

Tight DNA packaging protects against 'jumping genes,' potential cellular destruction

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UNC School of Medicine researchers discovered that the major developmental function of heterochromatin – a form of tight DNA packaging found in chromosomes – is likely to suppress activity of virus-like DNA elements known as transposons or "jumping genes," which can otherwise copy and paste themselves throughout the genome, potentially destroying important genes, and causing cancers and other diseases.

The discovery, published online in *Genes & Development*, clarifies the role of this basic feature of cell biology and adds to the scientific understanding of the different steps in heterochromatin formation. Disruption of these steps is associated with numerous diseases, including many cancers. Dissecting the mechanisms that cells use to build heterochromatin will help scientists therapeutically target the affected steps in these diseases, such as how disease-causing transposons can become active in cells.

"The repression of transposon mobilization is necessary to maintain [genome](#) stability, and we now think this repression may be the major developmental function of heterochromatin, rather than a role in controlling gene expression and cell proliferation," said Robert Duronio, PhD, professor of biology and genetics and senior author of the study. "This finding was very much unexpected."

Chromatin, essentially, is the spooled structure DNA takes when

packaged inside cells. The two broad forms of chromatin are euchromatin, a loose structure normally considered permissive for gene activity and the encoding of proteins; and heterochromatin, a tighter, denser packaging of DNA thought principally to suppress gene activity. The tightest and most stable form of heterochromatin, known as constitutive heterochromatin, is found mostly at the constricted region of [chromosomes](#), which is the region important for chromosome movement during cell division.

Although various functions have been attributed to heterochromatin, these functions have not been easy to confirm with definitive experiments. The standard experimental approach has been to observe what happens when heterochromatin formation is blocked, but the process that triggers the formation of heterochromatin is hard to block precisely.

The current model holds that heterochromatin forms when a protein called histone H3 is chemically modified – or methylated – at a key site. In principle, replacing normal histone H3 genes with mutant versions that can't be methylated at the key site would block heterochromatin formation and be an important test of the current model. In practice, however, it is virtually impossible to do this experiment in higher animals such as lab mice.

"Mice, as well as humans, have three different clusters of histone genes on different chromosomes, and so creating genetic manipulations at those different spots is very difficult, especially because there are other essential genes within those histone gene clusters," said Taylor J. R. Penke, a graduate student in the Duronio Lab who was first author of the study.

Fortunately, another standard lab animal, the *Drosophila* fruit fly, has a more targetable set of histone genes.

"The histone H3 genes we wanted to change are clustered in one location in the genome of a fruit fly, without other essential genes in the cluster, so they can all be removed at once and replaced with mutant histone H3 genes," said Penke.

For the new study, Penke, Duronio, and their colleagues used an advanced *Drosophila* genetics platform they developed last year to replace these histone H3 genes with mutant versions that don't permit the methylation that triggers heterochromatin formation.

The first surprise was that the *Drosophila* mutants did not all die before adulthood; about two percent survived. Among the surviving flies, there was a sharp drop in signs of heterochromatin in their chromosomes, especially where the histone H3 methylated proteins are normally concentrated. Moreover, despite the long-held assumption that heterochromatin regulates [gene activity](#), the UNC scientists found that gene expression in the mutants was mostly unchanged, even in the regions where the tight heterochromatin packaging of DNA had been relaxed.

There was one big change in the mutants, however. The regions of their chromosomes that would normally be strongly heterochromatic showed a jump in the activity of transposons. These DNA elements – whose evolutionary origins are murky but make up large fractions of plant and animal genomes – have a virus-like tendency to make copies of themselves by snipping themselves out of their original locations and re-inserting themselves elsewhere in the genome. Along with an increase in transposon activity, the team found signs that a key anti-transposon defense mechanism had been activated. That is, levels of piRNA transcripts – the precursors to small RNA molecules that bind to transposons to block their activity – were sharply increased.

Although transposons are thought to benefit their hosts in certain

circumstances, they clearly can cause harm. Duronio, Penke, and colleagues suspect that the 98 percent mortality among their *Drosophila* mutants and the high death rate thereafter among surviving flies were due largely to the effects of transposons inserting themselves in the genome and disrupting key genes.

"It seems that the major role for the methylation of histone H3 that triggers this type of heterochromatin is to keep transposons from jumping around and screwing up the genome," Duronio said.

Human histone H3 genes are quite similar to those in *Drosophila*, suggesting that their function has largely been conserved despite the evolutionary gulf between flies and humans. This suggests that *Drosophila* is a good model for the study of human histone function.

Understanding better how the genome normally defends itself from transposons should help scientists get a better handle on transposon-related diseases. Transposons can directly trigger cancerous changes in a cell, for example, by disrupting a tumor-suppressor gene or by causing a DNA break that destabilizes a large section of the chromosome. Cases of many other diseases, including hemophilia, have been linked to [transposons](#)' disruption of important genes.

"During embryonic and fetal development, there is normally a high-fidelity replication of the genome, and that is a significant mechanism for repressing cancer and other diseases. With studies like these, we're understanding how heterochromatin does its job in that respect," said Duronio, who is also associate dean for research at the UNC School of Medicine.

His lab plans to follow up with further studies of *Drosophila* histone genes, in particular a set of slightly different histone H3-family [genes](#) that exist apart from the main cluster and appear to have a role outside

constitutive [heterochromatin](#).

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