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Review Article

Transcriptional repression across mitosis: mechanisms and functions

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Transcription represents a central aspect of gene expression with RNA polymerase machineries (RNA Pol) driving the synthesis of RNA from DNA template molecules. In eukaryotes, a total of three RNA Pol enzymes generate the plethora of RNA species and RNA Pol II is the one transcribing all protein-coding genes. A high number of cis- and trans-acting factors orchestrates RNA Pol II-mediated transcription by influencing the chromatin recruitment, activation, elongation, and/or termination steps. The levels of DNA accessibility, defining open-euchromatin versus close-heterochromatin, delimits RNA Pol II activity as well as the encounter with other factors acting on chromatin such as the DNA replication or DNA repair machineries. The stage of the cell cycle highly influences RNA Pol II activity with mitosis representing the major challenge. In fact, there is a massive inhibition of transcription during the mitotic entry coupled with chromatin dissociation of most of the components of the transcriptional machinery. Mitosis, as a consequence, highly compromises the transcriptional memory and the perpetuation of cellular identity. Once mitosis ends, transcription levels immediately recover to define the cell fate and to safeguard the proper progression of daughter cells through the cell cycle. In this review, we evaluate our current understanding of the transcriptional repression associated with mitosis with a special focus on the molecular mechanisms involved, on the potential function behind the general repression, and on the transmission of the transcriptional machinery into the daughter cells. We finally discuss the contribution that errors in the inheritance of the transcriptional machinery across mitosis might play in stem cell aging.

Mechanisms involved on the transcriptional silencing associated with mitosis

More than 60 years ago, Prescott and Bender [1] first reported a drastic silence of transcription during mitosis by using nascent RNA labeling in HeLa cells (Figure 1A,B). The underlying mechanisms remained unknown until the late 90s, when seminal studies revealed the inactivation of general components of the transcriptional machinery during the mitotic entry through its direct phosphorylation [2–5] (Figure 1C). Parallel works evidenced a massive displacement of transcription factors from mitotic chromatin coupled with an increase on chromosome compaction driven by the loading of condensin complexes into the DNA [6,7]. A more recent study shows the activation, early in mitosis, of the positive transcription elongation factor b (pTEFb) [8], an essential complex for the transition of promoter-paused RNA Pol II into the active elongating variant. This activation triggers the clearance of RNA Pol II complexes already engaged with chromatin facilitating the transcriptional shutdown at the beginning of mitosis (Figure 1C). Although all these mechanisms might indicate a full abrogation of transcription, however, growing evidences have challenged this view demonstrating that transcription is not fully abolished in mitosis. First, several studies have reported the existence of active transcription running at centromeric regions of mitotic chromosomes with a crucial role on centromere cohesion, kinetochore assembly, and chromosome segregation [9,10] (Figure 1D). Both,

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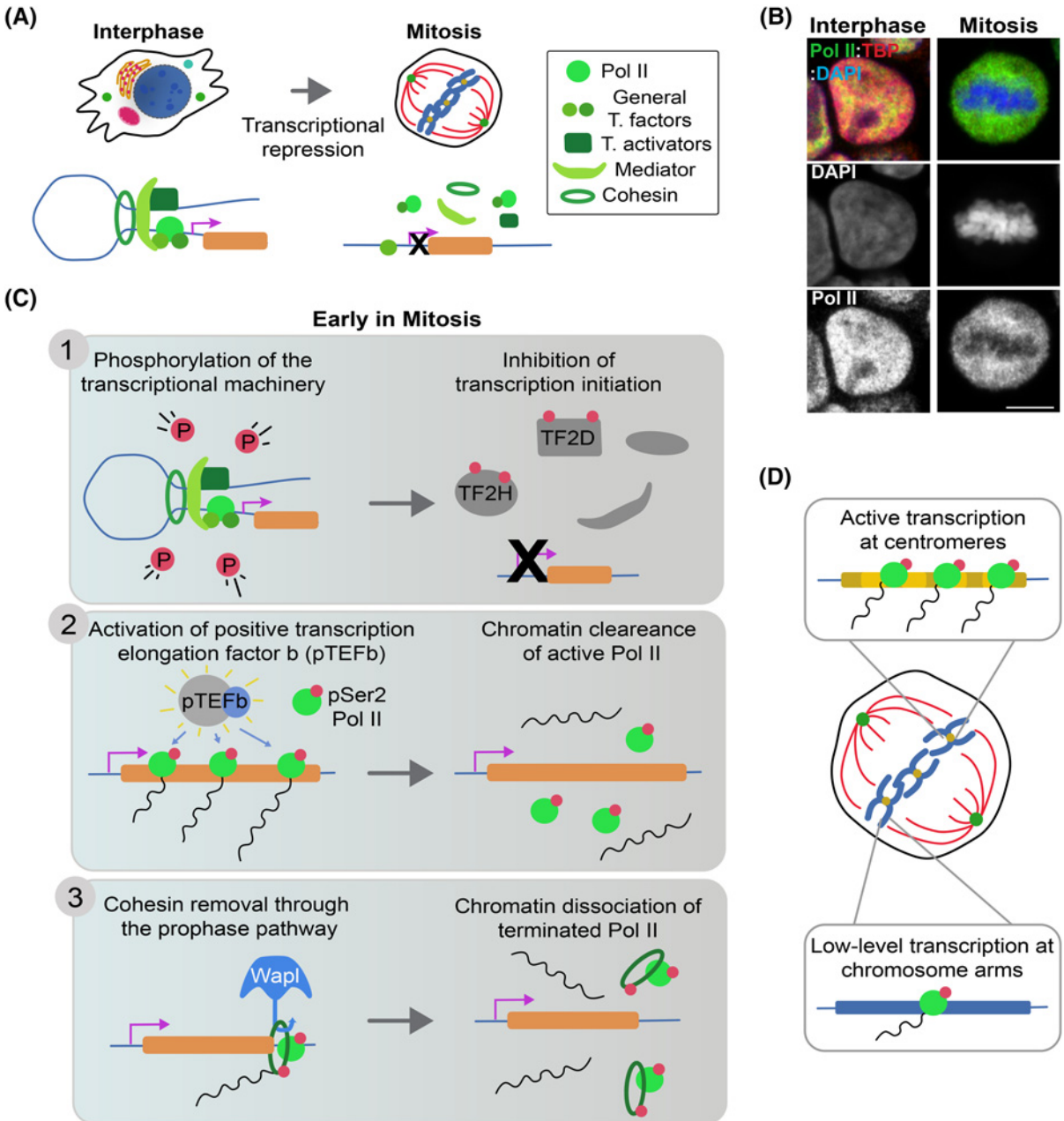

Figure 1. Transcriptional repression in mitosis: mechanisms and exceptions.

(**A**) Schematic representation of the transcriptional activity during interphase (left) and mitosis (right). Repression of transcription parallels with a selective chromatin displacement of the transcriptional machinery. (**B**) Subcellular localization of RNA Pol II (Pol II) and TATA-binding protein (TBP) by means of IF in HeLa cells in interphase (left) or mitosis (right). DAPI staining of DNA is included. Bars = 25 μM in all cases. (**C**) Schematic representation of the main mechanisms proposed to repress transcription early in mitosis. Phosphorylation of the transcriptional machinery (1), activation of the pTEFb complex (2), and the cohesin-based chromatin removal of RNA Pol II (3). (**D**) Active transcription persists at centromere regions and at chromosome arms of mitotic chromosomes.

the effect of transcription on chromatin remodeling and the role of nascent RNA, seems to play an important function at these chromosome regions [11–15]. One of these works revealed the molecular mechanism behind the specific retention of transcription at centromeres. While cohesin removal from chromosome arms favors

RNA Pol II dissociation from chromatin early in mitosis, selective retention of cohesin complexes at centromeres maintains active transcription at these regions [16] (Figure 1C). Second, a high-sensitive method to measure nascent RNA has revealed low levels of transcription still running along mitotic chromosomes. Importantly, the persistence of reduced transcription across mitosis seems to play an essential role on the transcriptional reactivation occurring once cell division finishes [17] (Figure 1D). Overall, all these efforts evidence the existence of synergistic mechanisms acting early in mitosis to selectively repress transcription (Figure 1). Unfortunately, many questions remain unresolved regarding the function that this general inhibition might play.

Why cells selectively repress transcription in mitosis?

Chromatin condensation was initially thought to be one of the main mechanisms behind the repression of transcription associated with mitosis [18]. This compaction might generate a chromatin state no longer accessible for the transcriptional machinery. However, genome-wide measurements on DNA accessibility in mitotic cells by ATAC-seq, together with DNase I treatments, have shown that condensed chromosomes maintain a moderate accessibility compatible with active transcription at least at promoter regions [19–21]. This opens the door for a functional-active role of repressing transcription in mitosis. In fact, pluripotent and committed cells show extensive abrogation of transcription associated with mitosis suggesting that the process plays a relevant function across development. Although a complete picture of the purpose/function of the massive transcription repression remains largely elusive, recent studies just started to shed some light into this question. Here, we discuss several nonexclusive scenarios.

To contribute on proper centromere function

Centromeres are highly repetitive areas of chromosomes with a fundamental role on sister chromatin segregation during mitosis. Interestingly, studies ranging from insect to vertebrate cells show retention of active transcription at these regions in mitosis [9,10,22]. The relative enrichment of transcription at centromeres might provide cells with a mechanism to allocate factors specifically at these regions and guarantee the accurate segregation of chromosomes (Figure 2A). Supporting this idea, active transcription has been shown to play a role on the centromeric localization of CENP-C (centromeric protein C), Sgo1 (Shugoshin 1), AurB (Aurora Kinase B), or ATR (Ataxia telangiectasia and Rad3-related) [11,23–25]. The mechanism behind the centromeric accumulation varies depending on the factor. For example, ATR interacts with centromeric R-loops, DNA–RNA hybrids that form through transcription, while Sgo1 binds nascent RNAs and RNA Pol II directly [24,25]. Independently of the mechanism involved, the presence of active transcription at centromeres in mitosis is shown to support the proper function of these factors and, ultimately, accurate chromosome segregation [10]. In contrast with all these evidences, a study using a large list of transcriptional inhibitors has proposed that the centromere misfunction is caused by the effect of these compounds on centromere integrity, rather than on *de novo* transcription [26]. Thus, the functional relevance of centromeric transcription specifically in mitosis still remains under debate.

A potential role on gene expression reprogramming

Mitosis plays a fundamental role in complex organisms as it constitutes the mechanism to generate the appropriate number of cells. Moreover, mitosis is key to originate cell diversity since most cell fate determination events scheduled during a developmental program occur following cell division [27,28]. On the other hand, cell diversity relies on the establishment of differential gene expression patterns meaning that mitosis provides the appropriate cellular and molecular framework to rewire gene expression. There are at least two potential mechanisms, likely interconnected, of how mitosis favor gene expression reprogramming. First, mitotic chromatin has been shown to be more responsive than interphase nuclei to reprogramming [29,30]. This phenomenon, termed mitotic advantage, relies on the singular composition of mitotic chromatin [30]. Both, chromatin displacement of most factors early in mitosis together with changes on histone epigenetic marks, would generate the unique mitotic plasticity [30,31]. Second, transcription constitutes a central aspect of gene expression and experiences a massive inhibition during mitosis. This general repression might compromise cell fate perpetuation but also favor the required reprogramming in cell fate determination events (Figure 2B). The potential relevance of this mechanism seems evident in the frame of asymmetric cell divisions (ACDs) that produce two daughter cells with different fates. It might be also relevant in symmetric mitosis in light of the differences found between G2 and G1 expression programs [16]. In line with this hypothesis, cells showing retention of

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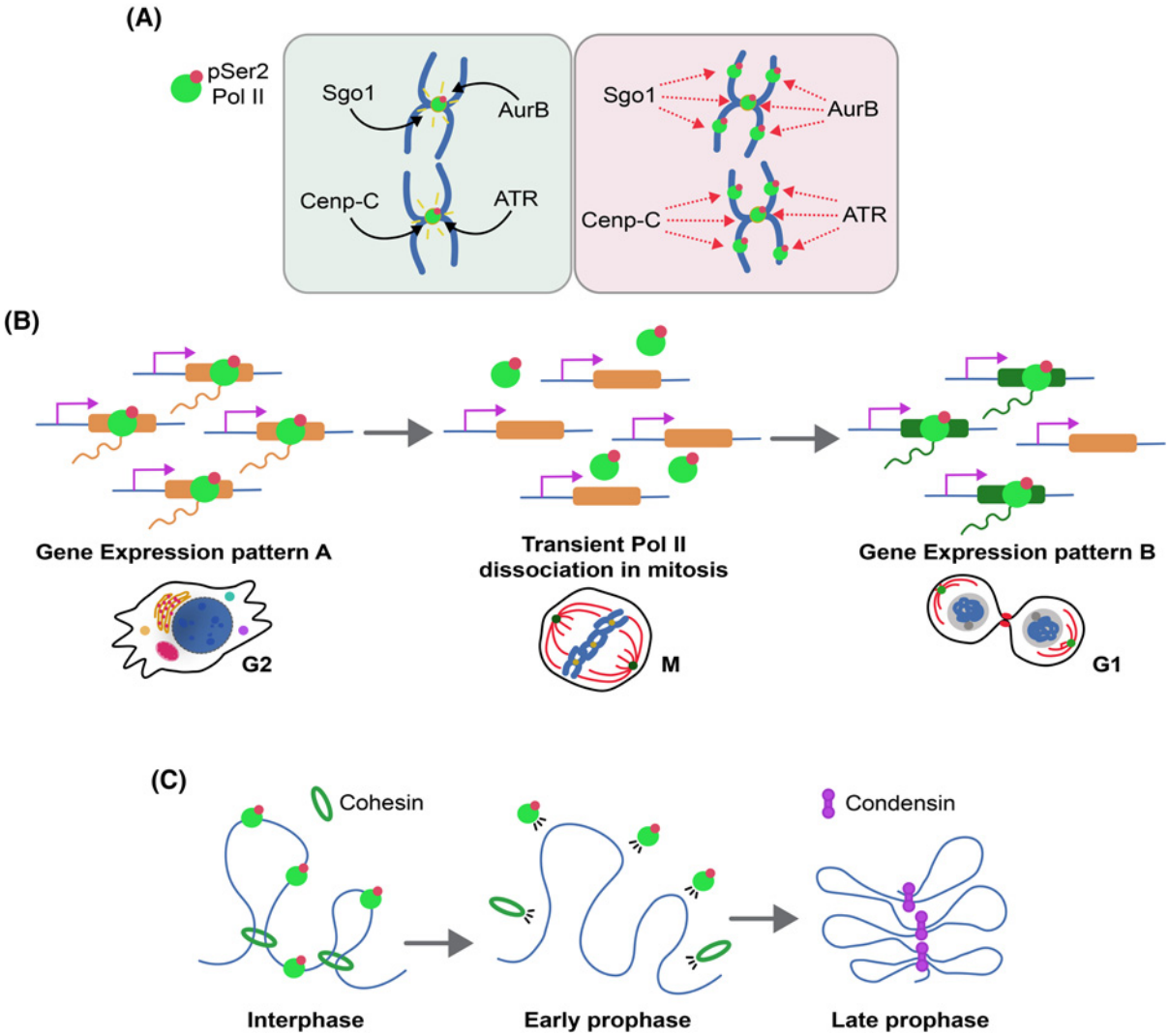

Figure 2. Functional significance of transcription repression in mitosis.

(**A**) The enrichment on active transcription at the centromere might facilitate the recruitment and localization of factors at these chromosome regions in mitosis (left). Retention of Pol II activity at chromosome arms disrupts the localization of centromere factors (right). (**B**) Transient repression of transcription during mitosis might facilitate the transition between differential gene expression programs. (**C**) Silencing transcription early in mitosis might favor the proper condensation of chromosomes driven by the chromatin loading of condensin complexes.

RNA Pol II activity along chromosome arms in mitosis fail to reprogram gene expression and show an aberrant G1 transcription profile that resembles the preceding G2 program. As a consequence, cells experience a delay on cell cycle progression [16]. Studies in yeast also reported that disruption of chromosome condensation early in mitosis causes RNA Pol II retention on chromosomes. This ultimately causes aberrant-ectopic transcription that disrupts the post-mitotic expression program [32]. Finally, the sequencing of nascent RNA from mitotic-arrested cells has revealed the existence of hundreds of transcripts showing increased transcription specifically in mitosis [17]. These results suggest that the selective silencing of transcription is key to generate a unique expression program proper of the mitotic stage. As stated above, the potential role of repressing transcription on gene expression reprogramming across mitosis seems especially attractive in the context of ACD. Unfortunately, a functional study evaluating the role of the mitotic-associated inhibition in this type of cell divisions is still missing.

To ensure the proper condensation and organization of mitotic chromatin

Chromatin strongly condenses when cells enter into mitosis to facilitate the asymmetric segregation of sister chromatids during anaphase. Early in prophase, the interphasic organization is rapidly lost and chromatin stacks following a spiral staircase of nested loops driven by condensin loading [33]. Contrary to a previous conception, measurement of chromatin accessibility by ATAC-seq has revealed similar values between asynchronous and mitotic-arrested cells [19,20]. In fact, single-cell analysis recently uncovered genome sites that remain open through mitosis, are occupied by bookmarking factors (see next section), and play a key role on post-mitotic activation of transcription [21]. Overall, the chromatin compaction associated with mitosis seems compatible with active transcription. It is then tempting to speculate that the topological stress associated with transcription elongation might disturb the proper condensation of chromosomes (Figure 2C). Under this scenario, a massive repression of transcription would help to overcome this conflict although evidences of such a mechanism remain largely elusive.

The rapid development on methods to investigate chromatin–chromatin interactions has recently uncovered, with unprecedent resolution, the organization and dynamics of the genome in 4D [34]. In essence, the genome divides into two large compartments, active (A) versus inactive (B), organized by domains that form through the accumulation of chromatin loops [34]. Analyses of chromatin contacts during the entrance and exit from mitosis evidence a high-complex re-configuration of the genome architecture across cell division [33,35]. Compartments and domains are lost within minutes in prophase [33]. At the beginning of anaphase/telophase, there is a rapid reconstitution and expansion of compartments while CTCF and cohesin orchestrate the formation of domains at later stages [35]. The role, if any, that the mitotic-associated inhibition and further re-activation of transcription might play on these genome rearrangements is unknown. Despite the lack of a functional connection between transcription and genome folding and organization, it is tempting to speculate that the large repression of transcription might influence mitotic genome rearrangements. In fact, several evidences demonstrate that transcription impacts the fine-scale level of chromatin interactions. First, transcription factors are fundamental in the formation of HUBS, short-range chromatin interactions involving two or more loci [36–38]. Second, single-nucleosome resolution of chromatin contacts using micro-C reported that transcription drives promoter–enhancer interactions [39]. Finally, transcription influences the dynamic and localization of cohesin complexes and, consequently, determines the formation and limits of chromatin loops and domains [40,41]. A large transcriptional inhibition might favor the complete resetting on the chromatin–chromatin contact network as cells transit through mitosis by fully dismantling fine-scale transcription-dependent interactions. Finally, it is important to note that transcription highly influences nucleosome positioning [42,43], which has been recently shown to play a role on 3D genome organization [44]. Repressing most transcription early in mitosis would potentially influence nucleosome rearrangement and genome organization during the transit of cells through mitosis. Whether this is required for proper transcriptional reprogramming associated with mitosis needs of future efforts.

Inheritance of the transcriptional machinery across mitosis

Once cell division terminates, transcription levels immediately increase to define the identity and to ensure the viability of nascent cells. Thus, there is an immediate demand on components of the transcriptional machinery by the daughter cells that might be satisfied, at least in part, through the inheritance and reuse of factors from the ancestor cell. Several evidences support such transmission through mitosis although a global view of which components are inherited, and which are not, together with the underlying mechanisms, remains uncomplete.

Chromatin bound factors: transcription bookmarking

The transmission of factors bound to the segregating chromosomes emerges as a straightforward mechanism, not only to transfer the transcriptional machinery from mother to daughter cells, but to demarcate where in the genome transcription must resume. This phenomenon is termed mitotic bookmarking and has been discussed in previous reviews [45,46]. In contrast with the previous conception of a large displacement of chromatin-associated factors, caused by fixation artifacts [20], recent approaches have revealed a high number of proteins linked to condensed chromatin in mitosis [47,48] (Figure 3A). In fact, recent proteomic data show widespread retention of transcription factors on mitotic chromatin indicating that the regulatory landscape is mostly preserved across mitosis [49,50]. General components of the transcriptional machinery, transcription

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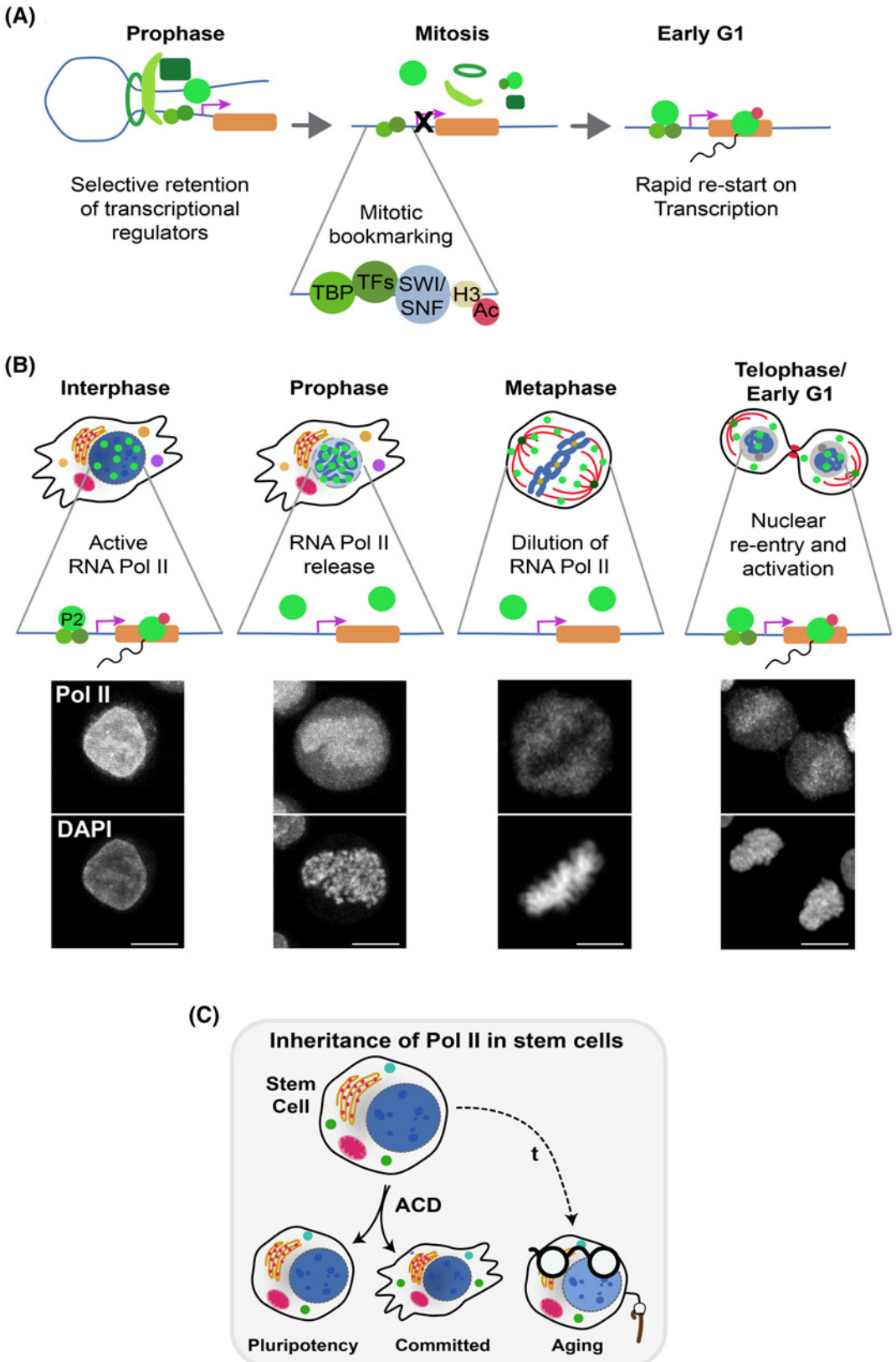

Figure 3. Inheritance of the transcriptional machinery across mitosis, insights into stem cell aging. Part 1 of 2

(**A**) Bookmarking factors, proteins, and epigenetic marks, remain associated with condensed chromatin during mitosis to

Figure 3. Inheritance of the transcriptional machinery across mitosis, insights into stem cell aging. Part 2 of 2

promote the rapid re-activation of transcription once cell division ends. (**B**) RNA Pol II (Pol II) transiently dissociates from condensing chromatin in mitosis, diffuse into the cytoplasm following the nuclear envelope breakdown, and re-enters the nuclei of daughter cells during the telophase-G1 transition. The mechanisms regulating the Pol II dynamics across this travel are poorly known. (**C**) Schematic diagram representing the transference of the transcriptional machinery during mitosis in stem cells. How the transfer occurs in asymmetric cell divisions (ACD), or whether errors on the transmission correlate with stem cell aging, remain unaddressed.

factors, or chromatin architectures and remodelers have been shown to operate as bookmarking factors by binding mitotic chromatin through sequence-specific and/or unspecific mechanisms [20,45–53]. Independently of the underlying mechanism, bookmarking proteins guarantee the rapid re-activation of transcription during the telophase-G1 transition. It is noteworthy that, in addition to proteins, certain epigenetic marks also persist on condensed chromatin across mitosis and collaborate on the transcriptional re-activation. So far, retention of the H3K27ac mark shows the highest correlation with nascent transcription during the onset of mitosis likely favoring the recruitment of transcriptional regulators as BRD4 [54,55].

Inheritance of transcription-associated factors transiently displaced from chromatin in mitosis (RNA Pol II)

In contrast with proteins bound to condensed chromatin (i.e. bookmarking factors), most components of the transcriptional machinery dissociate from chromatin early in mitosis [49]. Determining which factors are transferred to the daughter cells emerges as a regulatory layer with a clear potential to rewire gene expression as cells passage through mitosis. Here, we will focus on the mitotic transmission of the RNA Pol II enzyme. Data from IF or Chip-seq experiments show a massive clearance of RNA Pol II from condensing chromatin [16] (Figure 1B). It is key to remind that concomitant with chromatin displacement, the nuclear envelope disassembles (nuclear envelope breakdown, NEB) and RNA Pol II cellular concentration decreases as nucleoplasm and cytoplasm merge. At the end of mitosis, there is a sequential entry of components of the transcriptional machinery into the nuclei of daughter cells, including the RNA Pol II [55]. However, the mechanisms driving the recycling of the RNA Pol II across mitosis remain poorly understood. Although proteomic approaches have revealed the factors interacting with RNA Pol II specifically in mitosis [57], however, important aspects still remain unaddressed: (i) the mechanisms determining RNA Pol II dynamics following NEB; (ii) the mechanisms involved on safeguarding RNA Pol II complexes from degradation; (iii) the factors regulating the nuclear re-entry of RNA Pol II in the daughter cells; (iv) whether both nascent cells inherited balanced amounts of RNA Pol II, and the underlying mechanism, is also unresolved as well as if this might differ between symmetric and ACDs (Figure 3B).

Implications on stem cell aging

The self-renewal ability of adult stem cells is compromised during the aging process limiting their essential role on tissue repair and homeostasis maintenance [58]. Knowing the molecular mechanisms behind stem cell aging is then critical to improve the prevention and treatment of aging-related diseases. Several studies on the transcriptional reactivation of stem cells following mitosis have demonstrated the early transcription of genes required for pluripotency [47]. In fact, several transcription factors essential for the stemness maintenance act as bookmarking proteins that guarantee the cell fate preservation once mitosis ends [47,51]. It is then tempting to speculate that errors on the proper reactivation of transcription after mitosis might interfere with the rapid establishment of pluripotency in stem cells (Figure 3C). In this direction, global gene expression analyses comparing stem cells from young and old individuals show significant changes at the transcriptional level [58–60]. Unfortunately, whether age-related transcriptional changes are connected with the loss of the self-renewal capacity of stem cells is unknown. Future studies should address this question and evaluate whether errors on the inheritance of the transcriptional machinery across mitosis, and on the subsequent transcriptional re-activation, are connected with the pluripotency loss associated with aging. The existence of such a connection will definitely open the door to novel approaches for the early diagnosis and for the development of therapies to palliate the consequences of the aging process.

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Perspectives

- Studying how gene expression reprograms as cells transit through mitosis is essential to understand the proper and aberrant development of complex organisms.
- Recent advances have evidenced the highly dynamic and complex regulation of transcription during the passage of cells through mitosis.
- Combining cell cycle synchronization methods and proteomic approaches will provide a complete view of the mitotic transmission of the transcriptional machinery across mitosis. The use of models for both, symmetric and ACDs, will also provide essential insight into the transcriptional rewiring associated with development.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contributions

C.P.-R. conceive the work and C.P.-R. and A.C. wrote the manuscript.

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Abbreviations

ACDs, asymmetric cell divisions; ATAC-seq, assay for transposase-accessible chromatin sequencing; BRD4, Bromodomain-containing protein 4; Chip-seq, chromatin Immunoprecipitation sequencing; CTCF, CCCTC-binding factor; DNase I, DNA ribonuclease I; H3k27ac, acetylation of lysine 27 of histone H3; IF, immunofluorescence.

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