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Discovery Illuminates Surprising Flexibility of Chromosomes

For the first time, scientists have shown that a genetic element on one chromosome may direct gene activity on another chromosome. Howard Hughes Medical Institute (HHMI) researchers report that a multi-tasking master control region appears to oversee both a set of its own genes and a related gene on a nearby chromosome.

"In the past, people have thought that chromosomes acted independently," said senior author Richard Flavell, an HHMI investigator at the Yale University School of Medicine. "Now it's possible that regulatory regions on one chromosome can facilitate expression of genes on another chromosome."

The researchers report in an advance online publication on May 8, 2005, in the journal *Nature*, that evidence of a strong physical connection between two mouse chromosomes at a key region transforms an immature immune cell into one that can fight an invading pathogen.

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The researchers believe this neighborly association may turn out to be common among many closely coordinated genes that must work together in different parts of the body. Occasionally, such chromosomal intimacy could lead to inadvertent gene swapping, which could explain certain cancers caused by translocated genes, the researchers speculate.

The discovery came from studies of immune cells that patrol the body for signs of infection. Naïve T cells circulate through the blood and lymph nodes until they reach a node where another immune cell is waiting with a matching

antigen. This message calls the T cell to battle.

The signal triggers genetic activity that converts a naïve T cell into one of two types of helper cells armed with strategic molecular weapons for different situations. One type, T-helper-cell 1 (TH1), activates interferon-gamma to help kill cells that have been taken over by harmful bacteria or viruses. The other, T-helper-cell 2 (TH2), turns on interleukin-4 and other cytokines to destroy germs roving between cells.

On chromosome 11, the interleukin cytokines made by TH2 are spaced widely apart, but they are kept primed for action by one master control region on the same chromosome. Last year, researchers in Flavell's lab found that the control region and the genes were juxtaposed in the cell nucleus. Somehow, the chromosome contorted to bring all the genetic elements together.

Now, first author Charalampos "Babis" Spilianakis, a postdoctoral fellow in Flavell's laboratory, reports a similarly close connection between the same TH2 cytokine master control region on chromosome 11 and the start of the interferon-gamma gene on chromosome 10.

"We don't yet know the mechanism of interaction," Spilianakis said. Certain sections of chromosomes likely to be needed by the cell may gather together at different spots in the nucleus, ready and waiting for signals that activate their genes, he suggested.

To pinpoint the proximity of the chromosomes, Spilianakis used a powerful new technique developed by other researchers called chromosome conformation capture. He captured a freeze-frame of naïve CD4 cells in a test tube with formaldehyde. Then, he used an enzymatic scalpel to extract DNA in the immediate vicinity of the cytokine control region on chromosome 11. Subsequent genetic analysis revealed its coziness with the interferon gene on chromosome 10.

The team used a fluorescent technique to confirm that the consorting chromosomes were linking their DNA. "We think the TH2 control region on one chromosome regulates interferon-gamma on the other chromosome," Spilianakis said. The relationship between the chromosomes falls apart when the T cells have differentiated into helper cells, he said.

The researchers suspect the temporary chromosomal closeness keeps an essential set of genes on standby for rapid response.

The findings reinforce the growing importance of location for gene activity within the nucleus, Spilianakis said. Large loops of chromosomes containing active genes can extend outside of the usual location of a chromosome in the nucleus, other researchers have found. Other evidence suggests that regulatory elements may act by repositioning genes and their control regions

to more active transcription spaces within the nucleus.