FEBS Letters 589 (2015) 2867–2868

journal homepage: www.FEBSLetters.org

Editorial

3D genome structure. Organization of the nucleus in space and time

One of the major endeavors of modern biology is to understand how the spatial structure of genomes relates to the expression of genes. Research in this field is fostered by the rapid development of 3C-derived technologies, permitting to assay chromosome contacts in vivo.

The recent years have witnessed an ongoing race for resolution and coverage, assisted by the prowess of high throughput sequencing technologies. Every study has confirmed that genomes are structured in space, but how this structure ties in with gene expression is still an area of intense investigation.

Genome-wide analyses of 3D contacts by HiC revealed the existence of several substructures overlapping to some extent with chromatin domains. Most intriguing is the discovery that at 20–100 kb resolution the genomes of metazoans are segmented in so-called Topologically Associated Domains (TADs). In mammals, these megabase-scale domains are defined as contiguous segments with more contacts *within* than *between*. Even though TAD borders are fuzzy, they are remarkably stable between cell types and even between species. What TADs actually look like is presently unknown, and whether they fold as globules or as a succession of loops is debated. Nevertheless, there is strong agreement that chromosomes are segmented in space. TAD boundaries are enriched in binding sites for insulators, such as CTCF, cohesins, condensins and TFIIIC, but such sites are also found inside TADs and what makes the TAD boundaries function as such is another open question. The leading hypothesis is that compartments limit the action range of enhancers and provide a backbone for promoter–enhancer interactions, shielding away regulatory elements that should not come in contact with each other.

This organization may also explain cell-to-cell heterogeneity in gene expression. The TAD structure, as it appears on HiC interaction maps, represents an average configuration and the contacts that emerge at the population level may not all be present in the same cell. Consistent with this view, data from polymer physics suggest that TADs have variable structures between cells. Thus, a given enhancer–promoter contact may occur or not, depending on the configuration of the TAD they reside in, so the noise of gene expression may be the direct consequence of the cell to cell heterogeneity of genomic structures. Deeper understanding will come from technical progress ensuring complete analysis of genomic interactions in single cells and individual alleles. This information, combined with high-resolution fluorescence microscopy, will provide a detailed description of the heterogeneity within a cell population and of the response to external cues that change gene expression.

We can further speculate that chromatin modifications change the local stiffness of the chromatin, which in turn will have an impact on the probability that the TAD folds in a configuration or another. Interestingly, this model whereby histone modifications act at a structural level was the original proposal of the histone code hypothesis. It is noteworthy that such models may explain the spontaneous reactivation of latent viruses. The fluctuations of chromosome structures may accidentally put a latent virus in contact with an enhancer, starting a new cycle of infection. Yet, the relationships between the organization of the genome and the "nuclear fauna" are presently unexplored.

Another key aspect in the regulation of genes is their position in the nucleus. About 40% of the human genome lies in peripheral megabase-scale domains called Lamina Associated Domains (LADs). Chromosomes are a mosaic of domains locating at the center or at the periphery. The most striking feature of this organization is that silent genes reside mostly in LADs, while active genes tend to be at the center of the nucleus. This is true in different cell types of the same organism, so the LAD organization is fluid with respect to differentiation: genes travel inward or outward as they are turned on or off.

What force could explain the shuttling of genes? Actin, myosin and other ATP dependent movements have been postulated, but we would like to mention conformational entropy. Entropic forces merely represent the fact that systems at equilibrium explore equally all the configurations with the same energy. If these configurations are not uniform in space, patterns can emerge without energy expenditure.

Physics of confined polymers shows that compact and stiff parts tend to move towards the periphery, while open and flexible parts tend to move towards the center. This phenomenon, known as the "entropic centrifuge", reflects that there are more molecular configurations whereby compact and stiff parts are on the outside. An interesting feature of this model is that it naturally links the organization at different scales. Local changes to the compaction and stiffness of the chromatin can make a *locus* travel large distances and establish the polar organization of the genome. The crucial point is then to understand the mechanisms to specifically decompresses a region of the genome.

An important question regarding the spatial organization of the genome is whether or not the nucleus is a system at equilibrium. More precisely, how much of the observed organization can be explained by the physics of equilibrium? Depending on the answer, we may look for the source of this organization in the simple rules of physics, or in the complex toolbox of biology. In any event, natural selection has been acting on those structures for millions of years, we can thus expect that every feature has been put to use and optimized for some function of the cell. The sources of genome organization must be many, and the associated mechanisms must be diverse.

http://dx.doi.org/10.1016/j.febslet.2015.09.003

The recent technological advance still leaves a dimension of genome organization in the dark: time. The vast majority of the models of genome structure convey a static or statistical perspective. If genome folding is somewhat different in every cell, is it stable or does it keep fluctuating? Can the kinetics of conformational changes reveal something about the mechanisms at work? Those questions must be addressed in the context of a single cell. Major progress is thus expected to come from the developments of super-resolution microscopy.

More generally, the field is at a turning point, as the promising communication between molecular biologists and physicists has yet to become a dialogue. Polymer physics and structural biology have the potential to bring major contributions to our understanding of transcription and differentiation. If a common language can be found, the years ahead may reveal how the complexity of the nucleus emerges from simple physical laws.

Guillaume J. Filion
Miguel Beato
CRG, Barcelona, Spain
E-mail addresses: guillaume@genomearchitecture.com (G.J. Filion), miguel.beato@crg.eu (M. Beato)

Available online 9 September 2015