MOLECULAR BIOLOGY

# A Higher Order of Silence

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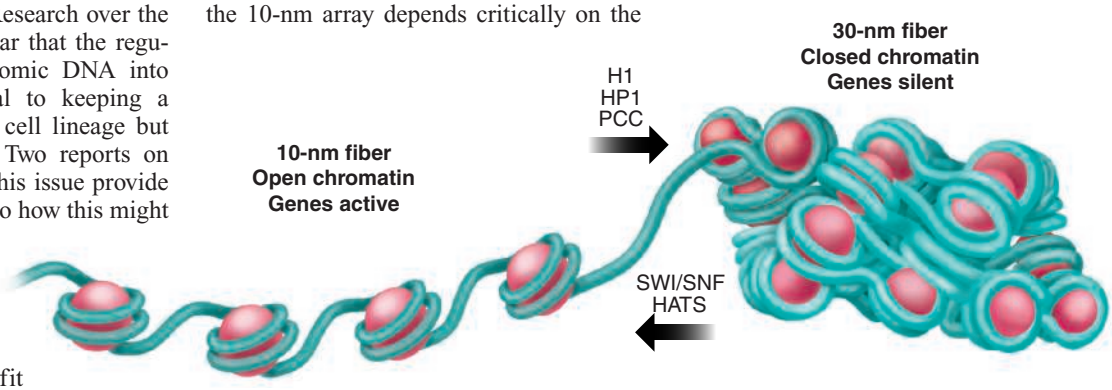
During the development of multicellular organisms, a single fertilized egg gives rise to a plethora of specialized cell types, which are the building blocks of distinct tissues. Because virtually all the cells in our body contain an identical genome, it is the discriminative reading of the genetic information that determines whether a cell is a muscle, skin, or nerve cell. In order to have the "right cell" at the "right place," it is essential that a chosen cellular gene expression program be maintained throughout cell division. Failures in cellular memory or epigenetic control can lead to serious developmental defects and diseases such as cancer. Research over the past decade has made clear that the regulated compaction of genomic DNA into chromatin is fundamental to keeping a gene turned "on" in one cell lineage but turned "off" in another. Two reports on pages 1571 and 1574 of this issue provide intriguing new insights into how this might be achieved (*1*, *2*).

The packaging of DNA into chromatin allows the DNA of human cells (about 2 m in length if stretched out) to fit into a nucleus with a diameter of only 10 μm. The basic repeat element of chromatin is the nucleosome, which consists of 147 base pairs (bp) of DNA wrapped 1.7 times around an octamer of histone proteins (two copies each of core histones H2A, H2B, H3, and H4). Core histones contain a trihelical histone fold domain that mediates histone-histone and histone-DNA binding, as well as unstructured amino-terminal tail domains that are subjected to extensive covalent modifications. Nucleosomes, connected by about 20 to 60 bp of linker DNA, form a 10-nm "beads-on-a-string" array, which can be compacted further into a "30-nm" chromatin fiber (see the figure) (*3*, *4*). Whereas the three-dimensional structure of the nucleosome is known in exquisite detail (*5*), the structure of the higher order 30-nm chromatin fiber is poorly understood.

One basic issue is the arrangement of the nucleosomes within the 30-nm fiber. Two classes of model have been proposed: (i) the "one-start helix" in which nucleosomes, connected by bent linker DNA, are arranged linearly in a higher order helix; and (ii) the "two-start helix" in which nucleosomes, connected by straight linker DNA, zigzag back and forth between two adjacent helical stacks. To distinguish between these two competing models of higher order chromatin folding, Dorigo and co-workers (*1*) developed an ingenious experimental approach using a fully defined in vitro system to generate regular nucleosomal arrays. Further compaction of the 10-nm array depends critically on the base of the histone H4 amino-terminal tails, believed to contact the histone H2A/H2B dimer of the neighboring nucleosome. Indeed, disulfide cross-links between a pair of cysteine residues that replaced selected amino acids in histone H4 and H2A stabilized the higher order chromatin structure. Next, Dorigo *et al*. digested the linker DNA connecting adjacent nucleosomes within the cross-linked compacted chromatin. Analysis of the length of the nucleosome stacks, now solely connected by internucleosomal cross-links, revealed a two-start rather than a one-start organization. This conclusion was corroborated by electron microscopy. In addition to important structural insights, this study shows that local interactions between nucleosomes can drive self-organization into a higher order chromatin fiber.

But what is the physiological relevance of higher order chromatin? Notably, the buffer conditions promoting formation of a 30-nm chromatin fiber reflect the in vivo environment better than do those that yield a 10-nm fiber. One basic premise of chromatin regulation is that genes are silenced through compaction of chromatin, which reduces the accessibility of DNA. In contrast, gene expression may require the "opening up" of chromatin. The Polycomb group (PcG) of gene repressors and the trithorax group (trxG) of gene activators are two antagonistic classes of proteins that may act through modulation of chromatin structure (*6*–*8*). Together, these factors maintain the gene expression patterns of key developmental regulators and hence are crucial players in cellular differentiation, stem cell renewal, and cancer. The trxG group includes members of the SWI/SNF family of adenosine triphosphate (ATP)–dependent chromatin remodeling factors, which use energy derived from ATP hydrolysis to open up chromatin. Conversely, in vivo studies suggest that PcG repression reduces DNA accessibility, but how this is achieved remains unclear (*6*–*9*).

In their study, Francis *et al*. (*2*) used electron microscopy to visualize the compaction of a nucleosomal array promoted by a core polycomb complex, named PCC. It will be of interest to determine whether PCC-induced compacted chromatin forms a bona fide two-start 30-nm fiber. One

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**Regulated chromatin folding directs gene expression.** A parsimonious model illustrating the transition from a 10-nm "beads-on-a-string" open chromatin formation to the next level of chromatin organization: the compacted 30-nm chromatin fiber. Depicted is one possible form of the chromatin fiber produced by a "two-start helix." Folding or unfolding of the chromatin fiber affects the accessibility of DNA to regulatory factors, which control gene expression. Whereas gene silencing factors such as the PCC complex, HP1, and H1 stabilize higher order chromatin folding, gene activators such as the SWI/SNF remodeling complexes and histone acetyl transferases (HATS) initiate chromatin unfolding.

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