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Epigenome orchestrates embryonic development

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The early stages of embryonic development shape our cells and tissues for life. It is during this time that our newly formed cells are transformed into heart, skin, nerve or other cell types. Scientists are finding that this process is largely controlled not by the genome, but by the epigenome, chemical markers on DNA that tell cells when to turn genes on and off.

Now, studying zebrafish embryos, researchers at Washington University School of Medicine in St. Louis have shown that the epigenome plays a significant part in guiding development in the first 24 hours after fertilization.

The research, which appears Feb. 20 in the journal *Nature Communications*, may deepen understanding of congenital defects and miscarriage.

The epigenome is a bit like software that makes sense of the DNA code hard-wired into each of the body's cells. While the DNA hardware is the same in each cell, differences in the epigenome—the software—differentiate brain cells from muscle, skin, eye or heart cells.

Using zebrafish as a model of vertebrate development, the new study is the first to map changes in the epigenome of whole embryos and their roles in gene regulation during the earliest hours of development.

"Our study suggests that an underappreciated fraction of the genome is

involved in gene regulation," said senior author Ting Wang, PhD, assistant professor of genetics. "Another surprising finding is that many of the important regions of DNA we identified are pretty far away from the genes they regulate.

"The field long has been focused on identifying genes that manufacture proteins," Wang added. "We are showing that the epigenome is just as important and is an area that is largely uncharted."

Wang is a principal investigator on the Roadmap Epigenomics Program, a national initiative to map the human epigenome, supported by the National Institutes of Health (NIH). Researchers leading this program recently published large data sets detailing information about human epigenetics.

"The human genome, like the zebrafish genome, is epigenetically regulated," Wang said. "But in humans, for ethical reasons, we can only look at tissues in childhood and adulthood and describe differences between cell types. With zebrafish, we can watch the developmental process as it unfolds."

To do so, Wang and first author Hyung Joo Lee, a graduate student in Wang's lab, studied zebrafish embryos at five intervals after fertilization, stopping at the 24-hour mark, when the embryos start to develop separate tissues.

At each of these points in time, the investigators measured several ways the epigenome regulates gene expression, one of the most important of which was with methyl groups. Methyl groups are organic compounds that attach to the DNA in different places. If many methyl groups are concentrated in a given area, the DNA is packaged away and gene expression is shut down. If the DNA is demethylated—with few or no methyl groups—genes are unpackaged and can be expressed.

Most studies of DNA methylation have focused on areas close to genes called promoters, which function like switches, turning gene expression on or off.

"But our data show that only 5 percent of DNA methylation changes happen in conventionally defined promoters," Wang said.

The scientists were surprised to discover the remaining 95 percent of the methylation changes happened in regions far from genes and their promoters, in parts of the genome considered noncoding because they don't tell the cell to make a particular protein.

Most of the changes in methylation at these distant sites involved losing methyl groups, which tends to increase gene expression. This gradual loss of methyl groups increased as the stages of development progressed, presumably turning on gene expression somewhere else. Using several techniques, the researchers were able to correlate the loss of methyl groups in one location with the dialing up of gene expression elsewhere.

This allowed them to statistically predict which noncoding regions of the genome were dialing up expression of distant genes. They determined these noncoding regions functioned as developmental enhancers, and they experimentally verified 20 of them in zebrafish. The data showed that these 20 enhancers drove expression of developmental genes in specific tissues, including the eye and parts of the brain and spinal cord.

The investigators pointed out that many developmental problems, whether they result in the loss of the embryo through miscarriage or in later disorders, can't be pinned to a particular gene.

"This study suggests that many diseases may have an epigenetic origin," Wang said. "Even if there is nothing wrong with the protein coding genes themselves, there are lots of different regulatory changes that could mess

up gene expression and lead to disease."

Wang noted that this study supports the trend of scientists finding more and more noncoding parts of the genome that play essential roles in gene regulation.

"I'm sure there are parts of the genome for which we may never find a function," he said. "But when we look deep, we can derive very complex regulatory relationships between noncoding regions and the distant genes they regulate."

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