

A Mechanism for Coordinating Genes

Chromosomes reach out and touch each other.

STUDYING HOW CELLS OF THE MOUSE IMMUNE SYSTEM MATURE and differentiate, researchers at Yale University recently discovered a surprising strategy. HHMI investigator Richard Flavell and his team observed the first instance of genes from separate chromosomes coordinating their activities by touching each other.

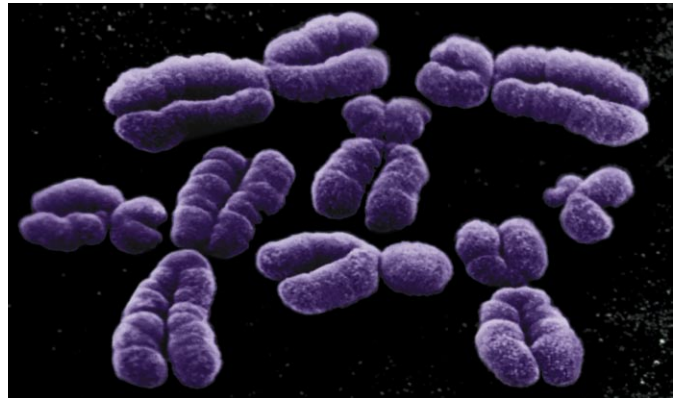
The researchers studied helper T cells (T_H cells), which can develop into T_{H1} or T_{H2} cells that use slightly different tactics—turning on distinct groups of genes—to fight infections. The Yale researchers had previously found out that in T_{H2} cells a master control element on chromosome 11—called the locus control region (LCR)—turns on three nearby but widely separated genes that encode interleukins (proteins the cells use to neutralize pathogens). With the aid of a recently developed method, called chromosome conformation capture, to map physical contacts between different regions of DNA, Flavell's group learned that the LCR orchestrates the activities of the three interleukin genes by actually contacting parts of all three genes.

At around the same time, the researchers noticed that early in development T cells produce small amounts of both the T_{H2} -specific interleukins and the T_{H1} -specific cytokine interferon- γ , whose gene lies on chromosome 10. (Cytokines are proteins that stimulate or inhibit the joint action of immune cells.) Because the interferon- γ and interleukin genes seemed to be regulated in concert, Flavell surmised that the LCR on chromosome 11 might somehow bind both its neighboring interleukin genes and the interferon- γ gene on chromosome 10. That was a bold hypothesis. “In the past, people have thought that chromosomes acted independently,” says Flavell. But the hunch turned out to be right.

Using fluorescent-microscope-imaging techniques, the Yale researchers directly witnessed the predicted regions of chromosomes 10 and 11 come in contact during early T_H cell development and then move apart as the cells committed to their final fates as T_{H1} or T_{H2} cells. The work was published in the June 2, 2005, issue of *Nature*.

Although questions remain about how the chromosome contacts regulate gene expression, the Flavell team suspects that the LCR serves to escort genes to regions of the cell's nucleus that offer a favorable environment for gene activation. Given nature's inherent efficiency, they speculate that chromosome contacts will prove to be a general mechanism for coordinating the activity of genes. ■

~ Paul Muhrad ~



IN CONTRAST TO THE SCENE IN THIS COLORIZED SCANNING ELECTRON MICROGRAPH, CHROMOSOMES IN A CELL'S NUCLEUS ARE SNUGLY PACKED—AND THEY AREN'T JUST RUBBING ELBOWS.

BIOPHOTO ASSOCIATES / PHOTO RESEARCHERS, INC.

IN BRIEF

(continued)

Leonard I. Zon, an HHMI investigator at Children's Hospital Boston, and his colleagues reported their findings in an article published in the October 2005 issue of the journal *Genes and Development*.

GETTING TO THE HEART OF CELL SIGNALING

Researchers have discovered new details about how one of the cell's most commonly used messenger molecules, cyclic AMP, can trigger several distinct responses within cells. The studies point the way toward new drug targets for heart disease and other disorders.

John D. Scott, an HHMI investigator at Oregon Health & Science University, and his colleagues published their findings in the September 22, 2005, issue of the journal *Nature*.

Cyclic AMP is a cellular chemical that, among other things, can control heart rate and muscle contraction. Cyclic AMP also regulates the passage of calcium through ion channels in

the cell membrane, another important cellular process in the heart.

In their new study, Scott and his colleagues explored a group of proteins called muscle-specific A-kinase anchoring protein (mA-KAP) complex, which acts as a sort of central molecular clearing house for cyclic AMP signals. An earlier study had found that mA-KAP includes phosphodiesterase, which Scott's study identified to be the key protein for regulating cyclic AMP signaling. Scott said their findings suggest that new treatments for heart disease could target phosphodiesterase to influence cyclic AMP signaling, since “changes in the cyclic AMP pathway are known to be linked to heart disease, and heart contraction is linked to calcium and cyclic AMP signaling.”

NEW FORM OF NERVE CELL PLASTICITY

Researchers have discovered a new form of synaptic plasticity, the changes to nerve cells in the brain that underlie learning and memory. The phenomenon, the scientists say, may help

govern how a single neuron integrates and processes multiple stimuli.

The researchers, led by HHMI investigators **Lily Yeh Jan** and **Yuh Nung Jan** at the University of California, San Francisco (UCSF), published their findings in the October 7, 2005, issue of *Cell*. Coauthors include the Jans' colleagues at UCSF and **Robert B. Darnell**, an HHMI investigator at the Rockefeller University.

In experiments designed to answer whether slow inhibition of electrical impulses between nerve cells undergoes long-term potentiation (LTP), long-lasting changes in the connectivity between two nerve cells, the Jans showed that the same pathway could generate LTP of both excitatory and inhibitory synapses. The scientists then wondered whether this plasticity might be controlled by a “master” regulatory protein. A good candidate, they thought, was a protein found in the brain called Nova-2 that controls a network of other proteins, many of which are involved in inhibitory synaptic transmission. Using mice engineered by the Darnell