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EXTRA VIEW

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Epigenetic countermarks in mitotic chromosome condensation

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ABSTRACT
Mitosis in metazoans is characterized by abundant phosphorylation of histone H3 and involves the recruitment of condensin complexes to chromatin. The relationship between the 2 phenomena and their respective contributions to chromosome condensation *in vivo* remain poorly understood. Recent studies have shown that H3T3 phosphorylation decreases binding of histone readers to methylated H3K4 *in vitro* and is essential to displace the corresponding proteins from mitotic chromatin *in vivo*. Together with previous observations, these data provide further evidence for a role of mitotic histone H3 phosphorylation in blocking transcriptional programs or preserving the 'memory' PTMs. Mitotic protein exclusion can also have a role in depopulating the chromatin template for subsequent condensin loading. H3 phosphorylation thus serves as an integral step in the condensation of chromosome arms.

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Introduction

A rapid increase in chromatin compaction during mitosis, known as chromosome condensation, is essential for the faithful distribution of identical genetic material between daughter cells. Chromosome condensation involves the recruitment of condensin complexes to chromatin[1] and is characterized by a pattern of posttranslational modifications (PTMs) in histones.[2-5] In prophase, the kinases Haspin and Aurora B phosphorylate T3, S10, and S28 of histone H3 through evolutionarily conserved mechanisms.[6-8] Even though chromosome condensation becomes evident at the onset of mitosis, H3 phosphorylation continues increasing from prophase to metaphase due to transactivation of Aurora B and a positive feedback loop involving Haspin.[9] In addition, other kinases can be recruited to ensure robust H3 phosphorylation.[10] Histone phosphorylation is so abundant that phosphorylation-dependent conformational changes were occasionally thought to drive chromatin condensation.[11] The discovery of condensins that promote condensation by physically wrapping the chromatin however has provided an alternative explanation,[12] which is now widely accepted. Although experiments on chromatin condensation *in vitro* reveal that phosphorylation of condensin I is the sole mitosis-specific modification required for the compaction of reconstituted chromatids,[13,14] accumulating evidence suggests that additional components contribute to this process *in vivo*.

One of the significant outcomes of chromatin condensation is the modulation of general gene transcription.[15] Although production of some non-coding RNAs continues at the centromere,[16] bulk transcription of spliced messengers is largely suppressed in mitosis and resumes at the end of cell division. Transcription programs require the association of histone readers in chromatin-associating proteins and complexes with regulatory PTMs such as methylated lysine.[17-19] Binding of methyllysine readers can in turn be modulated by removing the corresponding PTM or through a mechanism termed phospho/methyl switch.[20,21] (Fig. 1). The

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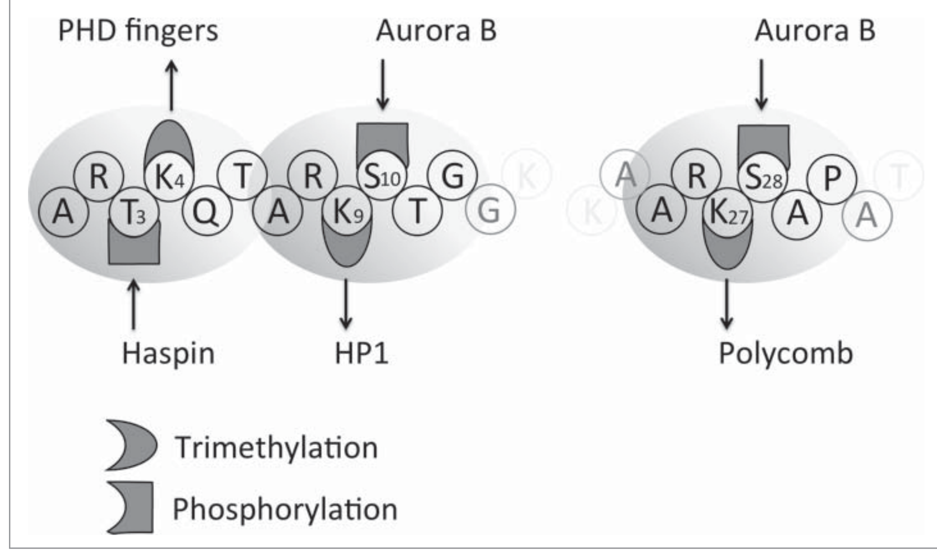

Figure 1. Haspin- and Aurora B-targeted threonine and serine sites in histone H3 tail. A wide array of cellular events requires posttranslational modifications on H3K4, H3K9 and H3K27 in interphase, however protein complexes that bind these PTMs can interfere with mitosis. Mitotic histone H3 phosphorylation at H3T3, H3S10 and H3S28 can pause the transcriptional programs, preserve the 'memory' PTMs, or play a role in preparing a chromatin template for condensins.

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phospho/methyl switch can displace reader-containing proteins from chromatin or prevent priming of demethylases and therefore preserve or "memorize" the methyllysine PTM. In contrast to demethylation that permanently erases an epigenetic modification, phosphorylation of serine and threonine residues adjacent to methyllysine provides a tool to temporarily prevent binding of reader proteins without affecting the PTM itself [20,22-24] A recent study that compared the behavior of methyllysine-interacting domains *in vitro* and *in vivo* revealed novel aspects of histone H3 phosphorylation, by linking the expulsion of reader proteins and chromatin condensation.[23]

Chromosome condensation in early mitosis

Prophase chromatin compaction coincides with histone phosphorylation[6-8] and dissociation of a wide array of nuclear proteins from chromatin.[20,23-26] Even organisms that divide by closed mitosis – without breakdown of the nuclear envelope – redirect a portion of nuclear proteins to the cytoplasm during chromosome segregation.[27] In contrast to protein expulsion in early mitosis, recruitment to prophase chromatin is limited to a specific subset of proteins, many of which have a role in directing mitosis progression. Of particular importance are the condensin complexes that form and stabilize chromatin loops[28] and the kinases that phosphorylate histone H3.[6,7]

Haspin is one of the main kinases to act on histones in early mitosis.[6] It phosphorylates T3 of histone H3 producing the epigenetic mark H3T3ph, which is recognized by Survivin, a component of the chromosomal passenger complex.[5,29,30] Survivin is required for the recruitment of Aurora B kinase and subsequent phosphorylation of H3S10 and H3S28.[7,8,29] Small molecule inhibition of Haspin has a marked effect on early mitosis and chromosome condensation,[23] but inhibition of Aurora B produces its effect only when decatenation and spindle attachment become important.[31] These data agree with the idea that Haspin acts upstream of Aurora B; inhibition of the former affects phosphorylation of both H3T3 and H3S10 *in vivo*, but inhibition of the latter still permits H3T3ph accumulation.

Mitotic H3 phosphorylation first occurs close to the pericentromeric heterochromatin and subsequently spreads out over the chromosome arms.[2-4] H3K4me3, a PTM enriched at transcription start sites, has been shown to decrease Haspin activity *in vitro*,[32-34] which may account for the delayed euchromatin condensation *in vivo*. The H3K9ac modification, linked to gene activation, suppresses H3 phosphorylation,[35] whereas the heterochromatin-associated H3K9me3 mark does not affect *in vitro* catalytic activities of Haspin and Aurora B.[33,34] Differential mitotic condensation of hetero- and euchromatin might have important functional consequences; whereas hardly any heterochromatin along chromosome arms is actively transcribed,

delayed euchromatin condensation shortens the time without general gene transcription. Even though the spatiotemporal patterns are different, many outcomes of H3T3 and H3S10 phosphorylation at the molecular level are similar – addition of a bulky negatively charged phosphate group can impede the function of the adjacent methyllysine PTM (Fig. 1). Eventually, H3T3ph and H3S10ph entirely cover the chromosomes from late prophase to metaphase. Maximum H3 phosphorylation and chromosome compaction coincide in metaphase and early anaphase,[36,37] suggesting that the 2 are functionally linked *in vivo*.

While the importance of histone phosphorylation *in vivo* has been documented, experiments on chromatin condensation *in vitro* suggest that histone phosphorylation is not essential for the actual process of condensation, which primarily depends on the loop-forming proteins condensins.[13,14] A minimal *in vitro* system functions without the H3 kinases and requires only core histones, topoisomerase, chaperones, and condensin.[14] Depletion of condensin by RNA interference in cells leads to a delay though not the loss of prophase chromatin condensation.[1] Likewise, conditional knockout cells without the SMC2 condensin subunit undergo residual albeit delayed chromatin compaction.[28] The resulting metaphase chromosomes are easily disrupted, suggesting structural differences between compacted chromosomes in the presence and absence of condensin. Interestingly, studies using immunofluorescence show that efficient *in vivo* deposition of condensin, particularly condensin I in prometaphase, requires a prior H3 phosphorylation by Aurora B,[7,38,39] (Fig. 2). Since conditional knockout cells without SMC2 undergo chromosome condensation only after nuclear envelope breakdown[28] condensin II – which enters the nucleus before mitosis in contrast to condensin I – probably contributes to prophase chromatin compaction, either by acting before or by collaborating with histone kinases. In agreement with this idea, depletion of the early condensin II, but not the late condensin I, partially reduces H3 phosphorylation.[40]

Maintaining and terminating chromatin condensation

In mid-mitosis, Haspin and Aurora B translocate to centromeres and their concentration along chromosome arms decreases.[9] Accordingly, histone H3 phosphorylation levels show a peak at metaphase and are gradually reduced after the metaphase-anaphase transition.[41] Despite the reduction in H3 phosphorylation, chromatin condensation persists until telophase, suggesting a relaxed requirement for H3 phosphorylation once chromatin condensation has reached a threshold. Even at the time when Haspin and Aurora B localize mainly at centromeres, an experimentally induced transient loss of H3S10ph along chromosome arms is quickly restored.[4] These data are consistent with the idea that metaphase re-phosphorylation of H3S10 on chromosome arms involves the continuous exchange of kinases,[42] and that residual low-level phosphorylation is important for sustained condensation. The continuous evolution of chromosomes during mitosis is reflected in the dynamic behavior of proteins associated with mitotic chromosomes. A general survey

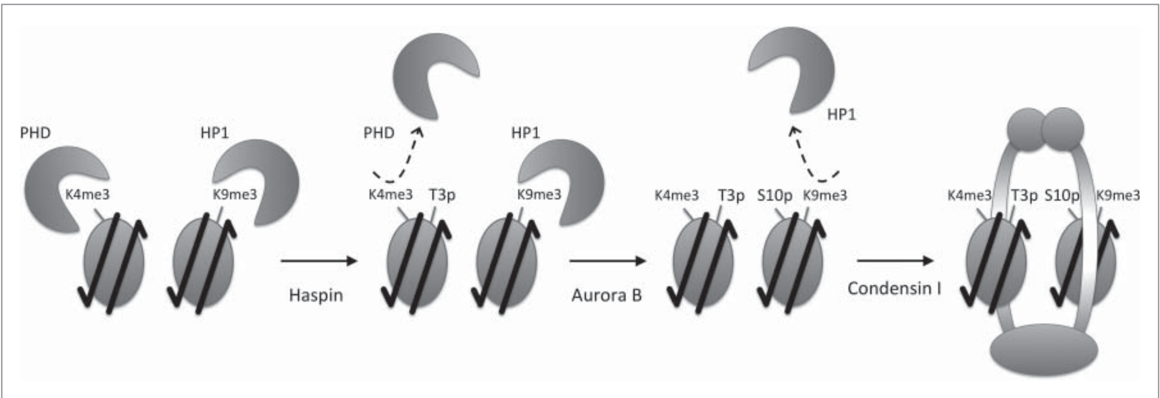

Figure 2. Sequential events control chromosome condensation *in vivo*. Early mitosis is characterized by phosphorylation of key residues in histone H3 by Haspin (left) and Aurora B (center), which coincide with the exclusion of a set of H3K4me3-specific and H3K9me3-specific reader proteins. The resulting template, which is less populated than interphase chromatin, can be readily compacted by mitotic condensins (right). The reader-containing proteins excluded from chromatin are depicted above the nucleosomes.

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identified hundreds of candidates,[43] the majority of which comprise several multicomponent complexes.[36] Interestingly, a large proportion of the associated proteins form part of the so-called chromosome periphery, which assembles around the chromosomes after nuclear envelope breakdown.[36]

The metaphase-anaphase transition marks a critical turning point in mitosis. It is controlled by the anaphase promoting complex and triggered by the proteasomal degradation of Cyclin B.[44] The same mechanism eliminates a fraction of Aurora B,[45] with the remaining part redistributing to the spindle midzone and midbody for the control of later events. Even though decatenation completes in early anaphase, chromatin compaction persists until late mitosis and could reduce resistance during poleward chromosome movement. During the second half of mitosis, PP1/Repo-man promotes gradual dephosphorylation of histone H3.[41] Residual H3 phosphorylation is nonetheless important in the second part of mitosis, as cells subjected to sub-optimal Haspin inhibition *in vivo* undergo chromosome condensation until anaphase but show extensive incorporation of PHD finger-containing proteins into telophase chromosomes.[23] Since Haspin inhibition reduces H3T3ph levels, its effect at the end of mitosis resembles the action of PP1/Repo-man – the removal of H3 phosphorylation. Controlling the balance between phosphorylation and dephosphorylation might thus be important until the end of mitosis and could protect chromatin from the premature recruitment of the methyllysine reader-containing proteins. In normal cells, the nuclear envelope reassembles around chromosomes when they are still condensed,[46] indicating that nuclear protein import resumes before chromatin decondensation. In addition, several studies have implicated ATPases in removing residual Aurora B, and thus the final traces of H3S10ph, from chromatin.[47,48] Complete chromatin decondensation thus comprises an active process instead of simple inactivation of condensation factors.

Concluding remarks

Over the past decade substantial progress has been made in our understanding of the physiologic importance of mitotic chromatin condensation, however many questions remain. For example, the precise role of histone H3 phosphorylation sites in chromatin condensation remains unclear, and we do not fully understand the antagonistic or cooperative effects and functional crosstalk involving phosphorylation and other histone PTMs. Further studies are also needed to examine whether the exclusion of reader-containing protein complexes from mitotic chromatin depends on collaboration between phosphorylation sites. Finally, a set of PHD finger-containing proteins show a notable tendency to accumulate on spindle microtubules, particularly on those adjacent to the spindle poles in metaphase and spindle midzone in late mitosis.[23] It will be interesting to investigate whether protein accumulation on microtubules is a mechanism to avert premature reassociation of histone readers with chromatin or to ensure equal distribution of important factors between daughter cells during mitosis.

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No potential conflicts of interest were disclosed.

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