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# Journal club

## 3D SOLUTIONS TO COMPLEX GENE REGULATION

As a postdoctoral researcher working on X-chromosome inactivation, I was greatly inspired by a series of studies in the early 1990s by Sedat and colleagues that used fluorescence microscopy to describe how changes in chromatin organization and nuclear positioning might be relevant to changes in gene expression and genome function during development.

At that time, I had been trying (and failing) to define the minimal region of the X chromosome — the X-inactivation centre (Xic) — that could trigger X inactivation. The prevailing view was that the Xic boiled down to just the 35 kb non-coding X inactive-specific transcript (*Xist*) gene and its immediate surroundings. However, even the largest DNA fragments containing the *Xist* gene (460 kb) that I tested in mice or embryonic stem cells could not induce random X inactivation when inserted into the genome as single copies (Heard *et al.* (1996); Heard *et al.* (1999)). Something was missing.

In 1996, Sedat and colleagues published a paper that completely changed the way I thought about the problem. Using DNA fluorescence *in situ* hybridization (FISH) to analyse the position of different regions along a chromosome relative to the nuclear envelope in the interphase nuclei of *Drosophila melanogaster* embryos, they discovered that some regions were consistently peripherally localized, whereas others were not. They postulated that this spatial organization of chromosomes in the nucleus could define large chromatin loops of approximately 1–2 Mb that partition the functions of the genome (such as gene expression and DNA recombination). The peripheral regions were later molecularly defined as lamina-associated domains (LADs) by Guelen *et al.* using the elegant DNA adenosine methyltransferase identification (DamID) approach. Some LADs are constitutive, whereas others appear in development when genes within them are silenced.

It was after reading the paper by Marshall *et al.* that I realized that the large *Xist* transgenes that I had been testing were missing key sequences that might be required to induce a particular chromatin structure or to guide the transgene towards a specific nuclear compartment: for example, the nuclear envelope. Although we are still trying to work out how developmental *Xist* regulation works and whether it actually involves association with the nuclear envelope or other compartments, it was the work of Sedat and colleagues that changed my perspective on the question of long-range control and led us to investigate the 3D nuclear and chromatin organization of the Xic.

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**ORIGINAL ARTICLES** Heard, E. *et al.* Transgenic mice carrying an *Xist*-containing YAC. *Hum. Mol. Genet.* **5**, 441–450 (1996) | Heard, E. *et al.* *Xist* yeast artificial chromosome transgenes function as X-inactivation centers only in multicopy arrays and not as single copies. *Mol. Cell. Biol.* **19**, 3156–3166 (1999) | Marshall, W.F. *et al.* Specific interactions of chromatin with the nuclear envelope: positional determination within the nucleus in *Drosophila melanogaster*. *Mol. Biol. Cell* 7, 825–842 (1996) | Guelen, L. *et al.* Domain organization of human chromosomes revealed by mapping of nuclear lamina interactions. *Nature* **453**, 948–951 (2008)