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Memory Is the Treasury and Guardian of All Things

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Transcriptional memory often relies on interactions with nuclear pore proteins. In this issue of *Molecular Cell*, Pascual-Garcia et al. (2017) describe hormone-induced developmental transcriptional memory in cells that have previously experienced ecdysone, mediated by Nup98-dependent enhancer-promoter looping.

Transcriptional regulation allows organisms to respond to their environment and cells to differentiate into tissues. Epigenetic forms of "memory" perpetuate a transcriptional state based on previous experiences through multiple cell divisions. The title of this piece, a quote attributed to the Roman philosopher Marcus Tillius Cicero (106–43 BC), articulates the practical and conceptual power of memory. Understanding how patterns of gene expression are established, maintained, and passed on through mitosis is critical to understand how organisms develop and are impacted by previous experiences. We have proposed that developmental memory, whereby transcriptional states established by previous stimuli are stably maintained, is distinct from transcriptional memory, whereby inducible genes remain poised for future expression based on a previous environmental stimulus. However, a study in this issue of *Molecular Cell* (Pascual-Garcia et al., 2017) explores an intriguing twist on this distinction: developmental transcriptional memory, in which hormone-induced genes are more rapidly or more strongly expressed in cells that have previously experienced the hormone. Furthermore, this form of memory utilizes components that have been implicated in other types of transcriptional memory, and the authors propose an exciting new model for how these players might work.

Epigenetic transcriptional memory is a deeply conserved mechanism that allows cells to mount a more rapid or robust transcriptional response to an environmental signal that they have experienced previously (Brickner et al., 2007; Light et al., 2010). This mechanism often involves a physical interaction with nuclear pore proteins (Nups) and was originally described in budding yeast, an organism in which it was first recognized that many active genes localize to the nuclear periphery through interaction with the nuclear pore complex (NPC; Casolari et al., 2004). Some of these genes remain associated with the NPC for several generations after repression, and this interaction enhances the rate of future transcriptional reactivation (Brickner et al., 2007; Light et al., 2010). Likewise, in HeLa cells, for up to four generations after experiencing interferon gamma (IFN-γ), hundreds of the genes exhibit stronger or faster induction in cells upon retreatment with IFN-γ (Gialitakis et al., 2010; Light et al., 2013). Transcriptional memory specifically requires Nup100 in yeast (Light et al., 2010), or its metazoan homolog Nup98 in HeLa cells (Light et al., 2013; Figures 1A and 1B). The interaction with Nups alters the chromatin structure of the promoters of these genes, permitting binding of a preinitiation form of RNA polymerase II preinitiation complex, poising them for future transcriptional reactivation (Light et al., 2013, 2010).

In yeast, flies, and mammals, both active and inactive genes interact with Nups (Casolari et al., 2004; Kalverda et al., 2010; Liang et al., 2013; Van de Vosse et al., 2013). However, the functional significance of these interactions has been unclear, particularly during development. Capelson and colleagues undertook a detailed ChIP-seq analysis of several Nups in *Drosophila* and found Nup binding at promoters, enhancers, and insulators. Similar results have recently been reported in mammals (Ibarra et al., 2016). To explore the functional significance of these binding sites, the authors focused on genes induced by the developmental hormone ecdysone. Prior to treatment with ecdysone, many of these promoters and enhancers are bound to Nup98, and the target genes localize at the nuclear periphery. Nup98-bound enhancers from the *Eip74* and *E23* genes show long-distance looping interactions with their respective promoters. Ecdysone treatment leads to a Nup98-dependent increase in the strength of this interaction. This suggested that Nup98 binding at these sites facilitates promoter-enhancer looping when the promoters are active (Figure 1C). However, knockdown of Nup98 had no effect on the expression of ecdysone target genes unless the treatment was repeated. If the ecdysone treatment was performed twice, with 24 hr of recovery, the second induction was much faster/stronger. Knockdown of Nup98 blocked this memory effect, resetting the system to the rate seen during the first induction. Thus, binding of Nup98 facilitated the formation of enhancer-promoter loops to poise a promoter for future re-activation.

This work both raises important questions for the future and may explain some perplexing and seemingly contradictory observations. Work in several organisms has been interpreted to suggest both a positive and a negative role for Nup-gene interactions in regulating transcription. This was also suggested to relate to whether the Nup-gene interactions occur in the nucleoplasm or at the nuclear periphery (Kalverda et al., 2010). However, if Nup binding to active genes can impact future expression, then interpreting the correlation between binding and transcriptional effects of knockdown becomes much more challenging. Consistent with this notion, many genes that are induced during differentiation of embryonic stem cells into neural precursor cells interact with Nup98 prior to their induction (Liang et al., 2013). The paper from Capelson and colleagues will

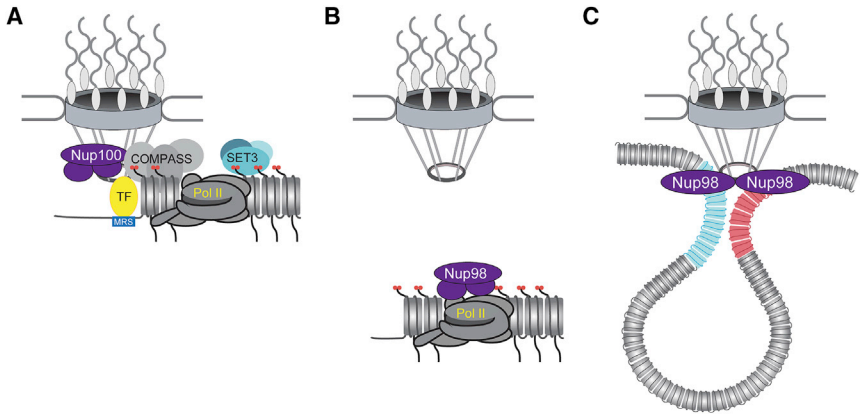

Figure 1. Nup98-Dependent Epigenetic Transcriptional Memory

(A) In yeast, some genes remain associated with the nuclear pore complex (NPC) for several generations after repression, specifically interacting with the Nup100 protein (homologous to metazoan Nup98). Memory is initiated by the binding of a specific transcription factor (yellow) to the MRS DNA-zip code, leading to changes in chromatin structure H3K4 (red) by the remodeling COMPASS complex (writer) and SET3C (reader) allowing preinitiation RNAPII binding, poising the promoter for future activation.

(B) IFN-γ-induced genes are primed for stronger reactivation in HeLa cells. After exposure to IFN-γ, the nuclear pore protein Nup98 binds to the promoters of genes with memory in the nucleoplasm. As with yeast genes that exhibit memory, genes that exhibit IFN-γ-induced memory are marked with H3K4me2 and associated with preinitiation RNAPII.

(C) Upon ecdysone induction, Nup98 mediates formation of an enhancer (blue)-promoter (red) loop, poising these genes for future reactivation.

influence how we think about these experiments in the future.

It remains to be seen if developmental and environmental transcriptional memory are distinct phenomena or a single phenomenon induced by different stimuli. IFN-γ memory also requires a physical interaction with Nup98 (Light et al., 2013), but a role for Nup98-dependent promoter-enhancer looping has not been examined. Although yeast *GAL1* memory is associated with a looping interaction between the 5′ and 3′ ends of the gene, this is not functionally equivalent to an enhancer-promoter loop. The promoters of genes that exhibit environmental transcriptional memory genes exhibit hypoacetylated nucleosomes that are di-methylated on H3, lysine 4 (H3K4me2) and poised, pre-initiation RNA polymerase II (Figures 1A and 1B; Gialitakis et al., 2010; Light et al., 2013). If Nup98-dependent enhancer-promoter looping leads to the same modification, that would suggest a unifying model. Given previous work from the Capelson group showing a physical interaction between Nup98 and the H3K4 methyltransferase Trx (Pascual-Garcia et al., 2014), this seems plausible. Regardless, Pascual-Garcia et al. have identified an exciting new mechanism of transcriptional memory in a developmental context that provides the first indication that Nup proteins can influence epigenetic states through chromosome folding.

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