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New Breakthrough in Understanding Gene Regulation

A team of researchers at the University of North Carolina, Chapel Hill Superfund Research Program (UNC SRP) Center and Yale University developed a new method to study DNA modifications that led them to a paradigm-shifting discovery of a new mechanism of gene regulation in mouse cells. The new method and resulting discoveries are important breakthroughs that open new possibilities for understanding gene regulation in mice and humans, particularly during development.

One way that cells regulate gene activity is through the chemical modification of DNA, known as epigenetic regulation. Enzymes add or remove methyl groups from individual DNA components, and those changes determine whether a gene will be activated. Epigenetic regulation plays an important role in development and disease. For example, epigenetic changes influence which genes are turned on and off during the development process from the fertilized egg into an organism. Epigenetic changes have been shown to occur after environmental exposure to harmful chemicals, and some have been linked to certain diseases.

The prevailing paradigm of epigenetic regulation in mammals (including mice and humans) focuses on one form of modified DNA called 5-methyl cytosine (5mC), particularly cytosine preceding guanine (CpG dinucleotides). The presence of 5mC is associated with gene silencing and reduced gene expression in mammalian cells. A different form of modified DNA, N6-methyladenine (N6-mA), is common in bacteria but has not been reported in mammals. In bacteria, N6-mA plays a role in gene activation.

James Swenberg, Ph.D., D.V.M., at the UNC SRP Center worked with a team of researchers to develop a new sophisticated method that allowed them to identify miniscule amounts of N6-mA in mouse embryonic stem (ES) cells – only 6 to 7 individual N6-mA bases per million adenines were detected in the entire mouse genome. The research team modified the single-molecule real-time (SMRT) sequencing technique to achieve a remarkable level of sensitivity. SMRT compares the rate of DNA replication at sites with modified DNA bases with the rate of replication at sites with non-modified DNA bases. The new approach, called SMRT-ChIP, amplifies results to allow detection of smaller amounts of modified DNA.

After identifying N6-mA in mouse ES cells, the researchers set out to learn more about where it is found in the genome and what its functions might be. To do this, they first identified the enzyme that removes the methyl group from N6-mA, rendering it inactive. Through a series of experiments, they identified Alkbh1 as an N6-mA methyltransferase.

They used Alkbh1 as a tool in additional experiments to explore possible functions of N6-mA. They learned that N6-mA acts as a gene silencer and reduces gene expression for 550 genes in mouse ES cells. This function is the direct opposite of the function of N6-mA in bacteria, where it activates gene expression. They also identified 37,581 sites where N6-mA binds to DNA, primarily in regions that are important for gene regulation. The large number of affected genes and DNA binding sites suggests that N6-mA may be very important for gene regulation.

These breakthroughs open new windows for understanding epigenetic regulation of gene expression and raise interesting questions about the evolution of gene regulation pathways. The new technique is a powerful tool for studying uncommon DNA modifications. Furthermore, the identification of N6-mA and its demethylating enzyme Alkbh1 in mouse ES cells provides paradigm-shifting information that sheds new light on epigenetic regulation during development and disease in humans. Understanding epigenetic regulation may help us understand how exposure to harmful chemicals in the environment leads to health effects and how we might prevent those effects.

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To learn more about this research, please refer to the following source:

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