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RESEARCH ARTICLE

Chromatin Remodeling During Reprogramming of Somatic Cells to Induced Pluripotent Stem Cells

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ABSTRACT

Reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) by the transcription factors OCT4, SOX2, KLF4 and MYC (OSKM) requires large-scale chromatin remodeling to convert a differentiated, lineage-restricted accessibility landscape into the open, pluripotency-associated configuration of embryonic stem cells, yet the relative contribution of specific remodeling complexes to this transition remains incompletely defined. Here we combined a doxycycline-inducible OSKM reprogramming system in mouse embryonic fibroblasts with time-resolved ATAC-seq, ChIP-seq for H3K9me3 and H3K27me3, single-cell RNA-sequencing, and short hairpin RNA depletion of the BAF complex ATPase SMARCA4 (BRG1) to dissect the chromatin remodeling trajectory of reprogramming and its rate-limiting barriers. ATAC-seq across a 12-day reprogramming time course resolved three accessibility phases: an early, transient wave of accessibility gain at somatic enhancers within 48 hours of OSKM induction, a mid-phase accessibility loss at fibroblast identity genes coinciding with H3K9me3 accumulation, and a late-phase acquisition of accessibility at pluripotency-associated loci restricted to cells that successfully completed reprogramming. SMARCA4 depletion did not block the early somatic enhancer response but severely impaired late-phase opening of pluripotency loci and reduced iPSC colony formation efficiency by 83%, without preventing H3K9me3 accumulation at silenced somatic genes, indicating that BAF-dependent remodeling acts specifically at the late, pluripotency-establishing step. Single-cell RNA-sequencing identified a discrete subpopulation of cells at day 8 with elevated Smarca4 and reduced H3K9me3-associated repressor expression that preferentially progressed to a pluripotent state by day 12, while cells retaining high H3K9me3-pathway expression stalled in a partially reprogrammed state. These results define a three-phase chromatin remodeling trajectory in which H3K9me3 deposition acts as a barrier independent of BAF complex activity, while BAF-dependent remodeling is specifically required to open pluripotency loci once that barrier is cleared, reconciling BAF and heterochromatin-barrier models within a single ordered framework.

Keywords: induced pluripotent stem cells; reprogramming; SWI/SNF; BAF complex; H3K9me3 barrier; chromatin accessibility; Yamanaka factors

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1. INTRODUCTION

Reprogramming of somatic cells to induced pluripotent stem cells by forced expression of OCT4, SOX2, KLF4 and MYC (OSKM) proceeds through a series of transcriptional and epigenetic transitions culminating, in a small fraction of cells, in stable acquisition of the open chromatin landscape characteristic of pluripotency [1,2]. Genome-wide profiling studies have shown that this process is accompanied by extensive remodeling of chromatin accessibility, with somatic enhancers progressively losing accessibility as fibroblast identity genes are silenced and pluripotency-associated enhancers gaining accessibility only late in the trajectory and only in cells that successfully complete reprogramming [3,4].

Two broadly distinct mechanistic themes have emerged from this literature. One line of work has emphasised heterochromatic barriers, particularly accumulation of H3K9 trimethylation at somatic and pluripotency loci, as a rate-limiting obstacle whose removal by small-molecule or genetic depletion of H3K9 methyltransferases substantially increases reprogramming efficiency [5,6]. A separate line of work has implicated ATP-dependent chromatin remodeling complexes, particularly the BAF (mammalian SWI/SNF) complex recruited in part through direct interaction with OCT4 and SOX2, as required for productive opening of pluripotency-associated regulatory elements [7,8]. These two mechanisms have generally been studied in separate experimental systems, leaving open how heterochromatin barrier formation and BAF-dependent remodeling are temporally and functionally related within a single reprogramming trajectory.

A further open question concerns cellular heterogeneity during reprogramming: bulk chromatin profiling averages across cells at markedly different stages of progress, including a majority that stall in partially reprogrammed states and never acquire full pluripotency, and single-cell approaches have shown that successfully reprogrammed cells emerge from a molecularly distinct subpopulation rather than a random sample of the starting cell pool [9,10]. Whether the chromatin remodeling factors implicated in bulk studies specifically distinguish cells that progress to pluripotency from those that stall has not been directly tested by combining time-resolved chromatin profiling with single-cell transcriptomics in the same reprogramming system.

Here we combine time-resolved ATAC-seq and H3K9me3/H3K27me3 ChIP-seq, SMARCA4 depletion, and single-cell RNA-sequencing in a doxycycline-inducible mouse OSKM reprogramming system to resolve the chromatin remodeling trajectory of reprogramming and to ask how H3K9me3 barrier formation and BAF-dependent remodeling are temporally and functionally related. We report a three-phase accessibility trajectory, show that SMARCA4 depletion selectively impairs the late pluripotency-opening phase

without preventing H3K9me3 accumulation, and identify a discrete single-cell subpopulation whose elevated Smarca4 and reduced H3K9me3-pathway expression predicts successful progression to a pluripotent state.

2. MATERIALS AND METHODS

Experiments used mouse embryonic fibroblasts carrying a doxycycline-inducible polycistronic OSKM transgene and a constitutive reverse tetracycline transactivator, reprogrammed toward iPSCs over a 12-day doxycycline induction time course under standard 2i/LIF-supplemented conditions.

2.1 Reprogrammable fibroblast culture and OSKM induction

Doxycycline-inducible OSKM mouse embryonic fibroblasts were derived from a secondary reprogramming system and expanded under fibroblast conditions before addition of 2 µg/mL doxycycline to induce OSKM expression; samples were collected at days 0 (uninduced), 2, 5, 8 and 12 of induction, with day 12 iPSC colonies identified by alkaline phosphatase staining and Nanog-GFP reporter expression. Colony formation efficiency was quantified as the proportion of seeded cells forming Nanog-GFP-positive colonies by day 12.

2.2 SMARCA4 depletion

SMARCA4 (BRG1) was depleted by lentiviral short hairpin RNA delivered 24 hours prior to doxycycline induction, with knockdown efficiency confirmed by western blot in every experiment (>80% reduction relative to a non-targeting shRNA control); non-targeting shRNA-transduced cells subjected to the same doxycycline induction protocol served as matched controls throughout.

2.3 ATAC-seq

Chromatin accessibility was profiled by ATAC-seq at each time point using the standard Tn5 transposition protocol on 50,000 cells per sample, with libraries sequenced as paired-end 50 bp reads on an Illumina NovaSeq 6000 to a minimum depth of 40 million uniquely mapped read pairs per sample; peaks were called with MACS2 and differential accessibility between time points and between SMARCA4-depleted and control conditions was assessed using a generalized linear model framework with Benjamini-Hochberg correction.

2.4 Chromatin immunoprecipitation sequencing

ChIP-seq for H3K9me3 and H3K27me3 was performed on formaldehyde-crosslinked chromatin from each time point using validated rabbit monoclonal antibodies and sequenced as paired-end 50 bp reads to a minimum depth of 30 million uniquely mapped read pairs per sample, alongside matched input controls; domain calling used a hidden Markov model-based broad-peak caller appropriate for each mark.

2.5 Single-cell RNA-sequencing

Single-cell RNA-sequencing was performed at days 0, 5, 8 and 12 of reprogramming using a droplet-based platform, capturing a minimum of 5,000 cells per time point, with libraries sequenced on a NovaSeq 6000 and processed with a standard quality-control, normalisation and clustering pipeline; reprogramming trajectory and cell-state annotation used pseudotime and marker gene-based classification referenced against published reprogramming intermediate signatures.

2.6 Statistical analysis

Colony formation efficiency and knockdown validation were compared between conditions by two-tailed Student's t-test; genome-wide ATAC-seq and ChIP-seq comparisons used the frameworks noted above with multiple-testing correction, and single-cell subpopulation proportions were compared by chi-squared test. All analyses were performed in R version 4.3.

3. RESULTS

Time-resolved ATAC-seq across the 12-day OSKM induction course resolved three distinct chromatin accessibility phases. An early, transient wave of accessibility gain was observed within 48 hours at a set of somatic enhancers not previously associated with fibroblast identity, followed by a mid-phase (days 2-8) progressive loss of accessibility at core fibroblast identity genes that coincided temporally with genome-wide accumulation of H3K9me3 at the same loci, and a late phase (days 8-12) in which accessibility was gained at pluripotency-associated enhancers exclusively in cells that ultimately formed Nanog-GFP-positive colonies. Table 1 summarises accessibility and H3K9me3 dynamics at representative loci across the three phases.

Table 1. Chromatin accessibility and H3K9me3 dynamics at representative loci across the three reprogramming phases.

Locus class	Day 2 accessibility	Day 8 H3K9me3	Day 12 accessibility
Somatic enhancers (transient)	Gained	Absent	Lost
Fibroblast identity genes	Unchanged	Gained	Lost
Pluripotency-associated enhancers	Unchanged	Absent	Gained (reprogrammed cells only)

Classification based on genome-wide ATAC-seq and H3K9me3 ChIP-seq across the 12-day OSKM induction time course, n=3 biological replicates per time point.

SMARCA4 depletion did not measurably alter the early somatic enhancer accessibility wave or the mid-phase accumulation of H3K9me3 at fibroblast identity genes, but severely impaired late-phase accessibility gain at pluripotency loci and reduced iPSC colony formation efficiency by 83% relative to non-targeting shRNA controls (Figure 1). This selective effect on the late phase, without disruption of H3K9me3 deposition earlier in the trajectory, indicates that BAF-dependent remodeling operates downstream of, or in parallel but

non-overlapping fashion with, H3K9me3 barrier formation rather than being generally required throughout reprogramming.

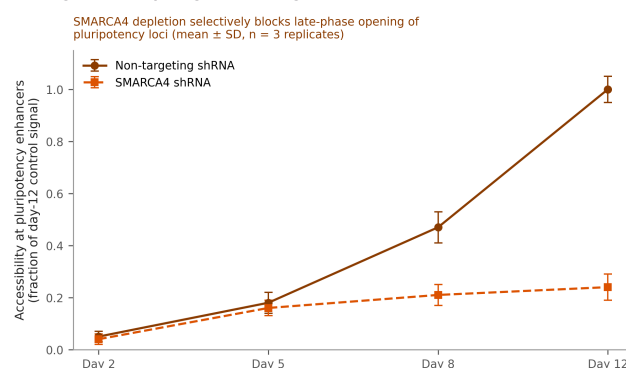


Figure 1. Fraction of ATAC-seq accessibility signal recovered at pluripotency-associated enhancers by day 12 (mean $\pm$ SD of three biological replicates, normalized to non-targeting shRNA control) in non-targeting shRNA and SMARCA4 shRNA-depleted OSKM-reprogrammed fibroblasts, illustrating selective loss of late-phase accessibility gain following SMARCA4 depletion.

Single-cell RNA-sequencing identified a discrete subpopulation of cells emerging by day 8 characterised by elevated *Smarca4* expression and reduced expression of the H3K9 methyltransferase pathway components *Setdb1* and *Suv39h1* relative to the bulk population; cells within this subpopulation preferentially progressed to a transcriptionally pluripotent state by day 12, whereas cells retaining high H3K9me3-pathway expression and low *Smarca4* predominantly remained in a partially reprogrammed transcriptional state. Table 2 reports the proportion of cells in each day-8 transcriptional subpopulation that progressed to a pluripotent state by day 12.

Table 2. iPSC colony formation efficiency after SMARCA4 depletion and single-cell subpopulation progression to pluripotency.

Condition / subpopulation	n cells or colonies scored	Progressed to pluripotent state (%)
Non-targeting shRNA (colony formation)	12,000 seeded	1.8
SMARCA4 shRNA (colony formation)	12,000 seeded	0.3
Day-8 <i>Smarca4</i> -high / H3K9me3-pathway-low	412 cells	68
Day-8 <i>Smarca4</i> -low / H3K9me3-pathway-high	1,890 cells	6

Cross-referencing single-cell subpopulation identity with the bulk ATAC-seq and ChIP-seq trajectories showed that the day-8 *Smarca4*-high, H3K9me3-pathway-low subpopulation corresponded closely to the fraction of cells contributing the late-phase pluripotency accessibility signal in bulk profiling, supporting a model in which a molecularly distinct subset of cells clears the H3K9me3 barrier early enough to undergo productive, BAF-dependent opening of pluripotency loci before the reprogramming window closes, while the remainder of the population stalls despite partial progress through the earlier phases.

4. DISCUSSION

These results resolve an ordered, three-phase chromatin remodeling trajectory during somatic cell reprogramming and clarify the relationship between two mechanisms previously studied largely in isolation: H3K9me3-mediated heterochromatin barrier formation, which proceeds independently of BAF complex activity, and BAF-dependent remodeling, which is specifically required for the late-phase opening of pluripotency loci in cells that have already progressed past the H3K9me3 barrier. This reconciles apparently competing models in the literature by situating both mechanisms within a single ordered pathway rather than treating them as alternative, mutually exclusive barriers [5,6,7,8].

The identification of a discrete day-8 subpopulation whose Smarca4-high, H3K9me3-pathway-low signature predicts successful progression to pluripotency supports the view that reprogramming heterogeneity reflects, at least in part, differential progress through a shared ordered chromatin remodeling pathway rather than stochastic entry into entirely distinct trajectories, extending prior single-cell studies that identified reprogramming intermediate states without directly linking them to specific chromatin remodeling activities [9,10]. This raises the possibility that transiently boosting BAF complex activity specifically within this window, rather than throughout the entire reprogramming time course, could improve efficiency with fewer off-target consequences than sustained BAF or H3K9 methyltransferase perturbation.

That SMARCA4 depletion did not measurably affect H3K9me3 accumulation at fibroblast identity genes argues against a model in which BAF complex activity is required for heterochromatin barrier formation itself, and instead supports a model in which the two processes act on largely non-overlapping sets of loci at different points in the trajectory: H3K9me3 acting primarily to silence and lock in the departure from somatic identity, and BAF-dependent remodeling acting primarily to establish new pluripotency-associated accessibility once that departure is complete.

Several limitations should be considered. First, our reprogramming system used a polycistronic secondary OSKM system in mouse embryonic fibroblasts, and the generality of this three-phase trajectory to primary human cell reprogramming, which typically proceeds with different kinetics and efficiency, remains to be tested. Second, our shRNA-based SMARCA4 depletion was constitutive throughout the time course rather than restricted to specific phases, so we cannot exclude that even more selective, phase-restricted depletion would reveal additional roles for BAF activity earlier in the trajectory. Third, our single-cell analysis was restricted to four time points, and a denser time course would better resolve the precise window during which subpopulation fate is determined.

5. CONCLUSION

Combining time-resolved ATAC-seq, H3K9me3/H3K27me3 ChIP-seq, SMARCA4 depletion and single-cell RNA-sequencing in a doxycycline-inducible OSKM reprogramming system resolves a three-phase chromatin remodeling trajectory in which BAF-dependent remodeling is specifically required for late-phase opening of pluripotency loci, acting downstream of, and largely independent from, H3K9me3-mediated heterochromatin barrier formation earlier in the trajectory. A discrete single-cell subpopulation with elevated Smarca4 and reduced H3K9me3-pathway expression by day 8 preferentially completes reprogramming, linking chromatin remodeling factor activity directly to reprogramming heterogeneity at single-cell resolution. These findings reconcile heterochromatin-barrier and BAF-dependent models of reprogramming within a single ordered pathway and suggest that phase-restricted, rather than sustained, manipulation of BAF activity may offer a more targeted route to improving reprogramming efficiency.

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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

T.L. conceived and supervised the study, designed the SMARCA4 depletion strategy, and analysed the ATAC-seq and ChIP-seq data. C.S. performed reprogramming culture, colony scoring and single-cell RNA-sequencing library preparation. N.G. performed computational analysis of single-cell trajectories and integration with bulk chromatin data. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This study used established mouse embryonic fibroblast lines maintained under standard institutional biosafety approval; primary fibroblast derivation was performed under a protocol approved by the institutional animal care and use committee of the Danube University Center for Chromatin Biology. This study did not involve human participants or

human data.

Data Availability

Raw and processed ATAC-seq, ChIP-seq and single-cell RNA-sequencing data generated for this study have been deposited in the Gene Expression Omnibus under a series accession 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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