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Remembering the past: Mitotic bookmarking in a developing embryo

Maelle Bellec[1], Ovidiu Radulescu[2] and Mounia Lagha[1]

Abstract

During development, transcriptional properties of progenitor cells are stably propagated across multiple cellular divisions. Yet, at each division, chromatin faces structural constraints imposed by the important nuclear re-organization operating during mitosis. It is now clear that not all transcriptional regulators are ejected during mitosis, but rather that a subset of transcription factors, chromatin regulators and epigenetic histone marks are able to 'bookmark' specific loci, thereby providing a mitotic memory. Here we review mechanisms of mitotic bookmarking and discuss their impact on transcriptional dynamics in the context of multicellular developing embryos. We document recent discoveries and technological advances, and present current mathematical models of short-term transcriptional memory.

Addresses

[1] Institut de Genetique Moleculaire de Montpellier, University of Montpellier, CNRS, Montpellier, France

[2] DIMNP, UMR CNRS 5235, University of Montpellier, Montpellier, France

Corresponding author: Lagha, Mounia (Mounia.lagha@igmm.cnrs.fr)

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Introduction

During development of multicellular organisms, transcriptional programs must be faithfully transmitted during each cellular division to ensure cell fate maintenance. Two steps of the cell cycle, mitosis and replication exhibit particular topological constraints, hindering stable inheritance of transcriptional repertoires. However it is now well established that mitosis is not always accompanied by a total erasure of past chromatin states, from mother to daughter cells [1]. On the contrary, memory of active and repressed chromatin states exists, both at the short-term between successive mitoses and in longer time scale through multiple generations [2].

In this review, we focus on recent advances in understanding how active states are transmitted through cellular divisions *in vivo*. We will discuss potential mechanisms and possible mathematical models of mitotic bookmarking and present their consequences in developing multicellular embryos.

Mechanisms of short-term memory have been also analyzed in the context of cultured cell lines and recent reviews summarize these findings [1,3]. Similarly, long-term memory of repressed states mediated by Polycomb family has been intensively reviewed and will not be discussed [4].

Mitosis, a challenging chromatin environment?

During mitosis, genome undergoes a dramatic metamorphose, resulting in clear morphological features of mitotic cells. This chromatin landscape was long thought to represent a hostile environment, incompatible with transcription and transcription factor binding [5].

However, recent studies using sensitive techniques nuance this view. While chromatin folding and compartmentalization are wiped out during mitosis [3,6], local accessibility can be maintained. ATAC-Seq experiments on mitotic *Drosophila* embryos revealed that patterns of accessibility are largely maintained through mitosis for several regulatory elements [7]. One may think that this is peculiar to the early fly embryo, where divisions are particularly fast. However genome accessibility is also widely preserved during mitosis in murine erythroblast cells, yet with local loci specific modulations [8]. Mitotic chromatin landscape has not yet been examined in vertebrate embryos, probably because of the relatively rapid loss in synchrony of divisions, operating as early as the 4-cell stage in zebrafish embryos [9]. This technical issue should be bypassed by recent developments of single cell technologies. Indeed, single cell Hi-C experiments were performed in Embryonic Stem Cells (ESCs) throughout the cell cycle thus revealing a much more dynamic picture of chromosome organization than previous bulk experiments with unsynchronized cells [10].

Mitotic bookmarking and development

Transmission of chromatin states from mother to daughter cells can be achieved passively or *via* active mechanisms. Among known active supports of mitotic memory, stand three classes of regulators: epigenetic histone marks/chromatin regulators, general transcription factors (GTF) and sequence specific transcription factors (TF) (Figure 1).

The vast majority of experiments aiming to assess mitotic retention of these particular factors has been performed in cultured cells with more or less conflicting conclusions, partly due to the level of purity of the mitotic population, cross linking conditions and to the methods of detection (global decoration by imaging versus specific binding assessed by ChIP). In this section, rather than providing an exhaustive survey of potential mitotic bookmarkers [1], we focus on potential supports for transmission of active chromatin states in the context of multicellular developing embryos (Figure 2).

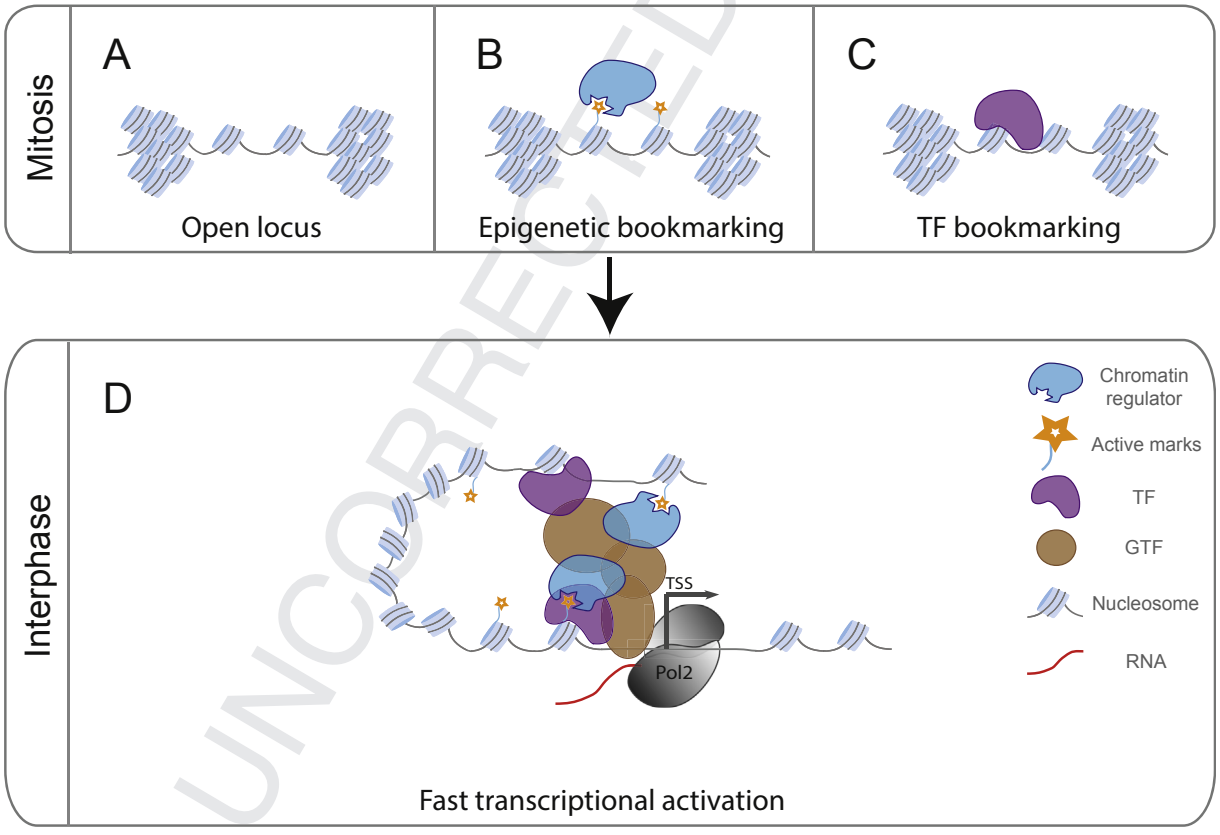
Passive mechanisms of mitotic bookmarking

So far, clear evidences of passive supports of memory are lacking. In a recent work, by monitoring transcriptional activation in living early *Drosophila* embryos, it was shown that experiencing transcription prior to mitosis does not always lead to a rapid post-mitotic activation [11]. With a mesodermal enhancer, memory of active transcriptional states is unequivocally occurring [12], while with a dorsal ectoderm enhancer, memory is not detected [11].

However, given the widespread maintenance of chromatin accessibility during mitosis in the fly embryo, a passive mechanism is plausible (Figure 1).

In interphase, gene expression seems to be partially regulated by local permissive or repressive environments, triggered by nuclear compartmentalization resulting from protein liquid–liquid demixing through phase separation [13] (e.g. HP1 in embryos [14]). The impact of phase separation during mitosis remains

Figure 1



Putative supports of memory of active genes/of transcriptional memory. Mutually non-exclusive mechanisms of mitotic bookmarking occurring at promoters and/or enhancers. A. Previously transcribing locus remains partially accessible during mitosis, thus facilitating post-mitotic re-activation. B. Histone marks and chromatin regulators (readers, writers) of an active chromatin state bind mitotic chromatin, thus 'bookmarking' particular loci for subsequent transcriptional activation. C. Transcription factors such as pioneer factors can associate to a subset of their targets during mitosis, consequently favoring their activation at mitotic exit. D. Through enhancer/promoter priming, all mechanisms illustrated in (A–C) lead to a rapid post-mitotic transcriptional activation.