**Role of compacted chromosome domains in establishing cell identity during animal development**

Dario Nicetto1 and Kenneth S. Zaret1

*1Institute for Regenerative Medicine, Epigenetics Program  
Department of Cell and Developmental Biology*  
*Perelman School of Medicine, University of Pennsylvania, Smilow Center for Translational Research,*  
*3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA*

A major aim of developmental biology is to understand the molecular processes that cause a fertilized egg to differentiate into the many types of cells seen in the adult organism. Since each type of cell has the same DNA, and therefore the same genes, cell differentiation is controlled by regulating which groups of genes are turned on in given cell. Equally important is that inappropriate genes are not expressed in a given cell. For example, liver cells must express genes that endow liver functions and not genes that endow bone or kidney functions. The cell-specific expression of genes is enabled by the DNA being efficiently packed around histone proteins to form a substance called "chromatin." Chromatin makes up the chromosomes and, broadly speaking, can be considered to exist in two physical states: an open, loosely packed, active configuration, “euchromatin”, and a closed, tightly packed, repressed configuration, “heterochromatin.” The open configuration of chromatin allows access by regulatory proteins that turn genes on, and the closed configuration prevents access by such regulatory proteins. Specific chemical modifications on histones are linked to each of the two chromatin forms and mark the capacity of the underlying DNA, and genes, to be active or silent. Notably, the addition of three methyl groups to the ninth amino acid (K=lysine) on histone H3, or H3K9me3 has been associated with chromatin compaction and repression of genes.

Whilepast studies on early embryonic cells in tissue cultures suggested a progressive accumulation of H3K9me3 and chromatin compaction upon differentiation, the dynamics of H3K9me3 and compaction during animal development, at genes, had not been described previously. To achieve this goal, Nicetto et al. (2019 Science) developed a new method to characterize changes in chromatin compaction, as well as assessed H3K9me3 and gene activity across all of the chromosomes, in various populations of cells from mouse embryos and adult tissues, at various days and weeks after fertilization.

Taking advantage of the different sensitivity of open and closed chromatin in being mechanically fragmented, Nicetto et al. (2019) separated the euchromatin and heterochromatin in embryonic and adult cells and mapped the developmental dynamics in chromatin compaction. They also mapped the dynamics in the H3K9me3 and in the expression of genes, at each developmental stage. Contrary to prior assumptions based on embryo cells in tissue culture, Nicetto et al. (2019) found that at eight days after fertilization, when the embryo cells in vivo have not yet begun to acquire a specific identity, the number of genes labeled with the methyl groups on H3K9me3 and exhibiting chromatin compaction was higher compared to earlier and later days. Many genes that were activated, going from embryonic to mature cells, showed a loss of chromatin compaction and H3K9me3.

To understand the mechanism responsible for the establishment of compacted domains, the authors genetically ablated, in embryonic precursors to liver cells, the enzymes that add the methyl groups on histone H3, and assessed the consequences. Embryonic liver cells depleted for the enzymes activated cell-inappropriate genes, and consequently mice lacking the enzymes expressed genes for bone and kidney in their liver, they were smaller than normal mice of the same age, and they died not long after birth.

Overall, the Nicetto et al. (2019) study indicates that repression of genes is an important mechanism in early animal development. If the H3K9me3 repressive mechanism is lost, upon deactivation of the proteins that establish compacted domains, the cell does not gain its proper identity and functions improperly. Understanding the dynamics in chromatin compaction and the role of the related enzymes will help us to instruct human embryonic stem cells to acquire specific identities at will, as well as to directly changes cell fates (trans-differentiation), by perturbing compacted chromatin at specific sites. Ultimately, these approaches can help control cell fate so to repopulate organs whose cells are malfunctioning, and alleviate human diseases.