important roles in mammalian physiology, growth and behaviour, and numerous diseases are associated with imprinting defects. Beyond their function, imprinted genes are appreciated as a useful and important model for the study of epigenetic regulation of gene expression, because they provide a natural system in which epigenetic modifications are the main determinants of a functional state.

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MILESTONE 16

The importance of wrapping

Nucleosomes are the basic building blocks of the eukaryotic nucleus, packaging DNA into the chromatin of individual chromosomes. The nucleosome consists of a histone octamer — a tetramer of histones H3–H4 and two dimers of histones H2A–H2B — around which the DNA string is wrapped approximately 1.8 times.

***In vitro* studies in the late 1970s with *Escherichia coli* RNA polymerase on bacteriophage DNA showed that transcription can proceed through regions of DNA organized into nucleosomes. Subsequent *in vitro* findings were to reveal that the transcription of other DNA templates was repressed by histones, especially when nucleosome density was increased. However, many believed that chromatin was transparent to RNA polymerase in living cells. Therefore, the idea that nucleosomes might be regulating gene transcription was generally dismissed by scientists in the 1980s, who were preoccupied with the ever-growing list of *cis*-acting sequences and associated factors that controlled gene transcription.**

An important hint that nucleosomes had a function other than packaging DNA came from Kornberg and colleagues, who found that nucleosomes assembling on gene promoters would themselves block initiation of transcription *in vitro*.

Scientists, however, remained sceptical and continued to ignore chromatin until a year later, when Han and Grunstein showed that nucleosome loss, through histone depletion, resulted in the increased transcription of numerous genes in yeast. This provided the first *in vivo* evidence that nucleosomes can repress gene activity. So, as interest grew in understanding how they regulated transcription, nucleosomes found themselves back in the test tube, with their individual histone components being chopped up and examined.

The Grunstein group laid the first cornerstone by showing that histone tails had specific functions. Studies on histone H4 revealed that its tail is dispensable for yeast growth, but is required to repress the activation of specific mating loci through the binding of a repressor protein. The same group showed that the H4 tail also had a gene-activating function and that histone modifications — namely acetylation at specific residues — were required for gene transcription. Now, of course, the post-translational modification of histone tails and their binding to regulatory proteins is a fundamental theme in transcriptional regulation (see Milestones 19 and 22).

So, what was once considered 'cellophane wrapping' now constitutes the 'nuts and bolts' of the transcription-regulatory apparatus. Science and the persistence of certain visionaries has once again proved that appearances can be deceptive, and that you might have to dig a little deeper and stare a little longer to uncover the function that lies at the core.

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