portance relative, say, to proportional abundance. Despite the formidable practical obstacles, some ecologists have tried to do just that, but have only deleted a fraction of species in the food web. These experiments in turn have revealed the difficulty in indexing the importance of species and in measuring their impacts on an ecosystem (*9*). The problem is implicit in Ernest and Brown's paper. Although *Chaetodipus* is already consuming almost as many seeds as the kangaroo rats once did, it may not match the kangaroo rat guild regarding other impacts on the desert ecosystem. Such impacts are loosely defined and could mean anything from changes in species richness to changes in nutrient fluxes, depending on the interests of the observer. There is no consensus on what to measure as an indicator of the importance of a species to an ecosystem, nor does such a consensus seem likely.

Another tricky problem is that the importance of a species might change in different places or at different times (*6*). Practical considerations limit the size of ecological experiments and therefore their domain of relevance. For example, studies of intertidal keystone predators are based on just a few meters of shoreline. But the intertidal ecosystem is highly variable, and a species that is a keystone predator in one area may not be in a neighboring area where, say, sandy overwash rather than predation controls species composition. So, a species that may be highly valuable in one place and at one time may or may not be important in another place or at another time.

The most successful exploration of how plants and animals control ecosystems comes from manipulating shallow lakes. Lakes are very convenient for large-scale ecosystem experiments, in part because their boundaries are clearly defined. Lake ecosystems also respond rapidly to manipulation. In a classic study of trophic cascades in a lake, changes in species and ecosystem characteristics triggered by manipulating piscivorous fish occurred in just 7 years (*10*). Contrast that with the long response time of Ernest and Brown's desert ecosystem. The result is that lake ecologists no longer argue about the relative importance of abiotic and biotic elements as regulators of ecosystem properties. Both are clearly important. The understanding gained by experimental manipulations, coupled with theoretical and technological advances, means that ecologists are able to make informed predictions and interventions to improve water and ecosystem quality. They have reached the stage where knowledge of the system, and the parts played by its component species, can be put into practice.

For the rest of the world, especially its terrestrial parts, our understanding is still rudimentary. We know from case studies that some rare species have very large effects on some ecosystem properties. We are a long way from identifying these species, or their potential impacts, with any confidence. The same is true, however, for the widely recognized problem of invading species (*2*). They too are idiosyncratic with respect to which ecosystems they invade, where, and with what effects. They can have enormous impacts on ecosystem properties. But predicting which species may become invasive, which ecosystems are liable to be invaded, and at what cost is still an important problem. Yet despite intensive study, the best general predictor of whether a species will become invasive, and to what effect, remains its history of invasiveness elsewhere (*2*). For native species in native ecosystems, well-documented case studies, such as the kangaroo rat in its desert ecosystem, could fulfill a similar role in warning of the potentially large consequences of losing influential rare species.

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PERSPECTIVES: MOLECULAR BIOLOGY

The Histone Modification Circus

Shelley L. Berger

There's an old circus routine that begins with a little car driven into the arena. One clown climbs out, then another emerges and another and another until the audience laughs and wonders how many more can possibly appear. The sequential discoveries of a series of distinct covalent modifications of histone proteins bring this absurd circus skit to mind. Several recent reports are beginning to bring order to the apparent chaos of the many histone modifications that are required for the regulation of gene expression. One of these reports, by Nakayama *et al.* (*1*) on page 110 of this issue, examines how histone modifications regulate the silencing of genes. The authors propose a chronological order for a dual histone modification step and elucidate how each modification contributes to gene silencing.

Histone proteins associate with DNA to form nucleosomes, permitting copious amounts of DNA to be neatly packaged into the nucleus. Histones are also direct regulators of gene expression because they can alter the accessibility of gene sequences in the DNA to components of the transcription and replication machinery that must bind to DNA to carry out their work. Addition of acetyl groups (acetylation) to amino acids in the amino terminus of histones provides a valuable model for understanding other histone modifications. The acetylation model is useful because acetylation strongly correlates with gene activation, and because many of the acetyltransferase enzymes that acetylate histones are coactivators of transcription, recruited to promoters by DNA-bound activators. From these observations a model emerges that elaborates the importance of acetylation in promoter-specific alterations of repressed chromatin. This model is substantiated by the finding that certain histone deacetylases—enzymes that remove acetyl groups from histones—are transcriptional corepressors that are recruited to chromatin by DNA-bound repressor proteins.

But why are there so many distinct types of histone modifications, and what is the precise mechanism through which they alter gene transcription? Indeed, the list of well-characterized modifications continues to grow, with the recent addition of phosphorylation (*2*, *3*) and ubiquitination (*4*, *5*). With the Nakayama *et al.* paper, another histone modification—methylation (the addition of methyl groups to histones)—now takes center stage (*1*, *6*, *7*). These investigators (*1*) describe the relation between histone methylation and deacetylation during gene silencing in the fission yeast. Their study builds upon the recent identification of the histone methyltransferases (enzymes that add methyl groups to histone amino acids) SuV39h1 in mammals, and its homolog Clr4 in yeast (*8*). Classical genetics had revealed that the genes encoding these enzymes and their relatives in the fly are required for maintaining certain chromosomal regions such as the centromeres in an inert (heterochromatic) state.

Nakayama *et al.* developed a specific antibody that detects methylation of amino acid lysine 9 (Lys-9) in histone H3, which is a substrate of the Clr4 methyltransferase in fission yeast. They used this antibody in chromatin immunoprecipitation assays to monitor specif-

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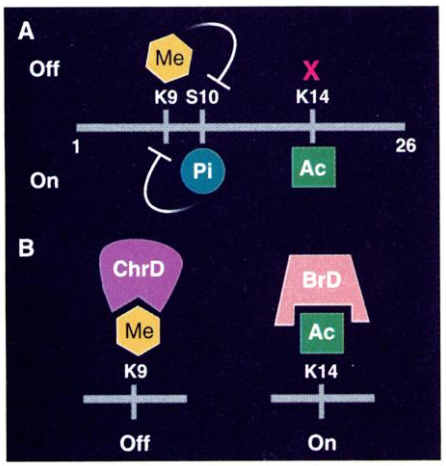

Modifying histones. Modifications to amino acid residues in histone protein H3 and the specialized domains of other proteins that bind to modified residues. **(A)** Dual modification of histone H3 occurs during gene silencing or gene activation. During gene silencing ("Off" state), Lys-9 (K9) is methylated (Me) and Lys-14 (K14) is deacetylated (X). During gene activation ("On" state), Ser-10 (S10) is phosphorylated and Lys-14 is acetylated. Methylation of Lys-9 blocks phosphorylation of Ser-10 and phosphorylation of Ser-10 blocks methylation of Lys-9. **(B)** As a result of these modifications, the chromodomain (ChrD) of regulatory proteins binds to methylated Lys-9 during gene silencing, and the bromodomain (BrD) of regulatory proteins binds to acetylated Lys-14 during gene activation.

ic DNA sequences associated with H3–Lys-9 methylation. The authors found that histone methylation at centromeres requires Clr4 methyltransferase activity and also depends on a histone deacetylase that specifically removes the acetyl moiety from the nearby Lys-14 of histone H3. Because Lys-14 is a common target of acetyltransferases associated with gene activation, these results suggest that deacetylation of Lys-14 leads to methylation of Lys-9 in an obligatory sequence. A second class of proteins, typified by HP1 (heterochromatin protein 1) in the fly, is also required for the maintenance of gene silencing. In fission yeast, the HP1 homolog Swi6 is localized to the heterochromatin of centromeres. The Nakayama *et al.* work (*1*), and a second study by Bannister *et al.* (*6*), demonstrate that localization of Swi6 to heterochromatin also requires Clr4 methyltransferase activity. Thus, it appears that deacetylation of H3 leads to its methylation, which then results in the localization of Swi6 to heterochromatin. Previous data have indicated that Swi6 expands across the heterochromatic region, presumably creating a unique silencing chromatin structure. Taken together, this work suggests an obligatory sequence of histone modifications that recruits structural proteins to DNA, resulting in the creation of heterochromatin.

The sequence of histone modifications during gene silencing—first, deacetylation of Lys-14, and then methylation of Lys-9—has a precedent in the dual ordered modifications of histone H3 during gene activation. Histone phosphorylation at serine-10 precedes and promotes acetylation at Lys-14 (*9*, *10*). Thus, together these studies of gene silencing and activation suggest that histone H3 exists in two modification states: an "Off" state characterized by methylation of Lys-9 and deacetylation of Lys-14, and an "On" state wherein Ser-10 is phosphorylated and Lys-14 is acetylated (see the figure). Interestingly, in vitro methylation of Lys-9 inhibits phosphorylation of Ser-10 and phosphorylation of Ser-10 inhibits methylation of Lys-9 (*8*). This dual arrangement could serve to reinforce gene silencing or activation in vivo.

The next compelling question is exactly how these histone modifications alter transcription. A recently advanced idea, the "histone code" hypothesis (*11*, *12*), holds that covalent modifications of histones constitute an intricate pattern that creates a docking surface with which the modules of other proteins can interact. Proteins containing these modules bind to chromatin to alter its structure, provide additional enzymatic activity, or to target other regulatory proteins. Initial support for the docking idea comes from histone acetylation: The bromodomain present in histone acetyltransferases and in other proteins that interact with chromatin binds with higher affinity to peptides bearing acetylated lysine than to unmodified peptides (*13*, *14*). Two recent papers (*6*, *7*) that also examine how histone methylation regulates the silencing of heterochromatin provide strong support for the docking proposal. These studies analyze a domain, called the chromodomain, found in heterochromatin-associated proteins, such as HP1 and Swi6. The chromodomain binds with high affinity to histone H3 peptides bearing methylated Lys-9 both in vitro and in vivo. Thus, a reciprocal docking mechanism may consist of, on the one hand, binding of a bromodomain to acetylated histone during gene activation, and on the other, binding of a chromodomain to methylated histone during gene silencing (see the figure). All chromodomain proteins, however, do not bind to methylated Lys-9 of histone H3 (*6*), prompting speculation that there may be additional patterns of histone modifications (and even other targeting mechanisms) (*15*) that specify the binding of other chromodomain proteins. A looming challenge will be to determine the histone modification "code" that specifies the binding to chromatin of numerous other domains in chromatin-associated proteins.

Thus, the silencing and activation of genes may require multiple modifications of histones, which generate unique surfaces for the binding of proteins that carry out further chromatin-related processes. The modification patterns that exist in these histones are just beginning to be decoded, yet it is already abundantly clear that the many distinct covalent modifications of chromatin, although initially confusing, are an important aspect of genomic regulation.

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PERSPECTIVES: SUPERCONDUCTIVITY

How Could We Miss It?

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In January of this year, the world of superconductivity was stunned by the announcement that the compound MgB_2 was superconducting at a critical temperature T_c of 39 K. Perhaps "astonished" is more accurate than "stunned," because every superconductivity laboratory in the world immediately began to make measurements on this new material and dash into print. Fifty preprints had been posted on the Web by the end of February—before the original paper was even published (*1*). On page 75 of this issue, Monteverde *et al.* (*2*) investigate the superconducting mechanism of MgB_2. The results show similarities with high-T_c oxide superconductors, although other measurements suggest that the material has more in common with low-T_c superconductors. This is an important question because it has proved extremely difficult to make useful wires out of high-T_c superconductors.

Superconductivity—in which the resistance of a material to electrical conduction becomes zero—has intrigued researchers since its discovery in 1911, but it took al-

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