Permanent changes in brain genes may not be so permanent after all

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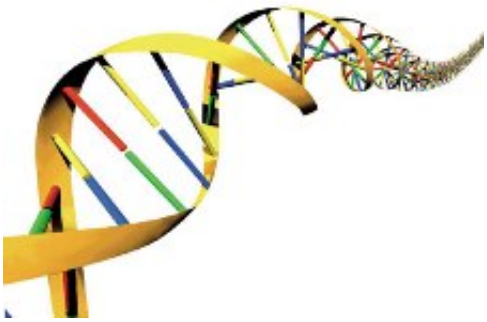

In normal development, all cells turn off genes they don't need, often by attaching a chemical methyl group to the DNA, a process called methylation. Historically, scientists believed methyl groups could only stick to a particular DNA sequence: a cytosine followed by a guanine, called CpG. But in recent years, they have been found on other sequences, and so-called non-CpG methylation has been found in stem cells, and in neurons in the brain.

Now, a team of researchers at Johns Hopkins has discovered that non-CpG methylation occurs later and more dynamically in neurons than previously appreciated, and that it acts as a system of gene regulation, which can be independent of traditional CpG methylation.

In a study described in the January 28 issue of *Nature Neuroscience*, the Hopkins team describes this new gene control mechanism and how it may contribute to Rett Syndrome, a nervous system disorder affecting mostly girls that causes problems with movement and communication.

The team, led by Hongjun Song, Ph.D., professor of neurology and director of Johns Hopkins Medicine's Institute for Cell Engineering's Stem Cell Program, had found non-CpG methylation prevalent in neurons, a finding that surprised them, since this wasn't found in any other cells besides stem cells.

By looking at what genes were being transcribed in neurons, he and his colleagues found that, like the form of methylation scientists had seen in stem cells, non-CpG methylation stops genes from being expressed. They also mapped the genome to find where non-CpG methylation happens, and found that it carves out its own niche, and are distributed in regions without CpG methlyation. "That was the first hint that maybe it can function independently of CpG methylation," Song says.

The new kind of methylation also seems to operate under different rules. Scientists have long thought methylation was final. Once a cytosine gets a methyl stuck to it, so the story went, that gene is shut off forever. "This became dogma," Song says. "Once cells become the right type, they don't change their identity or DNA methylation."

But non-CpG methylation seems to happen later, when the neuron is mature—and even after conventional wisdom said it was irreversible. The researchers learned this from an experiment in which they knocked out in adult mice the enzymes that attach methyl groups to DNA. They found the neurons still had just as much CpG methylation, but the non-CpG methylation dropped off. This suggests that non-CpG methylation is an active process, Song says, with methyl groups continually being taken off and put back on, adding to evidence that non-CpG methylation

may play more of a role in managing operations in mature cells.

The researchers also found a way that non-CpG methylation is similar to CpG methylation in one important way: it's read by MeCP2, an enzyme long identified as a player in methylation.

That's significant because a mutation in MeCP2 causes Rett Syndrome, and understanding DNA methylation is key to understanding this syndrome. The disorder occurs, Song says, when working copies of the gene for MeCP2 are silenced during development.

More information: www.nature.com/neuro/journal/v … nt/full/nn.3607.html

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