ID de Contribution: **28** Type: **Non spécifié**

Cell type specific chromatin domain organization reflects transcriptional competence in human mammary tumor cells

The spatial organization of chromatin in the nucleus is non-random and chromatin dynamics participate in regulating essential nuclear processes. 3D genome organization is a 'moderator' of long range interactions, in particular between regulatory elements such as enhancer-promoter contacts. Chromatin folding is thought to contribute to transcriptional regulation within topologically constrained domains of usually 1-2Mb.
We use estrogen inducible loci in human mammary tumour cells as a model system in which chromatin remodeling via looping allows priming of the gene environment for transcription activation. We mapped chromatin folding over several hundred kb around the estrogen responsive progesterone gene (PGR) using 3D DNA FISH and confronted these measurements with 5C data to establish models of domain organization. Our results indicate that rapid estradiol induction of PGR expression occurs in the context of pre-existing chromosomal architectures between the PGR coding region and an enhancer-spiked adjacent 300kb upstream gene desert. The groundstate domain architecture becomes stabilized and interactions between regulatory elements re-inforced, in response to estradiol signalling in estrogen receptor positive MCF7 cells. In a cell line, in which the receptor is not expressed, MDA-MB231, the entire domain around the silenced PGR gene is organised in a very different way with significantly less contacts between the enhancer region. It is tempting to speculate that this lack of organization permits silencing of PGR, or escape of hormono-regulation, in these mammary tumour cells which symbolise a more aggressive breast cancer ethiology.

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