NuRD complex in regulating DNA replication and/or subsequent chromatin assembly

at these chromosomal regions (FIG. 2). Interestingly, the Polycomb core complex PRC1, which localizes to pericentromeric heterochromatin in many cell types, is absent in lymphocytes containing NuRD foci, suggesting a unique role of the NuRD complex during lymphocyte proliferation. Coincidentally, cells derived from patients with immunodeficiency, centromeric instability and facial anomalies (ICF) syndrome, owing to a loss-of-function mutation in DNA methyltransferase 3B, have aberrant hypomethylated pericentromeric heterochromatin^{83,84}. However, B lymphocytes from these patients preferentially exhibit chromosomal instability, resulting in defective differentiation⁸⁵. It is plausible that an MBD2-containing NuRD complex targets the densely methylated regions at pericentromeric heterochromatin in lymphocytes to ensure proper chromatin assembly during cellular proliferation. Whether a similar mechanism is used by rapidly dividing tumour cells is unknown.

In addition to its involvement in chromatin assembly, the NuRD complex also regulates the G1/S cell cycle transition⁶⁹. The manipulation of the NuRD subunits CHD4 (REFS 69,81,86) and MTA2 (REF. 81) by RNA interference, or the manipulation of MTA1 by genetic means⁸⁷, can lead to a blockade at the G1/S phase transition and the accumulation of a p53 downstream effector, p21. In U2OS cells, the absence of the NuRD complex prevented deacetylation of p53. The accumulation of stabilized p53 protein resulted in increased expression of p21, leading to cell cycle arrest⁶⁹. By contrast, in mouse embryonic fibroblasts, the genetic depletion of *Mta1* led to a destabilization of p53. Nonetheless, p21 levels were also increased. Subsequent investigation revealed that, in the mouse embryonic fibroblasts and in mouse tissue, MTA1 and the NuRD complex directly regulate p21 levels via a p53-independent mechanism⁸⁵ (FIG. 2). It is currently unclear why these two studies, which describe a similar biological outcome, do so through different mechanisms. Further experimentation will be required to resolve these mechanistic discrepancies. Despite this, these analyses collectively indicate that the NuRD complex can have multiple roles at different stages of the cell cycle to regulate cell proliferation, and some functions seem to be cell type-specific events.

In the past year, several groups have also reported a novel function of the NuRD complex in regulating DNA damage responses, a role that had previously been ascribed to MTA1 (REF. 88). A genome-wide RNA interference screen in *Caenorhabditis elegans* identified *egr-1* (also known as *lin-40*), a homologue of the MTA genes, as a factor that protects against DNA damage that is induced by ionizing radiation⁸¹. Ionizing radiation results in chromosomal double-strand breaks (DSBs), and adequate DNA repair mechanisms are necessary to prevent apoptosis or aberrant transformation. The NuRD complex is rapidly recruited to sites of DSBs^{69,80,81,86}, and this is dependent on the activity of the poly(ADP ribose) polymerase (PARP), which incorporates poly(ADP ribose) (PAR) chains at sites of DNA damage^{69,80} (FIG. 2). The presence of PAR chains recruits several DNA repair proteins, as well as the NuRD complex. CHD4 was found to contain PAR-binding motifs in its amino-terminal region⁶⁹.

The depletion of CHD4 results in hypersensitivity to DNA damage resulting from ionizing radiation exposure, and the accumulation of unrepaired breaks at sites of DNA damage^{69,80,81}. Loss of CHD4 also results in CDC25A degradation and p21 accumulation, leading to cell cycle delay⁸⁶. CHD4- or MTA2-depleted cells failed to fully activate the G2/M checkpoint, owing to the inability of cells to activate the RNF8–RNF168-mediated histone ubiquitylation pathway, which is required for the accumulation of checkpoint and repair proteins, including BRCA1 (REFS 81,86). In addition to promoting DNA repair, there is also evidence that the presence of the NuRD complex at sites of DNA damage suppresses transcription⁸⁰. At sites of DNA damage, there is a rapid loss of nascent RNA and elongating RNA polymerase, which was not the case in CHD4- or MTA1-depleted cells⁸⁰. Collectively, these results suggest that the NuRD complex has a crucial role in the DNA damage response by both recruiting DNA repair proteins and promoting transcriptional repression, in order to facilitate the repair process. It is interesting that the NuRD complex has been implicated as an active regulator of both the G1/S and the G2/M progression checkpoints. These observations highlight the multiple roles of NuRD in chromosomal biology. During progression through the G1/S boundary, a defect in NuRD seems to result in deregulated transcription. During G2/M progression, disruption of NuRD results in a defect in histone modification that affects checkpoint control.

Targeting of NuRD subunits for cancer therapy?

Recent progress in understanding the function of NuRD subunits and their specificity in different types of cancer, as discussed above, should set the path for designing effective cancer therapeutic agents that target this complex. However, as the NuRD complex has roles in both promoting and suppressing tumour growth, even within the same tumour type, more knowledge of the fundamental biology downstream of NuRD will be required. Given the current state of the field, MTA1 would seem to be a prime therapeutic target. It is widely overexpressed in many types of cancer and is downstream of important pathways, such as MYC, in the transformation process^{38,39}.

The NuRD complex contains histone deacetylase subunits, so HDAC inhibitors may represent one potential therapeutic avenue for targeting NuRD function. A recent study showed that HDAC inhibitors have selective preference for different types of HDAC complexes⁸⁹, suggesting that targeting specific HDAC complexes may be feasible with enzyme inhibitors. However, it remains unclear whether one could selectively target tumour-promoting activities while sparing tumour-suppressive functions with this class of drugs.

As the NuRD complex frequently associates with tissue-specific transcription factors to regulate transcription, drugs modulating the activity or the interactions of these proteins may represent a more selective approach to inhibiting undesirable NuRD functions in cancer cells. Emerging evidence points to the possibility that post-translational modifications of NuRD subunits can modulate their function within the complex, potentially offering additional drug targets.

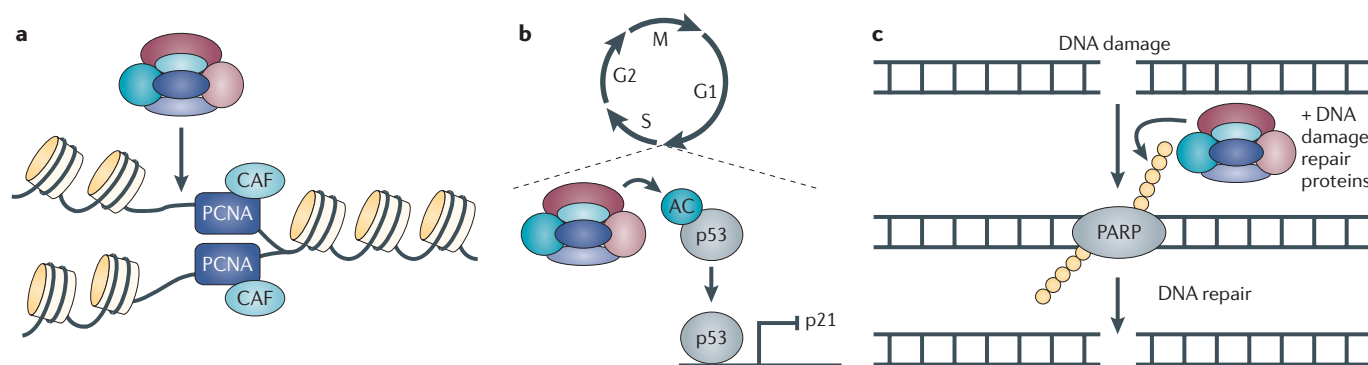


Figure 2 | **Non-transcriptional mechanisms by which the NuRD complex maintains genome stability.**

a | Colocalization of the nucleosome remodelling and histone deacetylase (NuRD) complex with DNA replication machinery such as CAF1 and proliferating cell nuclear antigen (PCNA) during the S phase of the cell cycle suggests a role of the complex in chromatin assembly during and/or after DNA replication⁷⁹. **b** | The NuRD complex promotes G1/S phase transition during cell cycle progression by promoting the deacetylation of p53. Loss of p53 function results in the inactivation of p21 to allow cell cycle progression⁶⁹. **c** | The recruitment of the NuRD complex to sites of DNA damage to facilitate the DNA repair process is shown. At sites of double-stranded breaks, poly(ADP ribose) polymerase (PARP) incorporates poly(ADP ribose) chains that can recruit the NuRD complex in addition to other DNA repair proteins to facilitate the repair process^{69,80}. AC, acetylation.

Conclusions and future directions

When the NuRD complex was first characterized, its subunit composition suggested a role in transcriptional repression. Although many examples of transcriptional repression have been demonstrated, it is now clear that the NuRD complex is multifunctional and participates in many aspects of chromosomal biology, including transcriptional activation, protein modification, DNA repair and DNA replication. In the context of cancer, the NuRD complex has roles in both promoting and suppressing tumorigenesis. As the interaction with other proteins represents a major mechanism of its functional specificity, how the NuRD complex might contribute to cancer development is dependent on cell type. The microenvironment and the transcriptional programme of each cell type will dictate the subunit composition of the NuRD complex and its interaction partners.

Given the broad role of the NuRD complex in cancer biology, it is surprising that the expression of the MTA1 subunit has only been shown to be deregulated during tumour progression in various types of cancer. Other chromatin modification complexes, such as the SWI/SNF complex and Polycomb repressive complexes, also have well-established roles in cancer^{47,48}. Several subunits of the SWI/SNF complex function as tumour suppressors, and loss-of-function mutations in these subunits have been found in various human cancers. By contrast, the Polycomb proteins have important roles in maintaining cancer stem cell populations, and cancer cells often have increased expression of Polycomb proteins. Similarly, mixed lineage leukaemia (MLL), a histone 3 lysine 4 methyltransferase that functions in a large nuclear complex, is frequently involved in chromosomal translocations in various haematopoietic malignancies⁹⁰. MLL fusions have also been found to impart leukaemic stem cell properties⁹⁰. As mentioned above, the NuRD complex has important roles in the maintenance and function of haematopoietic stem cells^{25,26}, so one can

speculate that it may also participate in regulating the transcriptional programme in leukaemic cells or other types of cancer stem cells.

As the NuRD complex is an integral component of the DNA repair machinery, one might anticipate the loss of NuRD complex function, particularly in tumour types that are characterized by chromosomal instability. Furthermore, ageing cells have loss of expression of CHD subunits⁹¹, which could contribute to genome instability and cancer susceptibility during cellular ageing. Indeed, loss of CHD4 expression has been observed in gastric and colorectal cancer cases with microsatellite instability⁹², supporting the role of the NuRD complex in the maintenance of genome integrity in these regions. However, loss-of-function mutations of the NuRD complex subunits have only been infrequently observed in cancer in limited studies^{92–95}. For example, a truncating mutation of HDAC2 has also been documented in sporadic carcinomas with microsatellite instability⁹⁵, although it is not clear whether the loss of HDAC2 function in these cases is in the context of the NuRD complex or other HDAC-containing nuclear complexes. Ongoing cancer genome-sequencing projects should provide insights into the prevalence of NuRD mutations in different types of cancer and reveal patterns of association of loss of function of specific subunits with unique aspects of tumour biology that are similar to those observed in other chromatin remodelling complexes.

Although mutations have not been observed in NuRD subunits with high frequency in cancer, it is possible that subunit composition of the NuRD complex is perturbed by signalling cascades in cancer cells without disrupting the expression level of individual subunits, leading to loss of function or aberrant genomic targeting of the complex. Recent reports showing the importance of acetylation of MTA1 in facilitating its interaction with oncogenic transcriptional complexes suggest that post-translational

modification on NuRD complex subunits may be crucial in determining its function. High-throughput screens of compounds with biological activity in tumour cells may lead to new insights into the contributions of the NuRD complex to tumorigenesis, as well as provide new therapeutic avenues. Furthermore, although the core composition of the NuRD complex is well characterized, only a handful of tissue-specific

transcription factors associating with the complex have been characterized. The identification of binding partners of different variant forms of the NuRD complex and the determination of genomic localization in both normal and abnormal tissue, a goal of current genome association studies, will facilitate the generation of models relating the biological functions of the NuRD complex to cancer.

1. Clapier, C. R. & Cairns, B. R. The biology of chromatin remodeling complexes. *Annu. Rev. Biochem.* **78**, 273–304 (2009).
2. Denslow, S. A. & Wade, P. A. The human Mi-2/NuRD complex and gene regulation. *Oncogene* **26**, 5433–5438 (2007).
3. Tong, J. K., Hassig, C. A., Schnitzler, G. R., Kingston, R. E. & Schreiber, S. L. Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. *Nature* **395**, 917–921 (1998).
4. Wade, P. A., Jones, P. L., Vermaak, D. & Wolffe, A. P. A multiple subunit Mi-2 histone deacetylase from *Xenopus laevis* cofractionates with an associated Snf2 superfamily ATPase. *Curr. Biol.* **8**, 843–846 (1998).
5. Xue, Y. *et al.* NuRD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. *Mol. Cell* **2**, 851–861 (1998).
6. Zhang, Y., LeRoy, G., Seelig, H. P., Lane, W. S. & Reinberg, D. The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities. *Cell* **95**, 279–289 (1998).
7. Wang, Y. *et al.* LSD1 is a subunit of the NuRD complex and targets the metastasis programs in breast cancer. *Cell* **138**, 660–672 (2009).
8. Wade, P. A. *et al.* Mi-2 complex couples DNA methylation to chromatin remodelling and histone deacetylation. *Nature Genet.* **23**, 62–66 (1999).
9. Brackertz, M., Boeke, J., Zhang, R. & Renkawitz, R. Two highly related p66 proteins comprise a new family of potent transcriptional repressors interacting with MBD2 and MBD3. *J. Biol. Chem.* **277**, 40958–40966 (2002).
10. Feng, Q. *et al.* Identification and functional characterization of the p66/p68 components of the MeCP1 complex. *Mol. Cell. Biol.* **22**, 536–546 (2002).
11. Marhold, J., Brehm, A. & Kramer, K. The *Drosophila* methyl-DNA binding protein MBD2/3 interacts with the NuRD complex via p55 and Mi-2. *BMC Mol. Biol.* **5**, 20 (2004).
12. Loyola, A. & Almouzni, G. Histone chaperones, a supporting role in the limelight. *Biochim. Biophys. Acta* **1677**, 3–11 (2004).
13. Brackertz, M., Gong, Z., Leers, J. & Renkawitz, R. p66a and p66b of the Mi-2/NuRD complex mediate MBD2 and histone interaction. *Nucleic Acids Res.* **34**, 397–406 (2006).
14. Hendrich, B. & Bird, A. Identification and characterization of a family of mammalian methyl-CpG binding proteins. *Mol. Cell. Biol.* **18**, 6538–6547 (1998).
15. Fujita, N. *et al.* MTA3 and the Mi-2/NuRD complex regulate cell fate during B lymphocyte differentiation. *Cell* **119**, 75–86 (2004).
This study is the first to demonstrate the association of the MTA subunit to a tissue-specific transcription factor for mediating transcriptional repression.
16. Le Guezennec, X. *et al.* MBD2/NuRD and MBD3/NuRD, two distinct complexes with different biochemical and functional properties. *Mol. Cell. Biol.* **26**, 843–851 (2006).
This study demonstrates that MBD2 and MBD3 form mutually exclusive NuRD complexes.
17. Saito, M. & Ishikawa, F. The mCpG-binding domain of human MBD3 does not bind to mCpG but interacts with NuRD/Mi2 components HDAC1 and MTA2. *J. Biol. Chem.* **277**, 35434–35439 (2002).
18. Hendrich, B. & Tweedie, S. The methyl-CpG binding domain and the evolving role of DNA methylation in animals. *Trends Genet.* **19**, 269–277 (2003).
19. Aguilera, C. *et al.* c-Jun N-terminal phosphorylation antagonises recruitment of the Mbd3/NuRD repressor complex. *Nature* **469**, 231–235 (2011).
This study demonstrates the protein–protein interaction property of the MBD domain within MBD3.
20. Hendrich, B., Guy, J., Ramsahoye, B., Wilson, V. A. & Bird, A. Closely related proteins MBD2 and MBD3 play distinctive but interacting roles in mouse development. *Genes Dev.* **15**, 710–723 (2001).
21. Yang, X. J. & Seto, E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. *Nature Rev. Mol. Cell Biol.* **9**, 206–218 (2008).
22. You, A., Tong, J. K., Grozinger, C. M. & Schreiber, S. L. CoREST is an integral component of the CoREST-human histone deacetylase complex. *Proc. Natl Acad. Sci. USA* **98**, 1454–1458 (2001).
23. Zhang, Y., Iatni, R., Erdjument-Bromage, H., Tempst, P. & Reinberg, D. Histone deacetylases and SAP18, a novel polypeptide, are components of a human Sin3 complex. *Cell* **89**, 357–364 (1997).
24. Ramirez, J. & Hagman, J. The Mi-2/NuRD complex: a critical epigenetic regulator of hematopoietic development, differentiation and cancer. *Epigenetics* **4**, 532–536 (2009).
25. Yoshida, T. *et al.* The role of the chromatin remodeler Mi-2p in hematopoietic stem cell self-renewal and multilineage differentiation. *Genes Dev.* **22**, 1174–1189 (2008).
This study investigated the function of the NuRD complex in haematopoietic stem cells using CHD4-conditional knockout mice.
26. Li, X., Jia, S., Wang, S., Wang, Y. & Meng, A. Mta3-NuRD complex is a master regulator for initiation of primitive hematopoiesis in vertebrate embryos. *Blood* **114**, 5464–5472 (2009).
27. Gao, H. *et al.* Opposing effects of SWI/SNF and Mi-2/NuRD chromatin remodeling complexes on epigenetic reprogramming by EBF and Pax5. *Proc. Natl Acad. Sci. USA* **106**, 11258–11263 (2009).
28. Williams, C. J. *et al.* The chromatin remodeler Mi-2p is required for CD4 expression and T cell development. *Immunity* **20**, 719–733 (2004).
29. Naito, T., Gomez-Del Arco, P., Williams, C. J. & Georgopoulos, K. Antagonistic interactions between Ikaros and the chromatin remodeler Mi-2p determine silencer activity and Cd4 gene expression. *Immunity* **27**, 723–734 (2007).
30. Hong, W. *et al.* FOG-1 recruits the NuRD repressor complex to mediate transcriptional repression by GATA-1. *EMBO J.* **24**, 2367–2378 (2005).
31. Gao, Z. *et al.* FOG-1-mediated recruitment of NuRD is required for cell lineage re-enforcement during haematopoiesis. *EMBO J.* **29**, 457–468 (2010).
32. Cismasiu, V. B. *et al.* BCL11B functionally associates with the NuRD complex in T lymphocytes to repress targeted promoter. *Oncogene* **24**, 6753–6764 (2005).
33. Grabarczyk, P. *et al.* Inhibition of BCL11B expression leads to apoptosis of malignant but not normal mature T cells. *Oncogene* **26**, 3797–3810 (2007).
34. Cobb, B. S. *et al.* Targeting of Ikaros to pericentromeric heterochromatin by direct DNA binding. *Genes Dev.* **14**, 2146–2160 (2000).
35. Kaji, K. *et al.* The NuRD component Mbd3 is required for pluripotency of embryonic stem cells. *Nature Cell Biol.* **8**, 285–292 (2006).
36. Zhu, D., Fang, J., Li, Y. & Zhang, J. Mbd3, a component of NuRD/Mi-2 complex, helps maintain pluripotency of mouse embryonic stem cells by repressing trophectoderm differentiation. *PLoS ONE* **4**, e7684 (2009).
37. Pencil, S. D., Toh, Y. & Nicolson, G. L. Candidate metastasis-associated genes of the rat 13762NF mammary adenocarcinoma. *Breast Cancer Res. Treat.* **25**, 13165–13174 (1993).
38. Nicolson, G. L. *et al.* Tumor metastasis-associated human MTA1 gene and its MTA1 protein product: role in epithelial cancer cell invasion, proliferation and nuclear regulation. *Clin. Exp. Metastasis* **20**, 19–24 (2003).
39. Zhang, X. Y. *et al.* Metastasis-associated protein 1 (MTA1) is an essential downstream effector of the c-MYC oncoprotein. *Proc. Natl Acad. Sci. USA* **102**, 13968–13973 (2005).
40. Toh, Y. & Nicolson, G. L. The role of the MTA family and their encoded proteins in human cancers: molecular functions and clinical implications. *Clin. Exp. Metastasis* **26**, 215–227 (2009).
41. Fujita, N. *et al.* MTA3, a Mi-2/NuRD complex subunit, regulates an invasive growth pathway in breast cancer. *Cell* **113**, 207–219 (2003).
This paper demonstrates that MTA family members form distinct NuRD complexes.
42. Kalluri, R. & Weinberg, R. A. The basics of epithelial-mesenchymal transition. *J. Clin. Invest.* **119**, 1420–1428 (2009).
43. Mazumdar, A. *et al.* Transcriptional repression of oestrogen receptor by metastasis-associated protein 1 corepressor. *Nature Cell Biol.* **3**, 50–57 (2001).
This paper shows that MTA1 expression can be upregulated by the heregulin–ERBB2 pathway in breast cancer cells and represses ER activity.
44. Molli, P. R., Singh, R. R., Lee, S. W. & Kumar, R. MTA1-mediated transcriptional repression of BRCA1 tumor suppressor gene. *Oncogene* **27**, 1971–1980 (2008).
45. Kumar, R. Another tie that binds the MTA family to breast cancer. *Cell* **113**, 142–143 (2003).
46. Zhang, H., Stephens, L. C. & Kumar, R. Metastasis tumor antigen family proteins during breast cancer progression and metastasis in a reliable mouse model for human breast cancer. *Clin. Cancer Res.* **12**, 1479–1486 (2006).
This paper demonstrates the opposing expression pattern of MTA1 and MTA3 during breast cancer progression.
47. Reisman, D., Glaros, S. & Thompson, E. A. The SWI/SNF complex and cancer. *Oncogene* **28**, 1653–1668 (2009).
48. Bracken, A. P. & Helin, K. Polycomb group proteins: navigators of lineage pathways led astray in cancer. *Nature Rev. Cancer* **9**, 773–784 (2009).
49. Jaye, D. L. *et al.* The BCL6-associated transcriptional co-repressor, MTA3, is selectively expressed by germinal centre B cells and lymphomas of putative germinal centre derivation. *J. Pathol.* **213**, 106–115 (2007).
50. Kusam, S. & Dent, A. Common mechanisms for the regulation of B cell differentiation and transformation by the transcriptional repressor protein BCL-6. *Immunol. Res.* **37**, 177–186 (2007).
51. Satterwhite, E. *et al.* The BCL11 gene family: involvement of BCL11A in lymphoid malignancies. *Blood* **98**, 3413–3420 (2001).
52. Liu, P. *et al.* Bcl11a is essential for normal lymphoid development. *Nature Immunol.* **4**, 525–532 (2003).
53. Wakabayashi, Y. *et al.* Bcl11b is required for differentiation and survival of $\alpha\beta$ T lymphocytes. *Nature Immunol.* **4**, 533–539 (2003).
54. Yang, J. *et al.* Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. *Cell* **117**, 927–939 (2004).
55. Peinado, H., Olmeda, D. & Cano, A. Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype? *Nature Rev. Cancer* **7**, 415–428 (2007).
56. Fu, J. *et al.* The TWIST/Mi2/NuRD protein complex and its essential role in cancer metastasis. *Cell Res.* **21**, 275–289 (2011).
57. Morey, L. *et al.* MBD3, a component of the NuRD complex, facilitates chromatin alteration and deposition of epigenetic marks. *Mol. Cell. Biol.* **28**, 5912–5923 (2008).

58. Srinivasan, R., Mager, G. M., Ward, R. M., Mayer, J. & Svaren, J. NAB2 represses transcription by interacting with the CHD4 subunit of the nucleosome remodeling and deacetylase (NuRD) complex. *J. Biol. Chem.* **281**, 15129–15137 (2006).
59. Adamson, E. D. & Mercola, D. Egr1 transcription factor: multiple roles in prostate tumor cell growth and survival. *Tumour Biol.* **23**, 93–102 (2002).
60. Abdulkadir, S. A. et al. Frequent and early loss of the EGR1 corepressor NAB2 in human prostate carcinoma. *Hum. Pathol.* **32**, 935–939 (2001).
61. Sancho, R. et al. JNK signalling modulates intestinal homeostasis and tumorigenesis in mice. *EMBO J.* **28**, 1843–1854 (2009).
62. Li, R. et al. ZIP: a novel transcription repressor, represses EGFR oncogene and suppresses breast carcinogenesis. *EMBO J.* **28**, 2763–2776 (2009).
63. Yoo, Y. G., Kong, G. & Lee, M. O. Metastasis-associated protein 1 enhances stability of hypoxia-inducible factor-1 α protein by recruiting histone deacetylase 1. *EMBO J.* **25**, 1231–1241 (2006).
64. Luo, J., Su, F., Chen, D., Shiloh, A. & Gu, W. Deacetylation of p53 modulates its effect on cell growth and apoptosis. *Nature* **408**, 377–381 (2000). **This paper was the first to demonstrate that the NuRD complex can regulate tumour suppressors via post-translational modifications.**
65. Moon, H. E., Cheon, H. & Lee, M. S. Metastasis-associated protein 1 inhibits p53-induced apoptosis. *Oncol. Rep.* **18**, 1311–1314 (2007).
66. Gururaj, A. E. et al. MTA1, a transcriptional activator of breast cancer amplified sequence 3. *Proc. Natl Acad. Sci. USA* **103**, 6670–6675 (2006).
67. Ohshiro, K. et al. Acetylation-dependent oncogenic activity of metastasis-associated protein 1 co-regulator. *EMBO Rep.* **11**, 691–697 (2010). **This paper shows that post-translational modification of MTA1 is important for its oncogenic activities.**
68. Balasenthil, S. et al. Identification of Pax5 as a target of MTA1 in B-cell lymphomas. *Cancer Res.* **67**, 7132–7138 (2007).
69. Polo, S. E., Kaidi, A., Baskcomb, L., Galanty, Y. & Jackson, S. P. Regulation of DNA-damage responses and cell-cycle progression by the chromatin remodelling factor CHD4. *EMBO J.* **29**, 3130–3139 (2010). **This paper demonstrates poly(ADP-ribose)-dependent recruitment of the NuRD complex to sites of DNA damage and shows that NuRD has a role in G1/S transition during the cell cycle by modulating p53 function.**
70. Olsen, J. V. et al. Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis. *Sci. Signal* **3**, ra3 (2010).
71. Choudhary, C. et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. *Science* **325**, 834–840 (2009).
72. Howard, G., Eiges, R., Gaudet, F., Jaenisch, R. & Eden, A. Activation and transposition of endogenous retroviral elements in hypomethylation induced tumors in mice. *Oncogene* **27**, 404–408 (2008).
73. Costello, J. F. et al. Aberrant CpG-island methylation has non-random and tumour-type-specific patterns. *Nature Genet.* **24**, 132–138 (2000).
74. McCabe, M. T., Brandes, J. C. & Vertino, P. M. Cancer DNA methylation: molecular mechanisms and clinical implications. *Clin. Cancer Res.* **15**, 3927–3937 (2009).
75. Zhang, Y. et al. Analysis of the NuRD subunits reveals a histone deacetylase core complex and a connection with DNA methylation. *Genes Dev.* **13**, 1924–1935 (1999).
76. Sansom, O. J., Maddison, K. & Clarke, A. R. Mechanisms of disease: methyl-binding domain proteins as potential therapeutic targets in cancer. *Nature Clin. Pract. Oncol.* **4**, 305–315 (2007).
77. Magdinier, F. & Wolffe, A. P. Selective association of the methyl-CpG binding protein MBD2 with the silent p14/p16 locus in human neoplasia. *Proc. Natl Acad. Sci. USA* **98**, 4990–4995 (2001).
78. Sansom, O. J. et al. Deficiency of Mbd2 suppresses intestinal tumorigenesis. *Nature Genet.* **34**, 145–147 (2003).
79. Helbling Chadwick, L., Chadwick, B. P., Jaye, D. L. & Wade, P. A. The Mi-2/NuRD complex associates with pericentromeric heterochromatin during S phase in rapidly proliferating lymphoid cells. *Chromosoma* **118**, 445–457 (2009).
80. Chou, D. M. et al. A chromatin localization screen reveals poly (ADP ribose)-regulated recruitment of the repressive polycomb and NuRD complexes to sites of DNA damage. *Proc. Natl Acad. Sci. USA* **107**, 18475–18480 (2010). **This paper also demonstrates poly(ADP-ribose)-dependent recruitment of NuRD complex to sites of DNA damage. It further suggests a role of the NuRD complex in repressing transcription at sites of DNA damage.**
81. Smeenk, G. et al. The NuRD chromatin-remodeling complex regulates signaling and repair of DNA damage. *J. Cell Biol.* **190**, 741–749 (2010).
82. Brehm, A. et al. The E7 oncoprotein associates with Mi2 and histone deacetylase activity to promote cell growth. *EMBO J.* **18**, 2449–2458 (1999).
83. Xu, G. L. et al. Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene. *Nature* **402**, 187–191 (1999).
84. Hansen, R. S. et al. The DNMT3B DNA methyltransferase gene is mutated in the ICF immunodeficiency syndrome. *Proc. Natl Acad. Sci. USA* **96**, 14412–14417 (1999).
85. Blanco-Betancourt, C. E. et al. Defective B-cell-negative selection and terminal differentiation in the ICF syndrome. *Blood* **103**, 2683–2690 (2004).
86. Larsen, D. H. et al. The chromatin-remodeling factor CHD4 coordinates signaling and repair after DNA damage. *J. Cell Biol.* **190**, 731–740 (2010).
87. Li, D. Q. et al. MTA1 coregulator regulates p53 stability and function. *J. Biol. Chem.* **284**, 34545–34552 (2009).
88. Li, D. Q. et al. E3 ubiquitin ligase COP1 regulates the stability and functions of MTA1. *Proc. Natl Acad. Sci. USA* **106**, 17493–17498 (2009).
89. Bantscheff, M. et al. Chemoproteomics profiling of HDAC inhibitors reveals selective targeting of HDAC complexes. *Nature Biotech.* **29**, 255–265 (2011).
90. Krivtsov, A. V. & Armstrong, S. A. MLL translocations, histone modifications and leukaemia stem-cell development. *Nature Rev. Cancer* **7**, 823–833 (2007).
91. Pegoraro, G. et al. Ageing-related chromatin defects through loss of the NURD complex. *Nature Cell Biol.* **11**, 1261–1267 (2009).
92. Kim, M. S., Chung, N. G., Kang, M. R., Yoo, N. J. & Lee, S. H. Genetic and expression alterations of CHD genes in gastric and colorectal cancers. *Histopathology* **58**, 660–668 (2011).
93. Bader, S. et al. MBD1, MBD2 and CGBP genes at chromosome 18q21 are infrequently mutated in human colon and lung cancers. *Oncogene* **22**, 3506–3510 (2003).
94. Zhu, Y., Harrison, D. J. & Bader, S. A. Genetic and epigenetic analyses of MBD3 in colon and lung cancer. *Br. J. Cancer* **90**, 1972–1975 (2004).
95. Ropero, S. et al. A truncating mutation of HDAC2 in human cancers confers resistance to histone deacetylase inhibition. *Nature Genet.* **38**, 566–569 (2006).
96. Musselman, C. A. et al. Binding of the CHD4 PHD2 finger to histone H3 is modulated by covalent modifications. *Biochem. J.* **423**, 179–187 (2009).
97. Mansfield, R. E. et al. Plant homeodomain (PHD) fingers of CHD4 are histone H3-binding modules with preference for unmodified H3K4 and methylated H3K9. *J. Biol. Chem.* **286**, 11779–11791 (2011).
98. Bouazoune, K. et al. The dMi-2 chromodomains are DNA binding modules important for ATP-dependent nucleosome mobilization. *EMBO J.* **21**, 2430–2440 (2002).
99. Durr, H., Flaus, A., Owen-Hughes, T. & Hopfner, K. P. Snf2 family ATPases and DExx box helicases: differences and unifying concepts from high-resolution crystal structures. *Nucleic Acids Res.* **34**, 4160–4167 (2006).
100. Pazin, M. J. & Kadonaga, J. T. SWI2/SNF2 and related proteins: ATP-driven motors that disrupt protein-DNA interactions? *Cell* **88**, 737–740 (1997).
101. Becker, P. B. & Horz, W. ATP-dependent nucleosome remodeling. *Annu. Rev. Biochem.* **71**, 247–273 (2002).
102. Thiagalingam, S. et al. Histone deacetylases: unique players in shaping the epigenetic histone code. *Ann. N. Y. Acad. Sci.* **983**, 84–100 (2003).
103. Jones, P. L. et al. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. *Nature Genet.* **19**, 187–191 (1998).
104. Nan, X., Campoy, F. J. & Bird, A. MeCP2 is a transcriptional repressor with abundant binding sites in genomic chromatin. *Cell* **88**, 471–481 (1997).
105. Oliver, A. W. et al. Crystal structure of the proximal BAH domain of the polybromo protein. *Biochem. J.* **389**, 657–664 (2005).
106. Humphrey, G. W. et al. Stable histone deacetylase complexes distinguished by the presence of SANT domain proteins CoREST/kiaa0071 and Mta-L1. *J. Biol. Chem.* **276**, 6817–6824 (2001).
107. Roche, A. E. et al. The zinc finger and C-terminal domains of MTA proteins are required for FOG-2-mediated transcriptional repression via the NuRD complex. *J. Mol. Cell. Cardiol.* **44**, 352–360 (2008).
108. Murzina, N. V. et al. Structural basis for the recognition of histone H4 by the histone-chaperone RbAp46. *Structure* **16**, 1077–1085 (2008).

Acknowledgements

The authors would like to thank members of the Wade laboratory for critical comments and suggestions for this manuscript. They apologize to those whose work is not cited owing to space limitations. The authors' research is funded by the Intramural Research Program of the US National Institute of Environmental Health Sciences, NIH (Project number Z01ES101965 to P.A.W.).

Competing interests statement

The authors declare no competing financial interests.

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