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FEATURE ARTICLE

Chromosome Interactions and Where to Find Them

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Cells face a perplexing challenge: Squeezing in two meters of DNA inside a nucleus a fraction of a millimetre wide. The cell achieves this by tightly wrapping DNA into structures known as chromosomes. The way chromosomes are localised within the nucleus can have implications for gene expression and is thus an area that is extensively researched. Two new studies, recently published in Nature by Stevens et al. (2017) and Beagrie et al. (2017), have elucidated the arrangement of chromosomes within the nucleus and their three-dimensional interactions. Their findings can potentially identify causes of mishaps in cancer and other genetic diseases.

When chromosomes are compacted into the nucleus, regions of DNA that are not adjacent in the sequence are brought closer together, allowing them to interact. Primarily, this is achieved through the formation of variably sized loops. Regions of DNA where these physical interactions are frequently known as topologically associated domains (TADs). Chromosome conformation capture experiments, such as Hi-C, can be used to show the interactions that occur within a TAD. Hi-C involves fragmenting the genome into smaller chunks and fusing ends of DNA segments that are in close proximity to each other. These joined DNA fragments can then be isolated, sequenced, and mapped to the known genome sequence. TADs tend to group regions of the genome that are of a similar state – for example, genes encoded in a TAD may all be actively expressed or they may all have been silenced.

Hi-C and Fluorescent Imaging

The study conducted by Stevens group is exciting as it provides one of the first genome-wide analyses of 3D interactions in individual cells. By combining Hi-C with fluorescent imaging, the Stevens group could map interactions onto the 3D genome architecture of mouse embryonic stem cells. In all cells studied, discrete chromosome territories could be seen, reinforcing previous studies, although the exact chromosome structure varied. This highlights the benefit of studying individual cells, as they provide insights to cellular heterogeneity. Some TADs, it has been suggested, may have highly dynamic structures, which could correlate to changes in gene expression.

Protein complexes are known to control changes in gene expression. The nucleosome remodelling and deactylase complex (NuRD) controls the expression of a specific subset of genes. A fascinating finding from Stevens group was that NuRD-regulated genes interact and cluster together, suggesting that there is function behind genome structure. Interestingly, the exact genes brought together varied amongst the cells. This was shown from Hi-C, as the interacting chromatin regions differed. Further work is now required to understand the factors driving the formation of NuRD clusters.

Genome Architecture Mapping

Beagrie et. al. used genome architecture mapping (GAM), a new genome-wide method to analyse chromatin contacts, in their study of mouse embryonic stem cells. In contrast to the Hi-C technique used by Stevens and colleagues, GAM involves sequencing DNA from a large collection of thin cryosections through the nucleus, without the requirement of joining DNA fragments together. The data collected replicates and reinforces the evidence for genome architecture from studies like that conducted by the Stevens group. However, the Beagrie group, by using GAM, could reveal three-way contacts across the genome. This major advantage is currently unattainable using the other chromatin capture methods, making GAM a desirable new technique. To make sense of all this data, Beagrie's group developed a mathematical model called SLICE that identifies the most specific chromatin contacts. By analysing these triplet contacts, it has been found that some chromatin contacts can connect up to three TADs containing highly active genes.

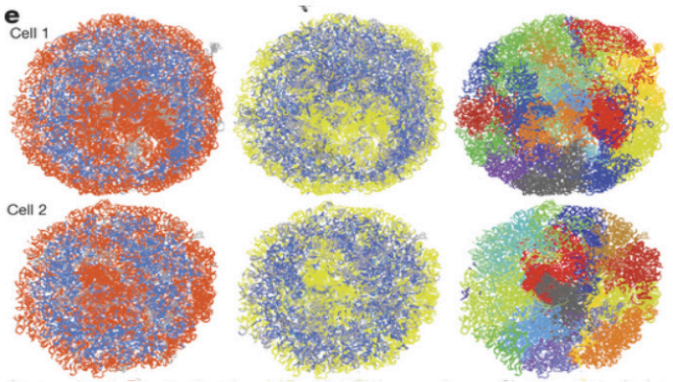

Figure 1. Chromosomes are arranged into discrete territories in the nucleus (Stevens et al., 2017).

In conjunction, these two new techniques are powerful tools to study the 3-D genome architecture. Once the locations of the interactions are fully mapped, analyses can be conducted to understand the function behind them. This is no trivial task and will require further experimentation into the specific DNA marks present in different TADs and analyses of the roles and expression levels of the genes present. By applying this to multiple cell types such as skin and liver cells, tissue-specific differences in interactions can then be discovered. Knowing the conserved interactions in each of these cell types will make identification of cancerous cells with damaged or duplicated chromosomes much easier. This has the potential to revolutionise the way cancer is both diagnosed and treated.

References:

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