A Dynamic Duo: RNA Polymerase II and SWI/SNF Engage in a Reciprocal Feedback Loop to Regulate Transcription Plasticity

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Plain Language Summary

The human body, like other multicellular organisms, is composed of diverse cell types differing in shape and function. Despite these differences, every cell contains the same DNA blueprint housed within the nucleus. This DNA encodes the instructions to build the entire organism. All multicellular beings originate from a single cell that divides and differentiates into various cell types. The key question arises: how do identical DNA blueprints result in distinct cell types like heart or skin cells? The answer lies in the specific DNA conformation within each cell type. DNA is not freely floating in the nucleus; it is compactly organized into chromatin, a structure composed of DNA wrapped around histone proteins, forming nucleosomes. The arrangement of this chromatin determines DNA accessibility. Through a process called remodeling, chromatin is compacted or loosened, exposing or hiding different DNA segments. This selective accessibility enables cells to read distinct DNA regions, producing unique proteins that define their structure and function. Protein synthesis begins with DNA transcription, where the DNA sequence is copied into messenger RNA (mRNA). This mRNA carries the instructions to the cellular machinery that synthesizes proteins. Given its critical role, transcription is tightly regulated by various mechanisms. This review focuses on two major players in transcription regulation and their interplay: SWI/SNF complexes and RNA Polymerase II (RNA Pol II). SWI/SNF refers to a family of protein complexes involved in chromatin remodeling. By sliding or evicting histones, SWI/SNF opens specific DNA regions for transcription. RNA Pol II, with the assistance of other proteins, reads the exposed DNA to produce mRNA. Recent studies reveal that SWI/SNF and RNA Pol II do not operate independently but influence each other's activities, either enhancing or suppressing transcription based on the DNA region and the protein to be produced. A gene, the DNA segment encoding a specific protein, is where this dynamic interaction occurs. The nature of SWI/SNF and RNA Pol II's influence varies across genes, reflecting the cell's requirement for distinct proteins. This regulation is vital for cellular functions, including responses to environmental changes and stress, which demand the transcription of different genes. Additionally, this mechanism allows cells to adapt, differentiate, and maintain homeostasis by quickly modulating gene expression. Newly discovered interactions between SWI/SNF and RNA Pol II reveal how this partnership ensures a fine-tuned, flexible balance in gene expression, enabling cells to meet their needs effectively. This adaptability is crucial for cell survival and specialization. Furthermore, as SWI/SNF dysfunction is implicated in approximately 20% of cancers, understanding these mechanisms could provide valuable insights into potential therapeutic strategies for targeting transcriptional dysregulation in cancer.

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Abstract

Transcriptional regulation in eukaryotes is a highly coordinated process involving the interplay between chromatin remodeling and RNA Polymerase II (RNA Pol II). Chromatin remodelers, like SWI/SNF (switch/sucrose non-fermentable) dynamically alter nucleosome positioning to regulate gene accessibility, while RNA Pol II is the machinery to transcribe genetic information. Despite extensive research into these processes individually, the mechanistic intricacies of their interactions remain underexplored. In this review, I discuss a novel model hypothesis: SWI/SNF chromatin remodeling and RNA Pol II are engaged in a reciprocal feedback loop that not only facilitates transcription but actively modulates transcription plasticity in response to cellular signals. Recent findings indicate that RNA Pol II and chromatin remodelers colocalize, especially during promoter-proximal pausing of RNA Pol II. SWI/SNF facilitates promoter accessibility, controls the release of RNA Pol II into the gene body, and plays a role in transcription elongation. These mechanisms, in turn, influence RNA Pol II's activity. By reviewing the latest literature, I highlight evidence of interdependent regulation, wherein changes in transcription dynamics induce corresponding alterations in chromatin structure and vice versa. Further, recent discoveries have uncovered new, emerging regulatory mechanisms influencing the feedback of SWI/SNF chromatin remodeling and RNA Pol II transcription. My hypothesis posits that this feedback loop plays a critical role in fine-tuning gene expression, allowing cells to respond rapidly and accurately to environmental and developmental cues. The proposed feedback loop expands the current view on SWI/SNF as a transcriptional activator, opening new avenues for research into SWI/SNF-RNA Pol II interactions as targets for therapeutic intervention.

Introduction

Chromatin remodeling plays a pivotal role in regulating transcription by RNA Polymerase II (RNA Pol II), a key enzyme responsible for transcribing protein-coding genes and some non-coding regions in eukaryotes (1). Chromatin, composed of DNA wrapped around histone proteins, exists in dynamic states that influence the accessibility of the underlying genetic code to transcription machinery (2). Tight, condensed chromatin (heterochromatin) typically represses transcription, whereas loosely packed chromatin (euchromatin) is associated with active transcription (3). Chromatin remodeling refers to the processes that alter chromatin structure, either by modifying histones or repositioning nucleosomes, thus controlling RNA Pol II access to gene promoters and regulatory regions. Multiple chromatin remodeling complexes, including SWI/SNF, ISWI, INO80, and NuRD, act in concert with histone modifications to enable or inhibit transcription by modifying nucleosome positioning and histone-DNA interactions (4). The activity of chromatin remodeling complexes is often mediated by transcription factors or coactivators, which help target remodelers to particular genes. This way they orchestrate the opening and

closing of chromatin at transcriptionally relevant sites thereby regulating and directing RNA Pol II activity (5).

The recruitment of RNA Pol II to gene promoters is only the first step in a highly regulated process. Once bound to the promoter, RNA Pol II must overcome the physical barrier posed by nucleosomes to elongate through chromatin (6). Chromatin remodelers and histone chaperones facilitate this process by repositioning nucleosomes and evicting histones, thus allowing RNA Pol II to traverse nucleosome-dense regions of genes (7). Importantly, chromatin remodeling does not only influence transcription initiation but also regulates the elongation, termination, and re-initiation cycles of RNA Pol II (8). Chromatin remodeling plays an essential role in the regulation of RNA Pol II transcription. Disruptions in these processes can lead to aberrant gene expression and are implicated in various diseases, including cancer and developmental disorders (9). Continued research into the molecular mechanisms governing chromatin remodeling and transcription will deepen our understanding of gene regulation and open new avenues for therapeutic intervention. In this review I will focus on a specific family of chromatin remodelers and their influence on RNA Pol II transcription: SWI/SNF (Switch/Sucrose Non-Fermentable). Subunits of these megadalton complexes are found to be mutated in 20% of all human cancers, hence it is of utmost importance to understand their function and regulation in health, and disease (10). To date, the mechanistic links between transcription, chromatin accessibility, and nucleosome remodeling remain poorly understood. This review will therefore address the following question: Does the role of SWI/SNF chromatin remodeling complexes extend beyond sole transcription activation, and how does this involvement influence transcriptional regulation? I hypothesize that SWI/SNF chromatin remodeling and RNA Pol II activity influence each other in both positive and negative directions, establishing a reciprocal feedback loop between the complexes which is essential for the precise regulation of transcription plasticity.

Main

SWI/SNF chromatin remodelers are transcription activators

SWI/SNF chromatin remodelers are ATP-dependent complexes that play a critical role in modifying chromatin structure, thereby regulating DNA accessibility for essential processes such as transcription, replication, and repair. First identified in yeast (*Saccharomyces cerevisiae*), these complexes are evolutionarily conserved across eukaryotes, albeit with increasing complexity in higher organisms. In yeast, SWI/SNF complexes are categorized into two subfamilies: Swi/Snf (11) and RSC (Remodels the Structure of Chromatin) (12). In contrast, higher eukaryotes have evolved the SWI/SNF chromatin remodelers into three distinct, so-called BAF (Brahma Associated Factor) complexes: canonical BAF (cBAF) (13), non-canonical BAF (ncBAF) (14,15), and polybromo-associated BAF (PBAF)(16).

At the core of these complexes are homologous ATPase subunits - BRG1 and BRM (SMARCA4/2) in mammals (17), Brahma in *Drosophila* (18), and Snf2/Sth1 in yeast (19,20) - essential for chromatin remodeling activity. While these complexes share fundamental structural components, they also possess unique subunits that confer functional specialization (21). For instance, the PBAF complex, closely related to the yeast RSC complex, contains the polybromo domain protein BAF180, which recognizes acetylated histones through multiple bromodomains (22). Accessory subunits such as ARID1A/B, BAF155 (SMARCC1), and BAF170 (SMARCC2) in mammals, along with Snf5 and Sfh1 in yeast, facilitate the recruitment of SWI/SNF complexes to specific genomic loci via interactions with transcription factors or histone modifications (23). This modular architecture enables the diverse SWI/SNF complexes to target distinct genomic regions, influencing various cellular processes, from gene activation to DNA repair(21). But despite their differences, the conserved mechanism of nucleosome remodeling through ATP hydrolysis highlights the evolutionary continuity and importance of these complexes in regulating chromatin structure and gene expression across species(24).

Mechanistically, SWI/SNF remodelers act by utilizing the ATPase activity of their catalytic subunits to disrupt histone-DNA interactions. This process involves ATP hydrolysis, which powers the movement or "sliding" of nucleosomes along the DNA or, in some cases, the ejection or partial unwrapping of nucleosomes (4). ATPase domains in these subunits contain helicase-like motifs that translocate DNA relative to the nucleosome, resulting in conformational changes that either shift the nucleosome or expose hidden DNA regions (25). Recent structural studies have revealed that SWI/SNF remodelers bind to nucleosomal DNA asymmetrically, with a hand-like architecture that grips the nucleosome and induces local torsional strain on the DNA, facilitating nucleosome remodeling (26).

SWI/SNF complexes play a crucial role as transcriptional activators by establishing nucleosome-depleted regions (NDRs) at gene promoters and enhancers, thus facilitating the binding of transcription factors and pre-initiation complex components, including RNA Pol II (27–29). These chromatin remodelers actively reposition or eject nucleosomes from regulatory regions, creating accessible sites for the transcriptional machinery (30). BRG1, the key catalytic ATPase in mammalian SWI/SNF complexes, is essential for this transcription activation, as demonstrated by the rapid reduction in transcription upon its acute depletion (27,31). SWI/SNF complexes dynamically maintain chromatin accessibility, continuously restoring NDRs, which are crucial for the persistent activity of regulatory elements such as enhancers and promoters (Figure 1). This function is essential for the binding of general transcription factors and RNA Pol II to form the preinitiation complex, which is critical for gene expression (32). At enhancers, SWI/SNF remodelers promote the creation of accessible chromatin

landscapes that enable enhancer-promoter communication, looping, and subsequent recruitment of coactivators necessary for transcriptional activation (33). By continuously modulating chromatin accessibility at these sites, SWI/SNF complexes ensure that RNAPII can effectively initiate and elongate transcription, which is critical for maintaining gene expression programs in development, differentiation, and stress responses (9). Thus, SWI/SNF complexes serve as vital gatekeepers of chromatin accessibility, actively remodeling nucleosomes to foster a transcriptionally permissive chromatin environment (Figure 1). The dynamic remodeling they provide prevents nucleosome reformation, ensuring that transcription factors and RNA Pol II can access target genes to initiate transcription. This interplay between SWI/SNF complexes, nucleosome dynamics, and RNAPII highlights their central role as an activator of transcription and underscores their importance in maintaining cellular homeostasis.

Interestingly, the recent development of fast-acting inhibitors for the SWI/SNF ATPase subunit Brg1 has enabled researchers to dissect the direct and secondary effects as well as the immediate and long-term effects of Brg1 loss (31,34,35). These advances have uncovered canonical and paradoxical changes in gene expression upon Brg1 inhibition, hinting towards previously unrecognized regulatory mechanisms of SWI/SNF which enable these complexes to activate and repress transcription (36). Here upon depletion of Brg1, some genes showed an upregulation, which is counterintuitive when thinking of SWI/SNF as an activator of transcription. Attempts to further elucidate the underlying mechanisms of SWI/SNF regulation and its influence on transcription have produced intriguing new insights, suggesting an interdependent regulation between SWI/SNF complexes and RNA Pol II (37). This compelling evidence of a more complex regulatory mechanism broadens our understanding of SWI/SNF's role in transcription and suggests promising advances in deciphering its implications in disease, as will be discussed in greater detail below.

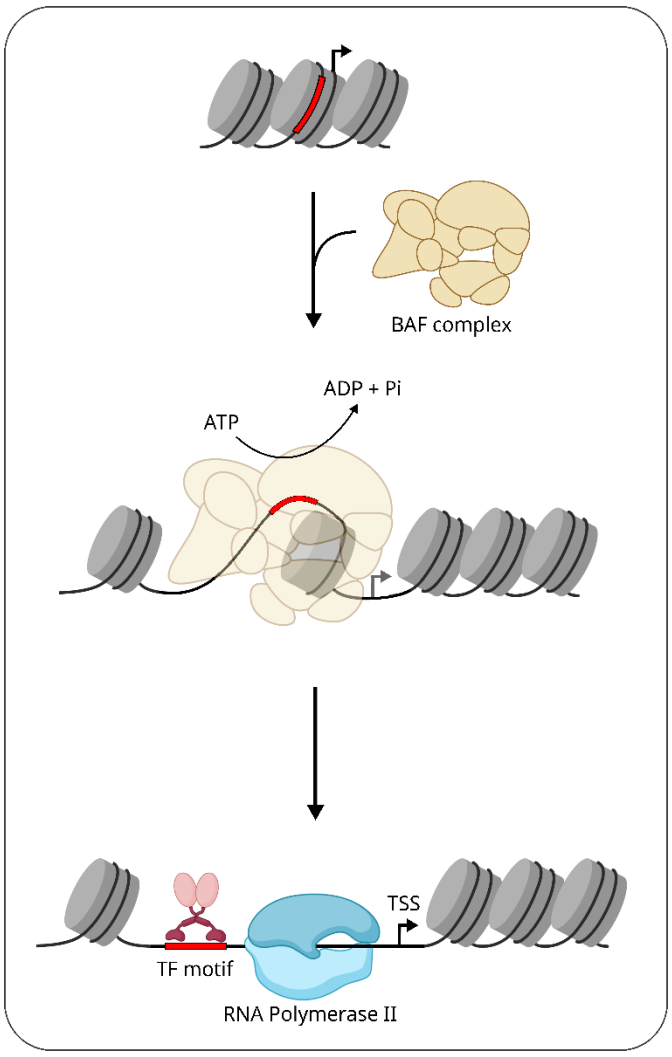

Figure 1: SWI/SNF promotes transcription initiation by establishing and maintaining nucleosome depleted regions: *This illustrates the process by which the BAF complex remodels chromatin to facilitate transcription initiation. Initially, DNA is tightly wrapped around nucleosomes (gray), blocking regulatory DNA elements (in red). The ATP-dependent BAF complex (in tan) binds to chromatin and, through ATP hydrolysis, repositions nucleosomes to expose transcription factor binding sites. This remodeling allows transcription factors (in red and pink) to bind, promoting the assembly of the transcription machinery (blue) at the transcription start site (TSS) and initiating gene transcription.*

SWI/SNF and RNA Pol II show interdependent regulation at promotor-proximal pause sites

To illuminate the to-date unclear mechanistic links between chromatin remodeling and transcription, researchers have investigated the interplay between SWI/SNF and RNA Pol II (36,37). Together these studies reveal a relationship between RNA Pol II activity and SWI/SNF chromatin remodeling, suggesting an interdependent regulation. Beyond continuously promoting transcription by increasing chromatin accessibility genome-wide (27,31), evidence is provided for SWI/SNF being recruited to promoter-proximal pausing RNA Pol II influencing chromatin dynamics at promoter sites (37). Further evidence emphasizes the dual role of SWI/SNF in both activating and repressing transcription. This activity appears to depend on the transcriptional state of the gene, inferring that the SWI/SNF regulatory influence on gene expression is a function of RNA Pol II occupancy (36).

Several recent reports have found evidence arguing against the role of SWI/SNF being purely an activator of transcription: Although Brg1 loss leads to the genome-wide loss of promoter accessibility, Brg1 loss also displays an activating effect for a subset of genes (29,38,39). To elucidate this paradoxical behavior, Pundhir *et al* leveraged previously published data sets of BRG1 genome occupancy and compared them to assay for transposase-accessible chromatin using sequencing (ATAC-seq) data and gene expression data from mouse embryonic stem cells (mESC) with Brg1 knockdown (KD) or after inhibition (36). In line with previous reports, ATAC-seq data displayed a decrease in promoter accessibility in mESC upon Brg1-KD. Interestingly, this loss in promoter accessibility did not always correlate with a reduction in gene expression resulting in two sets of genes with either canonical or paradoxical changes in gene expression upon loss of BRG1 and hence, a decrease in promoter accessibility. The activity of genes was determined according to the RNA Pol II occupancy at the promoter into high, average, low, and bivalent genes. When comparing the gene expression changes upon Brg1-KD in these four classes, strikingly genes with high and average gene activity showed the paradoxical upregulation upon Brg1 loss whereas genes with low activity and bivalent genes displayed a canonical downregulation. There was no difference in the absolute level of SWI/SNF occupancy at the TSS of the different classes (14,29). These opposite responses, along with the unchanged SWI/SNF occupancy at these gene promoters and the universal loss of promoter accessibility after Brg1 knockdown, suggest that SWI/SNF's role extends beyond providing promoter and enhancer access. Instead, it appears to have specific effects on genes based on promoter-proximal RNA Pol II occupancy. This finding suggests that SWI/SNF's impact on transcription might be modulated by a potential synergy with RNA Pol II, particularly with paused RNA Pol II at promoter-proximal sites (36).

Strikingly, concurring observations were made by Gilchrist *et al* when studying genes with high promoter-proximal pausing in *Drosophila* (40). They showed that lowly expressed, highly regulated genes are enriched in inherently nucleosome-favoring DNA sequences at the promoter and also show high levels of promoter-proximal pausing. This report would be in line with the requirement for active ATP-dependent chromatin remodeling to maintain accessibility at promoters with inherently nucleosome-favoring DNA sequences. Here a first link was suggested between the need for chromatin remodeling and promoter-proximal pausing of RNA Pol II which might imply an interconnected regulation.

Interestingly, further evidence for such an interconnected regulation of RNA Pol II and the SWI/SNF chromatin remodeling was brought by Brahma and Henikoff when investigating their interplay upon promotor-proximal pausing of RNA Pol II (37). The authors demonstrate that RNA Pol II promoter-proximal pausing, rather than simply representing a repressive mechanism, actively enriches promotors with the BAF complex, transcription factors (TFs), and general regulatory factors (GRFs). In line with previous reports, they could reveal a strong genome-wide colocalization between RNA Pol II and SWI/SNF, with SWI/SNF and promotor-proximal paused RNA Pol II showing the

strongest colocalization (36). To further test whether RNA Pol II, especially paused RNA Pol II, regulates SWI/SNF recruitment and occupancy at regulatory elements, this study leveraged special low-salt RNA Pol II-S5P CUT&Tag called CUTAC (Cleavage Under Targeted Accessible Chromatin). This new method leads to larger fragment sizes, improving the overall signal-to-noise ratio and sharpness of peaks, enabling more precise localization of initiating RNA Pol II (41). The resulting RNA Pol II-S5P CUTAC peaks correspond to RNA Pol II-occupied nucleosome-depleted regions (NDRs). To dissect how RNA Pol II regulates BAF occupancy the small molecule drugs Triptolide, Flavopiridol, and Actinomycin D were used to inhibit transcription initiation or elongation. Triptolide is a transcription initiation inhibitor that obstructs the ATP-dependent activity of XPB, essential for DNA translocation into the active site of RNA Pol II (42). Flavopiridol and Actinomycin D are inhibitors of transcription elongation but with two distinctly different mechanisms. Flavopiridol inhibits elongation by targeting the elongation factor subunit CDK9 of pTEFb which are kinases triggering pause-release (43). Actinomycin D on the other hand interacts with DNA to form a roadblock for elongating RNA Poll II anywhere on the gene (44,45). Upon Triptolide treatment, RNA Pol II-S5P and Brg1 occupancy at CUTAC peaks was lost, which implies that BAF occupancy is promoted by initiating RNA Pol II, either at RNA Pol II loading or promoter-proximal pausing. Inhibiting elongation by Flavopiridol and Actinomycin D was used to distinguish between the effects of loading or pausing RNA Pol II since they lead to the accumulation of paused RNA Pol II. Treatment cells with both inhibitors showed a rapid increase of paused RNA Pol II alongside the proportional increase in BAF occupancy at CUTAC peaks. These findings suggest that indeed promoter-proximal pausing of RNA Pol II promotes the recruiting of BAF chromatin remodeling complexes. To explore the function of BAF recruitment by paused RNA Pol II, researchers applied their previously established CUT&RUN.ChIP method to detect partially unwrapped nucleosomes in *S. cerevisiae*. CUT&RUN was performed for BRG1, combined with ChIP for histone PTMs, allowing the detection of both nucleosomal (>150 bp) and sub-nucleosomal (<120 bp) particles. Mapping these particles over CUTAC peaks showed BRG1's association with sub-nucleosome fragments, indicating its interaction with partially unwrapped nucleosomes. Notably, RNA Pol II elongation inhibition with Flavopiridol depleted sub-nucleosomal particles at CUTAC peaks, while fully wrapped nucleosomes in surrounding regions remained unchanged. Alongside the reduction in RNA Pol II-S5P CUTAC fragment sizes and the consistent levels of CUTAC signal, this suggests an increase in nucleosome spacing and emphasizes the role of BAF complex recruitment by RNA Pol II to partially unwrap and aid in evicting nucleosomes. Further by treating mESC with the BRG1 ATPase inhibitor BRM014, they could show a retention of partially unwrapped and BRG1-associated nucleosomes. This retention remained even upon dual treatment with BRM014 and Flavopiridol confirming that BRG1 is essential for the eviction of partially unwrapped nucleosomes.

Taken together these reports provide clear evidence for a marked increase in nucleosome eviction at the promoters with paused RNA Pol II, indicating that BAF is actively recruited to these sites to remodel chromatin and facilitate transcriptional re-initiation (Figure 2). The use of specific inhibitors of initiation and elongation allowed them to dissect the specific roles of RNA Pol II and BAF complex components in chromatin remodeling. These findings suggest that BAF partially unwraps nucleosomes in an RNA Pol II-dependent manner rather than simply increasing accessibility across the board. This evidence points towards regulatory feedback between RNA Pol II and BAF supporting a model of transcription control, whereby RNA Pol II activity and BAF activity dictate transcriptional outcomes in an interdependent manner. This highlights an interdependency between RNA Pol II and SWI/SNF activity in transcription regulation and presents a causal link between SWI/SNF chromatin remodeling and transcription by RNA Pol II.

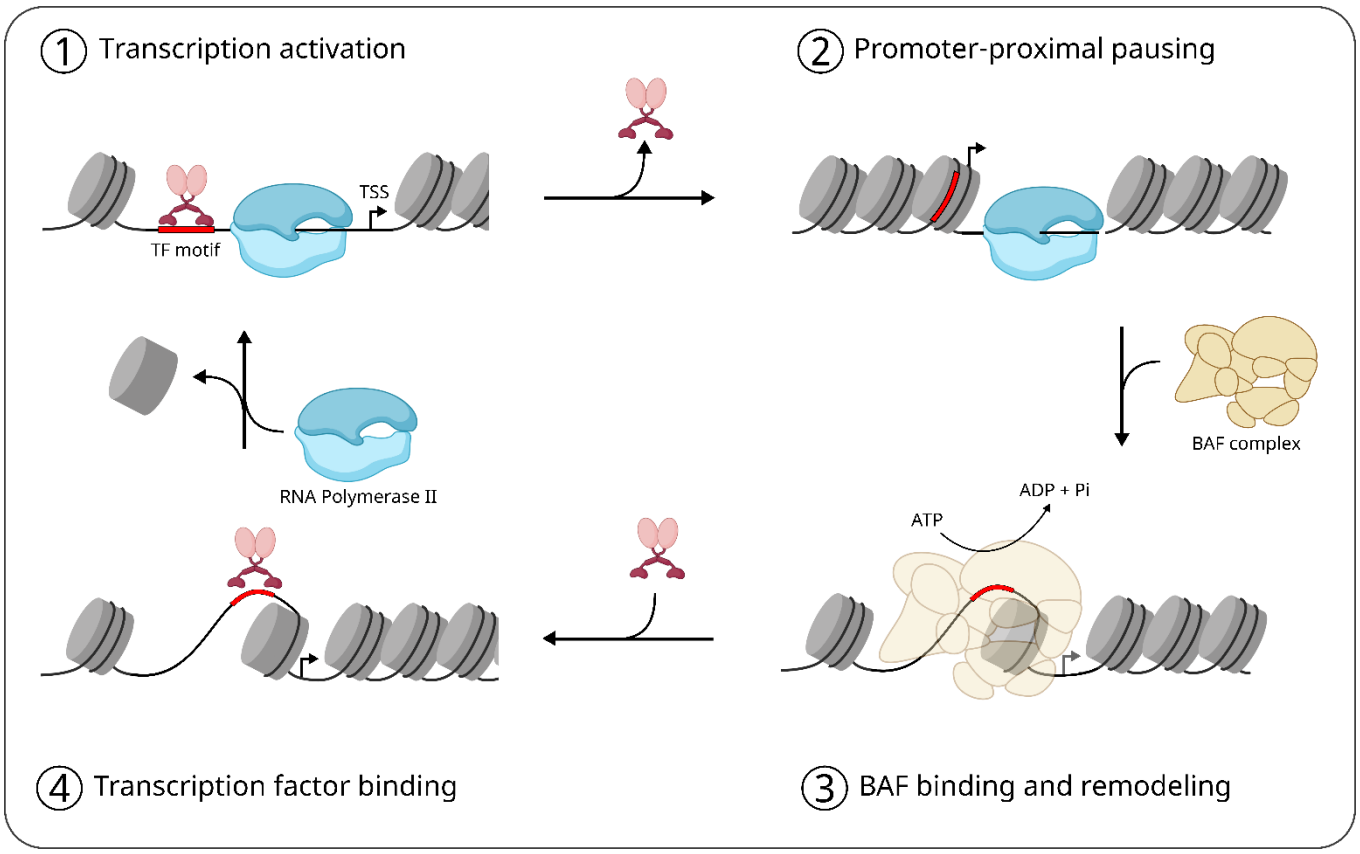

Figure 2: Interconnected transcription regulation by SWI/SNF and RNA Pol II at RNA Pol II promotor-proximal pausing: *This depicts the sequential process of transcription activation and chromatin remodeling upon promoter-proximal pausing of RNA Pol II.* ***(1)*** *Transcription Activation: The process begins with transcription factors binding to DNA motifs (TF motif, in red) near the transcription start site (TSS), facilitating the recruitment of RNA Polymerase II (blue) to initiate transcription.* ***(2)*** *Promoter-Proximal Pausing: RNA Polymerase II pauses shortly after initiation, with nucleosomes (gray) occluding regulatory DNA elements near the promoter region.* ***(3)*** *BAF Binding and Remodeling: The BAF complex (in tan) is recruited to the chromatin and, through ATP hydrolysis, repositions nucleosomes to expose the DNA region near the paused RNA Polymerase II.* ***(4)*** *Transcription Factor Binding: The chromatin remodeling by BAF allows further transcription factor binding to newly accessible DNA motifs, stabilizing RNA Polymerase II and facilitating further initiation. Adapted from Brahma and Henikoff, 2024.*

Mechanisms of interconnected SWI/SNF and RNA Pol II regulation beyond promoter-proximal pausing

While SWI/SNF chromatin remodeling complexes are well-recognized for their role in facilitating transcriptional activation (Figure 3/4), emerging studies reveal interactions with RNA Pol II through previously unexplored mechanisms. These include regulatory functions in transcriptional interference, interaction with long noncoding RNAs (lncRNAs), and facilitation of transcription elongation under specific chromatin contexts. These findings suggest additional mechanisms of interconnected SWI/SNF activity and RNA Pol II transcription. Here, I present mechanisms beyond those previously discussed at promoter proximal pausing sites and their possible roles in broader transcription regulation networks.

SWI/SNF complexes regulate transcriptional interference and gene repression

Recent advances have highlighted SWI/SNF complexes as critical regulators of transcriptional interference (TI) by promoting the expression of long undecoded transcript isoforms (LUTIs) (46). LUTI expression is a recently discovered mechanism in which an untranslated RNA transcript from an alternative upstream promoter (TSS^{DIST}) suppresses the expression of a nearby gene from the proximal promoter (TSS^{PROX}) (Figure 3/1) (47,48). The LUTI overlaps with the target gene's coding region and its expression induces chromatin modifications that hinder transcription factor access, creating a repressive chromatin environment at the TSS^{PROX} (49). LUTI-mediated TI allows cells to adjust gene expression in response to environmental changes, conserving resources by suppressing unnecessary

protein synthesis (50). Using a genetic screening approach in yeast, recent studies identified factors essential for LUTI expression by placing NDC80 LUTI upstream of HIS3 and ADE2 reporter genes. This setup facilitated the identification of "LUTI escape mutants," which all carried mutations in Swi/Snf subunits, suggesting its role in TI through LUTI-based gene repression. To investigate the mechanisms of Swi/Snf-driven LUTI repression, gene expression was compared between wild-type and LUTI escape mutants after inducing unfolded protein response (UPR), a cellular context where transcription isoform switching is common (48). Transcript isoforms were quantified using transcript leader sequencing (TL-seq) (51), revealing genes that switched from distal (TSS^{DIST}) to proximal (TSS^{PROX}) promoters in wild-type cells but not in LUTI escape mutants. Notably, the previously identified LUTI-regulated gene *HNT1* exhibited activating changes in nucleosome positioning at its TSS^{PROX} in wild-type cells, upon UPR induction (48). Additionally, Snf2 depletion resulted in reduced $HNT1^{LUTI}$ expression and increased $HNT1^{PROX}$ expression. These findings suggest two mechanisms of Swi/Snf-driven transcriptional interference: activation of distal promoters (TSS^{DIST}) and repression of proximal promoters (TSS^{PROX}) (46). This study highlights that Snf2's proper occupancy at the *HNT1* locus is critical for LUTI, linking co-transcriptional nucleosome remodeling by SWI/SNF to gene repression. However, the broader applicability of this mechanism and role in other stress-responsive genes requires further investigation.

SWI/SNF complexes interact with lncRNAs to activate or repress transcription

Recent studies have uncovered a direct interaction between SWI/SNF chromatin remodeling complexes and certain long non-coding RNAs (lncRNAs), which plays a crucial role in enhancing the specificity of SWI/SNF-mediated chromatin remodeling (52,53). Through this direct binding, lncRNAs can act as mediators between RNA Pol II and SWI/SNF, influencing transcriptional outcomes in a context-dependent manner. Depending on the specific interactions, these lncRNAs can either activate or repress transcription (52,54). This interplay between SWI/SNF complexes and lncRNAs introduces an additional layer of regulation, highlighting an RNA Pol II-dependent mechanism with significant implications for both physiological (54–56) and pathological (53,57,58) processes.

The recent discovery that lncRNA Xist interacts with the SWI/SNF complex provides valuable insights into X chromosome inactivation, showing how lncRNAs can modulate chromatin accessibility and drive genome-wide gene silencing (Figure 3/3) (59). Studies reveal that Xist RNA not only binds to SWI/SNF but also displaces its core subunit, BRG1, from the inactive X chromosome (Xi), enabling Xist to regulate the silencing of specific genomic regions (54). Ablating Xist RNA increases chromatin accessibility on Xi, as shown by ATAC-seq compared to wild-type cells. UV-RIP (60) and fRIP-qPCR (61) confirmed that SWI/SNF components directly interact with Xist RNA. Loss of Brg1 in Xist-ablated cells reduces chromatin accessibility across the genome, particularly on the X chromosome, where regions that gained accessibility after Xist ablation show a marked reduction. In vivo, Xist RNA-FISH combined with BRG1 immunostaining and nChIP-seq demonstrated that Xist RNA also actively repels BRG1, evicting SWI/SNF complexes from Xi chromosomes (54). These findings highlight a reciprocal regulation between RNA Pol II-mediated transcription and SWI/SNF, where Xist RNA expression inhibits SWI/SNF chromatin remodeling and expels the complex from chromatin, contributing to the silencing of the entire X chromosome.

Additionally, emerging research highlights an activating role for certain lncRNAs, such as SWINGN (SWI/SNF Interacting GAS6 enhancer Noncoding RNA), which recruit SWI/SNF complexes to promote transcription at specific promoters (53). Using ChIP-seq, RNA immunoprecipitation (RIP), and Hi-C data from human fibroblasts, it was shown that SWINGN binds to the SWI/SNF subunit SMARCB1. This recruits SWI/SNF, facilitating chromatin remodeling and increasing accessibility for transcriptional machinery. Notably, this effect was observed specifically at the GAS6 oncogene promoter, as revealed by ChIP-seq. Hi-C and 3C experiments further confirmed the enhancer-like role of the SWINGN locus in promoting GAS6 expression. These findings establish that the interaction between SWINGN and SWI/SNF, via SMARCB1, is essential for activating GAS6 expression (52).

The interaction between SWI/SNF complexes and lncRNAs, such as Xist and SWINGN, highlights the dual role of lncRNAs in modulating chromatin accessibility and transcription. Xist recruits SWI/SNF to the inactive X chromosome, inhibiting chromatin remodeling by displacing BRG1, while SWINGN activates transcription by recruiting SWI/SNF to promoter regions like GAS6.

While further research is needed to determine whether these examples represent unique or common regulatory mechanisms, they illustrate how lncRNA expression can either restrict or enhance chromatin accessibility, depending on the context, affecting gene expression regulation.

SWI/SNF complexes are facilitators of RNA Pol II transcription elongation

Beyond the described mechanisms that drive or repress transcription initiation of RNA Pol II through chromatin remodeling by SWI/SNF, a growing body of evidence suggests the integral role of SWI/SNF complexes in facilitating RNA Pol II elongation. Evidence suggests that SWI/SNF complexes aid RNA Pol II in overcoming nucleosome barriers that hinder its progression during transcription elongation, with reports indicating that these complexes associate with elongating RNA Pol II as potential elongation factors (Figure 3/5).

In vivo studies used episomal reporter vectors with a strong nucleosome positioning sequence placed between a gene promoter and a luciferase reporter gene to investigate the impact of SWI/SNF chromatin remodeling on RNA Pol II elongation (62). Hereby, as confirmed by ChIP-seq, strongly positioned nucleosomes lead to an accumulation of RNA Pol II at nucleosome positioning sequences and a reduction in the luciferase signal compared to control vectors lacking these sequences. Notably, ChIP-seq data also demonstrated BRG1 accumulation at nucleosome positioning sites, a phenomenon absent in vectors lacking the promoter sequence, thereby indicating that BRG1 recruitment is transcription-dependent. To determine whether BRG1 and, by extension, SWI/SNF chromatin remodeling activity, are required for RNA Pol II to overcome these positioned nucleosomes, researchers overexpressed wild-type BRG1 in cells containing vectors with and without nucleosome positioning sequences. In cells with nucleosome positioning sequences, BRG1 overexpression resulted in a marked increase in luciferase activity, suggesting that BRG1 facilitates RNA Pol II elongation by helping to overcome the nucleosome barrier. Importantly, BRG1 overexpression did not affect transcription initiation in control vectors without positioned nucleosomes, reinforcing the specific role of BRG1 in transcription elongation (62).

Earlier research into SWI/SNF involvement in promoter-proximal pausing and elongation on the Hsp70 gene revealed that the human heat shock factor 1 (HSF1) transcriptional activation domains promote RNA Pol II readthrough of paused complexes in vitro. This effect is maximized when SWI/SNF activity is present, suggesting SWI/SNF's involvement in both elongation and reinitiation following promoter-proximal pausing (63). These observations were further supported by the *in vitro* experiments of the same group showing that hHSF1 associates with the ATPase subunit BRG1 of hSWI/SNF. In addition, hSWI/SNF was recruited to a chromatin template by hHSF1 in a purified system. This recruitment was severely reduced when using an hHSF1 mutant which is associated with impaired activation of transcriptional elongation (64). These findings could be replicated *in vivo* in mouse embryonic fibroblasts in which mouse HSF1 was replaced with the human wild-type HSF1, a mutant associated with impaired initiation and a mutant associated with impaired elongation. Compared with the wild-type HSF1, the initiation mutant caused a two-fold reduction of *hsp70* RNA whereas the elongation mutant diminished the production of full-length RNA. Additionally, they were able to show that BRG1 recruitment was abolished by the elongation mutant and chromatin remodeling impaired (65). Later, in agreement with previous findings, another group could show in yeast that the elongation rate of RNA Pol II at the HSP82 gene is affected by Swi/Snf. It was reported that in heat-shocked cells carrying an inactivating mutation in the Snf2 subunit, despite the sixfold reduction in HSP82 transcription, the RNA Pol II occupancy within the HSP82 gene body was unchanged (66).

These experiments elegantly show that SWI/SNF complexes have the ability *in vitro* and *in vivo* to help RNA Pol II overcome nucleosome barriers. Further, they suggest that SWI/SNF complexes could play a role in the release of promotor-proximal paused RNA Pol II and might affect its elongation rate. While these experiments could neither show a direct association between elongating RNA Pol II and SWI/SNF nor could they uncover a mechanism for how SWI/SNF controls pause-release and elongation, these findings are still intriguing and might hint towards a model in which SWI/SNF directly or indirectly finetunes productive elongation of RNA Pol II in a context-specific matter. While these experiments did not directly demonstrate an association between elongating RNA Pol II and

SWI/SNF, nor did they uncover a precise mechanism by which SWI/SNF controls pause-release and elongation, the findings remain intriguing. They suggest a potential model in which SWI/SNF may directly or indirectly fine-tune the productive elongation of RNA Pol II in a context-dependent manner. This hypothesis is further supported by recent investigations into the canonical and non-canonical roles of BRG1 inactivation (36).

To explore the unexpected upregulation of certain genes following BRG1 inactivation, the Pundhir *et al* conducted ChIP-seq with reference exogenous genome (ChIP-Rx) (67) to examine initiating and elongating forms of RNA Pol II. Their quantitative analyses revealed that BRG1 inactivation shifted the ratio of initiating to elongating RNA Pol II towards elongation specifically in genes exhibiting paradoxical upregulation. Additionally, the analysis showed a strong positive correlation between BRG1 and the histone variant H3.3 at TSS-flanking nucleosomes. This histone variant is known to regulate promoter-proximal RNA Pol II recruitment and release through H3K27 acetylation deposition, mediated by CBP/p300 (68,69). Together, these findings provide a potential explanation for the upregulating effects observed upon BRG1 inactivation and suggest that SWI/SNF may selectively modulate RNA Pol II release kinetics by depositing histone variant H3.3 at TSS-flanking nucleosomes.

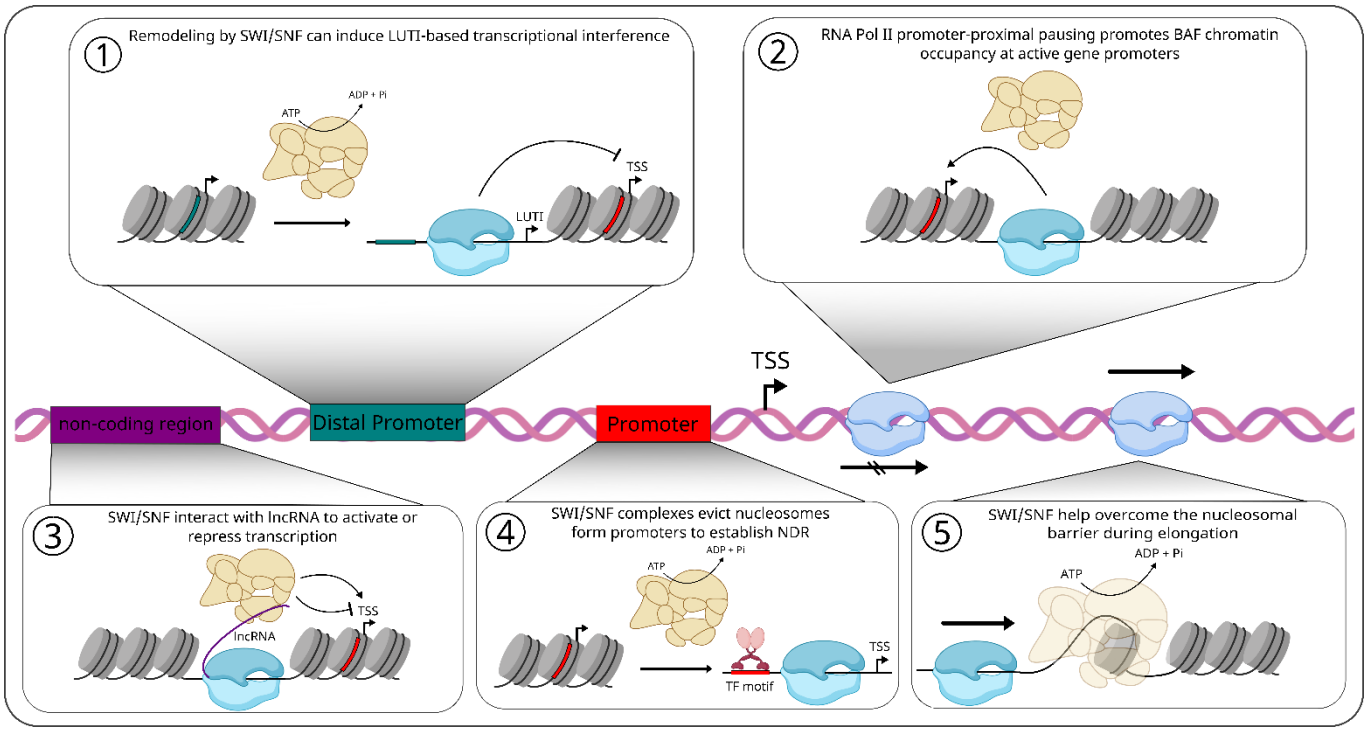

Figure 3: Illustration of the various roles of SWI/SNF chromatin remodeling complexes in transcriptional regulation, including transcriptional interference, promoter accessibility, and overcoming nucleosomal barriers during transcription: (1) *LUTI-Based Transcriptional Interference: SWI/SNF remodeling at distal promoters (green) can lead to Long Undecoded Transcript Isoform (LUTI) transcription, interfering with TSS proximal promoter (red) expression.* ***(2)*** *Promoter-Proximal Pausing: During promoter-proximal pausing, RNA Polymerase II (blue) recruits BAF (SWI/SNF complex) (tan) to maintain chromatin accessibility at active promoters by repositioning nucleosomes (grey) and stabilizing open chromatin states.* ***(3)*** *lncRNA Interaction: SWI/SNF complexes can also interact with long non-coding RNAs (lncRNAs) (purple) to either activate or repress transcription.* ***(4)*** *Establishment of Nucleosome-Depleted Regions (NDR): SWI/SNF complexes evict nucleosomes from promoters and enhancers, creating nucleosome-depleted regions (NDRs) that facilitate transcription factor binding at transcription start sites.* ***(5)*** *Overcoming Nucleosomal Barriers During Elongation: SWI/SNF complexes assist RNA Polymerase II in traversing nucleosomal barriers during transcription elongation.*

Biological Implications: SWI/SNF and RNA Pol II interdependence provides plasticity to highly regulated genes

As reviewed above, the coregulation of SWI/SNF chromatin remodeling and RNA Pol II activity may influence nearly every aspect of transcription. There is evidence for involvement in transcription initiation, promotor-proximal pausing, elongation, transcriptional interference, and regulation through lncRNA. This is exemplified by the role of SWI/SNF-RNA Pol II coregulation, in promoter-proximal pausing of RNA Pol II (37,40), SWI/SNF binding to lncRNA, the induction of unfolded protein response through transcriptional interference (46), and helping RNA Pol II to overcome nucleosome barriers in heat shock protein expression (63–65). This variety of mechanisms raises the question of whether they represent individual processes or a general regulatory mechanism.

Insights into the short-term effects of SWI/SNF inhibition suggest an essential role in maintaining promoter accessibility genome-wide. While other remodelers like EP400 can compensate for SWI/SNF loss at many loci, a subset of genes, primarily those involved in signaling, cell type definition, and developmental pathways, fail to regain promoter accessibility (35). These genes, typically lowly expressed with low promoter accessibility, depend on SWI/SNF activity for appropriate expression (70–72). Such genes often exhibit nucleosome-favoring DNA sequences, elevated paused RNA Pol II, enrichment of TATA-box motifs, and H3K4me1 histone marks - all hallmarks of SWI/SNF-dependent promoters (40). This structural composition renders their promoters inherently less accessible, requiring active remodeling to create nucleosome-depleted regions. Brahma and Henikoff have demonstrated that paused RNA Pol II recruits SWI/SNF in a mediator-dependent manner (37), underscoring the critical feedback between RNA Pol II and SWI/SNF in regulating these genes. This dynamic interplay enables differential regulatory strategies tailored to distinct gene types, reflecting their unique biological demands. Gene-intrinsic properties, such as nucleosome-favoring sequences, influence chromatin state and RNA Pol II activity, which in turn modulates SWI/SNF function (40,62,73–75). These intrinsic features clarify the necessity of chromatin remodeling at such promoters but raise questions about the mechanisms ensuring promoter-specific targeting.

Research in mouse embryonic stem cells (mESCs) reveals a strong correlation between promoter-proximal paused RNA Pol II, BRG1, and pluripotency transcription factors (TFs) such as NANOG and KLF4 at active promoters. Increasing NANOG and KLF4 levels under 2i culture conditions enhances chromatin accessibility by stabilizing nucleosome-depleted regions (NDRs), independent of BAF complex levels. These TFs regulate chromatin accessibility in a SWI/SNF-dependent manner (76–78). Mediators, including transcription factors (37,65), general regulatory factors (79), pioneer factors (80–82), and lncRNAs (52,54,55,58), guide SWI/SNF to specific genes in an RNA Pol II-dependent manner. These interactions allow spatio-temporal control of gene expression by targeting chromatin remodeling to loci requiring accessibility modulation (37,40). This model supports the role of SWI/SNF in adapting chromatin to gene-specific needs through interactions with RNA Pol II and mediators, underpinning the feedback loop's role in context-sensitive gene regulation.

In summary, the SWI/SNF-RNA Pol II feedback loop is essential for transcriptional plasticity, enabling precise gene regulation during development and rapid adaptation to environmental and physiological changes. By linking chromatin remodeling with transcriptional activity, this system balances transcriptional fidelity with flexibility, facilitating inducible or specialized gene expression while maintaining housekeeping gene stability. Its evolutionary conservation across species underscores chromatin remodeling as a cornerstone of gene expression adaptability and complexity.

Hypothesis Discussion: SWI/SNF and RNA Pol II engage in a feedback loop to regulate transcription

This review explored the question of whether the role of SWI/SNF chromatin remodeling complexes extends beyond simple transcription activation, specifically investigating if SWI/SNF and RNA Pol II engage in a reciprocal feedback loop that modulates transcriptional regulation. The hypothesis proposes that SWI/SNF chromatin remodeling and RNA Pol II activity influence each other in both positive and negative directions, establishing a reciprocal feedback loop, essential for meeting specific cellular and environmental demands. Through the lens of recent findings, this hypothesis finds robust support: SWI/SNF complexes

and RNA Pol II indeed appear to co-regulate one another to adapt transcription outcomes dynamically (37).

SWI/SNF and RNA Pol II engage in a reciprocal feedback loop that extends beyond chromatin remodeling and transcription initiation, enabling transcriptional plasticity in response to cellular and environmental changes (Figure 4). This dynamic feedback is modulated at each genetic locus by regulatory factors that recruit, enhance, or inhibit SWI/SNF activity, thereby influencing RNA Pol II activity (37,54,81). Conversely, RNA Pol II activity impacts SWI/SNF recruitment and function (52,62). Brahma and Henikoff propose that this interplay involves a dynamic equilibrium of association and dissociation, where RNA Pol II and SWI/SNF probe the genome for exposed promoter DNA. This model is supported by evidence of rapid turnover of SWI/SNF post-ATP hydrolysis (83,84) and of initiating and paused RNA Pol II (44,85). In PRC2-repressed heterochromatin, the absence of regulatory factors shifts the equilibrium toward dissociation, while active promoters favor association due to accessible chromatin and the presence of regulatory factor binding sites (86). These findings align with my hypothesis that the SWI/SNF-RNA Pol II feedback modulates this equilibrium in response to specific regulatory interactions. The variability in regulatory factors driving this dynamic shift likely reflects the distinct transcriptional demands of housekeeping versus highly regulated genes, which rely on SWI/SNF-RNA Pol II feedback to differing extents. Evidence suggests that lowly expressed, highly regulated genes depend heavily on this feedback loop, to add an extra layer of control (36,40). This feedback operates beyond promoter-proximal pausing, influencing transcriptional interference, initiation, and elongation (36,46,62). In contrast, housekeeping genes, which require stable expression, exhibit less regulated RNA Pol II progression, with minimal reliance on SWI/SNF and compensation of SWI/SNF loss by other chromatin remodelers (34,35,36,74). Pundhir et al. proposed that SWI/SNF in highly expressed genes may regulate RNA Pol II release kinetics by facilitating histone variant H3.3 deposition near transcription start sites, potentially explaining gene upregulation following BRG1 depletion, though further research is needed (36). However, EP400-mediated overcompensation of SWI/SNF loss in some genes offers an alternate explanation for the observed upregulation in highly expressed genes, hence the influence of this feedback on housekeeping genes remains elusive (34).

Among the key regulatory processes in which SWI/SNF and RNA Pol II can influence each other (Figure 4), evidence primarily highlights two as predominant: SWI/SNF facilitates transcription by establishing nucleosome-depleted regions and overcoming nucleosome barriers (Figure 4/4) as well as RNA Pol II, recruiting SWI/SNF to target its chromatin remodeling activity to specific loci (Figure 4/1). Although no direct interaction between SWI/SNF and RNA Pol II was reported, cumulative evidence indicates a strong correlation between RNA Pol II activity and SWI/SNF recruitment (27,31,62). Further, a great body of evidence shows that SWI/SNF-mediated chromatin remodeling is a key activator of transcription initiation (37,79). This activating feedback has been demonstrated across multiple genes, pathways and organisms, underscoring its fundamental role in transcriptional regulation. Conversely, inhibitory feedback between SWI/SNF and RNA Pol II, such as those mediated by lncRNA Xist (54) (Figure 4/2) or transcriptional interference (46) (Figure 4/3), appear to be involved only in the regulation of a limited number of processes. The sparse evidence supporting this inhibitory feedback may suggest that they are isolated phenomena with limited relevance to the general SWI/SNF–RNA Pol II feedback mechanism.

Evidence from yeast, drosophila, mouse, and human cells supports the evolutionary conservation of the SWI/SNF-RNA Pol II reciprocal feedback model, underscoring its biological significance (37,40,79). This model provides a framework for understanding the intricate interplay of SWI/SNF and RNA Pol II in regulating gene expression, crucial for maintaining cellular homeostasis and adaptation. Its implications are particularly relevant to SWI/SNF-related cancers, offering insights into disease mechanisms and informing the development of targeted therapies. By advancing this understanding, the model holds promise for more precise and effective treatments.

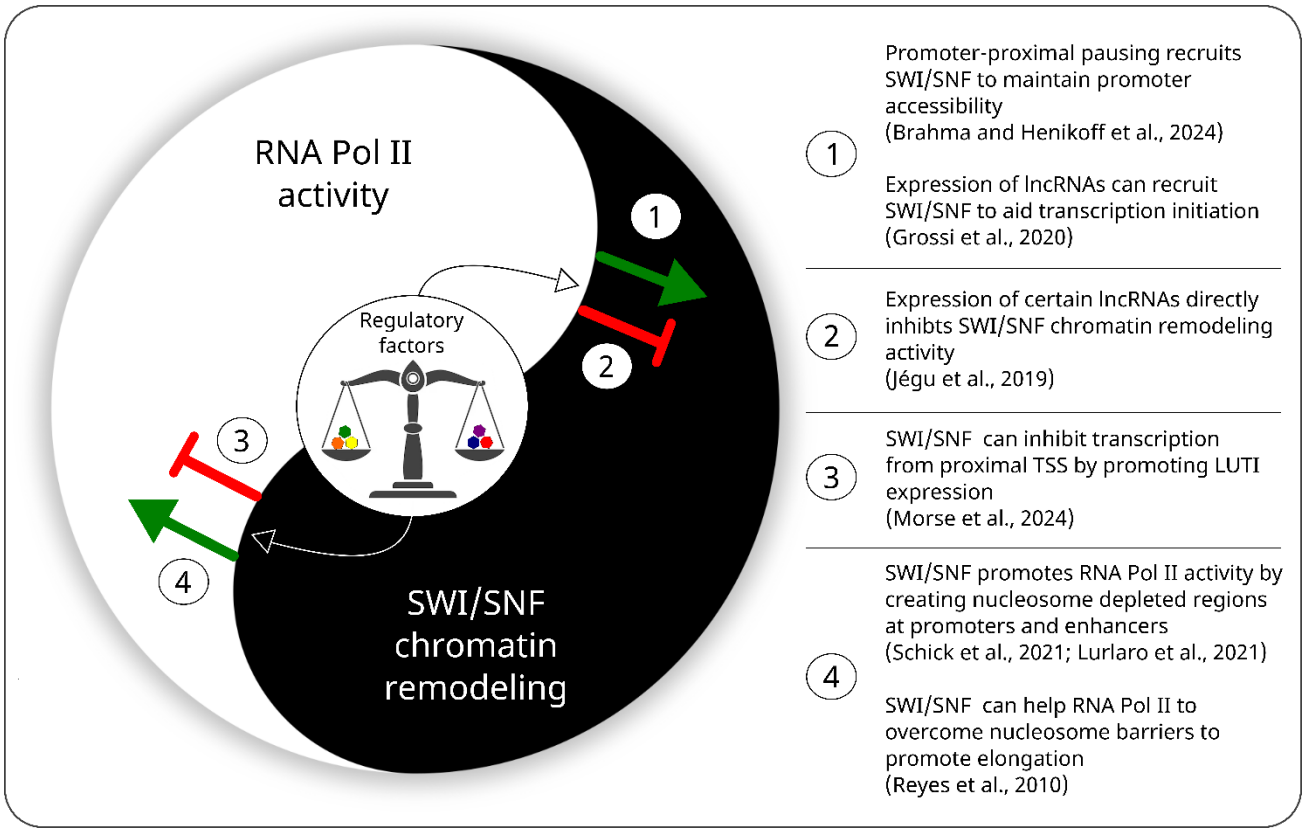

Figure 4: Depiction of the reciprocal feedback loop in which regulatory factors influence the equilibrium of RNA Pol II activity and SWI/SNF chromatin remodeling: *Regulatory factors turn the scale towards specific mechanisms shifting the RNA Pol II-SWI/SNF equilibrium.* ***(1)*** *RNA Pol II SWI/SNF in a context-specific, regulatory factor-dependent fashion (Brahma and Henikoff et al., 2024).* ***(2)*** *lncRNA (Xist) expression can directly inhibit SWI/SNF chromatin remodeling (Jégu et al., 2019).* ***(3)*** *LUTI (long undecoded transcript isoform) expression facilitated by SWI/SNF can inhibit transcription from proximal promoter (Morse et al., 2024).* ***(4)*** *SWI/SNF promotes transcription initiation by establishing nucleosome depleted regions and elongation by helping RNA Pol II to overcome nucleosome barriers (Schick et al., 2021; Lurlaro et al., 2021; Reyes et al., 2010).*

Challenges, Future Directions, and Open Questions

In exploring the SWI/SNF–RNA Pol II regulatory feedback loop, several technical and conceptual challenges limit our current understanding and open avenues for future research. Current techniques like chromatin ChIP/CUT&RUN, CUT&Tag, MNase-seq, and ATAC-seq have illuminated key aspects of RNA Pol II and SWI/SNF function. However, these methods generally capture only static snapshots or cumulative interactions within a population of cells, thus limiting their ability to reveal the real-time dynamics of SWI/SNF and RNA Pol II interactions. Specifically, promoter-proximal pausing by RNA Pol II, a phenomenon thought to prime certain genes for rapid activation (88), may contribute to transcriptional bursts, a mode of gene expression that is especially challenging to study with bulk assays (89). Although the contribution of promoter-proximal pausing to transcriptional bursts remains controversial, I showed that promoter-proximal pausing is especially important for the dynamic regulation of highly regulated genes. This dynamic regulation, likely mediated in part by SWI/SNF's transient chromatin remodeling, calls for more advanced tools capable of dissecting spatiotemporal changes in chromatin and transcription at a single-cell or even single-molecule resolution. Future directions in this area could benefit from live-cell imaging and single-molecule tracking techniques, which could offer new insights into the rapid, context-sensitive interplay between RNA Pol II and SWI/SNF complexes, particularly during the transition between pausing and elongation phases.

A key limitation is the predominant focus on BRG1, the core ATPase subunit shared by the three major mammalian SWI/SNF complexes: canonical BAF (cBAF), non-canonical BAF (ncBAF), and polybromo-associated BAF (pBAF) (90). Many studies use BRG1-targeting inhibitors, knockdowns, and antibodies,

overlooking the distinct subunit compositions and potentially unique roles of these complexes. This generalization obscures critical differences, as cBAF, ncBAF, and pBAF localize to different genomic regions and may regulate distinct pathways (91). Furthermore, the studies reviewed here span various model organisms, and while SWI/SNF structure and function are largely conserved, regulatory mechanisms may differ between species (92). Future research should distinguish between SWI/SNF subtypes to clarify their specific roles in RNA Pol II activity and gene expression regulation.

While this review centers on the SWI/SNF–RNA Pol II axis, gene regulation is also heavily influenced by higher-order chromatin conformations and enhancer-promoter interactions. Chromatin looping facilitates distal enhancer-promoter interactions, amplifying transcription in a spatially coordinated manner, and likely affects SWI/SNF and RNA Pol II dynamics. Given SWI/SNF's role in shaping 3D enhancer landscapes (93–95), this adds complexity to transcriptional regulation. Though beyond this review's scope, future studies could combine advanced chromosome conformation capture techniques (e.g., Hi-C) with real-time imaging to map SWI/SNF and RNA Pol II within the broader chromatin context.

Post-translational modifications of RNA Pol II, including phosphorylation, ubiquitination, and acetylation, add regulatory complexity by potentially influencing SWI/SNF recruitment and activity (96). These modifications may alter RNA Pol II's chromatin associations, guiding SWI/SNF to specific genomic loci in a signal-responsive manner (97). Understanding how these modifications affect SWI/SNF function could illuminate the feedback mechanisms underlying their interaction.

Additionally, further research is needed to clarify the mechanisms by which SWI/SNF, regulatory factors, and RNA Pol II interact. Although direct interactions between SWI/SNF and regulatory factors (80) or RNA Pol II and regulatory factiors (59) have been observed, the precise recruitment mechanism, particularly at promoter-proximal paused RNA Pol II, remains unclear. For example, while paused RNA Pol II promotes BAF and regulatory factor accumulation, no direct interaction was found in Brahma and Henikoff's study (37). Emerging evidence highlights the role of nascent RNA (98), BAF (99), and RNA Pol II (100) in forming transcriptional condensates, offering a novel perspective on how RNA Pol II activity and SWI/SNF interactions are regulated, with implications for drug discovery and molecular engineering.

Importantly, most evidence found on interdependent regulation of SWI/SNF and RNA Pol II was pointing towards both positively affecting each other’s activity. Processes shown to be involved in negative reciprocal feedback between the SWI/SNF and RNA Pol II are substantially less studied. These processes involve transcriptional interference and lncRNA which are emerging topics in gene regulation. To date, reports on these processes are detailed and convincing but still sparce in number (46,52,54). Further reports have suggested the role of SWI/SNF in transcription repression providing more evidence for negative feedback between SWI/SNF and RNA Pol II (101–104). These studies again focus on very specific loci and genes. Therefore, more research needs to be conducted in order to determine whether the observed negative feedback is a general regulatory mechanism or just an isolated phenomenon.

Finally, while this review focuses on SWI/SNF, other chromatin remodelers, such as NuRD and ISWI, may similarly interact with RNA Pol II or form composite networks with transcription factors (36,105,106). Additionally, remodelers like EP400/TIP60 can compensate for SWI/SNF loss, recovering promoter accessibility at many SWI/SNF targets. Consequently, the effects of long-term SWI/SNF loss do not fully represent its target spectrum (34). Expanding research to include other remodelers and their interplay with RNA Pol II could redefine transcriptional regulation as a dynamic equilibrium maintained by multiple interacting complexes.

Conclusion

The intricate relationship between SWI/SNF chromatin remodeling complexes and RNA Pol II underscores a sophisticated system of transcriptional regulation that extends beyond the conventional view of chromatin remodelers as sole activators of transcription. My review highlights a reciprocal feedback loop model where SWI/SNF complexes and RNA Pol II dynamically interact across multiple stages of transcription, mediated by a network of regulatory factors including lncRNAs, pioneer factors, and transcription factors. This interdependent system provides the cell with essential transcriptional plasticity, allowing for rapid and precise adaptation to changing physiological and environmental conditions.

This SWI/SNF - RNA Pol II feedback loop functions through gene-specific mechanisms, offering a flexible regulatory strategy that addresses the distinct transcriptional needs of different gene types. Highly regulated genes, for example, depend on specific recruitment signals and chromatin configurations to fine-tune RNA Pol II pausing, release, and elongation, often in response to stress signals or developmental cues. In contrast, housekeeping genes tend to operate within a streamlined SWI/SNF-RNA Pol II interaction that supports consistent expression, aligning with their critical roles in maintaining cellular homeostasis. Therefore, this reciprocal feedback loop provides plasticity to highly regulated genes while ensuring the consistent expression of highly expressed genes like housekeeping genes.

The diversity of these regulatory interactions is exemplified by studies showing gene- and locus-specific regulation of SWI/SNF by RNA Pol II activity. For instance, the Xist lncRNA directs SWI/SNF to participate in X-chromosome inactivation, while transcriptional interference mediated by SWI/SNF supports cellular stress responses. This feedback loop also incorporates intrinsic chromatin features as mechanism-deciding factors, such as nucleosome-favoring DNA sequences, further enhancing transcriptional control. Thus, rather than acting as a mere facilitator of promoter accessibility, SWI/SNF complexes respond to and influence RNA Pol II activity in a gene-context-dependent manner, finely tuning transcriptional outcomes based on the immediate demands placed on each gene.

Taken together, the reciprocal feedback SWI/SNF–RNA Pol II regulation model offers a robust framework for understanding the flexibility and precision of gene expression across cellular contexts. Evidence from studies across species suggests this mechanism is evolutionarily conserved, underscoring its critical role in maintaining transcriptional fidelity while enabling adaptive responsiveness. Future research into the exact mediators and signaling pathways that modulate this feedback loop will be crucial for a deeper understanding of how chromatin remodeling and transcriptional machinery collaboratively maintain cellular function, highlighting the broader significance of chromatin dynamics in the complex regulation of gene expression. The recent discoveries discussed in this review build the foundation to better understand the role of chromatin remodelers in transcription regulation in health and disease.

Statements and Acknowledgements

Hereby, I state that this review paper was written by one single author - Niklas Kupfer. Generative AI was used in accordance with the Utrecht University School Guidelines. Grammarly was used to improve flow, grammar, and spelling. Science Rabbit and Connected Papers were used for the initial literature search and reading. ChatGPT was used for literature search and improvement of writing flow.

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