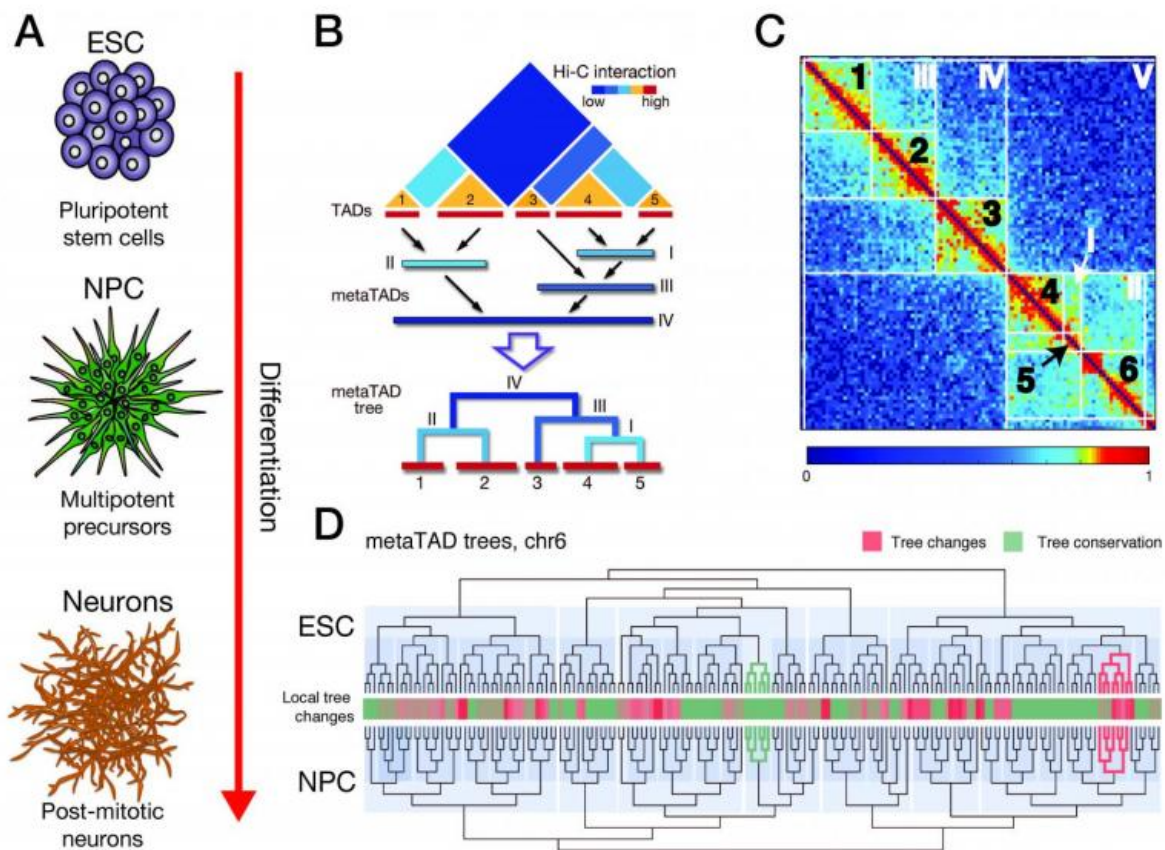


Changing architecture: A new understanding of the spatial organization

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(A) Scheme of mouse embryonic stem cells (ESC), neuronal progenitor cells (NPC) and differentiated neurons. (B) Meta-domains (metaTADs) are found by single-linkage clustering of individual topological domains (TADs), defining a hierarchical topology. (C) Contact map of part of a chromosome (Hi-C data) with domain and meta-domain structure indicated as white boxes. (D) Meta-domain trees for chromosome 6 in ESC (top) and NPC (bottom). The colour

heatmap between the trees indicates their local similarity. Two examples of highly similar (green) and dissimilar regions (red) are indicated. Credit: M. Schüler/A. Pombo

It has now been 15 years since scientists celebrated the completion of the human genome. At that point, scientists had determined the entire sequence of the genetic letters making up our DNA. It is now known that this was only an initial step in a long journey: in addition to the chemical letters, information is also encoded in the manner in which the DNA is packed inside the cell nucleus. A research team led by Ana Pombo from the Max Delbrück Center in Berlin-Buch, in collaboration with international colleagues from Italy, Canada and Great Britain, has now generated comprehensive 3D maps of the spatial organization of the mouse genome, from embryonic stem cells to fully developed neurons. The work has been published in the journal *Molecular Systems Biology*. In the future such maps might help track down genes that are involved in hereditary diseases.

Different cells of our body carry the same genetic information, written in the sequence of the genetic letters on our DNA. How the genes arranged on the long DNA thread are controlled has been the subject of many years of research. Which genes are used in a cell determines whether a cell develops for example into skin, or a heart or nerve cell; errors in gene regulation may result in disease.

It has become clear that the linear genetic text alone is not sufficient to understand the genome. "The three-dimensional organization of DNA is also very important," says Ana Pombo, head of the research group Epigenetic Regulation and Chromatin Architecture at the MDC. In mice, the genome thread is divided into 20 pairs of chromosome, which are in turn tightly packed in the [cell nucleus](#) in a non-random manner. "The

complex spatial folding of the DNA of the chromosomes controls the activity of genes," the scientist explains.

Over the last decade considerable progress has been made in determining the three-dimensional architecture of chromosomes. It is now known that they are divided into "topological" domains, i.e. into sections of DNA that come into direct contact more often than their genomic neighbors. "Until now the spatial structure has been studied in and around these domains," says Markus Schöler, postdoctoral researcher in Ana Pombo's group at the MDC and one of the first authors of the study. "However, we lacked a complete picture of how these domains interact with each other and whether such interactions are linked to gene function."

This is precisely the question addressed in the study by the researchers from the MDC. They took a detailed look at how the entire DNA is folded in the chromosomes and which regions preferentially contact each other. As a model, they investigated the development of mouse neurons from embryonic stem cells to a progenitor cell and differentiated neurons. For these three cell types, the researchers analyzed interaction maps, called Hi-C data: data that shows which regions touch each other within each chromosome.

Using this strategy, the researchers were able to put together a matrix of contacts for every chromosome in all three cell types. Their results showed that chromosomal domains are grouped in larger meta-domains. The folding of these meta-domains is not random - a crucial point. "Various regions on a chromosome come together because they have something in common," Pombo says. "Regions with similar functional properties contact each other, for example genes that are active, or that are regulated by the same mechanism."

To illustrate this, Pombo uses a thread to represent the string-like form

of DNA. In her hand, she forms several loops so that the thread meets again and again at the base of the loops. "This is where regions meet that have something in common," she explains. The looping arrangement illustrates a very important finding: it provides a means by which regions that are spaced far apart on the linear DNA can come into contact with each other. "For the first time we were able to determine specific, long-range contacts between domains across whole chromosomes," Pombo says.

The researchers represented this interaction as a tree-like hierarchy of domains that shows which region is in contact with which others. When they compared the tree diagrams of the [embryonic stem cells](#), neuronal progenitors and neurons they saw that during differentiation, many of the long-range contacts remain in place. However, other regions form new contacts, again based on common features. "Changes in gene activity correlate with changes in the spatial organization," Schüler says.

The scientists believe that in the future, this map of contacts might be used to help find the causes of genetic diseases. On the one hand, it could be used to localize chromosome rearrangements that play a role in conditions such as cancer. On the other, it might be possible to identify genes that are responsible for congenital diseases. This has been one result of numerous genome-wide studies carried out in recent years that have linked mutations to various diseases. However, for many of these genetic variants, the means by which they cause the particular disease has been unclear. They might, for example, change gene interactions instead of the genes themselves.

"Our maps increase the pool of targets on DNA that might be affected by a single mutation," Pombo says. The group's results make it possible to look up the other regions on the DNA with which a particular gene variant is in contact. The researchers from Berlin now want to pursue these relationships for neurological disorders such as autism and for

skeletal diseases.

More information: Hierarchical folding and reorganization of chromosomes are linked to transcriptional changes in cellular differentiation, msb.embopress.org/cgi/doi/10.15252/msb.20156492

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