Making memories that last a lifetime

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Neurobiologists have discovered a mechanism by which the constantly changing brain retains memories—from that dog bite to that first kiss. They have found that the brain co-opts the same machinery by which cells stably alter their genes to specialize during embryonic development.

Courtney Miller and David Sweatt reported their findings in the March 15, 2007 issue of the journal *Neuron*, published by Cell Press.

Their studies aimed at exploring whether a process called DNA methylation plays a role in forming memories. In this process, molecules called methyl groups are attached to genes, which switches them off. Conversely, lack of methyl groups enables the genes to remain activated.

Cells use methylation during embryonic development to selectively deactivate genes to enable the cells to specialize into different types as the embryo develops. Such regulation is dubbed "epigenetic," since it constitutes a layer of genetic control beyond the regulation inherent in the structure of genes themselves.

Methylation causes a permanent change in gene activity during development. So, while previous studies by Sweatt and others had hinted that the methylation mechanism remains active in adult brains, researchers had generally believed that methylation would not constitute a mechanism for long-term establishment of memories. However, as misregulation of DNA methylation occurs in some brain disorders like schizophrenia and forms of mental retardation, Miller and Sweatt designed experiments to test whether methylation specifically regulates

memory formation.

In their experiments, the researchers conditioned fearful memories in rats by giving the animals mild shocks when they were in a specific training chamber. The researchers could then test whether the rats remembered the conditioning by observing whether they froze when placed in the chamber.

Using drugs that inhibit methylation, the researchers showed that methylation was necessary for rats to form such memories. Particularly importantly, the researchers found that the level of methylation directly controlled the activity of genes known to either suppress or promote memory formation. The memory suppressor gene they studied is called protein phosphatase 1, and the memory-promoting gene is called reelin.

"To our knowledge, this study is the first to present evidence that DNA methylation, once thought to be a static process after cellular differentiation, is not only dynamically regulated in the adult nervous system but also plays an integral role in memory formation," concluded Miller and Sweatt. They wrote that their findings indicate that DNA methylation has been co-opted by the central nervous system as a "crucial step" in regulating gene activity involved in memory formation.

What's more, they noted, abnormal epigenetic regulation has been seen in cancer, some types of autism, and schizophrenia. Thus, they said their findings could aid in basic understanding of epigenetic mechanisms that underlie those disorders.

"The findings presented here may provide an important and relevant piece of data to the schizophrenia field, as they provide evidence that reelin methylation is subject to modulation in response to experience and environmental stimuli," wrote Miller and Sweatt.

More broadly, they wrote, their findings "indicate the importance of dynamic regulation of DNA methylation in behavioral changes brought about by the perception of environmental stimuli."

Source: Cell Press