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Serum starvation shifts TFIIIC binding to impact genome structure and function of human cells

Friday October 27, 2017; 10:00 am

Centre Génomique fonctionnelle Bordeaux – salle des conférences

Folding of the human genome from a fiber-like structure into a higher-order assembly is absolutely crucial for all nuclear processes[1]. Different kind of signaling and stress conditions, such as heat shock (HS) or serum starvation (SS) that can certainly impact nuclear functions might also reflect into changes underlining chromatin architecture[2]. CTCF and TFIIIC are genome insulators conserved from invertebrates to mammals that can act in regulating 3D genome organization[3]. However, thus far structural studies of genome organization have been primarily focused on the role of CTCF and very little on the interplay between mammalian insulators especially during stress conditions. Here we report that TFIIIC, besides its known role in RNA polymerase III (pol3) transcription, participates in 3D genome reshaping in normal and cancer cells in response to serum deprivation. Remarkably, we uncover a general reversible mechanism by which, following growth factor depletion, TFIIIC shifts its enrichment from tRNA genes to genomic regions harboring acetylated young Short-INterspersed Elements (SINE) close to pol2 promoters. We report that TFIIIC binding to these Alu is required to increase H3 Lysine-18 acetylation (H3K18ac) and establish proper DNA looping via interaction with pre-existing Cohesin and CTCF binding sites in order to sustain expression of a subset of genes that regulate nuclear, cell cycle and growth factor response in a serum-dependent manner. All together these data shed light on the complex role of TFIIIC and transposable elements in regulating gene expression and 3D organization in human, and expose a sophisticated way in which cells can re-utilize a factor of a growth-sensing machinery to rewire gene expression, epigenetic and 3D genome reorganization to communicate changes in nutrients availability.

References:

1 Bonev, B. & Cavalli, G. Organization and function of the 3D genome. Nat Rev Genet 17, 772, doi:10.1038/nrg.2016.147 (2016).

2 Li, L. et al. Widespread rearrangement of 3D chromatin organization underlies polycomb-mediated stress-induced silencing. Mol Cell 58, 216-231, doi:10.1016/j.molcel.2015.02.023 (2015).

3 Noma, K., Cam, H. P., Maraia, R. J. & Grewal, S. I. A role for TFIIIC transcription factor complex in genome organization. Cell 125, 859-872, doi:10.1016/j.cell.2006.04.028 (2006).