Stem cell researchers uncover previously unknown patterns in DNA methylation

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A previously unknown pattern in DNA methylation - an event that affects cell function by altering gene expression - has been uncovered for the first time by stem cell researchers at UCLA, a finding that could have implications in preventing some cancers and correcting defects in human stem cell lines.

The team of scientists discovered a relationship between DNA methylation and the positioning of nucleosomes, which compact and regulate access to DNA in the nucleus of a cell. The discovery was made using high-throughput DNA sequencing to study the sites on DNA where high levels of methylation were occurring, said Matteo Pellegrini and Steve Jacobsen, researchers with the Broad Stem Cell Research Center at UCLA and senior co-authors of the study.

The study appeared Sun., May 30, 2010 in the early online edition of the peer-reviewed journal *Nature*.

The processes required for the survival of a cell depend on the cell's ability to store and read the genetic information encoded in its DNA. Packaging the long DNA into a tiny nucleus is complicated because the DNA still needs to be accessible to the cell's molecular machinery. The molecules that compact DNA are called the nucleosome core particles. Each one has about 147 base pairs of DNA wrapped around it. This interaction forms a sort of scaffolding for compaction of the long DNA polymer, while allowing it to be accessible for events such as methylation.

DNA methylation is important in regulating genes that play a role in the differentiation of embryonic stem cells and in the development of some cancers, Jacobsen said.

"Changes in DNA methylation are behind a lot of what makes a stem cell a stem cell. As the cell differentiates, the DNA methylation tends to change. One aspect of understanding methylation is understanding its pattern and how it's laid out within the cell," said Jacobsen, a professor of molecular, cell and developmental biology and a Howard Hughes Medical Institute investigator.

In this study, the UCLA team found that the DNA wrapped around nucleosomes is more highly methylated than flanking DNA, which links adjacent DNA/nucleosome complexes.

"These results indicate that nucleosome positioning influences DNA methylation patterning throughout the genome and that DNA methyltransfereases (the enzymes that methylates DNA) preferentially target nucloesome-bound DNA," said Pellegrini, an associate professor of molecular, cell and developmental biology and an informatics expert.

The work was initially done in Arabidopsis, a mustard weed commonly used in plant research. Once the DNA methylation and nucleosome positioning patterns emerged, they repeated the work in human stem cells. Pellegrini and Jacobsen found similar patterns in the human stem cells.

One of the most important, unknown aspects of DNA methylation, Jacobsen said, is how the cell determines where the event occurs, and the pattern of nucleosome positions has emerged as an important determinant of methylation.

The findings could have implications in fighting cancer because DNA

methylation patterns go awry in cancer, often causing tumor suppressor genes to switch off. The more scientists know about the cellular mechanisms that lay down the correct DNA methylation patterns, the more that process can be manipulated. In the future, this type of research may lead to techniques that result in the ability to control the patterns that go awry and lead to cancer, thus preventing a malignancy.

And because DNA methylation is important in stem cell differentiation, this knowledge could lead to ways to correct defects in stem cells lines in the future.

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