Location matters, even for genes

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Moving an active gene from the interior of the nucleus to its periphery can inactivate that gene report scientists from the University of Chicago Medical Center in an article to be published early online Feb.13, 2008, in the journal *Nature*.

Attachment to the inner nuclear membrane, they show, can silence genes, preventing their transcription--a novel form of gene regulation.

"Several years ago, we and others described the correlation between nuclear positioning and gene activation," said study author Harinder Singh, Louis Block Professor of Molecular Genetics and Cell Biology and an Investigator in the Howard Hughes Medical Institute at the University of Chicago.

"With that in mind, we wanted to take the next step, to design an experiment that could test causality. Could we move a gene from the center of the nucleus to the periphery, we asked, and then measure the consequences of such repositioning?"

In mammalian nuclei, chromatin--a complex of DNA and associated proteins--is organized into structural domains through interactions with distinct nuclear compartments. In this study, the authors developed the molecular tools to take specific genes from these interior compartments, move them to the periphery and attach them to the nuclear membrane--which turned those genes off.

Not only were selected "test" genes that served as markers turned off

after being attached to the inner nuclear membrane, but also nearby "real" genes.

Singh's laboratory had become interested in studying the role of nuclear postioning in the control of gene activity based on work analyzing immunoglobulin heavy-chain genes. These genes are assembled by DNA recombination and code for proteins that are a crucial part of antibodies, produced in antibody-secreting lymphocytes or B-cells.

"In cells that don't produce antibodies, like fibroblasts or T-cells, these antibody genes are attached to the inner nuclear membrane and are not recombined or expressed," said Singh.

On the other hand, antibody genes are actively transcribed and recombined in developing B-cells, and therefore positioned in the nuclear interior, far away from the periphery.

Five years ago, Singh and colleagues reported in Science that even in developing B cells, antibody genes start off at the nuclear periphery. As young cells mature and prepare to produce antibodies, however, these genes move to the interior of the nuclei.

The exact ways in which positioning at the outer edge of the nucleus prevents gene expression are still unclear. The likely suspects, said Singh, are some of proteins that reside in the inner nuclear membrane.

These proteins may be involved in blocking transcription, he said. They accumulate at sites of attachment and come in contact with parts of certain silenced genes. "So we think that these proteins are part of the molecular machinery that is used for positioning genes at the inner nuclear membrane, as well as potentially for repressing them," he said.

In their Nature paper, Singh's team also showed for the first time that

this transcriptional repression was dependent on breakdown and reformation of the nuclear membrane during cell division.

The reorganizing of chromosomes occurs when cells divide. "This suggests that cell division is used not only to transmit the genetic information into daughter cells and create two equivalent cells," he said, "but it is also an opportunity for cells to reorganize their genomes in 3D space, sequestering parts of the genome at the nuclear periphery and rendering it inaccessible to transcription."

Singh and colleagues are now looking for examples of striking reorganization of the genome separated by one cell division--in which active genes, that will not be active after the cell divides, get pushed away from the interior to the periphery.

The lead author, Karen Reddy, a postdoctoral fellow in the Singh laboratory, proposes that, such compartmentalization "implies the existence of DNA segments that encode for 'nuclear addresses' acting like a nuclear zip code to direct or predispose genes to associate with specific regions within the nucleus. This could be tremendously important," she said, "for understanding the underlying cause of some diseases that result from mutations in genes encoding inner nuclear membrane proteins."

Source: University of Chicago

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