The tri-dimensional organization of the genome is clearly linked to its function as it varies during the cell cycle and upon differentiation in metazoan.

However, the causal relationship between nuclear organization and function remains often elusive. Budding yeast has proven to be an excellent model system for testing the functional role of higher-order chromatin organization. Extensive studies over the last two decades have revealed a dynamic yet well-defined organization of the yeast genome, which impacts on gene expression and genome stability through mechanisms that are still poorly understood (Taddei et al., 2012).

Using this model system, we ask two main questions:

1. **What determines the spatial and temporal behavior of chromatin?**

2. **How nuclear organization affects two essential functions of the genome: gene expression and the maintenance of genome integrity?**

To address the first question, we focus on the clustering of silent chromatin as a model of functional compartment in which the clustering of repetitive DNAs leads to the sequestration of general repressors of transcription, a phenomenon conserved from yeast to human (Meister & Taddei, 2013). Deciphering how such microenvironments are formed despite the absence of physical barrier to delimitate them, and what regulate their dynamics in relation to changes in genome activity is a key step in understanding how nuclear organization participates in nuclear
function. In budding yeast, heterochromatin is mainly found at telomeres that cluster in foci at the nuclear periphery in cycling cells. We have shown that the silencing factor Sir3 is a limiting factor for the clustering of telomeres and that Sir3 can promote telomere clustering independently of heterochromatin formation (Ruault et al., 2011). In order to gain insight into the physical mechanisms underlying the dynamics of silent chromatin we integrate our experimental data into quantitative models generating hypothesis that are then tested experimentally (Hoze et al., 2013).

We recently showed that chromosomes adopt distinct organizations according to the metabolic status of the cell (Guidi et al., 2015). In particular, following carbon source exhaustion, the telomeres of quiescent cells group into a unique focus or “hypercluster”, localized in the center of the nucleus, thus constraining the global organization in cells able to sustain long-term viability upon starvation.

We now aim at deciphering the mechanisms regulating the dynamics of nuclear architecture in relation to changes in genome activity and addressing how nuclear architecture impacts on chronological lifespan.

Combining cell biology, genetics and omics approach we investigate the interplay between the 3D folding of the genome, RNA expression (coding and non-coding) and the maintenance of genome stability upon major metabolic transitions and during prolonged quiescence.

Using advanced super-resolution microscopy and single molecule approaches, we study the dynamics and structure of chromatin and telomeric factors in order to decipher the physical parameters underlying telomere clustering in different metabolic states. We also develop
systematic genetic and proteomic screens to identify the molecular factors regulating silent chromatin formation and telomere clustering upon metabolic transitions or genotoxic stresses. We have identified a new pathway that links replication stress with the formation of heterochromatin (Dubarry et al., 2011). Similar observations have been reported in different organisms including human (Nikolov and Taddei 2015). Formation of heterochromatic structures at sites of replication stress may contribute to genome integrity by preventing collisions between the replication and transcription machineries.

As the analysis of yeast chronological lifespan and genome stability have been often predictive of processes influencing these essential processes in different species, we anticipate that basic principles will emerge from our studies with broad implications relevant in other organisms.

Key publications

Year of publication 2018

Antoine Hocher, Myriam Ruault, Petra Kaferle, Marc Descrimes, Mickaël Garnier, Antonin Morillon, Angela Taddei (2018 Oct 26)

*Expanding heterochromatin reveals discrete subtelomeric domains delimited by chromatin landscape transitions.*

*Genome research*: DOI: gr.236554.118

Year of publication 2015

Micol Guidi, Myriam Ruault, Martial Marbouty, Isabelle Loïodice, Axel Cournac, Cyrille Billaudeau, Antoine Hocher, Julien Mozziconacci, Romain Koszul, Angela Taddei (2015 Apr 2)

*Spatial reorganization of telomeres in long-lived quiescent cells.*


Year of publication 2014

Isabelle Loïodice, Marion Dubarry, Angela Taddei (2014 Mar 11)

*Scoring and manipulating gene position and dynamics using FROS in budding yeast.*

*Current protocols in cell biology / editorial board, Juan S. Bonifacino ... [et al.]*: Unit 22.17.1-14 : DOI: 10.1002/0471143030.cb2217s62

Year of publication 2013

Nathanaël Hozé, Myriam Ruault, Carlo Amoruso, Angela Taddei, David Holcman (2013 Apr 10)

*Spatial telomere organization and clustering in yeast Saccharomyces cerevisiae*
nucleus is generated by a random dynamics of aggregation-dissociation.
Molecular biology of the cell : 1791-800, S1-10 : DOI: 10.1091/mbc.E13-01-0031

Year of publication 2011

Marion Dubarry, Isabelle Loïodice, Chunlong L Chen, Claude Thermes, Angela Taddei (2011 Jul 5)
Tight protein-DNA interactions favor gene silencing.
Genes & development : 1365-70 : DOI: 10.1101/gad.611011

Myriam Ruault, Arnaud De Meyer, Isabelle Loïodice, Angela Taddei (2011 Feb 9)
Clustering heterochromatin: Sir3 promotes telomere clustering independently of silencing in yeast.
The Journal of cell biology : 417-31 : DOI: 10.1083/jcb.201008007