CELL BIOLOGY

Linker Histones, DNA's Protein Custodians, Gain New Respect

Gene mappers like to think of each chromosome as a shelf in a genomic library, with genes, regulatory sequences, and apparently meaningless DNA all lined up in a row. It's a useful picture, but the reality, in the cramped environs of the cell nucleus, is far less orderly—more like an overcrowded archive, with DNA and proteins wound and twisted into dense packages, called chromatin. Overseeing these masses of genetic information is a molecular bureaucracy, to which the cell's gene-regulating proteins have to appeal to gain access to their sequences. And among the more powerful functionaries in this bureaucracy are proteins called histones.

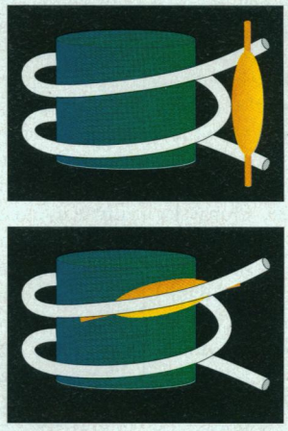
Once thought to be little more than passive supports for DNA, histones, in particular those called linker histones, are actually the custodians of these genetic packages, shifting the piles of records as needed to give other proteins access to specific bits of DNA (*Science*, 8 December 1995, p. 1589). Now a new series of findings, including one in this issue of *Science*, is sketching out how the linker histones manage the genome—and the picture is turning out to be more complex than researchers had thought.

While the linker histones were once thought to sit outside the DNA coils, blocking access to large stretches of DNA, a group led by biochemist Alan Wolffe of the National Institute of Child Health and Human Development in Bethesda, Maryland, reports on page 614 that at least some linker histones actually nestle inside the coils. This finding dovetails with work reported by Martin Gorovsky's lab at the University of Rochester. In the 9 August issue of *Cell*, they suggest that some histones may do more than block gene activation: Sometimes they may also promote it. These two reports imply, says Wolffe, that "a lot of [genetic] regulation is a lot more subtle [than we thought]."

As Gorovsky notes, however, the findings "are going against the conventional wisdom," and their conclusions aren't finding instant acceptance. "It remains to be seen how general they are," says Jean Thomas, a biochemist at Cambridge University in England, noting that both groups looked at specialized systems. If nothing else, the data now pouring out of these two labs and others have raised expectations that a revised, coherent picture of linker histones will soon be forthcoming. "It's just a question of waiting a bit longer and seeing how it turns out," Thomas adds.

The picture began taking shape some 20 years ago, as biochemists learned through electron microscopy, x-ray diffraction, and biochemical analyses that each chromosome's DNA is wound into a series of barrel-shaped masses called nucleosomes. Each nucleosome consists of eight core histones that act as a spool, with the DNA wound roughly twice around it. And each has a linker histone, which was thought to be positioned just outside the nucleosome and halfway along it, spanning the two coils of DNA "like a clamp," says Wolffe. Only by shifting this arrangement—or perhaps by removing the linker histone—could gene-regulating proteins gain access to their target sequences.

This traditional model implies that each linker histone has two different DNA binding sites, one for each turn of the DNA, and that picture has gained support from some recent data. Three years ago, structural biologist Venki Ramakrishnan of the University of Utah School of Medicine in Salt Lake City solved the crystal structure of one part of a linker histone known as the globular domain and identified two charged spots—likely binding sites—on opposite sides of the domain. Altering the chemistry of either site, Thomas's and Ramakrishnan's groups reported in the 1 July *EMBO Journal*, interfered with the ability of these altered proteins to assemble into full-fledged nucleosomes, implying that both sites play a role in stabilizing nucleosomes.



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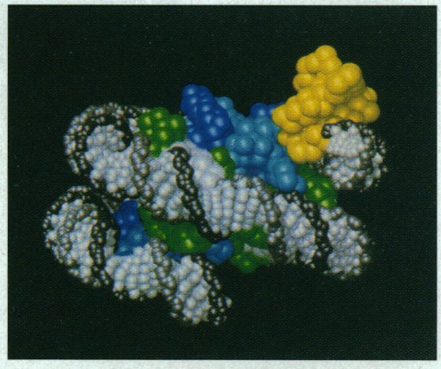


Nucleosomal views. The traditional view *(top)* puts the linker histone protein *(yellow)* outside the coiled DNA *(white, black)*; in a new model *(middle, bottom)*, it's inside and off-center.

Wolffe and his colleagues, however, have found at least one nucleosome that doesn't fit this picture. His group studied the function of a linker histone in *Xenopus*, a commonly studied frog, that interacts with DNA encoding a certain type of ribosomal RNA. For the experiment reported in this issue, he and Dmitry Pruss, now with Myriad Genetics in Salt Lake City, made a specially constructed copy of the DNA that includes molecular "hooks" attached to it at five widely spaced points. When hit with light, the hooks react, binding to nearby proteins.

Before activating the hooks, the researchers mixed the DNA with histones in the test tube, allowing *Xenopus* nucleosomes to assemble normally. Then they washed away bits of DNA that were not wrapped around nucleosomes and unattached nucleosomal protein, and treated what remained with light. The hooks grabbed onto any protein positioned nearby, enabling the researchers to map where the linker histones bind to the DNA.

"What we saw was a very selective interaction," Wolffe says. With each of the three kinds of linker histones tested, they observed that the linker histones attached to the DNA at only one place; they didn't seem to bind to both turns of the DNA coiled around the nucleosome. What's more, he says, "the linker histone contacts the core histones and the DNA in a much more intimate way [than was previously thought]." Building on the data, Gina Arents and Evangelos Moudrianakis of Johns Hopkins University in Baltimore created a new model of the nucleosome, one that positions the histone closer to one end of the nucleosome, and inside, not outside, the coiled DNA.

Independently, one of Wolffe's collaborators verified this intimacy using a very different experimental approach. Instead of modifying the DNA, biochemist Jeffrey Hayes of the University of Rochester in New York altered the linker histones by grafting on a molecule that cuts nearby DNA that is not bound to a protein. By activating this molecule in assembled nucleosomes, he knicked DNA where it extended beyond the linker histone. By analyzing that DNA, Hayes reported in the 17 September issue of *Biochemistry*, he was able to conclude that each linker histone lies underneath the spiral of DNA and away from the midpoint of the nucleosome. "[He] comes up with essentially the same position [as Wolffe]," Gorovsky notes.

"At least in this case, they've locked it down to an asymmetric structure," says biophysicist Ken van Holde at Oregon State University in Corvallis, but he and others point out that the structure may be a peculiarity of *Xenopus* nucleosomes. "I still have to be convinced there's just one binding site," adds Morton Bradbury, a structural biologist at the University of California, Davis, who notes that few results over the past 2 decades have contradicted the notion of two binding sites.

But if the new structure does prove to be widespread, it could support a new view of the role that the linker histones play in gene regulation—a role that is more complex than researchers have envisioned in the past. In their traditional position, outside the DNA spirals, the linker histones would act mainly to repress the activity of a large number of genes by blocking the access of regulatory proteins. But if the linker histones snuggle inside the DNA coils, they "may change the path of the DNA," notes Bradbury, which could make specific genes more accessible for transcription.

In keeping with this picture, Gorovsky and his colleague Xuetong Shen found signs that linker histones have both positive and negative effects on gene activity in a ciliated protozoan, *Tetrahymena thermophila*. These researchers eliminated the protozoan's linker histones, called H1 proteins, by knocking out the corresponding genes. They found that a gene known as *ngo-A*, expressed in normal *Tetrahymena* only during periods of starvation, was active all the time in the knockouts. That result fits in with the long-held view that linker histones slow down gene transcription.

But the loss of the H1 proteins had another, quite unexpected, effect on a gene called *CyP*. This gene codes for an enzyme involved in protein degradation. Like *ngo-A*, it becomes active during periods of starvation. But in starved knockouts, it was barely expressed at all. With these two findings, says Gorovsky, "we've clearly demonstrated that [the linker histone] can play a positive or negative role in gene expression."

The same is likely to be true of other linker histones, says Wolffe: "Far from being global repressors, [they] are quite specific in their effects." But not everyone is willing to make such sweeping statements. What Gorovsky sees "could well be a special case," says Bradbury, who points out that the *Tetrahymena* has unusual, shrunken linker histones that lack a globular domain altogether. "You've got to be careful about being too general."

Even at this stage, though, one thing is certain, says Gorovsky: The Byzantine bureaucracy of the chromosomes is looking even more intricate.

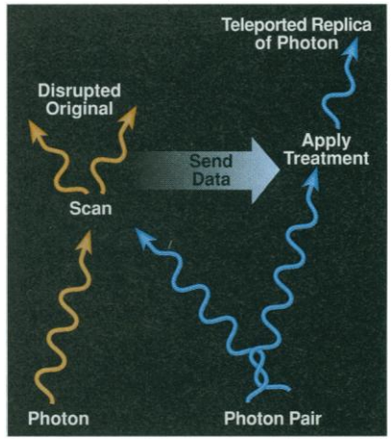
–Elizabeth Pennisi

QUANTUM MECHANICS

To Send Data, Physicists Resort to Quantum Voodoo

Tabloid journalists and writers of mystical self-help works will be happy to know there is an area of physics that holds a vague resemblance to voodoo. It involves one of the weirdest of quantum-mechanical paradoxes, in which two particles can be created simultaneously with their internal quantum states—their spin, for instance, or polarization—irrevocably "entangled." Quantum mechanics dictates that until a particular state is actually measured, it has no value at all. But when a measurement is made on one entangled particle, its partner instantly takes on the opposite value, even if it happens to be halfway across the universe at the time.

This is what Albert Einstein once referred to as "spooky action at a distance," and what Charles Bennett, an IBM fellow and renowned quantum mechanician, likens to voodoo. The entanglement establishes a unique connection between the two particles such that what Bennett calls the "quantum essence of the particle" passes from one to the other like a curse passing from a lock of hair back to its original owner. As quantum-mechanics researchers have shown lately, this quantum voodoo can be put to work in ways that are less maleficent but no less spooky, for transmitting data and even "teleporting" the quantum state of a particle, along with all the information it embodies.



Beam me over. In quantum teleportation, one entangled photon interacts with an unknown photon, yielding data that are transmitted to the other entangled photon to resurrect the unknown photon's quantum state.

Last June, for instance, physicists at the University of Innsbruck in Austria reported that they could convey one of three distinct "trits" of data through a single entangled photon, as opposed to the two binary bits that are all a photon can ordinarily handle. By the end of the year, the Innsbruck group hopes to use the same basic techniques to make the quantum state of a particle interacting with one entangled photon disappear, then reappear elsewhere in the other member of the entangled pair, without physically making the trip.

Weird as it all sounds, says Bennett, there is little suspense about these experiments. "We're almost certain what the results will be before we start, because everyone believes quantum mechanics," he says. Instead, there are practical reasons for attempting these feats. Teleportation, for instance, may play an important role in future computers based on quantum mechanics (*Science*, 7 July 1995, p. 28). And there's another kind of lure, says Bennett—the enticement of seeing the wildly counterintuitive predictions of quantum theory borne out.

Quantum voodoo of any kind starts with an entangled pair of photons. The Innsbruck physicists, led by Harald Weinfurter, produce them using a type of optical crystal that absorbs one high-energy, ultraviolet photon and emits in exchange two entangled low-energy photons. These photons are born with an irrevocable quantum link, which emerges, for example, when one of them passes through a polarized filter set at a particular angle. "The photons individually don't possess a definite polarization," says Los Alamos National Laboratory physicist Paul Kwiat, who works with the Innsbruck group, "and yet there's a definite polarization relationship between the two." If the filter is horizontally polarized, for instance, and one of the pair manages to pass through it, the other photon will instantly assume a vertical polarization.

The Innsbruck group has shown that they can exploit this relationship to get around the quantum-mechanical uncertainty principle, which ordinarily limits the amount of information that can be extracted from a single photon. While a photon's polarization, for example, can fall anywhere between 0° and 360° to infinite precision—so that in principle it can carry any of an infinite number of bits—the best any measurement can say is whether or not it will pass through a filter polarized at a particular angle. The result is one of two bits—a 0 or a 1. But by making joint measurements of an entangled photon and its partner, the Innsbruck group is able to do better.