Study affirms role of specialized protein in assuring normal cell development

February 26 2015

Scientists at NYU Langone Medical Center and New York University have demonstrated that a specialized DNA-binding protein called CTCF is essential for the precise expression of genes that control the body plan of a developing embryo.

The findings, to publish online February 27 in *Science*, focus on mouse brain cells that work to manage an animal's movements. The results add important details to how so-called Hox genes help cells keep their positions straight and in the right positions back to front.

Hox genes are arranged in particular clusters on an animal genome and only a subset of Hox genes are active in a given cell. Maintaining a precise "memory" from mother cell to daughter cell of active and inactive Hox genes is fundamental to establishing a normal body plan, the researchers report, and failure of that system produces a body part in the wrong anatomical position.

"Previous research has shown that CTCF acts as a key insulating barrier to prevent mistakes in cells as they multiply and differentiate," says Varun Narendra, the study's lead author, and a fifth-year graduate PhD student in developmental biology at NYU Langone and the Howard Hughes Medical Institute. "Now we have shown that correct positioning also depends on CTCF."

"The findings provide new insight into how cells faithfully transmit this organizational information as embryos develop, and into what goes

wrong when cellular development goes awry, thereby giving rise to abnormal cell development and diseases such as cancer," says senior study investigator Danny Reinberg, PhD, professor of biochemistry and molecular pharmacology at NYU Langone and a Howard Hughes Medical Institute investigator. "Information from this study could help lay the groundwork for therapies that address developmental missteps tied to Hox genes and their regulators."

CTCF is a so-called DNA-binding protein, which marks regions of DNA in animal genomes that serve as "insulators" or partitioning boundaries as cells package their DNA. What the researchers discovered is that CTCF binding ensures that segments of the genome that are packaged to be active do not interfere with neighboring segments that should not be active in the daughter cells they generate.

Using mouse embryonic stem cells that generate motor neurons as a model, the researchers found that CTCF isolates Hox genes from harmful activation. "We found that the activity of CTCF is to divide the Hox cluster into segments, allowing the cluster to fold into strict domains that are either active or inactive on either side of CTCF," Narendra adds.

To demonstrate that CTCF binding is necessary for correct Hox gene activation, the researchers removed the sites on the genome where CTCF would normally bind and showed that without that CTCF binding, the Hox cluster would not fold properly. As a result, motor neurons activated the wrong set of Hox genes.

"By altering the folding pattern of the Hox cluster, we altered the motor neurons' understanding of their anatomical position," says Esteban Mazzoni, PhD, a study co-investigator and assistant professor of biology and New York University. "In doing so, we also altered their ability to send nerve signals to the appropriate muscle targets."

Because the precise activation of Hox genes is essential for a cell's fate, "the research should prove extremely useful in developing novel embryonic stem cell-based therapies, Mazzoni adds.

More information: www.sciencemag.org/lookup/doi/ … 1126/science.1262088

Provided by New York University School of Medicine