Twist, slide and loop

Changes in nucleosomal DNA accessibility require ATP-dependent remodeling activities. The SWI/SNF and ISWI represent two chief conserved families of remodeling complexes, of which the human proteins BRG1 and SNF2h are representative. In *Molecular Cell*, Fan *et al.* show these two remodelers alter nucleosomal structure by distinct mechanisms. DNA accessibility in mononucleosomes was measured *in vitro* before and after exposure to BRG1 or SNF2h. SNF2h seems to slide the histone octamers along the DNA strand, perhaps by propagating small distortions in the helical twist—as can be imagined when the helix is transiently denatured and reannealed. In contrast, BRG1 seems to distort the nucleosome structure by creating DNA loops, even when constrained by neighboring nucleosomes. This has the effect of exposing the DNA to other factors, such as to transcription factors or recombinases, even when it is still in complexes with histones. Thus, ISWI remodelers may subtly change individual nucleosome translational positions on the DNA, whereas SWI/SNF activities might have a greater function in activating gene expression. *LAD*

Mol. Cell **11**, 1311–1322 (2003)

Oxidized guanine

Deamination of cytosine in DNA to uracil, and its subsequent removal by uracil-DNA glycosylase, can initiate somatic hypermutation of immunoglobulin (Ig) variable (V) regions. Guanine is frequently oxidized and removed by 8-oxoG DNA glycosylase (OGG1). Therefore, OGG1-dependent excision of oxidized guanine, which leaves an abasic site, could also contribute to hypermutation. In the *Journal of Immunology*, Gearhart and colleagues immunized OGG1-deficient mice and sequenced the V regions from the Ig heavy chain and κ loci. The frequency of hypermutation was similar in V regions from OGG-deficient and wild-type mice. In addition, the spectra of nucleotide changes were similar between the two groups and there was no increase in G:C→T:A transversions in the *Ogg*$^{-/-}$ clones, as might be expected if 8-hydroxyguanine remained in the DNA. Thus, OGG1 deficiency does not affect the frequency of hypermutation, indicating that oxidized guanine lesions are not involved in generating antibody diversity. *JDKW*

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Independent switching

Mismatch repair (MMR) proteins Msh2, MIh1 and Pms2 are involved in class-switch recombination (CSR). Analysis of Msh2- and MIh1-deficient B cells has shown that these two MMR proteins have different functions in CSR, but it is unclear if Msh2 is acting on a different pathway than MIh1. In the *Journal of Experimental Medicine*, Schrader *et al.* address this by analyzing CSR in Msh2 MIh1 double-deficient splenic B cells. The switching frequency of Msh2 MIh1 double-deficient B cells was reduced compared with that of cells deficient in either Msh2 or MIh1. Although Msh2 is believed to function earlier than MIh1 in the MMR pathway, the nucleotide sequences of the S -$S_{\gamma 3}$ junctions resemble junctions from MIh1-deficient cells. Substitution mutations that accompany CSR in the S regions are increased in Msh2 MIh1 double-deficient B cells compared with that of cells singly deficient in Msh2 or MIh1. These data therefore indicate that Mih1 functions independently of Msh2 in CSR. *JDKW*

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Acetylated RAG targets

V(D)J recombination occurs by precise targeting of immunoglobulin or T cell receptor loci in a lineage- and temporal-specific manner. How the proper genes are targeted for recombinase action remains unclear. In *Molecular and Cellular Biology*, Johnson *et al.* show that discrete changes in histone acetylation precede RAG-mediated recombination in the immunoglobulin loci. The pattern of histone H4 acetylation correlated with usage of the variable region genes throughout ontogeny; histones in the proximal J_H segments were more highly acetylated in fetal-liver-derived pro-B cells, whereas those of distal J_H segments were so in adult bone marrow cells. Importantly, expression of a transgene, which prevents rearrangement at the endogenous loci, was not accompanied by increased H4 acetylation. Thus, accessibility of the immunoglobulin loci seems to be regulated by sharp boundaries associated with histone H4 modification. *LAD*

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Replicative timing of silent genes

Nonexpressed genes are sequestered into heterochromatin and are thought to be replicated later in S phase than expressed genes. In *Nature Cell Biology*, Fisher's group reports that no correlation exists between gene replication and expression. Analysis of specific gene dosage at various stages of the cell cycle showed no differences in replicative timing between nonexpressing fibroblasts and various developing lymphocytes that did or did not express the gene product. *Cd4*, *Cd19* and *λ5* replicated in S1, whereas *Cd8α*, *Cd45*, *Rag1* and *Tdt* replicated in S2. Conversely, a λ5 transgene replicated late in S4 when integrated within γ-satellite DNA. Local DNA methylation was not sufficient to impose late replication onto silent genes. However, recruitment of silent genes to heterochromatin domains was accompanied by a lag in sister chromatid separation. Thus, apparent differences in the replicative timing are due to prolonged sister chromatid cohesion of inactive genes. *LAD*

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Remodeling with nuclear actin

Actin-related proteins (ARPs) found in the nucleus contribute essential but undefined functions to chromatin-remodeling complexes. In the *EMBO Journal*, Cairns and colleagues show ARPs heterodimerize through their actin-like domains, which are required for ARP function and assembly into SWI/SNF complexes, as cells are not viable upon their loss. Importantly, ARPs were not required for either ATPase activity, nucleosome binding or nucleosome remodeling *in vitro*, disproving earlier ideas of how ARPs may function. However, conditional mutants in nuclear ARP function were rescued by overexpression of a high-mobility group (HMG) protein, which subsequently was found to also associate with the remodeling complex. HMG proteins are known to introduce sharp bends in DNA. Thus, the genetic interactions indicate that ARP-HMG cooperativity is required for *in vivo* chromatin remodeling by an as-yet-undefined mechanism. *LAD*

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