



UNIVERSITÀ
DI TRENTO

Dipartimento di
Biologia Cellulare,
Computazionale e Integrata



Organizers:

Marta Biagioli
Fulvio Chiacchiera

Epigenetics Mondays Seminars

Every Monday from May 10th till June 14th

June 7th @ 2:00PM

ROOM A103

Alessio Zippo, Ph.D.

*Department of Cellular, Computational and Integrative Biology - CIBIO
- Group Leader, Laboratory of Chromatin Biology & Epigenetics*

Role of chromatin condensates in establishing nuclear architecture

Chromatin is a viscoelastic polymer organized in distinct compartments that modulate both the genetic and the nongenetic function of the genome, including its mechanical features. Chromatin compartments include biomolecular condensates whose dynamic establishment and functioning depends on multivalent interactions occurring among transcription factors, cofactors and basal transcriptional machinery. However how chromatin players contribute to determine nuclear architecture and its mechanical properties has not been addressed. By interrogating the effect of *KMT2D* haploinsufficiency in Kabuki Syndrome, we found that MLL4 contributes in the assembly of transcriptional condensates through liquid-liquid phase separation ¹. We determined that MLL4 maintains an equilibrium between transcriptional- and Polycomb-associated condensates, which is required for preserving the nuclear mechanical properties. Indeed, MLL4 loss-of-function (LoF) caused a PcG-mediated increment of nuclear mechanical stress, affecting YAP/TAZ nuclear accumulation and consequently the transcriptional regulation of its targets, including cohesin and condensing genes. MLL4 LoF impaired the correct chromatin compartmentalization of Polycomb proteins, altering nuclear architecture. By releasing the nuclear mechanical stress through the inhibition of the mechano-sensor ATR, we re-established the mechano-signaling of mesenchymal stem cells and their commitment towards chondrocytes both *in vitro* and *in vivo* ¹. This study supports the notion that in Kabuki Syndrome the haploinsufficiency of MLL4 causes an altered functional partitioning of chromatin, which determines the structure and the mechanical properties of the nucleus.

References:1 Fasciani, A. et al. MLL4-associated condensates counterbalance Polycomb-mediated nuclear mechanical stress in Kabuki syndrome. *Nature genetics* 52, 1397-1411, doi:10.1038/s41588-020-00724-8 (2020).