A spotlight on chromatin choreography

In 1996, Robinett et al. developed a way to visualize chromatin structure and dynamics in living cells.

As a postdoc studying chromosomal structure with David Agard and John Sedat in the late 1980s, Andrew Belmont had observed intriguing ultrastructural details in interphase nuclei. “We’d see large-scale fibers about 100 nanometers thick, and then there’d be a 10- to 30-nanometer-thick fiber looping out, which we thought might represent an active gene,” says Belmont. “However, we couldn’t rule out that these features were simply artifacts of fixation or sample preparation because we couldn’t identify the region that we were looking at.”

At the time, the only method available to identify a specific chromosomal region was in situ hybridization, in which a radioactive or fluorescently labeled nucleotide probe is annealed to complementary DNA or RNA sequences that have been denatured by chemicals or heat. The technique, first described in 1969 (1), enabled major advances in cytogenetics and genomic mapping (2). But it wasn’t suited to the application Belmont had in mind.

“One of the first experiments I did in my own lab was to perform a mock in situ hybridization and then take the sample to the electron microscope. I saw the chromatin structure was completely trashed at the ultrastructural level,” recalls Belmont. His group needed a way to label specific chromatin structures in cells that also preserved DNA ultrastructure. The approach they devised was described in a 1996 paper published in *JCB* (3).

The paper unveiled a genetic construct containing 256 lac operator repeats that, once integrated into a cell’s DNA, could be recognized by the lac repressor protein in both fixed and living cells. The site of lac repressor binding could then be visualized by indirect immunofluorescence or via fluorescently labeled nucleotide probe is annealed to complementary DNA or RNA sequences that have been denatured by chemicals or heat. The technique, first described in 1969 (1), enabled major advances in cytogenetics and genomic mapping (2). But it wasn’t suited to the application Belmont had in mind.

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