6ème Rencontre scientifique des Grands Causses

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Recueil des résumés

Contents

1

Dynamics of Nuclear Crowding and Electrostatic Effects on Chromatin

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I present an ongoing investigation on whether the electrostatic potential across the nuclear membrane or its fluctuations influences chromatin organization directly via condensation or indirectly through confinement and crowding, focusing on *Saccharomyces cerevisiae* across its growth cycle. In particular, we target key metabolic transitions such as glucose uptake, and will investigate the diauxic shift and entry into quiescence (Q phase), where major changes in nuclear architecture and metabolism occur. To test this, we are developing tools to quantify the electrical properties of the inner nuclear membrane and track their dynamics during these transitions. Using chemical and genetic perturbations of metabolic pathways, we will assess how shifts in membrane potential affect chromatin structure by high-resolution live imaging. Biophysical models will predict how electrostatic and crowding effects can shape chromatin conformation, the integration of models with experiments will allow the validations of hypothesis. This integrative approach aims to uncover how nuclear electrostatics modulate chromatin folding and cellular function during yeast growth phases.

2

Multiscale visualization of nucleolar chromatin in yeast Saccharomyces cerevisiae

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Spatial organization of chromosomes is crucial for genome stability, transcription, and proper mitotic segregation. By employing a range of imaging technologies, including random illumination microscopy and single molecule localization microscopy (SMLM), we conducted an in-depth exploration of the chromatin organization in budding yeast, with optical resolutions ranging from 250 nm to 50 nm. In silico models based on passively moving polymer chains and local tethering to nuclear landmarks explained much of the experimental data in yeast chromatin. We compared these models with our new imaging data of the nucleoplasmic and nucleolar chromatin. Chromatin fibers observed in the nucleoplasm showed some similarity with model prediction with a resolution of 150 nm. However, we visualized local clustering of chromatin in both the nucleoplasm and nucleolus, rather than the tube-like appearance predicted by polymer chain models. In the nucleolus, local clustering of ribosomal DNA (rDNA) chromatin is consistently observed from 150 nm resolution down to 50 nm. We also observed that actively transcribed rDNA spatially segregates from bulk nucleolar chromatin. Using correlative light and electron microscopy (CLEM), we found that local rDNA clustering is forming a specific nucleolar subdomain visible in transmission electron microscopy, the yeast equivalent of metazoan fibrillar center. We conclude that nucleolar chromatin forms a distinct sub-nucleolar compartment in yeast, supporting the model of a tripartite structural organization of the yeast nucleolus.

3

H. Flow, a 3D animation explaining how repeat sequences drive genome organization and condition gene expression

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Over 20 years ago, the scientific community identified the general mechanistic principles governing the establishment of open or closed chromatin domains in a given region of the eukaryotic genome, which either permit or prevent the expression of the underlying genes, respectively (1-5). The clustering of domains predominantly harboring closed chromatin forms the heterochromatin compartment, also known as the B compartment, while open chromatin forms the euchromatin or A compartment. This partitioning of chromatin within the nucleus was first observed by E. Heitz in the early 20th century using microscopy (6).
It was discovered that key to this partitioning are short DNA elements capable of nucleating and anchoring heterochromatin material (ProB elements) or, conversely, counteracting its assembly at the nucleosomal fiber, thereby seemingly repelling B-type chromatin (ProA elements) (1-5).
We showed that ProA and ProB elements are derived from repeat sequences (RepSeqs), in human and likely in all higher eukaryotes (7). In human, constitutive ProA RepSeqs are predominantly composed of Alu elements, whereas constitutive ProB RepSeqs consist of young L1s, some Endogenous Retroviruses (ERVs) and a panel of satellite DNA sequences, including AT-rich microsatellites, pericentromeric and subtelomeric satellites. Additionally, RepSeqs of all types with more indefinite character and, importantly, their derivatives known as "transcriptional enhancers", can switch between ProA and ProB functions and thereby act to open or close specific chromatin domains depending on the cellular context.
It thus appears that a major and previously unrecognized function of repeat sequences, which constitute the majority of the genome in higher eukaryotes, is to organize the genome into two distinct compartments, euchromatin and heterochromatin. This process is essential for the regulation of gene expression during cell differentiation and development, and for the prevention of diseases, most notably cancer.

While the key players have thus been identified, the mechanisms by which repeat sequences organize the genome and the molecular dynamics involved remain unclear. We will address this question through a 15-minute 3D animated video.

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4

How SMC5/6 controls chromatin dynamics in yeast

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résumé à venir

5

Extracellular matrix stiffness modulates nuclear lamina organisation and sets nuclear conditions for PRC2 repression

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Capability of cells to respond to tissue-level elasticity has important physiological and pathological implications. Stiffening of the extracellular matrix (ECM) promotes invasive behaviour of cancer cells, supports the transformation of fibroblasts into cancer-associated fibroblasts and primes stem cell differentiation programs. Here, we investigated how ECM stiffness modulates the Nuclear Lamina (NL) and its impact on gene expression programs, epigenetic marking and 3D genome organisation. By combining hydrogel cell culturing of primary fibroblasts, genomics and super-resolution microscopy, we found that ECM stiffness modifies composition of the NL, modulates long range chromatin interactions, induces changes in chromatin motion and regulates thousands of genes. We identified a specific set of genes coding proteins involved in pathways related to mechanical adaptation such as adhesion and signalling. These genes harbour an apparent bivalent chromatin signature and are expressed under soft condition while repressed in stiff condition through Polycomb Repressive Complex 2 (PRC2). We found that this stiffness-specific repression is tempered by mechanotransduction and the NL. This work uncovers mechano-dependent NL composition, changes in 3D genome organisation and in chromatin motion which underlie adaptative gene expression programs controlled through PRC2.