Transcriptional Memory: Staying in the Loop

Actively transcribed genes are organized into loops in which the 5′ and 3′ ends of the gene physically associate. Two new papers show that gene looping can persist after genes are repressed, promoting rapid reactivation of transcription, a phenomenon known as transcriptional memory.

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Transcription of genes results in dramatic changes in their physical architecture. In their promoters, nucleosomes are removed and remodeled [1]. Along their length, they become less condensed; in polytene chromosomes, active genes appear as 'puffs' [2]. Histones of the nucleosomes housed within the gene acquire characteristic post-translational modifications and these modifications are different at the beginning, middle and end of the gene [3]. Such changes in gene structure may promote transcription or regulate its fidelity [4–6].

Actively transcribed genes also fold (Figure 1). Experiments using Chromosome Conformation Capture (3C) reveal that the two ends of the gene are held in close proximity to each other [7]. This technique uses chemical cross-linking to trap interactions between regions of DNA that are physically near each other [8]. The existence of these gene loops was first observed in the budding yeast *Saccharomyces cerevisiae* [7,9] and has since been documented for human and virus genes [10,11]. In fact, thus far, every transcriptionally active gene analyzed by 3C has been found to be looped.

Because gene looping is a product of transcription but is not essential for transcription [12], its biological function has been enigmatic. However, two papers now provide a link between gene looping and a phenomenon known as transcriptional memory [13,14].

Transcriptional memory is best understood in the case of the galactose-inducible *GAL* genes in yeast [15,16]. These genes are activated much more rapidly if they have previously been expressed [17,18]. Furthermore, this effect is epigenetic; populations of cells retain transcriptional memory after one [18] or seven [17] cell division cycles, suggesting that this effect can survive DNA replication and that it can even be inherited.

Transcriptional memory is associated with changes in the subnuclear localization and chromatin state of the gene [15] (Figure 1). When activated, the *GAL1-10* locus changes from a nucleoplasmic localization to a more peripheral localization [19]. Upon repression, however, *GAL1-10* remains at the nuclear periphery for at least seven generations [17]. Furthermore, rapid reactivation of *GAL1* also requires the non-canonical histone variant H2A.Z [17] and the SWI/SNF chromatin remodeling complex [18]. H2A.Z is also essential for the persistent recruitment of genes to the nuclear periphery [17] (Figure 1). Therefore, chromatin state plays an essential role in the establishment or inheritance of transcriptional memory [17,18].

How might cells 'remember' previous transcription? It is possible that proteins produced under activating conditions can function as *trans*-acting factors to affect the future rate of transcription, perhaps by altering chromatin structure. This type of cytoplasmic inheritance would persist for as long as the *trans*-acting proteins persist. In fact, the Gal1 protein itself has been proposed to be such a factor, interfering with the Gal80 repressor after growth in galactose [20]. It is also possible that the physical alterations of gene architecture or folding that occur during transcription could persist for a period of time after repression and that this could mark the gene for more rapid reactivation. The two new studies find that gene

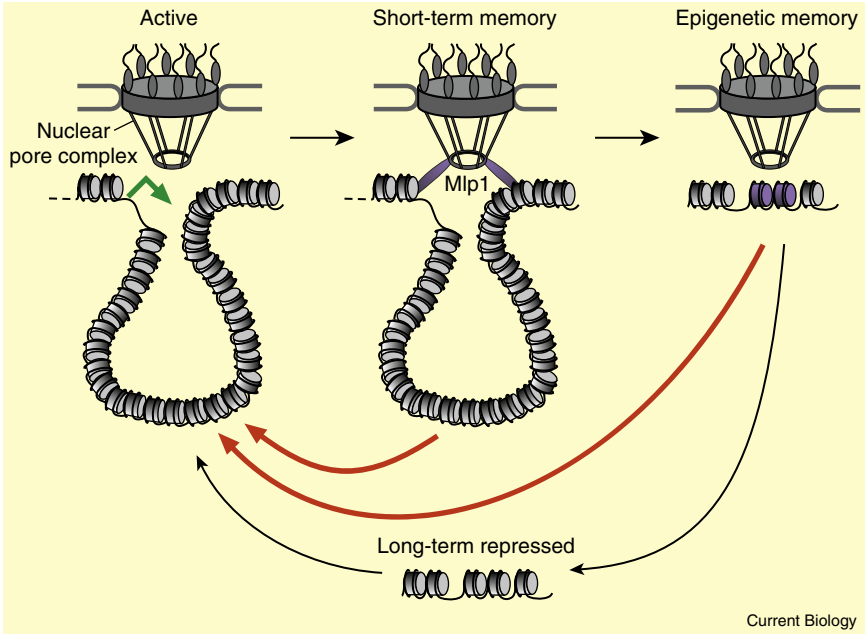

Figure 1. Model for transcriptional memory.

Upon activation, some genes relocalize from the nucleoplasm to the nuclear periphery. Transcription results in gene looping. After repression, genes can remain looped through interactions with the NPC-associated protein Mlp1. The looped gene can be rapidly reactivated (red arrow). Later, an epigenetically inherited memory 'state' exists that localizes at the nuclear periphery but is not looped. This form of transcriptional memory requires chromatin factors like the histone variant H2A.Z (purple nucleosomes) and may be regulated by *trans*-acting factors (see text).

looping can also be preserved and that this is important for transcriptional memory [13,14].

Analyzing several endogenous and artificial galactose-inducible genes in yeast, the most recent studies show that gene loops are maintained after transcription has been repressed [13,14]. For this reason, these post-transcriptional loops were named memory gene loops (MGLs) [14]. MGLs are important for transcriptional memory; in a mutant in TFIIB that blocks gene looping, *GAL* genes were activated normally but reactivation of these genes was defective [13,14]. This suggests that MGLs promote reactivation of certain genes, without affecting their initial activation. Thus, a physical product of transcription can persist to mark a transcribed gene and affect its future regulation.

Looping does not confer memory by itself; loss of SWI/SNF function blocked memory but did not affect MGLs. Therefore, SWI/SNF might function downstream of gene looping to promote reactivation. This suggests that MGLs could act to recruit SWI/SNF. If so, SWI/SNF recruitment would occur both during transcription and after repression. The distinct chromatin structure of a long-term repressed gene and a recently-repressed, looped gene could explain the different rate of RNA polymerase II association of these two forms of the gene.

Another fascinating aspect of this work is that Mlp1 (called TPR in mammalian cells), a protein associated with the nuclear pore complex (NPC), is required for maintaining MGLs and for transcriptional memory [14]. Mlp1 interacts with the 5′ and 3′ ends of the *HXK1* gene when the gene is active. Loss of Mlp1 had no effect on looping while the gene was being actively transcribed. However, Mlp1 was required to maintain the loop after repression (Figure 1). Rapid reactivation of transcription was also lost in cells lacking Mlp1. This suggests that Mlp1 has a role in MGL maintenance and transcriptional memory.

A number of fascinating questions arise from these papers that will drive future work. For example, if every gene is looped while it is transcribed, why do only some genes exhibit MGLs? Is there a function for gene looping that is unrelated to transcriptional memory? Why are some loops more stable than others? Could MGL stability and persistence be affected by growth conditions?

Because MGLs persist for one to four hours and transcriptional memory can persist for more than 12 hours, it becomes attractive to speculate that there may be more than one type of transcriptional memory (Figure 1). Perhaps MGL-mediated memory represents a short term, *cis*-acting memory that is followed by a longer-term epigenetic phase of memory. If so, then MGLs would mark the copy of the gene that was actually transcribed and the later phase might mark the descendents of that gene. This would reconcile the observations that memory can persist much longer than MGLs and that 'artificial' memory can be induced in *trans* by expression of Gal1 [17,20]. If this model is correct, it will be interesting to assess the extent to which these two phases of memory are independent.

Finally, gene looping and the chromatin components that are essential for transcriptional memory in yeast are conserved among eukaryotes. This suggests the possibility that both MGLs and transcriptional memory might also be conserved. If multicellular organisms also have transcriptional memory, then stresses or physiological signals that induce transcriptional responses from cells within tissues might have long-term effects on transcription, gene structure and tissue function.

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