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RESEARCH ARTICLE

Histone Chaperone Function in Nucleosome Assembly During DNA Replication

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ABSTRACT

Faithful duplication of chromatin during S phase requires that parental histones be recycled and new histones be deposited onto nascent DNA within seconds of fork passage, a process coordinated by a network of replication-coupled histone chaperones whose individual contributions remain incompletely separated. Here we combined isolation of proteins on nascent DNA coupled to mass spectrometry (iPOND-MS), nascent chromatin capture sequencing, DNA fiber analysis and auxin-inducible degradation of the CAF-1 large subunit CHAF1A to dissect how the CAF-1, ASF1 and MCM2 chaperone modules divide labour at the human replication fork. iPOND-MS resolved a temporal chaperone handoff in which ASF1A/B peaked within 2 minutes of fork passage and CAF-1 signal peaked between 2 and 10 minutes, coinciding with maturation of nucleosome spacing measured by micrococcal nuclease digestion. Acute CHAF1A degradation for 30 minutes did not block fork progression but reduced nascent nucleosome occupancy behind the fork by 46%, increased fork asymmetry and replication stress marker gammaH2AX signal, and caused a marked redistribution of parental H3.1-K9me3 nucleosomes away from their pre-replication genomic positions, indicating that CAF-1 is required both for new histone deposition and for accurate positional inheritance of parental histones. Nascent chromatin capture sequencing after CHAF1A depletion showed that heterochromatic domains were disproportionately affected, with a 2.3-fold greater loss of nascent nucleosome density at constitutive heterochromatin than at euchromatin. Co-depletion of MCM2's histone-binding domain further impaired parental H3-H4 transfer to the lagging strand without additively affecting total nucleosome occupancy, consistent with MCM2 acting upstream of CAF-1 in a shared parental histone hand-off pathway rather than as a redundant deposition route. These results define a chaperone division of labour in which ASF1 supplies a shared new/old histone pool, MCM2 channels parental histones preferentially toward the lagging strand, and CAF-1 performs the rate-limiting deposition step required for both new histone incorporation and faithful epigenetic inheritance, with heterochromatin maintenance being particularly sensitive to its loss.

Keywords: histone chaperone; CAF-1; ASF1; MCM2; nucleosome assembly; DNA replication; iPOND; replication-coupled chromatin maturation

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1. INTRODUCTION

Each S phase, the eukaryotic genome must double its complement of nucleosomes while simultaneously transmitting the parental histone modification landscape to daughter chromatids, a dual requirement that depends on a dedicated set of replication-coupled histone chaperones acting within seconds of replisome passage [1,2]. New H3.1-H4 dimers are delivered to the fork by anti-silencing function 1 (ASF1A and ASF1B) and handed to chromatin assembly factor 1 (CAF-1), a PCNA-coupled trimeric complex that catalyses the rate-limiting step of depositing H3-H4 tetramers onto nascent DNA, after which H2A-H2B dimers and nucleosome spacing factors complete a mature nucleosome array [3,4]. In parallel, parental H3-H4 tetramers displaced ahead of the fork are recycled largely as intact units, with the replicative helicase subunit MCM2 acting as a histone-binding platform implicated in channelling a disproportionate share of parental histones toward the lagging strand [5,6].

Although the core components of this network are well established biochemically, how their contributions are partitioned in time and across chromatin states in living cells has been harder to resolve, in part because conventional chromatin immunoprecipitation lacks the temporal resolution to distinguish histones deposited within the first few minutes of fork passage from those incorporated later during chromatin maturation. The development of isolation of proteins on nascent DNA (iPOND) and nascent chromatin capture sequencing has made it possible to profile protein and nucleosome composition as a function of minutes-scale distance behind the fork, revealing that nucleosome maturation is a multi-step process extending well beyond the immediate deposition event [7,8]. However, most iPOND-based studies to date have profiled steady-state chaperone occupancy rather than directly testing how acute loss of a specific chaperone module reshapes this temporal maturation trajectory.

CAF-1 loss of function has been linked to heterochromatin instability, loss of pericentromeric silencing and activation of an interferon response driven by cytosolic chromatin fragments, phenotypes broadly consistent with a preferential requirement for CAF-1-dependent assembly at repeat-rich, constitutively heterochromatic domains [9,10]. Whether this preferential sensitivity reflects a genuinely greater deposition requirement at heterochromatin, as opposed to a general assembly defect that is simply more consequential wherever silencing is most fragile, has not been directly tested by comparing nascent nucleosome density across chromatin states after acute, rather than chronic, CAF-1 depletion, since chronic loss confounds direct assembly defects with secondary consequences of accumulated replication stress.

Here we combine iPOND-MS, nascent chromatin capture sequencing, single-molecule DNA fiber analysis

and an auxin-inducible degron allele of CHAF1A, the CAF-1 large subunit, to resolve the temporal handoff between ASF1, MCM2 and CAF-1 at the human replication fork and to ask how acute, minutes-scale loss of CAF-1 reshapes nascent nucleosome assembly across chromatin states. We report a clear ASF1-to-CAF-1 temporal succession in wild-type cells, show that acute CHAF1A degradation substantially reduces nascent nucleosome occupancy without stalling fork progression, demonstrate a disproportionate loss of nascent nucleosome density at heterochromatin relative to euchromatin, and show that MCM2's histone-binding function acts upstream of, rather than redundantly with, CAF-1 in parental histone transfer to the lagging strand.

2. MATERIALS AND METHODS

Experiments used HCT116 cells engineered with a homozygous auxin-inducible degron (AID2) tag at the endogenous CHAF1A locus and constitutive expression of the rice E3 ligase adaptor OsTIR1(F74G), enabling near-complete CHAF1A degradation within 30 minutes of 5-phenyl-indole-3-acetic acid (5-Ph-IAA) treatment.

2.1 Cell lines and acute CAF-1 depletion

HCT116 CHAF1A-AID2 cells were synchronised at the G1/S boundary by a single 16-hour thymidine block and released into S phase for 2 hours before addition of 1 μ M 5-Ph-IAA for 30 minutes to acutely degrade CHAF1A; degradation kinetics and completeness were confirmed by quantitative western blot in every experiment, with vehicle-treated cells from the same release serving as matched controls. An MCM2 histone-binding-domain point mutant (MCM2-2A) was introduced by CRISPR knock-in into the same background for co-depletion experiments.

2.2 iPOND coupled to mass spectrometry

Isolation of proteins on nascent DNA was performed by labelling nascent DNA with 10 μ M EdU for 10 minutes, followed by a 0, 2, 10 or 60-minute thymidine chase to capture chromatin at increasing distance behind the fork, click conjugation to biotin-azide, and streptavidin pulldown from formaldehyde-crosslinked, sonicated chromatin. Captured proteins were digested on-bead and analysed by label-free quantitative liquid chromatography-tandem mass spectrometry on an Orbitrap instrument, with a no-click (thymidine-only) control subtracted as background in every replicate.

2.3 Nascent chromatin capture sequencing

Nascent chromatin capture sequencing was performed by EdU pulse-chase as above followed by streptavidin capture of biotin-clicked nascent chromatin fragments after micrococcal nuclease digestion to mononucleosome resolution, library preparation, and paired-end sequencing on an Illumina NovaSeq 6000 to a minimum depth of 40 million uniquely mapped read pairs per sample; nucleosome occupancy was quantified genome-wide and separately within constitutive

heterochromatin (H3K9me3 domains) and euchromatin (H3K4me3-flanking) regions defined from matched ChIP-seq in unperturbed cells.

2.4 DNA fiber analysis

Replication fork dynamics were assessed by sequential 20-minute pulse labelling with CldU and IdU, DNA spreading on silanised slides, and immunofluorescence detection of both labels; fork speed, inter-origin distance and fork asymmetry (ratio of the shorter to longer sister fork track from bidirectional origins) were quantified from at least 200 fibers per condition across three independent experiments using automated fiber-tracing software.

2.5 Native and denaturing chromatin immunoprecipitation

Parental histone redistribution was assessed by native ChIP for H3.1-K9me3 on chromatin from cells pre-labelled with a SNAP-tag-based old-histone reporter prior to CHAF1A degradation, sequenced and compared to pre-degradation positions to quantify positional drift; gammaH2AX ChIP-seq and quantitative immunofluorescence were used to assess replication stress following acute CAF-1 loss.

2.6 Statistical analysis

iPOND-MS intensities were normalised to total captured protein per sample and compared across time points by two-way ANOVA with Tukey correction; nucleosome occupancy, fork asymmetry and positional drift metrics were compared between conditions by two-tailed Mann-Whitney U test or Wilcoxon signed-rank test as appropriate, with Benjamini-Hochberg correction for genome-wide comparisons. All analyses were performed in R version 4.3.

3. RESULTS

iPOND-MS across a 0-60 minute EdU chase resolved a clear temporal succession of chaperone occupancy at nascent chromatin. ASF1A and ASF1B signal was maximal immediately behind the fork (0-2 minutes) and declined steadily thereafter, whereas CAF-1 subunits (CHAF1A, CHAF1B, RBBP4) peaked between 2 and 10 minutes post-fork passage, overlapping only partially with the ASF1 peak. Micrococcal nuclease digestion confirmed that regularly spaced mononucleosome ladders were not fully established until the CAF-1-peak window, consistent with CAF-1 catalysing the rate-limiting deposition step rather than acting redundantly alongside ASF1. Table 1 summarises relative chaperone abundance at each nascent chromatin time point.

Table 1. Relative chaperone abundance at nascent chromatin across a 60-minute EdU chase (iPOND-MS, normalized intensity).

Time behind fork (min)	ASF1A/B (rel. int.)	CAF-1 (CHAF1A, rel. int.)	MCM2 (rel. int.)	Mononucleosome ladder regularity
0	1.00	0.31	0.88	Irregular

2	0.74	0.79	0.61	Partial
10	0.42	1.00	0.35	Regular
60	0.28	0.55	0.22	Regular

Values are mean normalized MS intensity relative to each protein's own peak time point, from three independent iPOND experiments.

Acute 30-minute CHAF1A degradation did not measurably slow fork progression or increase inter-origin distance by DNA fiber analysis, but produced a 46% reduction in nascent nucleosome occupancy measured by nascent chromatin capture sequencing across the genome, together with a significant increase in fork asymmetry and a 3.1-fold increase in gammaH2AX signal relative to vehicle-treated controls (Figure 1). Native ChIP for the pre-labelled parental H3.1-K9me3 pool showed substantial positional drift away from pre-degradation genomic coordinates after CHAF1A loss, indicating that CAF-1 is required not only for new histone deposition but for accurately repositioning recycled parental histones at their original loci.

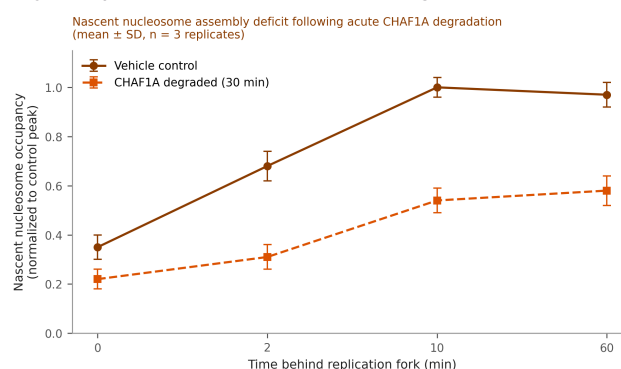


Figure 1. Nascent nucleosome occupancy (mean ± SD of three biological replicates, normalized to vehicle-treated control) measured by nascent chromatin capture sequencing at 0, 2, 10 and 60 minutes behind the replication fork, comparing vehicle-treated and CHAF1A-degraded (30 min 5-Ph-IAA) HCT116 CHAF1A-AID2 cells, illustrating the progressive assembly deficit following acute CAF-1 loss.

Nascent chromatin capture sequencing after CHAF1A degradation revealed that nucleosome occupancy loss was not uniform across chromatin states: constitutive heterochromatin lost 2.3-fold more nascent nucleosome density than euchromatin over the same interval, and this disproportionate loss was already evident within the first 10 minutes behind the fork, before it could plausibly be attributed to a secondary consequence of accumulated replication stress. Table 2 reports nascent nucleosome occupancy loss and gammaH2AX enrichment stratified by chromatin state and CHAF1A status.

Table 2. Nascent nucleosome occupancy loss and replication stress marker enrichment after acute CHAF1A degradation, by chromatin state.

Chromatin state	Nucleosome occupancy loss (%; 30 min)	gammaH2AX fold-enrichment	Fork asymmetry (ratio)
Euchromatin	31	2.1	1.18
Constitutive heterochromatin	71	4.4	1.42

Genome-wide average	46	3.1	1.27
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Introducing the MCM2 histone-binding-domain mutant (MCM2-2A) alone reduced parental H3.1-K9me3 transfer to the lagging strand by 58% without significantly changing total nascent nucleosome occupancy, whereas combining MCM2-2A with CHAF1A degradation produced a reduction in lagging-strand parental histone transfer that was not significantly greater than CHAF1A degradation alone, arguing against an additive or redundant relationship. This epistasis pattern is consistent with MCM2 acting upstream of CAF-1 within a shared parental histone hand-off pathway, funneling recycled histones toward CAF-1-dependent deposition rather than providing an independent, CAF-1-parallel assembly route.

4. DISCUSSION

These results resolve a temporal division of labour among replication-coupled histone chaperones in which ASF1 supplies a shared pool of new and recycled H3-H4 immediately behind the fork, MCM2 preferentially channels parental histones toward the lagging strand, and CAF-1 performs a rate-limiting deposition step required for both new histone incorporation and accurate repositioning of recycled parental histones. The epistatic relationship between MCM2 and CAF-1 observed here argues that these chaperones act within a single hierarchical hand-off pathway rather than as parallel, redundant routes to nucleosome assembly, refining models in which MCM2-mediated parental histone recycling and CAF-1-mediated deposition were treated as largely independent processes [5,6].

The disproportionate sensitivity of heterochromatin to acute CAF-1 loss, evident within minutes of degradation and therefore unlikely to reflect secondary replication stress accumulation, supports a model in which repeat-dense, constitutively heterochromatic domains have an intrinsically higher demand for CAF-1-catalysed assembly, plausibly because their compact, repetitive organisation offers fewer CAF-1-independent means of restoring nucleosome density after fork passage. This is consistent with prior reports linking chronic CAF-1 loss to pericentromeric derepression and an interferon response driven by cytosolic chromatin fragments [9,10], and suggests that at least part of that phenotype originates from a direct, acute assembly deficit at heterochromatin rather than solely from downstream consequences of prolonged replication stress.

That fork progression was not measurably impaired by acute CHAF1A loss, despite a substantial deficit in nascent nucleosome occupancy, indicates that replisome movement and nucleosome assembly are mechanistically uncoupled on this timescale in human cells, with under-assembled daughter chromatin persisting behind an advancing fork rather than acting as an obligate brake on its progression. The elevated gammaH2AX signal observed after CAF-1 loss may

instead reflect downstream genome instability arising from persistently under-packaged nascent DNA rather than a direct block to fork elongation, a distinction relevant to how CAF-1 loss is interpreted in the context of replication stress phenotypes reported in cancer and premature ageing models [2,9].

Several limitations should be considered. First, our acute-degradation design captures the immediate consequences of CAF-1 loss but cannot exclude that longer-term depletion produces additional, qualitatively different chromatin consequences mediated by compensatory pathways not engaged within 30 minutes. Second, our heterochromatin-versus-euchromatin comparison used H3K9me3 domains as a heterochromatin proxy and may not capture heterogeneity among heterochromatin subtypes (constitutive versus facultative, or pericentromeric versus subtelomeric). Third, the MCM2-2A epistasis experiments were performed in a single cell line background, and confirming this hierarchy in additional cell types would strengthen the generality of the proposed hand-off model.

5. CONCLUSION

Combining iPOND-MS, nascent chromatin capture sequencing, DNA fiber analysis and acute CHAF1A degradation resolves a temporal and functional hierarchy among replication-coupled histone chaperones in which ASF1 supplies new and recycled histones immediately behind the fork, MCM2 preferentially channels parental histones toward the lagging strand, and CAF-1 performs a rate-limiting deposition step required for both new histone incorporation and faithful parental histone repositioning, with heterochromatin showing disproportionate sensitivity to CAF-1 loss. These findings clarify that CAF-1 and MCM2 act within a single hierarchical pathway rather than redundant routes, and that fork progression and nucleosome assembly are mechanistically separable on a minutes timescale in human cells. Extending acute chaperone perturbation to additional cell types and chromatin states would help establish how general this assembly hierarchy is across the genome.

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publish, or preparation of the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

S.C. conceived and supervised the study, designed the CHAF1A degron strategy, and analysed the iPOND-MS and nascent chromatin capture data. E.L. performed DNA fiber analysis and generated the MCM2-2A knock-in line. P.C. performed native ChIP experiments and mass spectrometry sample preparation. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This study used an established human colorectal carcinoma cell line (HCT116) maintained under standard institutional biosafety approval; it did not involve animal procedures, human participants, or human data beyond the use of this widely distributed cell line.

Data Availability

Raw and processed iPOND-MS, nascent chromatin capture sequencing and ChIP-seq data generated for this study have been deposited in the Gene Expression Omnibus and PRIDE repositories under accessions available from the corresponding author on reasonable request. Analysis scripts supporting the findings of this study are available from the corresponding author upon request.

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