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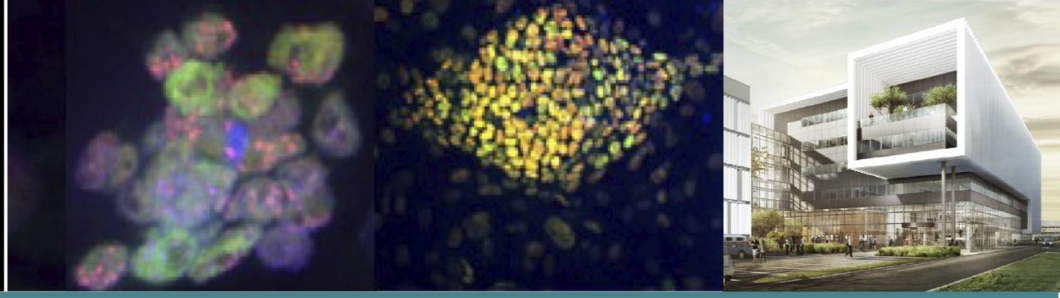

Chromatin Organisation Dynamics & Evolution

Monday
February 7TH 2022

11h A.M

Susan M. GASSER

Director of ISREC Foundation, Lausanne, Switzerland

Histone H3K9 methylation and HMTs in tissue-specific gene expression and genome stability

One of the fundamental structure-function questions in biology addresses the folding of the linear DNA molecule to achieve compaction while maintaining the ability to reveal specific sequences to repair enzymes or transcriptional activators. The levels of DNA compaction range from its wrapping around nucleosomes and compaction of the nucleosomal fiber, to the long-range segregation of chromatin into compartments. Both are shown to influence mechanisms of repair, replication and transcription, and both depend in part on the epigenetic modifications of histones. With respect to cell fate determination and epigenetic inheritance, we use the nematode *C. elegans* to study somatic and germline mechanisms of inheritance, and the impact of chromatin on genome stability. We have examined gut, hypoderm and muscle cell differentiation and the role of the nuclear envelope, lamin-associated chromatin, and the heterochromatic mark, H3K9me, on cell fate and tissue-specific gene expression. By depleting the major H3K9 HMT in muscle, we showed that differentiated, nondividing cells require the continual activity of the H3K9me HMT MET-2, and that its loss leads to the expression of germline genes and inappropriate tissue-specific genes. Misbinding of transcription factors drives aberrant gene expression. Loss of this H3K9me HMT also leads to the transcription of repeat elements, and a dramatic increase in genome instability due to an aberrant accumulation of R-loops, leading to sterility. This is aggravated by the loss of the exosome, of BRCA1/2 repair factors and checkpoint kinases involved in the repair of R-loop induced damage. Intriguingly, it is suppressed by expression of an activity dead MET-2 enzyme, suggesting a noncatalytic function for this HMT, which correlates with condensate or focus formation.

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Methot, S.P., Padeken, J. et al. (2021) ***Nature Cell Biol*. 23,** 1163–1175. https://doi.org/10.1038/s41556-021-00776-w.
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