# Surprise in genome structure linked to developmental diseases

August 18 2010

A team of researchers from Whitehead Institute, MIT, University of Colorado, and University of Massachusetts have discovered that each cell type in our bodies has a unique genome structure, which is due to a newly discovered mechanism that controls our genes. The protein complexes that generate this genome structure play a pivotal role in regulating gene transcription and cell state, and have been implicated in multiple developmental diseases.

"I think we have a fundamental new insight into the underlying causes of several neurological and developmental diseases, including Opitz-Kaveggia syndrome, Lujan syndrome and Cornelia de Lange syndrome," says Whitehead Institute Member Richard Young. "And it comes with a surprising new understanding of the control of genes."

According to the Young lab's paper, published online in *Nature* this week, a DNA loop formed at the beginning of cell-type-specific genes enables activation of these genes. Each cell type, such as skin cells, nerve cells, or embryonic stem cells, has its own gene expression program to maintain its cell state. For gene activation, regulatory factors and gene expression machinery, bound to two different parts of the DNA called the promoter and the enhancer, must come in contact. This contact, which is facilitated and maintained by protein complexes called Mediator and Cohesin, forms a set of DNA loops that is specific to each cell type.

"That's such a surprise," says Young, whose lab is deciphering the overall

cellular circuitry required to regulate gene expression and cell state. "We thought that a loop of DNA probably formed at the beginning of some genes—it's an old model—but we didn't expect that loops are formed by these complexes at active cell-type-specific genes."

Problems with this DNA loop structure can interfere with the activation of cell-type-specific genes, which can cause the cell to lose its normal state. Indeed, mutations in Mediator and Cohesin, the protein complexes that contribute to DNA loop formation, at cell-type-specific genes, can cause various developmental syndromes and diseases.

Finding this DNA loop structure in the genome was not the original goal for Michael Kagey, Jamie Newman, and Steve Bilodeau, who are postdoctoral researchers in the Young lab and co-first authors of the Nature paper. While looking for the genes required for embryonic stem cells to maintain their cell state, the trio found that Mediator and Cohesin were located uniquely at active, cell-type-specific genes. Mediator was already known to play some role in gene activation and Cohesin was known to hold chromosomes together. "We had no idea," says Newman, "that Mediator and Cohesin form a novel complex that generates stable DNA loops at active cell-type specific genes."

When the researchers knocked down Mediator or Cohesin in embryonic stem cells, the cells lost their defined embryonic stem cell state and started turning into other cell types.

"This gives us important new insights into how cells are able to maintain cell state," says Kagey. "We believe that Mediator and Cohesin function at different genes in different cell types to establish this cell-type-specific DNA structure and maintain cell state. Without that structure, the cells fail to maintain their normal cell state."

Bilodeau agrees.

"If you lose Mediator or Cohesin function in embryonic stem cells, you can't maintain proper cell state and inappropriate differentiation occurs" says Bilodeau. "We think this is the underlying problem in patients with Mediator or Cohesin mutations—you have a broad spectrum of developmental defects."

Cornelia de Lange patients, many of whom have defects in the Cohesin apparatus, have broad developmental defects, including severe intellectual disability, skeletal abnormalities, small stature, and gastrointestinal dysfunction. Patients with mutations in the Mediator apparatus have various neurological deficiencies.

"We hope these new insights into the control of cell-type-specific gene regulation will facilitate development of new therapeutics for patients with Mediator and Cohesin mutations," says Bilodeau.

**More information:** "Mediator and cohesin connect gene expression and chromatin architecture", *Nature*, August 19, 2010.

Provided by Whitehead Institute for Biomedical Research