

Uncovering the genetic mechanisms driving embryonic development

May 11 2017, by Kevin Mccullough



Ali Shilatifard, PhD, the Robert Francis Furchgott Professor and chair of the Department of Biochemistry and Molecular Genetics, was the senior author of the study that explored the activation of Hox genes in early embryonic development.

A new Northwestern Medicine study, published in *Genes and*

Development, has identified two DNA elements crucial to the activation of a set of genes that drive the early development of embryos, and which also play an important role in the development of cancer cells.

So-called Hox [genes](#) are a related group that control the body plan of a developing embryo; in humans, they regulate the orientation and structure of the vertebrae and spinal cord as well as the location and growth of limbs. Previously, however, the question of how Hox genes become activated, moving from a silent form to an active form, have been poorly-understood by scientists.

"Hox genes are not only crucial for the proper development of the embryo but also play essential roles in tumor formation and metastasis. Understanding the mechanisms that trigger the expression of Hox genes could help us develop novel therapeutic approaches against cancer," said first-author Kaixiang Cao, PhD, a postdoctoral fellow in the laboratory of Ali Shilatifard, PhD, the Robert Francis Furchgott Professor and chair of the Department of Biochemistry and Molecular Genetics.

In the study, the authors present several experiments that provide evidence for a model of embryonic development that utilizes multiple layers of regulation as a "fail-safe mechanism" to guarantee organisms develop properly.

First, the scientists identified two sequences of DNA, located in a so-called "gene desert" between functioning genes, and demonstrated how these sequences ensure activation of Hox genes.

Previously thought to be "junk DNA," the sequences of DNA found in gene deserts have recently been found to play important regulatory roles, and irregularities in these stretches of the genetic code have been associated with disease, including some forms of cancer.

After the scientists pinpointed these previously unidentified DNA sequences, named E1 and E2, they demonstrated they were acting as "shadow enhancers," and regulated the early expression of Hox genes.

Utilizing mouse embryonic stem cell models that had been modified to lack one or both of the sequences, the scientists showed that the two sequences worked redundantly: deletion of either the E1 or E2 sequence resulted in unaffected activation, but removing both E1 and E2 stopped the Hox genes from activating properly.

Separately, the scientists also demonstrated that a protein called SET1A, part of a family of enzymes called COMPASS, which have previously been shown to activate Hox genes, also regulates Hox gene activation: without SET1A, several Hox genes failed to activate.

According to the scientists, the E1/E2 regulation and the SET1A regulation of Hox genes appear to be independent of each other, and are part of a series of multiple regulatory processes that work together to fine-tune the activation of genes essential for the early growth of embryos.

"Future studies that identify small molecules targeting SET1A and factors functioning through the E1/E2 DNA sequences will be important for developing therapies for Hox gene disorders," Shilatifard said.

The project's insight into the process by which Hox genes are regulated, has the potential to identify targets for new treatments for developmental diseases caused by dysfunction in Hox genes, as well as forms of cancer that arise from Hox gene errors, according to the authors.

More information: Kaixiang Cao et al. SET1A/COMPASS and shadow enhancers in the regulation of homeotic gene expression, *Genes & Development* (2017). [DOI: 10.1101/gad.294744.116](https://doi.org/10.1101/gad.294744.116)

Provided by Northwestern University

Citation: Uncovering the genetic mechanisms driving embryonic development (2017, May 11)
retrieved 26 April 2024 from

<https://medicalxpress.com/news/2017-05-uncovering-genetic-mechanisms-embryonic.html>

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