Mechanisms of Nucleosome Dynamics In Vivo

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Nucleosomes function to tightly package DNA into chromosomes, but the nucleosomal landscape becomes disrupted during active processes such as replication, transcription, and repair. The realization that many proteins responsible for chromatin regulation are frequently mutated in cancer has drawn attention to chromatin dynamics; however, the basic mechanisms whereby nucleosomes are disrupted and reassembled is incompletely understood. Here, I present an overview of chromatin dynamics as has been elucidated in model organisms, in which our understanding is most advanced. A basic understanding of chromatin dynamics during normal developmental processes can provide the context for understanding how this machinery can go awry during oncogenesis.

Sequencing of tumor DNA has uncovered mutations and rearrangements of well-known tumor suppressor genes and oncogenes in a wide variety of human cancers, confirming much of what had been learned from decades of cancer research (Vogelstein et al. 2013). Such genetic insights verify the long-held assumption that cancer is not a single disease, but rather many diseases. Nevertheless, tumor DNA sequencing has also revealed a surprising number of likely driver mutations in a variety of shared chromatin components, sometimes seen in cancers that otherwise have little else in common (Pon and Marra 2015). From this epigenetic perspective, cancer might be viewed as a complex syndrome in which normal mechanisms that maintain chromatin homeostasis become disrupted in such a way that they may be subject to selection for uncontrolled proliferation. On the one hand, finding a chromatin basis for so many cancers has led to the hope for therapeutic

intervention to reverse the cancer phenotype, and other reviews discuss progress on these fronts. On the other hand, the complexity of the chromatin landscape makes it difficult to explain a wide variety of observations, some of which almost seem to lack a rational basis. For example, a histone modification that is present in all eukaryotic life, H3K79 methylation, can be essentially eliminated in the hematopoietic system in which it efficiently kills leukemia cells but has little effect on normal stem/progenitor cells (Daigle et al. 2011). Another example is a lysine-to-methionine mutation in the histone H3 tail that promotes a highly aggressive tumor when it occurs in a specific site in a child's brain (Wu et al. 2012), but a nearby mutation in the same histone tail results in a benign tumor when it occurs in a specific bone-forming cell of an adult (Behjati et al. 2013). To make sense of these and other issues raised by the discovery of mutations in chromatin regulators, we need

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to consider the molecular and developmental context in which the various components of the chromatin machinery normally function.

Here, I will survey chromatin dynamics during normal processes, focusing on those proteins and complexes that are most frequently mutated in cancer (Fig. 1). Most of our understanding of these processes comes from studies in model organisms, in which powerful genetic, biochemical, and genomic tools have long been applied. With the advent of new technologies, such as genome editing (Laufer and Singh 2015) and live super-resolution microscopy (Liu et al. 2015), the impact of traditional genetic studies of model organisms on understanding cancer genetics and epigenetics is likely to continue.

DISRUPTING AND REMODELING NUCLEOSOMES

The tight wrapping of DNA around the octameric core of nucleosomes requires their mobilization or eviction to make the DNA accessible

for replication, transcription, and repair to occur. Nucleosomes are completely disrupted every cell cycle before the DNA duplex passes through the replicative helicase, which separates the Watson and Crick strands for templated DNA synthesis, followed by reassembly on leading and lagging strands (Ramachandran and Henikoff 2015). Nucleosomes are also disrupted during passage of RNA polymerases, although the high density of nucleosomes over all but the most actively transcribed genes (Weintraub and Groudine 1976) implies that nucleosome disruption and reassembly during transcription must be very efficient. Considering that a nucleosome is an impenetrable barrier to the large RNA polymerase II (RNAPII) holoenzyme complex in vitro, how it can transcribe through a nucleosome in vivo remains incompletely understood (Teves et al. 2014). Another dynamic process that disrupts nucleosomes is remodeling by a class of DNA translocases related to the yeast switch-2/sucrose nonfermenting-2 (SWI2/SNF2) ATPase (Clapier and Cairns 2009).

Figure 1. Regulators of chromatin dynamics implicated in cancer. (P)BAF complexes catalyze nucleosome sliding and/or eviction, ATRX and DAXX promote replacement with H3.3 nucleosomes, CHD ATPases facilitate transcriptional elongation, and the PRC2 complex methylates the H3 amino-terminal tail at lysine-27 to stabilize nucleosomes.

Phylogenetic analysis of human and yeast members of the SWI/SNF superfamily reveals 11 distinct subfamilies, all with at least one human and one yeast member (Fig. 2). Four subfamilies, RAD54, RAD26, RAD16, and FUN30, are DNA translocases that function in DNA repair and/or recombination (Chen et al. 2012; Costelloe et al. 2012; Hinz and Czaja 2015; Li 2015; Waters et al. 2015), and MOT1 is dedicated to regulate TATA-binding protein by removing it from high-affinity sites (Wollmann et al. 2011; Zentner and Henikoff 2013). The other six subfamilies use nucleosomes as substrates for remodeling, and except for IRC5, which is as-yet uncharacterized, all have

been shown to perform distinct nucleosome mobilization reactions. CHD (chromo-helicase-DNA-binding), ISWI (imitation switch), and SNF2 subfamily translocases slide histone cores along the DNA duplex. Biochemical characterization of SNF2 and ISWI remodelers in yeast and *Drosophila* led to the realization that these different phylogenetic subgroups have rather different actions on nucleosomes: SNF2-class remodelers disrupt nucleosomes to facilitate activation, ISWI-class remodelers reposition and regularly space nucleosomes, and CHD-class remodelers help RNAPII transcribe through a nucleosome. These differences led to the realization that nucleosome dynam-

Figure 2. Phylogeny of SWI/SNF ATPase superfamily members in humans and yeast. Dendrogram shows that each subfamily is represented in both species. For example, the SNF2 subfamily includes the ATPase subunit for yeast RSC (Sth1) and SWI/SNF (Snf2) and for PBAF (SMARCA4=BRG1) and BAF (SMARCA2=BRM). For consistency, the SWISS-PROT name for each protein is used in the phylogeny. To obtain human and yeast members of the superfamily, ATRX_HUMAN was used as query versus human- and yeast-annotated SWISS-PROT amino acid sequences. Multiple alignment was performed using MAFFT with defaults, pruning with the MaxAlin option to maximize alignment quality, and a neighbor-joining tree was constructed using all 364 gap-free residues with the JTT amino acid substitution matrix. Ten distinct subfamilies were identified, each with at least one human and one yeast protein.

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ics can have a profound effect on gene expression.

Biochemical characterization of nucleosome remodelers has also distinguished them based on differences in subunit composition. Whereas the yeast Chd1 remodeler is a single subunit enzyme, Swr1 and Ino80 ATPases are each part of 14-subunit complexes. The SWR1 complex is dedicated to replacing canonical histone H2A with the H2A.Z histone variant, and the INO80 complex is capable of performing the reverse reaction (Watanabe and Peterson 2010). It is thought that these opposing reactions constitute a futile cycle in which H2A/H2B dimers, which flank the central (H3/H4)₂ tetramer in the nucleosome, are dynamically exchanged during transcription. Dynamic exchange of histone dimers is promoted by acetylation of histone H3K56 (Watanabe et al. 2013), an example of how chromatin remodeling, histone variants, and histone modifications can work together to dynamically maintain the chromatin landscape.

In the budding yeast, there are two SNF2-class remodeler complexes, RSC and SWI/SNF (Clapier and Cairns 2009). RSC is abundant, broadly distributed, and essential, whereas SWI/SNF is much less abundant than RSC and is nonessential. RSC is similar to the Polybromo (PBAF) complex, in having multiple subunits with bromodomains, a class of modules that bind to acetylated histone tails. In fact, eight of the 15 bromodomains encoded in the yeast genome are present in the RSC complex. SNF2 is similar to the BRM subunit of the BAF complex, which in mammals shares most of its subunits with PBAF. Yeast RSC and SWI/SNF have different catalytic subunits (Sth1 for RSC and Snf2 for SWI/SNF), and mammalian PBAF and BAF also have different catalytic subunits (BRG1 for PBAF and BRM for BAF), which suggest that the two complexes play different chromatin remodeling roles. However, *Drosophila* has only a single SNF2-class catalytic subunit, BRM, which suggests that these complexes are redundant at the basic biochemical level.

Most (P)BAF cancer mutations are found in subunits shared between the two complexes, which suggests that some common feature of SWI/SNF-class remodelers is responsible for

chromatin alterations characteristic of the oncogenic state (Kadoch et al. 2013). Insofar as >20% of all human cancers are found to harbor loss-of-function mutations in P-BAF or BAF complex subunits, elucidating the molecular mechanism of SNF2-class remodeling is crucial for understanding oncogenesis in these cancers.

The yeast RSC complex has been intensively studied both biochemically and structurally. RSC is several-fold larger than the nucleosome, and RSC is a powerful DNA translocase that hydrolyzes 3 ATPs per base pair with a step size of ~1 base pair (Eastlund et al. 2013). A model for RSC action is that it engulfs and unwraps the nucleosome up to the dyad axis by electrostatic attraction of DNA to its inner surface (Chaban et al. 2008; Lorch et al. 2010). Then Sth1 hydrolyzes ATP in a power stroke that releases the remaining histone–DNA contacts to pump through DNA, resulting in directional sliding of the histone octamer along DNA. This model is supported by the *in vivo* observation that RSC-bound nucleosomes are unwrapped up to the dyad axis, a putative RSC/nucleosome remodeling intermediate (Ramachandran et al. 2015). In some circumstances, RSC can evict a nucleosome core from the DNA entirely (Lorch et al. 2006), and the evidence that RSC facilitates the loss and replacement (turnover) of nucleosomes *in vivo* (Dion et al. 2007; Hartley and Madhani 2009) is consistent with eviction being an extreme manifestation of sliding in the context of a chromatin fiber that is densely packed with nucleosomes. These sliding and eviction capabilities of RSC can account for the well-established role of RSC in the generation of nucleosome-depleted regions genome-wide *in vivo* (Ganguli et al. 2014), which is a prerequisite for formation of a preinitiation complex that recruits RNAPII. We might view the SNF2-class remodelers as machines that clear nucleosomes from promoters so that transcription can initiate.

It is probable that *Drosophila* Brahma, the only SNF2-class remodeler in the fly genome (Tamkun et al. 1992), and mammalian PBAF and BAF complexes (Wilson and Roberts 2011) are likewise responsible for clearing nucleos-

comes from promoters. Moreover, the evidence that enhancers are also sites of enhancer RNA (eRNA) transcriptional initiation (Lai and Shiekhattar 2014) suggests that PBAF and BAF may serve a similar function at *cis*-regulatory sites in general. Thus, the central role of SNF2-class remodelers in transcription initiation throughout the genome may have made cells especially vulnerable to transcriptional misregulation when their function is altered by loss of a regulatory subunit (Kim and Roberts 2014). The fact that some individual subunits have been implicated in cell-type-specific functions of PBAF/BAF complexes (Hargreaves and Crabtree 2011) fits with the notion that cancer loss-of-function mutations in various subunits result in cell-type-specific misregulation of this powerful nucleosome clearing apparatus.

Tumor DNA sequencing has also led to the identification of driver mutations in ATRX (α -thalassaemia/mental retardation X-linked) (Picketts et al. 1996), which belongs to the RAD54 branch of the SWI/SNF superfamily of DNA translocases (Fig. 2). Germline homozygous loss-of-function ATRX mutations cause ATRX syndrome, in which an α -thalassaemia is associated with improper chromatin packaging of the α -globin CpG island promoter (Law et al. 2010). Little was understood about the mechanism of action of ATRX syndrome until tumor sequencing revealed that mutations in ATRX and in the associated DAXX histone chaperone are mutually exclusive driver mutations in ~4% of human cancers (Heaphy et al. 2011a; Jiao et al. 2011). Indeed, the study of these cancer mutations led to elucidation of the ATRX/DAXX nucleosome assembly pathway, a reversal of the usual paradigm in which basic science advances help to inform the mechanism of cancer drivers.

The Rad54 DNA translocase does not remodel nucleosomes, but studies of the Rad54-related ATRX ortholog in *Drosophila*, XNP, have suggested that ATRX translocation prepares the DNA substrate for assembly of histone H3.3 nucleosomes (Schneiderman et al. 2009, 2012). DAXX is a histone chaperone that is dedicated to the assembly of nucleosomes containing the

histone H3.3 variant, by depositing successive dimers of H3.3/H4 to form the central tetramer of octameric (H2A/H2B/H3.3/H4)₂ nucleosomes (Ray-Gallet et al. 2002; Drane et al. 2010; Lewis et al. 2010; Elsasser et al. 2012). The normal function of the ATRX-DAXX-H3.3 nucleosome assembly pathway is thought to be filling of gaps in the nucleosome landscape at sites where periodicities and base-compositional biases disfavor tight wrapping of nucleosomes (Fig. 2) (Schneiderman et al. 2009).

A unique feature of ATRX and DAXX mutations is that they are hallmarks of the alternative lengthening of telomeres (ALT) phenotype (Lovejoy et al. 2012). ALT is recognized as a less frequent alternative to telomerase activation that cancer cells can adopt to escape senescence, which likely accounts for the occurrence of ALT in a wide variety of cancers. ALT is readily detected using fluorescence in situ hybridization (FISH) with telomere DNA probes, seen as sporadic cells with extraordinarily long telomeres (Heaphy et al. 2011b). The precise mechanism whereby mutations in the H3.3 assembly pathway lead to the ALT phenotype has not been fully elucidated. However, a recent finding that CHK1-mediated phosphorylation of H3.3 serine-31, one of only four H3.3 residues not found in replication-coupled (RC) variants H3.1 and H3.2, is essential for the full ALT phenotype (Chang et al. 2015) raises the possibility that CHK1 kinase inhibitors might be used to specifically kill cancer cells driven by ATRX and DAXX mutations. ALT also sensitizes cells to ATR (ataxia telangiectasia and Rad3-related) protein kinase inhibitors (Flynn et al. 2015), presumably by reducing phosphorylation of histone H2A.X as part of the DNA damage response pathway. Thus, histone variant phosphorylation promises to be a more general regulatory paradigm that might be exploited in treating ALT-associated cancers.

MODIFYING NUCLEOSOMES

The surface of the nucleosome core and its histone tails are rich in basic residues that neutralize the strong negative charges of the DNA phosphate backbone. Whereas core surface ar-

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ginine side chains sit in the DNA minor groove to tightly wrap the duplex around the particle, lysines on the tails can undergo dynamic cycles of acetylation and deacetylation that neutralize and recharge the tails to facilitate active processes such as transcription (Wolffe 1992; Waterborg 2002). Charge neutralization is thus a universal function of acetylation. In addition, the acetyltransferases and deacetylases that mediate this process are often mutated or aberrantly expressed in cancer, and histone deacetylase (HDAC) inhibitors have been widely used in cancer chemotherapy (Ma et al. 2016). But whether histones themselves are the therapeutic targets of HDAC inhibitors is unclear, in that many nonhistone proteins, including metabolic enzymes, are regulated by acetylation (Downey and Baetz 2015). Furthermore, it has been proposed that a bulk function of histone tail acetylation is pH homeostasis, in which release of acetate and export from the cell reduces intracellular pH (McBrian et al. 2013). These observations complicate interpretation of HDAC inhibition studies.

Histone lysines also undergo cycles of methylation and demethylation, although on much slower time scales from cycles of acetylation and deacetylation. Whereas the half-life of an acetyl on a histone might be measured in seconds or minutes, the average methyl has a half-life that is nearly the same as the histone (Waterborg 1993, 2002). From a kinetic perspective, the stability of histone methylation makes it a strong candidate for a modification that perpetuates chromatin memory, one that can be selectively removed to allow for gene expression to occur. For example, ~70% of H3K27 lysines in the *Drosophila* genome are dimethylated by Polycomb repressive complex 2 (PRC2), which serves to prevent global unscheduled transcription (Lee et al. 2015), but only H3K27me3 is associated with regulated developmental silencing (Schwartz and Pirrotta 2013). To selectively derepress a gene without removing the histone, the UTX H3K27-specific demethylase may be targeted to demethylate H3K27 residues down to di- and monomethylation (Agger et al. 2007).

It is often asserted that histone methylation is “epigenetic” based on the analogy to DNA

methylation (Ptashne 2007). DNA methyls are inherited by the action of the Dnmt1 DNA methyltransferase, which faithfully methylates the cytosine of a CG dinucleotide on the newly replicated strand at the replication fork, but only when the parental cytosine on the opposite strand is methylated (Bestor 1996). However, unlike modifications of DNA, all DNA-binding proteins are removed in advance of DNA polymerization by the action of the replicative helicase. Therefore, all histones, whether old or new, must be deposited de novo on leading and lagging strands behind the replication fork. This means that inheritance of a modification cannot be assumed, and without direct evidence, it remains formally possible that all histone modifications are reestablished de novo as are the nucleosomes that they modify. Direct evidence for inheritance of a histone modification has been obtained in the case of the *Caenorhabditis elegans* germline, in which loss of the PRC2 complex that methylates H3K27 nevertheless allows for retention of H3K27me3 (Gaydos et al. 2014). Just how this feat of legerdemain at the replication fork is accomplished remains the subject of speculation (Ramachandran and Henikoff 2015).

EZH2 (enhancer-of-zeste homolog 2), the catalytic component of the mammalian PRC2 complex, is up-regulated in many cancers, and effective and safe inhibition of EZH2 is a major goal of pharmacological research (Koppens and van Lohuizen 2015). Other histone modifications, including acetylation and H3K4, H3K36, and H3K79 methylation, are associated with the transcriptionally active state, and some of the enzymes responsible for these modifications have been implicated in driving tumorigenesis (Bernt et al. 2011; Colon-Bolea and Crespo 2014; Riedel et al. 2015). From the perspective of cancer therapeutics, these activation-associated modifications represent attractive targets, insofar as inhibition of the enzymes that are involved in the gene activation process might be expected to down-regulate oncogenes that are aberrantly expressed in cancer. However, from a mechanistic perspective, possible roles of these “activating” modifications in mediating gene expression is more poorly understood than in

the case of “silencing” modifications. Specifically, the high-affinity binding of histone binder (“reader”) proteins, including Polycomb to H3K27me₃, and heterochromatin-associated protein 1 (HP-1) to H3K9me₂ and H3K9me₃, helps to immobilize nucleosomes (Canzio et al. 2011; Schwartz and Pirrotta 2013). Reducing nucleosome dynamics likely impedes transcriptional activation, which requires accessible DNA for transcription factors to bind. In contrast, histone-modifying enzymes that are enriched at active genes most likely act during the dynamic process of transcription, being associated with the carboxy-terminal domain of the large subunit of RNA polymerase II (Henikoff and Shilatifard 2011). Thus, these enzymes act on nucleosomes as they are being disrupted and reassembled by the machinery that moves a denaturation bubble forward as it adds RNA bases onto the growing RNA chain. As is the case for disruption of nucleosomes by replication fork passage, our understanding of nucleosome dynamics during transcription is far from complete.

An additional uncertainty in understanding the role of histone modifications in cancer is whether the modification of histones, as opposed to nonhistone proteins, is relevant to the cancer phenotype (Carlson and Gozani 2016). Moreover, cancer cell lines in which overexpression of the NSD2 SET domain-containing histone methyltransferase causes increases in H3K36 methylation also causes decreases in H3K27 methylation (Popovic et al. 2014). This anticorrelation could result from interference along the H3 tail, but might also be an indirect effect. As lysine methylation is a common regulatory modification of many proteins, including transcription factors (Levy et al. 2011; Carlson et al. 2015), it is also possible that the therapeutic target of NSD2 is instead a nonhistone protein, in which case these changes that occur on the lysine tail represent collateral damage with no physiological consequences. It should be kept in mind that calling these enzymes “histone” methyltransferases, demethylases, etc., does not necessarily reflect their *in vivo* activities, but rather the historical fact that the lysine richness of histones made them

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convenient substrates for use in biochemical purification. To avoid this misunderstanding, the accepted nomenclature for what was previously referred to as histone methyltransferases (HMTs) has been changed to “lysine” methyltransferases (KMTs) and so on for other chromatin-modifying enzymes (Allis et al. 2007).

A similar uncertainty as to physiological function applies to histone reader proteins, which bind their modified substrates sometimes with nanomolar affinities. In the case of Polycomb and HP-1, there is both genetic and biochemical evidence that their action includes preferential binding of methylated H3K27 and H3K9 lysines, respectively, including similar phenotypes for the orthologous modifying enzymes and reader proteins in *Drosophila* (Schotta et al. 2002; Schwartz and Pirrotta 2013). However, in other cases, the situation is ambiguous, for example, whether the various bromodomains found to preferentially bind acetylated histone tails actually bind these tails *in vivo*, and if they do, whether or not the binding is simply a consequence of the extraordinarily high concentration of acetylated histone lysines in the nucleus (Shi and Vakoc 2014). The development of reader protein inhibitors (Filipakopoulos et al. 2010) and ascertainment of their safety in the clinic will likely benefit from a better understanding of their physiologically relevant targets.

REPLACING CANONICAL HISTONES WITH VARIANTS

Most histones are rapidly synthesized from multicopy genes during S phase by specialized mRNA processing machineries and are deposited into nucleosomes immediately behind the replication fork (Marzluff et al. 2002). Other histones are synthesized throughout the cell cycle from ordinary genes and are incorporated into nucleosomes by dedicated histone chaperones (Henikoff and Smith 2015). These replication-independent (RI) histones include the aforementioned H3.3 histone variant, which is the exclusive substrate for RI assembly on chromosome arms, as are H3.1 and H3.2 the exclusive substrates for RC nucleosome assembly

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Figure 3. Phylogenies of histone variants in humans and yeast. All H3 (A), and H2A (B) variants annotated in SWISS-PROT are included (see the legend to Fig. 1 for details).

(Fig. 3A). Another notable histone variant is cenH3 (called CENP-A in mammals), which is the defining component of nucleosomes that form the chromatin foundation for the centromere. Most other RI histones are variants of H2A, including H2A.X, which is rapidly phosphorylated on a carboxy-terminal serine when DNA breaks in its vicinity, H2A.Z, which acts to weaken the nucleosome barrier to transcription, and macroH2A, H2A.B, and H2A.L, which are mammalian histone variants of uncertain function (Fig. 3B). The substitution of a histone variant for a canonical histone represents a profound change in nucleosome properties that can potentially affect nucleosome dynamics. For example, H2A.Z has a very different “docking domain” from H2A, which contacts H3/H4 in the nucleosome core and can affect its stability (Suto et al. 2000). Also, H2A.B forms a “short wrapper” nucleosome core that

makes fewer contacts with DNA, potentially reducing stability (Bao et al. 2004). macroH2A, which is enriched in silent chromatin, is unique among core histones in having a globular domain of uncertain function that protrudes from the canonical core (Costanzi and Pehrson 1998).

Until recently, histone variants have received much less attention in the cancer and chromatin field than histone modifications, which are catalyzed by many different modifying and demodifying enzymes and bound by reader proteins that provide attractive targets for small molecule drug development (Copeland et al. 2010; Filippakopoulos et al. 2010). However, tumor DNA sequencing studies have revealed unexpected roles for histone variants in promoting tumorigenesis. Specific driver mutations have been discovered in H3.3 genes that are characteristic of specific cancer types to an extraordi-

nary degree: H3.3K27M mutations are found in most diffuse midline gliomas (DIPGs) and many pediatric glioblastomas (Wu et al. 2012), and H3.3K36M mutations are driver mutations in nearly all chondroblastomas and H3.3G34W/L mutations in nearly all giant cell tumors of bone (Behjati et al. 2013). Whereas DIPGs are highly aggressive pediatric cancers, the bone tumors are less invasive and sometimes benign, and are also found in adults. All are likely gain-of-function mutations in that these tumors also express normal H3.3 copies. For example, in mammalian cells, expression of the H3.3K27M protein contributes to neoplastic transformation (Funato et al. 2014), and a similar neoplastic effect is seen for H3K36M/I mutations found in chondroblastomas (Lu et al. 2016). A gain-of-function interpretation of these phenotypes is also supported by studies in *Drosophila*, whereby introduction of the K27M mutation in an H3.3 transgene results in dominant Polycomb phenotypes, consistent with methionine-27 titrating the PRC2 complex (Lewis et al. 2013; Herz et al. 2014). Indeed, elucidation of the structure of a PRC2 complex homolog binding a histone H3K27M amino-terminal tail peptide shows that the mutation results in occlusion of the enzymatic active site by the neighboring H3R26 arginine side chain (Jiao and Liu 2015). Another candidate for mediating at least some of these cancers is the ZMYND11 zinc-finger tumor suppressor protein that specifically binds to both lysine-36 and (H3.3-specific) serine-31 (Wen et al. 2014).

Tumor sequencing and gene expression studies have also drawn attention to the possibility that RI nucleosome assembly pathway components might be potential drug targets, for example, the inhibition of the CHK1 and ATR kinases, which preferentially phosphorylate H3.3 and H2A.X in cancer cells (Chang et al. 2015). In the case of H2A.Z, overexpression is associated with poor prognosis in ER α breast cancer (Hua et al. 2008), and hyperacetylation of H2A.Z is a feature of deregulated promoters in prostate cancer (Valdes-Mora et al. 2012). Changes in macroH2A levels are also common in cancer. For example, the degree of malignancy in melanoma is inversely corre-

lated with macroH2A levels, and knockdown of macroH2A increases malignancy (Kapoor et al. 2010). As macroH2A nucleosomes are more compacted, it is attractive to consider that its presence in a nucleosome reduces dynamics (Chakravarthy et al. 2005), and so its loss can promote gene misexpression. However, just what role that global changes in macroH2A levels might have in tumor progression is complicated by the evidence that different splicing isoforms produced by two different macroH2A genes are associated with very different outcomes (Sporn and Jung 2012). It is possible that these complications arise from the differential abundances of these isoforms in different cancer cell types, rather than any difference in the action of the isoforms in compacting chromatin. Interestingly, macroH2A is negatively regulated by ATRX (Ratnakumar et al. 2012), and this raises the possibility that misregulation of macroH2A contributes to the ALT phenotype.

Whereas most RI histone variants are of interest because of their potential involvement in transcriptional regulation, cenH3 nucleosomes form the foundation of the centromere in the large majority of eukaryotes, and so are crucial for genome stability (Quenet and Dalal 2012). As cenH3 mislocalization can lead to the appearance of ectopic “neocentromeres,” and bridge-breakage-fusion cycles can result from a second centromere on a chromosome, overproduction of CENP-A in some cancers makes it a potential causative factor in aneuploidy (Lacoste et al. 2014; Athwal et al. 2015). Reducing CENP-A levels in cancer, for example, by targeting expression of its gene or inhibiting its incorporation into chromatin, may be a potential therapeutic strategy that would have little if any impact on nondividing cells.

CONCLUDING REMARKS

This survey of chromatin components involved in nucleosome dynamics of potential relevance to cancer underscores the intricate interrelationships between the major components, including DNA translocases, histone modifications and their reader proteins, and histone variants and their chaperones. For example, the

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Figure 4. Model for the concerted action of multiple chromatin regulators. (A) The Suv39h H3K9 methyltransferase is recruited by HP-1 protein, which binds preferentially to methylated H3K9. To perpetuate this mark when the nucleosome turns over, the ATRX-DNMT3L (ADD) "reader" domain, which binds with high specificity to methylated H3K9 on tails that entirely lack H3K4 methylation (because there are no H3K4 methyltransferases in this region of the genome). (B) ATRX provides the energy of ATP and works together with the H3.3-specific DAXX histone chaperone complex to incorporate the new nucleosome. The high local concentration of Suv39h results in a new nucleosome with the same H3K9 methylation as the nucleosome that was lost. (From Henikoff and Smith 2015; reprinted, with permission, from the authors.)

ATRX translocase, which is associated with the H3.3-specific DAXX chaperone has a dual-reader module that tightly binds di- or trimethylated lysine-9 and unmethylated lysine-4 on the histone 3 amino-terminal tail (Fig. 4) (Eustermann et al. 2011). Teasing out these interdependencies to understand how ATRX and DAXX mutations can drive ALT or how different H3.3 mutations can drive such different tumors as aggressive DIPGs and benign chondroblastomas requires a better understanding of the dynamic processes that these components normally carry out. Increases in nucleosome dynamics can also result in genome instability, as loss of nucleosomes exposes DNA and can result in double-strand breaks (Yang et al. 2015).

In this regard, studies of model organisms have the potential of providing insight into how disruption of normal developmental processes can result in cancer. For example, an important simplification of what otherwise seems to be a byzantine network of chromatin regulators involved in tumor progression originated with fly genetics. According to the central paradigm for *Drosophila* development, genes are heritably maintained in the silent state in *trans* by the product of the Polycomb locus (Lewis 1978). This paradigm was further elaborated with the discovery of additional loci in the Polycomb group (PcGs) that maintain developmental silencing (Schwartz and Pirrotta 2013), and in the trithorax group (trxGs) that maintain gene activity (Steffen and Ringrose 2014). Although originally described for maintaining silencing and expression of “homoeotic” master regulators of the anterior–posterior morphological axis, the paradigm applies generally to maintaining developmental memory in complex animals. Biochemical studies of PcGs showed them to consist of subunits of PRC1 complexes, which act to compact chromatin (Grau et al. 2011), and of the PRC2 complex, which methylates H3K27 to heritably maintain silencing (Schwartz and Pirrotta 2013). Biochemical studies of trxGs showed them to be chromatin remodelers, histone-modifying enzymes and other chromatin regulators that are associated with gene activity (Kingston and Tamkun 2006). Upsetting the balance between trxGs

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and PcGs that normally regulate developmental processes in *Drosophila* uncovers homoeotic phenotypes. Likewise, mutations in and silencing or misexpression of mammalian orthologs of trxGs and PcGs upsets the balance between them that normally maintains developmental homeostasis. A fuller understanding of the mechanisms whereby trxGs and PcGs affect nucleosome dynamics is needed to address the question of how mutation and misregulation of these proteins can drive tumorigenesis.

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