Scientists find clue to mechanisms of gene signaling and regulation

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Scientists have discovered a pattern in the DNA sequence of the mouse genome that may play a fundamental part in the way DNA molecules regulate gene expression. The research, led by Emory University scientists along with colleagues at Jacobs University, Bremen, Germany, will be published in the Aug. 22 Advance Online publication of the journal *Nature*.

Ever since scientists cracked the basic code of chemical bases that comprise the genome of humans and animals, scientists have been uncovering layers of other chemical modifications of gene functioning that can be inherited along with the DNA sequence. This field of discovery, called epigenetics, turns out to be just as important as the genetic sequence itself in controlling whether genes are turned on or off, which determines whether or not they manufacture proteins.

For the past several decades, scientists have known that DNA methylation, a biochemical reaction that adds a methyl group to DNA, is one of these epigenetic processes that marks genes for silencing, which means they do not manufacture proteins. Another kind of modification, called histone methylation, also marks histone proteins that are part of the complex packaging of DNA within the nucleus of cells.

How and where this critical selection process is accomplished--for either silencing or expression-- has been a mystery, however. DNA methylation occurs across the animal genomes, almost always at the C base position of a CG dinucleotide (sequence of two base pairs) in the genetic

sequence.

Most expressed genes are based on the simultaneous expression of two copies of a geneÑone from the mother and one from the father. A small subset of genes, however, are allele-expression specific, meaning only one copy of the gene is expressed, from either the mother or the father, with the gene from the other parent being methylated, or silenced. This kind of differential gene expression is called "imprinting." In the mouse genome, about 80 genes are imprinted.

The Emory and Bremen researchers discovered a biochemical pattern they believe may be a signal to the epigenetic machinery that a particular gene should be imprinted. In the regions of the genome where genes are imprinted, called differentially methylated regions, they found a repeat pattern (periodicity) of 8 to 10 base pairs between two CG dinucleotides. The periodicity is consistent with the structural information from the enzyme responsible for the methylation. The enzyme structure was solved by use of X-ray crystallography at the Advanced Photon Source of Argonne National Laboratory.

"We believe that this repeating pattern of 8 to 10 base pairs between CGs provides a signal for where the differential methylation should take place," says senior author Xiaodong Cheng, PhD, Emory professor of biochemistry and a Georgia Research Alliance eminent scholar. "So far only about 20 regions of differential methylation have been identified in the mouse genome, and we wanted to find out how those regions compared to the rest of the genome."

"Now we can use this new information to find out if any other areas with such 8 to 10 base pair repeats are also differentially methylated. We want to discover how many regions of differential methylation exist and whether or not this imprinting has any impact on disease development."

Scientists already have learned that cancer genes contain "islands" of CG concentrations that are abnormally methylated. Dr. Cheng and his colleagues will focus on these CG islands, trying to discover whether they contain the same repeating pattern as the differentially methylated regions.

Source: Emory University